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DEMEESTER FESTSCHRIFT

Introduction to Festschrift for Tom R DeMeester

Jeffrey Peters

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Although there are many measures of a successful surgical career: the patients we treat, the residents we train, the departments we build, or the knowledge we contribute, arguably one of the greatest is the "disciples" we leave behind. Through a career spanning well over 30 years, Tom DeMeester has taken joy and pride in inviting young surgeons from all over the world to join him for a year or two in the pursuit of excellence in the clinical care and research of esophageal and foregut disease. For those of us who had this unique experience (I had the pleasure of being Tom's first clinical esophageal fellow), we found a man with an uncompromising dedication to his work and life, providing an example of excellence not only in clinical care and research but also in life and leisure. Through these fellows, Tom's impact on the field of esophageal disease has been enormous. Through Tom and Carol's generous spirit and example, their impact on our lives has been equally significant.

In May 2008, on the eve of Tom's stepping down after 18 years as Chairman at the University of Southern California, we brought together these fellows along with a few friends and colleagues to celebrate Tom's contribution to us and to others. Tom has trained 122 esophageal fellows from 28 countries and six of the seven continents. As can be seen from the photograph accompanying this volume, most of them joined us in Pasadena, for a wonderful, once in a lifetime, 48 h of fellowship. The program included 47 presentations ranging from bile reflux to NOTES. All were excellent, and as a testament to Tom's impact, most were presented by individuals who have helped define the topic. The 18 papers found in this Festschrift volume were selected from among these talks and, as you will see, provide a fitting remembrance of the event and tribute to Tom DeMeester's career. We only regret that we could not publish them all. Enjoy!

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DEMEESTER FESTSCHRIFT

Personalized Treatment—The Promise of Molecular Genetics Diagnostics

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Neoplastic cell behavior occurs as a consequence of cumulative disruptions to the otherwise tightly controlled proliferation mechanisms normally in existence within the intracellular molecular environment. Cells become empowered with a number of specific characteristics[1] including the ability to replicate without limitation, resistance to growth inhibitors, receptivity to growth enhancers, evasion of programmed cell death, the development of new blood supplies, and the ability to spread through normal tissues and seed off new colonies.

It is ironic that while these features impart an overwhelming survival advantage to the cancer cell and its progeny, the impact on the person in whom they develop are potentially fatal. The degree, however, to which individual cancers cells display these characteristics varies substantially, even within tumors of the same tissue origin, and this is intrinsically dependant on the molecular pathway by which the normal cell ultimately became malignant. Each neoplastic characteristic is controlled by a gene, or set of genes, and the way in which these are corrupted determines the exact genotype, and hence phenotype of the cancer. This phenomenon, referred to as molecular heterogeneity, can be observed as variations in the microscopic/pathological and macroscopic/clinical features of both tumor and patient.

The basic principle of the "two-hit hypothesis", as first proposed by Knudson in 1971,[2] still largely holds true today. Sequential inactivation of tumor suppressor genes results in the failure of protein formation via the transcription–translation pathway, the loss of cell-proliferative inhibition and ultimate progression toward malignant behavior. This can occur as a consequence of direct damage to the gene itself, resulting in failure to produce a viable functioning product, or by actual gene-silencing through aberrant methylation of the gene promoter region. (Regulated methylation, and controlled activation of tumor suppressor genes are vital during embryogenesis and tissue-organ development, but becomes unrequited once this is complete).

Tumors therefore can develop as a consequence of gene inactivation through both genetic, and epigenetic mechanisms. The precise pathway by which a cell traveled along via genetic and/or epigentic routes across multiple genes to become cancerous determines it individual molecular signature,[3] and understanding this is fundamental to the ways in which we can develop novel diagnostic and therapeutic strategies which are presently discussed.

Early Detection and Surveillance

Prompt diagnosis is essential for the hope of potentially curative treatment. The recent detection of tumor related-DNA within circulating plasma[4] and other, easily attainable bodily fluids[5] could prove to be a vital means of non-invasively, but accurately confirming a suspected diagnosis, as well as obtaining detailed information on the biological nature of the lesion without the need for tissue biopsy. Furthermore, subsequent monitoring of possible disease recurrence following treatment can be facilitated by the detection of tumor-related DNA in this simple manner.[6]

Similarly, "at-risk" patients frequently undergo repeat investigations to keep pre-malignant lesions under surveil-

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lance, much of which proves to be unnecessary. Barrett's metaplasia is one such example, where the risk of neoplastic progression to adenocarcinoma is in the order of 1 in 100, causing many patients to undergo endoscopy and detailed biopsies on an annual basis, although in relatively few will an early cancer be detected. Numerous molecular events occur in the development of metaplastic tissues, and there is a substantial degree of molecular heterogeneity within the cells from different patients with Barrett's. Identifying which specific molecular events are consistently and reliably related to a higher risk of malignant progressions will eventually enable a more focused interrogation in these with lower risk patients having less frequent or being released from routine surveillance.

Predicting Prognosis

Estimating cancer-free survival is an inevitable question posed by patients about to embark on a recommended course of treatment. Currently this has to be evaluated, with varying degrees of accuracy, on the basis of numerous staging investigations that also help formulate the potential therapeutic modalities to be offered. More accurate information is then available if definitive, curative surgical resection is undertaken, based on the histopathological extent and nature of the lesion. Molecular characterization of the tumor DNA reveals detailed information on behavioral aspects of the cancer, such as its aggressiveness in the propensity it has to invade and metastasize and can therefore act as a further staging adjunct and help decide with greater confidence a proposed treatment protocol.[7,8]

Specific, tumor-related genetic and epigenetic alterations are being linked with variable clinical outcomes and this is likely to form the forefront of prognostic information available prior to embarking treatment, and will consequently influence how this is to be undertaken and ultimately followed up.

Gene-Based Therapy

How far can we modulate our proposed treatment strategies based on cellular–molecular information?

Pharmacogenomics

Drug therapy is an integral part of the treatment, either wholly or as an adjunct to surgery for most cancers. The infusion into the body of a highly toxic agent, with the aim of selectively destroying certain cells, while leaving others unaffected is at the moment a very crude method of cancer treatment. The basic rationale is to try and exploit the different and higher metabolic nature of neoplastic tissues, which can then selectively uptake these destructive agents. Inevitably, there will be uptake and destruction of normal cells too, which results in the debilitating symptoms, referred to a side-effects observed as a consequence of treatment.

Malignant cells may indeed be totally resistant to the chemotherapeutic agents offered, with no consequent benefit to the patient at all. Furthermore, the ability of the body to deal with these chemicals influences how this toxicity affects normal cells and thus clinical side-effects.

Based on tumor genotype, it will become possible to determine the sensitivity of a specific cancer cell to the different chemotherapeutic options available, in an identical manner to which specific anti-microbial therapy is offered for the "same" infection caused by a different bacterium with a unique profile of drug resistance.

The high levels of expression of certain proteins in some, but not all tumors of the same origin enable the use of specific drugs only for the lesions which will be sensitive to it. The selected use of Imatinib for leukemia, and Erlotinib for lung cancer both of which act on tyrosine kinase inhibitors, and Herceptin for breast cancer acting on *HER2* are examples of this emerging trend. This is not dissimilar to the use of hormonal therapy for certain breast and prostate cancers which display receptivity to circulating steroids.

Hegi et al.[9] recently demonstrated that the use of the toxic drug temolozide as an adjunct to radiotherapy for brain tumors is only of benefit if tumors show aberrant methylation of the tumor mismatch repair gene methylguanine methyltransferase. Thus, patients in whom such tumors have developed by an alternative pathway can be spared this unnecessary and toxic intervention.

Patients' ability to deal with circulating drugs depends on the efficacy of intrinsic metabolic enzymes to breakdown or inactivate these agents. Targeted, effective drug therapy therefore involves a molecular evaluation of the patient as well as the lesion. Examples of this include the breakdown of 6-mercaptopurine in the treatment of leukemia, which is dependent on the viability of thiopurine methyltransferase (TPMT), and 5-Fluoruracil, a common agent for many cancer treatments and dihydropyrimide dehydrogenase.

Screening for genetic defects in this enzyme prior to treatment allows the utilization of a patient-specific dose, being optimally effective and minimally inducive of toxic side-effects. This molecular-based, medical therapy is not just limited to cancer drugs, but indeed applies to all medication with potentially dangerous side-effects. Classes of drugs such as anti-coagulants and anti-depressives are

dependent on cytochrome p450 for their metabolism, and this too in future should be evaluated when offering a safe but effective prescription.

Chirogenomics

Can surgical therapy be influenced by molecular genetic information?

Prophylactic surgery has been offered to individuals with a perceived high-risk of developing an organ-based tumor, even if there is no clinical or macroscopic evidence of invasive disease. This may be the basis of essentially a detailed family history, or the recognition of clinical features where progression to neoplasia is deemed near inevitable. In these situations, it has been thought justifiable to surgically remove an entire, normal organ as a cancer preventative measure.

Major surgical resection of this form however is not without risk, and may indeed seem difficult to recommend to asymptomatic patients with no clinical evidence of disease. Operative mortality, surgical complications and the impact on quality of life and function following healthy organ resection have to be carefully considered, as well as the fact that despite a positive family history or a relationship to a syndrome, actual cancer progression does not occur in all individuals, and therefore, it is likely that some may in fact be undergoing what might have proven to be unnecessary surgery.

The identification of specific gene-related anomalies with these clinical conditions facilitates a much better informed decision-making process. Confirmation of the presence of a genetic or epigenetic defect within patients in addition to the clinical presentation makes the decision to undertake surgical intervention more justifiable, although there still remains a degree of variable penetrance, in other words, despite the presence of a molecular marker, absolute progression to cancer is not guaranteed, however the odds against this happening are substantially reduced. Table 1 gives a number of examples where molecular-genetic markers are now being utilized to this effect.

Prophylactic, gene-based surgery is likely to be the future for major cancer resection. The concept of waiting and watching for it to happen, and then dealing with the consequences, perhaps seems outdated when guaranteed prevention can be offered against possible cure. The need for radical resection including en-bloc tissue removal or lymph node field clearance no longer becomes an issue in this situation, and as a consequence, the morbidity that is unfortunately associated with radical, curative-intent cancer surgery is completely avoided. With this relief on the part of the surgical resection however comes a heightened challenge on the part of the surgeon to now offer essentially a major operation on a effectively healthy, asymptomatic patient with minimal or non-existent mortality and morbidity and little or no impact on patient quality of life, the duration of which is expected to be equivalent to that of normal individuals.

It is clear therefore, that as molecular science advances, surgeons must also constantly seek to improve their techniques and strategy to adapt to offering a different new kind of curative cancer surgery as well as deal with greater patient expectation. The development of minimally invasive approaches, which seek to make redundant the substantive trauma of open access surgery, has been a significant advance, and early results for oesophago-gastric cancers appear to be highly encouraging.[10]

Summary

Over the next decade we are likely to see the development of complete molecular profiles patterns for all common cancers, enabling accurate gene-based therapy, both medical and surgical to be offered to patients, specifically designed for an individual based on their tumor and personal molecular-genetic configuration. Surgical therapy

Table 1 Hereditary Cancers, Genes and Preventative Surgical Options

Clinical diagnosis	Gene defect	Organ affected	Surgical option
Familial adenomatous polyposis (FAP)	*APC*	Colorectal	Pan proctocolectomy
Multiple endocrine neoplasia (MEN) 2A	*RET*	Thyroid	Thyroidecotomy
Hereditary non-polyposis colorectal cancer (HNPCC)[a]	Mismatch repair genes		
Lynch I	*MSH2*, *MLH1*, *MSH6*	Colorectal	Pan proctocolectomy
Lynch II		Ovarian, endometrial	Oophorectomy, hysterectomy
Familial breast cancer	*BRCA1, BRCA2*	Breast	Bilateral mastectomy
Hereditary diffuse gastric cancer	*CDH1*	Stomach	Total gastrectomy

[a] Renamed more accurately as hereditary mismatch repair deficiency syndrome (HMRDS)

in particular has to evolve to meet the new demands of preventative and focused curative resection based on the new ideologies that this will generate.

References

1. Hanahan D, Weinberg RA. The hallmarks of cancer. [Review] [94 refs]. Cell 2000;100(1):57–70.
2. Knudson AGJ. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971;68:820–823.
3. Laird PW. Oncogenic mechanisms mediated by DNA methylation. [Review] [40 refs]. Mol Med Today 1997;3(5):223–229.
4. An Q, Liu Y, Gao Y, Huang J, Fong X, Li L et al. Detection of p16 hypermethylation in circulating plasma DNA of non-small cell lung cancer patients. Cancer Lett 2002;188(1–2):109–114.
5. Chan MW, Chan LW, Tang NL, Tong JH, Lo KW, Lee TL et al. Hypermethylation of multiple genes in tumor tissues and voided urine in urinary bladder cancer patients. Clin Cancer Res 2002;8 (2):464–470.
6. Leon SA, Shapiro B, Sklaroff DM, Yaros MJ. Free DNA in the serum of cancer patients and the effect of therapy. Cancer Res 1977;37(3):646–650.
7. Kawakami K, Brabender J, Lord RV, Groshen S, Greenwald BD, Krasna MJ et al. Hypermethylated APC DNA in plasma and prognosis of patients with esophageal adenocarcinoma. Journal of the National Cancer Institute 2000;92(22):1805–1811.
8. Lecomte T, Berger A, Zinzindohoue F, Micard S, Landi B, Blons H et al. Detection of free-circulating tumor-associated DNA in plasma of colorectal cancer patients and its association with prognosis. Int J Cancer 2002;100(5):542–548.
9. Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352 (10):997–1003.
10. Berrisford RG, Wajed SA, Sanders D, Rucklidge MW. Short-term outcomes following total minimally invasive oesophagectomy. Br J Surg 2008;95(5):602–610.

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DEMEESTER FESTSCHRIFT

Bile in the Esophagus—Model for a Bile Acid Biosensor

Dhiren Nehra

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Abstract Acid and bile acids form important constituents of the refluxed substances in patients who suffer from gastroesophageal reflux disease. Whilst 24h ambulatory pH monitoring using antimony or glass pH electrodes measures acid levels 5 cm above the gastroesophageal junction, there are no reliable methods of measuring other constituents of duodenal juices such as bile acids. Past studies in detection of bile acids have included esophageal aspiration studies with detection of bile acids with HPLC or indirect methods using fiber-optic bile sensor "Bilitec" to detect bilirubin in the bile. These methods have either been impracticable or unreliable for routine and accurate measurement of bile acid. More recently, impedance technology has been used to define "weakly" acid or alkaline reflux. There are many potential applications of biosensors of various types, and it is envisaged that a biosensor specific for bile acid would be a more practical tool for routine measurement. This paper looks at a model for development of a biosensor for bile acid based on molecular imprinted polymers.

Keywords Bile · Bile acid reflux · Bile acid biosensor · Alkaline reflux · Non acid reflux

Interest in bile acid reflux (Fig. 1—timeline) began with simple infusional studies with demonstration of chemically induced esophagitis in animal models.[1,2] Others demonstrated that metaplastic and carcinogenic changes could be induced by exposing the esophagus of rats to duodenogastric juices with or without a carcinogen.[3,4] There has been growing interest in the molecular effects of bile acid and acid exposure in Barretts cell lines with studies showing changes in gene expression CDx[5] and upregulation of oncogene c-myc.[6] Repeated exposure to acid and bile acids have been shown to increased proliferation through p38 and ERK MAPK pathways[7] and selectively induce colonic phenotype expression in Barretts cell lines.[8] Unconjugates bile acids have been shown to induce COX-2 expression in Barretts esophagus and adenocarcinoma through reactive oxygen species mediation.[9]

While pH probes were successfully developed to accurately monitor acid reflux, measurement of bile reflux has been difficult. Indirect evidence of increased bile in the stomach with aspiration studies[10] or dual pH monitoring[11] showed an association with esophagitis and Barretts. Presence of bile in the esophagus has also been demonstrated by using prolonged esophageal aspiration studies.[12–14] With HPLC separation of bile acids,[14] we have shown reflux of bile acids in concentrations greater than 200 μmol/l in 50% of the patients with severe esophagitis and Barrett's metaplasia. A wide spectrum of bile acids were detected, predominantly glycocholic and taurocholic acid. A significant proportion of the bile acids in patients with extensive mucosal injury were composed of the dehydroxylated taurodeoxycholic acid and the unconjugated cholic and deoxycholic acids. Secondary bile acids by dehydoxylation or deconjugation can occur by bacterial degradation, and these were shown in patients on PPI whose more neutral gastric environment can promote bacterial overgrowth.[15] However, direct aspiration studies are cumbersome and have not been used routinely in a clinical setting.

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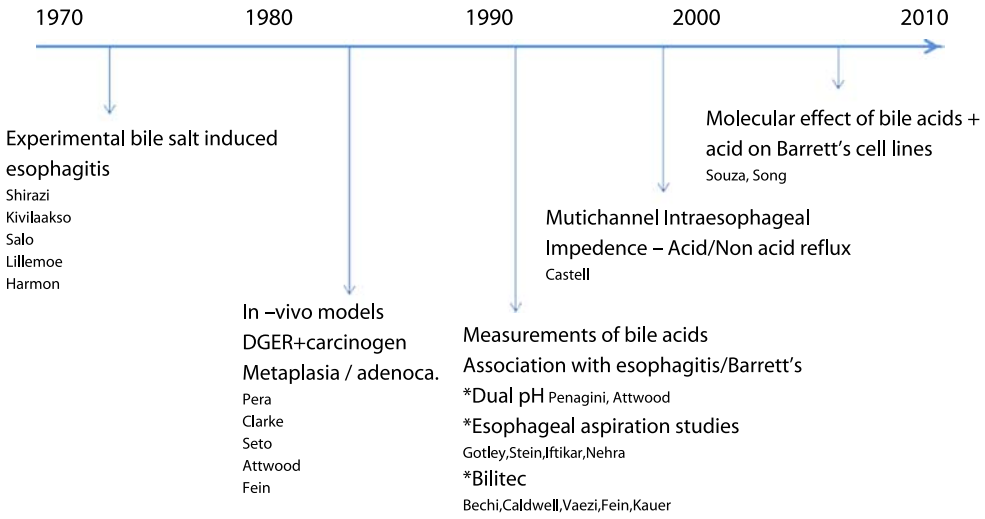
Figure 1 Bile reflux.



The "bilitec probe" was developed as a useful tool for detection of bilirubin in bile; however, the technology had limitations due to non-clearance of the probe and the requirement of a modified diet during the testing period. The current method of detecting acid and non-acid reflux with the usage of combined pH-impedance catheters has been more promising. The recordings have been successful in differentiating liquid acid reflux from liquid weakly acid or weakly alkaline reflux[16] but lacks in determining the composition of the refluxate.

Biosensors for Bile Acids

A biosensor specific for bile acid would seem to be a more practical tool for routine measurement. The system would be reliable with high specificity and sensitivity. It would have miniaturized components, easily tolerated by the patient and preferably incorporated within the current pH monitoring devices. Such a biosensor could be devised using molecular imprinting technology (MIP) (personal communication with Professor Anthony Turner, Department of Biosciences, Cranfield University, UK). MIPs are robust and inexpensive and possess the desired affinity and specificity for a wide range of target analytes. The commercial application of MIPs to the fields of separation and sensing is particularly promising to bile acid detection and treatment of bile reflux. MIP is a novel technique based on recognition characteristics of polymers that have complimentary size shape and binding site to specific substrates and have been applied to recognize steroids such as cholesterol and to bile acids which share the same four-ring nucleus as the steroid.[17] Three particular features make MIPs the target of this investigation: The striking resemblance of their binding properties (affinity and selectivity) to those of natural receptors; their unique stability, superior to that demonstrated by natural biomolecules; and their ease of preparation and adaptation to different practical applications.

The principle of MIP involves selection of polymer that is capable of forming non-covalent interactions with the template molecules such as glycocholic acid (Fig. 2). A

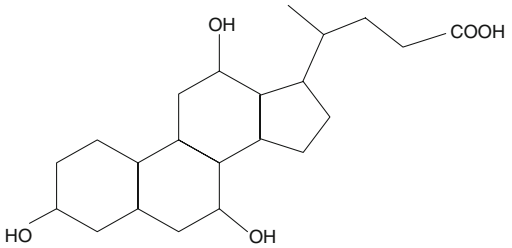


Figure 2 Sodium salt of cholic acid used as a template.[17]

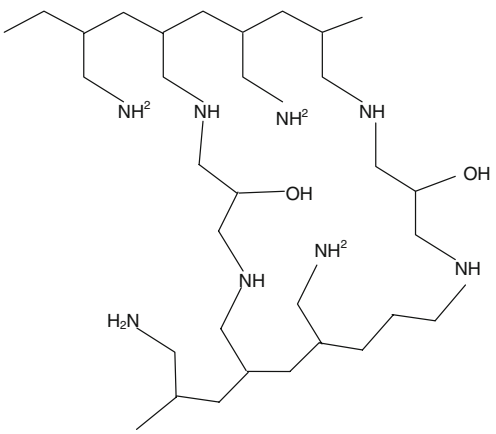


Figure 3 Imprinted polyammonium salt network containing binding sites complimentary to the shape of the bile acid skeleton.[17]

cross-linking agent such as ethylene glycol dimethacrylate is used to obtain imprinted polymer networks. These are subjected to a series of washing cycles to remove the template. The polymer is ground and sieved to particle with a size range of 65–100 μm, and the performance (affinity, specificity, capacity, and stability) is analyzed by chromatographic experiments, using model samples under acidic conditions similar to those existing in the human stomach and esophagus. These cholic imprinted polymer networks (Fig. 3) contain binding sites that mirror the carboxyl group and the shape of the parent steroid molecule. This forms the basis of a detection probe of bile acids. Polymeric sequestrants have been used for treating hypercholesteremia, but MIP has added therapeutic potential in the development of more potent and selective bile acid sequestrants to lower the concentrations of specific bile acids in the esophageal refluxate.

References

1. Salo J, Kivilaakso E. Contribution of trypsin and cholate to the pathogenesis of experimental alkaline reflux esophagitis. Scand J Gatroenterol 1984;19:875–881.
2. Lillemoe KD, Johnson LF, Harmon JW. Alkaline esophagitis: a comparison of the ability of gastroduodenal contents to injure the rabbit esophagus. Gastroenterol 1983;85:621–628.
3. Pera M, Brito MJ, Poulsom R, Riera E, Grande L, Hanby A, Wright NA. Duodenal-content reflux esophagitis induces the development of glandular metaplasia and adenosquamous carcinoma in rats. Carcinogenesis 2000;21(8):1587–1591.
4. Fein M, Peters JH, Chandrasoma P, Ireland AP, Oberg S, Ritter MP, Bremner CG, Hagen JA, DeMeester TR. Duodenoesophageal reflux induces esophageal adenocarcinoma without exogenous carcinogen. J Gastrointest Surg 1998;2(3):260–268.
5. Souza RF, Krishnan K, Spechler SJ. Acid, bile, and CDX: the ABCs of making Barrett's metaplasia. Am J Physiol Gastrointest Liver Physiol 2008;295(2):G211–G218.
6. Tselepis C, Morris CD, Wakelin D, Hardy R, Perry I, Luong QT, Harper E, Harrison R, Attwood SE, Jankowski JA. Upregulation of the oncogene c-myc in Barrett's adenocarcinoma: induction of c-myc by acidified bile acid in vitro. Gut 2003;52(2):174–180.
7. Jaiswal K, Lopez-Guzman C, Souza RF, Spechler SJ, Sarosi GA Jr. Bile salt exposure increases proliferation through p38 and ERK MAPK pathways in a non-neoplastic Barrett's cell line. Am J Physiol Gastrointest Liver Physiol 2006;290(2):G335–G342.
8. Bajpai M, Liu J, Geng X, Souza RF, Amenta PS, Das KM. Repeated exposure to acid and bile selectively induces colonic phenotype expression in a heterogeneous Barrett's epithelial cell line. Lab Invest 2008;88(6):643–651.
9. Song S, Guha S, Liu K, Buttar NS, Bresalier RS. COX-2 induction by unconjugated bile acids involves reactive oxygen species-mediated signalling pathways in Barrett's oesophagus and oesophageal adenocarcinoma. Gut 2007;56 (11):1512–1521.
10. Domellof L, Reddy B, Weisburger JH. Microflora and deconjugation of bile acids in alkaline reflux after partial gastrectomy. Am J Surg 1980;140:291–294.
11. Penagini R, Yuen H, Misiewicz JJ, Bianchi PA. Alkaline intraoesophageal pH and gastro-oesophageal reflux in patients with peptic oesophagitis. Scand J Gastroenterol 1988;23:675–678.
12. Gotley DC, Morgan AP, Ball D, Owen RW, Cooper MJ. Composition of gastro-oesophageal refluxate. Gut 1991;32:1093–1099.
13. Iftikhar SY, Ledingham S, Steele RJC et al. Bile reflux in columnar-lined Barrett's oesophagus. Ann R Coll Surg Engl 1993;75:411–416.
14. Nehra D, Howell P, Williams CP, Pye JK, Beynon J. Toxic bile acids in gastro-oesophageal reflux disease—Influence of gastric acidity. Gut 1999;44:598–602.
15. Theisen J, Nehra D, Citron D, Johansson J, Hagen J, Crookes PF, DeMeester S, Bremner CG, DeMeester TR, Peters JH. Suppression of gastric acid secretion in patients with gastroesophageal reflux disease results in bacterial overgrowth and deconjugation of bile acids. J Gastrointest Surg 2000;4:50–54.
16. Hila A, Agrawal A, Castell DO. Combined multichannel intraluminal impedance and pH esophageal testing compared to pH alone for diagnosing both acid and weakly acidic gastroesophageal reflux. Clin Gastroenterol Hepatol 2007;5 (2):172–177.
17. Huval CC, Bailey MJ, Braunlin WH et al. Novel cholesterol lowering polymeric drugs obtained by molecular imprinting. Macromolecules 2001;34:1548–1550.

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DEMEESTER FESCHRIFT

Emerging Concepts of Bile Reflux in the Constellation of Gastroesophageal Reflux Disease

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Abstract
Rationale Reflux of gastric and duodenal contents in patients with gastroesophageal reflux disease (GERD) has been postulated as a major cause of complications, such as Barrett's esophagus or malignant degeneration.
Findings We present a summary of experimental, clinical, and immunohistochemical studies that show that acid and bile reflux are increased in patients who suffer from GERD, are the key factor in the pathogenesis of Barrett's esophagus, and are possibly related to the development of esophageal adenocarcinoma.

Keywords Gastroesophageal reflux disease · Bile reflux · Esophageal adenocarcinoma

Introduction

Gastroesphageal reflux disease (GERD) is currently the most common benign disorder of the esophagus. In the Western world, 10% to 30% of the population suffers from GERD,[1] caused by symptomatic and nonsymptomatic reflux of intestinal contents into the esophagus. This can lead to inflammation of the esophageal mucosa. It is well accepted that GERD is a disease based on multiple factors. Loss of lower esophageal sphincter resistance and compromised esophageal clearance set the stage for prolonged exposure to the refluxate of gastric and duodenal juice.[2,3] The refluxed juice, that is, acid and duodenal components, individually or in combination, contributes to the development of GERD.[4] In animal and patient studies, it is shown that acid, particularly in combination with pepsin, can cause severe damage of the esophageal mucosa,[5–7] as in esophagitis and stenosis of Barrett's esophagus.[8] Further investigations of the role of bile reflux in the constellation of GERD give new insights into the development of esophagitis, Barrett's esophagus, and esophageal adenocarcinoma.

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Bile Salt Chemistry

The normal human liver converts an average of 0.78 to 1.29 mmol (300 to 500 mg) of cholesterol into bile acids daily.[9] These primary bile acids, cholate and chenodeoxycholate, are synthesized from cholesterol by hepatocytes in a ration of two to one. Three steps are involved in the pathway from cholesterol to primary bile acids: Insertion of a hydroxyl group into the 7α-position of cholesterol under the influence of the enzyme hydroxylase, a configurational change of the 3β-hydroxyl group to the 3α-position and, in the case of cholic acid, a 12α-hydroxylation and conversion of the 27-carbon cholesterol into a 24-carbon bile acid by oxidation and shortening of the side chain.

Secondary bile acids are formed as metabolic by-products of intestinal bacteria. In man, these include deoxycholic and lithocholic acid. Anaerobes, most importantly bacteroides and bifidobacteria, must be present in concentrations higher than 10^3/ml for significant degradation to occur. There are two mechanisms of bacterial metabolism: deconjugation and 7α-dehydroxylation, with the latter being the most common. Both deoxycholate and

lithocholate arise by colonic bacterial 7α-dehydroxylation of cholate and chenodeoxychlate, respectively.[10]

Prior to secretion into bile, 98% of bile acids are conjugated with taurine or gylcine in a ratio of about three to one. Because taurine availability is limited, glycine conjugation rises whenever there is an increased demand for bile acid synthesis. Conjugation, especially with taurine, increases the solubility of bile acids by lowering their pKa. Stated differently, at any given pH, conjugation results in a greater portion of the bile acid in its soluble and ionized form.[11] Interestingly, recent studies have shown that acidification of bile to below pH 2 resulted in a marked decrease of all bile acids commonly found in human bile.[12] This was due to an irreversible bile acid precipitation. The clinical implications of this finding may be twofold: (1) regurgitated bile acids may precipitate and become inactivated within an acidic gastric environment and, (2) given an alkaline environment, such as after gastrectomy or with acid suppression therapy, bile acids may remain in solution and can reflux into the esophagus causing esophageal mucosal injury. Inability to consistently alkalinize gastric juice with acid suppression medication allows a portion of the bile acids to remain in its ionized form, which is capable of crossing the epithelial cell membrane and damaging the mitochondria. Consequently, a gastric juice of pH <2 or >7 is less injurious than a pH between these extremes (Fig. 1).

Bile acid synthesis is regulated by feedback inhibition from reabsorbed bile acids reaching the liver via the portal vein. This circulating pool provides about 97% of the bile salts entering the biliary tree and duodenum. Bile acids that have been deconjugated before absorption are reconjugated before reentering the bile.[13] Intestinal absorption is the key event in the enterohepatic circulation, with maximal activity in the terminal quarter of the small intestine.[14] Absorption in the colon occurs, although it is much slower in the presence of normal colonic flora. The presence of deoxycholate in normal bile, which is virtually absent after colectomy, provides evidence for a colonic role in the normal enterohepatic circulation.[15] Colonic absorption is probably limited to the right colon, where the contents are liquid. This enterohepatic circulation maintains a composition of human bile consisting of 54% cholic, 31% chenodeoxycholic, and 15% deoxycholic acid, of which about 80% is conjugated with taurin and 20% to glycine.[16]

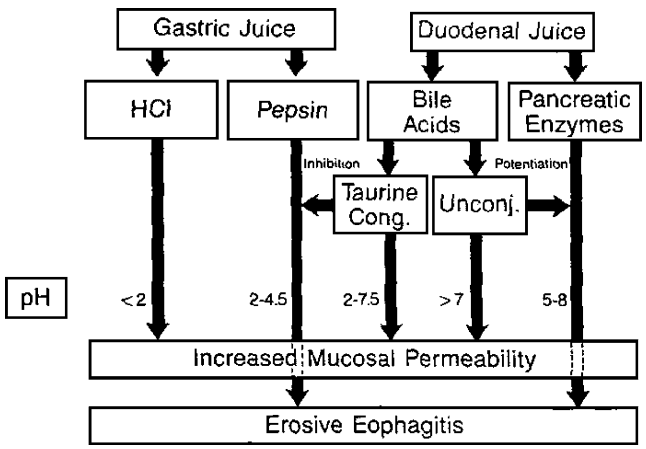

Figure 1 Potentially injurious contents of the esophageal refluxate depending on the pH.

Animal Studies

Using a dog model, Bremner et al.[17] were the first to demonstrate that a columnar epithelial metaplasia in the distal esophagus could result from prolonged reflux of acid. This finding was confirmed by Gillen et al.,[18] who studied canine esophageal mucosa under basal conditions and in the presence of gastroesophageal reflux. Under normal conditions, mucosal defects in the esophagus are regenerated by squamous epithelium. In the presence of gastroesophagealreflux of acid or a combination of acid and bile, regeneration is frequently by columnar epithelium. Lillimoe et al.[19] show that reflux of bile and pancreatic enzymes into the stomach can protect or augment esophageal mucosal injury. In a rabbit whose gastric acid secretion maintained an acid environment, the presence of bile salts attenuates the injurious effect of pepsin, and the acid gastric environment inactivates trypsin. Such a rabbit has bile-containing acid gastric juice that, when refluxed into the esophagus, injures the mucosal barrier and the epithelium but is less caustic than the reflux of acid gastric juice alone. In contrast, in a rabbit that has significant duodenogastric reflux, a more alkaline intragastric pH environment may be present and encourage the solubility of bile salts. This finding is supported by a study by Ireland et al.,[20] who manipulated rats so that the esophagus was exposed to reflux of gastric juice, duodenial juice, or a combination of both. In this rat model, the presence of gastric juice protected against the development of esophageal adenocarcinoma. The absence of gastric juice resulted in a threefold increase in the relevance of adenocarcinoma. The protective effect of the stomach seems to be related to the secretion of acid because there was a progressive increase in the prevalence of esophageal adenocarcinoma as the amount of gastric acid that was permitted to reflux with duodenal juice into the esophagus was reduced.

Human Studies

Because symptoms are not specific, the diagnosis of excessive duodenogastroesophageal reflux must be based

on objective parameters. Currently available methods to detect and quantify bile reflux objectively in the clinical situation of GERD include esophageal and gastric pH monitoring, aspiration studies, bilirubin monitoring, and impedance monitoring.

Esophageal pH Monitoring

Ambulatory 24-h esophageal pH monitoring has become the gold standard in the diagnosis of GERD.[21] In addition to a significantly increased acid exposure, patients who suffer from GERD also can have an increased esophageal exposure to bile, especially when Barrett's esophagus is present on endoscopy and histology (Fig. 2). On pH monitoring, this is indicated by the time pH >7.[22] The alkaline component of the refluxed juice seems to result from a contamination of the refluxed gastric content with excessive duodenogastric reflux.[23] Measurements of esophageal exposure to duodenal contents, however, are less dependable than the measurement of esophageal acid exposure.[24]

Gastric pH Monitoring

After the wide acceptance of 24-h esophageal pH monitoring for assessing gastroesophageal reflux, much work has focused on 24-h gastric pH monitoring as a clinical tool in the evaluation of gastroduodenal disorders. Because of the alkalinic nature of the duodenal content, measurement of alkaline peaks in the acid's gastric environment seemed an attractive method for detacting duodenogastric reflux. The interpretation of gastric pH recordings is, however, more difficult than that of esophageal recordings. This is because the gastric pH environment is determined by a complex interplay of acid and mucous secretion, ingested food, swallowed saliva, regurgitated duodenal, pancreatic, and biliary secretions, and the effectiveness of the mixing evacuating of the chyme.[25] Simple measurement of alkaline episodes on gastric pH monitoring, therefore, proved inaccurate in the detection of duodenogastric reflux. Fuchs et al. consequently developed a scoring system based on 16 parameters of the 24-h gastric pH record, identified by regression analysis, to better estimate the presence and quantity of duodenogastric reflux on the basis of gastric pH monitoring.[26] Validation studies showed that this composite score can completely differentiate the gastric pH profile of normal volunteers from patients who have objectively proven excessive duodenogastric reflux. Subsequent studies confirmed that this scoring system is superior to cholescintigraphy or clinical parameters in the detection of excessive duodengastric reflux.[25,27]

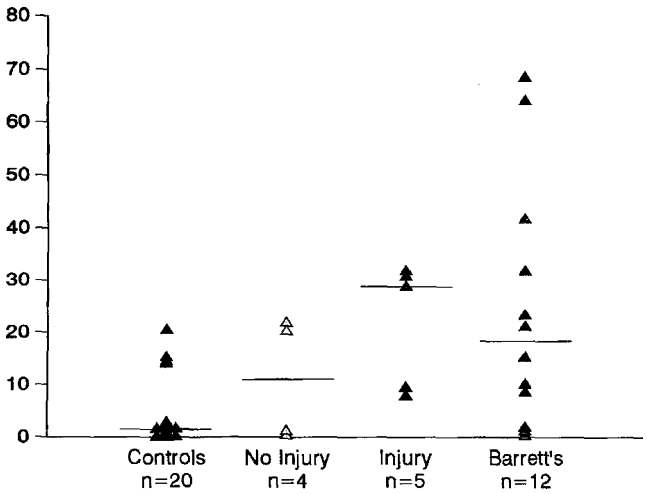

Figure 2 Percentage of total study period during which the esohageal mucosa of each subject was exposed to bilirubin (i.e., absorbance exceeded 0.14). Values of each subject are plotted and the median of each group is denoted by the *horizontal line*s. Patients with mucosal injury and Barrett's esophagus had a significantly higher bilirubin absorbance compared to controls ($p<0.04$, Mann–Whitney).

Aspiration and Chemical Analysis of Gastric Contents

Although many studies suggest excessive reflux of duodenal contents into the esophagus in patients who suffer from GERD, few have measured this directly. Using prolonged ambulatory aspiration in the distal esophagus, it can be shown that patients who have GERD and Barrett's esophagus have greater and more concentrated bile acid exposure to the esophageal mucosa than normal subjects (Fig. 3). This increased exposure occurs most commonly during the supine period while asleep and during the upright period after meals (Fig. 4).[22,28] Aspiration studies also deliver more details on the noxious effects of specific bile salts. Investigators identified the glycine conjugates of cholic, deoxycholic, and chenodeoxycholic acids as the predominant bile acids aspirated from the esophagus of patients who have GERD (Fig. 5). This is because glycine conjugates are three times more prevalent than taurin conjugates in normal human bile.

Bilirubin Monitoring

For reliable detection of duodenal contents in refluxed gastric juice, a fiber-optic system (Bilitec) for circadian monitoring of duodenogastroesophageal reflux was developed by Bechi et al.[29] Major advantages of the system are that it allows prolonged simultaneous measurements at multiple sites in the foregut on an ambulatory basis without interfering with normal physiology and it can be combined with pH monitoring (Fig. 6). With the Bilitec system, using bilirubin as a marker for duodenal juice, it is shown that patients who have reflux of acid gastric juice alone have less severe esophageal mucosal injury than patients who have reflux of

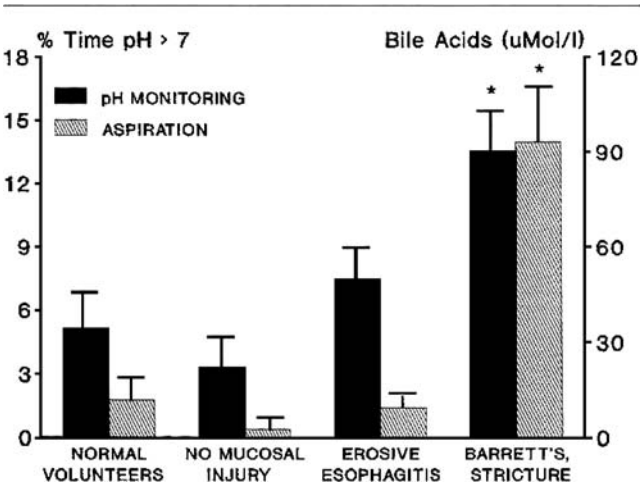

Figure 3 Total bile acid concentration in esophageal reflux aspirates and the time that the pH was above seven on ambulatory 24-h esophageal pH monitoring in normal volunteers (n=43), patients with GERD and no mucosal injury (n=14), patients with GERD and erosive esopagitis (n=25), and patients with GERD and stricture and/or Barrett's esophagus (n=13). *p<0.01 vs. patients with no mucosal injury.

gastric juice contaminated with duodenal components (Fig. 7).[4,30,31] Further, duodenal juice reflux into the esophagus is significantly more common in patients who have Barrett's esophagus compared with patients who have erosive esophagitis or patients with reflux who have no mucosal injury (Fig. 8). In addition, the mean percentage time of esophageal exposure to duodenal juice is significantly higher in patients who have Barrett's esophagus (Fig. 9).[4,30,31]

Simultaneous esophageal pH and bilirubin monitoring show that esophageal exposure to duodenal juice occurs at all pH values.[29,32] In patients who have GERD, duodenal content was detected within the esophagus 15% of the time when the pH was less than four, 19% of the time when the pH was between four and seven, and 6% of the time when

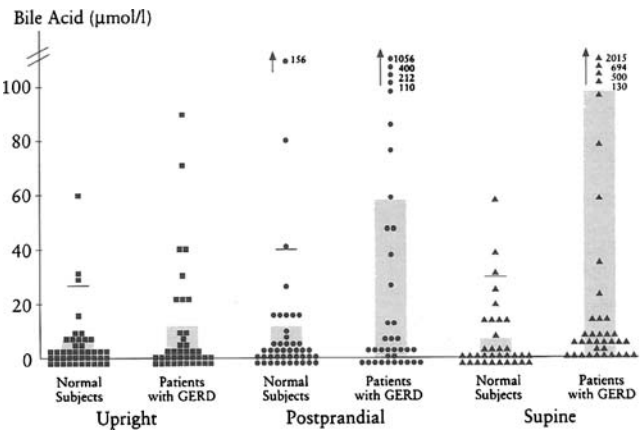

Figure 4 Peak bile acid concentration (µmol/L) for patients and normal subjects during upright, postprandial, and supine aspiration periods. *Shaded area* represents the mean and the *bar* represents he 95th percentile values.

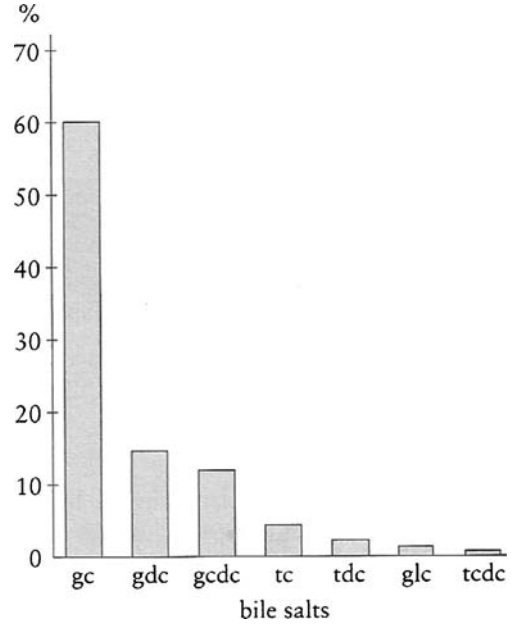

Figure 5 Prevalence of conjugated bile acids in samples with an aspirated volume greater than 3 ml (n=24). *gc*, glycocholic acid; *tc*, taurocholic acid; *gdc*, glycodeoxycholic acid; *tdc*, taurodeoxycholic acid; *gcdc*, glycochenodeoxycholic acid; *tcdc*, taurochenodeoxycholic acid.

the pH was higher than seven. An analysis of the cumulative period during which the esophagus was exposed to duodenal juice showed that the pH of the esophagus was between four and seven more than 87% of the time (Fig. 10). This pH is considered normal for the esophagus; consequently, such reflux goes undetected and unappreciated when analyzed by traditional criteria. The Bilitec technology, although not a quantitative measurement of bile reflux,[33] shows that 58% of the patients who have GERD have increased esophageal exposure of duodenal juice, that this exposure occurs most commonly when the esophageal pH is between four and seven, and that it is associated with severe esophageal mucosal injury.[32]

Impedance Monitoring

Impedance monitoring is a new diagnostic tool for GERD in which multiple impedance electrode pairs are placed on a standard pH catheter. It detects reflux of a liquid or gas bolus into the esophagus and can distinguish between acid and nonacid reflux episodes. A consensus conference on GERD monitoring concludes that combined pH and intraluminal impedance monitoring allows detection of all reflux events and gives the best possible evaluation of the function of the reflux barrier.[34] Using impedance monitoring, Tamhankar's group found, in normal subjects, that omeprazole treatment does not affect the number of reflux episodes or their duration. Rather, it converts acid reflux to less acid reflux, thus exposing the esophagus to altered gastric juice; they

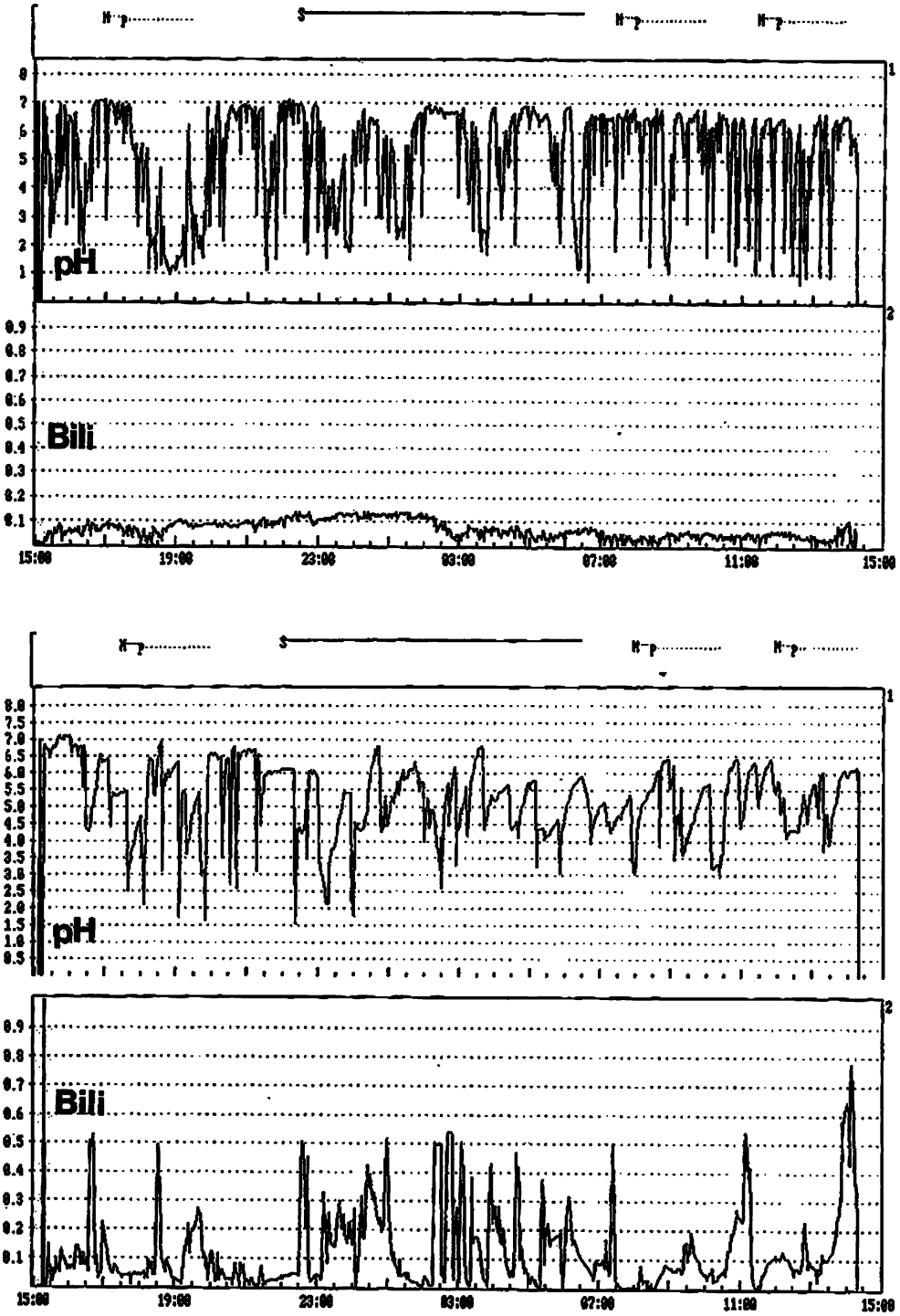

Figure 6 Combined ambulatory 24-h-esophageal pH and Bilitec monitoring. *Above*: isolated gastric reflux. *Below*: mixed gastric and duodenal reflux.

conclude that this observation may explain the persistence of symptoms and emergence of mucosal injury in patients on proton pump inhibitor therapy.[35]

Immunohistochemical Studies

Cyclooxygenase (COX)-2 is shown to be involved in chronic inflammation and epithelial cell growth. The role of COX-2 in various stages of Barrett's esophageal metaplasia and in response to pulses of acid and bile salts in an ex vivo organ culture system was investigated by Shirvani and coworkers.[36] There was a progressive increase in expression of COX-2 with disease progression from Barrett's metaplasia to dysplasia and adenocarcinoma. This increase indicates that COX-2 overexpression is an early event in the neoplastic transformation process of Barrett's columnar metaplasia. These studies show that bile and acid

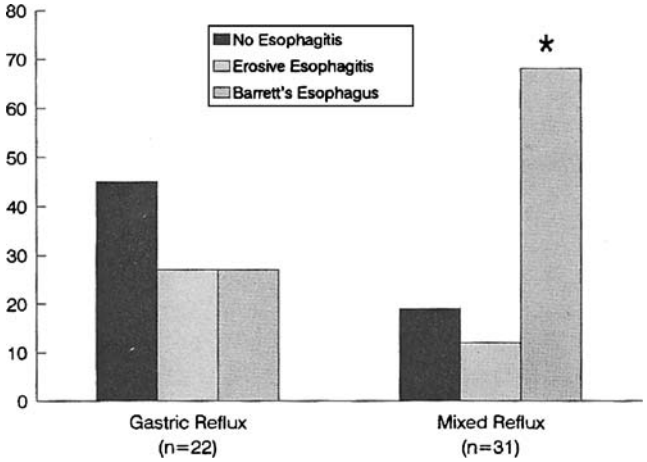

Figure 7 Prevalence of mucosal injury in patients with reflux of gastric juice only (gastric reflux) and in those with reflux of combined gastric and duodenal juices (mixed reflux) *$p<0.005$ vs. gastric reflux.

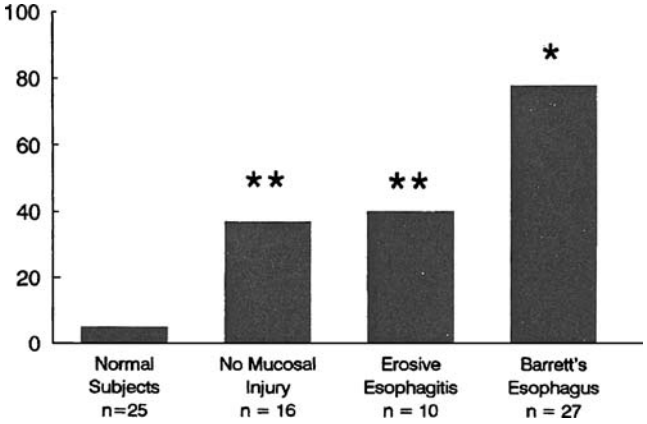

Figure 9 Prevalence of abnormal esophageal bilirubin exposure in healthy subjects and in patients with gastroesophageal reflux disease with varied degrees of mucosal injury.*$p<0.03$ vs. all other groups, **$p<0.03$ vs. healthy subjects.

could induce COX-2 expression in ex vivo human epithelial explants because COX-2 induction was increased significantly in the presence of acid and bile. The highest induction could be found when the explants were exposed to a 1-h pulse of bile salts, which, in part, could be related to protein kinase C activation by bile salts.[37]

Bile Reflux and the Development of Complications of GERD

Although esophageal pH monitoring provides indirect evidence of duodenal juice refluxing into the lower esophagus, the duodenal origin of such alkaline material has been demonstrated by the simultaneous detection of bile salts[38] and bile acids[39] in the esophagus of patients with esophagitis. Reflux complications such as esophagitis, stricture, and Barrett's esophagus have been shown to invariably occur in the presence of a mechanically defective sphincter and an increased esophageal exposure to both acid and alkalinity.[8] Furthermore, the severity of the complications was significantly higher in patients with acid/alkaline reflux as compared to those with only acid reflux or rarely only alkaline reflux. Although esophagitis and Barrett's esophagus can occur in patients who are achlorhidric or have had a total gastrectomy, the incidence and severity of complications is less.[40,41] It has been proposed that reflux of bile into the esophagus occurs because of the presence of a mechanically defective lower esophageal sphincter and increased duodengastric reflux. This is based on the observation that close to 100% of the patients with severe esophagus stricture or Barrett's esophagus have a mechanically defective sphincter and the correlation between the presence of complicated Barrett's esophagus and two markers of duodenoesophageal

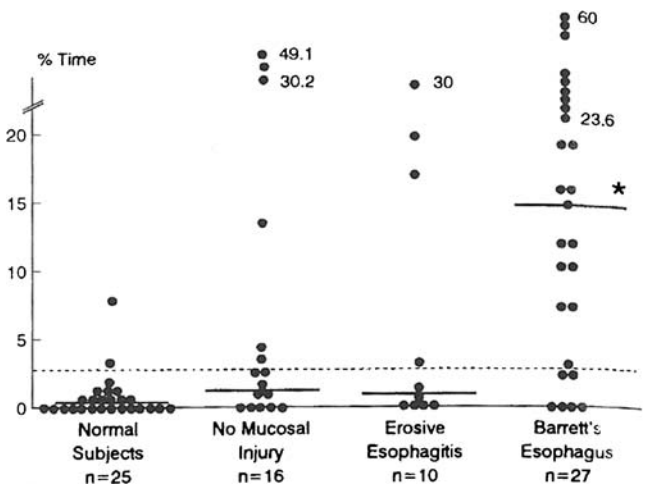

Figure 8 Duration of esophageal bilirubin exposure in healthy subjects and in patients with gastroesophageal reflux disease with varied degrees of mucosal injury. *$p<0.05$ vs. all other groups.

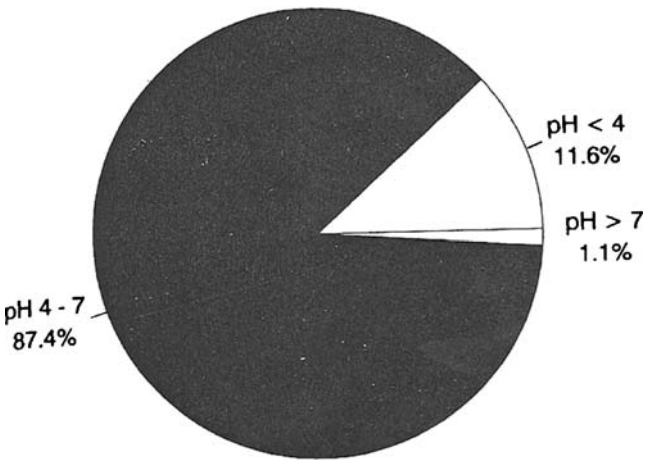

Figure 10 Esphageal luminal pH during bilirubin exposure.

reflux: elevated postprandial intragastric bile acid concentrations[42] and excessive pyloric regurgitation of radioactive TcHIDA.[23] These findings implicate duodenoesophageal reflux as the potential promoter in the pathogenesis of Barrett's metaplasia and esophageal adenocarcinoma. When patients with Barrett's esophagus are divided into those with no mucosal injury and those with esophageal stricture, ulcers, or dysplasia, the patients with complications showed a significantly higher time spent at pH >7, while the esophageal acid profile was similar in the two groups.[43] As expected, those with a high alkaline exposure also had a higher prevalence of duodengastric reflux. Direct evidence that duodenal juice refluxes into the distal esophagus of patients with esoghagitis and Barrett's has been shown in aspiration studies by Johnson et al.[38] and Stein et al.[22] Other investigators failed to identify the presence of bile in the distal esophagus during aspiration studies and cast doubt on these studies.[44] The use of a 24-h ambulatory esophageal aspiration probe confirmed the presence of bile in the esophagus.[28] These findings have been supported by bilirubin monitoring. This technique has demonstrated that normal subjects and patients with mild gastroesophageal reflux disease have a virtual absence of bilirubin in the distal esophagus, whereas patients with esophagitis, stricture, and Barrett's esophagus have bilirubin detectable in the lumen of the lower esophagus over 35% of the time.[30,32]

Barrett's Esophagus and its Association with Esophageal Adenocarcinoma

Since the introduction of H2 blockers, the incidence of Barrett's esophagus has increased. Esophageal adenocarcinoma has replaced squamous cell cancer as the predominant histologic type in most Western countries. Several lines of evidence suggest that the majority, if not all, of esophageal adenocarcinoma cases arise within Barrett's esophagus. Seventy percent of esophageal adenocarcinoma arise in conjunction with Barrett's metaplastic changes. The epidemiological features of esophageal adenocarcinoma are in striking contrast to those of squamous cell cancer and appear similar with or without Barrett's mucosal changes. Short-segment Barrett's metaplasia does occur, has similar physiologic characteristics to longer segment disease, and can result in malignancy. Finally, careful histologic examination demonstrates the majority of esophageal adenocarcinoma arising at or near the gastroesophageal junction in association with Barrett's metaplasia. Taken together these data strongly suggest, that gastroesophageal reflux and Barrett's metaplasia play a role in most instances of esophageal adenocarcinoma, and the recent increase in Barrett's esophagus and adenocarcinmoma may be related to the prevalent use of acid suppression therapy.

Summary

Gastric acid and bile acids are a particularly noxious combination when they interact with the mucosa of the upper intestinal tract. There is a critical pH range, between three and six, in which bile acids exist in their soluble, unionized form, can penetrate cell membranes, and accumulate within mucosal cells. At lower pH, bile acids are precipitated, and at a higher pH, bile acids exist in their noninjurious ionized form. Experimental, clinical, and immunohistochemical studies show that acid and bile reflux are increased in patients who suffer from GERD, are the key factor in the pathogenesis of Barrett's esophagus, and are possibly related to the development of esophageal adenocarcinoma.

References

1. The Gallop Organization. A Gallop Survey on Hearburn Across America. Princeton: Gallop Organization, 1988.
2. DeMeester TR, Stein HJ. Gastroesophageal reflux disease. In Moody FG, Jones RS, Kelly KA, Nahrwood DL, Skinner DB, eds. Surgical Treatment of Digestive Diseases, 2nd ed. Chicago: Year Book Medical, 1989, pp 65–108.
3. Stein HJ, DeMeester TR, Hinder RA. Outpatient physiological testing and surgical management of foregut motor disorders. Curr Probl Surg 1992;24:415–555.
4. Stein HJ, Kauer WKH, Feussner H et al. Bile acids as components of the duodenogastric refluxate: detection, relationship to bilirubin, mechanism of injury and clinical relevance. Hepatogastroenterology 1999;46:66–67.
5. Orlando RC, Powell DW, Carney CN. Pathophysiology of acute acid injury in rabbit esophagal epithelium. J Clin Invest 1981;68:286–293.
6. Goldberg HI, Dodds WJ, Gee S et al. Role of acid and pepsin in acute experimental esophagitis. Gastroenterology 1969;56:223–230.
7. Vaezi MF, Singh S, Richter JE. Role of acid and duodenogastric reflux in esophageal injury: a review of animal and human studies. Gastroenterology 1995;108:1897–1907.
8. Stein HJAP, DeMeester TR et al. Complications of gastroesophageal reflux disease: role of the lower esophageal sphincter, esophageal acid/alkaline exposure, and duodenogastric reflux. Ann Surg 1992;162:35–43.
9. Heaton KW. Bile salts. In Wright R, Alberti KGMM, Karran S, Millward-Sandler GH, eds. Livre and Biliary Disease. London: Saunders, 1979, pp 233–254.
10. Hofmann AF. The enterohepatic circulation of bile acids in man. Clin Gastroenterol 1977;6:3–24.
11. Harmon JW, Doong T, Gadacz TR. Bile acids are not equally damaging to the gastric mucosa. Surgery 1978;7:79–86.
12. Barthlen W, Liebermann-Meffert D, Feussner H, Stein HJ. Influence of pH on bile acid concentration in human, pig and commercial bile: implications for alkaline gastro-esophageal reflux. Dis Eso 1994;7:127–130.

13. Weiner IM, Lack L. Bile salt absorption; enterohepatic circulation. In Code CF, ed. Handbook of Physiology, vol. III. Baltimore: Williams and Wilkins, 1986, pp 1439–1455.
14. Dietschy JM. Mechanism for the intestinal absorption of bile acids. J Lip Res 1968;9:297–309.
15. Morris JS, Low-Beer TS, Heaton KW. Bile salt metabolism and the colon. Scand J Gastroenterol 1973;8:425–431.
16. Miettinen TA, Peltokallio P. Bile salts, fat, water and vitamin B12 excretion after ileostomy. Scand J Gastroenterol 1971;6:543–552.
17. Bremner C, Lynch V, Ellis F. Barrett's esophagus: congenital or required? An experimental study of esophageal mucosal regeneration in the dog. Surgery 1970;68:209–216.
18. Gillen P, Keeling P, Byrne P et al. Experimental columnar metaplasia in the canine esophagus. Br J Surg 1988;98:2120–2128.
19. Lillimoe K, Johnson L, Harmon J. Alkaline esophagitis: a comparison of the ability of components of gastroesophageal contents to injure the rabbit esophagus. Gastroenterology 1983;85:621–628.
20. Ireland A, Peters J, Smyrk T et al. Gastric juice protects against the development of esophageal adenocarcinoma in the rat. Ann Surg 1996;224:358–371.
21. Jamieson JR, Stein HJ, DeMeester TR et al. Ambulatory 24-hour esophageal pH-monitoring: normal values, optimal thresholds, specifity and reproducibilty. Am J Gastroent 1992;87:1102–1111.
22. Stein HJ, Feussner H, Kauer WKH et al. "Alkaline" gastroesophageal reflux: assessment by ambulatory esophageal aspiration and pH monitoring. Am J Surg 1994;167:163–168.
23. Attwood S, DeMeester TR, Bremner CG et al. Alkaline gastroesophageal reflux: implications in the development of complications in Barrett's columnar-lined lower esophagus. Surgery 1989;106:764–770.
24. Stein HJ. Characterization of acid and alkaline reflux in patients with Barrett's esophagus. Dis Esophagus 1993;105:107–111.
25. Stein HJ, DeMeester TR, Peters JH et al. Indications, technique, and clinical use of ambulatory 24-hour-gastric pH monitoring in a surgical practice. Surgery 1994;116:758–767.
26. Fuchs KH, Hinder RA, DeMeester TR et al. Computerized identification of pathologic duodenogastric reflux using 24-hour gastric pH monitoring. Ann Surg 1991;213:13–20.
27. Stein HJ, Hinder RA, DeMeester TR et al. Clinical use of 24-hour gastric pH monitoring vs. O-diisopropyl iminodiacetic acid (DISIDA) scanning in the diagnosis of pathologic duodenogastric reflux. Arch Surg 1990;125:966–971.
28. Kauer WKH, Peters JH, DeMeester TR et al. Composition and concentration of bile acid reflux into the esophagus of patients with gastroesophageal relfux disease. Surgery 1997;122:874–881.
29. Bechi P, Pucciani F, Baldini F et al. Long-term ambulatory enterogastric reflux monitoring. Validation of a new fiberoptic technique. Dig Dis Sci 1993;38:1297–1306.
30. Kauer WKH, Burdiles P, Ireland A et al. Does duodenal juice reflux into the esophagus of patients with complicated GERD. Am J Surg 1995;169:98–104.
31. Stein HJ, Kauer WKH, Feussner H et al. Bile reflux in benign and malignant Barrett's esophagus. Effect of medical acid suppression and fundoplication. J Gastrointest Surg 1998; 2:233–241.
32. Kauer WKH, Peters JH, DeMeester TR et al. Mixed reflux of gastric and duodenal juice is more harmful to the esophagus than gastric juice alone. Ann Surg 1995;4:525–533.
33. Ostrow J. Bilitec to quantitate duodenogastric reflux: is it valid. Gastroenterology 1995;108:1332–1334.
34. Sifrim D, Castell D, Dent J et al. Gastro-esophageal reflux monitoring: review and consensus report on detection and definitions of acid, non-acid, and gas reflux. Gut 2004;53:1024–1031.
35. Tamhankar AP, Peters JH, Portale G et al. Omeprazol does not reduce gastroesophageal reflux: new insights using multichannel impedance technology. J Gastrointest Surg 2004;8:888–896.
36. Shirvani V, Rodica O, Baljeet S et al. Cyclooxygenase 2 expression in Barrett's esophagus and adenocarcinoma: ex vivo induction of bile salts and acid exposure. Gastroenterology 2000;118:487–496.
37. Fitzgerald R, Omary M, Triafilopoulos G. Dynamic effects of acid on Barrett's esphagus. J Clin Invest 1996;98:2120–2128.
38. Johnsson F, Joelsson B, Floren C et al. Bile salts in the esophagus of patients with esophagitis. Scand J Gastroenterol 1988;23:712–716.
39. Gotley DC, Morgan AP, Cooper MJ. Bile acid concentration in the refluxate of patients with reflux esophagitis. Br J Surg 1988;75:587–590.
40. Morrow D, Passaro ER. Alkaline reflux esophagitis after total gastrectomy. Am J Surg 1976;132:287–291.
41. Hamilton SR, Yarkley JH. Regeneration of cardiac-type mucosa and acquisition of Barrett mucosa after esophagogastrostomy. Gastroenterol 1977;72:669–675.
42. Gillen P, Keeling P, Byrne PJ et al. Implication of duodenogastric reflux in the pathogenesis of Barrett's oesophagus. Br J Surg 1988;75:540–543.
43. DeMeester TR, Attwood S, Smyrk TC et al. Surgical therapy in Barrett's esophagus. Ann Surg 1990;212:528–542.
44. Mittal RK, Reuben A, Whitney JV et al. Do bile acids reflux into the esophagus. Gastroenterol 1987;92:371–375.

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DEMEESTER FESTSCHRIFT

Non-acid Gastroesophageal Reflux Measured Using Multichannel Intraluminal Impedance in Older Patients

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Abstract
Background Diagnosing gastroesophageal reflux disease is challenging in the older population, as comorbid conditions can obscure the disease.
Methods This prospective study included 97 participants: 25 healthy controls (group 1), 46 reflux patients aged 26–64 (group 2), and 26 patients over 65 (group 3). Esophageal motility was assessed using conventional esophageal manometry, and 24-h pH-metry and non-acid reflux episodes were assessed using multichannel intraluminal impedance.
Results Among the older patients (group 3), 34% had reflux disease. The rate of lower esophageal sphincter insufficiency in group 3 was comparable with that in group 2 and significantly different from group 1. Gastric 24-h pH-metry showed no significant differences between the groups. Esophageal pH-metry results for groups 1 and 3 differed significantly from those in group 2. Impedance assessment showed that older patients have non-acid reflux episodes in the recumbent position significantly more often in comparison with controls and reflux patients. Reflux patients and older patients had proximal reflux episodes significantly more often than healthy volunteers.
Conclusions Patients aged over 65 have non-acid reflux, particularly in the recumbent position, significantly more often than normal individuals and patients with reflux disease. Non-acid reflux may mimic a negative DeMeester score in older patients with severe reflux disease.

Keywords Aged · Gastroesophageal reflux · Esophageal pH monitoring · Impedance

Introduction

Older people represent an increasing proportion of the population in Western countries—currently 11–19% of the total.[1,2] There is a well-known association between aging and specific diseases, particularly in the gastrointestinal tract.[3] Although nearly 20% of the general population in the Western world suffer from gastroesophageal reflux,[4,5] the clinical implications of reflux in older patients are significantly different, as these patients are usually physically weaker.[6,7] Gastroesophageal reflux disease (GERD) is defined as symptoms or lesions caused by gastric contents refluxing back into the esophagus and higher, as far as the larynx, pharynx, and even possibly the mouth. The correlation between GERD and symptoms in younger and middle-aged patients is weak and extremely variable,[8–11] and the symptoms vary even more widely among older patients, whose perception of pain and discomfort may differ.[12–15] Multiple comorbid conditions may also mask reflux symptoms in older patients, and this increases the complexity of diagnosis and treatment.[16]

There are divergent views in the published literature regarding the relationship between age and gastric acidity. Some investigators have observed a decrease in gastric acid output among older patients if the gastric mucosa is affected by *Helicobacter pylori* infection, abnormal bacterial colonization, or medical treatment for gastric dysfunc-

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tion.[17,18]. Other groups have reported that, in the absence of pathological conditions such as these, gastric acidity and the volume of gastric acid output in older people was comparable to that in younger individuals.[19,20] However, the various investigators have used different measurement methods, and the results are therefore difficult to compare.

Few data are available regarding weak or non-acid gastroesophageal reflux in older patients, due to the shortcomings of conventional 24-h pH monitoring. The recent introduction of combined multichannel intraluminal impedance–pH monitoring has provided a reliable diagnostic tool for measuring bolus transport in combination with the concentration of refluxate at different levels in the upper gastrointestinal tract over a prolonged period, in an outpatient setting. The method can also be used in older patients, but few data are available on impedance measurements in older patients.[21,22] The purpose of this study was, therefore, to use multichannel intraluminal impedance methods to evaluate gastroesophageal reflux in patients aged over 65, in comparison with healthy volunteers and middle-aged reflux patients.

Materials and Methods

Study Population

The study population consisted of a total of 97 participants, who were divided into three groups:

- Group 1: a control group consisting of 25 healthy volunteers (16 women, nine men; average age 45 years, range 23–61).
- Group 2: 46 patients who had been referred due to symptoms of gastroesophageal reflux to the Department of Surgery at the University of Tübingen between October 2007 and April 2008 (16 women, 30 men; average age 45 years, range 26–64).
- Group 3: 26 older patients (17 women, nine men; average age 70 years, range 65–78).

The patients' average body mass indexes (BMI) were 24.5 in group 1, 28.0 in group 2, and 27.5 in group 3. Before inclusion in the study, the participants signed a written informed consent form based on the Helsinki Declaration.

Materials

Water-perfused Conventional Side Hole Manometry Catheter and System For correct positioning of the 24-h ambulatory pH-metry and impedance system, all of the participants underwent stationary water-perfused conventional esophageal manometry, as described in detail previously elsewhere.[23] The borders of the lower esophageal sphincter (LES) and esophageal contraction amplitudes were detected relative to baseline gastric pressure using a station pull-through technique. The manometry catheter used is a polyethylene tube with eight side holes (Mui Scientific, Strasbourg, France). The catheter is configured with four side holes circumferentially at the tip of the catheter and four side holes 5 cm apart from each other around the circumference. It is connected to a pneumohydraulic microcapillary pump that supplies pyrogen-free water through the capillary system at a rate of 0.6 ml/min (Arndorfer Medical Specialties, Greendale, WI, USA). The pump is linked to eight pressure transducers (Medex Medical, Rossendale, UK) that convert mechanical pressures into electrical signals. The signals are enhanced using an amplifier polygraph (Medtronic, Düsseldorf, Germany), and transferred to a personal computer that screens the signals.

pH-metry and Multichannel Intraluminal Impedance (MII) Two-channel pH-metry in combination with multichannel intraluminal impedance (MII) was used to evaluate the concentrations of gastric and esophageal content. The differences between monitoring esophageal refluxate and conventional testing have been described earlier in detail.[24] MII (Sandhill Scientific, Highland Ranch, CO, USA) assesses esophageal motor function and the effectiveness of bolus transits. The resistance between four paired bipolar impedance sensors alters when swallowed or refluxed material traverses the esophagus. MII is capable of distinguishing between acid, weak or non-acid, and gaseous (belching) refluxed material independently of the pH at various levels of the esophagus. In combined impedance and pH-metry, the instrument provides multifunctional assessment of esophageal and gastric contents.

Study Design Each participant was asked about symptoms of comorbid conditions in the upper gastrointestinal tract and previous surgery. Healthy volunteers were only enrolled if no symptoms were present and there was no history of abdominal surgery. Exclusion criteria were comorbidities such as heart failure, bleeding diathesis, esophageal varicosis, thrombosis, anticoagulopathy treatment, and a history of stroke or transient ischemic attacks. Patients were also excluded if informed consent was not provided. Seven days before the study, any use of drugs inhibiting gastric acid production or affecting gastric motility was discontinued. The patients had to fast overnight before measurements started.

Stationary manometry was carried out in a standardized fashion on each occasion. After the patient had fasted overnight, the manometry catheter was inserted intranasally until all of the side holes were in an intragastric position, so that the gastric baseline could be measured. Using a station pull-through technique, the catheter was then pulled back

through the high-pressure zone at the esophagogastric junction and the esophagus, up to the upper esophageal sphincter. The esophageal measurements were carried out with the patient in the recumbent position. LES relaxations and swallowing events were assessed using 5 ml water administered by syringe into the mouth. Lower esophageal sphincter pressure (LESP) was measured in the mid-expiratory position.[25]

After the borders of the LES had been identified, the proximal pH-metry electrode of the impedance probe was positioned 5 cm above the upper border of the LES manometrically during the same visit. The data from the instrument were then recorded in a data logger over a 24-h time period. The participants were not subject to any food restrictions and were able to continue their everyday life during this period, although they were not allowed to go to work. They received careful explanations of how to record any symptoms experienced. The data were analyzed twice—firstly with computer assistance, using the commercially available system's AutoScan facility, and secondly by an independent investigator who was familiar with MII measurements. The normal range for LESP was considered to be 15–24 mmHg, and a DeMeester Score <14.7 was regarded as normal.

Statistics Statistical analyses of esophageal motility, pH monitoring, and MII data were carried out using the commercial JMP program (SAS Institute, Cary, NC, USA). All data are expressed as medians. Frequency distributions were tested using the Shapiro–Wilk test. A level of $p<0.05$ was taken to denote statistical significance.

Results

Age and GERD Distribution

The median age was 70 in the older patients (group 3), 44.5 in group 2, and 45 in the control group (group 1). The difference in median age between groups 1 and 2 was not significant, but there was a significant difference between group 3 and the other two groups ($p<0.0001$). As assessed on the basis of symptoms and 24-h pH-metry, GERD was present in none of the participants in group 1, all of those in group 2 ($n=46$), and 34% of the older patients in group 3 ($n=9$) (Table 1).

Manometry Data

The contraction amplitudes for all patients in group 3 showed a reduction in distal esophageal contractions that was not statistically significant, although a trend was seen in comparison with group 1. In comparison with group 2, the difference was statistically significant ($p<0.09$). The nine patients in group 3 who had positive DeMeester scores were analyzed separately; in this subgroup of older patients, the contraction amplitude on channels 4 and 5 (distal esophagus) was significantly lower in comparison with normal individuals (group 1), but was comparable to that seen in group 2 ($p<0.003$).

Table 1 Demographic Data for the 97 Patients Included in the Study

	Healthy volunteers (group 1) ($n=25$)	GERD (group 2) ($n=46$)	Older patients (group 3) ($n=26$)
Female/male	16/9	16/30	17/9
Age (years)	45	45	70*
Age (range)	23–61	26–64	65–78
BMI (kg/m^2)	25	28	27
Hiatal hernia (n)	5	21	22
LESP (mmHg)	20	8*	7*

BMI body mass index, *GERD* gastroesophageal reflux disease, *LESP* lower esophageal sphincter pressure

*$p<0.0001$

The healthy volunteers in group 1 had a sufficient LESP. There was a statistically significant difference in the LESP between the control group and the patient groups ($p<0.0001$). Only 20% of the older patients in group 3 (5/26) had a sufficient LES (Fig. 1).

Gastric 24-h pH-metry

No significant differences were observed between normal individuals, patients with GERD, and older patients with regard to gastric acid exposure (total gastric acid exposure in percentage) in the upright and recumbent positions (Fig. 2). Additionally, no significant differences were detected between the groups with regard to gastric acid in the upright and recumbent positions.

Esophageal 24-h pH-metry (DeMeester Score)

The mean DeMeester scores were 5 in group 1, 22 in group 2, and 9 in group 3. There was a significant difference between the GERD patients in group 2 and the older patients in group 3 ($p<0.001$), but not between groups 1 and 3 (Fig. 3). The DeMeester score for the subgroup of older patients in group 3 with a positive DeMeester score was 39, significantly different from the score among normal individuals ($p<0.03$). In the 15 patients in group 3 who did not have a pathologically increased DeMeester score, the value was similar to that in healthy volunteers, at 6. LES insufficiency was not found to lead to a positive DeMeester score in this study.

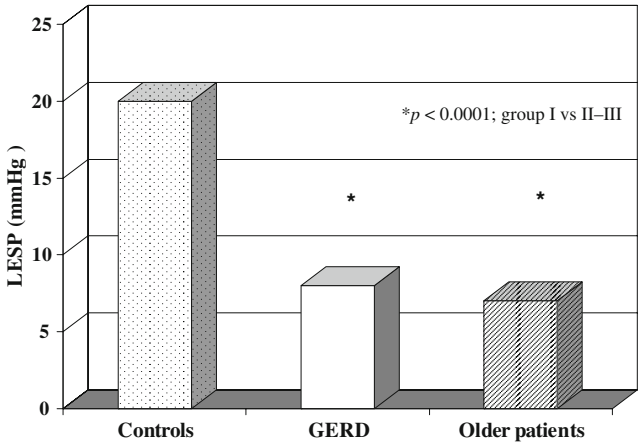

Figure 1 The median lower esophageal sphincter pressure (*LESP*) was significantly lower in patients with gastroesophageal reflux disease (*GERD*) and in older patients.

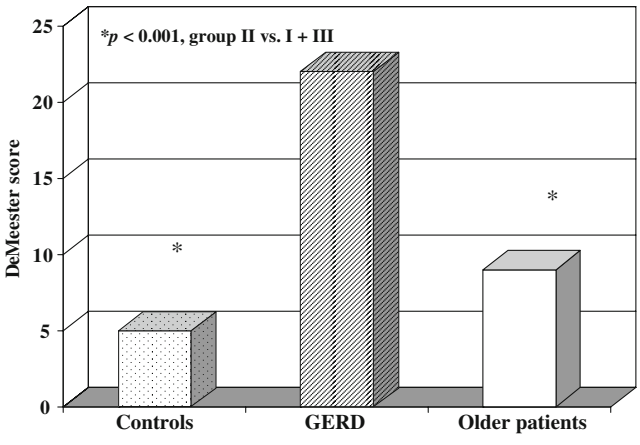

Figure 3 There were significant differences between patients with gastroesophageal reflux disease (*GERD*), older patients, and healthy volunteers with regard to esophageal acid exposure ($p<0.001$). Only 34% of the older patients in group 3 had a pathological DeMeester score.

Impedance Measurement

The 24-h impedance assessment showed that acid reflux episodes were more frequent in the upright position in comparison with the recumbent position. The numbers of acid reflux episodes in patients with GERD were significantly higher in comparison with normal individuals and older patients ($p<0.001$). The older patients in group 3 had a mean of 15 acid reflux episodes, while those with reflux in group 2 had a mean of 50 acid reflux episodes over the 24-h period (Fig. 4).

There were no differences between the groups with regard to the numbers of non-acid or weak reflux episodes experienced in the upright position (Fig. 5). In the recumbent position, however, significantly more non-acid reflux episodes were observed among the older patients, both in comparison with healthy volunteers (group 1) and in comparison with GERD patients ($p<0.03$) (Fig. 6).

In patients with GERD, the numbers of episodes of acid reflux traversing the esophagogastric junction and rising to the proximal part of the esophagus were significantly higher in comparison with groups 1 and 3 ($p<0.006$). There were no significant differences in the numbers of episodes of non-acid reflux migrating proximally up to an esophageal level of 15 cm (Fig. 7).

With regard to body position, proximal reflux episodes were observed more often in the recumbent position than in the upright position in older patients. The difference was statistically significant ($p<0.003$) (Fig. 8).

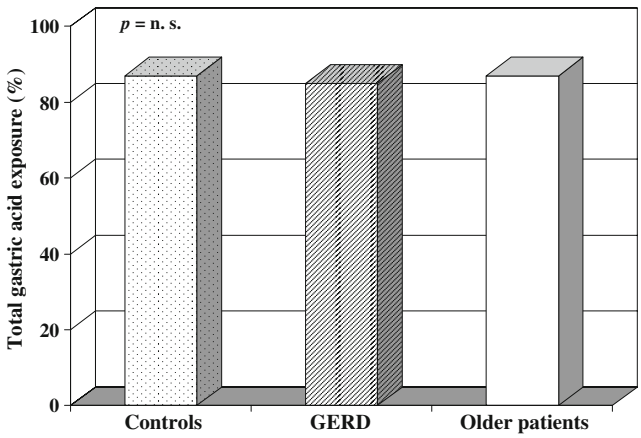

Figure 2 There were no significant differences between the groups with regard to gastric acid exposure. Gastroesophageal reflux disease (*GERD*).

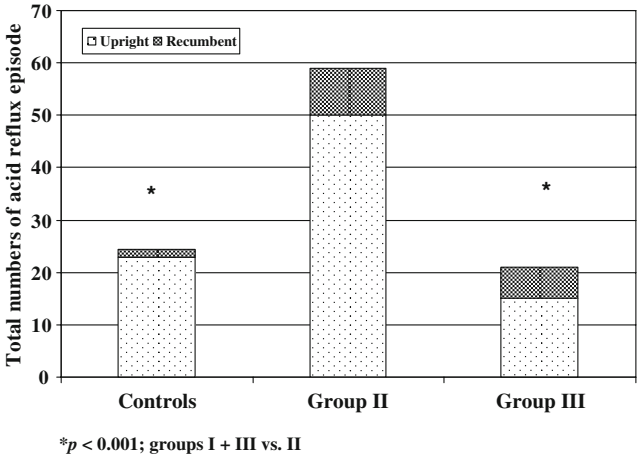

Figure 4 No significant differences were observed between healthy volunteers and older patients with regard to the numbers of reflux episodes experienced in the upright and recumbent positions, but there was a highly significant difference in comparison with patients with gastroesophageal reflux disease (GERD) ($p<0.001$).

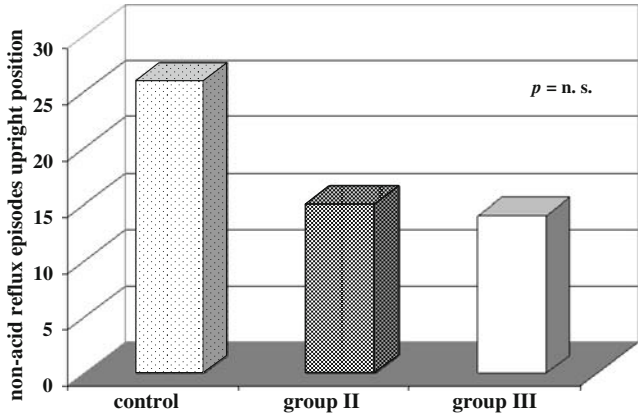

Figure 5 There were no significant differences between the groups with regard to non-acid reflux episodes in upright position.

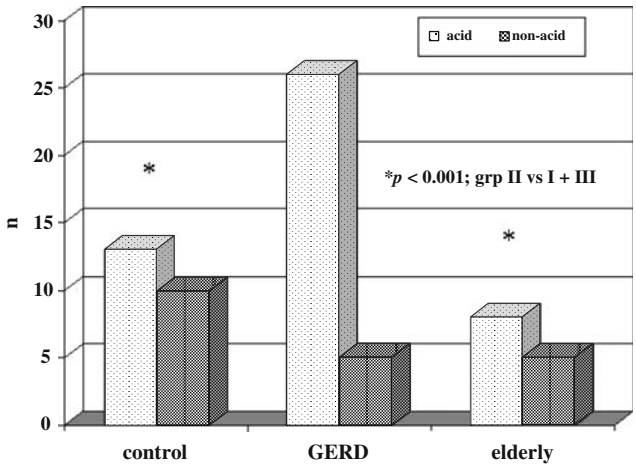

Figure 7 Numbers of acid and non-acid reflux episodes rising as far as 15 cm into the esophagus in the upright position. Gastroesophageal reflux disease (*GERD*).

Discussion

Observations in the field of gerontology[26] led to the view that increased life expectancy among the elderly is not associated with a continuation of adult physiology, but instead involves fundamental physiological changes. This led to changes in the allocation of health-care resources. Investigations of the physiological changes involved are still at an early stage, particularly in relation to the gastrointestinal tract, and increasingly detailed investigations are therefore needed. The present paper focuses on symptoms and assessment of GERD in patients aged over 65. In this series, 34% of older patients who were referred to a surgeon with noncardiac chest pain were found to have severe GERD, as demonstrated by a positive DeMeester score.

Esophageal contraction amplitudes showed an overall reduction in group 3, but the difference was not statistically significant. When the subgroup of older patients with a positive DeMeester score was analyzed separately, the data were found to be comparable to those for group 2. Contraction amplitudes were significantly reduced in the distal esophagus ($p<0.003$). It may therefore be concluded that, in this series, normal contractility was observed among older patients, while older patients with GERD had contraction amplitudes that were comparable with those seen in younger patients with GERD. This finding is in accordance with the results of earlier investigations.[27,28] However, this does not imply that ineffective motility, with a weak LES, must necessarily lead to GERD, as this study also shows.[29] In group 3, hiatal hernias were found in 87% of the patients during esophageal manometry and gastroscopy.

In contrast to the current clinical view that gastric acid secretion decreases with aging,[30] gastric acid production

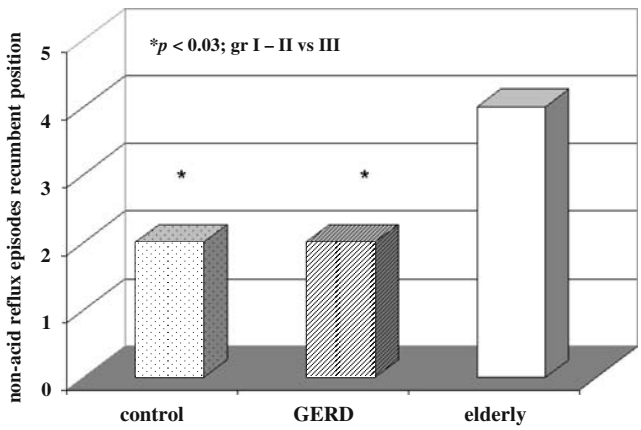

Figure 6 Non-acid reflux episodes in the recumbent position were significantly more frequent in the older patients in comparison with normal individuals and patients with gastroesophageal reflux disease (*GERD*) ($p<0.03$).

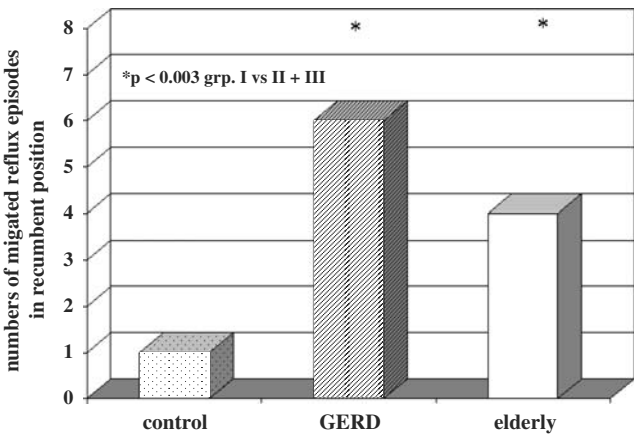

Figure 8 Reflux episodes in the recumbent position were more frequent in older patients and in patients with gastroesophageal reflux disease (*GERD*) in comparison with healthy volunteers.

following both meal stimulation[31] and gastrin-17 stimulation[32] is, in fact, similar or even higher in older patients in comparison with younger individuals. In the present study, 24-h gastric pH-metry showed no statistically significant differences with regard to gastric acid exposure between older patients and normal individuals or patients with GERD. This result might be related to a lower rate of *H. pylori* infection—an aspect that was not consistently investigated in this study, although the hypothesis has been raised by Goldschmiedt and coworkers.[32] Interestingly, however, there were no statistically significant differences in gastric acid exposure between patients with GERD (group 2) and older patients (group 3). This has only rarely been reported in the literature, although it is in accordance with data from a study of obese patients.[33]

Ambulatory impedance measurements of acid reflux episodes in the recumbent position showed a statistically significant difference between older patients and healthy volunteers ($p< 0.001$), but not between older patients and those with GERD. There were no statistically significant differences between groups 2 and 3 with regard to the frequency of acid reflux episodes, either in the upright or in the recumbent position. Older patients had significantly more frequent non-acid reflux episodes in comparison with normal individuals and middle-aged GERD patients ($p<0.03$). As the present series confirmed, this result may explain why esophageal acid exposure is not identified more often in older patients with acid reflux episodes and a positive DeMeester score.[34,35] Consistent with these findings, the total numbers of episodes of reflux (acid and non-acid) that migrated 15 cm up into the esophagus in the recumbent position were comparable among the older patients and patients with GERD, showing a significantly higher frequency in comparison with healthy volunteers ($p<0.003$).

Conclusion

The data from the present study show that a there is a high rate of non-acid reflux episodes in patients aged over 65. The significantly high frequency of non-acid reflux episodes in older patients with a negative DeMeester score may mimic severe GERD, although the level of baseline gastric acid secretion is not affected by age, as this study confirmed.

References

1. United States Department of Health and Human Services, Administration on Aging. Statistics on the aging population. Washington, DC: Administration on Aging. Available at: www.aoa.gov/prof/Statistics/statistics.asp (accessed August 7, 2007).
2. Giron MS, Wang HX, Bernsten C, Thorslund M, Winblad B, Fastbom J. The appropriateness of drug use in an older non-demented and demented population. J Am Geriatr Soc 2001;49:277–283. doi:10.1046/j.1532-5415.2001.4930277.x.
3. Crane SJ, Talley NJ. Chronic gastrointestinal symptoms in the elderly. Clin Geriatr Med 2007;23:721–734. doi:10.1016/j.cger.2007.06.003.
4. Locke GR 3rd, Tally NJ, Fett SL, Zinsmeister AR, Melton LJ 3rd. Prevalence and clinical spectrum of gastroesophageal reflux: a population-based study in Olmsted County, Minnesota. Gastroenterology 1997;112:1448–1456. doi:10.1016/S0016-5085(97)70025-8.
5. Dent J, El-Serag HB, Wallander MA, Johansson S. Epidemiology of gastro-oesophageal reflux disease: a systematic review. Gut 2005;54:710–717. doi:10.1136/gut.2004.051821.
6. Triadafilopolous G, Sharma R. Features of symptomatic gastro-esophageal reflux disease in elderly patients. Am J Gastroenterol 1997;92:2007–2011.
7. Ter RB, Johnston BT, Castell DO. Influence of age and gender on gastroesophageal reflux in symptomatic patients. Dis Esophagus 1998;11:106–108.
8. Wang JH, Luo JY, Dong L, Gong J, Zuo AL. Composite score of reflux symptoms in diagnosis of gastroesophageal reflux disease. World J Gastroenterol 2004;10:3332–3335.
9. Neumann H, Monkemueller K, Kandulski A, Malfertheiner P. Dyspepsia and IBS symptoms in patients with NERD, ERD and Barrett's esophagus. Dig Dis 2008;26:243–247. doi:10.1159/000121354.
10. Núñez-Rodríguez MH, Miranda Sivelo A. Psychological factors in gastroesophageal reflux disease measured by SCL-90-R questionnaire. Dig Dis Sci 2008 May 7 [Epub ahead of print].
11. Voutilainen M, Sipponen P, Mecklin JP, Juhola M, Färkkilä M. Gastroesophageal reflux disease: prevalence, clinical, endoscopic and histopathological findings in 1,128 consecutive patients referred for endoscopy due to dyspeptic and reflux symptoms. Digestion 2000;61:6–13. doi:10.1159/000007730.
12. Räihä IJ, Impivaara O, Seppälä M, Sourander LB. Prevalence and characteristics of symptomatic gastroesophageal reflux disease in the elderly. J Am Geriatr Soc 1992;40:1209–1211.
13. Räihä I, Hietanen E, Sourander L. Symptoms of gastro-oesophageal reflux disease in elderly people. Age Ageing 1991;20:365–370. doi:10.1093/ageing/20.5.365.
14. Tack J, Vantrappen G. The aging oesophagus. Gut 1997;41:422–424.
15. Collen MJ, Abdulian JD, Chen YK. Gastroesophageal reflux disease in the elderly: more severe disease that requires aggressive therapy. Am J Gastroenterol 1995;90:1053–1057.
16. Stanchev I, Pavlov K. Vutr Boles. Gastric secretion and acidity in elderly patients with duodenal peptic ulcer. 1987;26:46–49. in Bulgarian.
17. Salles N. Basic mechanisms of the aging gastrointestinal tract. Dig Dis 2007;25:112–117. doi:10.1159/000099474.
18. Feldman M, Cryer B, McArthur KE, Huet BA, Lee E. Effects of aging and gastritis on gastric acid and pepsin secretion in humans: a prospective study. Gastroenterology 1996;110:1043–1052. doi:10.1053/gast.1996.v110.pm8612992.
19. Manchikanti L, Colliver JA, Marrero TC, Roush JR. Assessment of age-related acid aspiration risk factors in pediatric, adult, and geriatric patients. Anesth Analg 1985;64:11–17.
20. Nakamura K, Ogoshi K, Makuuchi H. Influence of aging, gastric mucosal atrophy and dietary habits on gastric secretion. Hepato-gastroenterology 2006;53:624–628.
21. Castell DO, Tutuian R. The changing paradigm of GERD. Curr Gastroenterol Rep 2007;9:441–442. doi:10.1007/s11894-007-0056-6.
22. Tutuian R, Vela MF, Hill EG, Mainie I, Agrawal A, Castell DO. Characteristics of symptomatic reflux episodes on acid suppressive therapy. Am J Gastroenterol 2008;103:1090–1096. doi:10.1111/j.1572-0241.2008.01791.x.

23. Schneider JH, Kramer KA, Königsrainer A, Granderath FA. The lower esophageal sphincter strength in patients with gastroesophageal reflux before and after laparoscopic Nissen fundoplication. Dis Esophagus 2007;20:58–62. doi:10.1111/j.1442-2050.2007.00640.x.
24. Schneider JH, Kramer KM, Königsrainer A, Granderath FA. Ambulatory pH: monitoring with a wireless system. Surg Endosc 2007;21:2076–2080. doi:10.1007/s00464-007-9301-1.
25. Schneider JH, Crookes PF, Becker HD. Four-channel sleeve catheter for prolonged measurement of lower esophageal sphincter pressure. Dig Dis Sci 1999;44:2456–2461. doi:10.1023/A:1026630904455.
26. Davies I. Theories and general principles of aging. In Brocklehurst JC, Tallis RC, Fillit HM, eds. Textbook of Geriatric Medicine and Gerontology, 4th ed. New York: Churchill Livingstone, 1992, pp 61–70.
27. Grishaw EK, Ott DJ, Frederick MG, Gelfand DW, Chen MY. Functional abnormalities of the esophagus: a prospective analysis of radiographic findings relative to age and symptoms. AJR Am J Roentgenol 1996;167:719–723.
28. Sugiura M, Ohmae Y, Mogitate M, Kimura Y, Makino N, Kato T. Nippon Jibiinkoka Gakkai Kaiho. Relationship between globus sensation and esophageal clearance abnormalities in an elderly group. 2006;109:524–529. in Japanese.
29. Achem AC, Achem SR, Stark ME, DeVault KR. Failure of esophageal peristalsis in older patients with esophageal acid exposure. Am J Gastroenterol 2003;98:35–39. doi:10.1111/j.1572-0241.2003.07188.x.
30. Connor BA. Gastrointestinal disorders of the stomach and duodenum in the elderly. In Gelb AM, ed. Clinical Gastroenterology in the Elderly. New York: Dekker, 1996, pp 37–72.
31. Goldschmiedt M, Barnett CC, Schwarz BE, Kames WE, Redfern JS, Feldman M. Effect of age on gastric acid and serum gastrin concentrations in healthy men and women. Gastroenterology 1991;101:977–990.
32. Cryer B, Faust TW, Goldschmiedt M, Redfern JS, Lee E, Feldman M. Gastric and duodenal mucosal prostaglandin concentrations in gastric or duodenal ulcer disease: relationships with demographics, environmental, and histological factors, including *Helicobacter pylori*. Am J Gastroenterol 1992;87:1747–1754.
33. Schneider JME, Küper M, Saemann K, Königsrainer A, Schneider JH. Multichannel intraluminal impedance measurement of gastroesophageal reflux in patients with different stages of morbid obesity. Obes Surg. 2008. doi:10.1007/s11695-008-9624-6.
34. Gutschow CA, Bludau M, Vallböhmer D, Schröder W, Bollschweiler E, Hölscher AH. NERD, GERD, and Barrett's esophagus: role of acid and non-acid reflux revised with combined pH-impedance monitoring. Dig Dis Sci 2008 Apr 26 [Epub ahead of print], PMID 18438712.
35. Conchillo JM, Schwartz MP, Selimah M, Samsom M, Sifrim D, Smout AJ. Acid and non-acid reflux patterns in patients with erosive esophagitis and non-erosive reflux disease (NERD): a study using intraluminal impedance monitoring. Dig Dis Sci 2007, PMID 17934853.

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DEMEESTER FESTSCHRIFT

High-resolution Esophageal Manometry: Using Technical Advances for Clinical Advantages

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Abstract
Background High-resolution manometry (HRM) is a new technique to investigate the motor function of the esophagus. It differs from conventional manometry in recording pressures by solid state microtransducers at 12 points around the circumference at every centimeter of esophageal length, and displaying the data in pseudo-three-dimensional format using a topographic plot, where esophageal pressures within a given range are represented by different colors.
Rationale The large amount of data and the capacity to analyze and display it intuitively has afforded many new insights into esophageal dysfunction. Among these insights are the ability to distinguish three different subtypes of achalasia and predict their response to therapy, better understanding of the relationship between the lower esophageal sphincter (LES) and the crural diaphragm, the development of novel quantitative parameters to understand the nature of the dysfunction in non-specific esophageal motor disorders, and the elucidation of a newly described motility disorder characterized by failure of peristalsis at the transitional zone between the upper skeletal muscle and the more distal smooth muscle portion of the esophagus. It is also ideally suited to analysis of the effect of prokinetic medications. The method is quicker and less uncomfortable for patients and the analysis is visually appealing and intuitively comprehensible.
Conclusion Despite these potential advantages, there are currently no data to demonstrate a clinical advantage in treatment. The results of such studies will be crucial to the acceptance of this novel technology.

Keywords High-resolution manometry · Esophagus · Esophageal motor disorder · Esophageal manometry · Gastroesophageal reflux disease and achalasia

Introduction

The surgeon who treats benign esophageal diseases has a different mindset than the surgeon who merely excises the organ because it harbors a malignancy or is otherwise destroyed by disease. The former has to improve the function of the esophagus without removing it. Success in restoring function depends upon correct analysis of the underlying pathophysiology. The principal tool to aid the surgeon in this analysis is esophageal manometry. Conventional esophageal manometry has undergone very few changes in conduct or interpretation since the 1960s. However, in the past few years, several newer methods of studying esophageal function have been introduced: these include high-resolution manometry (HRM) and multilevel intraluminal impedance (MII). The focus of this manuscript is to review the technique and interpretation of HRM and assess if the technique offers any advantages over conventional manometry.

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Development of Manometric Technology

The first esophageal manometric study in a human subject was performed in 1883,[1] but the technique was of little

value in clinical practice until the introduction of the non-compliant pneumohydraulic infusion pump in 1960s.[2] A quarter of a century later, the application of solid-state miniaturized pressure transducers mounted on the manometric catheter facilitated the practical conduct of the study, but provided few interpretative insights. Disorders of the esophageal body and sphincters were recognized and classified on the basis of concepts derived from water-perfused catheter technology.

In parallel with improvements in catheter and transducer technology, advances in image processing and display were imported from expertise developed primarily in other physical sciences. Clinicians tended to be prominent in promoting improvements in catheter technology, but have been relatively slow to embrace the corresponding advances in software, which allows for novel modes of data presentation. For example, early attempts to construct a topographic plot of the esophagus,[3,4] aimed at giving a clearer visual representation of peristalsis, were met with skepticism.[5] Only recently has there been a user-friendly software system capable of providing an intuitive visual representation of esophageal function.

Conventional Manometry

Esophageal manometry is typically performed with a catheter with five pressure transducers placed 5 cm apart. A typical catheter is 4–5 mm in diameter and contains eight channels oriented round the circumference, each 0.6–0.8 mm in diameter, and perfused at a rate of 0.3–0.6 ml/min in order to record esophageal pressure waves with sufficient fidelity.

Limitations

Clinical Utility

Despite the physiologic insights into the function of the esophageal body and its sphincters, there remain many areas where conventional manometry does not provide the desired answers. In many patients with dysphagia, conventional manometric analysis is normal, or is described as showing a non-specific esophageal motor disorder (NEMD). Conversely, many patients with abnormal motility patterns are asymptomatic.[6,7] Achalasia stands out among the esophageal motility disorders as the most unequivocally identifiable pattern, and the only motility disorder with corresponding explanatory pathologic findings. The other motility disorders are rather poorly defined, can occur in asymptomatic individuals, and may vary with time.

Conventional manometry is also limited in its ability to predict bolus transport. The only agreed parameter, derived from simultaneous manometric and radiologic studies, is the need for peristaltic waves with amplitude of 30 mmHg or greater.[8]

Some of these limitations are inherent in the technique of conventional manometry. The entire esophageal body is usually sampled at only five or fewer points along its length. Localized or segmental abnormalities may be missed by such widely spaced transducers. The difficulties are even greater in analysis of the lower esophageal sphincter (LES) because of its short length and its frequent movement with swallowing and respiration. In this situation, axial movement of the sphincter proximal to the transducer may be misinterpreted as relaxation because the transducer is actually reflecting gastric pressure. The LES is traditionally assessed by pulling the transducer in a stepwise manner through the gastroesophageal junction, but this gives only static LES measurements and does not permit monitoring of sphincter function in real time.[9] It is slow to perform and prone to artifacts induced by the frequent swallowing associated with stepwise catheter movement. The accuracy and reproducibility of station pull-through can be improved by using the slow motorized pull-through technique, in which the catheter is pulled through at 1 mm per second, reducing swallow-induced artifacts, but this modification has not been widely adopted in practice.[10]

The 6-cm-long perfused sleeve introduced by Dent in 1976 allows continuous monitoring of the maximal LES pressure in real time, but it sacrifices anatomical information about the length of the LES and the length of the portion subjected to intra-abdominal pressure.[11] Further, the response rate of the sleeve is substantially slower than that of individual side holes, limiting its ability to detect rapid changes in pressure.

Water-perfused systems are relatively cheap, require little maintenance, and rarely malfunction. However, they are subject to many limitations. The need for constant infusion of water tends to be uncomfortable for patients when the sensors are located in the upper esophagus and pharynx, and may induce uncontrollable swallowing. It is also subject to inaccuracy because the side holes may not be consistently parallel to the bank of pressure transducers, especially in curved locations such as the pharynx or the EG junction. Consequently, reference to gastric baseline or atmospheric pressure may be inconsistent. The response rate of water-perfused systems is generally 300–400 mmHg/s, which may be adequate for the relatively slow changes in intraesophageal body pressure, but is of limited value in circumstances where the pressures change very rapidly, such as the upper esophageal sphincter (UES). In addition, the presence of even tiny bubbles of air in the

perfused fluid substantially reduces the response rate even further, and important changes in pressure may go undetected.

The introduction of solid-state pressure sensors mounted directly on the catheter has the potential to overcome many of these difficulties. Despite their high cost, they are valuable because they are independent of patient position, require no perfusion, and have a response rate many times faster than water-perfused sensors, approximately 4,000 mmHg/s.

Problems of Interpretation

Regardless of the fidelity with which signals are acquired and recorded, interpretation of motility tracings is prone to subjectivity and inter-observer variability. Even in major referral centers with prominent motility experts, there may be considerable disagreement between experienced observers in arriving at a diagnosis from a given motility tracing.[12] The most consistent results are obtained in normal subjects and in patients with achalasia. There is much greater discrepancy between observers in non-achalasia motor disorders. Variability also exists when the same observer is asked to review the same tracing some time later. Although computer-based interpretation of motility patterns avoids such variability, the diagnostic algorithms are only as good as the motility experts who create them, and in practice, the output of a computer-generated diagnosis is always supplemented by the physician's subjective analysis of the tracing. Paradoxically, the incorporation of more data points may actually simplify the picture by creating a topographic plot of the entire esophagus, which allows the physiologic status of the esophagus to be intuitively grasped at a glance. The concept is familiar to geographers who replace individual data points with contour plots of such parameters as temperature or pressure, giving an immediate overview of the weather status of the entire country.[13] Such contour plots are very amenable to modern computer analytical methods designed to manage large data sets.

High-Resolution Manometry

Principle

The simultaneous development of solid-state miniaturized transducers at very closely spaced intervals, coupled with the analytical capacity of modern sophisticated software systems has allowed the evolution of the latest species in the phylum of esophageal motility techniques, termed HRM. It is important to emphasize that it is not a completely new technology, but rather a natural development from conventional manometry. By greatly increasing the number of sensors and reducing the distance between them, it provides a comprehensive representation of the entire pressure profile along the esophagus. The concept of representing pressures as topographic contour plots was originally described using water-perfused catheters,[14] but the most widely available system uses a solid-state catheter (Sierra Scientific Instruments, Los Angeles, CA, USA).

Catheter Design

The commonly used catheter is 4.2 mm in diameter with sensors every centimeter along its 36-cm length. The pressures within the stomach, LES, esophageal body, UES, and pharynx can all be monitored simultaneously without the need for pull-through or repositioning of the catheter. The sensors measure pressure over a length of 2.5 mm. At each centimeter level, there is an array of 12 microtransducers around the circumference of the catheter (Fig. 1). The transducers have an extremely fast response characteristic and can record pressure changes as rapid as 6,000 mmHg/s and are generally accurate to within 1 mmHg. The outputs from the 12 circumferential pressure sensors at each centimeter level are averaged to give a mean value for that level. The data are smoothed by interpolation, and, using the supplied software, a topographic plot is made, in which pressures within a given narrow range are represented by different colors on the screen (Fig. 2).

Data Analysis and Presentation

There are two aspects of the software: One novel aspect of HRM is the mode in which the large amounts of data are

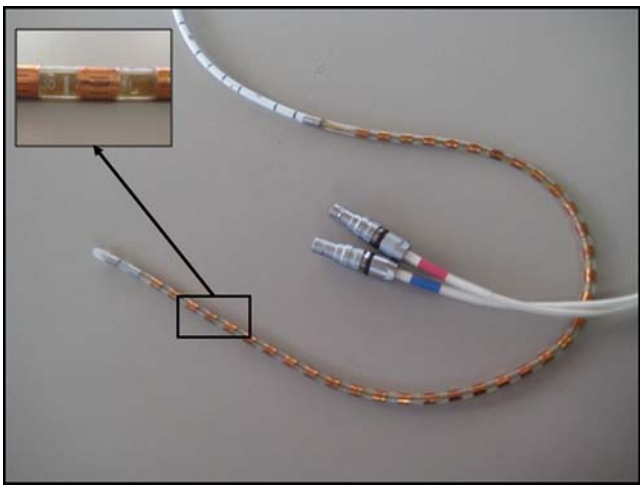

Figure 1 Solid-state manometric catheter with 36 levels of pressure sensors spaced at 1-cm intervals. At each centimeter level, there is an array of 12 circumferential microtransducers. The pressures are averaged to give a single value at each level.

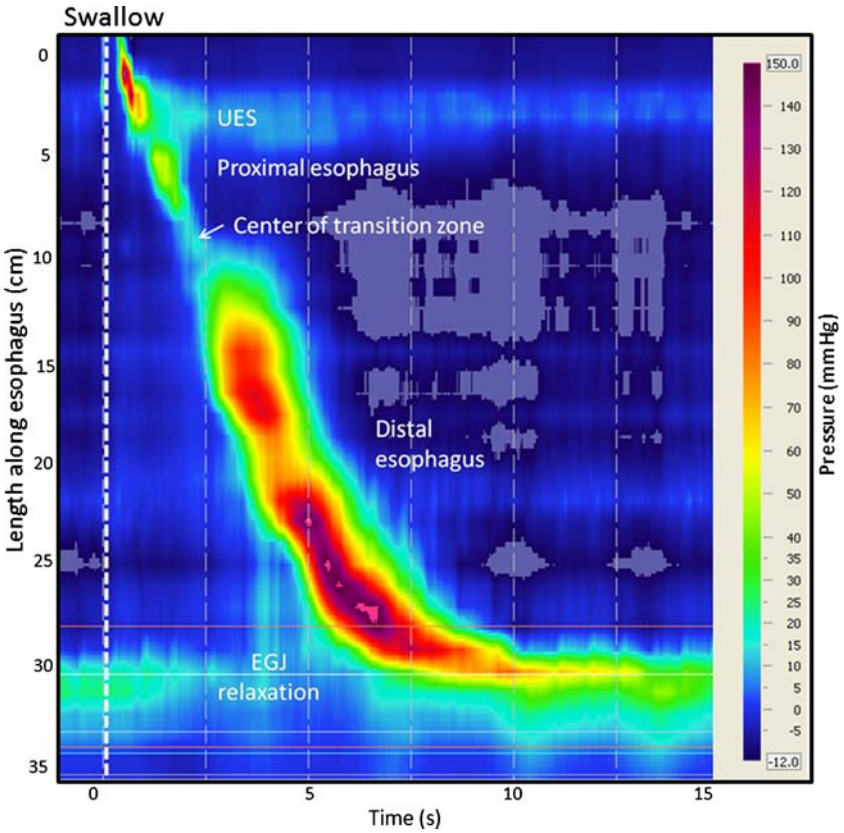

Figure 2 A sample of pressure topography of a swallow along the length of esophagus from the upper to the lower esophageal sphincters.

displayed. The pressure (z-axis), time (x-axis) and location within the esophagus (y-axis) are presented in a "pseudo-3-dimensional" format in which the pressures are plotted in the form of colored contours (Fig. 3a). The propensity of the human brain to recognize patterns makes this format intuitively easy to grasp by non-specialists and even patients. Some motility experts prefer the familiarity of conventional line tracings, and the current software makes this transition possible with a single click (Fig. 3b).

In addition to the advantage of the user-friendly visual representation, the software also permits the easy calculation of many new parameters. The baseline may be easily adjusted to either gastric pressure or atmospheric pressure depending on the area of interest. In addition, the closely spaced transducers straddling the lower esophageal sphincter can be treated like a virtual sleeve sensor, and detailed measures of the timing and extent of sphincter relaxation are simple to calculate. There are sufficient transducers along the length of the catheter to be able to distinguish true relaxation from mere upward movement of the sphincter off the transducer.

Study Protocol

The first phase of the study is a 25 seconds period of recording the resting status of the esophagus and determining the location and resting pressure profile of the sphincters. This is followed by ten swallows of 5 ml water, at 20-s intervals to assess esophageal body function, LES relaxation, and UES function. Some workers suggest the use of higher volumes of water (10 and 20 ml or even more) to increase the detection of pharyngeal dysfunction.[15]

New insights from HRM

Lower Esophageal Sphincter (LES)

Manometry has provided many insights into the function of the LES since its first description in 1956.[9] Although resting sphincter pressure was the first and principal parameter to be measured, useful physiologic insight was gained by measuring the total length over which the sphincter exerted its influence, and the portion of the sphincter subject to intra-abdominal pressure.[16] The dynamic function of the LES has been studied by using the perfused sleeve described by Dent.[17,18] As the techniques were refined, it became clear that phasic contraction of the crura of the diaphragm also contributed to the pressure at the LES, a concept popularly described as the "double sphincter" hypothesis.[19] In normal subjects, the LES is surrounded by the muscle of the crura, and this is easily recognizable as abrupt inspiratory spikes of pressure when the

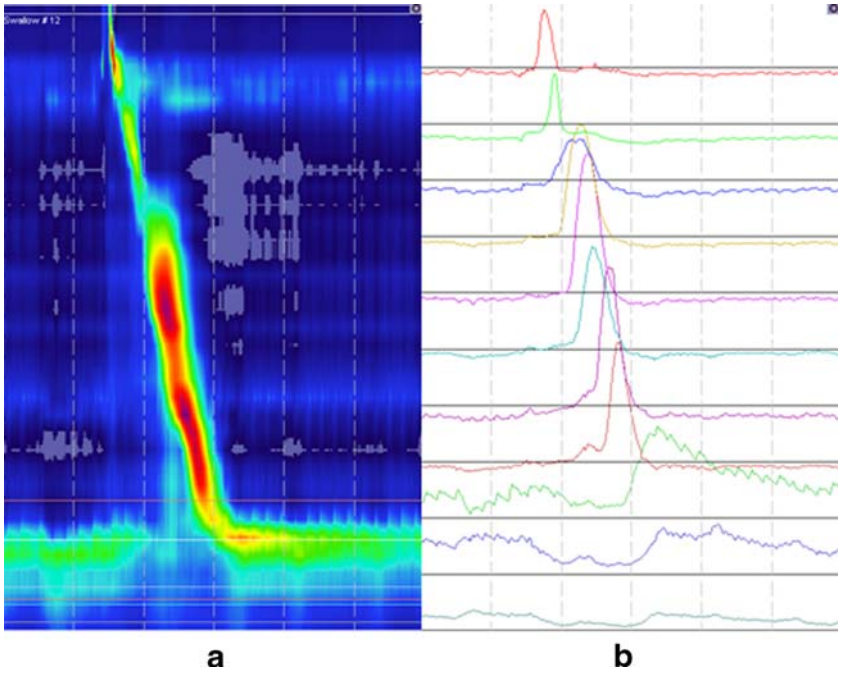

Figure 3 **a** Color contour mode and **b** conventional line tracing mode of the same swallow.

transducer is lying within the crura. In hiatal herniation, the crura and the intrinsic sphincter are not superimposed but axially separated, with the intrinsic sphincter lying somewhat more proximally, giving the "double-hump" appearance on a standard motility tracing. New insight into the relationship between the crura and the sphincter has recently been provided by HRM analysis.[20] Pandolfino and colleagues have classified the morphology of the EGJ into three major subtypes: type I with the crural diaphragm completely superimposed on the LES, type II having a 1–2-cm separation between the sphincter and the crural diaphragm, and type III where the separation between the sphincter and the diaphragm is greater than 2 cm. The same workers have recently reported that EGJ type III was rarely found in asymptomatic subjects or those with functional heartburn; however, it was a frequent finding in those with GERD. In addition, they also showed that expiratory esophagogastric junction pressure, LES-CD separation, and inspiratory pressure augmentation were all significantly associated with GERD, but only inspiratory pressure augmentation was an independent predictor of GERD.

Esophageal Body

The limitations of conventional manometric analysis of the esophageal body have prompted a re-examination of esophageal body function in the light of the insights provided by HRM. It has the potential to characterize esophageal contractions in a more precise fashion since the sensors are spaced very close to each other, thus reducing the risk of missing localized abnormalities.[21]

Classification of Esophageal Motor Disorders

This new technology has provided the opportunity to develop novel parameters for classifying functional abnormalities. Two such measures are the pressurization front velocity (PFV) and the distal contractile integral (DCI).[22] The PFV is calculated from the 30-mmHg isobaric contour plots by marking the distal temporal margin of the transition zone and the superior margin of the EGJ on the 30-mmHg isobaric contour and then calculating the slope between the two, expressed in centimeters per second. From an analysis of 75 normal subjects, the 95th percentile of normal for PFV is 4.5 cm/s. The DCI integrates other characteristics of the distal esophageal contraction, namely vigor, length, and persistence of the postdeglutitive pressurization in the distal esophagus, expressed as mmHg.s.cm. Patients with normal EGJ pressure, normal EGJ relaxation, normal PFV, and a DCI <5,000 mm Hg.s.cm are considered normal. Use of these two parameters has prompted the Northwestern group to propose a new classification of esophageal motor diseases termed the Chicago classification, summarized in the Table 1.[23] Note that the category of non-specific esophageal motility disorders (NEMD) has been abolished. This ought to be a positive step since NEMD has generally functioned as an umbrella term with minimal clinical utility.

Estimates of Esophageal Clearance

Conventional manometric estimates of bolus clearance generally depend on detection of peristaltic contractions of

Table 1 The Chicago Classification of Esophageal Motility

Normal[a]
Peristaltic dysfunction
Mild
Severe
Aperistalsis
Hypertensive peristalsis
Nutcracker
Segmental nutcracker
Spastic nutcracker
Nutcracker LES
Rapidly propagated pressurization
Spasm
Compartmentalized pressurization
Abnormal LES tone
Hypotensive
Hypertensive
Achalasia
Impaired deglutitive EGJ relaxation
Aperistalsis
Classic
Vigorous
Functional obstruction
Impaired deglutitive EGJ relaxation
Mild
Severe

[a] PFV <8 cm/s in >90% of swallows, DCI <5,000 mm Hg s cm, Normal EGJ pressure (10–35 mm Hg) and deglutitive relaxation (eSleeve 3-s nadir <15 mm Hg) adapted from Kahrilas et al.[23]

amplitude 30 mmHg or greater. HRM has the potential to predict bolus clearance by quantifying another important determinant of clearance, namely, the gradient between the intrabolus pressure and the opening pressure of the EG junction.[24] The time during which this gradient is positive, the flow permissive time (FPT), appears to be an important measure of clearance—a FPT value of less than 2.5 s has a sensitivity of 86% and specificity of 92% for predicting incomplete clearance. In contrast, the conventional manometric parameters, using a cut-off amplitude of 30 mm Hg, have a sensitivity of only 48% and specificity of 88%.[25]

Importance of Transitional Zone

The close spacing of the transducers during HRM has provided new insight into the function of the so-called transitional zone in the proximal esophagus. This zone, which appears to represent the junction of the skeletal and smooth muscle components of the esophageal body, was largely ignored by conventional manometric analyses. However, HRM has been used to characterize this region, and parameters such as the proximal contractile integral (PCI, by analogy with the DCI) can now quantify the profile of this area.[26] Although an isolated defect in this region is a rare cause of dysphagia, it may represent a distinct motility disorder.

Upper Esophageal Sphincter (UES)

HRM is ideally suited to the study of the pharynx and UES for several reasons: the extremely rapid pressure changes in the skeletal muscle of this area require transducers with this response rate: movement artifact is much greater in the UES than at the gastroesophageal junction, and a single transducer placed within the UES is likely to be displaced into the upper esophagus at the moment of sphincter opening. The output of single-point transducers may be unrepresentative because of a very asymmetrical configuration of the UES. Consequently, the availability of a catheter with a large number of closely spaced, circumferentially integrated, non-perfused transducers overcomes the chief limitations of conventional manometry. HRM has only recently been used to study the UES and oropharyngeal dysfunction.[27] Ghosh et al. have described newer parameters to characterize opening of the UES, but they have not been widely validated in clinical practice.[28]

Potential Clinical Advantages

Patient Discomfort and Easier Analysis

All workers appear to agree that HRM is quicker and more comfortable for patients than conventional manometry, but there are few data to substantiate this belief. The presence of recording channels from the pharynx to the stomach removes the need for the time-consuming pull-through technique and also facilities the positioning of the catheter. Elimination of the pull-through not only shortens the procedure time but also decreases the swallow simulation caused by catheter withdrawal, and this reduces the swallow-induced artifact of the recording.

In a study by Sadowski, a group of patients who underwent HRM were compared to those who had conventional manometry.[29] In this study, the total procedure time was 26% less in the HRM group, but they noted no significant difference in the discomfort scores for the two procedures. However, in this study, no patients experienced both procedures; therefore, a direct comparison was not possible. We have extensive experience of patients undergoing both HRM and conventional manometry, and there appears to be unanimous agreement that HRM is associated with a reduced degree of discomfort and is substantially quicker than conventional manometry. In addition, HRM

facilitates the detection of abnormal motor activity at least in the esophageal body, and in routine clinical studies, analysis sometimes proceeds simultaneously with data acquisition. Motivated patients who are familiar with the concepts of a topographic map for weather forecasts find it intuitively easy to recognize normal and abnormal peristaltic patterns within the esophageal body.

Placement of the conventional motility catheter in certain clinical situations, such as in a dilated esophagus or a large hiatal hernia, may be difficult because of curling of the catheter, often leading to the need to have it placed endoscopically. However, the HRM catheter is heavier and more rigid, making it easier to pass it into the stomach without endoscopic guidance. Once it is located in the stomach, the entire topography of the esophagus and the upper and lower sphincters is identifiable at a glance.

Improvement in Clinical Management

Although HRM provides more detailed information in a more patient-friendly way, it is not clear whether using HRM improves clinical management of patients with different benign esophageal disorders. To show clinical value would require case control studies with strong validation, using objective end points. At this time, most workers rely on individual case reports where it can be shown that HRM provided more clinically and physiologically relevant information than conventional manometry. The motor abnormalities found by HRM may have clinical significance, but the diagnosis sometimes does not fit the conventional manometry classification of motility disorder. Clouse and colleagues reported a 12% manometric disagreement and 5% diagnostic agreement between HRM and conventional manometry. In another publication from Zurich, the authors estimated that 10% of patients being investigated for endoscopy-negative dysphagia who had non-diagnostic conventional manometry received a definite diagnosis by HRM.[30] It is important to note that HRM findings, even if they provide a pathological basis for dysfunction and symptoms, may not lead to any improvement in treatment. There is, nevertheless, value in reaching a physiologically satisfying explanation for a patient's symptoms, since it may prevent unnecessary investigations or inappropriate treatments.

Effect of Medications

The information provided by HRM makes it a valuable tool in assessing the effect of some medications, most notably prokinetics. Tagaserod is a 5-HT4 receptor agonist with prokinetic effects on the gastro-intestinal tract. It has been shown to decrease postprandial acid reflux in patients with mild to moderate GERD.[31] While conventional manometry did not establish the physiological basis of this effect, the use of HRM revealed that Tegaserod promoted mid-esophageal contractility and shortened the proximal transition zone.[32] Another preliminary study suggests that HRM may identify specific dysmotility patterns that respond to specific pharmacologic intervention. For example, symptomatic focal spasm was shown to respond to sildenafil.[33]

The effects of surgery may also be better understood by HRM analysis. It has been postulated that HRM may be able to identify whether persistent or recurrent symptoms after surgical treatment of reflux disease or achalasia are due to persistent esophageal dysmotility or functional obstruction at the level of gastroesophageal junction induced by the surgery.[18]

Other Diagnostic Possibilities

Clinical Importance of Transitional Zone

Most physicians have tended to focus on the distal esophagus and LES when assessing dysphagia. However, the visually intuitive output from HRM studies has encouraged exploration of the esophageal transitional zone (TZ), easily recognized as the gap between the proximal one-third and the distal two-thirds of the esophageal body. Ghosh and colleagues developed a standardized method for quantifying the spatiotemporal dimensions of the TZ and by applying this method in a large series of patients, they concluded that TZ defects greater than 2 cm in length and 1 cm in duration were associated with otherwise unexplained dysphagia.[34]

Subtypes of Achalasia

Not all patients with achalasia respond with uniform success to standard modalities of treatment. This suggests that there may be subtypes of this esophageal motor disorder for which different treatments may be appropriate. This has been difficult to demonstrate with conventional manometry, since most workers rely on the standard parameters of aperistalsis and impaired LES relaxation. New studies of achalasia using HRM have revealed three distinct subtypes of this condition: (1) classic achalasia with minimal pressurization, (2) achalasia with esophageal compression, and (3) achalasia with spasm. These groups had different responses to medical or surgical therapies, with group 2 having the best response and group 3 the worst.[35]

HRM Limitation and Controversies

Compared to conventional manometry, HRM is more expensive, and since there are no outcome studies, the

cost-effectiveness of this procedure cannot be assessed. The catheter is expensive, but is reusable because, for each exam, it is covered with a disposable sterile plastic sheath. There are no reports in the literature of any disease being transmitted by the catheter.

The ease of the study and the straightforward analysis and report production makes it very popular in community-based centers. Concern has been expressed that this quality will encourage conduct and analysis of the study to be delegated to less experienced staff.

Currently available versions of the analytical software used to interpret HRM have focused the clinicians' attention on disorders of the esophageal body and UES, whereas the resting features of the LES are not easy to calculate. This has resulted from a tendency to downgrade the significance of the resting LES parameters in favor of dynamic activity, such as LES relaxation.[36] It is to be hoped that future versions of the analytical software will make calculation of resting LES pressure, length, and intra-abdominal length more accurate and intuitive. Although surgeons, most notably Dr. DeMeester, have long championed the significance of these measures of LES function, it is notable that, of all papers about high-resolution esophageal manometry that are currently identifiable on Medline, very few has come from a surgical center.

Like all manometric methods using intraluminal pressure transducers, HRM only provides information about the circular muscle contractions and ignores the contribution of the longitudinal muscles and muscularis mucosa in peristalsis and symptom generation. To a limited extent, these muscle layers have been studied using a high-frequency, intraluminal ultrasonographic probe (HFIUS), but their importance in disease has received little attention. Efforts to combine HFIUS with HRM[37] may be fruitful because they seem to be complementary procedures, providing a complete motor function assessment of the esophagus.

Future Horizons

The field of esophageal physiology has been rejuvenated by the introduction of the new technology of HRM. This technique has provided an adequate degree of spatial detail to characterize motor function of the esophagus. As a consequence, a new generation of researchers has begun to apply this new technology to the old questions in the field of esophagology. In particular, the work of Kahrilas and colleagues in Northwestern University has remarkably advanced our knowledge and understanding about esophageal motility. However, the potential exists to generate even further improvement with a recently available method called high-definition manometry (Sierra Scientific Instruments).[38] In this technique, the pressure transducers are grouped in four banks of four rings each, with the rings spaced 3 mm apart and the banks spaced 4 mm apart. There are 128 independent pressure recordings spanning 4.8 cm. The potential of this new technology in assessment of novel intraluminal antireflux treatments to augment the reflux barrier is very promising, and its developments are awaited with interest.

References

1. Kronecker H, Meltzer SJ. Der Schluckmechanismus, seine. Erregung und seine Hemmung. Arch Ges Anat Physiol 1883; (Suppl):328–332.
2. Arndorfer RC, Stef JJ, Dodds WJ, Hogan WJ. Improved infusion system for intraluminal esophageal manometry. Gastroenterology 1977;73:23–27.
3. Clouse RE, Staiano A, Alrakawi A, Haroian L. Application of topographical methods to clinical esophageal manometry. Am J Gastroenterol 2000;95(10):2720–2730.
4. Clouse RE, Prakash C. Topographic esophageal manometry: an emerging clinical and investigative approach. Dig Dis 2000;18 (2):64–74.
5. Holloway RH. Topographical clinical esophageal manometry: a better mousetrap or manometric overkill? Am J Gastroenterol 2000;95(10):2677–2679.
6. Kahrilas PJ, Clouse RE, Hogan WJ. American Gastroenterological Association technical review on the clinical use of esophageal manometry. Gastroenterology 1994;107(6):1865–1884.
7. Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. Gut 2001;49(1):145–151.
8. Kahrilas PJ, Dodds WJ, Hogan WJ. Effect of peristaltic dysfunction on esophageal volume clearance. Gastroenterology 1988;94(1):73–80.
9. Code CF, Fyke FE, Schlegel JF. The gastroesophageal sphincter in healthy human beings. Gastroenterologia 1956;86(3):135–150.
10. Campos GM, Oberg S, Gastal O et al. Manometry of the lower esophageal sphincter: inter- and intraindividual variability of slow motorized pull-through versus station pull-through manometry. Dig Dis Sci 2003;48(6):1057–1061.
11. Dent J. A new technique for continuous sphincter pressure measurement. Gastroenterology. 1976;71(2):263–267.
12. Nayar DS, Khandwala F, Achkar E et al. Esophageal manometry: assessment of interpreter consistency. Clin Gastroenterol Hepatol 2005;3(3):218–224.
13. Skelton RA. “Cartography”, History of Technology, vol. 6. Oxford, 1958, 612–614.
14. Clouse RE, Staiano A. Topography of the esophageal peristaltic pressure wave. Am J Physiol 1991;261:G677–G684.
15. Fox MR, Bredenoord AJ. Oesophageal high-resolution manometry: moving from research into clinical practice. Gut 2008;57 (3):405–423.
16. Zaninotto G, DeMeester TR, Schwizer W et al. The lower esophageal sphincter in health and disease. Am J Surg 1988;155 (1):104–111.
17. Dent J, Dodds WJ, Friedman RH et al. Mechanism of gastroesophageal reflux in recumbent asymptomatic human subjects. J Clin Invest 1980;65:256–267.
18. Dent J. Approaches to driving the evolving understanding of lower oesophageal sphincter mechanical function. J Smooth Muscle Res 2007;43(1):1–14.
19. Mittal RK. Current concepts of antireflux barrier. Gastroenterol Clin North Am. 1990;19(3):501–516.

20. Pandolfino JE, Kim H, Ghosh SK et al. High-resolution manometry of the EGJ: an analysis of crural diaphragm function in GERD. Am J Gastroenterol 2007;102(5):1056–1063.
21. Ghosh SK, Pandolfino JE, Zhang Q et al. Quantifying esophageal peristalsis with high-resolution manometry: a study of 75 asymptomatic volunteers. Am J Physiol Gastrointest Liver Physiol 2006;290(5):G988–G997.
22. Pandolfino JE, Ghosh SK, Rice J et al. Classifying esophageal motility by pressure topography characteristics: a study of 400 patients and 75 controls. Am J Gastroenterol 2008;103(1):27–37.
23. Kahrilas PJ, Ghosh SK, Pandolfino JE. Esophageal motility disorders in terms of pressure topography: the Chicago Classification. J Clin Gastroenterol 2008;42(5):627–635.
24. Ghosh SK, Kahrilas PJ, Lodhia N, Pandolfino JE. Utilizing intraluminal pressure differences to predict esophageal bolus flow dynamics. Am J Physiol Gastrointest Liver Physiol 2007;293(5): G1023–G1028.
25. Pandolfino JE, Ghosh SK, Lodhia N, Kahrilas PJ. Utilizing intraluminal pressure gradients to predict esophageal clearance: a validation study. Am J Gastroenterol 2008;103(8):1898–1905.
26. Ghosh SK, Janiak P, Fox M et al. Physiology of the oesophageal transition zone in the presence of chronic bolus retention: studies using concurrent high resolution manometry and digital fluoroscopy. Neurogastroenterol Motil 2008;20(7):750–759.
27. Takasaki K, Umeki H, Enatsu K, et al. Investigation of pharyngeal swallowing function using high-resolution manometry. Laryngoscope 2008;118(10):1729–1732.
28. Ghosh SK, Pandolfino JE, Zhang Q et al. Deglutitive upper esophageal sphincter relaxation: a study of 75 volunteer subjects using solid-state high-resolution manometry. Am J Physiol Gastrointest Liver Physiol 2006;291(3):G525–G531.
29. Sadowski DC, Broenink L. High-resolution esophageal manometry: a time motion study. Can J Gastroenterol. 2008;22 (4):365–368.
30. Fox M, Hebbard G, Janiak P et al. High-resolution manometry predicts the success of oesophageal bolus transport and identifies clinically important abnormalities not detected by conventional manometry. Neurogastroenterol Motil 2004;16 (5):533–542.
31. Kahrilas PJ, Quigley EM, Castell DO et al. The effects of tegaserod (HTF 919) on oesophageal acid exposure in gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2000;14 (11):1503–1509.
32. Fox M, Menne D, Stutz B et al. The effects of tegaserod on oesophageal function and bolus transport in healthy volunteers: studies using concurrent high-resolution manometry and videofluoroscopy. Aliment Pharmacol Ther 2006;24(7):1017–1027.
33. Fox M, Sweis R, Wong T, Anggiansah A. Sildenafil relieves symptoms and normalizes motility in patients with oesophageal spasm: a report of two cases. Neurogastroenterol Motil 2007;19 (10):798–803.
34. Ghosh SK, Pandolfino JE, Kwiatek MA, Kahrilas PJ.Oesophageal peristaltic transition zone defects: real but few and far between. Neurogastroenterol Motil 2008;20(12):1283–1290.
35. Pandolfino JE, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: A New Clinically Relevant Classification by High-Resolution Manometry. Gastroenterology 2008;135 (5):1526–1533.
36. Ayazi S, Hagen JA, Zehetner J, et al. The value of high resolution manometry in the assessment of the resting characteristics of the lower esophageal sphincter. J Gastrointest Surg 2009.
37. McCray WH Jr., Chung C, Parkman HP, Miller LS. Use of simultaneous high-resolution endoluminal sonography (HRES) and manometry to characterize high pressure zone of distal esophagus. Dig Dis Sci 2000;45(8):1660–1666.
38. Kahrilas PJ, Ghosh SK, Pandolfino JE. Challenging the limits of esophageal manometry. Gastroenterology 2008;134(1):16–18.

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DEMEESTER FESTSCHRIFT

A Controversy That Has Been Tough to Swallow: Is the Treatment of Achalasia Now Digested?

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Abstract Esophageal achalasia is a rare neurodegenerative disease of the esophagus and the lower esophageal sphincter that presents within a spectrum of disease severity related to progressive pathological changes, most commonly resulting in dysphagia. The pathophysiology of achalasia is still incompletely understood, but recent evidence suggests that degeneration of the postganglionic inhibitory nerves of the myenteric plexus could be due to an infectious or autoimmune mechanism, and nitric oxide is the neurotransmitter affected. Current treatment of achalasia is directed at palliation of symptoms. Therapies include pharmacological therapy, endoscopic injection of botulinum toxin, endoscopic dilation, and surgery. Until the late 1980s, endoscopic dilation was the first line of therapy. The advent of safe and effective minimally invasive surgical techniques in the early 1990s paved the way for the introduction of laparoscopic myotomy. This review will discuss the most up-to-date information regarding the pathophysiology, diagnosis, and treatment of achalasia, including a historical perspective. The laparoscopic Heller myotomy with partial fundoplication performed at an experienced center is currently the first line of therapy because it offers a low complication rate, the most durable symptom relief, and the lowest incidence of postoperative gastroesophageal reflux.

Keywords Achalasia · Dysphagia · Heller myotomy · Laparoscopic surgery · Endoscopic dilation

Introduction

Esophageal achalasia is a rare neurodegenerative disease of the esophagus and lower esophageal sphincter (LES) that leads to dysphagia and other associated symptoms. The incidence of achalasia in western populations is one to three per 100,000 people.[1,2] Patients with achalasia present to the gastroenterologist within a spectrum of disease severity related to the progressive pathological changes affecting the esophagus, such as grades of esophageal dilation, and associated conditions, such as esophageal diverticulum.[3] Because achalasia is rare and the spectrum of disease severity is wide, few randomized controlled clinical trials have properly delineated the best treatment strategy. The safety, effectiveness, and durability of current treatment options, including pharmacologic, endoscopic, and surgical therapy, varied widely. Until the late 1980s, endoscopic dilation was considered first-line therapy;[4] but after minimally invasive surgical techniques were introduced toward the end of the last century, expert opinion shifted. Currently, most experts agree that first-line therapy should be laparoscopic myotomy with partial fundoplication, performed by an experienced surgeon, and that endoscopic methods should be reserved as an alternative to surgery for patients who are poor surgical candidates, refuse an operation, and possibly patients for whom surgery fails.[5–13] In this paper, we review the current understanding of the pathophysiology of achalasia, standard and emerging diagnostic tools, and outline the various treatment options before and after the development of minimally invasive

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surgical techniques, with an emphasis on symptom relief and complications.

Pathophysiology

Achalasia, though rare, is possibly the most studied and best described motility disorder of the esophagus, yet its pathogenesis remains incompletely understood. It is a neurodegenerative disorder affecting the function of the muscle of the esophageal body and LES, as well as the vagal trunks and dorsal vagal nuclei.[14] The pathogenesis stems from an idiopathic and irreversible loss of postganglionic inhibitory neurons in Auerbach's myenteric plexus.[15] The resulting imbalance toward cholinergic stimulation[15,16] causes loss of LES relaxation and failure of the esophageal body peristalsis after swallowing, giving the condition the name achalasia, a Greek word meaning "failure to relax".

There are no well described effects of achalasia outside the abnormalities seen in the esophagus, LES, and the vagus nerves.[17] Whether the failure of esophageal body peristalsis is secondary to the obstruction caused by nonrelaxing LES or is a primary defect of the esophageal body is also still debated. Achalasia can present at any age, but incidence increases during the second and third decades of life. There is no evidence that the disease has a predilection for a particular race or gender.

Despite considerable investigation, the cause of ganglion cell degeneration in achalasia is still unknown. Possible associations have been described with class II human leukocyte antigen DQw1, implicating an autoimmune mechanism[16] or an inflammatory reaction due to a viral infection such herpes, measles, poliomyelitis, varicella zoster, and human papilloma virus.[14,18,19] Supporting an immune-mediated response to a virus in a genetically susceptible population are data that from Boeckxstaens et al.[20] who produced clonal proliferation of cytotoxic T cells taken directly from the gastroesophageal junction (GEJ) of patients with achalasia in response to herpes virus-1 (HSV-1). As suggested by this evidence, a smoldering HSV-1 infection could cause a myenteric plexitis and eventual self-mediated neuronal destruction in a genetically susceptible patient. Whether the mechanism of neuronal destruction is an autoimmune or infectious process and which virus(es) can lead to neuronal destruction is still unclear.

There is mounting evidence that the main downstream effect of neuronal destruction is an alteration in the neurotransmitter nitric oxide (NO) pathway. NO is the dominant small molecule mediating relaxation of the LES.[21] NO activity decreases due to loss of the inhibitory neurons that release NO and thus decreased relaxation of the LES.[22] These inhibitory neurons are thought to be severely impaired, while interestingly, their cholinergic counterparts are less affected.[23] In humans, this pattern was shown by comparing the response of the LES in patients with achalasia with that in healthy controls, after intravenous injection of several well-defined pharmacologic stimuli. The LES of achalasia patients was more sensitive than that of healthy controls to methacholine and pentagastrin. Edrophonium increased the LES pressure in achalasia patients but had no significant effect on control patients, whereas atropine increased the LES pressure in both groups.[23] Furthermore, nitric oxide synthase (NOS) knockout mice display consistently higher resting LES pressure and failure of relaxation of the LES in response to swallowing,[24] which is a similar manometric pattern to that of many patients with achalasia. Finally, GEJ biopsies from patients with achalasia display a complete absence of NOS containing neurons.[25]

Ultimately, degeneration of the myenteric plexus produces a functional defect causing loss of esophageal body peristalsis and failure of relaxation of the LES in response to swallowing. These abnormalities in motility produce the slowed transit of solids and liquids, resulting in the dysphagia that is most often the primary, but not the sole complaint, of patients. Swallowed material pools above the LES, causing irritation of the esophageal mucosa and regurgitation, and may contribute to dilation of the esophagus proximal to this outflow obstruction. In addition to dysphagia and esophageal mucosal changes, this pattern of dysmotility reliably produces manometric and radiologic findings that are required for the diagnosis of achalasia.[26–29]

Diagnosis

The most common presenting symptom of achalasia is dysphagia, which can often become so debilitating that profound weight loss occurs. However, the primary symptom of achalasia in up to 40% of patients may be regurgitation of undigested food, unexplained chest pain, "heartburn" mimicking reflux, cough, or recurrent pneumonia. The standard current workup of a patient suspected of having esophageal achalasia consists of a barium esophagram, esophageal manometry, and upper endoscopy.[30]

The *barium esophagram* can be a window into the static structure and the dynamic function of the esophagus. The mechanical outflow obstruction created by the LES leads to dilatation of the esophageal body that narrows sharply to form a classic "bird's beak" appearance seen on esophagram. Retained food is often seen in the esophagus and transit of barium past the LES is slow. Radiographic findings suggestive of achalasia have a specificity of about 75%.[17,31] As the disease progresses, often dilation worsens and the esophagus can take on a sigmoidal shape with

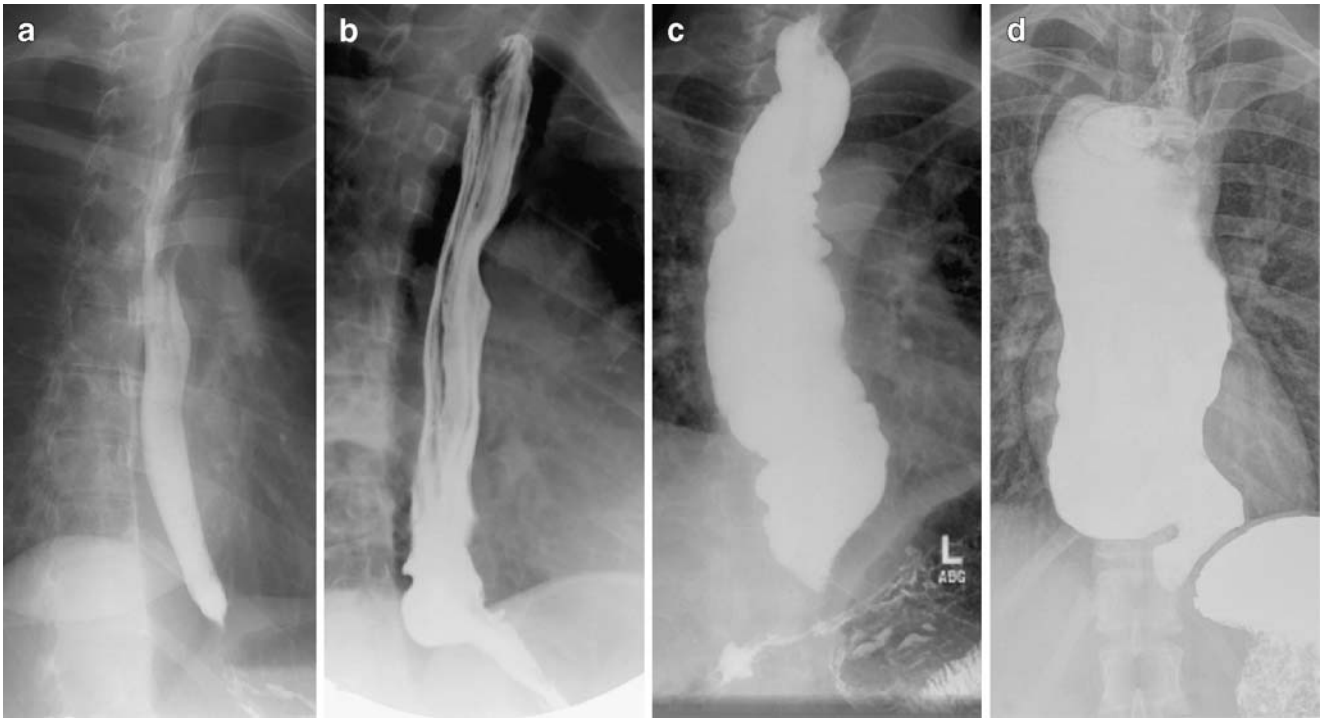

Figure 1 Examples of progressive dilation of the esophagus in different patients with achalasia. **a** Normal diameter esophagus leading to a bird's beak at the LES. **b** Minimal esophageal dilation (from 4 to 7 cm). **c** Progressive esophageal dilation (from 7 to 10 cm) with preserved esophageal axis. **d** Greater dilation (>10 cm) and initial sigmoidal course of the distal esophagus.

various degrees of dilation (Fig. 1). A sigmoid esophagus is defined as dilation of the distal esophagus to more than 10 cm in diameter and/or one that takes a tortuous course through the chest towards the GEJ. Another sign of longstanding esophageal outflow obstruction is the development of esophageal pulsion diverticula that produces external compression on the esophagus (Fig. 2).

Standard stationary esophageal manometry is currently the gold standard for diagnosing achalasia. Manometry is important for differentiating achalasia from other esophageal motility disorders such as diffuse esophageal spasm, hypertensive LES, or nutcracker esophagus.[32] Findings on manometry that suggest the diagnosis are (1) absence of peristalsis of the distal two thirds of the esophageal body and (2) incomplete LES relaxation in response to deglutition.[33] The LES is hypertensive in approximately 50% of cases,[34] but it can also be normo or hypotensive; consequently, elevated resting LES pressure is not required for the diagnosis of achalasia.[33] The diagnosis does require the finding of an aperistaltic esophagus;[33,35] although aperistalsis of the esophageal body is not a finding specific to achalasia, as it can be seen in diabetes, gastroesophageal reflux disease, and collagen vascular diseases.

Manometric diagnosis of achalasia may be a challenge in a small subset of patients with variants of the disease such as vigorous achalasia. Vigorous achalasia is thought to be an early stage of the disease.[36,37] LES pressure and the amplitude of the simultaneous aperistaltic contractions are significantly higher in vigorous achalasia than in "classic" achalasia, and the repetitive ("mirror image") waves are more frequent.[38]

Newer techniques such as high-resolution manometry (HRM) and multichannel intraluminal impedance monitoring can be used to study esophageal function and have helped clinicians further classify patients with achalasia and

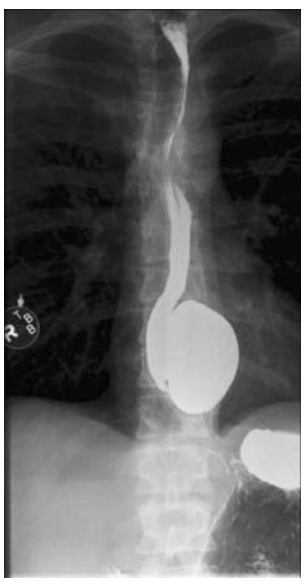

Figure 2 A barium esophagram showing a normal caliber esophagus with a large epiphrenic diverticula in a patient with achalasia.

possibly guide treatment.[39,40] High-resolution manometry records the pressure generated by the entire length of the esophagus and reports this information as a topographical plot. These data allow for more accurate definition of the contractile elements of deglutition as they are traced from the pharynx to the stomach.[41,42] In a recent study evaluating 213 patients with achalasia, HRM was used to classify the disease into three subtypes based on the function of the contractile elements: In type I (classic) achalasia (21.2% of patients), there was no distal esophageal pressurization to greater than 30 mmHg in greater than or equal to eight of the ten test swallows; in type II achalasia (with compression; 49.5% of patients), at least two test swallows were associated with an esophageal pressurization to greater than 30 mmHg; and in type III, patients (spastic; 29.3% of patients) had two or more spastic contractions with or without periods of compartmentalized pressurization.[42] Using logistic regression, the investigators related these subtypes to treatment response and showed that patients with type II achalasia were the least likely to report poor symptom improvement or require further therapy within 12 months of the initial treatment. Symptom relief was obtained in 71% of type II patients after endoscopic injection of botulinum toxin (EBTI), 91% after endoscopic dilation (ED), and 100% after Heller myotomy. Type I patients had a good response to therapy 56% of the time, whereas type III patients had a good response only 29% of the time.[42]

Multichannel intraluminal impedance pH monitoring entails positioning a series of electrodes inside the esophagus and measuring the resistance to flow of electricity between these electrodes.[43] If the esophageal lumen is filled with air, the impedance is high relative to a lumen filled with fluid. This test can also follow the dynamic impedance of a food bolus after deglutition, and during the same swallow, manometry results can be recorded. Achalasia results in a dilated and fluid-filled esophageal lumen with slowed transit of food boluses, so measuring the intraluminal impedance adds to the information about the amplitude and progression of muscle contractions gained from manometry.[35,43]

Patients being evaluated for achalasia often describe the sensation of gastroesophageal reflux (GER) or heartburn, either in addition to or in place of dysphagia. Most achalasia patients likely do not have actual reflux of gastric contents through the GEJ, but rather they experience this sensation as a direct result of fermentation of retained food in the distal esophagus and regurgitation. Fermentation is the breakdown of carbohydrates into acids or alcohol under the right conditions, and this can take place in the esophagus of a patient with esophageal outflow obstruction. Crookes et al.[44] showed that chewed samples incubated in vitro with saliva but never exposed to gastric acid slowly ferment. The pH of these samples gradually drops to around 4, but usually not below that. They also showed that achalasia patients can have pH tracings that mimic this gradually decreasing pH, or they can have sharp dips in pH more characteristic of actual reflux events. Therefore, to make the diagnosis of reflux in a patient with achalasia, the pH must drop below 3 or the tracing must display sudden sharp drops in pH; otherwise, the decreasing pH is likely a product of retained food fermenting in the distal esophagus. This is an important diagnostic distinction because it is the unusual patient who has both achalasia and GER. Crookes et al. looked at 20 patients before surgery for achalasia and found that five (20%) had abnormally high esophageal acid exposure. Of those five patients, only one (5%) had sudden pH drops characteristic of GER.[44] Evidence is lacking, but theoretically, these patients might be at a higher risk for postprocedure reflux, and should be counseled accordingly.[45]

Diagnostic upper endoscopy must be performed in all patients suspected having achalasia, although it may be normal in up to 44% of cases.[17] It is an indispensable part of the workup because primary, idiopathic achalasia must be differentiated from secondary, or pseudoachalasia. Endoscopy is required for this discrimination because manometric findings in pseudoachalasia can be indistinguishable from those in primary achalasia.[46] Pseudoachalasia can develop as a result of a parasitic infection by the leishmanial forms of *Trypanosoma cruzi* (Chagas' achalasia), which occurs most often in South Africa and South America,[47,48] or in cases of a malignant disease of the distal esophagus and the gastric cardia or peri-esophageal tumors.[47–49] Pseudoachalasia has also been associated with mesenchymal tumors, secondary amyloidosis, peripheral neuropathy, or neurological disorders resulting from brain tumors, lymphoma, and encephalitis.[31,50,51] Further causes include iatrogenic conditions such as an incorrectly constructed or tight fundoplication during antireflux procedures (ARPs) and placement of laparoscopic adjustable gastric banding for the treatment of morbid obesity (Fig. 3).[31,50,51] Although rare, esophageal and gastric malignancies may occur in patients with long-standing achalasia,[38,52] so a retroflexed view of the GEJ with routine distal esophageal and cardia biopsies should be obtained to ensure that all mucosal abnormalities are identified. Furthermore, some authors have recommended endoscopic ultrasound and/or a computed tomography scan in older patients and patients with advanced disease to uncover small, submucosal lesions, which might otherwise go undetected by other diagnostic tests.[53]

Nonspecific findings on chest X-ray may include mediastinal widening, presence of an air-fluid level in the midesophagus, absence of a gastric air bubble, and abnormal pulmonary markings due to chronic aspiration.

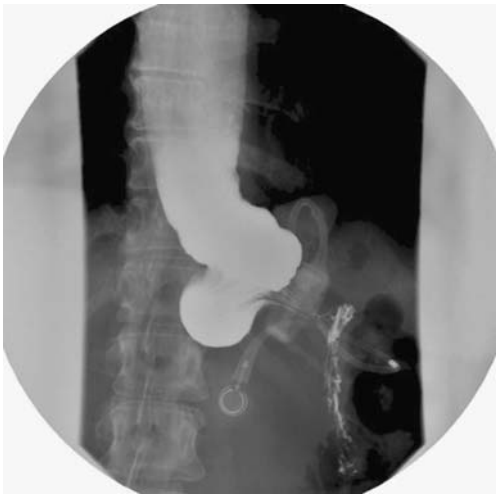

Figure 3 A barium esophagram in a patient with a gastric band causing pseudoachalasia. The esophagus is dilated and empties barium slowly.

After treatment, timed barium swallow (TBS) is an additional tool to evaluate esophageal emptying and correlate it with patient symptoms. During TBS, the patient is instructed to drink 150 ml of barium as quickly as comfortable within a time interval of 30 to 45 s. Spot films of the esophagus are taken 1 and 5 min after ingestion of the barium. The area of the barium column is measured on timed digital images. Esophageal emptying is then calculated by comparing the area of the residual barium column on the 1- and 5-min images.[54] Oezcelik et al.[55] evaluated the TBS of 30 patients at 3 and 6 months after myotomy to access esophageal emptying. They correlated the TBS results with patient reported symptom relief and found that esophageal emptying as measured by standard means did not change significantly after myotomy, but initial esophageal clearance improved dramatically (by 81%) and this correlated well with symptom improvement.

In summary, the diagnosis of achalasia is often suggested by history, barium esophagram, and upper endoscopy. Stationary esophageal manometry is currently the gold standard. Because achalasia represents a spectrum of disease, manometric findings can vary and the addition of HRM, impedance manometry, and pH-impedance can further classify the pathological state and may assist the clinician during these diagnostic dilemmas. Twenty-four hour pH monitoring can identify the unusual patient with GER prior to treatment.

Treatment

Several treatment options for esophageal achalasia are available. The overall health of the patient, coupled with the patient's expectations for symptom relief, must be considered to ensure a proper treatment plan. Treatment strategies attempt to relieve the obstructive nature of the LES at rest and after swallowing, to allow a more normal transit of liquids and solids, while taking great care not to induce GER. Currently, there is no available treatment to correct the dysmotility of the esophagus and LES created by the disease. Treatment options consist of pharmacologic therapy, endoscopic therapy, and surgery.

Pharmacologic Therapy

The goal of pharmacological therapy, the only noninvasive treatment for achalasia, is to lower the resting LES pressure. Because drug absorption is impaired due to the poor esophageal emptying, sublingual medications are preferred. Sublingual calcium channel blockers (nifedipine) and sublingual isorbide dinitrates (nitrates) are the two most common medications used.[56,57] Less commonly used medications include anticholinergics, beta-blockers, beta-adrenergic agonists (carbuterol, terbutaline, cimetropium bromide), nitroglycerine, and theophylline (aminophylline).[58–61]

In collected outcomes for 229 patients treated with pharmacologic therapy, we found that symptoms improved in 61% of patients after use of nifedipine and 70% of patients after use of nitrates.[116–123] Manometry was used to document LES pressure before and after drug therapy in all trials in different subsets of patients. A transient decrease in LES pressure was documented in 46% of patients when manometry was performed. This transient effect seemed to be better after nitrate use than after nifedipine use, as measured by the transient mean decrease in LES pressure (baseline pressure−posttherapy pressure)×100, which was 66% after nitrates but only 38% after nifedipine. Nitrates also seemed better than nifedipine with regard to the time to maximum effect (25 vs 9 min), but the duration of effect was longer for nifedipine (40 vs 30 min).

The short clinical response and common presence of side effects such as headache, dizziness, tachycardia, hypotension, nausea, and ankle edema were limiting problems with pharmacological therapy. It should be considered only for patients who decline or are considered too frail for endoscopic or surgical treatment options.

Endoscopic Therapy

Achalasia was first described in the literature in 1672 by Sir Thomas William, and the first described treatment for achalasia (then called "cardiospasm") was performed in London, by Thomas Willis. Of note, other notable accomplishments of Thomas Willis include numbering the cranial nerves and identifying the vascular arcade of the brain that is now called the Circle of Willis. In 1674, he described treatment of cardiospasm by forceful passage of a

piece of whalebone padded with a sponge through the LES.[62] With the advent of modern endoscopic techniques, endoscopic dilation was first-line therapy for achalasia until the advent of minimally invasive surgery in the 1980s.[63] Endoscopic treatments are directed at relieving the obstruction caused by the LES and now include endoscopic botulinum toxin injection (EBTI), described in 1991,[64] or endoscopic dilation (ED) of the LES.

EBTI decreases tonic and swallow-induced LES pressure by inhibiting acetylcholine release from the inhibitory cholinergic presynaptic nerve innervating the LES.[65] As reported in a recent systematic review,[66] EBTI relieves symptoms in 79% of patients surveyed up to 1 month after treatment, but unfortunately, the symptom relief declines to 70% at 3 months, 53% at 6 months, and 41% after 12 months.[66] Due to this progressive return of dysphagia, almost half (47%) of the patients undergoing EBTI required repeat injection.[66] Relief of dysphagia was found to be somewhat better if a second injection was planned at a 1-month interval after the first, but again, symptom relief was not durable and symptoms returned in 66% of patients at 2 years.[67] Primary failure of EBTI can also be due to antibody formation that causes resistance to the acetylcholine injection in 26% of patients.[68–70] In addition to these primary failures, EBTI leads to fibrosis of the mucosa and muscle layers that could make the myotomy, during a future surgical therapy, considerably more challenging.[71,72]

The other mode of endoscopic therapy is ED, and the current method of choice for dilation is a controlled pneumatic dilation.[63,73–75] Other older dilation methods have gradually been abandoned as they were associated with a higher perforation rate.[66] During controlled pneumatic dilation, a balloon is placed across the LES under direct endoscopic or fluoroscopic visualization. The balloon is inflated for 1 to 3 min, to a pressure of 300 mmHg (10–12 psi). To obtain an acceptable therapeutic effect, dilation to a diameter of at least 3.0 up to 4.0 cm must be performed.

The goal of ED is similar to the goal of any surgical therapy, as they both attempt to produce a controlled division of the esophageal muscle while leaving the mucosa intact. Review of the literature shows that dilator size, the amount of pressure applied, and duration of dilation were inconsistent between endoscopists and symptom relief seems to be dependent on these variables. ED is a relatively safe procedure and the most serious complication of the currently used methods of ED is perforation of the esophagus, which was seen in 1.6% of patients in a review of 1,065 patients, but the perforation rate can be as high as 12% using older dilation techniques.[66] Symptom relief has been related to the ability of the procedure to decrease the resting LES pressure by more than 10 mmHg, or produce a reduction of ≥50% of LES pretreatment pressure.[76]

A recent Cochrane Review, published in 2008, comprised of six randomized controlled trials including 178 patients, looked at symptom recurrence after ED vs EBTI at 1, 6, and 12 months after treatment. This review found that 30% of patients undergoing ED experienced symptom recurrence and treatment failure at 12 months vs 74% of EBTI patients.[77]

A recent systematic review and meta-analysis of 105 articles reporting on 7,855 patients treated for achalasia showed that symptom relief after ED was obtained in 85% of patients at 1 month and declined with time to 68% at 12 months and 58% at 1.5 years (Table 1).[66] Symptom relief was better for ED than for EBTI (68% vs 41%, odds ratio (OR) 3.4; 95% confidence interval (CI) 1.2–9.8; P= 0.02), and the need for further procedures was lower after ED than after EBTI (25% vs 47%; OR 2.6; 95% CI 1.05–6.5; P=0.04).[66]

In addition to dysphagia recurrence, patients undergoing ED can experience the onset of GER, with 33% of patients reporting symptomatic GER at 4 years.[78–80] When 24-h pH monitoring was used as a proxy, more than 30% of patients had an increase in episodes and duration of reflux.[44,81]

In summary, published evidence shows that ED is consistently more durable than EBTI, but that after ED, symptoms recur in 42% of patients and about 30% of all of the patients treated with ED require further therapy. Prior to any surgical intervention, knowledge of the patient's history of previous endoscopic therapies at the GEJ is important to the surgeon because some experts propose that ED and EBTI lead to fibrosis of the mucosa and muscular layers of

Table 1 Symptom Improvement After Initial Treatment of Achalasia by Therapeutic Endoscopy (Adapted from Campos et al.[66])

Treatment	Number of studies	Number of patients	Symptom improvement at (numbers are mean[a] % and range)				
			≤1months	3months	6months	≥12months	≥36months
Endoscopic injection of botulinum toxin	9	315	78.7 (64–93)	70.0 (55–83)	53.3 (44–57)	40.6 (10–55)	n/a
Endoscopic pneumatic balloon dilation	15	1,065	84.8 (56–97)	n/a	73.8 (51–97)	68.2 (38–90)	58.4 (33–70)

n/a data were not recorded for these time points in the studies used to compile the systematic review and meta-analysis

[a] Weighted averages of the sample prevalence in each of the studies, with weights equal to the number of patients

the esophagus. Less predictable symptom relief has been reported in patients who have been previously treated with endoscopic therapy,[72,82] which could be due to the greater technical difficulty of doing the operation in these patients. To avoid mucosal perforation in these cases, the location of the GEJ and the proper dissection planes must be identified during the myotomy.

Surgical Therapy

The initial attempts to treat achalasia with an operation in the early twentieth century combined several modifications of gastroesophageal junction reconstructions (cardioplasties) to esophageal resections.[83] Those techniques failed due to high operative morbidity and excessive postoperative gastroesophageal reflux and led to the development of distal esophageal myotomy. The first successful surgical myotomy of the lower esophagus and lower esophageal sphincter was reported in 1913, by the German surgeon Ernest Heller.[84] His original technique used anterior and posterior myotomies extending for 8 cm or more along the distal esophagus and GEJ through a left thoracoabdominal approach. Although this technique was successful in improving dysphagia, excessive gastroesophageal reflux resulted. In 1918, the Dutch surgeon Zaaijer[85] described a modification of Heller's original technique to a single, anterior cardiomyotomy that has remained the myotomy of choice until now. Based on Heller's original idea, many surgeons performed the distal esophageal and LES myotomy through a left thoracotomy[86] as a way to perform an appropriate myotomy while attempting to preserve the natural anatomical antireflux components of the gastroesophageal junction, such as the His angle and the phrenoesophageal membrane, thereby possibly preventing postoperative GER. Both the transabdominal and transthoracic techniques have been used since.

The end of the last century witnessed the shift from open surgery in the chest and abdomen towards thoracoscopic and laparoscopic surgery. The myotomies performed through both approaches have evolved in parallel[87,88] into minimally invasive procedures through the chest and abdomen. The first laparoscopic Heller myotomy was described by Shimi et al. in 1991.[89]

One advantage of the transabdominal operation is that it makes it easier to create a fundoplication because better exposure of the structures of the GEJ can be obtained. Thoracoscopic myotomy is also more technically challenging the transabdominal, because the myotomy must be performed perpendicular to the course of the esophagus. Finally, as discussed below, the thoracoscopic approach is associated with a higher incidence of postoperative GER, making the laparoscopic operation the preferred approach performed at most experienced centers.[87,90,91]

A 2009 systematic review and meta-analysis of the surgical options summarized 64 articles, including 4,871 patients (Table 2).[66] Regression analysis confirmed that the laparoscopic approach yielded similar symptom relief to the open thoracic operation (89% vs 83%; OR 1.3; 95% CI 0.8–2.0; P=0.3) and the open abdominal operation (89% vs 84%; OR 1.1; 95% CI 0.5–2.5; P=0.8), but better relief than then the thoracoscopic operation (89% vs 78%; OR 1.9; 95% CI 1.1–3.7; P=0.048) and also ED (89% vs 56%; OR 5.9; 95% CI 3.7–9.3; P=<0.01).[66]

In a recently published study of over 400 consecutive patients, Zaninotto et al. reported their experience with laparoscopic Heller myotomy and Dor fundoplication. Similar to results previously reported by other authors,[92,93] the best predictor of a dysphagia relief was preoperative LES pressure >30 mmHg.[94]

Some authors have debated the need to perform an ARP after the myotomy.[95–97] The 2009 systematic review and meta-analysis also evaluated the development of postoperative GER and found that adding an antireflux procedure after laparoscopic myotomy dramatically decreased the incidence of GER symptoms from 31% down to 9% (OR 4.3; 95% CI 1.9–9.7; P=0.001) without altering the resolu-

Table 2 Results (Symptom Improvement and Postoperative GER) After Surgical Treatment for Achalasia (Adapted from Campos et al.[66])

Treatment	Months follow-up (range)	Number of studies	Number of patients	Mean symptom improvement[a] % (range)		Mean prevalence[a] of GER (range)	
				No ARP	With ARP	No ARP	With ARP
Transthoracic myotomy	102.0 (57–172)	13	842	85.1 (66–97)	80.2 (66–97)	29.2 (4–66)	13.6 (0–28)
Thoracoscopic myotomy	36.4 (12–72)	8	211	77.6 (31–94)	n/a	28.3 (15–60)	n/a
Transabdominal myotomy	87.4 (8–190)	10	732	64.4 (57–66)	89.7 (73–100)	28.5 (21–64)	7.5 (0–15)
Laparoscopic myotomy	35.4 (8–83)	39	3,086	89.9 (86–100)	90.3 (77–100)	31.5 (11–60)	8.8 (0–44)

ARP antireflux procedure, *n/a* data not collected for at that time points in the studies used to compile the meta-analysis, *GER* postprocedure gastroesophageal reflux symptoms

[a] Weighted averages of the sample prevalence in each of the studies, with weights equal to the number of patients

tion of dysphagia (90% vs 90%; OR 1.6; 95% CI 0.74–3.3; P=0.23).[66] When measured by 24-h pH monitoring, the incidence of GER after laparoscopic myotomy without fundoplication was 42% vs 15% after laparoscopic myotomy with fundoplication (OR 4.2; 95% CI 1.5–12.8; P=0.01). The addition of an ARP seems crucial for satisfactory outcome in the treatment of achalasia, and the addition of a fundoplication does not increase morbidity.[98–100]

Selecting the proper treatment course for a given patient requires analysis of the rates of complication of all of the treatment options. With pneumatic balloon dilation, currently the accepted standard, the perforation rate is 1.6%.[66] Systematic review of the results of 3,086 patients who had laparoscopic myotomy found that complications were reported in 6% and death in 0.1%.[66] Intraoperative perforation of the esophageal or gastric mucosa was reported in about 7%.[66] Most of those injuries were repaired during the index operation, and only 19 patients, or 0.7%, experienced symptoms from perforation postoperatively. When overall complication rates reported after laparoscopic myotomy are compared with ED, differences are possibly related to an innate more invasive nature of the laparoscopic surgery, but differences in baseline patient characteristics and severity of the disease likely have an impact on the results of each method reported. A 2001 decision analysis for the treatment of achalasia evaluated four strategies for the initial management of achalasia: (1) laparoscopic Heller myotomy and partial fundoplication, (2) pneumatic dilatation, (3) botulinum toxin injection, and (4) thoracoscopic Heller myotomy[101]. According to the analysis, laparoscopic myotomy with fundoplication was the proper first treatment strategy unless the patient's risk of operative mortality was higher than 0.7%.

Surgical Technique

Laparoscopic Myotomy

Laparoscopic myotomy has proven over time to be the approach that consistently produces the most durable symptom relief.[99,100] The operation begins with trocar placement similar to that for any laparoscopic operation taking place at the GEJ.[100] The gastrohepatic ligament and the phrenoesophageal membrane are opened to expose the esophagus. The anterior vagus nerve is carefully identified and preserved as the dissection is carried out in clockwise fashion around the anterior esophagus. The anterior fat pad covering the GEJ may be removed to facilitate the myotomy.

In most cases, posterior esophageal dissection is not needed. Leaving the posterior attachments intact also provides an anchor to help keep the GEJ in the proper anatomic location. A posterior dissection is only performed in patients who have large concomitant hiatal hernias so that the hernia can be reduced into the abdominal cavity and the crura can be repaired properly.

The myotomy is begun by bluntly dividing the longitudinal muscle fibers of the esophagus with graspers (Fig. 4), scissors, or the hook. The myotomy is carried cephalad for at about 6 cm and through the longitudinal and circular muscle fibers down to the esophageal submucosa and extended 2 cm in the caudal direction from the GEJ on the anterior stomach to ensure complete division of the sling fibers, making the total length of the myotomy about 8 cm (Fig. 5). A gastric extension that is too short is one important cause of failure of the myotomy to relieve dysphagia. The gastric extension is also the part of the myotomy where the most mucosal perforations occur because the plane between the submucosa and the muscularis is not as pronounced in this location. Any mucosal perforation should be primarily repaired with interrupted absorbable suture.

Antireflux Procedure

After the myotomy is completed, an antireflux procedure is performed to prevent postoperative GER by recreating the His angle and keeping the GEJ inside the abdominal cavity. A 360° Nissen fundoplication has been used in selected series;[98,102,103] however, a Nissen fundoplication may hinder esophageal clearance, resulting in progressive postoperative dilatation of the aperistaltic esophagus and recurrent dysphagia. Although a few centers with significant experience in esophageal surgery still advocate a Nissen fundoplication after myotomy,[103] most do not recommend it due to reported reoperation rates as high as 29%.[10,32,86,104–108]

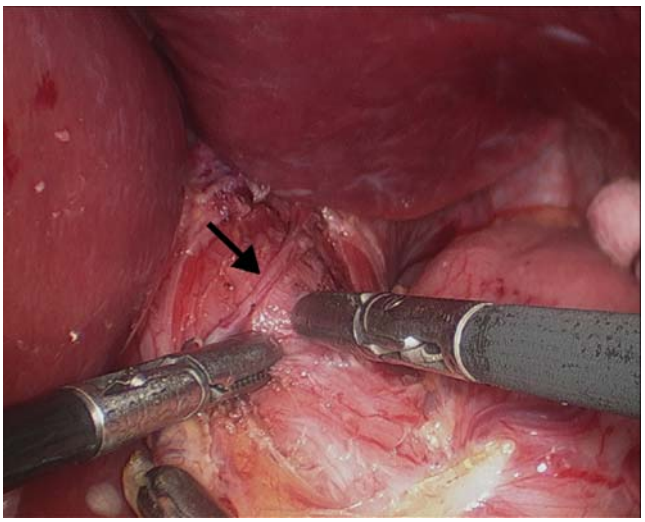

Figure 4 The anterior vagus nerve (*arrow*) is identified and preserved. Then two graspers are used to begin the myotomy just above the GEJ.

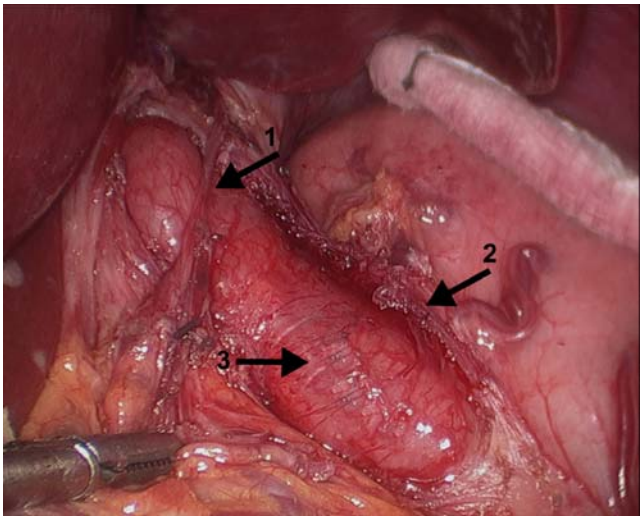

Figure 5 A completed 8-cm myotomy is shown. *Arrow 1* points to the anterior vagus nerve. *Arrow 2* points to the left edge of the myotomy. *Arrow 3* points to the exposed esophageal submucosa.

Two partial fundoplications have been used with equipoise, a posterior fundoplication (Toupet fundoplication) and an anterior fundoplication (Dor fundoplication). The *Toupet fundoplication* seems to provide an appropriate antireflux barrier. The theoretical advantages of the Toupet fundoplication are that due to its anatomical configuration, (1) it keeps the edges of the myotomy pulled apart, thus preventing scarring and recurrent dysphagia, and (2) that it can be performed just after the lower esophagus has been pulled downward and straightened, thus improving passage through the cardia and again minimizing postoperative dysphagia.[109] The drawbacks of the Toupet fundoplication are the need for circumferential dissection of the gastroesophageal junction and the possibility that diverticula will develop at the site of the myotomy years after surgery because the fundoplication does not cover the myotomy site.[110]

Proponents of the *Dor fundoplication* argue that the procedure is faster because the posterior esophageal attachments may be left in place.[109] Another advantage is that a properly constructed Dor fundoplication can prevent post operative reapproximation of the myotomy.[111] Furthermore, covering the myotomy with the fundoplication may seal inadvertent mucosal injury and prevent future development of diverticulae at the site of the myotomy. The Dor fundoplication is described in detail elsewhere,[100] and it is described briefly below.

Dor Fundoplication

The creation of the fundoplication begins with a complete mobilization of the fundus of the stomach, including division of the short gastric vessels all the way to the His angle. This dissection is required to permit the creation of the proper geometry of the fundoplication. Two vertical rows of sutures secure the gastric fundus to the left and right edges of the myotomy to create the fundoplication. Initially, the inferior edge of the left side of the esophageal myotomy is sutured to the medial gastric fundus. Then

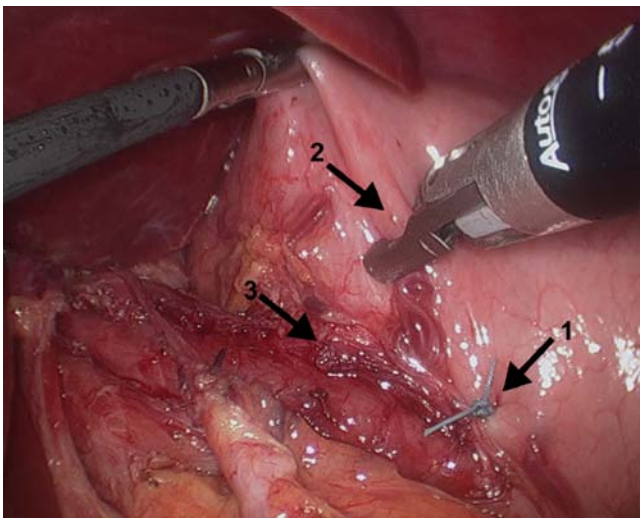

Figure 6 The creation of a Dor fundoplication. The first suture from the anterior portion of the fundus to the left edge of the myotomy (*arrow 1*). The second suture will anchor the fundoplication and part of the myotomy in the abdomen by apposing the fundus (*arrow 2*) to the left crus (not shown) and then to left edge of the myotomy (*arrow 3*).

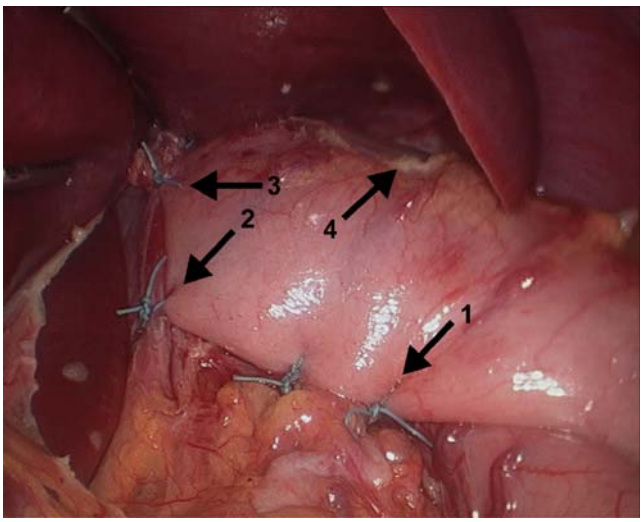

Figure 7 The completed Dor fundoplication. *Arrows 1 and 2* show the suture line that anchors the fundoplication to the right edge of the myotomy. *Arrow 2* incorporates the fundus, the right crus to the right edge of the myotomy. *Arrow 3* points the suture that secures the fundoplication to the diaphragm. *Arrow 4* points to the divided short gastric vessels that are brought into an anterior position as the fundoplication is created. This reinforces the need for a complete mobilization of the gastric fundus for the proper configuration of the fundoplication.

(Fig. 6), a stitch is placed from a superior portion of the gastric fundus to the left diaphragmatic crus and then the left side of the myotomy about 2 to 3 cm cephalad of the first suture. Two to 3 cm cephalad to the previous suture, a suture secures the left side of the myotomy to the gastric fundus without incorporating the crus. Attention to the geometric arrangement of the fundus produced during this step is important because the reconstructions of the His angle, in addition to having an intra-abdominal GEJ, are what provide the major antireflux barriers. A final suture, again on the left and cephalad to the last, brings the fundus to the left edge of the myotomy, this time just below the myotomy apex.[100]

A suture line is then created down the right edge of the myotomy. The first suture secures the superior right edge of the myotomy to a bite of gastric fundus. The suture line is continued caudally down the right myotomy edge. The second suture incorporates the right diaphragmatic crus to the fundus and the myotomy edge. Two final sutures on the right side bring the fundus to the inferior edge of the myotomy, and the exposed mucosal surface should now be completely covered by the fundus at this point. One or two sutures should then be placed to secure the superior aspect of the fundus to the anterior esophageal hiatus to prevent anterior herniation of the fundoplication into the chest (Fig. 7).

Persistent postoperative dysphagia can be the result of the following technical factors: (1) the myotomy is too short distally, (2) the myotomy is too short proximally, or (3) the fundoplication has been constructed incorrectly. Some patients may develop recurrent dysphagia after a symptom-free interval. This type of failure may be due to gastroesophageal reflux and the development of peptic stricture, healing, and fibrosis of the distal portion of the myotomy.[112]

Treatment of advanced stages of achalasia is somewhat controversial when the esophagus has dilated severely and its course in the chest becomes sigmoidal. Some authors have proposed that the gross pathology of the esophagus is so advanced that it will not respond to myotomy and fundoplication and therefore requires esophageal resection. However, recent studies suggest that these patients may have good outcomes after myotomy and fundoplication, although studies with long-term follow-up are still lacking.[113–115] Esophagectomy may need to be contemplated in selected cases.

Summary

Achalasia is a debilitating motility disorder of the esophageal body and LES. The standard diagnostic workup includes a barium esophagram, esophageal manometry, and diagnostic upper endoscopy. The diagnosis cannot be made without the finding of an aperistaltic esophagus on manometry. Impedance testing and high-resolution manometry may prove to be useful adjuncts in the future because patient characteristics are highly variable at the time of presentation. Achalasia can be treated with pharmacologic therapy, EBTI or ED, or surgery. The treatment course should be selected based on the patient's age, overall state of health, and expectations for recovery. Pharmacologic and EBTI therapy can reduce dysphagia, but unfortunately, symptom relief is often not durable. ED provides a longer interval of symptom relief than EBTI, but dysphagia commonly returns and often requires further intervention. ED was considered first-line therapy for achalasia until the late 1980s, when minimally invasive surgery was introduced. Most centers have since adopted the laparoscopic Heller myotomy with a partial fundoplication as the procedure of choice for treating achalasia. This operation provides durable symptom relief with a low rate of complications and infrequent development of postoperative GER.

References

1. Ruffato A, Mattioli S, Lugaresi ML, Lugaresi ML, D'Ovidio F, Antonacci F, Di Simone MP. Long-term results after Heller–Dor operation for oesophageal achalasia. Eur J Cardiothorac Surg 2006;29:914–919.
2. Podas T, Eaden J, Mayberry M, Mayberry J. Achalasia: a critical review of epidemiological studies. Am J Gastroenterol 1998;93:2345–2347.
3. Birgisson S, Richter JE. Achalasia: what's new in diagnosis and treatment? Dig Dis 1997;15(Suppl 1):1–27.
4. Bennett JR, Hendrix TR. Treatment of achalasia with pneumatic dilatation. Mod Treat 1970;7:1217–1228.
5. Bonatti H, Hinder RA, Klocker J, Neuhaser B, Klaus A, Achem SR, de Vault K. Long-term results of laparoscopic Heller myotomy with partial fundoplication for the treatment of achalasia. Am J Surg 2005;190:874–878.
6. Rosemurgy A, Villadolid D, Thometz D, Kalipersad C, Rakita S, Albrink M, Johnson M, Boyce W. Laparoscopic Heller myotomy provides durable relief from achalasia and salvages failures after botox or dilation. Ann Surg 2005;241:725–733. discussion 733–725.
7. Frantzides CT, Moore RE, Carlson MA, Maden AK, Zografakis JG, Keshavarian A, Smith C. Minimally invasive surgery for achalasia: a 10-year experience. J Gastrointest Surg 2004;8:18–23.
8. Zaninotto G, Costantini M, Molena D, Buin F, Carta A, Nicoletti L, Ancona E. Treatment of esophageal achalasia with laparoscopic Heller myotomy and Dor partial anterior fundoplication: prospective evaluation of 100 consecutive patients. J Gastrointest Surg 2000;4:282–289.

9. Oelschlager BK, Chang L, Pellegrini CA. Improved outcome after extended gastric myotomy for achalasia. Arch Surg 2003;138:490–495. discussion 495–497.
10. Patti MG, Fisichella PM, Perretta S, Galvani C, Gorodner MV, Robinson T, Way LW. Impact of minimally invasive surgery on the treatment of esophageal achalasia: a decade of change. J Am Coll Surg 2003;196:698–703. discussion 703–695.
11. Patti MG, Tamburini A, Pellegrini CA. Cardiomyotomy. Semin Laparosc Surg 1999;6:186–193.
12. Deb S, Deschamps C, Allen MS, Nichols FC, Cassivi SD, Crownhart BS, Pairolero PC. Laparoscopic esophageal myotomy for achalasia: factors affecting functional results. Ann Thorac Surg 2005;80:1191–1194. discussion 1194–1195.
13. Ackroyd R, Watson DI, Devitt PG, Jamieson GG. Laparoscopic cardiomyotomy and anterior partial fundoplication for achalasia. Surg Endosc 2001;15:683–686.
14. Nguyen NQ, Holloway RH. Recent developments in esophageal motor disorders. Curr Opin Gastroenterol 2005;21:478–484.
15. Goldblum JR, Whyte RI, Orringer MB, Appelman HD. Achalasia. A morphologic study of 42 resected specimens. Am J Surg Pathol 1994;18:327–337.
16. Wong RK, Maydonovitch CL, Metz SJ, Baker JR Jr. Significant DQw1 association in achalasia. Dig Dis Sci 1989;34:349–352.
17. Howard PJ, Maher L, Pryde A, Cameron EW, Heading RC. Five year prospective study of the incidence, clinical features, and diagnosis of achalasia in Edinburgh. Gut 1992;33:1011–1015.
18. Castagliuolo I, Brun P, Costantini M, Rissetto C, Palu G, Costantino M, Baldan N, Zaninotto G. Esophageal achalasia: is the herpes simplex virus really innocent? J Gastrointest Surg 2004;8:24–30. discussion 30.
19. Castex F, Guillemot F, Talbodec N, Colombel JF, Paris JC, Cortot A. Association of an attack of varicella and an achalasia. Am J Gastroenterol 1995;90:1188–1189.
20. Boeckxstaens GE. Achalasia: virus-induced euthanasia of neurons? Am J Gastroenterol 2008;103:1610–1612.
21. Zayat EN, Schuster MM. Nitric oxide—a major player in esophageal motility. Am J Gastroenterol 2000;95:1584–1585.
22. Tutuian R, Castell D. Review article: oesophageal spasm—diagnosis and management. Aliment Pharmacol Ther 2006;23:1393–1402.
23. Holloway RH, Dodds WJ, Helm JF, Hogan WJ, Dent J, Armdorfer RC. Integrity of cholinergic innervation to the lower esophageal sphincter in achalasia. Gastroenterology 1986;90:924–929.
24. Sivarao DV, Mashimo HL, Thatte HS, Goyal RK. Lower esophageal sphincter is achalasic in nNOS(−/−) and hypotensive in W/W(v) mutant mice. Gastroenterology 2001;121:34–42.
25. Mearin F, Mourelle M, Guarner F, Salas A, Riveros-Moreno V, Moncada S, Malagelada JR. Patients with achalasia lack nitric oxide synthase in the gastro-oesophageal junction. Eur J Clin Invest 1993;23:724–728.
26. Balaji NS, Peters JH. Minimally invasive surgery for esophageal motility disorders. Surg Clin North Am 2002;82:763–782.
27. Kraichely RE, Farrugia G. Achalasia: physiology and etiopathogenesis. Dis Esophagus 2006;19:213–223.
28. Dogan I, Mittal RK. Esophageal motor disorders: recent advances. Curr Opin Gastroenterol 2006;22:417–422.
29. Gockel I, Bohl JR, Junginger T. Achalasia: new insights in pathogenesis. Am J Gastroenterol 2006;101:202–203.
30. Richter JE. Oesophageal motility disorders. Lancet 2001;358:823–828.
31. Stylopoulos N, Bunker CJ, Rattner DW. Development of achalasia secondary to laparoscopic Nissen fundoplication. J Gastrointest Surg 2002;6:368–376. discussion 377–378.
32. DeMeester TR. Surgery for esophageal motor disorders. Ann Thorac Surg 1982;34:225–229.
33. Wong RKH, Maydonovitch CL. Achalasia. In Castell DO, Richter J, eds. The esophagus, 3rd ed. Philadelphia: Lippincott, WIlliams and Wilkins, 1999, pp 185–213.
34. Pandolfino JE, Kahrilas PJ. AGA technical review on the clinical use of esophageal manometry. Gastroenterology 2005;128:209–224.
35. Agrawal A, Hila A, Tutuian R, Castell DO. Manometry and impedance characteristics of achalasia. Facts and myths. J Clin Gastroenterol 2008;42:266–270.
36. Creamer B, Ellis FH Jr., Olsen AM. Cardiospasm (achalasia of the cardia). Am J Surg 1957;93:299–307.
37. Bondi JL, Godwin DH, Garrett JM. "Vigorous" achalasia. Its clinical interpretation and significance. Am J Gastroenterol 1972;58:145–155.
38. Camacho-Lobato L, Katz PO, Eveland J, Vela M, Castell DO. Vigorous achalasia: original description requires minor change. J Clin Gastroenterol 2001;33:375–377.
39. Spechler SJ, Castell DO. Classification of oesophageal motility abnormalities. Gut 2001;49:145–151.
40. Goldenberg SP, Burrell M, Fette GG, Vos C, Traube M. Classic and vigorous achalasia: a comparison of manometric, radiographic, and clinical findings. Gastroenterology 1991;101:743–748.
41. Kahrilas PJ, Sifrim D. High-resolution manometry and impedance–pH/manometry: valuable tools in clinical and investigational esophagology. Gastroenterology 2008;135:756–769.
42. Pandolfino JE, Kwiatek MA, Nealis T, Bulsiewicz W, Post J, Kahrilas PJ. Achalasia: a new clinically relevant classification by high-resolution manometry. Gastroenterology 2008;135:1526–1533.
43. Bredenoord AJ, Tutuian R, Smout AJ, Castell DO. Technology review: esophageal impedance monitoring. Am J Gastroenterol 2007;102:187–194.
44. Crookes PF, Corkill S, DeMeester TR. Gastroesophageal reflux in achalasia. When is reflux really reflux? Dig Dis Sci 1997;42:1354–1361.
45. Cheadle WG, Vitale GC, Sadek S, Cuschieri A. Evidence for reflux in patients with achalasia. Dis Surg 1988;5:1–4.
46. Lemme EM, Domingues GR, Pereira VL, Firman CG, Pantoja J. Lower esophageal sphincter pressure in idiopathic achalasia and Chagas disease-related achalasia. Dis Esophagus 2001;14:232–234.
47. Boeckxstaens GE, Jonge WD, van den Wijngaard RM, Benninga MA. Achalasia: from new insights in pathophysiology to treatment. J Pediatr Gastroenterol Nutr 2005;41(Suppl 1):S36–S37.
48. Koberle F. Chagas' disease and Chagas' syndromes: the pathology of American trypanosomiasis. Adv Parasitol 1968;6:63–116.
49. Moonka R, Patti MG, Feo CV, Arecerito M, De Pinto M, Horgan S, Pellegrini CA. Clinical presentation and evaluation of malignant pseudoachalasia. J Gastrointest Surg 1999;3:456–461.
50. Del Genio A, Fei L, Di Martino N, Napolitano V, Landolfi V, Maffettone V, Fusco F, Ruggiero R. Acute aperistaltic megaesophagus as a complication of Nissen fundoplication: a case report. Ital J Surg Sci 1984;14:135–138.
51. Gockel I, Eckardt VF, Schmitt T, Junginger T. Pseudoachalasia: a case series and analysis of the literature. Scand J Gastroenterol 2005;40:378–385.
52. Proctor DD, Fraser JL, Mangano MM, Calkins DR, Rosenberg SJ. Small cell carcinoma of the esophagus in a patient with longstanding primary achalasia. Am J Gastroenterol 1992;87:664–667.
53. Ziegler K, Sanft C, Friedrich M, Gregor M, Riecken EO. Endosonographic appearance of the esophagus in achalasia. Endoscopy 1990;22:1–4.
54. de Oliveira JM, Birgisson S, Doinoff C, Einstein D, Herts B, Davros W, Obuchowski N, Koehler RE, Richter J, Baker ME. Timed barium swallow: a simple technique for evaluating

esophageal emptying in patients with achalasia. AJR Am J Roentgenol 1997;169:473–479.
55. Oezcelik A, Hagen JA, Halls JM, Leers JM, Abate E, Ayazi S, Zehetner J, DeMeester SR, Banki F, Lipham JC, DeMeester TR. An improved method of assessing esophageal emptying using the timed barium study following surgical myotomy for achalasia. J Gastrointest Surg 2008;13:14–18.
56. Hoogerwerf WA, Pasricha PJ. Pharmacologic therapy in treating achalasia. Gastrointest Endosc Clin N Am 2001;11:311–324. vii.
57. Wen ZH, Gardener E, Wang YP. Nitrates for achalasia. Cochrane Database Syst Rev 2004:CD002299. doi:002210.001002/14651858.CD14002299.pub14651852.
58. Wong RK, Maydonovitch C, Garcia JE, Johnson LF, Castell DO. The effect of terbutaline sulfate, nitroglycerin, and aminophylline on lower esophageal sphincter pressure and radionuclide esophageal emptying in patients with achalasia. J Clin Gastroenterol 1987;9:386–389.
59. DiMarino AJ Jr., Cohen S. Effect of an oral beta2-adrenergic agonist on lower esophageal sphincter pressure in normals and in patients with achalasia. Dig Dis Sci 1982;27:1063–1066.
60. Marzio L, Grossi L, DeLaurentiis MF, Cennamo L, Lapenna D, Cuccurullo F. Effect of cimetropium bromide on esophageal motility and transit in patients affected by primary achalasia. Dig Dis Sci 1994;39:1389–1394.
61. Penagini R, Bartesaghi B, Negri G, Bianchi PA. Effect of loperamide on lower oesophageal sphincter pressure in idiopathic achalasia. Scand J Gastroenterol 1994;29:1057–1060.
62. Willis T. Pharmaceutice rationalis sive diatribe de medicamentorum operationibus in human corpore. London: Hagae Comitis, 1674.
63. Witzel L. Treatment of achalasia with a pneumatic dilator attached to a gastroscope. Endoscopy 1981;13:176–177.
64. Jankovic J, Brin MF. Therapeutic uses of botulinum toxin. N Engl J Med 1991;324:1186–1194.
65. Roberts KE, Duffy AJ, Bell RL. Controversies in the treatment of gastroesophageal reflux and achalasia. World J Gastroenterol 2006;12:3155–3161.
66. Campos GM, Vittinghoff E, Rabl C, Takata M, Gadenstatter M, Lin F, Ciovica R. Endoscopic and surgical treatments for achalasia—a systematic review and meta-analysis. Ann Surg 2009;249:45–57.
67. Annese V, Bassotti G, Coccia G, Dinelli M, D'Onofrio V, Gatto G, Leandro G, Repici A, Testoni PA, Andriulli A. A multicentre randomised study of intrasphincteric botulinum toxin in patients with oesophageal achalasia. GISMAD Achalasia Study Group. Gut 2000;46:597–600.
68. Pasricha PJ, Rai R, Ravich WJ, Hendrix TR, Kalloo AN. Botulinum toxin for achalasia: long-term outcome and predictors of response. Gastroenterology 1996;110:1410–1415.
69. Fishman VM, Parkman HP, Schiano TD, Hills C, Dabezies MA, Cohen S, Fisher RS, Miller LS. Symptomatic improvement in achalasia after botulinum toxin injection of the lower esophageal sphincter. Am J Gastroenterol 1996;91:1724–1730.
70. Annese V, Basciani M, Perri F, Lombadi G, Frusciante V, Simone P, Andrulli A, Vantrappen G. Controlled trial of botulinum toxin injection versus placebo and pneumatic dilation in achalasia. Gastroenterology 1996;111:1418–1424.
71. Morino M, Rebecchi F, Festa V, Garrone C. Preoperative pneumatic dilatation represents a risk factor for laparoscopic Heller myotomy. Surg Endosc 1997;11:359–361.
72. Portale G, Costantini M, Rizzetto C, Guirroli E, Ceolin M, Salvador R, Ancona E, Zaninotto G. Long-term outcome of laparoscopic Heller–Dor surgery for esophageal achalasia: possible detrimental role of previous endoscopic treatment. J Gastrointest Surg 2005;9:1332–1339.
73. Abir F, Modlin I, Kidd M, Bell R. Surgical treatment of achalasia: current status and controversies. Dig Surg 2004;21:165–176.
74. Vaezi MF, Richter JE. Current therapies for achalasia: comparison and efficacy. J Clin Gastroenterol 1998;27:21–35.
75. Rai RR, Shende A, Joshi A, Mathur A, Nijhawan S. Rigiflex pneumatic dilation of achalasia without fluoroscopy: a novel office procedure. Gastrointest Endosc 2005;62:427–431.
76. Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. Gastroenterology 1992;103:1732–1738.
77. Leyden JE, Moss AC, MacMathuna P. Endoscopic pneumatic dilation versus botulinum toxin injection in the management of primary achalasia. Cochrane Database Syst Rev 2006:CD005046.
78. Wehrmann T, Jacobi V, Jung M, Lembcke B, Caspary WF. Pneumatic dilation in achalasia with a low-compliance balloon: results of a 5-year prospective evaluation. Gastrointest Endosc 1995;42:31–36.
79. Aguilar-Paiz LA, Valdovinos-Diaz MA, Flores-Soto C et al. Prospective evaluation of gastroesophageal reflux in patients with achalasia treated with pneumatic dilatation, thoracic or abdominal myotomy. Rev Invest Clin 1999;51:345–350.
80. Karamanolis G, Sgouros S, Karatzias G, Papdopoulou E, Vasiliadis K, Stefanidis G, Mantides A. Long-term outcome of pneumatic dilation in the treatment of achalasia. Am J Gastroenterol 2005;100:270–274.
81. Mainie I, Tutuian R, Castell DO. The limitations of pH monitoring for detecting gastroesophageal reflux. Clin Gastroenterol Hepatol 2006;4:1184. author reply 1185.
82. Smith CD, Stival A, Howell DL, Swafford V. Endoscopic therapy for achalasia before Heller myotomy results in worse outcomes than heller myotomy alone. Ann Surg 2006;243:579–584. discussion 584–576.
83. Zanardi F, Tempini GB. Stenosis of the cardia and esophageal achalasia; a case treated with total cardioplasty. Minerva Chir 1952;7:293–297.
84. Heller E. Extramukose Cardioplastik beim chronischen Cardiospasmus mit Dilatation des Osophagus. Mitteil Grengeb Med Chir 1914;2:141–149.
85. Zaaijer JH. Cardiospasm in the aged. Ann Surg 1923;77:615–617.
86. Tomlinson P, Grant AF. A review of 74 patients with oesophageal achalasia: the results of Heller's cardiomyotomy, with and without Nissen fundoplication. Aust N Z J Surg 1981;51:48–51.
87. Pellegrini C, Wetter LA, Patti M, Leichter R, Mussan G, Mori T, Bernstein G, Way LW. Thoracoscopic esophagomyotomy. Initial experience with a new approach for the treatment of achalasia. Ann Surg 1992;216:291–296. discussion 296–299.
88. Rosati R, Fumagalli U, Bonavina L, Segalin A, Montorsi M, Bona S, Peracchia A. Laparoscopic approach to esophageal achalasia. Am J Surg 1995;169:424–427.
89. Shimi S, Nathanson LK, Cuschieri A. Laparoscopic cardiomyotomy for achalasia. J R Coll Surg Edinb 1991;36:152–154.
90. Codispoti M, Soon SY, Pugh G, Walker WS. Clinical results of thoracoscopic Heller's myotomy in the treatment of achalasia. Eur J Cardiothorac Surg 2003;24:620–624.
91. Lee JM, Wang CH, Huang PM, Hsu HH, Chen JS, Lee CJ, Lee YC. Enduring effects of thoracoscopic Heller myotomy for treating achalasia. World J Surg 2004;28:55–58.
92. Torquati A, Richards WO, Holzman MD, Kennneth W. Laparoscopic myotomy for achalasia. Predictors of successful outcome after 200 cases. Ann Surg 2006;243:587–593.
93. Arain MA, Peters JH, Tmhankar AP, Portale G, Almogy G, DeMeester SR, Crookes PF, Hagen JA, Bremner CG, DeMeester TR. Preoperative lower esophageal sphincter pressure affects

outcome of laparoscopic esophageal myotomy for achalasia. J Gastrointest Surg 2004;8:328–334.
94. Zaninotto G, Costantini M, Rizzett C, Zanatta Z, Guirroli E, Portale G, Nicoletti L, Battaglia G, Ruol A, Ancona E. Four hundred laparoscopic myotomies for esophageal achalasia, a single center experience. Ann Surg 2008;248:986–993.
95. Lyass S, Thoman D, Steiner JP, Phillips E. Current status of an antireflux procedure in laparoscopic Heller myotomy. Surg Endosc 2003;17:554–558.
96. Avtan L, Avci C, Guvenc H, Igci A, Ozmen V. Laparoscopic myotomy for oesophageal achalasia—adding an antireflux procedure is not always necessary. Int J Clin Pract 2005;59:35–38.
97. Ramacciato G, D'Angelo FA, Aurello P, Del Gaudio M, Varotti G, Mercantini P, Bellagamba R, Ercolani G. Laparoscopic Heller myotomy with or without partial fundoplication: a matter of debate. World J Gastroenterol 2005;11:1558–1561.
98. Rebecchi F, Giaccone C, Farinella E, Campaci R, Morino M. Randomized controlled trial of laparoscopic Heller myotomy plus Dor fundoplication versus Nissen fundoplication for achalasia long-term results. Ann Surg 2008;248:1023–1030.
99. Society for Surgery of the Alimentary Tract. Esophageal achalasia. SSAT patient care guidelines. J Gastrointest Surg 2004;8:367–368.
100. Campos GM, Ciovica R, Takata M. Laparoscopic myotomy. Oper Tech Gen Surg 2006;8:161–169.
101. Urbach DR, Hansen PD, Khajanchee YS, Swanstrom LL. A decision analysis of the optimal initial approach to achalasia: laparoscopic Heller myotomy with partial fundoplication, thoracoscopic Heller myotomy, pneumatic dilatation, or botulinum toxin injection. J Gastrointest Surg 2001;5:192–205.
102. Topart P, Deschamps C, Taillefer R, Duranceau A. Long-term effect of total fundoplication on the myotomized esophagus. Ann Thorac Surg 1992;54:1046–1051. discussion 1051–1042.
103. Falkenback D, Johansson J, Oberg S, Kjellin A, Wenner J, Zilling T, Johnsson F, Von Holstein CS, Walther B. Heller's esophagomyotomy with or without a 360 degrees floppy Nissen fundoplication for achalasia. Long-term results from a prospective randomized study. Dis Esophagus 2003;16:284–290.
104. Richards WO, Torquati A, Holzman MD, Khaitan L, Byrne D, Lutfi R, Sharp KW. Heller myotomy versus Heller myotomy with Dor fundoplication for achalasia: a prospective randomized double-blind clinical trial. Ann Surg 2004;240:405–412. discussion 412–405.
105. Wills VL, Hunt DR. Functional outcome after Heller myotomy and fundoplication for achalasia. J Gastrointest Surg 2001;5:408–413.
106. Jamieson WR, Miyagishima RT, Carr DM, Stordy SN, Sharp FR. Surgical management of primary motor disorders of the esophagus. Am J Surg 1984;148:36–42.
107. Stipa S, Fegiz G, Iascone C, Paolini A, Moraldi A, De Marchi C, Chieco PA. Heller–Belsey and Heller–Nissen operations for achalasia of the esophagus. Surg Gynecol Obstet 1990;170:212–216.
108. Limpert PA, Naunheim KS. Partial versus complete fundoplication: is there a correct answer? Surg Clin North Am 2005;85:399–410.
109. Perrone JM, Frisella MM, Desai KM, Soper NJ. Results of laparoscopic Heller–Toupet operation for achalasia. Surg Endosc 2004;18:1565–1571.
110. Dobashi Y, Goseki N, Inutake Y, Kawano T, Endou M, Nemoto T. Giant epiphrenic diverticulum with achalasia occurring 20 years after Heller's operation. J Gastroenterol 1996;31:844–847.
111. Raiser F, Perdikis G, Hinder RA, Swanstrom LL, Filipi CJJ, McBride PJ, Katada N, Neary PJ. Heller myotomy via minimal-access surgery. An evaluation of antireflux procedures. Arch Surg 1996;131:593–597. discussion 597–598.
112. Ware J, Snow K, Kosinski M, Gandek B. SF-36 health survey: manual and intrepretation guide. Boston: The Health Institute, New England Medical Center, 1993.
113. Gaissert HA, Lin N, Wain JC, Frankhauser G, Wright CD, MMathisen DJ. Transthoracic Heller myotomy for esophageal achalasia: analysis of long-term results. Ann Thorac Surg 2006;81:2044–2049.
114. Mineo TC, Pompeo E. Long-term outcome of Heller myotomy in achalasic sigmoid esophagus. J Thorac Cardiovasc Surg 2004;128:402–407.
115. Sweet MP, Nipomnick I, Gasper WJ, Bagatelos K, Ostroff JW, Fisichella PM, Way LW, Patti MG. The outcome of laparoscopic Heller myotomy for achalasia is not influenced by the degree of esophageal dilatation. J Gastrointest Surg 2008;12:159–165.
116. Gelfond M, Rozen P, Keren S, Gilat T. Effect of nitrates on LOS pressure in achalasia: a potential therapeutic aid. Gut 1981;22:312–318.
117. Rozen P, Gelfond M, Salzman S, Baron J, Gilat T. Radionuclide confirmation of the therapeutic value of isosorbide dinitrate in relieving the dysphagia in achalasia. J Clin Gastroenterol 1982;4:17–22.
118. Bortolotti M, Labo G. Clinical and manometric effects of nifedipine in patients with esophageal achalasia. Gastroenterology 1981;80:39–44.
119. Traube M, Dubovik S, Lange RC, McCallum RW. The role of nifedipine therapy in achalasia: results of a randomized, double-blind, placebo-controlled study. Am J Gastroenterol 1989;84:1259–1262.
120. Traube M, Hongo M, Magyar L, McCallum RW. Effects of nifedipine in achalasia and in patients with high-amplitude peristaltic esophageal contractions. Jama 1984;252:1733–1736.
121. Coccia G, Bortolotti M, Michetti P, Dodero M. Prospective clinical and manometric study comparing pneumatic dilatation and sublingual nifedipine in the treatment of oesophageal achalasia. Gut 1991;32:604–606.
122. Gelfond M, Rozen P, Gilat T. Isosorbide dinitrate and nifedipine treatment of achalasia: a clinical, manometric and radionuclide evaluation. Gastroenterology 1982;83:963–969.
123. Bortolotti M, Coccia G, Brunelli F, Sarti P, Mazza M, Bagnato F, Barbara L. Isosorbide dinitrate or nifedipine: which is preferable in the medical therapy of achalasia? Ital J Gastroenterol 1994;26:379–382.

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DEMEESTER FESTSCHRIFT

Achalasia—If Surgical Treatment Fails: Analysis of Remedial Surgery

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Abstract
Introduction Heller myotomy leads to good–excellent long-term results in 90% of patients with achalasia and thereby has evolved to the "first-line" therapy. Failure of surgical treatment, however, remains an urgent problem which has been discussed controversially recently.
Materials and Methods A systematic review of the literature was performed to analyze the long-term results of failures after Heller's operation with emphasis on treatment by remedial myotomy.
Discussion Other reinterventions and their causes after failure of surgical treatment in patients with achalasia are discussed.

Keywords Myotomy · Achalasia · LES · Laparoscopic myotomy · Heller myotomy

Introduction

Achalasia is a rare motor disorder of the esophagus characterized by the loss of peristalsis and an inability of the lower esophageal sphincter (LES) to relax—resulting in dysphagia, regurgitation, chest pain, and weight loss—the clinical hallmarks. As the etiology of achalasia still remains elusive, none of the current therapeutic options is able to the reverse the underlying neuropathology or associated impaired LES relaxation; thus, they remain strictly palliative. Targeting to reduce the LES resting pressure, all treatment modalities result in facilitating esophageal emptying by gravity—alleviating the symptoms associated with achalasia and preventing complications of retention. Results of prospective long-term investigations by Eckardt et al. showed that a postinterventional LES resting pressure of less than or equal to 10 mmHg was the most significant predictor of a favorable long-term remission.[1,2] In 90% of patients with achalasia, good to excellent long-term results have been reported after Heller myotomy with antireflux plasty—using an open transabdominal or transthoracic or a laparoscopic or thoracoscopic approach.[3–13] Minimally invasive surgery has influenced the treatment of achalasia more than any other gastrointestinal disorder. Laparoscopic Heller myotomy thereby has led to a significant change in the treatment algorithm of achalasia. Due to the high success rate of myotomy, it has been advocated as the "first line" therapy for achalasia, especially in younger patients <40 years.

Myotomy after failed pneumatic dilation has also proven significantly superior compared to patients with an "ideal" outcome in the course of only one dilatation.[14]

Thus, only one controlled trial has compared pneumatic dilation versus Heller myotomy, reporting 95% nearly complete symptom resolution in the surgical group and only 51% in the dilation group ($p>0.01$) after 5 years.[15] Results of a European prospective-randomized multicenter trial comparing laparoscopic myotomy with pneumatic dilation are about to be published.

The adequate myotomy should include 6–7 cm of the distal esophagus and be extended at least 2 cm on the gastric fundus, combined either with a 180° anterior (Dor) or a 270° posterior (Toupet) partial fundoplication. Data by Oelschlager et al. showed better clinical results when

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performing a Toupet fundoplication and an extended 3-cm myotomy on the gastric side than those obtained with a Dor fundoplication and a shorter 1.5-cm myotomy.[16] However, it is difficult to interpret whether the improvements in outcomes were due to the sequential learning curve, the extension of the myotomy or the change in fundoplication.[16]

The operative procedure ought to be performed with careful attention to technical details to ensure completeness of the myotomy, to prevent later healing of the myotomy, and to avoid a too radical myotomy that might result in the development of gastroesophageal reflux (GER). Early operation before the progression of megaesophagus is recommended.

Through the reported high efficacy of Heller myotomy, it remains a matter of debate how to deal with failed surgery in patients with achalasia, which can be—according to the chronology of symptoms—divided into persistent and recurrent achalasia.

In detail, the following subgroups of failed surgical treatment for achalasia requiring reoperation can be identified:

1. Persistent achalasia or early recurrence (incomplete myotomy, early fused or healed myotomy, early scarring or fibrosis)
2. Failure of the co-combined antireflux procedure (hypercalibrated or floppy wrapping, "slipped fundoplication," disruption of the wrap, paraesophageal hernia)
3. GER
4. Late recurrence of achalasia (late scarring or fibrosis, late fused or healed myotomy, progression to megaesophagus—with or without siphon formation)
5. Progression to esophageal cancer (adenocarcinoma in Barrett's esophagus following myotomy with GER, squamous cell carcinoma)
6. Other (e.g., mucosal hernia, "diverticulization" of the mucosa, misdiagnosis at first operation, e.g., diffuse esophageal spasm, in which condition a routine myotomy is inadequate)

The aim was to analyze the long-term results of failures after Heller's operation with emphasis on treatment by remedial myotomy and to discuss other reinterventions and their causes after failure of surgery in patients with achalasia.

Materials and Methods

A systematic review of the literature was conducted including articles published in the English literature only and reflecting the time period from 1966 to August 31st, 2008. The search concentrated on the following databases and online catalogs: *PubMed*, *Web of Science*, *Cochrane Library*, and *Current Contents Connect*. Key terms searched for were "achalasia—treatment of surgical failure", "remyotomy/re-do myotomy and achalasia," "achalasia and relapse," and "remedial/revisional surgery for achalasia". Only series reporting on follow-up and focusing on long-term results after remedial myotomy following Heller's operation were included in this analysis. Electronic searches identified 16 studies eligible for the above mentioned criteria.[17–32]

Results

Table 1 summarizes original articles reporting on persistent achalasia or early recurrence following open or minimally invasive Heller myotomy. With respect to articles of authors with multiple chronological series,[18–21,23,24] only those ones with the largest number of patients (latest report) and/or the most detailed follow-up have been taken into account for this table.[18,23]

The largest series, reporting on 43 patients with repeated myotomy for a failed esophagomyotomy by Gayet and Fékété, followed up on their patients over a mean interval of 14 years after the last operation.[23] Of the 43 patients described, $n=32$ had inadequate primary myotomy, $n=3$ interstitial sclerosis, $n=3$ dolichomegaesophagus, $n=2$ diffuse esophageal spasm (DES), and $n=3$ secondary extended achalasia. Long-term results were "good" in 79%, "fair" in 9%, and a "poor" outcome in 12%. Reoperation in most cases was performed as a longer myotomy at the same site as the previous one or on the opposite side by a repeat laparotomy if a technical error was suspected. Only in patients in whom access to the esophagus was impeded by periesophageal sclerosis, a thoracotomy was opted for. Indications for a left transthoracic approach in this series were the confirmation by preoperative diagnostics that the initial myotomy had been performed correctly or if the myotomy needed to be extended in cases of DES. The transition from DES to achalasia with recurrent dysphagia has been described and requires reoperation with extension of the myotomy to include the LES.[33]

The second largest series presenting results of reoperative procedures for achalasia by Ellis at al. showed an "overall improvement" rate of 79%, including all other indications for reoperation ($n=66$) in addition to remyotomy (such as antrectomy and Roux-Y diversion ($n=17$), revision of fundoplication ($n=10$), fundoplication ($n=5$), esophagectomy ($n=5$), and miscellaneous ($n=4$)).[18] In an earlier publication with a follow-up period of 1 month to 13 years (average, 5 years) after revisional myotomy, 12/18 patients (66.7%) revealed improved symptoms and the rate of poor results was rather high with 33.3%.[19] Due to the relatively poor outcome following remyotomy or extension of a

Table 1 Original Articles Reporting on Persistent Achalasia or Early Recurrence Following Open or Minimally Invasive Heller Myotomy

Author (year)	Journal	Pat. (*n*)	Procedures (*n*)	Interval between 1 and 2 myotomy	Follow-up after 2 myotomy	Major complications (%)	Long-term results
Nelems (1980)	Can J Surg	6 *n*=6: incomplete myotomy	6 *n*=6: myotomy completed and Belsey repair	n.r.	n.r.	n.r.	3/6: exclllent (+) 3/6: good (+)
Mercer/Hill (1986)	Can J Surg	8 *n*=8: unsuccesful myotomy	Remidial operations individualized (=repeat Heller myotomy with/without antireflux operation [Hill-repair])	24 (3–48) months[a]	16 months[a]	0	9/12: improved (=good results)[a] 1/12: fair (=continuous dysphagia and dilatation)[a] 2/12: poor result[a] *n*=2 required a subsequent operation for relief of dysphagia
Gayet/ Fékété (1991)	Hepatogastroenterol	43 *n*=32: inadequate primary myotomy *n*=3: interstitial sclerosis *n*=3: DME *n*=2: diffuse spasm *n*=3: secondary extended achalasia	43 *n*=34: transabdominal remyotomy with antireflux procedure *n*=42: remyotomy at the same site as the initial myotomy	1–29 years	14 years (mean)	0	34/43 (79%): good (+) 4/43 (9%): fair (+) 5/43 (12%): poor (+)
Kiss/Vörös (1996)	Surg Today	12 *n*=6: failure of myotomy (HM not long and deep enough or "healed") *n*=6: failure of myotomy and megaesophagus	12 *n*=6: remyotomy with antireflux procedure *n*=3: remyotomy *n*=2: remyotomy and esophagoplication *n*=1: distal resection of the esophagus and esophagojejunostomy	n.r.	n.r.	0	23/29: excellent or good (+)[b] 3/29: fair (+)[b]
Ellis FH Jr. (1997)	Chest Surg Clin N Am	23	23	n.r.	n.r.	n.r.	Overall improvement rate of 79%[c]

		n=16: incomplete	remyotomy either by extension of an inadequate myotomy or a redo procedure neccessitated by healing of the initial myotomy				
		n=7: healed					
Bove (2001)	Hepatogastroenterol	18	18	1–14 years[d]	at least 3 years[d]	*n*=1: pneumonia	10/20: excellent (+)[d]
		n=12: inadequte myotomy	left transthoracic access, wide myotomy from inferior edge of the pulmonary vein 1 cm into the stomach, always with Belsey Mark IV antireflux-plasty			*n*=1: pleural spillage	5/20: good (+)[d]
		n=6: cause of failure could not be demonstrated					3/20: sufficient (+)[d]
							2/20: unsatisfactory/ no improvement (+)[d]
Gorecki (2002)*	Surg Endosc	5	5	18 (3–26) months (median)	14 (6–56) months (median)	0	1/5: excellent (+)
		n=4: incomplete myotomy lower pole	*n*=3: laparoscopic Heller-extension				4/5: good (+)
		n=1: incomplete myotomy and obstruction by Dor fundoplication	*n*=2: laparoscopic Heller-extension and Toupet				
Robinson (2003)*	J Laparoendosc Adv Surg Tech A	3	3	n.r.	18 months (average)	n.r.	5/5: excellent or good (+)
		n=3: incomplete myotomy	*n*=3: laparoscopic remyotomy and Dor fundoplication				
Duffy (2003)*	Surg Endosc	5	5	18 (6–59) months (median)	4 (2–26) months (median)	0	2/5: excellent (+); dysphagia grade 0
		n=5: incomplete myotomy at gastric site	*n*=3: laparoscopic remyotomy and Toupet				3/5: good (+); dysphagia grades I and II
			n=1: laparoscopic remyotomy and Dor				
			n=1: laparoscopic remyotomy				

Table 1 (continued)

Author (year)	Journal	Pat. (*n*)	Procedures (*n*)	Interval between 1 and 2 myotomy	Follow-up after 2 myotomy	Major complications (%)	Long-term results
Iqbal (2006) *	Dis Esophagus	15[e]	15[e]	23 (3–52) months (mean)	30 (6–100) months (mean)	*n*=3: mucosal perforation	Symptom resolution: 40–89%[e,f]
		(*n*=11: achalasia,	*n*=11: remyotomy and Dor (achalasia)	(*n*=14)[e,f]	(*n*=14)[e,f]	*n*=1:	pneumothorax
	excellent post-OP result: 50% (*n*=4 pat. with fibrosis), 75%						
		n=1: DES, *n*=3: HTLES)					(*n*=5 pat. with incomplete myotomy), 33% (*n*=3 pat. with
		n=4: fibrosis	*n*=4: extended remyotomy and Dor (DES, HTLES)				incomplete myotomy and fibrosis, 0–50% (*n*=3 pat. with other causes)
		n=5: incomplete myotomy					satisfaction score: 1.0–3.2 [0–4][e,f]
		n=3: incomplete myotomy and fibrosis					
	n=3: other						
Gockel (2007)	Arch Surg	12	13	15 (4–156) months (median)	38 (2–206) months (median)	0	median Eckardt score: 1 (0–5) [0–12]
		n=11: incomplete myotomy	*n*=11: extended remyotomy and Dor				BMI (kg/m2): 27.3 (22.2–35.3)
		n=1: incomplete myotomy and fibrosis					max. esophageal diameter (mm): 25.0 (20–60)
			n=2: dorsal myotomy and posterior partial fundoplication				min. diameter of gastric cardia (mm): 10.0 (5–12)
							LES resting pressure (mmHg): 8.3 (4.0–10.4)

Schuchert (2008)*	Ann Thorac Surg	11	11 *n*=11: remyotomy with partial fundoplication		12 (0.5–83) months[g]	n.r.	n.r.	7/11: palliated successfully 4/11: required subsequent esophagectomy

n.r. not reported; *pat.* patient; *DME* dolichomegaesophagus; *HM* Heller myotomy; *DES* diffuse esophageal spasm; *HTLES* hypertensive lower esophageal sphincter; *series reporting on laparoscopic remyotomy; *[]* normal values in brackets

(+) scoring system used: excellent: completely asymptomatic, good: absence of symptoms except under certain circumstances (such as hurried eating or stressful conditions), fair: persistence of preoperative symptoms, although less severe than preoperatively, poor: persistence or worsening of symptoms or the development of new disabling symptoms

[a] Long-term results refer to a total of 12 patients, four of whom had other reasons for remedial Heller myotomy than unsuccessful myotomy (*n*=2: complication of myotomy [*n*=1: large hiatal hernia post-OP with secondary esophageal spasm, *n*=1: myotomy too far distally with development of GERD, ulcerative esophagitis and peptic stricture] and *n*=2: an incorrect primary therapy).

[b] Long-term results refer to a total of 29 patients (33 procedures), of whom 17 patients had other causes (*n*=1: Barrett's dysplasia, *n*=5: esophageal stricture, *n*=6: esophageal stricture and megaesophagus, *n*=2: planocellular esophageal cancer, *n*=1: adenocarcinoma, n=2: megaesophagus as a condition following Heller-Belsey's operation) than failure of myotomy with (*n*=6) and without (*n*=6) megaesophagus.

[c] Long-term results refer to a total of 66 patients, of whom *n*=41 had other procedures than remyotomy (*n*=17: antrectomy and Roux-en-Y diversion, *n*=10: revision of fundoplication, *n*=5: fundoplication, *n*=5: esophagectomy, *n*=4: miscellaneous).

[d] Long-term results refer to a total of 20 patients (*n*=18: transthoracic remyotomy and Belsey Mark IV antireflux plasty, *n*=2: Belsey Mark IV antireflux plasty in patients with GER)

[e] Operative redo-procedures and follow-up refer to 11 patients with achalasia, 1 patient with diffuse esophageal spasm and three patients with hypertensive lower esophageal sphincter

[f] One patient was lost of follow-up, *n*=14 patients with complete follow-up

[g] Mean time to failure after first operation of all patients (*n*=23) in addition to remyotomy (*n*=11) (=patients with no improvement in dysphagia, esophagectomy)

previously performed myotomy, they performed a discriminant analysis, including age, sex of patients, the interval between the original and the reoperation, as well as the cause of symptoms necessitating reoperation, which failed to disclose any predictors of good results.[19]

Publications on failure of laparoscopic myotomy and the need for reoperation include fewer patient numbers and shorter follow-up, if reported at all.[26–28,30,32,34–36] One of the two largest series on laparoscopic reoperation reported on by Iqbal et al. comprised 11 patients with achalasia[3] (others included had hypertensive lower esophageal sphincter and one had DES) and showed an overall symptom resolution of 40–89%.[30] In this study, the interval between the first and the second operation was rather short with a mean of 23 (3–52) months and a mean follow-up of 30 months. Reasons for revisional myotomy were fibrosis (n=4), incomplete myotomy (n=5), and incomplete myotomy plus fibrosis (n=3). In a recent study by Schuchert et al., seven out of 11 patients with redo-myotomy following minimally invasive myotomy were palliated successfully, whereas four out of 11 required subsequent esophagectomy.[32] Laparoscopic redo procedures as published by Duffy,[28] Gorecki,[27] and Robinson[26] exhibit similar good results in a rather short-term follow-up.

Discussion

Failures requiring postoperative treatment in patients with achalasia are reported with an incidence between 0% and 14% in open and minimally invasive series,[19,23,37] although—probably due to the learning curve—the rate in latter series seems to be slightly higher. No data exist on the impact of pneumatic dilation and botulinum toxin injection prior to reoperation following myotomy on long-term outcomes. Although no prospective-randomized studies comparing pneumatic dilation, botulinum toxin injection, and remedial myotomy in patients with failure after Heller's operation are available in the current literature, it is well accepted that—if a surgical–technical failure is assumed, as in most cases reported an incomplete or healed myotomy—the patient should be reoperated again. Comparisons of long-term results of reoperations after failure of Heller myotomy are made difficult due to a great variety of operative re-procedures, follow-up intervals, and the lack of standardized symptom scores as well as the incomplete use of objective measurements such as esophageal manometry, 24-h pH monitoring, and radiologic parameters. Although to be interpreted with caution due to the limited number of patients reported in the series of this review, a mixture of the results with other remedial procedures than remyotomy in some studies, different kinds of added antireflux procedure in revisional surgery and the type of objective assessment, the reported overall success rate is high—following open and minimally invasive remyotomy, and is liable to duplicate the good results of primary myotomy with respect to the symptomatic, radiologic, and manometric outcome.[31]

The best treatment for failed Heller myotomy is the prevention of failures. This can be achieved by routine use of intraoperative endoscopy to ensure that all muscle fibers have been separated properly, by an adequate length of the myotomy extending 2 to 3 cm on the gastric fundus, division of the short gastric vessels to perform a tension-free partial fundoplication—either according to Dor or Toupet—in order to prevent reflux and keep the edges of the myotomy wide open. Additional findings such as epiphrenic diverticulum or hiatal hernia should be repaired simultaneously. Diffuse esophageal spasm associated with achalasia requires extended myotomy best performed via a transthoracic route.

Persistent Achalasia or Early Recurrence

The most frequently reported reason for "early" reoperation in achalasia following Heller myotomy is inadequate myotomy (either upward or downward) or sclerosis and fibrosis of the myotomy fused or healed at an early stage. Incomplete myotomy on the gastric side as seen in Figs. 1 and 2 is often caused by the fear of producing mucosal injury, which typically occurs just below the esophagogastric junction, where the muscular layer diminishes. Failure to mobilize the underlying mucosa for one third to half of its circumference may lead to healing or early fusion of the myotomy resulting in persistent or early recurrent dysphagia. The impact of fibrosis—either as a primary finding or as a secondary development after myotomy—as well as postoperative sclerosis have not yet been fully understood and further prospective histopathologic studies of specimens taken at the first and the redo-operation should examine these aspects more closely. In contrast to these early postoperative phenomena, the development of a peptic stricture usually requires a much longer interval of months to years to occur. In the experience of Mercer and Hill, more than half of the reoperative procedures were necessitated by an incomplete or healed myotomy.[17]

The finding of periesophageal sclerosis or fibrosis as a reason for fused or healed myotomy at an early stage might be related to imperfect hemostasis during the initial Heller's operation.[21,23] Diagnosis of interstitial esophageal sclerosis by radiologic or endoscopic examination is difficult, and in some cases, it can also be associated with esophagitis. Thus, the development of early scarring or fibrosis and re-fusion of the muscular edges of the myotomy has not been fully elucidated so far. Ellis and Olsen proposed that post-Heller scar formation complicates the course primarily

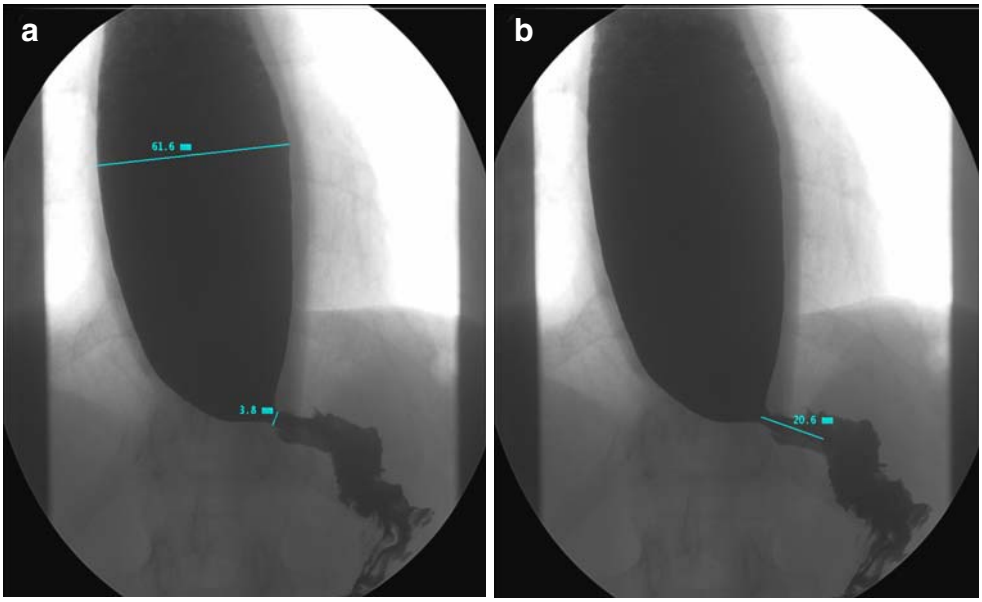

Figure 1 **a**,**b** 49-year-old patient (♂) with two previous laparoscopic cardiomyotomies in an outside institution (2006 + 2007) and recurrent achalasia since 7/2007. Barium esophagogram (2/2008) revealed a relatively short narrow zone with diameter 3.8 mm at the esophagogastric junction. Remyotomy was performed 3/2008, and the previous myotomy was extended distally (+ Dor). The patient is completely free of symptoms ever since and gained 8 kg of weight since remedial (third) myotomy.

through reapproximation of the cut edges of the distal musculature.[38] In cases of revisional surgery, they found it "surprisingly difficult to identify the site of the previous myotomy." In the series reported by Liu et al., periesophageal fibrosis was the second cause for reoperating after modified Heller esophagomyotomy alone or plus modified Belsey Mark IV antireflux procedure.[39] Rosati et al. support limiting dissection in the parahiatal area and preserving the anatomical attachments of the region in order to prevent both postoperative reflux and fibrosis.[12] Others contend that postmyotomy lateral submucosal dissection of the muscular edges reduces the incidence of fusion by further spreading of the cut muscular wall. Intraoperative mucosa perforation and consecutive repair has not been shown to be associated with a pathologic course influencing the final result.[40]

Even the event of scarring or fibrosis in patients with no previous surgery continues to be discussed controversially: smaller but significant amounts of spontaneous deep fibrosis have been reported in primary achalasia cases. Lendrum[41] studied 13 patients with achalasia at autopsy and found no scarring in or around the narrow segment of the esophagus, but both Rake[42] and MacCready[43] stated that one of two autopsy cases revealed considerable fibrosis of the muscularis propria. Freeman[44] emphasized the

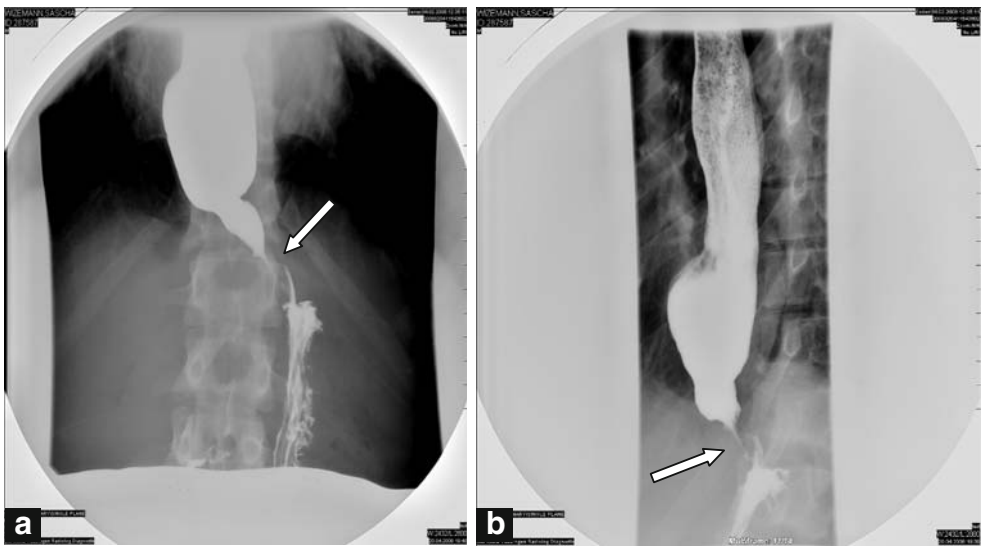

Figure 2 **a,b** 18-year-old patient (♂) with previous laparoscopic Heller myotomy in an outside institution (2006) and recurrent achalasia since 2007 with repeated unsuccessful pneumatic dilations postoperatively. Barium esophagogram (1/2008) showed a short narrow segment just above the cardia. Remyotomy was performed 3/2008, and muscle fibers cut at the previous site of the myotomy, which was extended 2.5 cm on the gastric cardia accomplished by Dor semifundoplication. The patient has a good swallowing function since remedial myotomy as well as weight gain, while dysphagia and regurgitation have been eliminated.

frequency of muscle atrophy in the vicinity of fibrosis between the two layers, although the usual interpretation is that such atrophy is merely a late response to esophageal retention, following a period of compensatory muscular hypertrophy.[45,46] Goldblum et al.[47] showed a secondary degeneration and fibrosis in 29/42 esophageal resectates with achalasia. Our own recent analyses of biopsies taken from the high pressure zone of the distal esophagus in patients undergoing surgery for achalasia revealed an association between the duration of symptoms prior to the operation and the degree of fibrosis.[48] The crucial interpretational problem is whether intramuscular fibrosis can properly be considered part of the "retention esophagitis" that is rather frequently associated with untreated achalasia and often enough persists following Heller myotomy. Unfortunately, one can rarely find information on this matter in reports of surgical treatment of the disease. The amount of intramural fibrosis and periesophageal fibrosis added by the manipulation of Heller's operation is less well known. In the paper by Steichen et al.,[49] such fibrosis was considered a likely sequel to the operation unless precluded by gentle technique: post-Heller recurrences were "due mainly to periesophageal scarring and constriction, secondary to dissection in that region."

Alternatively to remedial Heller myotomy after failure of surgery, Guarner and Gavino proposed the modified Heyrowsky operation associated with fundoplication, especially in patients with repeated unsuccessful myotomies.[50] This procedure, including a latero-lateral anastomosis performed between the gastric fundus and the dilated lower segment of the esophagus, had been discarded almost immediately after its introduction in 1913 because of the severe reflux it had produced.[51] In combination with a 360° fundoplication covering the anastomosis in six patients, five of whom had undergone multiple previous cardiomyotomies, the long-term results of Guarner and Gavino showed no gastroesophageal reflux in any patient, and only one patient developed infrequent dysphagia.[50]

Failure of the Co-Combined Antireflux Procedure

A major controversy relates to the type of fundoplication added to the myotomy associated with unsuccessful outcome after myotomy. Common failures of myotomy associated to the co-combined antireflux procedure are hypercalibrated or floppy wrapping, "slipped fundoplication," disruption of the wrap, and development of paraesophageal hernia.

To perform or not to perform an antireflux procedure along with myotomy at all has been a matter of debate for a long time, and a metaanalysis failed to demonstrate a significant difference between wrapped and nonwrapped patients.[52] Ellis, the pioneer of the transthoracic approach, advocated a limited (<1 cm) gastric myotomy *without* an antireflux procedure[53] and in contrast to the previously reported low reoperation rate of 2.9% in patients with Heller's operation[19] at a very late follow-up, symptomatic improvement markedly deteriorated in the course of time with this approach, and the rate of excellent results progressively decreased from 54% at 10 years to 32% at 20 years.[54]

Nissen fundoplication may ultimatively lead to dysphagia, and a partial fundoplication is usually recommended in association with myotomy. Advocates of the Dor semifundoplication argue that the procedure is easier than a Toupet antireflux plasty, as the posterior esophageal attachments and the short gastric vessels may be kept untouched. Furthermore, it may protect against potential intraoperative unrecognized mucosal leaks. On the other side, authors advocating the Toupet procedure argue with the benefit of providing a better antireflux barrier and of keeping the edges of the myotomy distracted, in order to prevent postoperative recurrent dysphagia that may result from healing or refusion of the myotomy borders. The "ideal" added antireflux plasty to esophagomyotomy and the associated induction of additional scar/fibrosis formation is a matter of ongoing discussion and a prospective-randomized study is desirable for further clarification.

GER

Complications of Heller myotomy may also develop, when it is carried too far distally. Jara et al. have correlated the incidence of gastroesophageal reflux with the length of the myotomy performed on the stomach: if it was longer than 2 cm, reflux was always present postoperatively.[55]

The gastroesophageal junction becomes incompetent, and reflux occurs. Due to disordered or absent motility in the body of the esophagus in achalasia, prolonged contact of acid with the esophageal mucosa causes severe esophagitis.

Overzealous hiatal dissection, resulting in an iatrogenic hiatal hernia may also cause reflux esophagitis. To avoid this situation, the myotomy should be performed without mobilizing the gastroesophageal junction. If the phrenoesophageal bundles are damaged during surgery, the gastroesophageal junction and/or the concomitant semifundoplication is free to migrate into the mediastinum. The latter will cause a paraesophageal hernia or "slipped fundoplication."

Gastroesophageal reflux deteriorates outcomes of Heller myotomy in the course of time and was the most frequent cause of failure with a reported incidence of 20.9% in very long-term follow-up after a mean of 190 months as reported by Csendes et al.[56]

Most patients can be successfully treated conservatively with proton pump inhibitor medication. However, development of peptic stricture in this setting is a major therapeutic challenge and surgical reinterventions are frequently re-

quired. Antrectomy and Roux-en-Y diversion for severe postoperative GER, frequently with resection of stricture, was the next most common operation in 25.8% of 66 reoperative procedures for failure after esophagomyotomy (with remyotomy being the most frequent) in a series reported by Ellis et al.[18] Picchio et al.[57] achieved good long-term results in 85% of 21 operated patients with jejunal interposition for peptic stenosis of the esophagus following esophagomyotomy for achalasia. Reflux esophagitis secondary to myotomy was the most common cause in 21 out of 37 patients with esophagogastric resection after Heller's myotomy as described by Gayet and Fékété.[23]

Late Recurrence of Achalasia and Progression to Megaesophagus

The cause of late scarring or fibrosis, late fused, or healed myotomy—especially with regard to histopathological examinations—has not been fully understood. Refibrosis can be secondary to external fibrotic tissue that involves the myotomy site or internal fibrosis from gastroesophageal reflux. As GERD is often associated with a peptic (internal) stricture and will develop in the late course of myotomy, it can be easily differentiated from external fibrosis, which usually occurs in the medium follow-up after the original operation for achalasia. The transition from early scarring and early fibrosis seems to be fluently and can be, similar to the chronologically early variant, associated to surgical manipulation, bleeding, extensive paraesophageal scar, and adhesion formation. The type of (semi-)fundoplication added to the myotomy has been reported to affect the incidence of fibrosis significantly in the long run.

Patients requiring reoperation after cardiomyotomy in the form of esophagectomy—due to irreversible progression of the disease and development of megaesophagus, are usually older and have a longer duration of the disease and a longer interval between the first and the redo operation as compared to patients with remyotomy for failure of Heller's operation.[31] Although the functional results after primary myotomy in patients with a dilated sigmoid-shaped megaesophagus continue to be discussed controversially in the literature,[58,59] general consensus exists regarding the surgical procedure for advanced megaesophagus with or without siphon formation after prior myotomy. Resections of the esophagus as a result of a dolichomegaesophagus are described in the literature with a frequency of 8% to 9% in relation to the total number of treated achalasia patients,[19,60] whereas this frequency in patients with Chagas disease is markedly higher (14%).[61]

The resection and reconstruction of megaesophagus following myotomy in the long-term course lead to a marked functional improvement with elimination of dysphagia. These decompensated end stages of achalasia are usually irreversible and cannot be improved by conservative or nonresecting surgical procedures. The choice of the operative approach and the type of interposition are strongly determined by the type of previous surgery. Esophagectomy—open[62–66] or minimally invasive[32,67–69]—with gastric pull-up or colon interposition is the preferred procedure and can be performed with low morbidity, leading to symptomatic relief and restoration of alimentation and quality of life.

Progression to Esophageal Cancer

It is questionable if progression to esophageal cancer following Heller myotomy (adenocarcinoma in Barrett's esophagus or squamous cell carcinoma) is a failure of surgery or a failure of follow-up. Since the original report by Fagge in 1872,[70] the risk of developing esophageal squamous cell carcinoma in patients with long-standing achalasia has been estimated to occur from 1% up to 33% of patients.[71–75] Streitz et al. reported a prevalence of esophageal squamous cell carcinoma of 3.7%, a risk that was found to be 14.5 times greater than an age- and sex-adjusted control group.[74] Development of adenocarcinoma after myotomy in the sequelae of Barrett's esophagus might be due to a too long myotomy and only few case reports on this association are available.[76,77]

Comment

Remyotomy is of high efficacy in patients with failure after Heller's operation. However, the best treatment for patients with achalasia should be to prevent symptom recurrence by adequate primary therapy. Intraoperative endoscopy is valuable to control the completeness and proper length of the myotomy. When symptoms—especially dysphagia—do persist or recur after a short interval following Heller myotomy, intensive examinations, namely barium esophagogram, upper gastrointestinal endoscopy, functional testing with esophageal manometry, and—in cases with suspected development of gastroesophageal reflux—24-h pH monitoring are mandatory to determine the cause of failure exactly. Individualized remedial surgery is required to correct the problem. Further prospective-randomized studies should focus on comparing—in patients with similar diameters of the esophagus and presurgical treatment—the length of the myotomy, the type of added antireflux procedure and histopathologic/immunohistochemic findings with regard to scarring in untreated and repeatedly myotomized patients. Laparoscopic revision for failed Heller myotomy is feasible with low morbidity and results are encouraging. Reoperation for achalasia may require esophagectomy to relieve symptoms if other measures fail.

References

1. Eckardt VF, Aignherr C, Bernhard G. Predictors of outcome in patients with achalasia treated by pneumatic dilation. Gastroenterology 1992;103:1732–1738.
2. Eckardt VF, Gockel I, Bernhard G. Pneumatic dilation for achalasia: late results of a prospective follow-up investigation. Gut 2004;53:629–622. doi:10.1136/gut.2003.029298.
3. Gockel I, Junginger T, Eckardt VF. Long-term results of conventional Heller-myotomy in patients with achalasia: a prospective 20-year analysis. J Gastrointest Surg 2006;10:1400–1408. doi:10.1016/j.gassur.2006.07.006.
4. Costantini M, Zaninotto G, Guirroli E, Rizzetto C, Portale G, Ruol A, Nicoletti L, Ancona E. The laparoscopic Heller-Dor operation remains an effective treatment for esophageal achalasia at a minimum 6-year follow-up. Surg Endosc 2005;19:345–351. doi:10.1007/s00464-004-8941-7.
5. Moreno Gonzales E, Garcia Alvares A, Landa Garcia I, Gutierrez M, Rico Selas P, Garcia Garcia I, Jover Navalon JM, Ari Diaz J. Results of surgical treatment of esophageal achalasia. Multicenter retrospective study of 1856 cases. Int Surg 1988;73:69–77.
6. Csendes A, Braghetto I, Mascaro J, Henriquez A. Late subjective and objective evaluation of the results of esophagomyotomy in 100 patients with achalasia of the esophagus. Surgery 1988;104:469–475.
7. Desa LA, Spencer J, McPherson S. Surgery for achalasia cardiae: the Dor operation. Ann R Coll Surg Engl 1990;72:128–131.
8. Bonavina L, Nosadini A, Bardini R, Baessato M, Peracchia A. Primary treatment of esophageal achalasia. Long-term results of myotomy and Dor fundoplication. Arch Surg 1992;127:222–227.
9. Picciocchi A, Cardillo G, D'Ugo D, Castrucci G, Mascellari L, Granone P. Surgical treatment of achalasia: a retrospective comparative study. Surg Today 1993;23:855–859. doi:10.1007/BF00311361.
10. Mattioli S, Di Simone MP, Bassi F, Pilotti V, Felice V, Pastina M, Lazzari A, Gozzetti G. Surgery for esophageal achalasia. Long-term results with three different techniques. Hepatogastroenterology 1996;43:492–500.
11. Graham AJ, Finley RJ, Worsley DF, Dong SR, Clifton JC, Storseth C. Laparoscopic esophageal myotomy and anterior partial fundoplication for the treatment of achalasia. Ann Thorac Surg 1997;64:785–789. doi:10.1016/S0003-4975(97)00628-0.
12. Rosati R, Fumagalli U, Bona S, Bonavina L, Pagani M, Peracchia A. Evaluating results of laparoscopic surgery for esophageal achalasia. Surg Endosc 1998;12:270–273. doi:10.1007/s004649900649.
13. Patti MG, Fisichella PM, Perretta S, Galvani C, Gorodner MV, Robinson T, Way LW. Impact of minimally invasive surgery on the treatment of esophageal achalasia: a decade of change. J Am Coll Surg 2003;196:698–703. doi:10.1016/S1072-7515(02)01837-9.
14. Gockel I, Junginger T, Bernhard G, Eckardt VF. Heller myotomy for failed pneumatic dilation in achalasia: How effective is it. Ann Surg 2004;239:371–377. doi:10.1097/01.sla.0000114228.34809.01.
15. Csendes A, Braghetto I, Henriquez A, Cortes C. Late results of a prospective randomised study comparing forceful dilatation and oesophagomyotomy in patients with achalasia. Gut 1989;30:299–304. doi:10.1136/gut.30.3.299.
16. Oelschlager BK, Chang L, Pellegrini CA. Improved outcomes after extended gastric myotomy for achalasia. Arch Surg 2003;138:490–497. doi:10.1001/archsurg.138.5.490.
17. Mercer CD, Hill LD. Reoperation after failed esophagomyotomy for achalasia. Can J Surg 1986;29:177–180.
18. Ellis FH Jr. Failure after esophagomyotomy for esophageal motor disorders. Causes, prevention, and management. Chest Clin N Am 1997;7:477–488.
19. Ellis FH Jr, Crozier RE, Gibb SP. Reoperative achalasia surgery. J Thorac Cardiovasc Surg 1986;92:859–865.
20. Ellis FH Jr, Gibb SP. Reoperation after esophagomyotomy for achalasia of the esophagus. Am J Surg 1975;129:407–412. doi:10.1016/0002-9610(75)90185-3.
21. Patrick DL, Payne WS, Olsen AM, Ellis FH Jr. Reoperation for achalasia of the esophagus. Arch Surg 1971;103:122–1228.
22. Nelems JM, Cooper JD, Pearson FG. Treatment of achalasia: esophagomyotomy with antireflux procedure. Can J Surg 1980;23:588–589.
23. Gayet B, Fékété F. Surgical management of failed esophagomyotomy (Heller's operation). Hepatogastroenterol 1991;38:488–492.
24. Fékété F, Breil P, Tossen JC. Reoperation after Heller's operation for achalasia and other motility disorders of the esophagus: a study of eighty-one reoperations. Int Surg 1982;67:103–110.
25. Bove A, Corbellini L, Catania A, Chiarini S, Bongarzoni G, Stella S, De Antoni E, De Matteo G. Surgical controversies in the treatment of recurrent achalasia of the esophagus. Hepatogastroenterol 2001;48:715–717.
26. Robinson TN, Galvani CA, Dutta SK, Gorodner MV, Patti MG. Laparoscopic treatment of recurrent dysphagia following transthoracic myotomy for achalasia. J Laparoendosc Adv Surg Tech A 2003;13:401–403. doi:10.1089/109264203322656487.
27. Gorecki PJ, Hinder RA, Libbey JS, Bammer T, Floch N. Redo laparoscopic surgery for achalasia: Is it feasible. Surg Endosc 2002;16:772–776. doi:10.1007/s00464-001-8178-7.
28. Duffy PE, Awad ZT, Filipi CJ. The laparoscopic reoperation of failed Heller myotomy. Surg Endosc 2993;17:1046–1049.
29. Kiss J, Vörös A, Szirányi E, Altorjay A, Bohák A. Management of failed Heller's operations. Surg Today 1996;26:541–545. doi:10.1007/BF00311564.
30. Iqbal A, Tierney B, Haider M, Salinas VK, Karu A, Turaga KK, Mittal SK, Filipi CJ. Laparoscopic reoperation for failed Heller myotomy. Dis Esophagus 2006;19:193–199. doi:10.1111/j.1442-2050.2006.00564.x.
31. Gockel I, Junginger T, Eckardt VF. Persistent and recurrent achalasia after Heller myotomy. Analysis of different patterns and long-term results of reoperation. Arch Surg 2007;142:1093–1097. doi:10.1001/archsurg.142.11.1093.
32. Schuchert MJ, Luketich JD, Landreneau RJ, Kilic A, Gooding WE, Alvelo-Rivera M, Christie NA, Gilbert S, Pennathur A. Minimally-invasive esophagomyotomy in 200 consecutive patients: factors influencing postoperative outcomes. Ann Thorac Surg 2008;85:1729–1734. doi:10.1016/j.athoracsur.2007.11.017.
33. Vantrappen G, Janssens J, Hellemans J, Coremans G. Achalasia, diffuse esophageal spasm, and related motility disorders. Gastroenterology 1979;76:450–457.
34. Patti MG, Molena D, Fisichella PM, Whang K, Yamada H, Perretta S, Way LW. Laparoscopic Heller myotomy and Dor fundoplication for achalasia. Analysis of successes and failures. Arch Surg 2001;136:870–877. doi:10.1001/archsurg.136.8.870.
35. Patti MG, Pellegrini CA, Horgan S, Arcerito M, Omelanczuk P, Tamburini A, Diener U, Eubanks TR, Way LW. Minimally invasive surgery for achalasia. An 8-year experience with 168 patients. Ann Surg 1999;230:587–594. doi:10.1097/00000658-199910000-00014.
36. Zaninotto G, Costantini M, Portale G, Battaglia G, Molena D, Carta A, Costantino M, Nicoletti L, Ancona E. Etiology, diagnosis, and treatment of failures after laparoscopic Heller myotomy for achalasia. Ann Surg 2002;235:186–192. doi:10.1097/00000658-200202000-00005.
37. Perrone JM, Frisella MM, Desai KM, Soper NJ. Results of laparoscopic Heller-Toupet operation for achalasia. Surg Endosc 2004;18:1565–1571.
38. Ellis FH Jr, Olsen AM. Achalasia of the Esophagus. Philadelphia: W.B. Saunders Co., 1969, p 215.

39. Liu HC, Huang BS, Hsu WH, Huang CJ, Hou SH, Huang MH. Surgery for achalasia: long-term results in operated achalasic patients. Ann Thorac Cardiovasc Surg 1998;4:312–320.
40. Costantini M, Rizzetto C, Zanatta L, Finotti E, Amico A, Nicoletti L, Guirroli E, Zaninotto G, Ancona E. Accidental mucosal perforation during laparoscopic Heller-Dor myotomy does not effect the final outcome of the operation (2008) SSAT abstract M1530, Digestive Disease Week, May 18–21, San Diego
41. Lendrum FC. Anatomic features of the cardiac orifice of the stomach with special reference to cardiospasm. Arch Intern Med 1937;59:474–511.
42. Rake GW. On the pathology of achalasia of the cardia. Guys Hosp Rep 1927;77:141–150.
43. MacCready PB. Cardiospasm: report of two cases with post-mortem observations. Arch Otolaryng 1935;633–647.
44. Freeman EB. Chronic cardiospasm: report of fatal case with pathological findings. South Med J 1933;26:71–76.
45. Beattie WJH. Achalasia of the cardia with a report on ten cases. St Bart Hosp Rep 1931;64:39–84.
46. Walton AJ. The surgical treatment of cardiospasm. Br J Surg 1925;12:701–737. doi:10.1002/bjs.1800124807.
47. Goldblum JR, Whyte RI, Orringer MB, Appelman HD. Achalasia. A morphologic study of 42 resected specimens. Am J Surg Pathol 1994;18:327–337.
48. Gockel I, Bohl JR, Doostkam S, Eckardt VF, Junginger T. Spectrum of histopathologic findings in patients with achalasia reflects different etiologies. J Gastroenterol Hepatol 2006;21:727–733. doi:10.1111/j.1440-1746.2006.04250.x.
49. Steichen FM, Heller E, Ravitch MM. Achalasia of the esophagus. Surgery 1960;47:846–876.
50. Guarner V, Gavino J. The Heyrowsky operation associated with fundoplication for the treatment of patients with achalasia of the esophagus after failure of the cardiomyotomy. Surg Gynecol Obstet 1983;157:450–454.
51. Heyrowsky H. Casuistik und Therapie der idiopathischen Dilatation der Speiseröhre, Oesophagogastroanastomose. Arch Chir 1913;100:703–715.
52. Lyass S, Thoman D, Steiner JP, Phillips E. Current status of an antireflux procedure in laparoscopic Heller myotomy. Surg Endosc 2003;17:554–558. doi:10.1007/s00464-002-8604-5.
53. Ellis FH Jr, Crozier RE, Watkins E Jr. Operation for esophageal achalasia. Results of esophagomyotomy without an antireflux operation. J Thorac Cardiovasc Surg 1984;88:344–351.
54. Ellis FH Jr. Oesophagomyotomy for achalasia: a 22-year experience. Br J Surg 1993;80:882–885. doi:10.1002/bjs.1800800727.
55. Jara FM, Toledo-Pereyra LH, Lewis JW, Magilligan DJ. Long term results of esophagomyotomy for achalasia of the esophagus. Arch Surg 1979;114:935–936.
56. Csendes A, Braghetto I, Burdiles P, Korn O, Csendes P, Henríquez A. Very late results of esophagomyotomy for patients with achalasia. Clinical, endoscopic, histologic, manometric and acid reflux studies in 67 patients for a mean follow-up of 190 months. Ann Surg 2006;243:196–203. doi:10.1097/01.sla.0000197469.12632.e0.
57. Picchio M, Lombardi A, Zolovkins A, Della Casa U, Paolini A, Fegiz G, Mihelson M. Jejunal interposition for peptic stenosis of the esophagus following esophagomyotomy for achalasia. Int Surg 1997;82:198–200.
58. Pechlivanides G, Chrysos E, Athanasakis E, Tsiaoussis J, Vassilakis JS, Xynos E. Laparoscopic Heller cardiomyotomy and Dor fundoplication for esophageal achalasia. Arch Surg 2001;136:1240–3. doi:10.1001/archsurg.136.11.1240.
59. Patti MG, Feo CV, Diener U, Tamburini A, Arcerito M, Safadi B, Way LW. Laparoscopic Heller myotomy relieves dysphagia in achalasia when the esophagus is dilated. Surg Endosc 1999;13:843–847. doi:10.1007/s004649901117.
60. Miller DL, Allen MS, Trastek VF, Deschamps C, Pairolero PC. Esophageal resection for recurrent achalasia. Ann Thorac Surg 1995;60:922–925. doi:10.1016/0003-4975(95)00522-M.
61. Pinotti HW, Cecconello I, da Rocha JM, Zilberstein B. Resection for achalasia of the esophagus. Hepatogastroenterology 1991;38:470–473.
62. Orringer MB, Marshall B, Stirling MC. Transhiatal esophagectomy for benign and malignant disease. J Thorac Cardiovasc Surg 1993;105:265–277.
63. Deveney EJ, Lannettoni MD, Orringer MB, Marshall B. Esophagectomy for achalasia: patient selection and clinical experience. Ann Thorac Surg 2001;72:854–858. doi:10.1016/S0003-4975(01)02890-9.
64. Peters JH, Kauer WK, Crookes PF, Ireland AP, Bremner CG, DeMeester TR. Esophageal resection with colon interposition for end-stage achalasia. Arch Surg 1995;130:632–637.
65. Watson TJ, DeMeester TR, Kauer WK, Peters JH, Hagen JA. Esophageal replacement for end-stage benign esophageal disease. J Thorac Cardiovasc Surg 1998;115:1241–1249. doi:10.1016/S0022-5223(98)70205-3.
66. Glatz SM, Richardson JD. Esophagectomy for end stage achalasia. J Gastrointest Surg 2007;11:1134–1137. doi:10.1007/s11605-007-0226-8.
67. Palanivelu C, Rangarajan M, Jategaonkar PA, Maheshkumaar GS, Anand NV. Laparoscopic transhiatal esophagectomy for "sigmoid" megaesophagus following failed cardiomyotomy: Experience of 11 patients. Dig Dis Sci 2008;53:1513–1518. doi:10.1007/s10620-007-0050-8.
68. Luketich JD, Nguyen NT, Weigel T, Ferson P, Keenan R, Schauer P. Minimally invasive approach to esophagectomy. JSLS 1998;2:243–247.
69. Luketich JD, Fernando HC, Christie NA, Buenaventura PO, Keenan RJ, Ikramuddin S, Schauer PR. Outcomes after minimally invasive esophagomyotomy. Ann Thorac Surg 2001;72:1909–1912. doi:10.1016/S0003-4975(01)03127-7.
70. Fagge CH. A case of simple stenosis of the esophagus, followed by epithelioma. Guys Hosp Rep 1872;17:413–415.
71. Aggestrup S, Holm JC, Sorensen HR. Does achalasia predispose to cancer of the esophagus. Chest 1992;102:1013–1016. doi:10.1378/chest.102.4.1013.
72. Meijssen MAC, Tilanus HW, van Blankenstein M, Hop WC, Ong GL. Achalasia complicated by oesophageal squamous cell carcinoma: a prospective study in 195 patients. Gut 1992;33:155–158. doi:10.1136/gut.33.2.155.
73. Peracchia A, Segalin A, Bardini R, Ruol A, Bonavina L, Baessato M. Esophageal carcinoma and achalasia: prevalence, incidence and results of treatment. Hepatogastroenterology 1991;130:514–516.
74. Streitz JM, Ellis FH, Gibb SP, Heatley GM. Achalasia and squamous cell carcinoma of the esophagus: analysis of 241 patients. Ann Thorac Surg 1995;59:1604–1609. doi:10.1016/0003-4975(94)00997-L.
75. Brücher BL, Stein HJ, Bartels H, Feussner H, Siewert JR. Achalasia and esophageal cancer: incidence, prevalence, and prognosis. World J Surg 2001;25:745–749. doi:10.1007/s00268-001-0026-3.
76. Ruffato A, Mattioli S, Lugaresi ML, D'Ovidio F, Antonacci F, Di Simone MP. Long-term results after Heller-Dor operation for oesophageal achalasia. Eur J Cardiothorac Surg 2006;29:914–919. doi:10.1016/j.ejcts.2006.03.044.
77. Gaissert HA, Lin N, Wain JC, Fankhauser G, Wright CD, Mathisen DJ. Transthoracic Heller myotomy for esophageal achalasia: analysis of long-term results. Ann Thorac Surg 2006;81:2044–2049. doi:10.1016/j.athoracsur.2006.01.039.

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DEMEESTER FESTSCHRIFT

Rudolf Nissen (1896–1981)-Perspective

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Abstract
Introduction Rudolf Nissen was one of the outstanding general surgeons of the last century. Between the years 1921 and 1933, he was the pupil and protégé of the famous surgeon Ferdinand Sauerbruch. He was nominated professor of surgery in 1930. Forced by the Nazi-Regime to resign his position, Nissen emigrated in 1933 first to Turkey and then in 1939 to the USA. Here, he held positions in hospitals at New York. Having been appointed to the Chair of Surgery at the University of Basle, Switzerland, he returned to Europe in 1952. Nissen was a critical prolific writer and excellent researcher, surgeon, and teacher.
Conclusion The first successful pneumectomy and lung lobectomy in man, as well as the description of surgical pathophysiology and treatment of gastroesophageal reflux disease, including hiatus hernia, are considered to be his most important pioneer work.

Keywords Nissen–Rossetti fundoplication · Surgery · Gastroesophageal · Reflux disease

Background: Education

Rudolf Nissen was born September 9, 1896 in Neisse, Schlesien, Germany. His father, a gifted general surgeon and friend of the famous professor of surgery Johann von Mikulicz-Radecki, owned a large building in which the hospital and the home of the family was accommodated. As he writes in his memoirs,[1] this background left its marks on his life. With this history, is it not clear that the "surgeon virus" infected him early in life ?

Living in a wealthy, cultivated home, the esthetic education by his parents, and the stern Prussian discipline, he was taught in the Catholic Gymnasium of Neisse, which created a social restraint. The topics at school covered ancient but not living languages, a fact that would make his life in English speaking countries difficult. At the age of 17, Nissen matriculated at the Medical Faculty of the German Universities of Breslau and Munich.[1,2] In 1914, he was called into the active armed service and participated as a military doctor in the first World War. He endured a war injury, a lung lesion from which he never recovered completely.[1–3]

After the war, he re-entered the studies of Medicine and finished with the doctor degree. In 1921, Nissen joined the staff of the University Clinic at Munich where he came to the attention of the famous Professor Ferdinand Sauerbruch, Chair of the Department of Surgery at that time. Sauerbruch was impressed with the shy, well-educated and hard working intelligent young doctor who soon became his favorite pupil and protégé[1–3] in Munich and later in Berlin (1927), where Sauerbruch was appointed to the Chair of Surgery at the most renowned German hospital, the Charité.

Nissen guided the solution of diagnostic problems rather by observation than from laboratory results, and his

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capacity for grasping the significance of concepts was unbelievable. He emphasized careful handling of tissues and careful hemostasis, which supported uneventful recovery. Much of his attention was directed to the pathophysiology and the surgical treatment of lung disease, such as tuberculosis, empyema, bronchiectases, and lung emphysema on which he published outstanding pioneering work. He performed the first lobectomy (1930) and the first pneumectomy (1931)—both of which presented a successful outcome.[4,5] During this stage of career, Nissen had become known as a brilliant surgeon.[2,3]

His work at the Charité came to an end, abrupt and unexpected! The assumption of power by the Nazi regime forced Nissen to resign his position. He abandoned his career in Germany, emigrated to Turkey (1933–1939), and then to the USA (1939–1952). In Turkey, he was offered and took over the Chair of Surgery at the University of Istanbul; in the USA, he hold positions in New York hospitals.[1–3]

During the period of emigration, in the 1930s to 1950s, fell the operations and the observations that were going to be of great importance for Nissen's later pioneering work on gastroesophageal reflux surgery.[6]

Nissen's milestones on the track to GER surgery

Milestone 1: Gastric Wall Plication over a Witzel fistula (1937)

At Istanbul—it was in the year 1937—Nissen met a case that should be one of the first milestones on the track to develop antireflux surgery. He had to operate on a bleeding chronic ulcer in the terminal esophagus and cardia, which penetrated into the diaphragm and pericardium. Nissen transpleurally mobilized and resected the patient's cardia and incorporated the esophageal remnant similar to a valve of a Witzel fistula into the stomach and added a gastropexy. Then, he fashioned two lateral folds and wrapped them over the gastrostoma; the recovery was uneventful. What appeared strange to Nissen was: "lack of the cardia" but "no symptoms of esophagitis even in the long term ?"[6]

At that time, the knowledge about esophagitis was poor. Until the 1950s, heartburn, regurgitation, and dysphagia were regarded as a result of a hiatal hernia. Attempts, however, to reduce the hernia and close the diaphragmatic crura did not solve the problem of esophagitis.

Concept of Incompetent Cardia as a Cause of Esophagitis (1951)

The British thoracic surgeon Philip Allison (1908–1974) is considered to be the first to link the symptoms of esophagitis to an incompetent cardia (1951).[7] Allison proposed gastropexy in order to keep the cardia in the normal position within the abdomen, but this, again, did not avoid reflux; consequently, this treatment was abandoned and Allisons' idea disputed.

Meanwhile, in the USA, Nissen has gained a great experience in visceral and hiatus hernia surgery and also gained a great reputation as a technically excellent and innovative general surgeon. Therefore, in 1952, he was appointed to the Chair of Surgery at the University of Basle, Switzerland and returned to Europe.[1–3]

Milestone 2: Gastric Wall Plication over an Incompetent Cardia to Avoid Reflux

One of his new patients at Basle was a lady with unbearable gastroesophageal reflux symptoms. Nissen decided to correct the defective sphincter. He remembered his case of 1937 and recognized the value of the previous experiences in Istanbul and New York, and he agreed with Allison's suggestion[7] of esophagitis being caused by reflux through an incompetent cardia.

Because of his own and the observations of others that not all patients with hernia suffered from esophagitis,[8–10] Nissen had obtained an igniting spark and had his own vision on surgical techniques and principles. For him, the competent cardia, that is, the intact gastroesophageal transition, acted as a flap valve that allowed unhindered transport of food from the esophagus into the stomach but prevented reflux of gastric content. He concluded that any treatment must be directed definitely toward the incompetent cardia. Therefore, he decided to operate on the lady with a technique of what is called the "original Nissen antireflux operation".[11–13]

The Classical Nissen Technique (1956)

Following the experience of 1937, Nissen divided the short gastric vessels, wrapped a portion of the stomach wall on the cardia, recreated a new valve that he inserted into the esophagus by a stitch, and added a gastropexy,[10,11] which

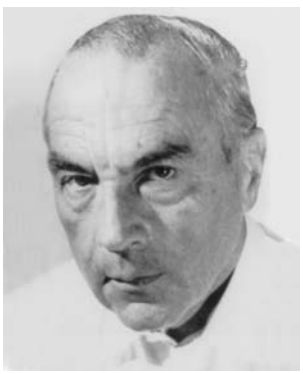

Figure 1 Rudolf Nissen pictured at time of the creation of the antireflux surgery.

prevented the sliding element (but not the lower esophageal sphincter incompetence). Because of several failures, Nissen discarded the classical technique in favor of the Nissen–Rossetti modification.[13]

In his hospital, Nissen had met a young superactive radiologist whose main interest concerned esophageal diseases, and whose knowledge on esophageal function and physiology was extraordinary. Nissen was quick to realize that this was the person to work with and convinced him to join the studies and to become a surgeon. The name of the young doctor was Mario Rossetti (1927–2008), who rapidly became very fond of Nissen and the right person for the project. Nissen became Rossetti's mentor. Finally, both men became not only coworkers but lifelong friends.

Milestone 3: Complete Plication of the Gastric Fundus Around the Cardia

The Nissen–Rossetti Antireflux Operation, Concept, and Principles

In association with Rossetti, Nissen now used the anterior wall of the gastric fundus alone to build up a complete 360° fundic wrap around the terminal esophagus and the cardia. The details of the original Nissen–Rossetti fundoplication are described by Nissen et al.[12] and Rossetti himself in Mastery of Surgery.[13] Nissen abandoned gastropexy and seldom repaired the hiatus. He considered the bulk of plication too large to enter the chest.

Perspective

The next decades following Nissen's and Rossetti's contributions on the fundoplication as treatment against gastroesophageal reflux can be labeled "the age of surgical experimentation and technical development" (Fig. 1).

Careful anatomic studies gave evidence of the presence of a muscular equivalent at the location of the cardia,[14] and specific reactivity of the musculature at the cardia and terminal esophagus[12] confirmed the concept and function of the modified technique. This follows not only the principle of a one-way valve but becomes a true substitute for the lower esophageal sphincter.[11–13]

Nissen demanded, and it came true, that reproducible, methodical investigations were performed, which would allow precise analysis of the normal sphincter and of fundoplication. These were manometrical pressure monitoring,[15–17] standard reflux tests (pH measurement),[18,19] and endoscopic evaluation of esophagitis.

Subsequently, a great number of surgeons developed different techniques to cure gastroesophageal reflux disease. Some did not stand the test of time and were gradually abandoned. More durable methods including the laparoscopic repair achieved good results.[2,13,18,20]

However, despite warnings, the fundoplication was occasionally made too narrow or too long. As a consequence, postoperative symptoms developed, such as dysphagia, persistent gas bloat, and inability to vomit and belch. Occasionally, chronic reflux esophagitis leading to Barrett's disease was caused by an incomplete wrap. All this contributed to unnecessary high complication rates.[12,13,21–23]

Summary

Rudolf Nissen and Mario Rossetti proved their concept and principle about gastroesophageal antireflux surgery. They showed that fundoplication was a safe operation, that it does not affect esophageal motility or transit provided that the wrap is correctly done, that the fundic wrap develops its own dynamic motion, i.e., an independent contraction effect. The operation results in reflux symptoms and esophagitis disappearing in 80–97% of the patients.

The Nissen–Rossetti fundoplication results in a reasonably long-term success rate in chronic reflux disease with a fundic wrap as the main determinant of outcome.

References

1. Helle Blätter Nissen R. Helle dunkle Blätter. Erinnerung eines Chirurgen. Stuttgart: Deutsche Verlagsanstalt, 1969.
2. Liebermann-Meffert D, Nissen R. Reminiscences 100 years after his birth. Dis Esophagus 1996;9:237.
3. Liebermann-Meffert D, Stein HJ. Rudolf Nissen and the World Revolution of Fundoplication. Heidelberg: Barth Verlag, 1999.
4. Nissen R. Die chirurgische Behandlung des bedrohlichen Mediastinalemphysems. Zbl Chir. 1930;57:1023.
5. Nissen R. Extirpation eines ganzen Lungenflügels. Zbl Chir. 1931;58:3003.
6. Nissen R. Erlebtes aus der Thoraxchirurgie. Stuttgart: Thieme, 1955
7. Allison PR. Refluxesophagitis, sliding hernia and the anatomy of repair. Surg Gynecol Obstet 1951;92:419.
8. Nissen R. Die chirurgisch-klinische Bedeutung der Refluxoesophagitis. Thoraxchirurgie. 1953;1:199.
9. Hiebert CA, Belsey R. Incompetency of the gastric cardia without radiologic evidence of hiatal hernia. J Thorac Cardiovasc Surg 1961;42:352.
10. Nissen R, Rossetti M. Zur Indikation der Fundoplikatio und Gastropexie bei der Hiatushernie. Schweiz Med Wochenschr. 1954;84:439.
11. Nissen R. Eine einfache Operation zur Beeinflussung der Refluxoesophagitis. Schweiz Med Wschr. 1956;86:59.
12. Nissen R, Rossetti M, Siewert R (eds). Fundoplicatio und Gastropexie bei Refluxkrankheit und Hiatushernie. Indikation. Technik. Ergebnisse. 2.Aufl. Stuttgart New York: Thieme, 1981.
13. Rossetti ME, Liebermann-Meffert D. Nissen–Rossetti Fundoplication (open procedure). In Baker RJ, Fischer JE, eds. Mastery of surgery, Chapt. 60. Philadelphia: Lippincott, Williams and Wilkins, 2001, pp 764–777.

14. Liebermann-Meffert D, Allgöwer M, Schmid P, Blum A. Muscular equivalent of the lower esophageal sphincter. Gastroenterology 1979;76:31.
15. Fyke FE, Code CF, Schlegel JF. The gastroesophageal sphincter in healthy human beings. Gastroenterol Basel 1956;86:135.
16. Winans CS, Harris LD. Quantitation of lower sphincter competence. Gastroenterology 1967;52:113.
17. Pope CE. A dynamic test of sphincter strength. Its application to the lower esophageal sphincter. Gastroenterology 1967; 52:179.
18. DeMeester TR, Johnson LE, Kent AH. Evaluation of current operation for the prevention of gastroesophageal reflux. Ann Surg 1974;180:511.
19. Johnson LE, DeMeester TR. Twenty-four-hour pH monitoring of the distal esophagus. Am J Gastroenterol 1974;62:325.
20. Luostarinen M, Isolauri J, Laitinen J et al. Fate of Nissen fundoplication after 20 years. A clinical, endoscopical, and functional analysis. Gut 1993;34:1015. doi:10.1136/gut.34.8.1015.
21. Donahue PE, Bombeck CT. The modified Nissen fundoplication—reflux prevention without gas bloat. Chir Gastroenterol 1977;11:15.
22. Siewert R, Blum AL (eds). Postoperative syndromes after surgery of the upper and lower esophageal sphincter. In: Clinics in gastroenterology. Philadelphia: Saunders, 1979
23. Negre JB. Post-fundoplication symptoms. Do they restrict the success of Nissen fundoplication? Ann Surg 1983;198:689. doi:10.1097/00000658-198312000-00005.

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DEMEESTER FESTSCHRIFT

Proton Pump Inhibitors in the Management of GERD

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Abstract
Introduction Management of gastroesophageal reflux disease (GERD) is based on the concept that gastric contents, principally acid and pepsin, are responsible for symptoms of reflux and esophageal injury. Pharmacologic treatment is based on the principle that controlling intragastric pH will affect esophageal healing and subsequently symptom relief.
Results and Discussion Control of pH can be accomplished with antisecretory agents, principally proton pump inhibitors (PPIs). The majority of patients respond to a single daily dose of a PPI; however, some will require higher doses, and a small percentage are "refractory" to twice daily dosing of these drugs. The success of these agents, and in fact the reasons for "failure," is elucidated by understanding the mechanism of action of PPIs and the effect of dose timing and meals on their efficacy.
Conclusion Awareness of new concerns regarding potential side effects of PPIs when used long-term require careful thought as GERD is a chronic disease with most needing some form of medical treatment over time. This article reviews the pharmacologic properties of PPIs and the impact on the treatment of GERD.

Keywords Proton pump inhibitors · GERD · Pharmacologic properties

Introduction

It is estimated that 30–40% of the US population have some symptoms of gastroesophageal reflux disease (GERD).[1] The most common symptoms are heartburn and/or regurgitation with an unknown number of patients with extra-esophageal symptoms, such as cough, laryngitis, or wheezing.[2,3] Chronic, frequent heartburn is the major risk factor for the development of esophageal adenocarcinoma, the fastest rising cancer in white men in the USA.

GERD is caused by the retrograde movement of gastric contents, mainly acid and pepsin, into the esophagus thereby causing symptoms of reflux and injury to the esophageal mucosa. Antisecretory agents, such as proton pump inhibitors (PPIs), increase intragastric pH thereby promoting esophageal mucosal healing and subsequent symptom relief. Understanding the mechanism of action of PPIs and the importance of dose timing in relation to meals is critical to optimize treatment for GERD. A majority of patients respond to a single daily dose of PPI. However, there are those who will require higher doses of medication and a small percentage that are considered refractory to PPIs. PPIs are safe medications with a low side effect profile; however, there is a new concern regarding the potential for long-term effects of these medications in the treatment of a chronic GERD sufferers. This article will explain the pharmacology of PPIs and their impact on the treatment of GERD.

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Acid Production

The parietal cell is the key player of acid secretion in the stomach responsible for an average of 2 L of gastric acid daily.[4] It expresses receptors for stimulators of acid secretion, including gastrin released from G cells, acetylcholine released from the vagus nerve, and histamine. Gastrin and acetylcholine cause the release of histamine from enterochromaffin-like cells (ECL). Activation of gastrin and acetylcholine receptors results in the activation of the protein kinase C phosphoinositide signaling pathway. Histamine leads to activation of adenylate cyclase and increase in cyclic AMP.[5,6] Both of these signaling pathways regulate a series of kinase cascades that control the acid secreting, H+/K+ATPase (proton pump), the target of the PPI.

PPIs inhibit only active pumps. A single dose of a PPI does not inhibit all pumps and does not result in profound inhibition of acid secretion. Acid production is inhibited with subsequent PPI doses, taking 5–7 days to achieve a steady state. Acid inhibition is never complete because of continued synthesis of new proton pumps. When PPIs are given twice daily, more active proton pumps are exposed to drug, and steady-state inhibition of gastric acid secretion is achieved more rapidly and more complete.[7]

PPIs are weak bases, incompletely absorbed, and have short half lives (0.6–1.9 h).

PPIs accumulate and activate in the acid environment at the secretory canalicular surface of the parietal cell. The inactive benzimidazole is converted to a cationic tetracyclic sulfonamide, which bind to the alpha subunit of the H+ K+ ATPase enzyme, irreversibly inhibiting acid production in about 70% of active pumps.[5,8] Acid secretion returns when new H+ K+ ATPase molecules are converted from inactive status in the tubulovesicle to active form at the canalicular surface.[9] This averages 36–72 h. PPIs decrease daytime, nocturnal, and meal-stimulated acid secretion.[10] The slower a PPI is cleared from the plasma; the more of it is available to be delivered to the proton pump.[11]

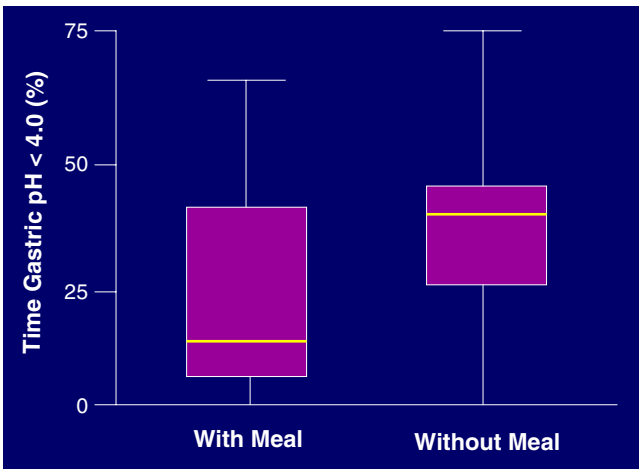

Figure 1 Percentage time for which gastric pH <4 when taking PPI (either omeprazole 20 mg or lansoprazole 30 mg) each morning, either 15 min before a breakfast meal or without food and drink (except for water), until 12 noon. In this box-and-whiskers plot, the median values are indicated as the *transverse line within the box*, the interquartile range as the *vertical extent of the box*, and total range as the *whiskers*. Acid suppression was significantly more effective when medication was taken with breakfast than without ($p<0.01$).

Table 1 Relationship Between Percent Time pH >4.0 and Healing of Erosive Esophagitis

Healing status	Mean % time intragastric pH>4.0[a]	*P* value
Healed	61.3	0.0002
Not healed	42.2	

Consistent with ITT analysis: 64.5% vs. 47.6% ($p=0.0003$). Overall erosive esophagitis was healed in 69.9% of patients at 4 weeks

ITT intention to treat

[a] Mean number of hours with valuable data was 23.64 h

All available PPIs are indicated for once daily dosing, usually in the morning. Food affects the bioavailability of each molecule, so it is our practice to recommend that all PPIs be given prior to meals for optimal efficacy. This is based on the concepts outlined above and results of intragastric pH studies in which superior daytime pH control (time intragastric pH>4) was seen when the PPI was taken before breakfast compared to an empty stomach (Fig. 1).[11]

PPIs are responsible for inhibiting gastric acid secretion, thereby decreasing potential damage to the esophageal mucosa. In addition, by raising gastric pH, the conversion of pepsinogen to pepsin, another player of mucosal damage, is inhibited. As one would expect, greater duration of gastric acid suppression affords greater healing rates of erosive esophagitis (Table 1).

Most patients respond to once-a-day PPI. However, some patients, particularly those with extraesophageal symptoms or complicated disease need higher doses. Splitting the dose and giving a PPI twice daily, before breakfast and dinner, results in superior nocturnal intragastric pH control, when compared to a double dose given once daily (Fig. 2).

Pharmacodynamic Effects

Omeprazole (also available over the counter at a 20 mg dose), lansoprazole, pantoprazole, rabeprazole, esomeprazole, and the newest PPI omeprazole sodium bicarbonate immediate release (IR-OME, Zegerid®) are all available for the treatment of GERD. PPIs inhibit daytime, nocturnal, and meal-stimulated acid secretion to a significantly greater

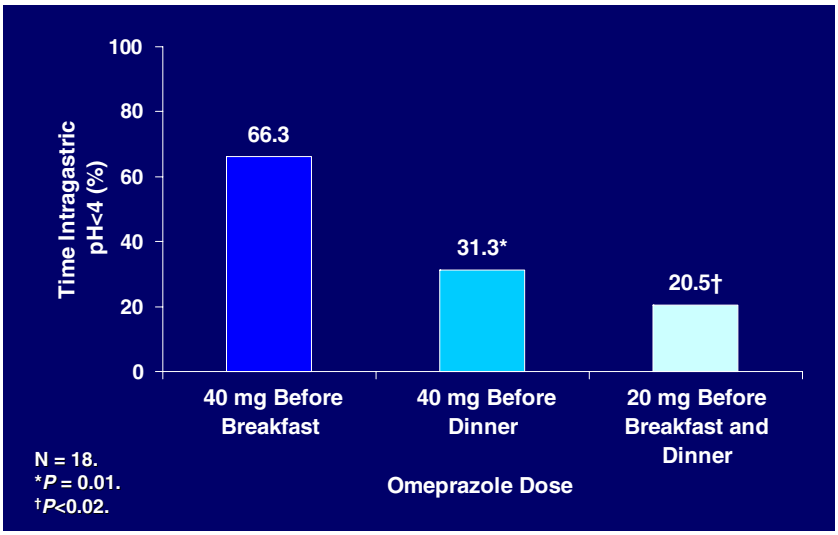

Figure 2 Bar graph showing percent time nocturnal pH <4 (10P-6A) for three different dose regimens of omeprazole. All result in equal daytime pH control. Results are similar with all proton pump inhibitors.

degree than H_2RAs and have largely replaced these agents in antireflux therapy.

Usually, delayed release PPIs are administered before the first meal of the day. If a second dose is needed, it should be given before the evening meal. With the exception of IR-OME, bedtime dosing is discouraged because proton pumps are not stimulated to a great degree during the sleeping period. When PPIs are administered twice daily, more active proton pumps are exposed to drug, and steady-state inhibition of gastric acid secretion is quicker and more complete. Daily dosing of PPIs are thus more effective than on demand or intermittent dosing in maintenance of symptom relief and healing of erosive esophagitis.

Patients with *Helicobacter pylori* gastritis involving the gastric corpus have enhanced overnight intragastric pH control with PPIs compared to those who are *H. pylori* negative.[12] However, *H. pylori* infection has little effect on pH control and thus has no role in the management of GERD. We do not routinely test for *H. pylori* in our GERD patients and find that it has no effect on outcome.

Immediate-Release Omeprazole

The newest PPI, immediate-release omeprazole sodium bicarbonate (IR-OME), offers another option for nighttime heartburn sufferers. IR-OME suspension, when administered at bedtime, achieved enhanced control of nocturnal gastric pH when compared to pantoprazole 40 mg.[13] Additionally, IR-OME given prior to breakfast and dinner, was found to be more effective in controlling overnight pH as compared to twice daily pantoprazole.[13]

An open-label, randomized, crossover study (N=54) compared intragastric pH with IR-OME suspension 40 mg, lansoprazole 30 mg, and esomeprazole 40 mg given at bedtime (10:00 P.M.) on an empty stomach for 7 days.[14] In the first half of the nighttime, intragastric pH >4 were higher after IR-OME compared to esomeprazole or lansoprazole ($p<0.001$, both comparisons).[15] Acid control with IR-OME was significantly better than lansoprazole ($p<0.001$) and comparable to esomeprazole for the entire nighttime period. The percentage of time with gastric pH >4 for the entire 24-h period was 43.6% after treatment with IR-OME vs. 59% with esomeprazole ($p<0.001$) and 27.8% with lansoprazole ($p<0.001$), when compared with both IR-OME and esomeprazole (Table 2).[14]

This study further supports the longstanding suggestion that delayed release PPIs are not optimally effective when given at bedtime. Lansoprazole offered a slow onset of overnight control with little increase the next day. Esomeprazole had a slower onset, with little time pH >4 in the first part of the sleeping period, however, had excellent 24-h control. As such, delayed release PPIs are best given before the evening meal if control is needed overnight.[16]

Side Effects of PPIs

PPIs have a low side effect profile and are considered to be safe medications. Frequent side effects seen in trials include headache, abdominal pain, and diarrhea. However, they are no greater in frequency than placebo.[15]

The increased levels of gastrin from gastric acid suppression and its trophic effects on stomach mucosa have also been a concern. Fundic gland polyps, while seen in a small number of patients, have not been shown to lead to a negative outcome. In the absence of observational and case–control studies, we do not change or stop PPIs due to fundic gland polyps unless the patient requests an alternative approach. We do not perform surveillance endoscopies unless a patient has a change in symptoms.

Table 2 Percent Time pH >4 Overnight with Bedtime Dosing of PPIS

Treatment	2200–2400 hours	First half of the night, 2200–0200 hours	2200–0400 hours	Entire nighttime period, 2200–0600 hours
IR-OME 40 mg	32.3 (6.6–94.1)	51.9 (16.8–88.7)	62.6 (26.0–88.1)	53.4 (31.3–90.3)
Lansoprazole 30 mg	0.0 (0.0–0.3)[a]	12.0 (0.0–32.1)[a]	26.6 (2.8–43.9)[a]	34.2 (13.3–52.2)[a]
Esomeprazole 40 mg	0.1 (0.0–14.8)[a]	30.1 (5.1–48.6)[a]	46.5 (29.5–64.1)	54.9 (38.2–68.6)

*p value <0.001 when compared with IR-OME using the Wilcoxon signed rank test

Increased incidence of gastric carcinoids, once thought to be of concern, have not been proven to be true. Vitamin B12 deficiency was thought to be a potential problem but has not been shown in well-done studies except in patients with multiple endocrine neoplasias.[17]

Several newer issues have been raised, especially in regards to infectious diseases. Pneumonia has been reported to be higher in patients on PPI (and H_2RAs) as compared to the patients not on treatment. The odds ratio for pneumonia was 1.8 compared to those not on PPI.[18] The patients in the study had multiple comorbidities, making these results difficult to interpret. Additionally, case–control studies have reported an increase in the prevalence of *Clostridium difficile* infection while on PPIs. Odds ratios from 1.3 to 5.1 for infection have been reported.[19–21] An increase in infection has not been substantiated in direct observational studies nor has the mechanism for this increase been elucidated. More importantly, the overall incidence of *C. difficile* infection in the general population is still quite low, so any small increase is unlikely to be a major clinical problem. Nonetheless, we must increase our awareness of the potential for *C. difficile* infection in patients on PPI, especially if they are on antibiotics, hospitalized, or in chronic care facilities.

A recent study reports an increase in the odds ratio for hip fractures for patients taking a PPI.[22] There was increased risk if a patient was taking a PPI long term and on more than once a day dosing.[23] The study states the multiple confounders were accounted for, including the severity and number of comorbid conditions in the comparator groups. Two other studies support this association. While the association is plausible, it has not been proven to be causal. Although the number of hip fractures is low, if confirmed, these data may affect the way we use PPIs long term particularly in patients at risk for fracture. At present, we remind patients at risk to discuss preventative measures with their primary care providers and use the lowest effective dose needed.

It is important to note that, in an observational study (N= 230) in which patients were followed while on continuous PPI, in doses of 20–160 mg/day for up to 11 years, none of the side effects above were seen.[24]

Multiple dose–response, meal, and dose timing pharmacodynamic studies reinforce the following key principles for clinical practice:

- Daytime control of intragastric pH is superior to nighttime control when PPIs are given in the morning.[25] A single daily dose given in the morning before breakfast will help most patients. A PPI given before dinner improves nighttime pH control without effect on daytime pH control.[16] Bedtime dosing of IR-OME will shift this curve to better overnight pH control compared to daytime.[14] Symptom studies are not available to compare these dose timings.
- Intragastric pH studies support superiority of acid control with twice daily dosing compared to double dose once daily in patients needing higher doses than approved by the FDA.[16]
- We recommend that all PPIs be dosed prior to meals for optimal efficacy. Our own data found superior daytime pH control (time intragastric pH >4) when PPI was taken before breakfast compared to an empty stomach.[11] Despite knowing these data, the appropriate timing of a meal is still under emphasized by clinicians. Patients often use PPIs in the morning and do not eat breakfast, taking their drug after a meal or at bedtime. A small adjustment in timing to before dinner, or eating breakfast *after* the morning dose, may improve clinical outcome. Consider IR-OME in patients needing nighttime control, especially the early hours after going to sleep.
- Optimal intragastric pH control is the key to effective treatment. Better control results in improved outcomes.[26]

Summary

PPIs are safe and effective agents for GERD. A single daily dose works for most. All available PPIs offer excellent symptom relief and healing of erosive esophagitis both short and long term. Esomeprazole 40 mg once daily offers small improvements in erosive esophagitis healing and symptom relief at 4 and 8 weeks compared to omeprazole 20 mg,[27] lansoprazole 30 mg,[28] and pantoprazole 40 mg.[29] The clinical importance of these statistical differences

continues to be debated. In practice, cost usually guides therapy. Omeprazole OTC is equal in strength to standard FDA approved dose by prescription. IR-OME offers options for patients with nighttime heartburn and off label as an on-demand PPI. Optimal efficacy of PPIs should ideally be given before a meal. Higher doses, if needed, should be given in split dose taking advantage of improved pH control when given twice daily. Careful vigilance and more studies are needed to evaluate the potential for side effects in those on long-term therapy. Until more studies are available, PPIs remain the treatment of choice for clinical management for the vast majority of patients with GERD.

References

1. Locke GR, Talley NJ, Fett SL et al. Prevalence and clinical spectrum of gastroesophageal reflux: a population based study in Olmstead county, Minnesota. Gastroenterology 1997;112:1448.
2. Stanghellini V. Relationship between upper gastrointestinal symptoms and lifestyle, psychosocial factors and comorbidity in general population; results from the Domestic/International Gastroenterology Surveillance Study (DIGEST). Scand J Gastroenterol Suppl 1999;231:29–37.
3. Fennerty MB. Extraesophageal gastroesophageal reflux disease. Presentations and approach to treatment. Gastroenterol Clin North Am 1999;28:861–873.
4. Robinson M. Review article: Current perspectives on hypergastrinaemia and enterochromaffin-like-cell hyperdysplasia. Aliment Pharmacol Ther 1999;13(suppl 5):5–10.
5. Massoomi F, Savage J, Destache CJ. Omeprazole: a comprehensive review. Pharmacotherapy 1993;13(1):46–59.
6. Maton PN. Omeprazole N. Engl J Med 1991;324(14):965–975.
7. Bell NJV, Burget D, Howden CW et al. Appropriate acid suppression for the management of gastro-oesophageal reflux disease. Digestion 1992;51(suppl 1):59–67.
8. Lew EA. Review article: Pharmacokinetic concerns in the selection of anti-ulcer therapy. Aliment Pharmacol Ther 1999;13 (suppl 5):11–16.
9. Bensancon M, Simon A, Sachs G et al. Sites of action of the gastric H, K-ATPase with extracytoplasmic thiol reagents. J Biol Chem 1997;272:22438–22446.
10. Klinkenberg-Knol EC, Festen HPM, Meuwissen SGM. Pharmacological management of gastro-oesophageal reflux disease. Drugs 1995;49:695–710.
11. Hatlebakk JG, Katz PO, Castell DO. Proton pump inhibitors: better acid suppression when taken before a meal than without a meal. APT 2000;14(10):1267–1272.
12. Katsube T, Adachi K, Kawamura A et al. *Helicobacter pylori* infection influences nocturnal gastric acid breakthrough. Aliment Pharmacol Ther 2000;14(8):1049–1056.
13. Castell D, Bagin R, Goldlust B, Major J, Hepburn B. Comparison of the effects of immediate-release omeprazole powder for oral suspension and pantoprazole delayed-release tablets on nocturnal acid breakthrough in patients with symptomatic gastro-oesophageal reflux disease. Aliment Pharmacol Ther 2005;21 (12):1467–1474.
14. Katz PO, Koch FK, Ballard ED, Bagin RG, Gautille TC, Checani GC, Hogan DL, Pratha VSV. Comparison of the effects of immediate-release omeprazole oral suspension, delayed-release lansoprazole capsules and delayed-release esomeprazole capsules on nocturnal gastric acidity after bedtime dosing in patients with night-time GERD symptoms. Aliment Pharmacol Ther 2007;25: 197–205.
15. Physicans' Desk Reference. Product information for all proton pump inhibitors, 60th edn. Thomson PDR: Montvale, NJ, 2006
16. Hatlebakk JG, Katz PO, Kuo B et al. Nocturnal gastric acidity and acid breakthrough on different regimens of omeprazole 40 mg daily. Aliment Pharmacol Ther 1998;12:1235–1240.
17. Howden CW. Vitamin B12 levels during prolonged treatment with proton pump inhibitors. J Clin Gastroenterol 2000;30(1):29–33.
18. Laheij RJF, Sturkenboom MCHM, Hassing RJ et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA 2004;292(16):1955–1960.
19. Dial S, Alrasadi K, Manoukian C et al. Risk of *Clostridium difficile* diarrhea among hospital inpatients prescribed proton pump inhibitors: cohort and case-control studies. CMAJ: Can Med Assoc J 2004;171(1):33–38.
20. Dial S, Delaney JAC, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*- associated disease. JAMA 2005;294 (23):2989–2995.
21. Williams C, McColl KEL. Review article: Proton pump inhibitors and bacterial overgrowth. Aliment Pharmacol Ther 2006;23(1):3–10.
22. Targownik LE, Lix LM, Metge CJ et al. Use of proton pump inhibitors and risk of osteoporosis-related fractures. CMAJ 2008;179(4):319–326.
23. Yang Y-X, Lewis JD, Epstein S, Metz DC. Long-term proton pump inhibitor therapy and risk of hip fracture. JAMA 2006;296 (24):2947–2953.
24. Klinkenberg-Knol E, Nelis F, Dent J et al. Long-term omeprazole treatment in resistant gastroesophageal reflux disease. Gastroenterology 2000;118:661–669.
25. Tutuian R, Katz PO, Castell DO. A PPI is a PPI is a PPI: Lessons from prolonged intragastric pH monitoring. Gastroenterol 2000;118:A17.
26. Katz PO, Ginsberg GG, Hoyle PE, Sostek MB, Monyak JT, Silberg DG. Relationship between intragastric acid control and healing status in the treatment of moderate to severe erosive oesophagitis. Aliment Pharmacol Ther 2007;25(5):5617–5628.
27. Richter JE, Kahrilas PJ, Johanson J et al. Efficacy and safety of esomeprazole compared with omeprazole in GERD patients with erosive esophagitis: a randomized controlled trial. Am J Gastroenterol 2001;96:656–665.
28. Castell DO, Kahrilas PJ, Richter JE et al. Esomeprazole (40 gm) compared with lansoprazole (30 mg0 in the treatment of erosive esophagitis. Am J Gastroenterol 2002;97(3):575–583.
29. Labenz J, Armstrong D, Lauritsen K et al. A randomized comparative study of esomeprazole 40 mg versus pantoprazole 40 mg for healing erosive oesophagitis: the EXPO study. Aliment Pharmacol Ther 2005;21(6):739–746.

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DEMEESTER FESTSCHRIFT

Is There a Role for Anything Other Than a Nissen's Operation?

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Abstract
Background The Nissen fundoplication is the most frequently applied antireflux operation worldwide. The aim of this review was to compare laparoscopic Nissen with partial fundoplication.
Methods Nine randomized trials comparing several types of wraps were analyzed, four for the comparison Nissen vs. Toupet and five for the comparison Toupet or Nissen vs. anterior fundoplication. Similar comparisons in nonrandomized studies were also included.
Results Dysphagia rates and reflux recurrence were not related to preoperative esophageal persistalsis independent of the selected procedure. Overall, Nissen fundoplication revealed slightly better reflux control, but was associated with more side effects, such as early dysphagia and gas bloat. Advantages of an anterior approach were only reported by one group. A significantly higher reflux recurrence rate for anterior fundoplication was observed in all other comparisons.
Conclusion Tailoring antireflux surgery according to esophageal motility is not indicated. At present, the relevant factor for selection of a Nissen or Toupet fundoplication is personal experience. Anterior fundoplication offers less effective long-term reflux control.

Keywords Antireflux surgery · Gastroesophageal reflux disease · Esophageal motility

Introduction

Gastroesophageal reflux disease (GERD) is of major medical and socioeconomic importance. Clinical manifestations of this disease range from mild and infrequent symptoms to more serious complications such as Barrett's esophagus or cancer of the esophagus. The incidence of reflux disease, as well as the incidence of esophageal adenocarcinoma, is growing.[1]

Therapeutic options are medical treatment with acid-suppressive drugs, endoscopic augmentation of the lower esophageal sphincter and surgical antireflux procedures. Since the introduction of laparoscopic fundoplication in the early 1990s, there has been an exponential growth in the number of patients being referred for operation despite the availability of proton-pump inhibitors. In randomized studies, antireflux surgery was at least as effective as medical treatment.[2,3] The laparoscopic approach has largely replaced open surgery for reflux, with the benefit of a more rapid recovery. This has been shown in many randomized controlled trials and summarized in two reviews.[4,5]

The most common antireflux operation procedure worldwide is laparoscopic Nissen fundoplication.[4–8] It has been shown to be safe, effective, and durable. Potential side effects are gas bloat, early satiety, dysphagia, and flatulence. The choice of surgical technique to provide optimal reflux control while minimizing side effects remains controversial. Some surgeons favor partial fundoplication. These authors argue that a partial fundoplication is more physiological, allowing venting of air from the stomach, and therefore reducing the rate of side effects.

To define the role of other techniques of fundoplication, the outcome of laparoscopic total fundoplication was compared with partial fundoplication. The analysis was

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based on all published randomized controlled trials (RCTs) on laparoscopic fundoplication and long-term nonrandomized studies with similar comparisons. Since the meta-analysis from Catarci et al.,[4] six additional RCTs and three follow-up reports have been published.

Randomized Controlled Trials

Nine randomized trials comparing several types of wraps in laparoscopic antireflux surgery were identified, four for comparison Nissen vs. Toupet and five for comparison Toupet or Nissen vs. anterior fundoplication. Nissen vs. Toupet was evaluated in one study from Birmingham, Alabama, USA[9]; one from Hamburg, Germany[10–12]; one from Charleroi, Belgium;[13] and one from Berkshire, UK.[6] Nissen was compared to anterior fundoplication in three trials from Adelaide, Australia,[14–17] and one from Cape Town, South Africa.[18] The author from Cape Town had also worked together with the authors from Adelaide.[19] One study from Gothenburg, Sweden[20,21] examined Toupet vs. anterior fundoplication. In three studies, choice of procedure was stratified based on results of esophageal manometry (normal or ineffective esophageal peristalsis).[6,10,14] Details of these studies are shown in Table 1.

The outcomes considered were: overall morbidity and mortality, length of operation, incidence of reoperation for any failure, and patients' satisfaction (Table 2). Specific symptoms included dysphagia, reflux recurrence, and gas bloat (Table 3). Presence of postoperative dysphagia was separated into three groups: new onset, early onset (≤3 months) and persistent (≥1 year). Postoperative recurrence of GERD was reported by the recurrence of symptoms and by clinical findings (endoscopy and/or pH-metry).

In all RCTs comparing Nissen with Toupet procedure, hiatal repair and division of short gastric vessels was performed for both types of wraps. A bougie was used by every investigator, sizes 34, 36, 40, and 56. Two studies excluded patients with esophageal motility disorders, the other two stratified patients by esophageal motility. Length of follow-up was 1 year, two times 2 years and 3 years (Table 1). There were no perioperative deaths. No significant differences were found in operative morbidity and length of surgical procedure. A very high reoperation rate (15%) was reported in one study after Nissen fundoplication.[11] In most of these patiens, the indication for reoperation was a recurrent hernia with dysphagia and/or reflux recurrence. Reoperation rates were very low and not different in the other studies. The Visick score was constantly high in all studies without any significant difference at the final follow-up (Table 2).

While two studies reported very low dysphagia rates with no significant differences for persistent dysphagia,[9,13] Booth et al., as well as Fibbe et al., found a significantly higher rate of postoperative persistent dysphagia in the Nissen group (Table 3). These two studies also reported

Table 1 RCTs: Details of the Studies

Author	Year	Period	Follow up [months]	Procedures	Hiatal repair	Bougie [French]	DSGV	No. of Patients	Esophageal Motility Disorders
Laws[9]	1997	NR	27	Nissen	Yes	40	Yes	23	Excluded
				Toupet			Yes	16	Excluded
Fibbe[10–12]	2001/2	1999–2000	4–24	Nissen	Yes	36	Yes	100	50/100
	2008			Toupet	Yes	36	Yes	100	50/100
Guerin[13]	2007	1998–2002	12–36	Nissen	Yes	34	Yes	77	Excluded
				Toupet	Yes	34	Yes	63	Excluded
Booth[6]	2008	1998–2001	12	Nissen	Yes	56	Yes	64	26/64
				Toupet	Yes	56	Yes	63	26/63
Watson[14,16]	1999	1995–1997	6	Nissen	Yes	52	No	53	11/53
	2005		60	Anterior	Yes	None	No	53	11/53
Watson[15]	2004	2000–2003	6	Nissen	Yes	52–60	Yes	52	Excluded
				Anterior	Yes	None	No	60	Excluded
Spence[17]	2006	1999–2003	12	Nissen	Yes	52	No	39	Excluded
				Anterior	No	None	No	40	Excluded
Baigrie[18]	2005	1999–2001	24	Nissen	Yes	56	No	84	NR
				Anterior	Yes	NR	No	79	NR
Lundell[20,21]	2003	NR	12	Toupet	Yes	None	Yes	48	NR
	2007		65	Anterior	Yes	None	No	47	NR

DSGV division of the short gastric vessels, *NR* not reported

Table 2 Results of RCTs

Author	Procedures	No. of Patients	Morbidity	Operation Time [min]	Reoperation	Visick score (I–II) [%]
Laws[9]	Nissen	23	0	155	0	91.3
	Toupet	16	2	162	1	93.8
Fibbe[10–12]	Nissen	100	5	45	15*	85
	Toupet	100	1	50	4*	85
Guerin[13]	Nissen	77	1	NR	NR	90.5
	Toupet	63	3	NR	NR	88.9
Booth[6]	Nissen	64	0	81	0	92
	Toupet	63	1	89	1	91
Watson[14,16]	Nissen	53	8	58	3	78
	Anterior	53	10	60	3	86
Watson[15]	Nissen	52	4	87	0	83
	Anterior	60	5	80	1	87
Spence[17]	Nissen	39	7	55	4	68
	Anterior	40	2	60	2	80
Baigrie[18]	Nissen	84	NR	53	4	98
	Anterior	79	NR	59	6	93
Lundell[20,21]	Toupet	48	NR	NR	1	93*[a]
	Anterior	47	NR	NR	5	59*

*$p<0.05$

[a] No Visick Score; % of patients, who would have surgery again

Table 3 Results of RCTs: Specific Symptoms

Author	Procedures	No. of Patients	Dysphagia			Recurrence		Gas bloat symptoms
			New-Onset (a)	Early (b)	Persistent (c)	Symptoms	Clinical findings	
Laws[9]	Nissen	23	NR	2	0	NR	1	NR
	Toupet	16	NR	1	0	NR	0	NR
Fibbe[10–12]	Nissen	100	23	NR	**19**[a]	25	**42/144**[a]	n.s.[1]
	Toupet	100	10	NR	**8**[a]	17	**22/144**[a]	
Guerin[13]	Nissen	77	NR	**9**[a]	2	4	NR	1
	Toupet	63	NR	**21**[a]	0	3	NR	4
Booth[6]	Nissen	64	14	21	**16**[a]	14	3/76	44
	Toupet	63	9	12	**5**[a]	14	5/76	39
Watson[14,16]	Nissen	53	NR	NR	14	5	NR	**38**[a]
	Anterior	53	NR	NR	9	10	NR	**22**[a]
Watson[15]	Nissen	52	NR	5	**5**[a]	**4**[a]	2	47
	Anterior	60	NR	2	**0**[a]	**19**[a]	4	39
Spence[17]	Nissen	39	NR	28	**19**[a]	3	NR	**31**[a]
	Anterior	40	NR	24	**5**[a]	4	NR	**17**[a]
Baigrie[18]	Nissen	84	NR	**56**[a]	4	0	NR	n.s.[1]
	Anterior	79	NR	**38**[a]	0	10	NR	
Lundell[20,21]	Toupet	48	n.s.[1]	n.s.[1]	n.s.[1]	**11**[a]	**9/26**[a]	[a]
	Anterior	47				**26**[a]	**22/27**[a]	

NR not reported, *n.s.*[1] Reported scores were not significant, no number of patients given

[a] Significant difference

more frequent new-onset dysphagia after Nissen fundoplication. Of note, in one study, early-onset dysphagia was more frequent following Toupet fundoplication.[13] Information on severity of dysphagia was inconsistent and, in most cases, either endoscopic dilatation or no treatment at all was sufficient. Only one study showed a statistically significant number of endoscopic dilatations (one or more) after Nissen vs. Toupet fundoplication (14 patients vs. five patients).[11] Stratification according to esophageal motility showed no differences for patients with or without esophageal motility disorders.[6,10–12]

In general, three RCTs revealed the same reflux control for both procedures without statistically significant differences. Only Fibbe et al. reported a higher rate of recurrent reflux symptoms in the Nissen group. Furthermore, these authors reported that pathological pH-metry findings were more frequent after Nissen fundoplication, mostly as a consequence of a recurrent hernia. These findings were the indication for a reoperation in most patients and resulted in the higher reoperation rate after Nissen fundoplication. There were no differences in gas bloat symptoms reported in three of these four studies.

There were four RCTs comparing Nissen with anterior fundoplication. Hiatal repair was always done, except for the anterior fundoplication in one study.[17] Short gastric vessel division is not necessary for anterior fundoplication. In these comparisons, it was only performed on Nissen patients in one study.[15] Two studies excluded patients with esophageal motility disorders,[15,17] one study included 20% of patients with esophageal motility disorders,[14] and in one study, esophageal motility was not measured in every patient.[18] Follow-up was 6 months and 1, 2, and 5 years each (Table 1).

Mortality was nil and similar rates of perioperative morbidity and operation time were found. Reoperation rates were between 2% and 8% with no significant differences. However, Baigrie et al., as well as Spence et al., performed all reoperations after Nissen fundoplication due to severe dysphagia, while all reoperations after anterior fundoplication were done because of recurrent reflux. Patients' satisfaction levels after surgery were high in both groups with no significant differences (Table 2).

Dysphagia was significantly more frequent after Nissen fundoplication in two of the four studies.[15,17] Baigrie et al. described a significant difference for early onset dysphagia, but only slightly higher rates for persistent dysphagia following a Nissen. In contrast, rate of reflux recurrence tended to be higher after anterior fundoplication in three studies with a significant difference in one. As mentioned above, the indications for reoperations were related to these differences. Significantly more patients suffered from gas bloating in the Nissen group in two studies.[16,17]

Finally, Lundell et al. compared the Toupet procedure with anterior fundoplication with a 5-year follow-up. No deaths occurred after surgery. No detailed information is given on morbidity and length of surgery, and no significant differences in the dysphagia rates and gas bloating were shown. Reflux recurrence rates were higher after anterior fundoplication (60.5% vs. 24.4%). This was in correlation with results of pH-metry, when performed after surgery. In these cases, pathological acid reflux was evident in more than 80% of patients after anterior fundoplication. However, reoperation was performed in only a small number of patients. In accordance with the reflux recurrence, Visick score was significantly higher after Toupet fundoplication.

Nonrandomized Studies

It is impossible to summarize all nonrandomized studies that have been published on laparoscopic fundoplication. Criteria for the selected papers were the total number of patients, the length and rate of follow-up, and/or the comparison of different procedures. The search results for "anterior fundoplication" were mainly studies reporting on surgical treatment of achalasia, paraesophageal hernia, or antireflux surgery in children. However, there are some institutions that apply anterior fundoplication as the standard procedure. It was reported to be a good therapeutic option for selected patients with endoscopically negative esophagitis.[22]

Details of the selected studies are shown in Table 4. In contrast to the randomized studies, data on morbidity, operation time, and Visick score were reported infrequently and were, therefore, not listed in the table. The Nissen–Rosetti modification that adds a caudal fixation of the wrap to the stomach was evaluated in two reports.[23,24] A hiatal repair was done in almost all selected studies except for on the patients with Toupet fundoplication in five studies. Bougie size was 50 or more and used for all Nissen and most Toupet patients. About half of the patients had a division of the short gastric vessels. Patients with esophageal motility disorders were sometimes excluded,[23] others used a "tailored approach": In patients with normal esophageal motility, a Nissen fundoplication was applied; in those with motility disorders, a partial fundoplication was applied. However, esophageal motility was not evaluated in all patients. The follow-up time and rate and the most important endpoints—dysphagia and reflux recurrence—are summarized in Table 5. Follow-up time was up to 10 years and follow-up rates range from 47% to 100%.

A significantly higher dysphagia rate after Nissen fundoplication was observed for the Nissen–Rosetti in two studies reporting on this modification.[23,24] Kamolz et al. and Patti et al. reported slightly higher dysphagia rates after

Table 4 Nonrandomized Controlled Trails: Details of the Studies

Author	Year	Period	Procedures	Hiatal repair	Bougie [French]	DSGV	No. of Patients	Esophageal Motility Disorders
Hunter[23]	1996	1991–1993	Nissen	Yes	56	Yes	46	Excluded
			Niss.–Ros.	Yes	52–56	No	55	Excluded
			Toupet	No	54–60	No	83	Excluded
Coster[28]	1997	1992–1995	Nissen	Yes	60	No	125	NR
			Toupet	Yes	60	No	101	NR
Bell[32]	1999	1993–1997	Toupet	No 31 Ant. 31 Pos. 81	No	(75/121) reported	143	Included
Fernando[26]	2000	1991–1997	Nissen	Yes	52–56	Yes	163	23/151
			Toupet	Yes	54–58	Yes	43	21/33
Pessaux[24]	2000	1992–1996	Nissen	Yes	50	Yes	423	11/53
			Niss.–Ros. Toupet	Yes	50 50	No No	655 392	11/53
Kamolz[29,41]	2000	1992–1996	Nissen	Yes	56–60	No	104/107	Excluded
	2002		Toupet	No	54–60	No	65/68	Included
Oleynikov[30]	2002	1994–1997	Toupet	No	52	Yes	39	39/39
		1999–2000	Nissen	Yes	52	Yes	57	57/57
Patti[27]	2004	1992–1999	Nissen	Yes	56	Yes	94	Excluded
			Toupet	Yes	56	Yes	141	Included
		1999–2000	Nissen	Yes	56	Yes	122	55/122
Fein[25]	2008	1992–1997	Nissen	Yes	54	Yes	88	Excluded
			Toupet	Yes	54	Yes	10	NR
			Anterior	Yes	No	No	22	NR

DSGV division of the short gastric vessels, *NR* not reported

Table 5 Results of Non-RCTs: Specific Symptoms

Author	Follow up [months]	Follow up [%]	Dysphagia			Reccurence		
			Nissen (+)	Toupet (+)	+/−	Nissen (+)	Toupet (+)	+/−
Hunter[23]	3	100	●[a]	–	●	–	–	–
Coster[32]	30	64.3	●[a]	–	–	–	–	●
Bell[32]	5–51	96.5	–	–	–	–	●[e]	–
Fernando[26]	12–43	69.0	–	●	–	–	●	–
Pessaux[24]	3–24	94.6	–	–	●	–	–	●
Kamolz[29,41]	12–60	60.0[b]	–	–	●[c]	–	–	●[f]
Oleynikov[30]	3–24	46.5[b]	–	●[d]	–	–	–	●[f]
Patti[27]	67+/− 2,223+/− 10	100	–	–	●[c]	–	●	–
Fein[25]	120	87	–	–	●	–	●	–

(+) more dysphagia/recurrence, ● significant differences

[a] Nissen–Rossetti

[b] Percentage of patients undergoing clinical evaluation

[c] Slightly higher dysphagia rate after Nissen fundoplication

[d] Better reduction of dysphagia after Nissen fundoplication

[e] Only patients undergoing Lap. Toupet procedure investigated

[f] Slightly higher recurrence rate after Toupet fundoplication

standard Nissen fundoplication. Fernando et al. found a significantly higher dysphagia rate after Toupet fundoplication. Of note, Oleynikov described that preoperative dysphagia improved more after total than after partial fundoplication. Dysphagia rate was similar for the different types of wraps in the other studies.[23–25] None of the studies described differences in dysphagia rate for patients with or without esophageal motility disorder.

No nonrandomized study reports that the recurrence rate is higher for a Nissen than for a Toupet. Three papers reported a significantly higher recurrence rate for the Toupet fundoplication.[25–27] Four of the studies,[24,28–30] with a very large number of patients in the study from France, showed no significant differences in the recurrence rate. Bell et al. and Horvath et al.[31] described a very high recurrence rate after Toupet fundoplication, especially for patients with severe esophagitis or Barrett's esophagus. When evaluated, the "tailored concept" disappointed because of the higher rate of reflux recurrence after Toupet and no increased dysphagia rates after Nissen fundoplication for impaired esophageal peristalsis.[24,25,30] The most common indication for reoperation was reflux recurrence. In accordance with the data on reflux recurrence, higher reoperation rates were reported for Toupet fundoplication in two studies.[27,32] There was no significant difference in the other studies.

Discussion

Laparoscopic total fundoplication is the most commonly performed procedure in the surgical treatment of GERD. Partial fundoplications have been advocated and popularized to avoid some of the postoperative side-effects of a total fundoplication. Despite nine RCTs with a substantial number of patients and numerous nonrandomized studies on the outcome of laparoscopic fundoplication, the optimal operative approach has not yet been identified.

There are several reasons for the inconsistency of the data of these various studies. First, the operative technique is not standardized. A Nissen is not a Nissen. The hiatoplasty is different in many studies, bougies of several sizes are used, ranging from 32 to 60, and various fixations of the wrap on the esophagus, the stomach, or the hiatal crus are used. For partial fundoplications—anterior and posterior—the extent of the wrap is also not identical in these studies. Second, the patient selection may introduce a bias in these studies; e.g., some authors excluded patients with a brachyesophagus. When comparing motility disorders of the esophagus, the definition of impaired peristalsis on manometry is not standardized. Third, outcome is related to the experience of the institution. Fourth, symptoms are usually the applied endpoint of the studies. It is almost impossible to define and characterize symptoms in a general standardized manner. Another important parameter is the length of follow-up. For example, in a randomized study comparing anterior with posterior fundoplication, only 10% of patients reported severe heartburn 1 year after anterior fundoplication, but the rate rose to 22% after 5 years.[20,21] Only two randomized studies included a 5-year follow-up.

Therefore, even the results of the meta-analysis that revealed some advantages for the Toupet fundoplication were interpreted with caution.[4] The authors recommended waiting for data with a longer follow-up before drawing definitive conclusions.[4] This meta-analysis and the included three original studies, new reports on ongoing randomized trials with a longer follow-up, and recently published reports on further randomized trials, and many nonrandomized trials have been carefully reevaluated. The following conclusions on the selection of the type of fundoplication could be drawn from the currently available data:

Many centers have used the so-called "tailored approach" for years. It was assumed that a partial fundoplication would offer less resistance in patients with reduced pump function, thus lowering the dysphagia rate.[33–35] Two RCTs,[6,10] as well as a RCT on open antireflux surgery,[36,37] focused on this subject and clearly demonstrated that tailoring antireflux surgery according to the esophageal motility is not indicated. Unspecific esophageal motility disorders have no effect on the results of antireflux surgery. A Nissen fundoplication can be successfully applied even in patients with aperistaltic esophagus.[19,37] However, there is not yet enough data to define the optimal procedure in patients with specific motility disorders such as scleroderma, where most surgeons prefer to perform a Toupet fundoplication.

Comparing laparoscopic Nissen with Toupet fundoplication, dysphagia rate after Nissen was higher in the two RCTs.[6,10] This was related to more frequently reported preoperative dysphagia in one study.[6] Of note, there were also no differences in gas bloat. In nonrandomized studies, Nissen fundoplication was associated with more side effects, such as early dysphagia and gas bloat. Especially gas bloat symptoms usually decrease after more than 2 years. Postoperative scar tissue formation leading to later narrowing of the esophageal hiatus may occur in the second or third week, and may lead to late dysphagia independent of the type of wrap[38]; e.g., at the 5-year follow-up of a study on open fundoplication, there was a tendency towards more dysphagia following partial compared to total fundoplication.[39] Recent observations have shown that the wrap itself is less involved in delayed dysphagia than its transhiatal migration.[11] The etiology of dysphagia is multifactorial, although an abnormal preoperative manometric pattern is definitely a poor predictor of postoperative

new-onset or persistent dysphagia. There was no difference in reflux recurrence in three of the four randomized studies, and slightly better reflux control after Nissen fundoplication in nonrandomized studies. In summary, there is no clearly characterized overall advantage of one procedure over the other and the results are strongly related to the specific technique of the institutions. Therefore, the relevant factor for selection of a Nissen or Toupet fundoplication is personal experience.

The comparison of Nissen or Toupet with anterior fundoplication reveals significant differences in both randomized and nonrandomized studies. Only studies from one group showed an equal reflux control with advantages for the anterior approach because of fewer side effects[14,15] even in the 5-year follow up.[40] The two other RCTs[20,21] showed—like many other non-RCTs—a dramatically higher rate of reflux recurrence after the anterior approach. As a rule, the effects of each of the applied fundoplication procedures show a gradual steady decline over time. This explains why the technique with the greatest benefit initially remains superior in the long-term. As anterior fundoplication offers less effective long-term reflux control, it cannot be recommended as the standard antireflux procedure.

In comparison to these findings, the results of the meta-analysis 2004 from Catarci[4] for the comparison of Nissen with partial fundoplication included six studies with open procedures. No differences had been described for any of the evaluated parameters except for a higher reoperation rate after a Nissen, which resulted from the extremely high numbers of reoperations in the institution contributing the largest study.[10] These differences were not observed in the six new studies. The authors of the study with the high reoperation rate discuss the strict follow-up combined with an early indication for redo surgery as an explanation for these high reoperation rates.[11] They observed a high failure rate for the hiatal repair, causing failure of total fundoplication. Herniation of the wrap resulted in a higher dysphagia rate, as well as a higher reflux recurrence rate in the recently reported 2-year follow-up of these patients.[11] The identification of institution-specific problems after one type of operation is another argument for the selection of the procedure according to personal experience.

The surgical treatment of large hiatal hernia or an upside-down stomach was not part of this evaluation. The results for different types of wraps in these patients may differ from the above described results in classical GERD. Here, the most important issue is the closure of the hiatus, and the importance of a mesh is a relevant issue to be further studied. The function of the wrap in these patients is an augmentation of the hiatal closure and not primarily an antireflux barrier. At present, the best type of fundoplication for this closure is not yet identified.

Conclusions

The comparison of different types of wraps for antireflux surgery is limited by the fact that the operative technique is not standardized. Nevertheless, it has been consistently shown that tailoring antireflux surgery according to esophageal motility is not indicated. At present, there is no clearly characterized advantage of one procedure over the other. Therefore, the relevant factor for selection of a Nissen or Toupet fundoplication is personal experience. Finally, there is significance evidence that anterior fundoplication offers less effective long-term reflux control.

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References

1. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97:142–146.
2. Lundell L, Miettinen P, Myrvold HE, Hatlebakk JG, Wallin L, Malm A, Sutherland I, Walan A. Seven-year follow-up of a randomized clinical trial comparing proton-pump inhibition with surgical therapy for reflux oesophagitis. Br J Surg 2007;94:198–203. doi:10.1002/bjs.5492.
3. Lundell L, Attwood S, Ell C, Fiocca R, Galmiche JP, Hatlebakk J, Lind T, Junghard O. Comparing laparoscopic antireflux surgery with esomeprazole in the management of patients with chronic gastro-oesophageal reflux disease: a 3-year interim analysis of the LOTUS trial. Gut 2008;57:1207–1213. doi:10.1136/gut.2008.148833.
4. Catarci M, Gentileschi P, Papi C, Carrara A, Marrese R, Gaspari AL, Grassi GB. Evidence-based appraisal of antireflux fundoplication. Ann Surg 2004;239:325–337. doi:10.1097/01.sla.0000114225.46280.fe.
5. Lundell L. Therapy of gastroesophageal reflux: evidence-based approach to antireflux surgery. Dig Dis 2007;25:188–196. doi:10.1159/000103883.
6. Booth MI, Stratford J, Jones L, Dehn TC. Randomized clinical trial of laparoscopic total (Nissen) versus posterior partial (Toupet) fundoplication for gastro-oesophageal reflux disease based on preoperative oesophageal manometry. Br J Surg 2008;95:57–63. doi:10.1002/bjs.6047.
7. Dallemagne B, Weerts J, Markiewicz S, Dewandre JM, Wahlen C, Monami B, Jehaes C. Clinical results of laparoscopic fundoplication at ten years after surgery. Surg Endosc 2006;20:159–165. doi:10.1007/s00464-005-0174-x.
8. Dassinger MS, Torquati A, Houston HL, Holzman MD, Sharp KW, Richards WO. Laparoscopic fundoplication: 5-year follow-up. Am Surg 2004;70:691–694.
9. Laws HL, Clements RH, Swillie CM. A randomized, prospective comparison of the Nissen fundoplication versus the Toupet fundoplication for gastroesophageal reflux disease. Ann Surg 1997;225:647–653. doi:10.1097/00000658-199706000-00002.

10. Fibbe C, Layer P, Keller J, Strate U, Emmermann A, Zornig C. Esophageal motility in reflux disease before and after fundoplication: a prospective, randomized, clinical, and manometric study. Gastroenterology 2001;121:5–14. doi:10.1053/gast.2001.25486.
11. Strate U, Emmermann A, Fibbe C, Layer P, Zornig C. Laparoscopic fundoplication: Nissen versus Toupet two-year outcome of a prospective randomized study of 200 patients regarding preoperative esophageal motility. Surg Endosc 2008;22:21–30. doi:10.1007/s00464-007-9546-8.
12. Zornig C, Strate U, Fibbe C, Emmermann A, Layer P. Nissen vs Toupet laparoscopic fundoplication. Surg Endosc 2002;16:758–766. doi:10.1007/s00464-001-9092-8.
13. Guerin E, Betroune K, Closset J, Mehdi A, Lefebvre JC, Houben JJ, Gelin M, Vaneukem P, El Nakadi I. Nissen versus Toupet fundoplication: results of a randomized and multicenter trial. Surg Endosc 2007;21:1985–1990. doi:10.1007/s00464-007-9474-7.
14. Watson DI, Jamieson GG, Pike GK, Davies N, Richardson M, Devitt PG. Prospective randomized double-blind trial between laparoscopic Nissen fundoplication and anterior partial fundoplication. Br J Surg 1999;86:123–130. doi:10.1046/j.1365-2168.1999.00969.x.
15. Watson DI, Jamieson GG, Lally C, Archer S, Bessell JR, Booth M, Cade R, Cullingford G, Devitt PG, Fletcher DR, Hurley J, Kiroff G, Martin CJ, Martin IJ, Nathanson LK, Windsor JA. Multicenter, prospective, double-blind, randomized trial of laparoscopic nissen vs anterior 90 degrees partial fundoplication. Arch Surg. 2004;139:1160–1167. doi:10.1001/archsurg.139.11.1160.
16. Ludemann R, Watson DI, Jamieson GG, Game PA, Devitt PG. Five-year follow-up of a randomized clinical trial of laparoscopic total versus anterior 180 degrees fundoplication. Br J Surg 2005;92:240–243. doi:10.1002/bjs.4762.
17. Spence GM, Watson DI, Jamiesion GG, Lally CJ, Devitt PG. Single center prospective randomized trial of laparoscopic Nissen versus anterior 90 degrees fundoplication. J Gastrointest Surg. 2006;10:698–705. doi:10.1016/j.gassur.2005.10.003.
18. Baigrie RJ, Cullis SN, Ndhluni AJ, Cariem A. Randomized double-blind trial of laparoscopic Nissen fundoplication versus anterior partial fundoplication. Br J Surg 2005;92:819–823. doi:10.1002/bjs.4803.
19. Baigrie RJ, Watson DI, Myers JC, Jamieson GG. Outcome of laparoscopic Nissen fundoplication in patients with disordered preoperative peristalsis. Gut 1997;40:381–385.
20. Hagedorn C, Jonson C, Lonroth H, Ruth M, Thune A, Lundell L. Efficacy of an anterior as compared with a posterior laparoscopic partial fundoplication: results of a randomized, controlled clinical trial. Ann Surg 2003;238:189–196.
21. Engstrom C, Lonroth H, Mardani J, Lundell L. An anterior or posterior approach to partial fundoplication? Long-term results of a randomized trial. World J Surg 2007;31:1221–1225. doi:10.1007/s00268-007-9004-8.
22. Gockel I, Heintz A, Domeyer M, Kneist W, Trinh TT, Junginger T. Nichterosive und erosive gastroöphageale Refluxerkrankung. Langzeitergebnisse der laparoskopischen anterioren Semifundoplikatio. Chirurg 2007;78:35–39. doi:10.1007/s00104-006-1246-8.
23. Hunter JG, Swanstrom L, Waring JP. Dysphagia after laparoscopic antireflux surgery. The impact of operative technique. Ann Surg 1996;224:51–57. doi:10.1097/00000658-199607000-00008.
24. Pessaux P, Arnaud JP, Ghavami B, Flament JB, Trebuchet G, Meyer C, Huten N, Champault G. Laparoscopic antireflux surgery: comparative study of Nissen, Nissen–Rossetti, and Toupet fundoplication. Societe Francaise de Chirurgie Laparoscopique. Surg Endosc. 2000;14:1024–1027. doi:10.1007/s004640000248.
25. Fein M, Bueter M, Thalheimer A, Pachmayr V, Heimbucher J, Freys SM, Fuchs KH. Ten-year Outcome of Laparoscopic Antireflux Surgery. J Gastrointest Surg 2008;1893–1899. doi:10.1007/s11605-008-0659-8.
26. Fernando HC, Luketich JD, Christie NA, Ikramuddin S, Schauer PR. Outcomes of laparoscopic Toupet compared to laparoscopic Nissen fundoplication. Surg Endosc 2002;16:905–908. doi:10.1007/s004640080007.
27. Patti MG, Robinson T, Galvani C, Gorodner MV, Fisichella PM, Way LW. Total fundoplication is superior to partial fundoplication even when esophageal peristalsis is weak. J Am Coll Surg 2004;198:863–869. doi:10.1016/j.jamcollsurg.2004.01.029.
28. Coster DD, Bower WH, Wilson VT, Brebrick RT, Richardson GL. Laparoscopic partial fundoplication vs laparoscopic Nissen–Rosetti fundoplication. Short-term results of 231 cases. Surg Endosc 1997;11:625–631. doi:10.1007/s004649900408.
29. Kamolz T, Granderath FA, Bammer T, Wykypiel H Jr, Pointner R. "Floppy" Nissen vs. Toupet laparoscopic fundoplication: quality of life assessment in a 5-year follow-up (part 2). Endoscopy 2002;34:917–922. doi:10.1055/s-2002-35309.
30. Oleynikov D, Eubanks TR, Oelschlager BK, Pellegrini CA. Total fundoplication is the operation of choice for patients with gastroesophageal reflux and defective peristalsis. Surg Endosc 2002;16:909–913. doi:10.1007/s00464-001-8327-z.
31. Horvath KD, Jobe BA, Herron DM, Swanstrom LL. Laparoscopic Toupet fundoplication is an inadequate procedure for patients with severe reflux disease. J Gastrointest Surg. 1999;3:583–591. doi:10.1016/S1091-255X(99)80079-1.
32. Bell RC, Hanna P, Mills MR, Bowrey D. Patterns of success and failure with laparoscopic Toupet fundoplication. Surg Endosc 1999;13:1189–1194. doi:10.1007/PL00009618.
33. DeMeester TR, Peters JH. Errors and dangers of laparoscopic antireflux surgery. Chirurg 1993;64:230–236.
34. Freys SM, Fuchs KH, Heimbucher J, Thiede A. Tailored augmentation of the lower esophageal sphincter in experimental antireflux operations. Surg Endosc 1997;11:1183–1188. doi:10.1007/s004649900565.
35. Hunter JG, Trus TL, Branum GD, Waring JP, Wood WC. A physiologic approach to laparoscopic fundoplication for gastroesophageal reflux disease. Ann Surg 1996;223:673–685. doi:10.1097/00000658-199606000-00006.
36. Lundell L, Abrahamsson H, Ruth M, Rydberg L, Lonroth H, Olbe L. Long-term results of a prospective randomized comparison of total fundic wrap (Nissen–Rossetti) or semifundoplication (Toupet) for gastro-oesophageal reflux. Br J Surg 1996;83:830–835. doi:10.1002/bjs.1800830633.
37. Rydberg L, Ruth M, Abrahamsson H, Lundell L. Tailoring antireflux surgery: A randomized clinical trial. World J Surg 1999;23:612–618. doi:10.1007/PL00012356.
38. Watson DI, de Beaux AC. Complications of laparoscopic antireflux surgery. Surg Endosc 2001;15:344–352. doi:10.1007/s004640000346.
39. Hagedorn C, Lonroth H, Rydberg L, Ruth M, Lundell L. Long-term efficacy of total (Nissen–Rossetti) and posterior partial (Toupet) fundoplication: results of a randomized clinical trial. J Gastrointest Surg 2002;6:540–545. doi:10.1016/S1091-255X(02)00037-9.
40. Wijnhoven BP, Watson DI, Devitt PG, Game PA, Jamieson GG. Laparoscopic Nissen fundoplication with anterior versus posterior hiatal repair: long-term results of a randomized trial. Am J Surg 2008;195:61–65. doi:10.1016/j.amjsurg.2006.12.046.
41. Kamolz T, Bammer T, Wykypiel H Jr, Pasiut M, Pointner R. Quality of life and surgical outcome after laparoscopic Nissen and Toupet fundoplication: one-year follow-up. Endoscopy 2000;32:363–368. doi:10.1055/s-2000-9000.

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DEMEESTER FESTSCHRIFT

Genetics in the Pathogenesis of Esophageal Cancer: Possible Predictive and Prognostic Factors

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Abstract
Introduction Esophageal adenocarcinoma is the most rapidly increasing cancer in Western countries. Like esophageal squamous-cell carcinoma, these tumors are often detected at an advanced stage, requiring a multimodal concept. Despite improvements in detection, surgical resection, and (neo-) adjuvant therapy, the overall survival of esophageal cancer remains lower than other solid tumors. In fact, just 30–40% of the patients with advanced esophageal cancer benefit from a neoadjuvant therapy. Therefore, predictive/prognostic markers are needed to allow tailored multimodality therapy with increased efficacy.
Discussion In recent years, there has been an exponential growth in our understanding of the cellular and molecular events associated with cell cycle regulation, programmed cell death, angiogenesis, and tumor growth. In this review, the classification of Hanahan and Weinberg is used concerning the six essential changes in carcinogenesis, i.e., the six hallmarks of cancer: (1) self-sufficiency in growth signals; (2) insensitivity to antigrowth signals; (3) avoidance of apoptosis; (4) limitless replicative potential; (5) sustained angiogenesis; and (6) tissue invasion and metastasis.
Conclusions According to these six steps, this review provides an update of the most recent data about predictive/prognostic molecular markers in patients with esophageal cancer.

Keywords Esophageal adenocarcinoma · Neoadjuvant therapy · Predictive/prognostic molecular markers

Introduction

Esophageal adenocarcinoma is currently the most rapidly increasing cancer in the USA and Western Europe.[1–3] This type of tumor as well as esophageal squamous-cell carcinoma is frequently detected at an advanced stage, requiring a multimodal concept. Despite improvements in its detection, surgical resection, and (neo-) adjuvant therapy, the overall survival of esophageal cancer remains low.[4–6] Actually, two meta-analyses by Greer et al. and Gebski et al., analyzing randomized trials of neoadjuvant chemotherapy/chemoradiation prior to surgery for patients with esophageal cancer, showed only modest survival advantages.[7,8] Moreover, other authors demonstrated that only patients with a complete pathological response to neoadjuvant therapy seem to have a survival benefit, while patients who do not respond to neoadjuvant therapy appear to have an inferior prognosis compared with patients who undergo only surgery.[9,10] Consequently, there is a great need for prognostic/predictive markers to allow a tailored multimodality approach with increased efficacy.

Over recent years, molecular markers have been identified using innovative, molecular driven technologies to identify predictive and prognostic markers in patients with esophageal cancer undergoing multimodality therapy. In order to further discuss these molecular factors, in this review the classification of Hanahan and Weinberg (Fig. 1) is used concerning the six essential changes in carcinogenesis, i.e. the six hallmarks of cancer: (1) self-sufficiency in

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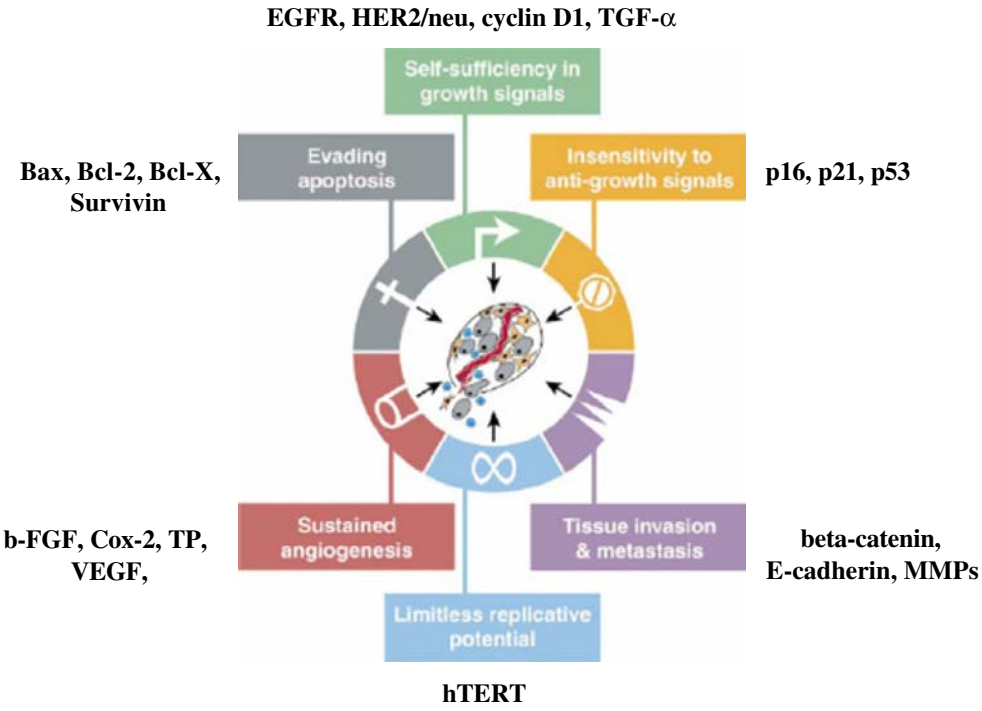

Figure 1 Possible predictive and prognostic factors in esophageal cancer according to the six hallmarks of cancer (modified from Hanahan and Weinberg[11]).

growth signals; (2) insensitivity to antigrowth signals; (3) avoidance of apoptosis; (4) limitless replicative potential; (5) sustained angiogenesis; and (6) tissue invasion and metastasis.[11] According to these six steps, this review provides an update of the most recent data about predictive/prognostic molecular markers in patients with esophageal cancer.

Self-Sufficiency in Growth Signals

Cancer cells can free themselves from dependence on exogenous growth signals by producing their own growth factors or by altering the growth-factor receptors and their signaling pathways. A number of studies suggest that the human epidermal growth factor receptors 1 and 2 (EGFR/HER2/neu) are important prognostic factors in esophageal cancer.[12–17] Actually, Yacoub et al. demonstrated in 1997 that high intratumoral EGFR protein expression of patients with esophageal cancer was significantly related with poor clinical outcome.[12] Inada et al. showed in esophageal cancer patients a significant correlation between EGFR expression and the depth of tumor invasion, the number of lymph node metastases, and survival rate.[13] Other studies from Gibson et al. and Wilkinson et al. confirmed these results.[14,15] Consequently, these data have clinical significance allowing us to use novel targeted therapies in esophageal cancer. A recent clinical trial with cetuximab, an anti-EGFR targeting drug, in combination with common antitumoral therapies has shown promise and should be evaluated in further studies.[16] HER2/neu seems also to have prognostic impact in esophageal cancer as shown by Polkowski et al.[17] They analyzed the prognostic value of HER2/neu in 41 patients with gastroesophageal junction tumors and revealed that HER2/neu staining was significantly associated with the stage of disease. In addition, Brien et al. demonstrated that HER-2/neu gene amplification, determined by fluorescence in situ hybridization, correlates with shortened survival and independently predicts poor outcome in patients with Barrett's adenocarcioma.[18] The transforming growth factor-α (TGF-α), which also belongs to the family of growth factors, appears to have also prognostic value in esophageal cancer. Aloia et al. demonstrated in esophageal cancer patients that a low intratumoral protein expression of TGF-α was significantly related to cancer-specific death and negative clinical outcome.[19]

Moreover, growth factor receptors seem also to be predictive factors in patients with esophageal cancer. Miyazono et al. assessed the potential of quantitative EGFR and HER2/neu mRNA expression in patients with esophageal cancer to predict histopathologic response to neoadjuvant radiochemotherapy followed by surgical resection.[20] The authors showed that low intratumoral expression levels of HER2/neu were significantly associated with better histopathologic response to neoadjuvant therapy compared with high HER2/neu expression levels, while EGFR did not predict the degree of histopathologic response to neoadjuvant radiochemotherapy. Similar findings were shown by Akamatsu et al. analyzing the significance of HER2/neu protein expression as a predictive factor in the neoadjuvant therapy of patients with esopha-

geal squamous cell carcinoma.[21] Patients that did respond to the preoperative therapy had a significantly lower intratumoral protein HER2/neu expression compared with patients that were nonresponders.

Other mechanisms in which malignant tumors acquire self-sufficiency are mediated by the production of cell cycle regulators, like cyclin D1. Kuwahara et al. demonstrated that cyclin D1-negative patients with esophageal cancer had a longer survival rate compared with patients having a cylin D1-positive staining.[22] Others also reported high intratumoral cyclin D1 protein expression to be a poor prognostic factor of esophageal squamous cell carcinomas.[23]

Insensitivity to Antigrowth Signals

The most important mechanism by which tumor cells become insensitive to antigrowth signals is the inactivation of tumor-suppressor genes. This antiproliferative event can occur through different mechanisms, including mutation, loss of heterozygosity, or promoter hypermethylation. Ikeda et al. demonstrated in patients with esophageal squamous cell carcinoma undergoing surgical therapy that the intratumoral protein expression of the tumor-suppressor gene p53 was an independent prognostic factor.[24] Patients with a negative staining of p53 had a significantly longer overall survival than patients with high p53 protein expression. Sturm et al. investigated the prognostic value of the tumor suppressor genes p16 and p53 in 53 patients with curative resected esophageal squamous cell carcinoma and revealed that high expression levels of p16 were significantly associated with longer survival.[25] Finally, a study by Brock et al. assessed aberrant methylation patterns in esophageal adenocarcinoma patients and found a strong trend towards shorter survival for patients whose primary tumors were methylated for p16.[26]

Tumor-suppressor genes appear to also have predictive value in patients with esophageal cancer. Shimada et al. revealed in a study with 59 esophageal cancer patients who received neoadjuvant therapy followed by esophagectomy that positive p53 staining in the pretherapeutic biopsies was associated with minor histopathologic response to chemotherapy.[27] In a study by Nakashima et al. about patients with esophageal squamous cell carcinoma, the correlation between intratumoral p21 and p53 protein expression and response to preoperative chemotherapy was investigated.[28] The authors showed that positive staining of p21 in the absence of p53 is associated with histological response to preoperative chemotherapy. In addition, Sohda et al. demonstrated that combined analysis of protein expression of p21 and p53 is a useful marker of sensitivity to response to preoperative radiochemotherapy in patients with esophageal cancer.[29]

Avoidance of Apoptosis

The capability of tumors to expand is determined not only by the rate of cell proliferation but also by the rate of cell attrition. Apoptosis (programmed cell death) represents the major source of this attrition. Important regulators of apoptosis are the members of the Bcl-2 family, including Bax, Bcl-2, and Bcl-X.[30–32] In a study by Takayama et al., analyzing the intratumoral protein expression levels of Bcl-2 and Bcl-X in 86 patients with esophageal cancer, a significant correlation of these two factors with different histopathological markers was found.[30] In addition, multivariate analysis revealed high Bcl-X expression to be an independent negative prognostic factor. Raouf et al. demonstrated in 48 patients with Barrett's adenocarcinoma receiving preoperative radiochemotherapy followed by esophagectomy that the intratumoral Bcl-2 expression was significantly associated with survival but not with response to neoadjuvant radiochemotherapy.[31] Finally, Ikeguchi et al. investigated the prognostic value of Bax protein expression in 141 esophageal cancer patients with or without adjuvant radiochemotherapy.[32] High intratumoral Bax expression correlated with favorable prognosis in patients receiving postoperative treatment.

Recent studies suggest that a member of the inhibitor of apoptosis protein gene family, survivin, is a useful predictive factor in the neoadjuvant therapy of esophageal cancer. Kato et al. analyzed the intratumoral survivin gene expression in 51 patients with esophageal cancer and revealed in patients with partial response to neoadjuvant chemotherapy a significantly lower survivin expression than in patients having no response.[33] Interestingly, a recent study of our working group demonstrated that intratumoral survivin protein expression was significantly down-regulated during neoadjuvant therapy of esophageal cancers, and elevated survivin levels after preoperative therapy were significantly associated with a minor histopathologic response and prognosis.[34] These data suggest that failure in down-regulation of intratumoral survivin expression following neoadjuvant chemoradiation in esophageal cancer needs therapeutic strategies to reduce survivin expression or block survivin mediated pathways to increase the histopathologic response rate and prognosis.

Limitless Replicative Potential

Malignant cells must destabilize the intrinsic mechanisms that limit the proliferative capacity of normal cells to become deathless. Malignant tumors achieve this subversion mainly due to the stabilization of telomere length via the overexpression of telomerase. Actually, quite a few studies have shown that there is a stepwise increase in the

expression of the telomerase reverse transcriptase catalytic subunit (hTERT) in the pathogenesis of esophageal adenocarcinoma, but there are no studies available showing a prognostic value of hTERT in esophageal cancer.[35,36]

Sustained Angiogenesis

Sustained angiogenesis is essential for the development, progression, and metastasis of malignant tumors. Evidence suggests that angiogenetic factors, like cyclooxygenase-2 (Cox-2), basic fibroblast growth factor (b-FGF), and vascular endothelial growth factor (VEGF), are potential prognostic factors in esophageal cancer patients. Of these three factors, VEGF seems to be the most important player in angiogenesis.[37] In a recent publication by Kleespies et al., four studies were presented showing high intratumoral protein expression of VEGF to be an independent negative prognostic factor in esophageal squamous cell cancer.[38] On the other hand, studies in esophageal adenocarcinoma fail to give prognostic information of VEGF expression patterns.[38]

Cox-2, a rate-limiting enzyme in the conversion of arachidonic acid to prostaglandins, has been shown to sequentially increase in the metaplastic–dysplastic sequence leading to esophageal adenocarcinoma.[37] Furthermore, Kuo et al. demonstrated in 96 patients with squamous cell carcinoma of the esophagus undergoing surgical therapy that intratumoral Cox-2 overexpression was significantly correlated with fewer metastases and less advanced tumor stage.[39] Finally, Takatori et al. revealed in 228 patients with esophageal cancer that Cox-2 overexpression was significantly correlated with depth of tumor invasion, disease stage, and survival.[40]

Another angiogenetic factor, b-FGF, was also reported to have prognostic impact in esophageal caner: in 79 patients with this malignant disease, Han et al. demonstrated intratumoral protein expression to be significantly correlated to a greater depth of tumor invasion, more lymph-node metastasis, and a higher tumor–node–metastases stage.[41] Similar findings were described by Barclay et al. showing that overexpression of b-FGF is associated with tumor recurrence and reduced survival after surgical therapy for esophageal cancer.[42]

Some angiogenetic factors seem also to be important predictive markers in the neoadjuvant therapy of esophageal cancer. In fact, in a study with 56 esophageal cancer patients that received preoperative radiochemotherapy, Imdahl et al. demonstrated VEGF protein expression to be significantly correlated with response to preoperative therapy: patients with a complete response showed a significantly lower intratumoral VEGF expression compared with patients with partial or no response.[43] Besides VEGF, the angiogenetic factor thymidine phosphorylase (TP) was shown to be a useful predictive marker in the multimodality treatment of esophageal cancer. Shimada et al. investigated the ability to predict response to radiochemotherapy in patients with esophageal squamous-cell cancer with intratumoral protein expression levels of TP and VEGF in pretreatment tumor biopsies.[44] They revealed that partial response is negatively associated with intratumoral TP and VEGF protein expression. Kulke et al. investigated whether Cox-2 and VEGF protein expression levels are associated with histopathologic response and overall survival in 46 patients with esophageal cancer receiving neoadjuvant radiochemotherapy followed by surgical resection.[45] In patients with squamous cell carcinoma, low Cox-2 expression correlated significantly with histopathologic response. These findings were confirmed by Xi et al. showing high Cox-2 protein expression to be significantly associated with minor response to neoadjuvant therapy and poor prognosis in patients with esophageal cancer.[46]

Invasion and Metastasis

Abnormalities in cell–cell adhesion molecules, such as the cadherin glycoproteins, play an important role in the mechanisms whereby cancer cells become invasive and metastasize. The prognostic impact of these cell–cell adhesion molecules in esophageal cancer was assessed by Krishnadath et al. in 65 esophageal adenocarcinomas analyzing the intratumoral expression of E-cadherin and alpha- and beta-catenin.[47] They demonstrated that the protein amount of E-cadherin and beta-catenin were significant prognosticators for survival independent of disease stage.

Another parameter of the invasive and metastatic capability involves extracellular proteases, which can destroy the surroundings of the tumor cell. In fact, matrix metalloproteinases and their inhibitors have been reported to have close associations with tumor invasion and metastasis. A study by Murray et al. investigated the presence of matrix metalloproteinase-1 (MMP-1), matrix metalloproteinase-2, and matrix metalloproteinase-9 (MMP-9) in esophageal cancer by immunohistochemistry and revealed that the presence of MMP-1 was associated with a particularly poor prognosis and was an independent prognostic factor.[48] Sharma et al. were able to show in a study with 65 esophageal squamous cell carcinoma patients undergoing surgical therapy that high intratumoral protein expression of matrix metalloproteinase-11 and low expression of tissue inhibitor of matrix metalloproteinase 2 correlated significantly with shorter disease-free survival.[49] Finally, Tanioka et al. studied the correlation of matrix metalloproteinase-7 (MMP-7) and MMP-9 protein expres-

sion with clinicopathologic factors and prognosis in 55 patients with esophageal carcinomas.[50] They demonstrated that high MMP-7 expression was significantly correlated with the presence of nodal metastasis, and high MMP-9 expression was significantly correlated with the depth of tumor invasion, lymphatic permeation, nodal metastasis, and pathologic differentiation grade.

Conclusion

In recent years, a great number of molecular markers have been identified in the pathogenesis of esophageal cancer which could be used as potential predictive and prognostic markers. These markers are mainly involved in the six hallmarks of cancer: (1) self-sufficiency in growth signals; (2) insensitivity to antigrowth signals; (3) avoidance of apoptosis; (4) limitless replicative potential; (5) sustained angiogenesis; and (6) tissue invasion and metastasis. However, the current results are mainly generated retrospectively, so that prospective studies are needed to validate and confirm those markers. Finally, the major goal in the multimodality treatment of esophageal cancer could be achieved: an individualized therapy for every single patient with the most optimal benefit.

References

1. Jemal A, Siegel R, Ward E et al. Cancer statistics, 2007. CA Cancer J Clin. 2007;57:43–66. doi:10.3322/canjclin.57.1.43.
2. Wei JT, Shaheen N. The changing epidemiology of esophageal adenocarcinoma. Semin Gastrointest Dis. 2003;14:112–127.
3. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst. 2005;97:142–146.
4. Ando N, Ozawa S, Kitagawa Y et al. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann Surg. 2000;232:225–232. doi:10.1097/00000658-200008000-00013.
5. Whooley BP, Law S, Murthy SC et al. Analysis of reduced death and complication rates after esophageal resection. Ann Surg. 2001;233:338–344. doi:10.1097/00000658-200103000-00006.
6. Refaely Y, Krasna MJ. Multimodality therapy for esophageal cancer. Surg Clin North Am. 2002;82:729–746. doi:10.1016/S0039-6109(02)00029-4.
7. Gebski V, Burmeister B, Smithers BM et al. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. Lancet Oncol. 2007;8:226–234. doi:10.1016/S1470-2045(07)70039-6.
8. Greer SE, Goodney PP, Sutton JE et al. Neoadjuvant chemoradiotherapy for esophageal carcinoma: a meta-analysis. Surgery. 2005;137:172–177. doi:10.1016/j.surg.2004.06.033.
9. Zacherl J, Sendler A, Stein HJ et al. Current status of neoadjuvant therapy for adenocarcinoma of the distal esophagus. World J Surg. 2003;27:1067–1074.
10. Brucher BL, Stein HJ, Zimmermann F et al. Responders benefit from neoadjuvant radiochemotherapy in esophageal squamous cell carcinoma: results of a prospective phase-II trial. Eur J Surg Oncol. 2004;30:963–971.
11. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell. 2000;100:57–70. doi:10.1016/S0092-8674(00)81683-9.
12. Yacoub L, Goldman H, Odze RD. Transforming growth factor-alpha, epidermal growth factor receptor, and MiB-1 expression in Barrett's-associated neoplasia: correlation with prognosis. Mod Pathol. 1997;10:105–112.
13. Inada S, Koto T, Futami K et al. Evaluation of malignancy and the prognosis of esophageal cancer based on an immunohistochemical study (p53, E-cadherin, epidermal growth factor receptor). Surg Today. 1999;29:493–503. doi:10.1007/BF02482343.
14. Wilkinson NW, Black JD, Roukhadze E et al. Epidermal growth factor receptor expression correlates with histologic grade in resected esophageal adenocarcinoma. J Gastrointest Surg. 2004;8:448–453. doi:10.1016/j.gassur.2004.01.006.
15. Gibault L, Metges JP, Conan-Charlet V et al. Diffuse EGFR staining is associated with reduced overall survival in locally advanced oesophageal squamous cell cancer. Br J Cancer. 2005;93:107–115. doi:10.1038/sj.bjc.6602625.
16. Safran H, Suntharalingam M, Dipetrillo T et al. Cetuximab with concurrent chemoradiation for esophagogastric cancer: assessment of toxicity. Int J Radiat Oncol Biol Phys. 2008;70:391–395. doi:10.1016/j.ijrobp.2007.07.2325.
17. Polkowski W, van Sandick JW, Offerhaus GJ et al. Prognostic value of Lauren classification and c-erbB-2 oncogene overexpression in adenocarcinoma of the esophagus and gastroesophageal junction. Ann Surg Oncol. 1999;6:290–297. doi:10.1007/s10434-999-0290-2.
18. Brien TP, Odze RD, Sheehan CE et al. HER-2/neu gene amplification by FISH predicts poor survival in Barrett's esophagus-associated adenocarcinoma. Hum Pathol. 2000;31:35–39. doi:10.1016/S0046-8177(00)80195-1.
19. Aloia TA, Harpole DH Jr, Reed CE et al. Tumor marker expression is predictive of survival in patients with esophageal cancer. Ann Thorac Surg. 2001;72:859–866. doi:10.1016/S0003-4975(01)02838-7.
20. Miyazono F, Metzger R, Warnecke-Eberz U et al. Quantitative c-erbB-2 but not c-erbB-1 mRNA expression is a promising marker to predict minor histopathologic response to neoadjuvant radiochemotherapy in oesophageal cancer. Br J Cancer. 2004;91:666–672.
21. Akamatsu M, Matsumoto T, Oka K et al. c-erbB-2 oncoprotein expression related to chemoradioresistance in esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2003;57:1323–1327. doi:10.1016/S0360-3016(03)00782-X.
22. Kuwahara M, Hirai T, Yoshida K et al. p53, p21(Waf1/Cip1) and cyclin D1 protein expression and prognosis in esophageal cancer. Dis Esophagus. 1999;12:116–119. doi:10.1046/j.1442-2050.1999.00034.x.
23. Itami A, Shimada Y, Watanabe G, Imamura M. Prognostic value of p27(Kip1) and CyclinD1 expression in esophageal cancer. Oncology. 1999;57:311–317. doi:10.1159/000012067.
24. Ikeda G, Isaji S, Chandra B et al. Prognostic significance of biologic factors in squamous cell carcinoma of the esophagus. Cancer. 1999;86:1396–1405. doi:10.1002/(SICI)1097-0142(19991015)86:8<1396::AID-CNCR3>3.0.CO;2-H.
25. Sturm I, Petrowsky H, Volz R et al. Analysis of p53/BAX/p16(ink4a/CDKN2) in esophageal squamous cell carcinoma: high BAX and p16(ink4a/CDKN2) identifies patients with good prognosis. J Clin Oncol. 2001;19:2272–2281.
26. Brock MV, Gou M, Akiyama Y et al. Prognostic importance of promoter hypermethylation of multiple genes in esophageal adenocarcinoma. Clin Cancer Res. 2003;9:2912–2919.
27. Shimada Y, Watanabe G, Yamasaki S et al. Histological response of cisplatin predicts patients' survival in oesophageal cancer and

p53 protein accumulation in pretreatment biopsy is associated with cisplatin sensitivity. Eur J Cancer. 2000;36:987–993. doi:10.1016/S0959-8049(00)00049-6.
28. Nakashima S, Natsugoe S, Matsumoto M et al. Expression of p53 and p21 is useful for the prediction of preoperative chemotherapeutic effects in esophageal carcinoma. Anticancer Res. 2000;20:1933–1937.
29. Sohda M, Ishikawa H, Masuda N et al. Pretreatment evaluation of combined HIF-1alpha, p53 and p21 expression is a useful and sensitive indicator of response to radiation and chemotherapy in esophageal cancer. Int J Cancer. 2004;110:838–844. doi:10.1002/ijc.20215.
30. Takayama T, Nagao M, Sawada H et al. Bcl-X expression in esophageal squamous cell carcinoma: association with tumor progression and prognosis. J Surg Oncol. 2001;78:116–123. doi:10.1002/jso.1130.
31. Raouf AA, Evoy DA, Carton E et al. Loss of Bcl-2 expression in Barrett's dysplasia and adenocarcinoma is associated with tumor progression and worse survival but not with response to neoadjuvant chemoradiation. Dis Esophagus. 2003;16:17–23. doi:10.1046/j.1442-2050.2003.00281.x.
32. Ikeguchi M, Maeta M, Kaibara N. Bax expression as a prognostic marker of postoperative chemoradiotherapy for patients with esophageal cancer. Int J Mol Med. 2001;7:413–417.
33. Kato J, Kuwabara Y, Mitani M et al. Expression of survivin in esophageal cancer: correlation with the prognosis and response to chemotherapy. Int J Cancer. 2001;95:92–95. doi:10.1002/1097-0215(20010320)95:2<92::AID-IJC1016>3.0.CO;2-9.
34. Vallböhmer D, Kuhn E, Warnecke-Eberz U et al. Failure in downregulation of intratumoral survivin expression following neoadjuvant chemoradiation in esophageal cancer. Pharmacogenomics. 2008;9:681–690. doi:10.2217/14622416.9.6.681.
35. Morales CP, Lee EL, Shay JW. In situ hybridization for the detection of telomerase RNA in the progression from Barrett's esophagus to esophageal adenocarcinoma. Cancer. 1998;83:652–659. doi:10.1002/(SICI)1097-0142(19980815)83:4<652::AID-CNCR4>3.0.CO;2-M.
36. Lord RVN, Salonga D, Danenberg KD et al. Telomerase reverse transcriptase expression is increased early in the Barrett's metaplasia, dysplasia, adenocarcinoma sequence. J Gastrointest Surg. 2000;4:135–142. doi:10.1016/S1091-255X(00)80049-9.
37. Vallböhmer D, Peters JH, Kuramochi H, Oh D, Yang D, Shimizu D, DeMeester SR, Hagen JA, Chandrasoma PT, Danenberg KD, Danenberg PV, DeMeester TR. Molecular determinants in targeted therapy for esophageal adenocarcinoma. Arch Surg. 2006;141:476–481. doi:10.1001/archsurg.141.5.476.
38. Kleespies A, Guba M, Jauch KW, Bruns CJ. Vascular endothelial growth factor in esophageal cancer. J Surg Oncol. 2004;87:95–104. doi:10.1002/jso.20070.
39. Kuo KT, Chow KC, Wu YC. Clinicopathologic significance of cyclooxygenase-2 overexpression in esophageal squamous cell carcinoma. Ann Thorac Surg. 2003;76:909–914. doi:10.1016/S0003-4975(03)00717-3.
40. Takatori H, Natsugoe S, Okumura H et al. Cyclooxygenase-2 expression is related to prognosis in patients with esophageal squamous cell carcinoma. Eur J Surg Oncol. 2008;34:397–402. doi:10.1016/j.ejso.2007.04.011.
41. Han B, Liu J, Ma MJ, Zhao L. Clinicopathological significance of heparanase and basic fibroblast growth factor expression in human esophageal cancer. World J Gastroenterol. 2005;11:2188–2192.
42. Barclay C, Li AW, Geldenhuys L et al. Basic fibroblast growth factor (FGF-2) overexpression is a risk factor for esophageal cancer recurrence and reduced survival, which is ameliorated by coexpression of the FGF-2 antisense gene. Clin Cancer Res. 2005;11:7683–7691. doi:10.1158/1078-0432.CCR-05-0771.
43. Imdahl A, Bognar G, Schulte-Monting J, Schoffel U, Farthmann EH, Ihling C. Predictive factors for response to neoadjuvant therapy in patients with oesophageal cancer. Eur J Cardiothorac Surg. 2002;21:657–663. doi:10.1016/S1010-7940(02)00044-1.
44. Shimada H, Hoshino T, Okazumi S et al. Expression of angiogenic factors predicts response to chemoradiotherapy and prognosis of oesophageal squamous cell carcinoma. Br J Cancer. 2002;86:552–557. doi:10.1038/sj.bjc.6600129.
45. Kulke MH, Odze RD, Mueller JD, Wang H, Redston M, Bertagnolli MM. Prognostic significance of vascular endothelial growth factor and cyclooxygenase 2 expression in patients receiving preoperative chemoradiation for esophageal cancer. J Thorac Cardiovasc Surg. 2004;127:1579–1586. doi:10.1016/j.jtcvs.2003.12.034.
46. Xi H, Baldus SE, Warnecke-Eberz U et al. High cyclooxygenase-2 expression following neoadjuvant radiochemotherapy is associated with minor histopathologic response and poor prognosis in esophageal cancer. Clin Cancer Res. 2005;11:8341–8347. doi:10.1158/1078-0432.CCR-04-2373.
47. Krishnadath KK, Tilanus HW, van BM et al. Reduced expression of the cadherin-catenin complex in oesophageal adenocarcinoma correlates with poor prognosis. J Pathol. 1997;182:331–338. doi:10.1002/(SICI)1096-9896(199707)182:3<331::AID-PATH860>3.0.CO;2-D.
48. Murray GI, Duncan ME, O_Neil P et al. Matrix metalloproteinase-1 is associated with poor prognosis in oesophageal cancer. J Pathol. 1998;185:256–261. doi:10.1002/(SICI)1096-9896(199807)185:3<256::AID-PATH115>3.0.CO;2-A.
49. Sharma R, Chattopadhyay TK, Mathur M, Ralhan R. Prognostic significance of stromelysin-3 and tissue inhibitor of matrix metalloproteinase-2 in esophageal cancer. Oncology. 2004;67:300–309. doi:10.1159/000081331.
50. Tanioka Y, Yoshida T, Yagawa T et al. Matrix metalloproteinase-7 and matrix metalloproteinase-9 are associated with unfavourable prognosis in superficial oesophageal cancer. Br J Cancer. 2003;89:2116–2121. doi:10.1038/sj.bjc.6601372.

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The Molecular Pathogenesis of Barrett's Esophagus: Common Signaling Pathways in Embryogenesis Metaplasia and Neoplasia

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Abstract Although Barrett's esophagus has been recognized for over 50 years, the cellular and molecular mechanisms leading to the replacement of squamous esophageal epithelium with a columnar type are largely unknown. Barrett's is known to be an acquired process secondary to chronic gastroesophageal reflux disease and occurs in the presence of severe disruption of the gastroesophageal barrier and reflux of a mixture of gastric and duodenal content. Current hypothesis suggest that epithelial change occurs due to stimulation of esophageal stem cells present in the basal layers of the epithelium or submucosal glands, toward a columnar epithelial differentiation pathway. The transcription factor CDX2 seems to play a key role in promoting the cellular biology necessary for columnar differentiation, and can be induced by bile salt and acid stimulation. Several cellular signaling pathways responsible for modulation of intestinal differentiation have also been identified and include WNT, Notch, BMP, Sonic HH and TGFB. These also have been shown to respond to stimulation by bile acids, acid or both and may influence CDX2 expression. Their relative activity within the stem cell population is almost certainly responsible for the development of the esophageal columnar epithelial phenotype we know as Barrett's esophagus.

Keywords Barrett's esophagus · Metaplasia · Neoplasia

Evolution of Our Understanding of the Pathogenesis of Barrett's Esophagus

Norman Barrett[1] described the condition which bears his name in 1950. He believed that he was observing a congenitally short esophagus and an intrathoracic stomach.[2] In fact, Barrett erroneously wrote in 1950, that the sections of the gastrointestinal tract are defined by their mucosa, and therefore the esophagus is "that part of the foregut distal to the cricopharyngeal sphincter which is lined by squamous epithelium".[1] Philip Allison, in 1953, by carefully examining seven esophagectomy specimens identified that it was actually the tubular esophagus lined with columnar epithelium.[3] Hayward expanded the concepts of the epithelium at the gastroesophageal junction in a report, largely without supporting data, hypothesizing that the lower 1–2 cm of the esophagus is normally lined by a mucus-secreting columnar epithelium that has the ability to resist acid-peptic digestion.[4] He suggested that this mucosa is present to prevent squamous epithelial digestion at the junction, to provide a buffer between squamous epithelium and acid-pepsin producing fundic mucosa.

Although well recognized by the 1960s, the pathogenesis of the columnar lined esophagus and whether it was congenital or acquired remained unclear. A seminal animal study published by Bremner et al. in 1970 concluded correctly that it was likely an acquired condition although incorrectly that it occurred via "growth" of gastric mucosa into the esophagus. He commented that "the squamous epithelium destroyed by gastroesophageal reflux is replaced, through creeping substitution, by columnar cells of gastric or junctional origin".[5] Subsequent studies have left little question that Barrett's esophagus may develop following healing of damaged esophageal epithelium. Hanna et al. prospectively followed a cohort of 172 patients with baseline erosive esophagitis in an effort to ascertain the proportion with Barrett's esophagus detected upon re-

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endoscopy 8–12 weeks later.[6] Twelve percent of those with baseline erosive disease but no Barrett's initially had histologically confirmed Barrett's with intestinal metaplasia at re-endoscopy. Throughout the 1980s and early 1990s Barrett's esophagus was defined by the presence of greater than 3 cm of columnar lined esophagus containing intestinal metaplasia (IM) on histology. Further refinement came in the late 1990s when short segment Barrett's was identified redefining Barrett's as any esophageal columnar lining containing IM.

As the understanding of stem cell biology unfolded in the late 1990s and early 2000s the possibility that Barrett's esophagus developed via a stem cell response and its subsequent altered differentiation into the epithelial phenotype we recognize as Barrett's emerged. Whether this was true or not, and how it might occur, remained unclear. Two possible mechanisms have been identified and supporting studies published; (1) seeding of site of epithelial injury with bone marrow stem cells and their subsequent columnar differentiation and (2) a pathologic response of stem cells present in the basal layer of the esophageal squamous epithelium and/or submucosal ducts. The bone marrow stem cell hypothesis is supported by the fascinating observation, published in 2002, of epithelial cells of donor origin (male) in the mucosa of the gastroesophageal junction of a female patient following bone marrow transplantation.[7] This provides proof of principle that bone marrow derived stem cells may populate the esophageal epithelium, although does not prove that it is the predominant mechanisms of clinical Barrett's esophagus. Serosi and Spechler provided experimental support of this concept showing that bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus.[8] They concluded that "our study suggests the fascinating possibility that there may be circulating stem cells that hone in on areas if injury to repair damaged tissue and that the progenitor cell for Barrett's may be a circulating stem cell".

Although stem cells of the esophagus and other portion of the GI tract have not been conclusively isolated, considerable evidence suggests that the basal layer of esophageal epithelium contain pluripotent cells that give rise to progressively differentiated cells capable of repopulating the epithelium on a regular basis (Fig. 1).[9] The characteristics which define esophageal stem cells are slowly emerging and definitive identification and tissue culture may be on the horizon.[10] Evidence also suggests that, given the relatively superficial location of the stem cell compartment along with the epithelial erosion known to occur secondary to gastroesophageal reflux, esophageal stem cells are likely exposed to luminal contents. The current prevailing hypothesis is that;

> Barrett's esophagus occurs via abnormal differentiation of esophageal epithelial stem cells exposed to gastric juice by the chronic epithelial erosion and injury of gastroesophageal reflux disease.

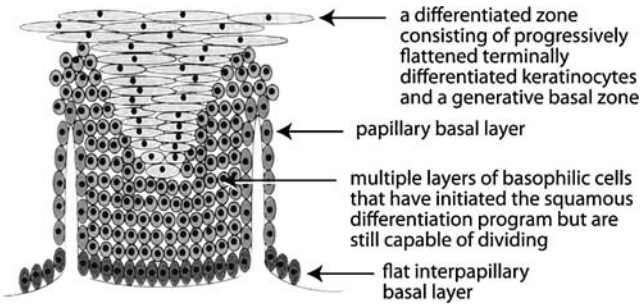

Figure 1 Schematic representation of the esophageal epithelium (from Seery,[9] Fig. 1).

The Emergence of a Key Transcription Factor

In the mid 1990s, Shu and colleagues at the University of Pennsylvania identified the transcription factor CDX2, a member of the caudal family of homeodomain genes known to function in early developmental events in *Drosophila*, as a fundamental component of both the establishment and maintenance of the intestinal cellular phenotype.[11,12] CDX2 has been shown to be an important transcriptional regulator of embryonic differentiation and maintenance of normal adult small intestine and colonic epithelium.[13,14] CDX2 is specifically expressed in the small and large intestines, and has been shown to activate other intestinal differentiation genes including MUC2.[15,16] CDX2 is not expressed in normal esophageal mucosa but is abundantly re-expressed in intestinal metaplastic mucosa in the esophagus (i.e., Barrett's esophagus).[17,18]

Immunohistochemical staining studies have recently confirmed that CDX2 protein is overexpressed in human Barrett's epithelium.[19] Knock-out mice homozygous for the absence of CDX2 die in utero although those that are heterozygotes develop colonic polyps which show squamous differentiation.[20] These observations suggest that CdX-2 may be critical in the gastrointestinal tract to maintain columnar epithelium. Gene transfection studies have shown that inducing CDX2 expression in mouse gastric mucosa can induce the transformation of gastric mucosa into an intestinal mucosa phenotype (i.e., intestinal metaplasia).[21] Animal studies have further suggested that gastroesophageal reflux may enhance CDX2 expression in rat esophageal keratinocytes.[22]

Studies of CDX2 gene expression in human esophageal biopsy specimens reveal an increase at each step in the development of Barrett's esophagus.[23] Laser capture micro-

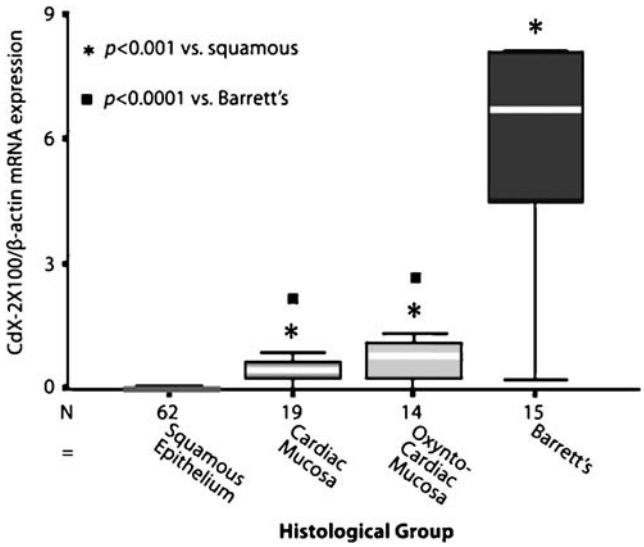

Figure 2 Relative Cdx-2 mRNA in the different histological groups. The *boxes* show the 25th and 75th percentile (interquartile) ranges. Median values are shown as a *horizontal bar* in each box. The *whiskers* show levels outside the 25th and 75th percentile (from Vallbohmer et al.,[23] Fig. 2).

dissected biopsies obtained at the gastroesophageal junction in patients with symptoms of GERD including normal squamous mucosa, cardiac mucosa, oxynto-cardiac mucosa, intestinal metaplasia, and duodenum revealed increasing levels of CDX2 mRNA. After expression levels of CdX-2 were measured in each tissue type by quantitative RT-PCR. Consistent with its known function, CdX-2 gene expression levels were highest in duodenal mucosa and nearly absent in squamous epithelium. There was a stepwise increase in CdX-2 gene expression from cardiac to Barrett's epithelium (Fig. 2). Expression levels of cardiac and oxynto-cardiac mucosa were 40–70 times higher and Barrett's mucosa 400 times higher than that of squamous epithelium.

Until recently, it seemed unlikely that a single transcription factor may be responsible for a change as dramatic as that of Barrett's esophagus. While other factors may be involved (see below), recent studies in which pluripotent cells functionally identical to embryonic stem cells were produced via transfection of only four key transcription factors makes such a hypothesis considerably more plausible.[24] Thus an experimental focus on CDX2 and other key transcription factors known to effect intestinal differentiation may improve our understanding of the pathogenesis of Barrett's epithelium.

The Abundant Evidence for a Role of Bile Salts in Barrett's Pathogenesis

Bile salts, or more accurately, duodenal content, have been implicated in the pathophysiology of esophageal mucosal injury for decades. Risk factors for the development of Barrett's esophagus have been extensively studied and include a long-standing history of reflux symptoms (>5 years),[25] a hiatal hernia which is usually large,[26] a defective lower esophageal sphincter and profound reflux of gastric juice into the lower esophagus.[27] Patients who reflux not only gastric acid, but also components of duodenal juice have a markedly higher prevalence of Barrett's metaplastic changes.[28] The latter was first shown in the 1970s as studies using 24-h ambulatory pH monitoring showed a higher prevalence of "alkaline" reflux in patients with esophagitis and Barrett's esophagus.[29] In a study of esophageal acid and bilirubin exposure in patients with and without intestinal metaplasia in a short segment of esophageal columnar lining, abnormal esophageal bilirubin exposure, and duration of symptoms were the only two determinants significantly associated with the presence of intestinal metaplasia.[30] These early observations were confirmed by ambulatory spectrophotometric monitoring of esophageal bilirubin exposure and esophageal aspiration studies, both of which showed a high esophageal exposure to duodenal content and bile salts particularly in patients with Barrett's epithelium.

Using prolonged ambulatory aspiration techniques directly measuring luminal bile salts, patients with gastroesophageal reflux disease have greater and more concentrated bile acid exposure to the esophageal mucosa than normal subjects.[31] This increased exposure occurs most commonly during the supine period while asleep, and during the upright period following meals. Chemical analysis identified the glycine conjugates of cholic acid, deoxycolic, and chenodeoxycholic acids as the predominant bile acids aspirated from the esophagus of patients with GERD, although appreciable amounts of taurine conjugates of these bile acids can also be found (Fig. 3). Other bile slats were identified but in small concentrations. The bile acid concentration (μmol/lit) aspirated from the esophagus in patients was appreciable often exceeding 100 μm/lit over a single 24-h time period (Fig. 4).

Finally, numerous other studies have shown significant effects of bile salts and other components of gastroesophageal reflux on cellular physiology, including activation of protein kinase C and nuclear transcription factors.[32–34] These findings, in concert with the strong link between gastroesophageal-reflux disease and esophageal adenocarcinoma suggests that bile salts play a role in the pathophysiology of Barrett's metaplasia and esophageal adenocarcinoma.

The Molecular Pathogenesis of Barrett's; Investigations Linking Bile Salts to CDX2 Expression and Intracellular Signaling

Interest has recently been focused on signaling pathways known to be active in cellular differentiation during

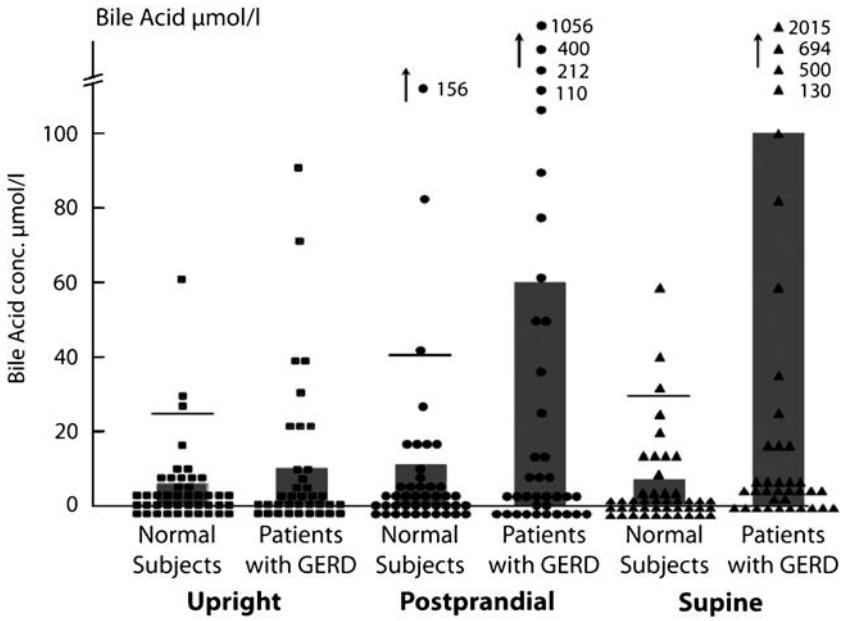

Figure 3 Peak bile acid concentration (µmol/l) for patients and normal subjects during upright, postprandial, and supine aspiration periods. The *shaded area* represents the mean and the *bar* the 95th percentile values. (From Kauer et al.,[31] Fig. 4).

embryonic development, which may also play a role in human disease and cancer.[35] During embryogenesis, the esophagus is lined with a columnar epithelium which later differentiates into a squamous epithelium as the foregut develops. It seems likely that Barrett's esophagus may represent differentiation of the epithelium via signaling mechanisms similar to those active embryologically, pathologically activated in response to injury from exposure to refluxate. The literature suggests that the Wnt, bone morphogenic protein, transforming growth factor-β, hedgehog, notch, NFκB, and epidermal growth factor pathways play an important role in this process.[36,37] The fundamental hypothesis is that intestinal metaplasia of the esophageal epithelium occurs via the activation of genes that play a role in the embryological development of the foregut.

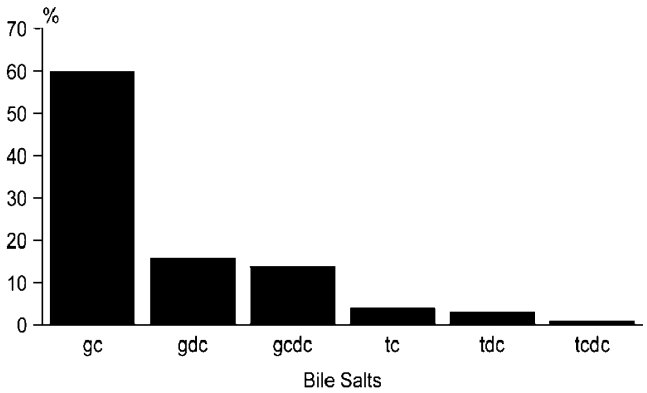

Figure 4 Prevalence of conjugated bile acids in samples with an aspirated volume greater than 3 ml (n=24).*GC* glycocholic acid, *TC* taurocholic acid, *GDC* glycodeoxycholic acid, *TDC* taurodeoxycholic acid, *GCDC* glycochenodeoxycholic acid, *TCDC* taurochenodeoxycholic acid, *GLC* glycolithocholic acid (from Kauer et al.,[31] Fig. 5).

As outlined above the presence of bile acids in the refluxed material has been consistently observed in patients with Barrett's esophagus, strongly suggesting that they are important in its pathogenesis. The exact molecular mechanisms underlying this intestinal metaplastic and/or differentiation process remains largely unknown.

Our initial studies investigated the effect of primary and secondary bile acids on CDX2 mRNA expression in human esophageal cells.[38] Four different human esophageal cell lines: (1) squamous, immortalized by SV40 (Het-1A), (2) adenocarcinoma (SEG-1), and (3) squamous cell carcinoma (HKESC-1 and HKESC-2), were exposed in cell culture for 1–24 h to 100–1,000 µM deoxycholic, chenodeoxycholic, and glycocholic acid. Total RNA was extracted before and after bile acid treatment and CDX2 mRNA expression was determined by quantitative real time and reverse transcription PCR. CDX2 mRNA expression was absent before bile

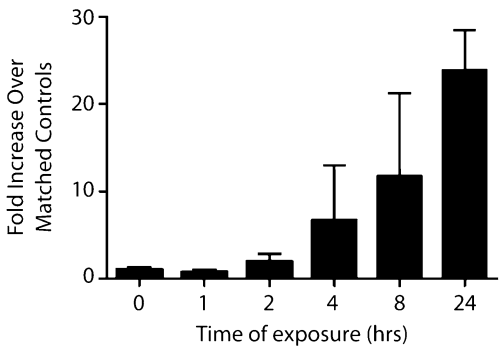

Figure 5 Fold increase over matched controls in CDX2 mRNA by real-time PCR in SEG-1 cells treated with deoxycholic acid, monoclonal antibody 528, and no treatment—all for 24 h (* and ^ denote a statistically significant difference, p<0.05; from Hu et al.,[38] Fig. x).

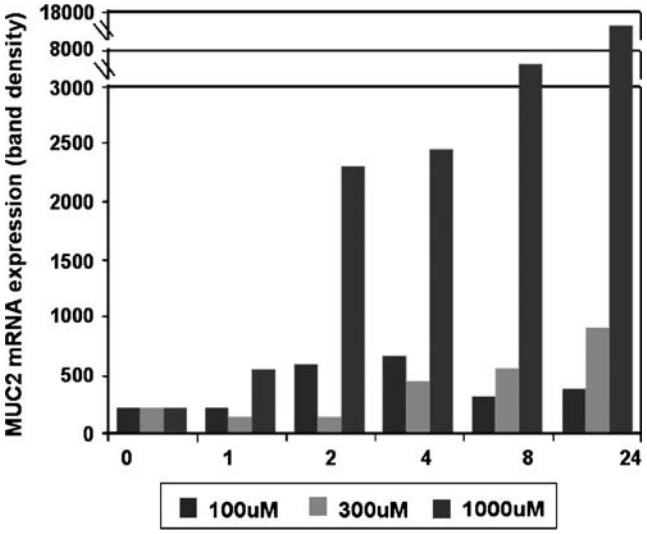

Figure 6 Relative MUC2 gene expression in HET-1A cells following stimulation with 100–300 uM deoxycholic acid. Adapted from Hu et al.,[39] Fig. 4).

acid exposure in all cell lines. CDX2 expression increased in a dose and time dependent fashion with deoxycholic and chenodeoxycholic but not glycocholic acid in all four cell lines (Fig. 5). The maximal induction of CDX2 expression was seen in SEG-1 adenocarcinoma cells. These findings show that secondary bile acid stimulation upregulates CDX2 gene expression in both normal and cancer cell lines and support the role of bile acids in the pathogenesis of Barrett's esophagus.

We next investigated the effect of bile salt stimulation on MUC2 mRNA, a "downstream" gene and protein characteristic of the phenotype of Barrett's epithelium.[39] Goblet cells serve as the histological hallmark identifying Barrett's epithelium microscopically and contain mucin. Ten to 12 mucin genes have been identified, each coding for the protein core of a specific mucin type. Genes coding for the secreted mucins lie in a cluster on chromosome 11.p15.5 and include MUC2, MUC5, and MUC6.[40] MUC glycoproteins are variably expressed along the gastrointestinal tract. MUC1 has been shown to be expressed in intestinal goblet cells and enterocytes, MUC3 in intestinal enterocytes, MUC5 in gastric foveolar and mucous neck cells and MUC 6 in gastric antral and fundic gland epithelium. We chose to study the MUC2 protein as it is secreted from the goblet cells in BE, has been shown to be present in and relatively specific for human Barrett's epithelium, and likely plays an important role in the cytoprotection against reflux of gastroduodenal contents including bile acids. These data show that, even in immortalized normal esophageal squamous cells (Het-1A) and esophageal squamous carcinoma cells (HKESC-1 and 2), deoxycholic acid stimulation can activate MUC2 transcription (Fig. 6). Moreover, MUC2 mRNA upregulation correlated very well with CDX2 upregulation. The simultaneous upregulation of

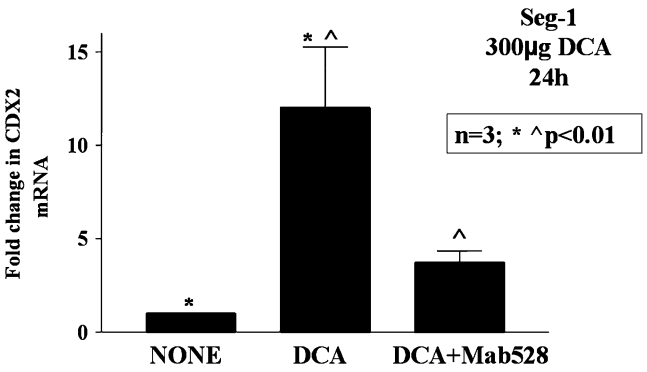

Figure 7 Real-time PCR of relative CDX2 mRNA expression in SEG-1 cells treated with 100 uM DCA at pH 5 or pH 7 with or without Mab528. **a** SEG-1 cells were incubated for up to 24 h at pH 5 or pH 7 with or without 100 uM DCA or **b** for 24 h at pH 5 with or without 100 uM DCA, with or without 5 ug/ml Mab528 (528). Total RNA was isolated from cell lysates, reversed transcribed to cDNA and subjected to real time PCR analysis. Values obtain for control at pH 7 alone were set at 1 for (**a**) and those obtained for control at pH 5 were set at 1 for (**b**). Values are means ± SEM; *p<0.001 compared to all others. n=3–8 (from Avissar,[47] Fig. 5).

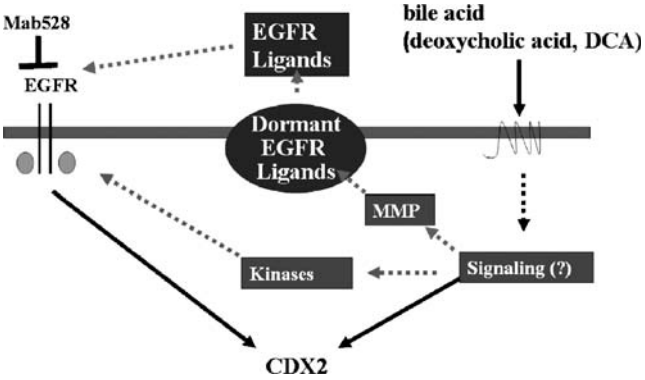

Figure 8 Suggested mechanisms for CDX2 induction by DCA in SEG1 cells. *Broken lines* pathways not directly tested, *solid lines* pathways tested, *red lines* likely do not occur, *blue lines* likely to occur (from Avissar,[47] Fig. 8).

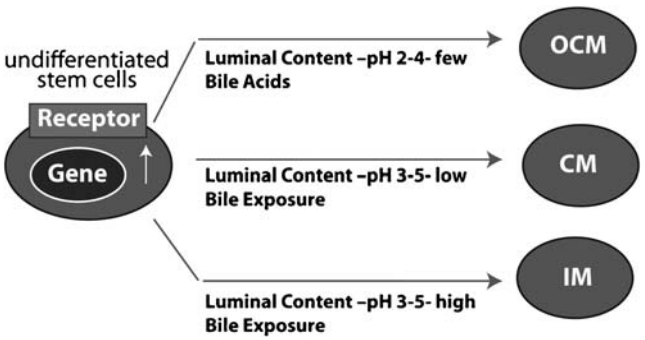

Figure 9 Conceptual schema of stem cell differentiation leading to various esophageal epithelial types.

both CDX2 and MUC2 after DCA exposure in esophageal cells is consistent with previous findings of other groups showing CDX2 is directly involved in the transcriptional regulation of the MUC2 gene in gastric and colon cancer cells.[41,42]

Stimulated by the observation that bile salts activate the epidermal growth factor receptor in colon cancer cell lines,[43] and interested in dissecting out putative signaling pathways in which CDX2 gene may be activated, we next studied the effect of epidermal growth factor receptors (EGFR) activation and blockade on bile salt stimulated CDX2 expression in SEG1 cells. The EGFR are a family of receptor tyrosine kinases including four members, EGFR/ErbB1/HER1, ErbB2/Neu/HER2, ErbB3/HER3, and ErbB4/HER4.[44] All EGFRs have in common an extracellular ligand-binding domain, a single membrane-spanning region, and a cytoplasmic protein tyrosine kinase domain. Activation of EGFRs is controlled by expression of their ligands.[45] The EGFR ligands are members of the EGF-related peptide growth factor family. There are a number of EGFR-specific ligands, each of which contains an EGF-like domain that confers binding specificity. Ligand binding to EGF receptors induces formation of homo- and heterodimers leading to activation of the intrinsic kinase domain and subsequent phosphorylation on specific tyrosine residues within the cytoplasmic tail. EGFR phosphorylation leads to the activation of intracellular pathways, including the mitogen-activated protein kinase and the phosphatidylinositol-3 kinase (PI-3K) pathways both implicated in the molecular pathogenies of Barrett's epithelium.[46]

We exposed human mucosal epithelial cells (SEG-1) for 0 to 24 h with up to 300 μM deoxycholic acid (DCA) at pH 7 or 5 with or without antibodies against the EGFR ligand-binding site (Fig. 7).[47] Acid (pH 5) increased the induction of CDX2 mRNA expression caused by DCA. CDX2 mRNA induction was markedly reduced by EGFR blockade with Mab528. Each treatment (pH 5, DCA or pH 5 plus DCA) activated the EGFR on all tyrosines tested, but in different time courses. Phosphorylation by DCA was inhibited by Mab528 and activation of EGFR by DCA at pH 5 resulted in EGFR degradation, while that by DCA alone did not. These data show that CDX2 induction by DCA with or without an acidic milieu occurs through ligand-dependent transactivation of the EGFR. The later may occur through membrane perturbation induced by bile salts and consequent release of receptor ligands (Fig. 8).[48] The variations in EGFR degradation pattern observed with DCA or DCA at pH 5 indicate that differential transactivation pathways may occur.

Conclusion

Despite the identification of Barrett's epithelium over 50 years ago, few details of its pathogenesis are known. The identification of CDX2 as a key transcriptional regulator and studies dissecting its activation are rapidly evolving, as is our understanding of its potential pathogenesis. Current evidence supports the hypothesis that luminal contents including acid and bile salts trigger signaling cascades in either circulating, epithelial, or submucosal stem cells, toward differentiation into the epithelial phenotype seen at the gastroesophageal junction including the intestinal metaplasia of Barrett's esophagus (Fig. 9). The rapid re-epithelialization with squamous mucosa following circumferential radiofrequency ablation via new technology may provide yet further insights into its biology. Much is yet to be learned of this fascinating and potential lethal disease process.

References

1. Lord RVN. Norman Barrett, "Doyen of esophageal surgery". Ann Surg 1999;229:428–439.
2. Barrett NR. Chronic peptic ulcer of the esophagus and "oesophagitis". Br J Surg 1950;38:175–182.
3. Allison P, Johnstone A. The oesophagus lined with gastric mucous membrane. Thorax 1953;8:87–101.
4. Hayward J. The lower end of the oesophagus. Thorax 1961;16:36–41.
5. Bremner CG, Lynch VP, Ellis H. Barrett's esophagus: congenital or acquired? An experimental study of esophageal mucosal regeneration in the dog. Surgery 1970;68:209–216.
6. Hanna S, Rastogi A, Weston AP, Totta F, Schmitz R, Mathur S, McGregor D, Cherian R, Sharma P. Detection of Barrett's esophagus after endoscopic healing of erosive esophagitis. Am J Gastroenterol 2006;101:1416–1420.
7. Körbling M, Katz RL, Khanna A, Ruifrok AC, Rondon G, Albitar A, Champlin RE, Estrov Z. Hepatocytes and epithelial cells of donor origin in recipients of peripheral-blood stem cells. N Engl J Med 2002;346:738–746.
8. Sarosi G, Brown G, Jaiswal K, Feagins LA, Lee E, Crook TW, Souza RF, Zou YS, Shay JW, Spechler SJ. Bone marrow progenitor cells contribute to esophageal regeneration and metaplasia in a rat model of Barrett's esophagus. Dis Esoph 2008;21:43–50.
9. Seery JP. Stem cells of the esophageal epithelium. J Cell Sci 2002;115:1783–1789.
10. Croagh D, Phillips WA, Redvers R, Thomas RJS, Kaur P. Identification of candidate murine esophageal stem cells using a combination of cell kinetic and cell surface markers. Stem Cells 2007;25:313–318.
11. Suh E, Chen L, Taylor J, Traber PG. A homeodomain protein realted to caudal regulates intestine specific gene transcription. Mol Cell Biol 1994;14:7340–7351.
12. Suh E, Traber PG. Am intestine-specific homeobox gene regulates proliferation and differentiation. Mol Cell Biol 1996;16:619–625.

13. Lorentz O, Duluc I, Arcangelis AD, Simon-Assmann P, Kedinger M, Freund J-N. Key role of the Cdx2 homeobox gene in extracellular matrix-mediated intestinal cell differentiation. J Cell Biol 1997;139(6):1553–1565.
14. Guo RJ, Suh ER, Lynch JP. The role of Cdx proteins in intestinal development and cancer. Cancer Biol Ther 2004;3:593–601.
15. Steininger H, Pfofe DA, Muller H, Haag-Sunjic G, Fratianu V. Expression of CDX2 and MUC2 in Barrett's mucosa. Pathol Res Pract 2005;201(8–9):573–577.
16. Uesaka T, Kageyama N, Watanabe H. Identifying target genes regulated downstream of CDX2 by microarray analysis. J Mol Biol 2004;337:647–660.
17. Groisman GM, Amar M, Meir A. Expression of the intestinal marker Cdx2 in the columnar-lined esophagus with and without intestinal (Barrett's) metaplasia. Mod Pathol 2004;17(10):1282–1288.
18. Phillips RW, Frierson HF Jr, Moskaluk CA. Cdx2 as a marker of epithelial intestinal differentiation in the esophagus. Am J Surg Pathol 2003;27:1442–1447.
19. Moons LMG, Bax DA, Kuipers EJ, et al. The homeodomain protein CDX2 is an early marker of Barrett's oesophagus. J Clin Pathol 2004;57(10):1063–1068.
20. Tamai Y, Nakajima R, Ishikawa T, Takaku K, Seldin MF, Taketo MM. Colonic hamartoma development by anomalous duplication in Cdx2 knockout mice. Cancer Res 1999;59:2965–2970.
21. Silberg DG, Sullivan J, Kang E, et al. Cdx2 ectopic expression induces gastric intestinal metaplasia in transgenic mice. Gastroenterology 2002;122(3):689–696.
22. Kazumori H, Ishihara S, Rumi MAK, Kadowaki Y, Kinoshita Y. Bile acids directly augment caudal related homeobox gene Cdx2 expression in oesophageal keratinocytes in Barrett's epithelium. Gut 2006;55:16–25. doi:10.1136/gut.2005.066209.
23. Vallbohmer D, DeMeester SR, Peters JH, Oh DS, Kuramochi H, Shimizu D, Hagen JA, Danenberg KD, Danenberg PV, DeMeester TR, Chandrasoma PT. Cdx-2 expression in squamous and metaplastic columnar epithelia of the esophagus. Dis Esophagus 2006;19(4):260–266.
24. Takahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S. Induction of pluripotent stem cells from adult human fibroblasts by defined factors. Cell 2007;131:1–12.
25. Lieberman DA, Oehike M, Helfand M, the GORGE consortium. Risk factors for Barrett's esophagus in community-based practice. Am J Gastroenterol 1997;92:1293–1297.
26. Cameron AJ. Barrett's esophagus; prevalence and size of hiatal hernia. Am J Gastroenterol 1999;94:2054–2059.
27. Stein HJ, Barlow AP, DeMeester TR. Complications of gastroesophageal reflux disease. Role of the lower esophageal sphincter, esophageal acid and acid/alkaline exposure, and duodenogastric reflux. Ann Surg 1992;216:35–43.
28. Kauer WK, Peters JH, DeMeester TR, Ireland AP, Bremner CG, Hagen JA. Mixed reflux of gastric and duodenal juices is more harmful to the esophagus than gastric juice alone. The need for surgical therapy re-emphasized. Ann Surg 1995;222:525–531.
29. Pellegrini CA, DeMeester TR, Wernly JA, Johnson LF, Skinner DB. Alkaline gastroesophageal reflux. Am J Surg 1978;135:177–184.
30. Oberg S, Peters JH, DeMeester TR, Lord RV, Johanson J, Theisen J, Bremner CG. Determinates of intestinal metaplasia within the columnar lined esophagus. Arch Surg 2000;135:651–656.
31. Kauer WK, Peters JH, DeMeester TR, Feussner H, Ireland AP, Stein HJ, Siewert RJ. Composition and concentration of bile acid reflux into the esophagus of patients with gastroesophageal reflux disease. Surgery 1997;122(5):874–881.
32. Kaur BS, Triadafilopoulos G, Kaur BS, Triadafilopoulos G. Acid- and bile-induced PGE(2) release and hyperproliferation in Barrett's esophagus are COX-2 and PKC-epsilon dependent. Am J Physiol Gastrointest Liver Physiol 2002;283(2):G327–G334.
33. Anisfeld AM, Kast-Woelbern HR, Lee H, et al. Activation of the nuclear receptor FXR induces fibrinogen expression: a new role for bile acid signaling. J Lipid Res 2005;46(3):458–468.
34. Souza RF, Krishman K, Spechler SJ. Acid, bile and CDX; the ABC's of making Barrett's metaplasia. Am J Physiol Gastrointest Liver Physiol 2008;295:211–218.
35. Radtke F, Clevers H. Self-renewal and cancer of the gut: two sides of a coin. Science 2005;307:1904–1909.
36. Scoville DH, Sato T, He XC, Li L. Current view: intestinal stem cells and signaling. Gastroenterology 2008;134:849.
37. Milano F, Van Baal JWPM, Buttar NS, Rygiel AM, De Kort F, Demars CJ, Rosmolen WD, Bergman JJGHM, Van Marle J, Wang KK, Peppelenbosch MP, Krishnadath KK. Bone morphogenetic protein 4 expressed in esophagitis induces a columnar phenotype in esophageal squamous cells. Gastroenterology 2007;132:2412–2421.
38. Hu Y, Williams VA, Gellerson O, Jones C, Watson TJ, Peters JH. The pathogenesis of Barrett's esophagus; secondary bile acids upregulate intestinal differentiation factor CDX2 expression in esophageal cells. J Gastrointest Surg 2007;11:827–834.
39. Hu Y, Jones C, Gellerson O, Williams V, Watson TJ, Peters JH. The pathogenesis of Barrett's esophagus; deoxycholic acid upregulates goblet specific gene MUC2 in concert with CDX2 in human esophageal cells. Arch Surg 2007;142:540–545.
40. Strous GJ, Dekker J. Mucin-type glycoproteins. Crit Rev Biochem Mol Biol 1992;27(1–2):57–92.
41. Yamamoto H, Bai YQ, Yuasa Y. Homeodomain protein CDX2 regulates goblet-specific MUC2 gene expression. Biochem Biophys Res Commun 2003;300:813–818.
42. Mesquita P, Jonckheere N, Almeida R, Ducourouble MP, Serpa J, Silva E, Pigny P, Silva FS, Reis C, Silberg D, Van Seuningen I, David L. Human MUC2 mucin gene is transcriptionally regulated by Cdx homeodomain proteins in gastrointestinal carcinoma cell lines. J Biol Chem 2003;278:51549–51556.
43. Merchant NP, Rogers CM, Trivedi B, Morrow J, Coffey RJ. Ligand-dependent activation of the epidermal growth factor receptor by secondary bile acids in polarizing colon cancer cells. Surgery 2005;138:415–421.
44. Zhang H, Berezov A, Wang Q, et al. ErbB receptors: from oncogenes to targeted cancer therapies. J Clin Invest 2007;117(8):2051–2058.
45. Pal SK, Pegram M, Pal SK, Pegram M. Epidermal growth factor receptor and signal transduction: potential targets for anti-cancer therapy. Anticancer Drugs 2005;16(5):483–494.
46. Jaiswal K, Lopez-Guzman C, Souza RF, Spechler SJ, Sarosi GA. Bile salt exposure increases proliferation through p38 and ERK MAPK pathways in a non-neoplastic Barrett's cell line. Am J Physiol Gastrointest Liver Physiol 2006;290:G335–G342.
47. Avissar NE, Toia L, Hu Y, Watson TJ, Jones C, Raymond DP, Matousek A, Peters JH. Bile acid alone, or in combination with acid, induces CDX2 expression through activation of the epidermal growth factor receptor (EGFR). J Gastrointest Surg 2009;13(2):212–222.
48. Samira JL, Akare S, Ali MA, Mash EA, Meuillet E, Martinez JD. Deoxycholic acid induces intracellular signaling through membrane perturbations. J Biol Chem 2006;281:14948–14960.

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DEMEESTER FESCHRIFT

Radiofrequency Ablation of Barrett's Esophagus

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Abstract
Introduction Barrett's esophagus (BE) is known to be due to chronic gastroesophageal reflux disease and is a precursor of esophageal adenocarcinoma.
Discussion The ability to eliminate BE is appealing, given the neoplastic potential of this condition and the continued increase in incidence of adenocarcinoma involving the esophagus and esophagogastric junction, a highly lethal disease. While a number of endoscopic technologies targeting metaplastic or neoplastic esophageal mucosa have been introduced into the clinical marketplace, most have not been widely adopted. Radiofrequency ablation recently was developed and holds appeal as a reliable, minimally invasive, inexpensive, and well-tolerated technique to destroy pathologic esophageal epithelium.
Conclusion The available data show its efficacy and safety in the short-term, though more mature follow-up is needed to demonstrate its durability in the long-term and its cost-effectiveness in ultimately saving lives.

Keywords Barrett's esophagus · Radiofrequency ablation · Esophageal adenocarcinoma · Gastroesophageal reflux disease

Introduction

The incidence of esophageal adenocarcinoma (EAC) continues to increase at an alarming rate in the USA and Western Europe. The relationship between gastroesophageal reflux disease (GERD) and EAC has been well established; patients with chronic GERD symptoms have been found to have an eightfold increased risk for development of EAC compared to an age- and sex-matched control population.[1] Chronic exposure of the esophageal squamous mucosa to gastric contents can lead to intestinal metaplasia (IM), also known as Barrett's esophagus (BE), characterized by columnar epithelium with goblet cells. Patients with BE have a risk of developing EAC that is 30–125 times greater than the general population.[2] Current thought is that BE progresses through the intermediate stages of low-grade dysplasia (LGD) and high-grade dysplasia (HGD) before becoming invasive EAC. Recent data suggest that the risk of non-dysplastic BE progressing to EAC is in the range of 0.5% per patient-year, while the risk of progression to dysplasia runs approximately 0.9% per patient-year.[3] Once HGD develops, the risk of cancer progression rises dramatically, with most series estimating the annual risk between 5% and 10% per patient.[4]

Despite the malignant potential of BE, the standard management paradigm for non-dysplastic BE or BE with LGD has been observation with lifelong surveillance endoscopies and biopsies, in addition to control of the underlying GERD by medical or surgical means. Such a "watch and wait" strategy, however, does not reliably reduce or remove BE.[5] In addition, the current standard of care in most centers for treatment of BE with HGD or early

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EAC is esophagectomy, a procedure associated with significant morbidity, high mortality in inexperienced hands, and a potential negative impact on long-term gastrointestinal function and quality of life. Thus, the ability to eliminate BE holds appeal in an effort to prevent the development of esophageal malignancy and to avoid the complications associated with esophageal resection.

While a number of endoscopic therapies (Table 1) have been devised to allow resection or ablation of metaplastic or neoplastic esophageal mucosa, the fact that no such therapy has become the mainstay of treatment is, on some levels, surprising. Perhaps the explanation lies in the fact that an effective, safe, minimally invasive, easily reproducible and well-tolerated technique has not until recently been developed. With the introduction of radiofrequency (RF) ablation into clinical practice, a technology may now be available that satisfies many of the requirements of the ideal Barrett's ablation procedure (Table 2).

Current Radiofrequency Ablation Devices and Techniques

Radiofrequency ablation for BE is performed utilizing either of two FDA-approved devices, the HALO^{360} and HALO^{90} (Figs. 1 and 2), both manufactured by BÂRRX Medical, Inc. (Sunnyvale, California). The devices utilize narrow (250 μm width each), tightly spaced (250 μm intervening distance) electrodes attached to a RF energy generator. The HALO technology allows rapid delivery of high power energy with reliable energy density control and depth of tissue penetration.

For circumferential BE, initial ablation typically is attempted with the HALO^{360} balloon-based ablation catheter (Fig. 1). This device consists of 60 bipolar electrode rings, wrapped over a 3 cm distance around a 4 cm balloon, that deliver ablative (radiofrequency) energy to tissue. The balloon dilates the esophagus to a predetermined pressure (0.5 atm), flattening the esophageal wall to a standardized tension and allowing uniform energy delivery to the mucosa over a large surface area (>30 cm^2). A high power (300 W), ultrashort (300 ms) burst of energy is then applied to allow ablation to a uniform depth at approximately the level of the muscularis mucosae (1,000 μm).

The procedure commences with standard flexible esophagoscopy under moderate sedation or general anesthesia to assess the Barrett's segment, carefully looking for areas of mucosal nodularity, ulceration, or epithelial irregularity that might suggest associated neoplasia. The gastroesophageal junction (GEJ) and length of BE are mapped relative to the distance from the incisors and the mucosa is washed with 1% *N*-acetylcysteine. A flexible guidewire up to 0.038 in. in diameter is then advanced through the biopsy channel of the endoscope into the stomach and the endoscope is withdrawn. A sizing balloon on a catheter is advanced over the guidewire and initially positioned 10 cm above the GEJ. The balloon is inflated automatically to a predetermined pressure (4 psi, 27.58 kPa) upon pushing a pedal and a diameter estimate is provided on an automated display. This number is recorded and the process repeated at 1 cm increments, progressing distally until the stomach is entered

Table 1 Methods of Barrett's Ablation

Thermal
Heating technologies
Multipolar electrocautery (MPEC)
Argon plasma coagulation (APC)
Laser
Radiofrequency (RF) ablation
Freezing technologies (cryotherapy)
Non-thermal laser: photodynamic therapy (PDT)
Resectional
Endoscopic resection (ER)
Surgical mucosectomy
Esophagectomy

Table 2 Features of the Ideal Barrett's Ablation Technology

Endoscopic
Automated
Inexpensive
Quick and reliable to perform
Well tolerated
Treats to a uniform depth limited to mucosa
Removes all Barrett's in a single session
Able to be re-applied (if necessary)
Causes no complications
Leads to no subsequent buried glands
Eliminates the need for surveillance

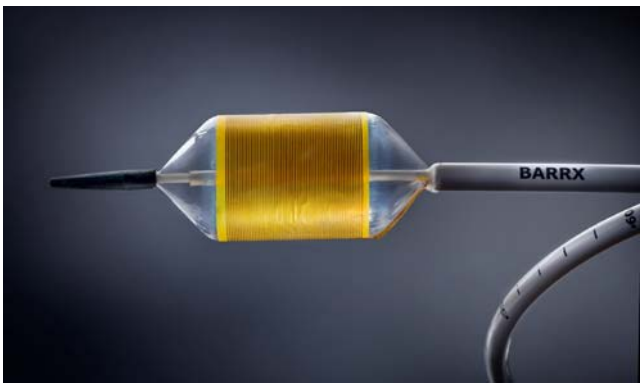

Figure 1 HALO^{360}.

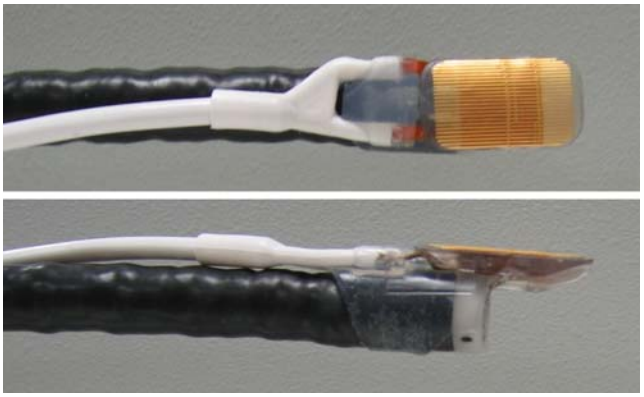

Figure 2 HALO^{90}.

(typically noted by a large incremental increase in the diameter estimate as the tubular esophagus is passed and the more bulbous stomach entered.) All of the recorded esophageal diameter estimates are reviewed and an ablation catheter chosen based on the smallest of the diameters recorded. The HALO^{360} comes in 22, 25, 28, 31, and 34 mm outer diameters.

The appropriate ablation catheter is then advanced over the guidewire and the endoscope reinserted to allow precise positioning of the electrodes under endoscopic visualization. Ablation commences at the most proximal portion of the BE and proceeds in a distal fashion. Once appropriate positioning is confirmed, suction is applied via the endoscope, the balloon is automatically inflated by pushing a foot pedal and the energy current is then activated by pushing a second pedal. Standard dosimetry for the HALO^{360} is 10 J per cm^2 (at 300 W per cm^2) for non-dysplastic BE and 12 J per cm^2 for dysplastic BE. The electrode is 3 cm in length and applies the current sequentially at 1 cm increments in less than 1 s total. The balloon is automatically deflated and immediate mucosal slough is noted. The catheter is then advanced just less than 3 cm to allow slight overlap with the last segment ablated. The process of balloon inflation and RF ablation is repeated. Treatment continues until the entire Barrett's segment has been ablated, though the current recommendation is to treat no more than 6 cm at one session for fear of excessive post-procedural pain with more extensive application.

The catheter is withdrawn and the balloon/electrodes cleaned thoroughly with water. The endoscope is reinserted and the mucosa irrigated and debrided of all coagulum; the tip of the endoscope can be used to assist with mechanical debridement. The endoscope is withdrawn, the catheter reinserted over the guidewire, and the endoscope again advanced to allow repetition of the entire ablation process a second time. Upon completion of the procedure, the remaining coagulum is allowed to slough on its own without the need for repeat debridement.

The HALO^{90} (Fig. 2) endoscope-based catheter is typically used for secondary focal ablation of non-circumferential "tongues" or "islands" of IM. The device, measuring 20 mm long and 13 mm wide, is mounted on an articulated platform, attached to the tip of a standard flexible adult upper endoscope and introduced transorally as per standard upper endoscopy. The microelectrode array is similar in pattern and spacing to the HALO^{360} device. The catheter is positioned under direct visualization, with tissue apposition achieved by upward deflection of the endoscope tip. Differences compared to the HALO^{360} include the fact that the ablation zone is smaller (approximately 2.6 cm^2), no esophageal sizing is necessary (as the HALO^{90} does not utilize a catheter-based balloon), and the recommended energy level is 12 J per cm^2 and 40 W per cm^2 for both dysplastic and non-dysplastic BE. The technique as currently recommended also differs in that the energy is delivered twice to each region, the coagulum cleaned/debrided, and the energy again applied twice, for a total of four applications (as compared to two with the HALO^{360}). The HALO^{90} also may be utilized to treat the esophagus in a circumferential fashion, particularly in the region of the GEJ, where the anatomy may not allow successful apposition of the HALO^{360} device with the target mucosa.

Results of Preclinical and Clinical Trials

For RF ablation, or any other technology, to become an accepted therapy for BE, a number of critical questions need to be addressed:

1. Does it work?
2. Is it safe and well tolerated?
3. Is it reliable and reproducible?
4. Is it durable?
5. In what situations should it be used?
6. Does it save lives?
7. Is it cost effective?

The available data have shown clear affirmative answers to the first three of these questions, while experience is accumulating to answer the remainder.

Animal and Preclinical Human Studies

The initial studies of RF ablation of esophageal mucosa using a circumferential, balloon-based electrode were performed on swine.[6] In the first experiments, varying energy densities were assessed for completeness of esophageal epithelial ablation, ablation depth, and stricture formation. The results showed complete removal of esophageal epithelium at energy density settings of 9.7–

29.5 J/cm^2. Settings of 9.7 and 10.6 J/cm^2 produced no strictures, while more than 20 J/cm^2 produced a stricture in each case. Settings of 5 and 8 J/cm^2 spared the muscularis mucosae, whereas 10 J/cm^2 injured the muscularis mucosae while sparing the submucosa.

Studies to assess the efficacy and safety of RF ablation using the HALO^{360} were then performed on patients undergoing a total esophagectomy for esophageal adenocarcinoma.[7] RF energy was applied to the non-malignant esophageal mucosa at 8, 10, and 12 J/cm^2 in 13 patients immediately prior to surgery. Within the proximal esophagus, a single RF application was administered, while two applications were administered within the distal esophagus. Histologic assessment of the resected esophageal specimens allowed determination of the completeness of epithelial ablation and ablation depth. A dose–response was found for ablation depth, with an energy level of 8 J/cm^2 leading to mid-epithelial injury, 10 J/cm^2 leading to injury down to the lamina propria, and 12 J/cm^2 leading to injury down to the muscularis mucosae. In addition, 100% ablation was found using 10 J/cm^2 (following two ablations) or 12 J/cm^2 (following one or two ablations). No ablation extended beyond the muscularis mucosae and a second application did not significantly alter ablation depth.

In a similar study, RF ablation was undertaken immediately prior to esophagectomy in eight patients undergoing resection for Barrett's with HGD.[8] Energy levels of 10, 12, and 12 J/cm^2 were randomly selected, and patients were treated variously with two, three, or four applications per zone within the region of HGD. On histologic assessment, IM and HGD were completely eradicated in nine out of ten ablation zones, the one incomplete ablation occurring at the margin of an ablation zone and resulting from incomplete overlap of applications. The maximum ablation depth was the muscularis mucosae, though superficial submucosal edema was noted at an energy level of 14 J/cm^2 and four ablations per zone.

The data from these studies were used to determine the energy density and number of ablations per zone in subsequent clinical trials of both dysplastic and non-dysplastic IM.

Clinical Trials

RF Ablation of Non-dysplastic BE

The first multicenter trial of RF ablation using the HALO^{360} device for non-dysplastic BE was published in 2007.[9] In the first phase of the trial (AIM-I), the safety, feasibility, tolerability, and dose–response of RF ablation was assessed over 2–3 cm segments of BE in 32 patients at five centers using randomized energy levels of 6, 8, 10, or 12 J/cm^2. The median procedure time was 24 min for the initial ablation session and no subsequent strictures, perforations, or pleural effusions were noted. All patients were treated with esomeprazole (Nexium, AstraZeneca LP, Wilmington, Delaware) 40 mg twice a day for 1 month after any ablation procedure, and 40 mg per day at all other times during the follow-up period. Complete clearance of IM was noted in 67% of patients at 10 J/cm^2 and 55% at 12 J/cm^2 at 12-months follow-up.

Based on these "dosimetry phase" data, an "effectiveness phase" (AIM-II, 70 patients) was undertaken to assess the efficacy of ablating 2–6 cm segments of BE. An energy level of 10 J/cm^2 delivered twice per session was chosen based on the AIM-I results. The follow-up algorithm called for endoscopic biopsies at 1 and 3 months post-ablation, with repeat circumferential ablation using the HALO^{360} at 4 months if IM persisted. Endoscopic biopsies were repeated at 6 and 12 months after initial ablation. Up to three focal ablation sessions were allowed after the 12-month biopsies for persistent IM, targeting endoscopically visible BE or irregularity at the GEJ. Final biopsies were performed at 30 months after initial ablation. Complete clearance of IM was noted in 70% of patients at 12-months follow-up, and 98% of patients at 2.5-years follow-up.[10] No strictures, perforations or pleural effusions were encountered, and no buried glandular mucosa was detected in 4,306 biopsy fragments.

RF for Dysplastic BE

Several series have reported outcomes following RF ablation of dysplastic BE. The first trial assessing the feasibility and efficacy of RF ablation for LGD (AIM-LGD Trial) assessed 10 patients for 24-months post-treatment.[11] Patients underwent initial circumferential ablation with focal ablation at 12 months if IM persisted. At 24-months follow-up, 100% of patients were found to have a complete response (CR) for dysplasia and 90% a CR for all IM (Fig. 3).

A series from the Netherlands assessed 11 patients undergoing RF ablation for HGD, six having undergone prior endoscopic resection (ER) for focal mucosal nodules.[12] The median length of BE was 5 cm. Patients underwent a median of two circumferential ablations with the HALO^{360} and an additional two focal ablations using the HALO^{90}. No strictures or serious complications were observed. A CR for dysplasia and IM was noted in all patients. During a median follow-up of 14 months after the last treatment session and a median of two surveillance endoscopies, none of the patients had recurrence of dysplasia or endoscopic signs of recurrent BE.

A multicenter US registry of patients undergoing ablation for Barrett's with HGD was reported in 2008.[13] A total of 142 patients from 16 centers were followed with

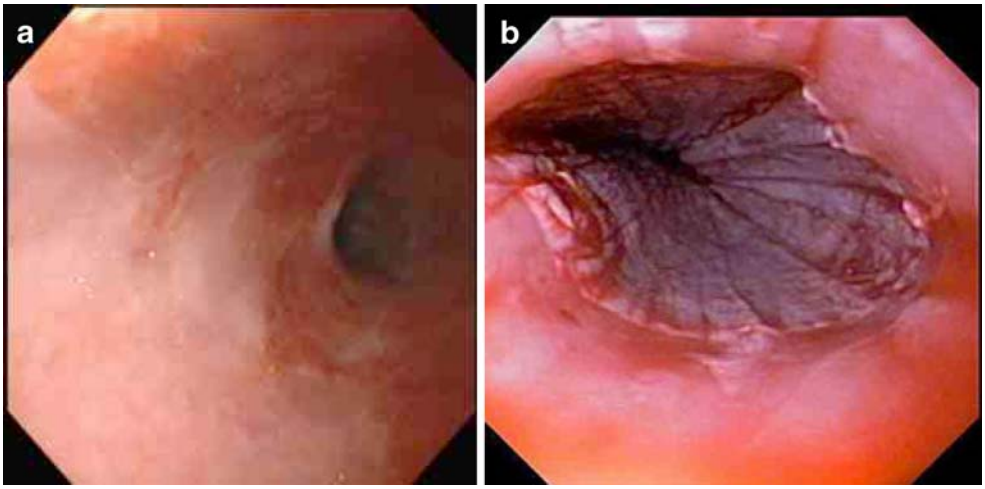

Figure 3 **a** Barrett's esophagus, pre-treatment. **b** Mucosal slough, post-treatment.

a 6 cm median length of BE. In 92 patients who underwent at least one follow-up biopsy session, the CR for HGD was 90.2% and the CR for IM was 54.3% at a median of 12 months. A single, asymptomatic, post-treatment esophageal stricture (0.4%) was reported and no buried glands were found on subsequent esophageal biopsies.

Finally, a multicenter trial of RF ablation was opened in 2006 for patients with both LGD and HGD. One-hundred twenty-seven patients, 64 with LGD and 63 with HGD, were enrolled from 20 centers and randomized in a 2:1 fashion to undergo ablation or sham treatment. Preliminary results of the trial were presented in abstract form at Digestive Disease Week 2008.[14] Of 35 patients treated with ablation and undergoing follow-up endoscopic biopsies at 12 months, a CR for IM was found in 29 (83%) after a median of four treatment sessions. Of the six patients with residual IM, all had down-grading of dysplasia and none had persistent HGD.

RF in Combination with ER for Early EAC

A recent report from the Netherlands assessed outcomes in 44 patients with BE and HGD or early EAC.[15] Thirty-one patients first underwent endoscopic resection (ER), 16 with early EAC, 12 with HGD, and three with LGD. The worst histology remaining after any ER and prior to the first ablation was HGD in 32, LGD in ten and no dysplasia in two. A complete histologic eradication of all dysplasia, as well as complete endoscopic and histologic clearance of IM, was achieved in 98% after a median of one circumferential ablation session, two focal ablation sessions, and rescue ER in three patients. Complications occurred during ER in five patients, including four mild bleeding episodes managed with endoscopic techniques, and one esophageal perforation treated with endoscopic clips and placement of a covered esophageal stent. Four patients (9%) developed dysphagia after ablation, improved after a median of three endoscopic dilatations; all had undergone widespread ER. After a median follow-up of 21 months, no dysplasia had recurred. In 1,475 follow-up biopsies obtained from neosquamous epithelium, only one (0.07%) revealed buried glandular mucosa. These results demonstrate that stepwise circumferential and focal RF ablation, with or without adjunctive ER to assess and treat focal nodules, is safe and effective at eradicating dysplasia and IM at short- to medium-term follow-up.

Discussion

The ability to ablate BE holds strong appeal, given the neoplastic potential of this condition and the continued increase in incidence of adenocarcinoma involving the esophagus and esophagogastric junction, a highly lethal disease. While a number of endoscopic technologies targeting metaplastic or neoplastic esophageal mucosa have been introduced into the clinical marketplace, most have not been widely adopted. Prior to the introduction of RF ablation, the available endoscopic thermal ablative modalities, such as multipolar electrocautery (MPEC), argon plasma coagulation (APC), and laser therapy, suffered from several pitfalls including the "point and shoot" nature of the applications and inconsistent depth of tissue penetration. The techniques also suffered from the inability to treat all regions of the corrugated surface area of the esophageal lining in a uniform fashion. As a result, utilization of such technologies led to the possibility of both undertreatment (i.e., persistent BE) and overtreatment (i.e., excessive depth of tissue injury leading to esophageal stricturing or perforation). While photodynamic therapy (PDT) allowed for more diffuse and uniform treatment of pathologic mucosa, it suffered the same problems with inconsistent depth of tissue injury.

RF ablation recently was introduced into clinical practice and has been quickly adopted. The available data have

shown both a high rate of success at elimination of BE and an excellent safety profile, with a very low rate of esophageal strictures, perforations, bleeding, or subsequent buried sub-squamous glands. Success rates at achieving a CR for ablation of both dysplastic and non-dysplastic IM have been excellent in short- to medium-term follow-up, though multiple treatment sessions may be required. In addition, the procedure is minimally invasive, reliable, quick to learn and perform, easy to administer, reproducible, relatively inexpensive, and well-tolerated. Accordingly, RF ablation with the HALO^{360} and HALO^{90} devices satisfies many of the requirements of the ideal ablation technique and appears to be superior to other technologies in many respects.

A number of issues require additional study, however, for RF ablation to become considered a standard of care for treatment of non-dysplastic or dysplastic BE. As the technology is relatively new, long-term success rates at maintaining ablation have yet to be demonstrated. Whether complete ablation is essential or partial ablation is adequate, in particular leaving IM at the "difficult to ablate" region of the GEJ, requires longer follow-up on large cohorts of patients. Given the relative infrequency of the development of esophageal adenocarcinoma in patients with BE, the issue of whether ablation should be considered for all patients or merely a subset deemed to be at high risk for neoplastic progression will need to be elucidated. Perhaps with improvements in our understanding of the molecular biology and natural history of BE, our ability to risk-stratify the individual patient will mature and allow for tailored therapy. The ability to exclude an occult focus of invasive carcinoma that penetrates deep to the RF ablation zone (i.e., muscularis mucosae) will be important, particularly when ablation is considered for HGD and the chance of occult malignancy is significant. The best form of reflux control, medical or surgical, to prevent recurrent IM needs to be assessed as well as the best timing of antireflux surgery relative to ablation. Finally, and of great importance, the issue of whether long-term surveillance needs to be undertaken in cases of proven eradication of IM needs careful consideration.

Ultimately, for RF ablation to survive and be proven an effective long-term therapy for BE, experience will need to show that lives are saved and at a reasonable cost. The experience, to date, suggests that the technology is here to stay and is clinically safe, effective, and reliable as an ablation tool in select circumstances.

References

1. Lagergren J, Bergstrom R, Lindgren A, Nyren O. Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. N Engl J Med 1999;340:825–831.
2. Reid BJ. Barrett's esophagus and adenocarcinoma [review]. Gastroenterol Clin North Am 1991;20:817–834.
3. Sharma P, Falk GW, Weston AP et al. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. Clin Gastroenterol Hepatol 2006;4:566–572.
4. Rastogi A, Puli S, El-Serag HB, Bansal A, Wani S, Sharma P. Incidence of esophageal adenocarcinoma in patients with Barrett's esophagus and high-grade dysplasia: a meta-analysis. Gastrointest Endosc 2008;67:394–398.
5. Gurski RR, Peters JH, Hagen JA et al. Barrett's esophagus can and does regress after antireflux surgery: a study of prevalence and predictive features. J Am Coll Surg 2003;196:706–713.
6. Ganz RA, Utley DS, Stern RA, Jackson J, Batts KP, Termin P. Complete ablation of esophageal epithelium with a balloon-based bipolar electrode: a phased evaluation in the porcine and in the human esophagus. Gastrointest Endosc 2004;60:1002–1010.
7. Dunkin BJ, Martinez J, Bejarano PA et al. Thin-layer ablation of human esophageal epithelium using a bipolar radiofrequency balloon device. Surg Endosc 2006;20:125–130.
8. Smith CD, Bejarano PA, Melvin WS, Patti MG, Muthusamy R, Dunkin BJ. Endoscopic ablation of intestinal metaplasia containing high-grade dysplasia in esophagectomy patients using a balloon-based ablation system. Surg Endosc 2007;21:560–569.
9. Sharma VK, Wang KK, Overholt BF et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. Gastrointest Endosc 2007;65:185–195.
10. Fleischer DE, Overholt BF, Sharma VK et al. Endoscopic ablation of Barrett's esophagus: a multicenter study with 2.5-year follow-up. Gastrointest Endosc 2008;68:867–876.
11. Sharma VK, Kim HJ, Das A, Dean P, DePetris G, Fleischer DE. A prospective pilot trial of ablation of Barrett's esophagus with low-grade dysplasia using stepwise circumferential and focal ablation (HALO system). Endoscopy 2008;40:380–387.
12. Gondrie JJ, Pouw RE, Sondermeijer CMT et al. Stepwise circumferential and focal ablation of Barrett's esophagus with high-grade dysplasia: results of the first prospective series of 11 patients. Endoscopy 2008;40:359–369.
13. Ganz RA, Overholt BF, Sharma VK et al. Circumferential ablation of Barrett's esophagus that contains high-grade dysplasia: a U.S. multicenter registry. Gastrointest Endosc 2008;68:35–40.
14. Lightdale CJ, Overholt BF, Wang KK, et al. Predictors and quantitative assessment of incomplete response after radiofrequency ablation for dysplastic Barrett's esophagus: analysis of randomized sham-controlled clinical trial (the AIM dysplasia trial). Presented at Digestive Disease Week, San Diego, CA, May, 2008.
15. Pouw RE, Gondrie JJ, Sondermeijer CM et al. Eradication of Barrett esophagus with early neoplasia by radiofrequency ablation, with or without endoscopic resection. J Gastrointest Surg 2008;12:1627–1637.

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DEMEESTER FESTSCHRIFT

Evaluation and Treatment of Superficial Esophageal Cancer

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Abstract
Introduction Adenocarcinoma of the esophagus is the fastest increasing cancer in the USA, and an increasing number of patients are identified with early-stage disease. The evaluation and treatment of these superficial cancers differs from local and regionally advanced lesions.
Methods This paper is a review of the current methods to diagnose, stage, and treat superficial esophageal adenocarcinoma.
Results Intramucosal adenocarcinoma can be effectively treated with endoscopic resection techniques and with less morbid surgical options including a vagal-sparing esophagectomy. However, submucosal lesions are associated with a significant risk for lymph node metastases and are best treated with esophagectomy and lymphadenectomy.
Discussion There has been a major shift in the treatment for Barrett's high-grade dysplasia and superficial esophageal adenocarcinoma in the past 10 years. New therapies minimize the morbidity and mortality of traditional forms of esophagectomy and in some cases allow esophageal preservation. Individualization of therapy will allow maximization of successful outcome and quality of life with minimization of complications and recurrence of Barrett's or cancer.

Keywords Superficial esophageal cancer · Adenocarcinoma of the esophagus · Chronic gastroesophageal reflux disease · Barrett's esophagus · Dysplasia · Endoscopic resection

Introduction

Adenocarcinoma of the esophagus is the fastest increasing cancer in the USA, and the latest statistics suggest that in white men the increase from 1975 to 2004 exceeded 460%.[1,2] A similar alarming increase has been noted in white women but at a lower rate (335%).[2] The increased incidence is occurring across all stages and all age groups. It is projected that there will be 16,470 new patients diagnosed with esophageal cancer in the USA in 2008, with the majority of these being adenocarcinoma.[2] A similar trend has also been reported in other western countries.[3]

Esophageal adenocarcinoma develops as a consequence of chronic gastroesophageal reflux disease, and the precursor lesion of this cancer is Barrett's esophagus. Barrett's esophagus is a metaplastic transformation of the normal squamous lining of the distal esophagus into a premalignant, intestinalized columnar mucosa. The incidence of Barrett's esophagus is also increasing, and since many patients with Barrett's are in a surveillance program, there are more patients with high-grade dysplasia and superficial adenocarcinoma presenting for therapy. Both high-grade dysplasia and intramucosal adenocarcinoma, while potentially lethal, are curable lesions.[4–6] Previously, cure of these lesions was reliably accomplished only with esophagectomy. However, new technologies now allow endoscopic therapy with esophageal preservation in appropriate patients. However, determining the optimal therapy for patients with high-grade dysplasia or superficial esophageal cancer requires a thorough understanding of the disease process; the pros, cons, and pitfalls of each therapy; and the expected results.

The first fundamental issue with regards to the treatment of suspected high-grade dysplasia and intramucosal adenocarcinoma is to confirm the diagnosis with repeat biopsies and expert pathological review and to carefully inspect the Barrett's mucosa during endoscopy. New endoscopic modalities including narrow band imaging and enhanced

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magnification likely will prove valuable for finding areas of dysplasia and superficial cancer, but nonetheless a critical task is to look for any nodules, ulcers, or irregularities in the columnar mucosa. Such areas are particularly at risk to harbor a cancer. If a random biopsy shows adenocarcinoma but no nodule or visible abnormality was seen endoscopically, we have shown that the lesion is confined to the mucosa in nearly all circumstances.[7] In contrast, if a biopsy showing adenocarcinoma came from a visible lesion, the cancer cannot be assumed to be limited to the mucosa, regardless of the size or appearance of the lesion. Even very small lesions may penetrate into the submucosa; thus, the endoscopic appearance of a lesion cannot be used to determine the "T" stage. Instead, the "T" stage of a lesion is best determined with endoscopic ultrasound and/or endoscopic resection.

Staging Superficial Esophageal Cancer

Local/regional staging of esophageal adenocarcinoma is best done with endoscopic ultrasound. Standard 7.5 and 12 MHz endoscopic ultrasound probes can accurately assess the depth of invasion once the tumor has gone through the submucosa and also provide information on the presence of abnormal or enlarged lymph nodes. However, neither the standard probes nor newer high-resolution 20 MHz probes are able to accurately distinguish intramucosal from submucosal tumor invasion.[8] Currently, the only method to accurately and reliably determine the depth of invasion of a superficial lesion is endoscopic resection. Endoscopic resection (ER) excises a disc of esophageal (or gastric) wall down to the muscularis propria and provides a specimen for histologic review that includes both mucosa and submucosa. In this way, ER can reliably determine the "T" stage of superficial esophageal lesions.[9] Although several techniques have been proposed for ER, one popular method involves the use of a cap that fits over the end of a standard endoscope. Developed by Dr. Inoue from Japan, these caps are available in various sizes and configurations (flat versus angled) and come with a complete kit for the procedure by Olympus®.[10] Using the large cap for ER, lesions up to 1.5 cm in size can be excised in one piece. Piecemeal excision of a lesion is acceptable but raises the potential for incomplete resection and makes pathologic evaluation of the resection margins impractical. Although ER can be performed with conscious sedation, I prefer to have the patient intubated and under general anesthesia in the operating room to minimize the risk of aspiration. The procedure is quick, and patients are typically discharged home a few hours later. In order to accurately determine margins, I have found it best to personally orient the specimen for the pathologist and have it pinned and fixed for permanent rather than frozen section. Experience at our center and elsewhere has demonstrated that patients with negative margins on the ER specimen reliably have had complete resection of the tumor.[9,11] However, tumor at the cauterized margin of the specimen indicates the potential for residual tumor in the esophagus. A positive lateral margin can be addressed with further endoscopic intervention, but a positive deep margin is an indication for esophagectomy in most circumstances.

Intramucosal Versus Submucosal Tumor Invasion

Accurately determining the depth of invasion is critical to treatment planning for superficial esophageal cancer. A disturbing trend in the gastrointestinal literature is to only call a tumor invasive once it penetrates into the submucosa, and in some centers even superficial submucosal invasion is thought to be treatable with endoscopic techniques.[12,13] This attitude is dangerous, since esophageal adenocarcinoma is one of the deadliest cancers known to man, and a few microns of invasion can dramatically alter the risk of lymph node metastases. In patients with only high-grade dysplasia, lymph node metastases and systemic disease has not been reported, and this is the only lesion from which patients can be assured that they have been cured with adequate therapy. As soon as a focus of adenocarcinoma breaches the basement membrane and enters the lamina propria below the epithelial layer, it is an invasive cancer, and lymph node metastases, systemic disease, and death can occur and have been reported.[4] However, numerous surgical series have evaluated the risk of lymph node metastases with intramucosal tumors, and it is clear that they are rare, approximately 2%.[4,5,14] The low prevalence of nodal metastases with intramucosal cancer allows resection of the lesion without lymphadenectomy. We recently showed that survival was equivalent in patients after a vagal-sparing esophagectomy without lymph node dissection and after an en bloc esophagectomy with systematic thoracic and abdominal lymphadenectomy.[15] Thus, for intramucosal tumors, endoscopic therapy is a reasonable option and indeed is likely to be the preferred therapy in most patients. However, invasion of a tumor through the muscularis mucosa into the submucosa increases the risk of lymph node metastases to approximately 30%, and therapies that do not include a lymphadenectomy are potentially inadequate.[16,17]

Endoscopic Mucosal Resection as Primary Therapy for Esophageal Adenocarcinoma

Christian Ell and colleagues in Wiesbaden Germany have been leading the world in the endoscopic management of

intramucosal adenocarcinoma. They initially reported excellent survival in 100 highly selected patients with intramucosal adenocarcinoma treated by ER alone and have subsequently expanded this experience to 349 patients with 5 years of follow-up.[12,18] These patients were carefully screened to have only well-differentiated intramucosal tumors without evidence of lymphovascular invasion. The majority of patients had short-segment Barrett's, and despite relatively short-term follow-up, there was a high rate (11%) of metachronous tumor development. This rate will undoubtedly increase with longer follow-up and would also almost certainly be higher if more patients with long-segment Barrett's esophagus were part of the study. Thus, patients with Barrett's and one focus of adenocarcinoma are at high risk for a synchronous or metachronous tumor.

In our initial experience with endoscopic resection, all patients had an esophagectomy after the visible lesion was excised by EMR. In addition to the endoscopy at the time of the ER, all patients had multiple endoscopies and biopsies prior to the esophagectomy, and yet on final pathology, two of seven patients (29%) had an additional (undetected) cancer in the resected specimen.[9] This reality is almost certainly part of the explanation for the significant risk of metachronous lesion development in the reports by Ell and colleagues where only the visible adenocarcinoma was resected and the surrounding Barrett's was not ablated.[18,19] In an effort to reduce the risk of metachronous tumor development, Wang and colleagues combined ER with photodynamic therapy to ablate the residual Barrett's. They reported that no new or recurrent cancers developed in 16 patients during a median follow-up of 13 months, although residual Barrett's was present in 47% of the patients.[20] Consequently, ablation of any residual Barrett's is recommended in patients that have had a therapeutic ER for intramucosal adenocarcinoma. Recently, radiofrequency ablation devices have become available (Halo® 360 and 90) that provide effective ablation of Barrett's with a low risk of stricture formation or buried Barrett's. Early experience with ablation for high-grade dysplasia alone or after endoscopic resection of an intramucosal cancer in several centers with small numbers of patients is promising and in my opinion is the procedure of choice when esophageal preservation is planned.[21–23]

High-Risk Intramucosal Tumors and Low-Risk Submucosal Lesions?

Although the overall prevalence of lymph node metastases with an intramucosal adenocarcinoma of the esophagus is low, it has been proposed that markers for an increased risk include poor differentiation and lymphovascular invasion.[18] It is likely that in the future molecular markers that portend an increased risk for nodal metastases will be identified, but at this point histologic markers are all that are available, and their significance remains disputed. Using these histologic features of low risk, Pech and colleagues have recently reported that superficial submucosal invasion in "low risk" tumors can safely be treated with endoscopic resection.[24] While this strategy may be acceptable in very high surgical risk patients, those with acceptable risk likely have a higher risk of an involved node and death from cancer with a therapy that does not include a lymphadenectomy than they do with appropriate surgical resection. Ideally, techniques will be developed that allow identification of patients with and without lymph node metastases with submucosal tumors so that endoscopic therapy can be safely extended to a larger proportion of patients. Currently, the safest approach from an oncologic standpoint is to recommend esophagectomy for all patients with submucosal tumor invasion that are operative candidates. In keeping with this philosophy, most centers consider tumor penetration deeper than the muscularis mucosa a contraindication to endoscopic therapy.

Gastroesophageal Reflux and Endoscopic Therapy for High-Grade Dysplasia or Intramucosal Adenocarcinoma

Barrett's develops as a consequence of gastroesophageal reflux, and ablation of Barrett's does not alter the environment that precipitated the development of Barrett's. Typically, it is recommended that after ablation therapy patients go on twice daily proton pump inhibitor medication to promote regeneration of squamous mucosa, and this strategy has proven effective in my experience. A more aggressive approach was taken by Ell and colleagues who treated patients after endoscopic resection with pH-guided proton pump inhibitor therapy.[18] However, the efficacy of medical therapy, pH guided or otherwise, for prevention of Barrett's recurrence after ablation remains unproven. Not surprisingly, many patients with Barrett's require large doses of proton pump inhibitors to be adequately acid-suppressed. This speaks to the severity of reflux disease in these patients, and as impedance studies have demonstrated, adequate acid suppression does not equate to elimination of alkaline or weak acid reflux events.[25,26] One has to suspect that life-long maintenance of this degree of intensive medical therapy will be difficult in the majority of patients, and antireflux surgery is likely to be a more effective long-term strategy.

It is also important to realize that caution must be used when using the traditional 5-year survival mark to evaluate the success of endoscopic therapy for high-grade dysplasia or superficial esophageal cancer, since many of these patients have a lot of years ahead of them, and cure from

one or even several Barrett's cancers may not be the end of the story. Barrett's esophagus develops as a consequence of gastroesophageal reflux, and elimination of Barrett's without concomitant elimination of the reflux in these patients may be similar to pulling weeds out of a garden and expecting them never to grow again. This concern is highlighted by surgical series that have shown that almost 50% of patients that have an esophagectomy with gastric pull-up for high-grade dysplasia or adenocarcinoma redevelop columnar mucosa above the anastomosis in what had been histologically proven squamous mucosa at the time of the reconstruction.[27,28] The development of intestinal metaplasia is less common but also does occur. Importantly, the risk of developing Barrett's was higher in patients that had their esophagectomy for adenocarcinoma compared to those that had an esophagectomy for squamous cancer, suggesting a potential genetic susceptibility to reflux injury and metaplasia in the squamous mucosa of some patients.

Endoscopic Therapy for High-Grade Dysplasia and Intramucosal Adenocarcinoma of the Esophagus: Important Considerations

When considering a new therapy such as endoscopic resection and/or ablation for high-grade dysplasia or superficial adenocarcinoma, there are several things that must be avoided. First, we want to avoid finding a highly curable lesion in a patient and then treat it ineffectively with the new therapy and lose the patient to the disease process. Second, we want to avoid creating a whole new set of problems for the patient with the new therapy that they did not originally have, and third, the new therapy should not make it harder to definitely treat the process if the new therapy proves ineffective. Early results suggest that endoscopic resection and radiofrequency ablation address these concerns better than photodynamic therapy, which was associated with a 30% rate of significant esophageal stricture development, inconsistent eradication of Barrett's, frequent subsquamous or buried Barrett's, and suggestions that the most genetically abnormal clones of Barrett's were those most likely to persist after therapy.[29–32]

While Ell has adopted the approach that endoscopic therapy for high-grade dysplasia and intramucosal adenocarcinoma is essentially always the preferred therapy, in my opinion there are several considerations that should be used to assist the patient and physician in the decision regarding whether endoscopic therapy or esophagectomy is the best approach in that patient's particular circumstance. These considerations can be divided into tumor factors, esophageal factors, and patient factors.

The important tumor factors are that there is only high-grade dysplasia or intramucosal cancer and that any visible lesion has been completely excised with a negative deep margin. High-risk features for nodal metastases should be absent or considered in the decision to continue with endoscopic therapy, and there should be no evidence of lymphatic spread by endoscopic ultrasound or other modality. The esophageal factors are more complex, but the first over-riding consideration is that the esophagus has to be worth saving. A patient with end-stage reflux manifest by severe regurgitation symptoms, large nonreducing hiatal hernia, dysphagia, and poor esophageal body function and bolus transport on physiologic testing is, in my opinion, a poor candidate for esophageal preservation. In my opinion, this patient would be best treated with vagal-sparing esophagectomy. Other esophageal factors to consider include high-grade dysplasia that proves refractory to ablation or recurrence of dysplastic Barrett's after initial complete ablation. Lastly, there are a number of patient factors that need to be considered. Patients need to be fully informed of the pros and cons as well as the risks and benefits of both options for therapy (esophageal preservation versus esophagectomy), and they need to understand that esophageal preservation requires a significant commitment by both the patient and the physician. Follow-up endoscopies and biopsies need to be frequent (every 3 months initially) and lifelong since the natural history of endoscopic therapy for these lesions is not yet known. Furthermore, the patient has to be able to live with the uncertainty that a hidden or buried adenocarcinoma may show up in an advanced stage that may not be curable and that, secondary to recurrence or complications of the endoscopic therapy, the patient may at some point require an esophagectomy anyway. Endoscopic therapies that resect or ablate dysplastic Barrett's or intramucosal cancers are not without complications including a risk for perforation, stricture formation, buried Barrett's beneath the neosquamous epithelium, recurrent or persistent areas of Barrett's, induction of alterations in esophageal body motility, and the potential that ablative therapy could select out the most genetically abnormal or aggressive clones of Barrett's.[29,32] Furthermore, endoscopic therapy may complicate a subsequent esophagectomy if resection of the esophagus becomes necessary. Another consideration is that effective control of reflux may be necessary to prevent recurrence of Barrett's, and thus patients that select endoscopic therapy for high-grade dysplasia or intramucosal adenocarcinoma may eventually be recommended to have antireflux surgery. Consequently, the decision to treat high-grade dysplasia or intramucosal adenocarcinoma with endoscopic therapy cannot be made or taken lightly.

Esophagectomy for High-Grade Dysplasia or Intramucosal Adenocarcinoma

Esophagectomy has been and remains the standard of care for the cure of patients with high-grade dysplasia or intramucosal adenocarcinoma. Esophagectomy removes the diseased esophagus and essentially eliminates the risk of recurrent high-grade dysplasia and death from esophageal adenocarcinoma. Furthermore, it is a one-time therapy, with little or no need for subsequent endoscopies or interventions in most patients. Commonly, the esophagus is removed with a transhiatal esophagectomy, but minimally invasive procedures are becoming more frequent. One drawback to most methods of removing the esophagus is that the vagus nerves are divided during the procedure, and this leads to dumping and post-vagotomy diarrhea in up to 30% of patients.[33] We have switched to a vagal-sparing technique to resect the esophagus in patients who do not require a lymphadenectomy including those with high-grade dysplasia or intramucosal adenocarcinoma. This procedure was initially described by Dr. Akayma in Japan, and with this technique, the esophagus is stripped out of the mediastinum inside–out.[34] We have shown that, with a vagal-sparing technique, vagal integrity is maintained, the risk of dumping and post-vagotomy diarrhea is minimized, and the morbidity of esophagectomy is decreased.[15,35] The vagal-sparing esophagectomy can be done as an open trans-abdominal or a laparoscopic approach, requires no mediastinal dissection, and either the stomach or the colon can be used for esophageal replacement. In comparison to a transhiatal or en bloc resection, we recently showed that the vagal-sparing esophagectomy is associated with a shorter hospital stay and reduced incidence of complications, especially infectious complications.[36] A number of interesting animal studies have demonstrated an important role for the vagus nerves in the regulation of the systemic response to infection and have shown that vagotomy impairs survival in animals that are given an infectious challenge.[37,38] Furthermore, the vagus nerves have been shown to participate in a neuroimmunologic pathway that regulates immune response during feeding.[39] Consequently, in addition to avoiding dumping and diarrhea symptoms, preservation of the vagus nerves during esophagectomy likely is associated with maintenance of other more global gastrointestinal and immune functions.

Quality of Life with Esophageal Preservation Versus Esophagectomy

A final important issue is long-term quality of life in patients treated for high-grade dysplasia or intramucosal adenocarcinoma since they are likely to be cured of their disease. Quality of life in patients with Barrett's is variable, but many have severe reflux disease with the accompanying problems of regurgitation, nocturnal aspiration, and dysphagia. The assumption that any esophageal preserving therapy is going to be better than the alternative therapy of an esophagectomy in everyone with early esophageal adenocarcinoma is unproven and likely untrue, and the concept that an esophagectomy should be avoided at all cost or used only as a last resort is unfounded. The often-quoted mortality of 5–15% for an esophagectomy is not supported by current series in patients with high-grade dysplasia or intramucosal adenocarcinoma where mortality is 0–1%.[15,40,41] Esophagectomy remains the standard of care for both high-grade dysplasia and early adenocarcinoma, and that quality of life after esophagectomy is excellent in most patients.[42] Currently, quality of life after endoscopic therapy for high-grade dysplasia or intramucosal cancer remains unstudied, and future reports likely will add important information that aids the decision for and selection of patients to have endoscopic rather than surgical therapy for these conditions.

Conclusions

In light of the recent advances in endoscopic technology that allow esophageal preservation and the new, less invasive and potentially less morbid surgical techniques to remove the esophagus, it is time that we alter our approach to the evaluation of patients with high-grade dysplasia and superficial esophageal adenocarcinoma. In addition to determining the stage of the cancer and assessing the overall health of the patient, we should also evaluate the pathophysiologic abnormalities associated with the patient's reflux disease. In particular, an assessment should be made of the function of the stomach, lower esophageal sphincter, and esophageal body, as well as the size of the hiatal hernia, length of Barrett's, and presence and severity of reflux symptoms. Esophageal preservation might be the preferred therapy in a patient with few symptoms, a small hiatal hernia, normal esophageal body function, and a short segment of Barrett's with a low-risk intramucosal carcinoma. In contrast, patients that are poor candidates for esophageal preservation are those that present with multifocal high-grade dysplasia or intramucosal adenocarcinoma and have severe reflux symptoms or dysphagia, long-segment Barrett's with a large, fixed hiatal hernia, and poor esophageal body motility. These patients are best treated with a vagal-sparing esophagectomy. Thus, the decision to treat high-grade dysplasia or intramucosal cancer endoscopically or with an esophagectomy should take into consideration not just the stage of the lesion but the pathophysiology of the esophagus and the severity of the underlying reflux disease. To advocate one therapy as

always being the best is to take a step backward in an age of increasing individualization of therapy. Rather than a one-size-fits-all approach, our understanding of tumor biology and esophageal physiology in conjunction with patient preference should be used to determine the best therapy for an individual patient, preserving the esophagus in those where it makes sense and removing the esophagus when necessary to adequately address not only the cancer but the background pathophysiology that precipitated the development of the malignancy. This approach will require a balanced and updated understanding of the advantages and disadvantages of both endoscopic and surgical therapies by the surgeons and gastroenterologists that treat these patients.

References

1. Pohl H, Welch HG. The role of overdiagnosis and reclassification in the marked increase of esophageal adenocarcinoma incidence. J Natl Cancer Inst 2005;97(2):142–146.
2. Brown LM, Devesa SS, Chow W-H. Incidence of adenocarcinoma of the esophagus among white Americans by sex, stage, and age. J Natl Cancer Inst 2008;100(16):1184–1187.
3. Crane LMA, Schaapveld M, Visser O, et al. Oesophageal cancer in The Netherlands: increasing incidence and mortality but improving survival. Eur J Cancer 2007;43(9):1445–1451.
4. Oh DS, Hagen JA, Chandrasoma PT, et al. Clinical biology and surgical therapy of intramucosal adenocarcinoma of the esophagus. J Am Coll Surg 2006;203(2):152–161.
5. Rice TW, Blackstone EH, Goldblum JR, et al. Superficial adenocarcinoma of the esophagus. J Thorac Cardiovasc Surg 2001;122(6):1077–1090.
6. Stein HJ, Feith M, Bruecher BL, et al. Early esophageal cancer: pattern of lymphatic spread and prognostic factors for long-term survival after surgical resection. Ann Surg 2005;242(4):566–573. discussion 573–5.
7. Nigro JJ, Hagen JA, DeMeester TR, et al. Occult esophageal adenocarcinoma: extent of disease and implications for effective therapy. Ann Surg 1999;230(3):433–440.
8. May A, Gunter E, Roth F, et al. Accuracy of staging in early esophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. Gut 2004;53:634–640.
9. Maish MS, DeMeester SR. Endoscopic mucosal resection as a staging technique to determine the depth of invasion of esophageal adenocarcinoma. Ann Thorac Surg 2004;78:1777–1782.
10. Tada M, Inoue H, Yabata E, et al. Colonic mucosal resection using a transparent cap-fitted endoscope.[see comment]. Gastrointest Endosc 1996;44(1):63–65.
11. Prasad GA, Buttar NS, Wongkeesong LM, et al. Significance of neoplastic involvement of margins obtained by endoscopic mucosal resection in Barrett's esophagus. Am J Gastroenterol 2007;102(11):2380–2386.
12. Pech O, Behrens A, May A, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008;57(9):1200–1206.
13. Schembre DB, Huang JL, Lin OS, et al. Treatment of Barrett's esophagus with early neoplasia: a comparison of endoscopic therapy and esophagectomy.[see comment]. Gastrointest Endosc 2008;67(4):595–601.
14. Liu LMDP, Hofstetter WLMD, Rashid AMDP, et al. Significance of the depth of tumor invasion and lymph node metastasis in superficially invasive (T1) esophageal adenocarcinoma. Am J Surg Pathol 2005;29:1079–1085.
15. Peyre C, DeMeester SR, Rizzetto C, et al. Vagal-sparing esophagectomy: the ideal operation for intramucosal adenocarcinoma and Barrett's with high-grade dysplasia. Ann Surg 2007;246:665–674.
16. Rice TW, Zuccaro G Jr, Adelstein DJ, et al. Esophageal carcinoma: depth of tumor invasion is predictive of regional lymph node status. Ann Thorac Surg 1998;65(3):787–792.
17. Nigro JJ, Hagen JA, DeMeester TR, et al. Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy [see comments]. J Thorac Cardiovasc Surg 1999;117(1):16–23. discussion 23–5.
18. Ell C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer).[see comment]. Gastrointest Endosc 2007;65(1):3–10.
19. Ell C, May A, Gossner L, et al. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology 2000;118(4):670–677.
20. Buttar N, Nijhawan P, Krishnadath K, et al. Combined endoscopic mucosal resection (EMR) and photodynamic therapy (PDT) for esophageal neoplasia within Barrett's esophagus. Gastroenterology 2000;118:A405.
21. Sharma VK, Wang KK, Overholt BF, et al. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients.[see comment]. Gastrointest Endosc 2007;65(2):185–195.
22. Lang L. Radiofrequency ablation is effective treatment for dysplasia in Barrett's esophagus. Gastroenterology 2008;135(1):6.
23. Hernandez JC, Reicher S, Chung D, et al. Pilot series of radiofrequency ablation of Barrett's esophagus with or without neoplasia. Endoscopy 2008;40(5):388–392.
24. Manner H, May A, Pech O, et al. Early Barrett's carcinoma with "low-risk" submucosal invasion: long-term results of endoscopic resection with a curative intent. Am J Gastroenterol 2008;103(10):2589–2597.
25. Tamhankar AP, Peters JH, Portale G, et al. Omeprazole does not reduce gastroesophageal reflux: new insights using multichannel intraluminal impedance technology. J Gastrointest Surg 2004;8(7):890–897. discussion 897–8.
26. Katz PO. Review article: the role of non-acid reflux in gastro-oesophageal reflux disease. Aliment Pharmacol & Ther 2000;14(12):1539–1551.
27. Lord RV, Wickramasinghe K, Johansson JJ, et al. Cardiac mucosa in the remnant esophagus after esophagectomy is an acquired epithelium with Barrett's-like features. Surgery 2004;136(3):633–640.
28. Oberg S, Johansson J, Wenner J, Walther B. Metaplastic columnar mucosa in the cervical esophagus after esophagectomy. Ann Surg 2002;235:338–345.
29. Krishnadath KK, Wang KK, Taniguchi K, et al. Persistent genetic abnormalities in Barrett's esophagus after photodynamic therapy. Gastroenterology 2000;119(3):624–630.
30. Overholt BF, Panjehpour M, Halberg DL. Photodynamic therapy for Barrett's esophagus with dysplasia and/or early stage carcinoma: long-term results.[see comment]. Gastrointest Endosc 2003;58(2):183–188.
31. Prasad GA, Wang KK, Halling KC, et al. Correlation of histology with biomarker status after photodynamic therapy in Barrett esophagus. Cancer 2008;113(3):470–476.
32. Overholt BF, Wang KK, Burdick JS, et al. Five-year efficacy and safety of photodynamic therapy with Photofrin in Barrett's high-grade dysplasia.[see comment]. Gastrointest Endosc 2007;66(3):460–468.

33. Orringer MB, Marshall B, Chang AC, et al. Two thousand transhiatal esophagectomies: changing trends, lessons learned. Ann Surg 2007;246(3):363–372. discussion 372–4.
34. Akiyama H, Tsurumaru M, Kawamura T, Ono Y. Esophageal stripping with preservation of the vagus nerve. Int Surg 1982;67 (2):125–128.
35. Banki F, Mason RJ, DeMeester SR, et al. Vagal-sparing esophagectomy: a more physiologic alternative. Ann Surg 2002;236(3):324–335. discussion 335–6.
36. Peyre CG, DeMeester SR, Rizzetto C, et al. Vagal-sparing esophagectomy: the ideal operation for intramucosal adenocarcinoma and barrett with high-grade dysplasia. Ann Surg 2007;246 (4):665–671. discussion 671–4.
37. Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000;405(6785):458–462.
38. van Westerloo DJ, Giebelen IAJ, Florquin S, et al. The cholinergic anti-inflammatory pathway regulates the host response during septic peritonitis. J Infect Dis 2005;191(12):2138–2148.
39. Luyer MD, Greve JWM, Hadfoune Mh, et al. Nutritional stimulation of cholecystokinin receptors inhibits inflammation via the vagus nerve. J Exp Med 2005;202(8):1023–1029.
40. Ferguson MK, Naunheim KS. Resection for Barrett's mucosa with high-grade dysplasia: implications for prophylactic photodynamic therapy. J Thorac Cardiovasc Surg 1997;114(5):824–829.
41. Headrick JR, Nichols FC 3rd, Miller DL, et al. High-grade esophageal dysplasia: long-term survival and quality of life after esophagectomy.[see comment]. Ann Thorac Surg 2002;73 (6):1697–1702. discussion 1702–3.
42. Williams VA, Watson TJ, Herbella FA, et al. Esophagectomy for high grade dysplasia is safe, curative, and results in good alimentary outcome. J Gastrointest Surg 2007;11(12):1589–1597.

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DEMEESTER FESTSCHRIFT

Esophagectomy Without Mortality: What Can Surgeons Do?

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Abstract
Introduction Surgical resection remains the mainstay treatment for patients with localized esophageal cancer. It is, however, a complex procedure. Mortality rate used to be high, but in recent years, death rate has been reduced to below 5% in specialized centers.
Methods Outcome of esophagectomy can be improved by paying attention to (1) appropriate patient section, (2) choice of surgical techniques and their execution, and (3) optimizing perioperative care. A volume–outcome relationship is also evident. Surgeons can perform esophagectomy without mortality, but a multi-disciplinary team management is essential to achieve this goal.

Keywords Esophagectomy · Surgical resection · Volume–outcome relationship

Introduction

Surgical resection remains the mainstay treatment for patients with localized esophageal cancer. It is justified only when acceptably low morbidity and mortality rates can be achieved; otherwise, the benefits gained by those who survive the operation are offset by the deaths of others.[1] A volume–outcome relationship is evident in complex surgery like esophagectomy; in dedicated high-volume centers, resection mortality rate of 2–3% can be achieved.[2–8] It is also true that the overall mortality rate still approximates 10% when results from multicenter trials and national figures are included.[9,10] It is thus important to appraise the factors leading to such diverse results, and seek ways to improve this.

The outcome of esophagectomy is mainly related to: (1) selecting appropriate patients for resection and optimizing the patients' physiologic status before surgery, (2) choice of surgical techniques and their execution, and (3) perioperative care.

Risk Assessment and Patient Selection for Esophagectomy

Assessing a patient's fitness is often based on the surgeons' experience and intuition rather than an exact science. Objective scores have been developed to aid this process using various statistical methods.[11,12] Using a composite score compromising general status, poor cardiac, hepatic, and respiratory function as independent predictors of postoperative death, one group of investigators reduced postoperative mortality rate from 9.4% to 1.6%.[3,12] It is uncertain if patient selection based on a "strict" mathematical scoring system is better than that of surgeons and anesthesiologists' assessments alone. They are more likely to be complimentary to each other. When patients with squamous cell cancers and adenocarcinomas are compared, they may have different risk profiles, in part related to their dissimilar

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etiological factors. The main risks for the former group seem to be pulmonary and hepatic, related to smoking and alcohol consumption, while for the latter, cardiac risk factors may be more important, associated with obesity.[3] The focus of perioperative care has to be adjusted for these two types of patients.

Once a patient is selected for surgical resection, optimizing his or her physiological status should be an important goal of preoperative preparation. However, what one could achieve is usually limited. Patients with impaired liver reserve related to chronic alcoholism or hepatitis cannot be made better, and pulmonary damage from chronic smoking is mostly irreversible. Patients should still be made to stop smoking and abstain from alcohol and intensive chest physiotherapy applied. Patients with reversible airway obstructive disease should have their bronchodilator therapy optimized. One potentially "treatable" adverse factor is cardiac ischemia; when significant coronary atherosclerotic stenosis is found, revascularization by percutaneous coronary angioplasty is a definite beneficial therapeutic strategy. Patients with high-grade esophageal malignant stricture may have lost substantial amount of their body weight. Providing high caloric and high protein dietary supplement, even in the form of nasogastric tube feeding, will improve their general physique in a relatively short time.

Choice of Surgical Procedure

There are different surgical approaches for esophagectomy, including the transhiatal approach, esophagectomy via a left or right thoracotomy, or in recent years, minimally invasive surgery involving thoracoscopy and/or laparoscopy. There is also a choice of the organ (stomach, colon, and jejunum) used to restore intestinal continuity, the route taken to place the conduit (intrathoracic, orthotopic, retrosternal, or subcutaneous), and the location of the esophageal anastomosis (neck or chest). The intended extent of lymphadenectomy plays an important role in this decision-making. When considering radical lymphadenectomy, the physiological reserve of the patient has to be taken into account, as such an operation may not be appropriate in a high-risk patient.[13] The various combinations of surgical options have to be carefully chosen for individual patient.

The debate on whether a transthoracic or a transhiatal resection is to be used has been ongoing. Proponents of transhiatal resection believe that surgical resection for esophageal cancer is mostly palliative, and a cure is a chance phenomenon for only those with very early tumors. The operating time is also shorter, and postoperative morbidity is less. Equivalent survival to transthoracic resection is claimed.[14] Conversely, surgeons who practice transthoracic esophagectomy consider the open approach to be safer, with less chance of injury to the tracheo-bronchial tree, thoracic duct, recurrent laryngeal nerves, azygous vein, and aorta.[15] A more thorough lymphadenectomy leads to better staging and also longer survival, but at the same time, extensive lymphadenectomy may lead to more postoperative complications.

The largest randomized trial comparing the two approaches to date compared 106 patients who underwent transhiatal esophagectomy with 114 patients who had the transthoracic approach for mid-lower third/cardia adenocarcinomas. Pulmonary complication rates were 27% in the former group compared to 57% in the later. Ventilation time, intensive care, and hospital stay were longer in the transthoracic group. There were, however, no significant differences in in-hospital mortality at 2% and 4%. Significantly more lymph nodes were dissected in the transthoracic group (16 vs. 31). There was a trend toward a survival benefit with the transthoracic approach at 5 years: disease-free survival was 27% compared with 39%, overall survival was 29% compared with 39%. There was also no difference in quality of life in the long run between both groups.[16] A subsequent follow-up study showed that for Siewert type I tumors (true esophageal), an estimated survival benefit of 14% (5-year survival 37% vs. 51%) was evident (though statistically insignificant), while this was absent for type II (true cardia/gastroesophageal junction) cancers (5-year survival 31% and 27%). In addition, in patients with limited nodal disease (one to eight metastatic nodes), a significant survival benefit existed (5-year survival 23% vs. 64%). This effect was not found for patients without nodal metastases or in those with more than eight positive nodes, suggesting that extended lymphadenectomy provides survival benefits in patients with limited spread.[17] Further convincing evidence for the benefit of lymphadenectomy is also shown in a recent international multicenter study involving 2,303 patients from both western and eastern centers, which demonstrated on multivariate analysis that both the number of involved nodes as well as the number of nodes removed at operation were of prognostic significance.[18]

It does seem that the advent of transhiatal esophagectomy came at a time when esophagectomy was a high-risk operation with high mortality rates, and this "less invasive" method probably contributed to reducing overall death rates. With improvement in surgical techniques and perioperative care, it seems that in most experienced centers, when selected appropriately, both procedures can be carried out safely, and the margin of benefit in reducing morbidity for most patients with the transhiatal operation is not overwhelming. There is also increasing evidence of the benefits of radical lymphadenectomy in recent years. With these considerations, the transthoracic approach with radical nodal dissection

should be the procedure of choice in patients with good risk and limited localized disease.

In Asian countries, the transhiatal vs. transthoracic debate has not been a major controversy. This is because the type of cancers are mostly advanced tumors of the middle and upper esophagus. In these patients, from a purely technical and safety standpoint, the transhiatal method is much less suitable except in early tumors. Mediastinal lymph node dissection is also deemed to be more important, given the more proximally located tumors, and these stations cannot be reached from the abdomen. Thus, transthoracic resection remains the surgical approach of choice.

Minimally invasive surgery (MIS) as applied to esophagectomy, like the transhiatal approach, aims at reducing the trauma of surgical access further. What is potentially better than the transhiatal approach is that when a thoracoscopic phase is used, a thorough mediastinal nodal dissection can be performed as well. By reducing the size of the wounds, cardiopulmonary complications may be further reduced, without sacrificing the extent of lymphadenectomy. Indeed, with the magnification offered by thoracoscopy, some investigators have claimed better and more meticulous nodal dissection with the MIS approach.[19,20]

Many different MIS approaches in esophagectomy have been devised, including various combinations of thoracoscopy, laparoscopy, mediastinoscopy, and laparoscopic-assisted (with minilaparotomy or hand-port devices) or thoracoscopic-assisted methods (with minithoracotomy). The myriad of surgical methods implies a lack of consensus on which is superior.[21] The most popular is perhaps thoracoscopic esophagectomy with gastric mobilization via a laparotomy and cervical esophago-gastrostomy.[20,22–25] Most performed the thoracoscopic procedures using a lateral position, though some also advocated a prone position for improved exposure, since the lung and blood naturally fall away from the operating field.[25–27]

Contraindications for thoracoscopic procedures may include extensive pleural adhesions and bulky or locally infiltrative tumors, especially those in close proximity with the tracheo-bronchial tree. Some surgeons do not recommend the procedure in patients with prior irradiation because tissue planes may be obscured,[28] while others do not find this prohibitive.[23] In many series, early-stage cancers or patients with high-grade dysplasia were preferentially selected, partly because of the technical ease with which these tumors can be resected.[29,30] In a large series of 222 patients, two thirds of patients had cancer of stage II and below; 21% had high-grade dysplasia.[31]

The lack of tactile control is probably a contributory factor in some intraoperative complications, such as bleeding from the azygous vein[32] and from intercostal vessel,[33] injury to the aorta,[34] tracheo-bronchial tree,[35,36] and recurrent laryngeal nerve.[37] On the contrary, the increased magnification and excellent visualization offered by thoracoscopy might in fact help lessen complications. Less blood loss[22] and reduction in transient recurrent laryngeal nerve palsy from 80% to 18% were reported.[38] As surgical techniques mature and instrumentation improves, the chance of intra-operative mishaps will likely reduce.

Most published studies include small number of patients, with the exception of a few which included more than 100 patients.[23,25,27,31,39] Direct comparisons of results with patients who underwent conventional esophagectomy, either in concurrent or historical cohorts of patients, are also uncommon. When benefits are found, these included blood loss, shortened intensive care or hospital stay, analgesic requirement, spirometric and pulmonary function derangements,[20,40–42] and biochemical changes.[43] Some authors also reported less morbidities, such as less recurrent laryngeal nerve injury and pulmonary[38] and cardiac complications,[35,44] but certainly these advantages are not universally accepted.[39] Short- to medium-term quality-of-life scores are probably only comparable to that of the open procedure.[45,46] A learning curve exists for such complicated procedures,[38,47] and for most series, the full technical potential may not have been realized.

The place of MIS esophagectomy remains controversial and is evolving. What is certain is that, with the complexity, these techniques should be investigated in centers experienced with open method of esophagectomy.

The tumor resection phase of an esophagectomy must be carried out with care; direct damage to important structures such as the tracheo-bronchial tree or aorta will have disastrous immediate consequences, while injuring the thoracic duct will lead to chylothorax[48] or recurrent laryngeal nerves predisposing patients to aspiration and pneumonia after surgery.

Recovery from esophagectomy depends to a large extent on the reconstructive phase. The most common surgical complication after esophagectomy is still anastomotic leak and can reach 30%,[49] although in experienced centers, leak rates of below 5% can be achieved. Most leaks are probably related to technical faults,[11,50] such as tension between the conduit and the esophageal stump, ischemia of the conduit because of rough handling and poor preparation, and suboptimal anastomotic technique. The intrinsic vascular perfusion of the stomach can be enhanced by certain methods, such as "ischemic pre-conditioning," whereby partial mobilization of the gastric conduit is followed by a second-stage anastomosis later. The perfusion of the stomach could be shown to improve in the interim period.[51] Although an interesting concept and potentially useful, existing wide range of leak rates (from 2–3% to 30%) suggest much improvement could be made by other means, even without ischemic conditioning. It would perhaps be ideal if one could identify the right patients on whom to

perform ischemic conditioning, so that such elaborate preparation can be selectively applied.

The actual method of anastomosis is less important than its proper application. Stapled anastomosis is popular for intrathoracic anastomosis, while the hand-sewn technique is preferred in the neck. There is no evidence from randomized trials that leak rates differ between stapled and hand-sewn anastomoses, but the circular stapler may give rise to more strictures.[52] The linear stapler has also been advocated in the neck. One group reduced their cervical leak rate from 10–15% using a hand-sewn technique to 2.7% using linear staples with a side-to-side anastomosis.[53] With experience, however, the hand-sewn method is as safe, if not more so, and certainly less expensive. Leak rate was 3% in our patients who had an intrathoracic anastomosis, 35% of whom died, resulting in an overall leak-related mortality of 1% out of all patients who had esophagectomy.[50,54]

The route of reconstruction is in part related to the surgical approach for resection. When a cervical anastomosis is chosen, a choice exists for placing the conduit in the orthotopic, retrosternal, or subcutaneous route. The subcutaneous route is rarely used because it is cosmetically unsightly. The retrosternal route has variably been shown to be associated with increased or similar cardiopulmonary morbidity and mortality rates.[55–57] The retrosternal route is 2–3 cm longer compared to the orthotopic route[58] but is rarely of relevance because the esophageal replacement conduit is usually of sufficient length. Some suggest that the tight space at the thoracic inlet in the neck could cause potential constriction on the conduit and recommend partial manubrium, clavicular head, and first rib resection,[59] although the author has found this unnecessary.

Technical variables play an important role in the genesis of postoperative complications. Complications, such as anastomotic leaks (largely technique-related) and recurrent laryngeal nerve injury, for instance, are related to higher incidences of postoperative pulmonary morbidities. At the author's center, pulmonary complications occurred in 10% of patients without technical complications and in 38% of patients who developed such morbidities; mortality rates were 3.3% and 9.2%, respectively.[60] Multivariate analyses also demonstrated that a long operating time was related to pulmonary complications, and increasing intraoperative blood loss was related to postoperative mortality.[61] In sum, the meticulous and expeditious execution of an esophagectomy and its subsequent reconstruction is of paramount importance in lessening complication and mortality rates.

Perioperative Care

With adequate preoperative workup, serious cardiac events like myocardial infarction should be rare. Pulmonary complications remain the most common and serious postoperative morbidity. Most report a respiratory morbidity rate of about 20%.[10] Pneumonia and respiratory failure occur in 15.9% of our patients and are responsible for 55% of hospital deaths. Predictive factors include advanced age, supracarinal tumor location, and lengthened operating time. The increased chance of pulmonary complications associated with supracarinal tumors is in part related to the prevalence of recurrent laryngeal nerve injury, which reduces the effectiveness of glottic closure on coughing, diminishes airway protection, and predisposes to aspiration. Long-term quality of life is also impaired.[62] Neoadjuvant therapy did not lead to increased morbidity.[61] Measures to improve respiratory outcome include cessation of smoking preoperatively, chest physiotherapy, avoidance of recurrent laryngeal nerve injury, cautious fluid administration to avoid fluid overload, use of smaller chest tube,[63] early ambulation, regular bronchoscopy, and early tracheostomy to provide easy access should there be sputum retention despite regular bronchoscopic clearance.[64] Epidural analgesia is invaluable in postoperative pain relief and should be the standard of care after esophagectomy.[65] In a retrospective study at the author's unit, the use of epidural analgesia led to a reduction of major pulmonary complications from 22% to 13%.[65]

As discussed in the previous section, anastomotic leak remains one of the most common and deleterious complications after esophagectomy. Early detection of anastomotic leaks is important so that timely intervention can be instituted; sometimes a high index of suspicion is important when other seemingly unrelated complications develop, such as atrial fibrillation.[66] Atrial arrhythmia is common, affecting about 20% of patients. In itself, atrial fibrillation is benign; rather, it serves as a marker for more serious underlying pulmonary and septic surgical complications.[66] Occurrence of atrial arrhythmia should prompt thorough search for a more ominous underlying cause. In 1946, in the article published by Ivor Lewis on esophagectomy, he commented on the postoperative course of one patient: "On the third day arrhythmia of the heart was present…. In the next two days his respiration increased, moist sounds developed at the bases, and he died six days after the operation." He further wrote: "I now think this case might have been saved by timely and repeated bronchoscopic suction. The cardiac arrhythmia… probably had little to do with his death."[67] Thus, the significance of atrial arrhythmia as a "complication marker" has long been recognized. Treatment principles dictate adequate drainage, whether by radiological, endoscopic, or surgical means. Recent use of a removable plastic stent in sealing anstomotic leaks holds promise as a "minimally invasive method" of leak management.[68] Maintenance of nutritional status is important, preferably via the enteral route, either by a fine-bore

nasoduodenal tube placed endoscopically or by feeding jejunostomy. Improvements in the management of leaks have led to reduction in leak-related mortality. At the author's unit, anastomotic leak rate was 16% in the 1960s to 1970s, 61% of whom died, resulting in a leak-related mortality of 9.8%.[54] In the 1980s, leak rate was 3.5%, of whom 35% died, a leak-related mortality of 1.2%,[50] while in the late 1990s, leak occurred in 3.2% of patients, and none died as a result.[69]

Other surgical complications like chylothorax and herniation of bowel through the diaphragmatic hiatus are rare but should be recognized early, and both are corrected by surgical re-exploration. Early exploration is more likely to be successful than expectant treatment.[70]

Summary

In summary, achieving esophagectomy without mortality depends on realistic patient selection, versatility in the choice of surgical procedure, its meticulous and expeditious execution, vigilant and proactive postoperative care, timely and aggressive intervention, and most of all, multidisciplinary team work involving surgeons, anesthesiologists, intensivists, and other health care workers. An obvious volume–outcome relationship exists,[8,71] but it is the dedicated care of individuals which matters most.

References

1. Wong J. Esophageal resection for cancer: the rationale of current practice. Am J Surg 1987;153:18–24.
2. Law S, Kwong DL, Kwok KF, Wong KH, Chu KM, Sham JS, Wong J. Improvement in treatment results and long-term survival of patients with esophageal cancer: impact of chemoradiation and change in treatment strategy. Ann Surg 2003;238:339–348.
3. Siewert JR, Stein HJ, Feith M, Bruecher BL, Bartels H, Fink U. Histologic tumor type is an independent prognostic parameter in esophageal cancer: lessons from more than 1,000 consecutive resections at a single center in the Western world. Ann Surg 2001;234:360–367.
4. Hagen JA, DeMeester SR, Peters JH, Chandrasoma P, DeMeester TR. Curative resection for esophageal adenocarcinoma: analysis of 100 en bloc esophagectomies. Ann Surg 2001;234:520–530.
5. Altorki N, Kent M, Ferrara C, Port J. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann Surg 2002;236:177–183.
6. Ando N, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann Surg 2000;232:225–232.
7. Birkmeyer JD, Siewers AE, Finlayson EV, Stukel TA, Lucas FL, Batista I, Welch HG, Wennberg DE. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346:1128–1137.
8. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349:2117–2127.
9. Medical Research Council Oesophageal Cancer Working Party. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727–1733.
10. Bailey SH, Bull DA, Harpole DH, Rentz JJ, Neumayer LA, Pappas TN, Daley J, Henderson WG, Krasnicka B, Khuri SF. Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg 2003;75:217–222.
11. Law SY, Fok M, Wong J. Risk analysis in resection of squamous cell carcinoma of the esophagus. World J Surg 1994;18:339–346.
12. Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of oesophagectomy for resectable oesophageal cancer. Br J Surg 1998;85:840–844.
13. Law S, Wong J. What is appropriate treatment for carcinoma of the thoracic esophagus? World J Surg 2001;25:189–195.
14. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies: changing trends, lessons learned. Ann Surg 2007;246:363–372.
15. Katariya K, Harvey JC, Pina E, Beattie EJ. Complications of transhiatal esophagectomy. J Surg Oncol 1994;57:157–163.
16. Hulscher JB, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. N Engl J Med 2002;347:1662–1669.
17. Omloo JM, Lagarde SM, Hulscher JB, Reitsma JB, Fockens P, van Dekken H, ten Kate FJ, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the mid/distal esophagus: five-year survival of a randomized clinical trial. Ann Surg 2007;246:992–1000.
18. Peyre CG, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM, Holscher A, Lerut T, Law S, Rice TW, Ruol A, van Lanschot JJ, Wong J, DeMeester TR. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 2008;248:549–556.
19. Akaishi T, Kaneda I, Higuchi N, Kuriya Y, Kuramoto J, Toyoda T, Wakabayashi A. Thoracoscopic en bloc total esophagectomy with radical mediastinal lymphadenectomy. J Thorac Cardiovasc Surg 1996;112:1533–1540.
20. Osugi H, Takemura M, Higashino M, Takada N, Lee S, Kinoshita H. A comparison of video-assisted thoracoscopic oesophagectomy and radical lymph node dissection for squamous cell cancer of the oesophagus with open operation. Br J Surg 2003;90:108–113.
21. Law S. Minimally invasive techniques for oesophageal cancer surgery. Best Pract Res Clin Gastroenterol 2006;20:925–940.
22. Law S, Fok M, Chu KM, Wong J. Thoracoscopic esophagectomy for esophageal cancer. Surgery 1997;122:8–14.
23. Yamamoto S, Kawahara K, Maekawa T, Shiraishi T, Shirakusa T. Minimally invasive esophagectomy for stage I and II esophageal cancer. Ann Thorac Surg 2005;80:2070–2075.
24. Law SY, Fok M, Wei WI, Lam LK, Tung PH, Chu KM, Wong J. Thoracoscopic esophageal mobilization for pharyngolaryngoesophagectomy. Ann Thorac Surg 2000;70:418–422.
25. Smithers BM, Gotley DC, McEwan D, Martin I, Bessell J, Doyle L. Thoracoscopic mobilization of the esophagus. A 6 year experience. Surg Endosc 2001;15:176–182.
26. Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. J R Coll Surg Edinb 1992;37:7–11.
27. Palanivelu C, Prakash A, Senthilkumar R, Senthilnathan P, Parthasarathi R, Rajan PS, Venkatachlam S. Minimally invasive

esophagectomy: thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position—experience of 130 patients. J Am Coll Surg 2006;203:7–16.
28. Nakatsuchi T, Otani M, Osugi H, Ito Y, Koike T. The necessity of chest physical therapy for thoracoscopic oesophagectomy. J Int Med Res 2005;33:434–441.
29. Bernabe KQ, Bolton JS, Richardson WS. Laparoscopic hand-assisted versus open transhiatal esophagectomy: a case-control study. Surg Endosc 2005;19:334–337.
30. Espat NJ, Jacobsen G, Horgan S, Donahue P. Minimally invasive treatment of esophageal cancer: laparoscopic staging to robotic esophagectomy. Cancer J 2005;11:10–17.
31. Luketich JD, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCaughan JS, Litle VR, Schauer PR, Close JM, Fernando HC. Minimally invasive esophagectomy: outcomes in 222 patients. Ann Surg 2003;238:486–494.
32. Peracchia A, Rosati R, Fumagalli U, Bona S, Chella B. Thoracoscopic dissection of the esophagus for cancer. Int Surg 1997;82:1–4.
33. Collard JM, Lengele B, Otte JB, Kestens PJ. En bloc and standard esophagectomies by thoracoscopy. Ann Thorac Surg 1993;56:675–679.
34. Cuschieri A. Thoracoscopic subtotal oesophagectomy. Endosc Surg Allied Technol 1994;2:21–25.
35. Bumm R, Feussner H, Bartels H, Stein H, Dittler HJ, Hofler H, Siewert JR. Radical transhiatal esophagectomy with two-field lymphadenectomy and endodissection for distal esophageal adenocarcinoma. World J Surg 1997;21:822–831.
36. Kawahara K, Maekawa T, Okabayashi K, Hideshima T, Shiraishi T, Yoshinaga Y, Shirakusa T. Video-assisted thoracoscopic esophagectomy for esophageal cancer. Surg Endosc 1999;13:218–223.
37. Dexter SP, Martin IG, McMahon MJ. Radical thoracoscopic esophagectomy for cancer. Surg Endosc 1996;10:147–151.
38. Akaishi T, Kaneda I, Higuchi N, Kuriya Y, Kuramoto J, Toyoda T, Wakabayashi A. Thoracoscopic en bloc total esophagectomy with radical mediastinal lymphadenectomy. J Thorac Cardiovasc Surg 1996;112:1533–1540.
39. Shiraishi T, Kawahara K, Shirakusa T, Yamamoto S, Maekawa T. Risk analysis in resection of thoracic esophageal cancer in the era of endoscopic surgery. Ann Thorac Surg 2006;81:1083–1089.
40. Taguchi S, Osugi H, Higashino M, Tokuhara T, Takada N, Takemura M, Lee S, Kinoshita H. Comparison of three-field esophagectomy for esophageal cancer incorporating open or thoracoscopic thoracotomy. Surg Endosc 2003;17:1445–1450.
41. Nguyen NT, Follette DM, Wolfe BM, Schneider PD, Roberts P, Goodnight JE. Comparison of minimally invasive esophagectomy with transthoracic and transhiatal esophagectomy. Arch Surg 2000;135:920–925.
42. van den Broek WT, Makay O, Berends FJ, Yuan JZ, Houdijk AP, Meijer S, Cuesta MA. Laparoscopically assisted transhiatal resection for malignancies of the distal esophagus. Surg Endosc 2004;18:812–817.
43. Fukunaga T, Kidokoro A, Fukunaga M, Nagakari K, Suda M, Yoshikawa S. Kinetics of cytokines and PMN-E in thoracoscopic esophagectomy. Surg Endosc 2001;15:1484–1487.
44. Bumm R, Holscher AH, Feussner H, Tachibana M, Bartels H, Siewert JR. Endodissection of the thoracic esophagus. Technique and clinical results in transhiatal esophagectomy. Ann Surg 1993;218:97–104.
45. Osugi H, Takemura M, Lee S, Nishikawa T, Fukuhara K, Iwasaki H, Higashino M. Thoracoscopic esophagectomy for intrathoracic esophageal cancer. Ann Thorac Cardiovasc Surg 2005;11:221–227.
46. Leibman S, Smithers BM, Gotley DC, Martin I, Thomas J. Minimally invasive esophagectomy: short- and long-term outcomes. Surg Endosc 2005;203:428–433.
47. Osugi H, Takemura M, Higashino M, Takada N, Lee S, Ueno M, Tanaka Y, Fukuhara K, Hashimoto Y, Fujiwara Y, Kinoshita H. Learning curve of video-assisted thoracoscopic esophagectomy and extensive lymphadenectomy for squamous cell cancer of the thoracic esophagus and results. Surg Endosc 2003;17:515–519.
48. Lo OS, Law S, Chu KM, Wong J. Chylothorax after esophagectomy. Surgery 2003;133:340–341.
49. Hsu HK, Hsu WH, Huang MH. Prospective study of using fibrin glue to prevent leak from esophagogastric anastomosis. J Surg Assoc ROC 1992;25:1248–1252.
50. Whooley BP, Law S, Alexandrou A, Murthy SC, Wong J. Critical appraisal of the significance of intrathoracic anastomotic leakage after esophagectomy for cancer. Am J Surg 2001;181:198–203.
51. Holscher AH, Schneider PM, Gutschow C, Schroder W. Laparoscopic ischemic conditioning of the stomach for esophageal replacement. Ann Surg 2007;245:241–246.
52. Law S, Fok M, Chu KM, Wong J. Comparison of hand-sewn and stapled esophagogastric anastomosis after esophageal resection for cancer: a prospective randomized controlled trial. Ann Surg 1997;226:169–173.
53. Orringer MB, Marshall B, Iannettoni MD. Eliminating the cervical esophagogastric anastomotic leak with a side-to-side stapled anastomosis. J Thorac Cardiovasc Surg 2000;119:277–288.
54. Lorentz T, Fok M, Wong J. Anastomotic leakage after resection and bypass for esophageal cancer: lessons learned from the past. World J Surg 1989;13:472–477.
55. Bartels H, Thorban S, Siewert JR. Anterior versus posterior reconstruction after transhiatal oesophagectomy: a randomized controlled trial. Br J Surg 1993;80:1141–1144.
56. Gawad KA, Hosch SB, Bumann D, Lubeck M, Moneke LC, Bloechle C, Knoefel WT, Busch C, Kuchler T, Izbicki JR. How important is the route of reconstruction after esophagectomy: a prospective randomized study. Am J Gastroenterol 1999;94:1490–1496.
57. van Lanschot JJ, van Blankenstein M, Oei HY, Tilanus HW. Randomized comparison of prevertebral and retrosternal gastric tube reconstruction after resection of oesophageal carcinoma. Br J Surg 1999;86:102–108.
58. Ngan SYK, Wong J. Lengths of different routes for esophageal replacement. J Thorac Cardiovasc Surg 1986;91:790–792.
59. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann Surg 1999;230:392–400.
60. Ferri LE, Law S, Wong KH, Kwok KF, Wong J. The influence of technical complications on postoperative outcome and survival after esophagectomy. Ann Surg Oncol 2006;13:557–564.
61. Law S, Wong KH, Kwok KF, Chu KM, Wong J. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 2004;240:791–800.
62. Baba M, Aikou T, Natsugoe S, Kusano C, Shimada M, Nakano S, Fukumoto T, Yoshinaka H. Quality of life following esophagectomy with three-field lymphadenectomy for carcinoma, focusing on its relationship to vocal cord palsy. Dis Esophagus 1998;11:28–34.
63. Law S, Boey JP, Kwok KF, Wong KH, Chu KM, Wong J. Pleural drainage after transthoracic esophagectomy: experience with a vacuum system. Dis Esophagus 2004;17:81–86.
64. Whooley BP, Law S, Murthy SC, Alexandrou A, Wong J. Analysis of reduced death and complication rates after esophageal resection. Ann Surg 2001;233:338–344.
65. Tsui SL, Law S, Fok M, Lo JR, Ho E, Yang J, Wong J. Postoperative analgesia reduces mortality and morbidity after esophagectomy. Am J Surg 1997;173:472–478.

66. Murthy SC, Law S, Whooley BP, Alexandrou A, Chu KM, Wong J. Atrial fibrillation after esophagectomy is a marker for postoperative morbidity and mortality. J Thorac Cardiovasc Surg 2003;126:1162–1167.
67. Lewis I. The surgical treatment of carcinoma of the esophagus with special reference to a new operation for growths of the middle third. Br J Surg 1946;34:18.
68. Freeman RK, Ascioti AJ, Wozniak TC. Postoperative esophageal leak management with the Polyflex esophageal stent. J Thorac Cardiovasc Surg 2007;133:333–338.
69. Law S, Suen DT, Wong KH, Kwok KF, Wong J. A single-layer, continuous, hand-sewn method for esophageal anastomosis: prospective evaluation in 218 patients. Arch Surg 2005;140:33–39.
70. Merrigan BA, Winter DC, O'Sullivan GC. Chylothorax. Br J Surg 1997;84:15–20.
71. Dimick JB, Pronovost PJ, Cowan JA, Lipsett PA. Surgical volume and quality of care for esophageal resection: do high-volume hospitals have fewer complications? Ann Thorac Surg 2003;75:337–341.

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DEMEESTER FESTSCHRIFT

Minimally Invasive Esophagectomy

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Abstract
Introduction Minimally invasive esophagectomy has gained popularity over the past two decades. The procedural goal is to decrease the high overall morbidity of a traditional open esophageal resection. The entire spectrum of open esophagectomy techniques has been successfully replicated in a minimally invasive fashion.
Discussion Esophagectomy remains one of the most technically challenging operations, and developing the skills necessary for minimal invasive esophagectomy is associated with a steep learning curve. Minimally invasive approaches show most promise for benign disease and select early esophageal cancers, but their role in more advanced cancer remains controversial due to lack of long-term results.
Conclusion As minimally invasive esophagectomy matures, its true value in both benign and malignant disorders will become better defined.

Keywords Esophagectomy · Minimally invasive surgery · Perioperative morbidity

Introduction

Esophagectomy remains one of the most complex and technically challenging surgical procedures. Indications for surgery range from end-stage benign disorders of the esophagus to cancer. Unfortunately, esophagectomy, even when performed by expert surgeons, is associated with high rates of perioperative morbidity, including anastamotic leaks, pneumonia, and tachyarrythmias. Fortunately, operative mortality has progressively declined in spite of the high rate of complications related to the surgery. Consequently, esophageal resection is often viewed as a last resort treatment strategy. In addition, esophagectomy has been identified as a volume-sensitive procedure, and efforts are currently being made to direct patients to high-volume providers practicing at high-volume institutions.

The concept of minimally invasive surgery was based on the assumption that surgical morbidity could be decreased if incisions were smaller and that this could be done without reducing the therapeutic quality of the procedure performed. This philosophy is an extension of the well-known surgical principle of gentle tissue handling to minimize damage and also aims to decrease the psychological impact of surgery for patients. Indeed, "key-hole" surgery has revolutionized our approach to surgical problems as well as enhanced acceptance of these procedures by patients and referring physicians. Applying these concepts has lead to well-documented decreases in tissue trauma, lessened stress response, improved recovery, and increased patient satisfaction for a wide variety of surgical procedures.

However, achieving proficiency in minimally invasive surgery can be challenging, and patient benefits may not be immediately apparent. Nearly all minimally invasive procedures experience an initial increase in complications during the so-called learning curve. For these reasons, acceptance of minimal access techniques has been mixed

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for more complicated procedures such as esophagectomy, an operation for which the incisions are not necessarily the source for the majority of complications.

In the early days of minimally invasive surgery, a few pioneers ventured forth to conquer the esophagus. Naturally, diseases limited to the abdominal esophagus were pursued first. It did not take long for the benefits of laparoscopy to be realized for disorders of the distal esophagus such as gastroesophageal reflux disease and achalasia.[1–3] Soon, Cuschieri and Collard separately published the first thoracoscopic esophageal mobilizations for esophagectomy in the early 1990s.[4,5] The first totally endoscopic esophagectomies were reported by DePaula in 1995 and Swanström in 1997 via a transhiatal approach.[6,7] Finally, Luketich finished off the 1990s by reporting combined thoracoscopic/laparoscopic approaches to minimally invasive esophagectomy.[8]

Today, a wide variety of techniques have been developed and refined such that, now, the full spectrum of open esophagectomy options have been adapted to minimally invasive surgery. The goals of minimally invasive esophagectomy (MIE) are to replicate and even to exceed the therapeutic results of open surgery, to decrease associated morbidity, hospital stay, and postoperative pain, facilitate recovery, and improve psychological acceptance of surgical treatment for patients.

Indications

Benign indications for esophagectomy include persistent dysphagia due to refractory peptic stricture, end-stage achalasia and other motor disorders with anatomic abnormalities, multiple redo antireflux operations, and occasionally perforations. The rationale of embarking on such a radical treatment for a non-lethal disorder of the esophagus is largely to provide improved quality of life. The decision to proceed is usually a last resort measure after years of failure of alternative therapies. MIE arguably may make its biggest impact in this group of patients. In comparison to those with cancer, these patients often are in better health, have not had concurrent chemotherapy or radiation, and do not need a major oncologic dissection. Overall, theoretically, these patients have more reserve to tolerate surgery, and they need less surgery.

Indications for cancer are more controversial. Esophagectomy without extensive lymphadenectomy has been shown to have excellent results in the setting of high-grade dysplasia and intramucosal cancer.[9,10] MIE is ideal in this setting using the techniques described above for benign disease but is in direct competition with endoscopic therapies such as endoscopic mucosal resection and ablation despite relative paucity of long-tern outcomes data.[11,12] MIE for more advanced cancer is gaining acceptance as techniques are refined and results comparable to open operations accumulate.[8,13–19]

Minimally Invasive Esophagectomy Techniques

As there has never been a consensus regarding the superiority of any of the various open esophagectomy techniques, it is not surprising that there is no agreement on the best MIE approach either. It can be stated however, that minimally invasive adaptations of every conceivable approach to esophageal resection have been reported (Table 1).

Transhiatal MIE utilizes laparoscopic abdominal dissection and preparation of the gastric conduit followed by a cervical anastamosis created via a traditional open approach in the neck (Fig. 1). Mediastinal dissection of periesophageal lymph nodes, including those in the subcarinal station, can be accessed through the hiatus, if needed, utilizing the lighting and magnification afforded by the laparoscopic technology.[7] The esophageal specimen can be removed through the neck incision obviating the requirement for an extraction incision in the abdomen. Some surgeons prefer to combine the laparoscopic transhiatal approach with a mini-laparotomy to facilitate gastric tube creation as well as to remove the specimen. Finally, the esophagus can also be removed from the mediastinum via an inversion technique with or without division of the vagus nerves (Fig. 2).[10,20] In these operations, the phrenoesophageal ligament is divided, and the esophagus is inverted from the neck using a large vein stripper.

Many prefer a thoracoscopic approach when extensive mediastinal dissection of the esophagus is required such as for cancer. This operation is typically performed through the right chest, with patients positioned in lateral decubitus or prone.[21,22] (Figure 3) Single lung ventilation via a double lumen endotracheal tube can be used or, alternatively, standard laparoscopic trocars can be used along with positive pressure carbon dioxide insufflation to deflate the lung. Thoracoscopy can be used as part of a minimally invasive “three-hole” esophagectomy, where the procedure begins in the chest and ends with laparoscopy and a cervical anastamosis or as part of the Ivor Lewis esophagectomy where the esophagogastric anastamosis resides in the chest. In this procedure, the specimen is removed through a mini-thoracotomy, and the anastamosis is created above the azygus vein.[14]

Combinations of open and minimally invasive techniques are also an option, such as laparoscopy with thoracotomy or thoracoscopy with laparotomy. These so-called hybrid techniques are applied for a variety of reasons, such as prior surgery in either cavity, surgeon experience, and comfort level or simply surgeon preference.

Although the goal of minimally invasive surgery is to perform the equivalent open operation without omitting critical steps for the sake of an incision, some aspects, considered by many as routine for open esophagectomy,

Table 1 Minimally Invasive Esophagectomy Techniques

Thoracoscopic/laparoscopic esophagectomy with cervical anastamosis
Thoracoscopic/laparoscopic esophagectomy with thoracic anastamosis
Total laparoscopic transhiatal esophagectomy
Laparoscopic inversion esophagectomy (with or without preservation of vagal nerves)
Thoracoscopic esophageal mobilization with laparotomy and cervical anastamosis (hybrid)
Laparoscopic gastric mobilization with thoracotomy and intrathoracic anastamosis (hybrid)

have fallen out of favor as the approaches have been refined. Specifically, the performance of a pyloroplasty has been found unnecessary in the presence of a sufficiently narrow gastric conduit (3 cm).[23] Secondly, selective placement of feeding jejunostomy tubes has been adopted, as return to oral alimentation has been rapid after procedures such as vagal sparing esophagectomy.[10,24] Lastly, many surgeons do not remove the azygus vein during a thoracoscopic mediastinal lymph node dissection. While all of these esophagectomy adjuncts could be performed safely with minimally invasive techniques, identifying them as potentially optional, no doubt, streamlines the operation and provides yet another avenue to decrease potential morbidity whether the esophagus is removed through an open or minimally invasive approach.

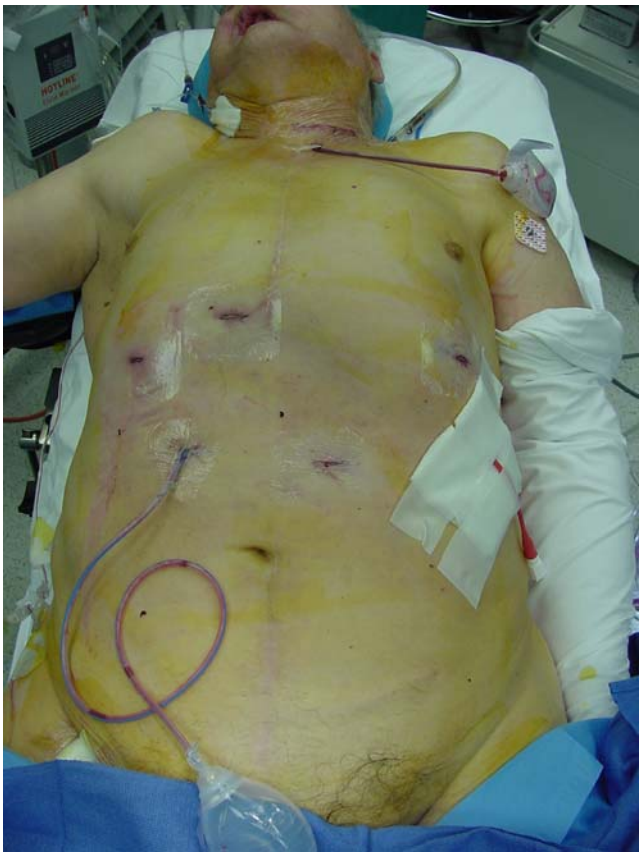

Figure 1 Final view of patient after minimally invasive transhiatal esophagectomy demonstrating laparoscopic incisions, abdominal, and cervical drains and feeding jejunostomy tube.

A minimally invasive inversion esophagectomy, sparing the vagus nerves when possible, should be the procedure of choice for refractory benign disease. This transhiatal operation is the least invasive esophagectomy, requires less operative time, and has excellent functional outcomes.[20,24] Feeding tube placement can be determined based on the individual patient's nutritional status before surgery. The chest need not be violated for benign disease, unless there is concern for an inadequate gastric conduit length to perform a safe cervical anastamosis such as a history of multiple previous fundoplications.

Results

The primary goal of MIE is to decrease surgical morbidity associated with the open approach. No direct comparative trials have been performed between open and MIE and may be difficult due to the wide variety of techniques available

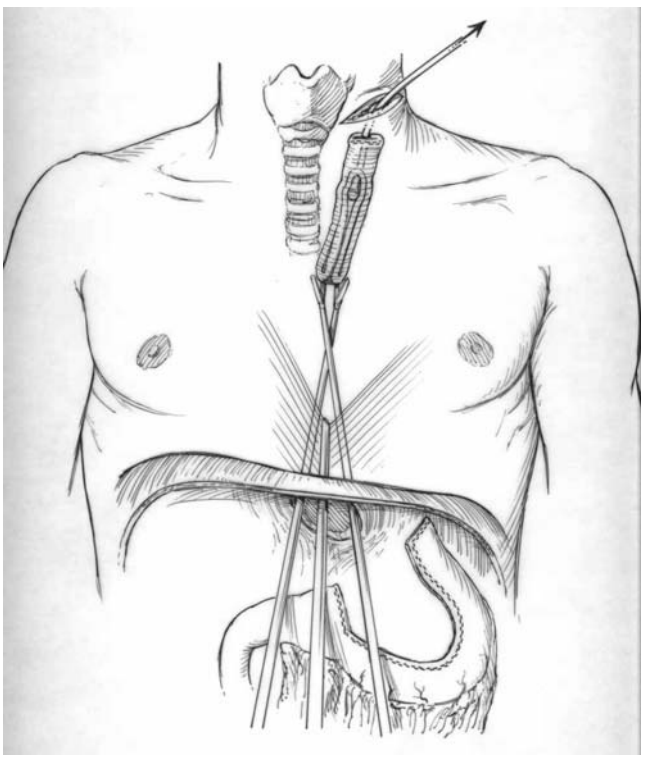

Figure 2 Transcervical inversion esophagectomy using a vein stripper to remove the esophagus through the cervical incision.

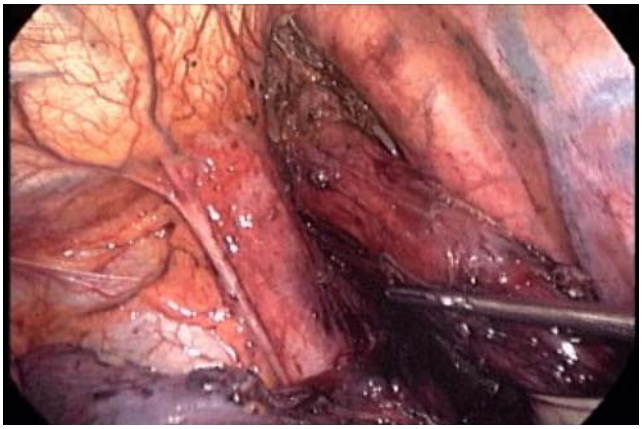

Figure 3 Thoracoscopic view of distal esophageal mobilization in prone position.

and the relative low number of procedures performed. At present, the data shows that mortality rates and the incidence of complications reported are essentially equivalent for both techniques (Table 2). It is likely that any benefit of MIE is overshadowed by the persistent rate of complications independent of the approach such as anastamotic leaks. It seems conceivable that, in the absence of such complications, patients with the minimally access approach enjoy quicker recovery with return to normal activities and decreased long-term pain when compared to patients with similarly uncomplicated open procedures. This, however, has yet to be proven.

MIE has been demonstrated as feasible for esophageal cancer resection, but the oncologic value and safety is often questioned especially following radiation. The debate over optimal surgical approach for esophageal cancer, regardless of technique, continues despite accumulating evidence in support of radical lymphadenectomy.[31–34] Few MIE series report lymph node retrieval or long-term results (Table 3). From a technical and biological standpoint, the outcomes of open and minimally invasive esophageal resection for cancer should be equivalent. Improved lighting and visibility along with magnification afforded by minimally invasive equipment may prove superior for meticulous dissection and lymph node harvest. However, until large series report long-term survival by stage, the true oncologic value of MIE for cancer will remain controversial.

Minimally Invasive Esophagectomy Learning Curve

As with all procedures, there are inherent technical challenges faced when applying a new technique. Esophagectomy is a complex, technically challenging procedure fraught with potential pitfalls in nearly every step of the procedure. Many of the largest open series discuss the fact that morbidity and mortality decrease with experience.[25,29,30] Technical complication rates have also been shown to negatively impact cancer specific survival.[27] As such, esophagectomy has been designated an operation best left in the hands of experts at

Table 2 Review of Surgical Outcomes of Esophagectomy

Author	Technique	n	Mortallity	Overall Morbidity	Pneumonia	Cardiac Arrythmia	Anastamotic Leak	Graft Ischemia	Chylothorax
Hofstetter et al. 2002[25]	Open	994	7	NR	NR	NR	9	NR	NR
Bailey et al. 2003[26]	Open	1,777	10	49.5	21	NR	NR	0.8	NR
Rizk et al. 2004[27]	Open	510	NR	NR	NR	NR	21	1	NR
Portale et al. 2006[28]	Open	263	4.5	NR	10	16	12	2	3
Orringer et al. 2007[29]	Open	2,007	3	NR	2	NR	12	2	1
Low et al. 2007[30]	Open	340	0.3	45	NR	13	3.8	0	4
Williams et al. 2007[9]	Open	35	0	37	8	3	9	0	3
Smithers et al. 2007[17]	Open	114	2.6	NR	27.8	18.4	8.7	1.7	6.1
Luketich et al. 200[38]	MIE	222	1.4	NR	7.7	NR	11.7	3.2	3.2
Nguyen et al. 2003[13]	MIE	46	4.3	17.4	2	NR	4	0	0
Bizekis et al. 2006[14]	MIE	50	6	NR	10	14	6	0	2
Palanivelu et al. 2006[15]	MIE	130	1.5	20.8	1.5	5.4	2.3	0	0.8
Collins et al. 2006[16]	MIE	25	4	32	12	16	12	0	4
Smithers et al. 2007[17]	MIE	23	0	NR	30	26	4	4	4
Fabian et al. 2007[18]	MIE	22	4.5	23	5	19	14	5	0
Sunpaweravong et al. 2008[19]	MIE	28	3.5	32	21	NR	7	0	NR

All values reported as percentages

n number, *MIE* minimally invasive esophagectomy, *NR* not reported

Table 3 Oncologic Outcomes of Minimally Invasive Esophagectomy

	Lymph node retrieval	Percent 3-Year Survival
Cadiere et al.[35]	29	NR
Luketich et al.[8]	16	36
Berrisford et al.[36]	21	50[a]
Fabian et al.[18]	16	NR
Smithers et al.[17]	17	22
Nguyen et al.[13]	11	57
Palanivelu et al.[15]	18	45
Yamamoto et al.[37b]	28	52

NR not reported

[a] Estimation based on predicted median survival of 35 months

[b] Represents only the mediastinal nodes

high-volume centers. Little is written regarding the learning curve for MIE directly, but it has been suggested that it may be more than 50 procedures.[14,38]

Ideally, MIE should be relegated to surgeons experienced in both advanced laparoscopy/thoracoscopy and surgical oncology for esophageal cancer. Combined teams of specialists, including minimally invasive surgeons, thoracic surgeons, and surgical oncologists, can be helpful especially during the first several cases. Dedication to mastery of several MIE techniques allows the operation to be tailored to the individual patient using the least invasive approach matched to the pathology at hand. Certainly, the extent of oncologic resection should be based on the tumor, not the technique, and should be the primary goal particularly during the learning curve for MIE. Minimally invasive approaches to all GI diseases are very popular with patients and referring physicians—it makes sense for all high-volume esophageal surgery programs to adopt minimally invasive techniques and to master the learning curve as rapidly as possible.

Discussion

Learning curve issues aside, MIE for benign disease makes undeniable sense, and without a less invasive alternative for pre- and early malignancies, it is likely that endoscopic therapies will replace surgery for this indication. The controversy of course is the treatment of invasive cancers. Open esophagectomy remains the most effective treatment for esophageal cancer with current 5-year survival rates reported approximately 50% in several selective series.[28,30,39] This is a dramatic improvement over the past few decades when survival rates were consistently less than 20%. In fact, curative resection is possible for the *majority* of patients presenting with early esophageal adenocarcinoma. Cancers that have not penetrated the muscularis mucosa rarely spread to regional lymph nodes or beyond making it not only possible, but likely, that cure can be achieved with resection.[40] On the other hand, advancements in flexible endoscopic therapies are rapidly defining their role in early esophageal cancer treatment with techniques such as endoscopic mucosal resection and radiofrequency ablation,[11,12] calling the role of traditional esophagectomy into question. Esophageal preserving techniques show great promise as a definitive treatment option for small, superficial lesions in practices dedicated to intensive surveillance protocols but long-term outcomes are largely unknown. Esophagectomy remains the only method to completely remove all at risk mucosa without the need for serial follow-up monitoring. Esophagectomy without extensive lymphadenectomy has been shown to have excellent results in the setting of high-grade dysplasia and intramucosal cancer.[9,10] MIE is ideal in this setting particularly inversion esophagectomy with preservation of the vagal nerves when possible. Individual patient characteristics need to be considered when contemplating the pursuit of esophageal preserving techniques over a MIE. Factors that may favor endoscopic mucosal resection include unifocal disease, short segment Barrett's esophagus, normal esophageal function, absence of anatomic derangements such as diverticuli, large hiatal hernia, or persistent stricture.

Cancers that extend into and beyond the submucosal layer have a progressively higher rate of lymphatic involvement and distant metastasis. To combat these larger cancers, more extensive resection is required. Open esophagectomy remains the gold standard treatment for this disease. Improvements in chemoradiation protocols have been reported as effective adjuncts to surgical therapy. Today, a multimodality approach to esophageal cancer is common and preferred for tumors extending beyond the submucosa or with suspected lymph node involvement.[41] Unfortunately, the majority of patients with stage III esophageal adenocarcinoma still succumb to the disease despite the treatment modality.

As a result of research endeavors aimed at determining the most effective chemoradiation treatments, some patients who were deemed unfit for surgery or who simply refused surgery were cured without esophageal resection. Although these findings were initially limited to investigational protocols, over the years, the practice of offering definitive chemoradiation for potential cure has spread. When confronted with the potential 20–50% major morbidity rates reported in the esophagectomy literature and the historically

limited potential for cure, many patients and oncologists simply remove surgery as an option even for some with stage II disease. This decision is often made without surgical consultation and is supported by various articles citing outdated mortality and cure rates.[42] MIE provides a more palatable surgical approach to esophageal cancer resection, provided that there is dedication to its development and commitment to oncologic principles.

Conclusions

MIE has been gaining popularity since the first reports nearly two decades ago. Similar to open surgery, several techniques exist including totally laparoscopic transhiatal or transthoracic resections as well as combination, or hybrid, techniques. Much as with open esophageal surgery, no consensus has been reached regarding the superiority of any particular MIE adaptation. Comprehensive esophageal programs typically rely on the minimally invasive approach that best reflects their institutional approach or treatment algorithm. Currently, no significant decrease in operative morbidity has been proven for MIE compared to its open counterpart, but no direct, randomized trials have been done.

The least invasive esophagectomy technique is the inversion esophagectomy with or without preservation of the vagal nerves. This procedure is suitable for benign esophageal disease and early esophageal cancer, as extended lymphadenectomy is not required. Most reports of MIE for more advanced cancers include a thoracic dissection. The role for MIE in these cancers is controversial but will likely become more defined as the procedures mature beyond its steep learning curve and long-term outcome data becomes available.

References

1. Dallemagne B, Weerts JM, Jehaes C, Markiewicz S, Lombard R. Laparoscopic Nissen fundoplication: preliminary report. Surg Laparosc Endosc 1991;1(3):138–143.
2. Cuschieri A. Laparoscopic antireflux surgery and repair of hiatal hernia. World J Surg 1993;17(1):40–45.
3. Cuschieri A, Hunter J, Wolfe B, Swanström LL, Hutson W. Multicenter prospective evaluation of laparoscopic antireflux surgery. Preliminary report. Surg Endosc 1993;7(6):505–510.
4. Cuschieri A, Shimi S, Banting S. Endoscopic oesophagectomy through a right thoracoscopic approach. J R Coll Surg Edinb 1992;37(1):7–11.
5. Collard JM, Lengele B, Otte JB, Kestens PJ. En bloc and standard esophagectomies by thoracoscopy. Ann Thorac Surg 1993;56 (3):675–679.
6. DePaula AL, Hashiba K, Ferreira EA, de Paula RA, Grecco E. Laparoscopic transhiatal esophagectomy with esophagogastroplasty. Surg Laparosc Endosc 1995;5(1):1–5.
7. Swanström LL, Hansen P. Laparoscopic total esophagectomy. Arch Surg 1997;132(9):943–947. (discussion 947–949).
8. Luketich JD, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCaughan JS, Litle VR, Schauer PR, Close JM, Fernando HC. Minimally invasive esophagectomy: outcomes in 222 patients. Ann Surg 2003;238(4):486–494.
9. Williams VA, Watson TJ, Herbella FA, Gellersen O, Raymond D, Jones C, Peters JH. Esophagectomy for high grade dysplasia is safe, curative, and results in good alimentary outcome. J Gastrointest Surg 2007;11(12):1589–1597.
10. Peyre CG, DeMeester SR, Rizzetto C, Bansal N, Tang AL, Ayazi S, Leers JM, Lipham JC, Hagen JA, DeMeester TR. Vagal-sparing esophagectomy: the ideal operation for intramucosal adenocarcinoma and barrett with high-grade dysplasia. Ann Surg 2007;246 (4):665–671. (discussion 671–674).
11. Ell C, May A, Gossner L, Pech O, Günter E, Mayer G, Henrich R, Vieth M, Müller H, Seitz G, Stolte M. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. Gastroenterology 2000;118(4):670–677.
12. Sharma VK, Wang KK, Overholt BF, Lightdale CJ, Fennerty MB, Dean PJ, Pleskow DK, Chuttani R, Reymunde A, Santiago N, Chang KJ, Kimmey MB, Fleischer DE. Balloon-based, circumferential, endoscopic radiofrequency ablation of Barrett's esophagus: 1-year follow-up of 100 patients. Gastrointest Endosc 2007;65(2):185–195.
13. Nguyen NT, Roberts P, Follette DM, Rivers R, Wolfe BM. Thoracoscopic and laparoscopic esophagectomy for benign and malignant disease: lessons learned from 46 consecutive procedures. J Am Coll Surg 2003;197(6):902–913.
14. Bizekis C, Kent MS, Luketich JD, Buenaventura PO, Landreneau RJ, Schuchert MJ, Alvelo-Rivera M. Initial experience with minimally invasive Ivor Lewis esophagectomy. Ann Thorac Surg 2006;82(2):402–406.
15. Palanivelu C, Prakash A, Senthilkumar R, Senthilnathan P, Parthasarathi R, Rajan PS, Venkatachlam S. Minimally invasive esophagectomy: thoracoscopic mobilization of the esophagus and mediastinal lymphadenectomy in prone position—experience of 130 patients. J Am Coll Surg 2006;203(1):7–16.
16. Collins G, Johnson E, Kroshus T, Ganz R, Batts K, Seng J, Nwaneri O, Dunn D. Experience with minimally invasive esophagectomy. Surg Endosc 2006;20(2):298–301.
17. Smithers BM, Gotley DC, Martin I, Thomas JM. Comparison of the outcomes between open and minimally invasive esophagectomy. Ann Surg 2007;245(2):232–240.
18. Fabian T, Martin JT, McKelvey AA, Federico JA. Minimally invasive esophagectomy: a teaching hospital's first year experience. Dis Esophagus 2008;21(3):220–225.
19. Sunpaweravong S, Chewatanakornkul S, Ruangsin S. Initial experience and result of thoracoscopic and laparoscopic esophagectomy. J Med Assoc Thai 2008;91(8):1202–1205.
20. Jobe BA, Reavis KM, Davis JJ, Hunter JG. Laparoscopic inversion esophagectomy: simplifying a daunting operation. Dis Esophagus 2004;17(1):95–97.
21. Dapri G, Himpens J, Cadière GB. Minimally invasive esophagectomy for cancer: laparoscopic transhiatal procedure or thoracoscopy in prone position followed by laparoscopy? Surg Endosc 2008;22 (4):1060–1069.
22. Fabian T, Martin J, Katigbak M, McKelvey AA, Federico JA. Thoracoscopic esophageal mobilization during minimally invasive esophagectomy: a head-to-head comparison of prone versus decubitus positions. Surg Endosc 2008;22(11):2485–2491.
23. Swanström LL. Minimally invasive surgical approaches to esophageal cancer. J Gastrointest Surg 2002;6(4):522–526.
24. Banki F, Mason RJ, DeMeester SR, Hagen JA, Balaji NS, Crookes PF, Bremner CG, Peters JH, DeMeester TR. Vagal-sparing esophagectomy: a more physiologic alternative. Ann Surg 2002;236 (3):324–335. (discussion 335–336).

25. Hofstetter W, Swisher SG, Correa AM, Hess K, Putnam JB Jr, Ajani JA, Dolormente M, Francisco R, Komaki RR, Lara A, Martin F, Rice DC, Sarabia AJ, Smythe WR, Vaporciyan AA, Walsh GL, Roth JA. Treatment outcomes of resected esophageal cancer. Ann Surg 2002;236(3):376–384.
26. Bailey SH, Bull DA, Harpole DH, Rentz JJ, Neumayer LA, Pappas TN, Daley J, Henderson WG, Krasnicka B, Khuri SF. Outcomes after esophagectomy: a ten-year prospective cohort. Ann Thorac Surg 2003;75(1):217–222.
27. Rizk NP, Bach PB, Schrag D, Bains MS, Turnbull AD, Karpeh M, Brennan MF, Rusch VW. The impact of complications on outcomes after resection for esophageal and gastroesophageal junction carcinoma. J Am Coll Surg 2004;198(1):42–50.
28. Portale G, Hagen JA, Peters JH, Chan LS, DeMeester SR, Gandamihardja TA, DeMeester TR. Modern 5-year survival of resectable esophageal adenocarcinoma: single institution experience with 263 patients. J Am Coll Surg 2006;202(4):588–596. (discussion 596–598).
29. Orringer MB, Marshall B, Chang AC, Lee J, Pickens A, Lau CL. Two thousand transhiatal esophagectomies: changing trends, lessons learned. Ann Surg 2007;246(3):363–372.
30. Low DE, Kunz S, Schembre D, Otero H, Malpass T, Hsi A, Song G, Hinke R, Kozarek RA. Esophagectomy—it's not just about mortality anymore: standardized perioperative clinical pathways improve outcomes in patients with esophageal cancer. J Gastrointest Surg 2007;11(11):1395–1402. (discussion 1402).
31. Nigro JJ, Hagen JA, DeMeester TR, DeMeester SR, Peters JH, Oberg S, Theisen J, Kiyabu M, Crookes PF, Bremner CG. Prevalence and location of nodal metastases in distal esophageal adenocarcinoma confined to the wall: implications for therapy. J Thorac Cardiovasc Surg 1999;117(1):16–23.
32. Schwarz RE, Smith DD. Clinical impact of lymphadenectomy extent in resectable esophageal cancer. J Gastrointest Surg. 2007;11(11):1384–1393.
33. Altorki NK, Zhou XK, Stiles B, Port JL, Paul S, Lee PC, Mazumdar M. Total number of resected lymph nodes predicts survival in esophageal cancer. Ann Surg. 2008;248(2):221–226.
34. Peyre CG, Hagen JA, DeMeester SR, Altorki NK, Ancona E, Griffin SM, Hölscher A, Lerut T, Law S, Rice TW, Ruol A, van Lanschot JJ, Wong J, DeMeester TR. The number of lymph nodes removed predicts survival in esophageal cancer: an international study on the impact of extent of surgical resection. Ann Surg 2008;248(4):549–556.
35. Cadiere GB, Torres R, Dapri G, Capelluto E, Hainaux B, Himoens J. Thoracoscopic and laparoscopic oesophagectomy improves the quality of extended lymphadenectomy. Surg Endosc 2006;20:1308–1309.
36. Berrisford RG, Wajed SA, Sanders D, Rucklidge MW. Short-term outcomes following total minimally invasive oesophagectomy. Br J Surg 2008;95(5):602–610.
37. Yamamoto S, Kawahara K, Maekawa T, Shiraishi T, Shirakusa T. Minimally invasive esophagectomy for stage I and II esophageal cancer. Ann Thorac Surg 2005;80(6):2070–2075.
38. Decker G, Coosemans W, De Leyn P, Decaluwé H, Nafteux P, Van Raemdonck D, Lerut T. Minimally invasive esophagectomy for cancer. Eur J Cardiothorac Surg 2009;35:13–21.
39. Bonavina L, Via A, Incarbone R, Saino G, Peracchia A. Results of surgical therapy in patients with Barrett's adenocarcinoma. World J Surg 2003;27(9):1062–1066.
40. Oh DS, Hagen JA, Chandrasoma PT, Dunst CM, Demeester SR, Alavi M, Bremner CG, Lipham J, Rizzetto C, Cote R, Demeester TR. Clinical biology and surgical therapy of intramucosal adenocarcinoma of the esophagus. J Am Coll Surg 2006;203(2):152–161.
41. Ajani JA, Barthel JS, Bekaii-Saab T, Bentrem DJ, D'Amico TA, Fuchs CS, Gerdes H, Hayman JA, Hazard L, Ilson DH, Kleinberg LR, McAleer MF, Meropol NJ, Mulcahy MF, Orringer MB, Osarogiagbon RU, Posey JA, Sasson AR, Scott WJ, Shibata S, Strong VE, Swisher SG, Washington MK, Willett C, Wood DE, Wright CD, Yang G. NCCN esophageal cancer panel. Esophageal cancer. J Natl Compr Canc Netw 2008;6(9):818–849.
42. Suntharalingam M. Definitive chemoradiation in the management of locally advanced esophageal cancer. Semin Radiat Oncol 2007;17(1):22–28. (review).

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DEMEESTER FESTSCHRIFT

Is Esophagectomy the Paradigm for Volume–Outcome Relationships?

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Abstract
Introduction Esophagectomy is considered one of the most complicated, difficult to perform, and physiologically altering operations performed by surgeons.
Discussion Outcome, not only depends upon surgeon and hospital volume but also involves a "supporting cast" of health professionals, such as physical therapy and ICU. The complementary skill set of the surgeon may also influence esophagectomy outcomes.
Conclusions Young surgeons can perform esophagectomy with low mortality while their volume increases if they engage and involve all of the components in this paradigm.

Keywords Esophagectomy · Outcomes assessment · Esophageal neoplasm · Treatment outcome · Clinical competence

Esophagectomy is considered one of the most complicated, difficult to perform, and physiologically altering of the myriad of operations performed by surgeons. The surgical mortality of esophagectomy remains as high as 18% in spite of significant improvements in the technical aspects of the operation and the perioperative care of patients undergoing esophagectomy. Two recent studies using the Medicare administrative database showed that mortality rates as low as 8.1% can be accomplished in "high-volume centers" or with "high-volume surgeons."[1,2]

These two studies are part of countless papers and articles that have examined the inverse relationship between volume and mortality in a variety of surgical procedures, since it was first described by Luft et al.[3] in their landmark article in the New England Journal of Medicine. However, as most surgeons and physicians have realized, this relationship has significant variability,[4] and it remains unclear how and why this interaction occurs. Yet, despite the considerable variability and controversy surrounding the volume–outcome relationship it has seeped into the conscientiousness of the public who are told to ask their prospective surgeon, "how many of these procedures do you perform each year?" and "what are your outcomes?"

Recently graduated surgeons are acutely aware of the volume–outcome relationship because no one begins his or her career as a high-volume surgeon. If you are fortunate to have joined a high-volume practice, the answers to these questions from your prospective patients will likely reflect the outcomes of your group. However, if you are building a practice or program, the answers may be in taking a closer look at the factors affecting the volume–outcome relationship. Thus, the purpose of this paper is as follows:

- To examine the volume–outcome relationship
- To determine if esophagectomy is the paradigm for volume-outcome relationships
- To describe the perspective of a young esophageal surgeon trying to build a high-volume center.

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The Volume and Outcome Relationship

For many years, it was widely accepted that with more experience comes improved or better results despite the fact that there was little or no statistical support for this assertion. Luft et al.,[3] in 1979, was the first to examine the hospital volume–outcome relationship. After selecting 12 procedures of differing complexity and expected mortality ranging from total hip replacement to coronary artery bypass grafting, nearly 425,000 patient records over 2 years were examined. A clear overall association was seen for the selected 12 procedures showing a decrease in the expected death rate with increasing volume. This was the first evidence supporting a volume–outcome relationship.

However, closer scrutiny of the 12 procedures showed that three major groups or trends emerge: group 1, procedures where more volume led to a falling death rate; group 2, procedures where the death rate plateaus after 10–50 procedures have been performed; and group 3, procedures where volume and death rate were independent. This suggested that, although volume and outcome are inversely related, certain procedures were more dependent on volume than other procedures. In group 1 in the study of Luft et al., where more volume led to a falling death rate, the procedures were generally more complex and less common.

However, every surgeon feels that their cases are complex, so which procedures fall into this category? In a more recent study, Birkmeyer et al.,[1] using Medicare data, showed, for the 14 procedures evaluated, that higher hospital volume led to improved outcomes. The procedures were selected because they were relatively complex, had a significant mortality rate, and were performed electively. Six of the procedures were cardiovascular, and eight were oncologic. The impact of volume on outcome was varied and depended on the procedure. However, pancreatic resection (16.3% vs. 3.8%), esophagectomy (20.3% vs. 8.4%), and pneumonectomy (16.1% vs. 10.7%) showed significantly higher mortality differences between high- and low-volume hospitals when compared to the other procedures.

These findings clearly established the relationship between hospital volume and outcome, but the contribution of one key factor—the surgeon—had not been clearly delineated in these studies. Birkmeyer et al.,[2] in a subsequent paper, used a similar database of nearly 480,000 patients undergoing eight cardiovascular and oncologic operations to examine the impact of the surgeon on volume and outcome. Overall, a similar relationship between volume and outcome was noted—higher volume surgeons had an inverse relationship with operative mortality. Like hospital volume, the surgeons' outcomes were procedure-dependent, and pancreatic resection and esophagectomy had significantly greater differences between high- and low-volume centers. The odds of dying after pancreatic resection in a low-volume hospital were 3.61 times higher than for a high-volume hospital and 2.3 times higher for esophagectomy.

The surgeon also influenced the hospital's volume–outcome relationship, and this too varied by procedure. For some procedures such as aortic valve replacement, the surgeon's volume accounts for 100% of the hospital's outcome, whereas for lung resection, only one quarter of the hospital's outcome was dependent on the surgeon.[2] Thus, for procedures that require the use of hospital services such as physical therapy, respiratory therapy, and intensive care and with longer hospital stays, the impact of hospital volume on outcome was higher. For pancreatic resection, surgeon volume has a greater influence on outcome and less reliance on hospital services. For esophagectomy, even though surgeon volume has significant influence on outcome, there is a higher reliance on other hospital services that influence patient outcome. Thus, esophagectomy is an ideal procedure for examining the volume–outcome relationship.

Esophagectomy is the Paradigm

The volume–outcome relationship for esophagectomy has been confirmed in multiple studies using hospital volume and, to a lesser extent, surgeon volume.[5] The results are consistently the same and demonstrate an improvement in mortality when the volume of esophagectomy rises, and, while both hospital and surgeon volume are independent predictors of outcome, accounting for one volume measure did not over come the effect of the other—meaning that a low-volume surgeon in a high-volume center will still have higher mortality rates than a colleague with high volumes.

For surgeons performing these more complex procedures on less common diseases, the volume outcome relationship is more complicated than simply having higher volumes to achieve better outcomes. The central figures in this relationship are the surgeon and the hospital, but there are many factors that also influence the patient's outcome.[6] This can range from the patient's co-morbidities[7] and the severity of illness[8] to the surgeon's specialty training and complementary skills. It also involves, the "supporting cast" from the hospital, including ICU, nursing, physical therapy, and nutrition. These factors create a new paradigm around which the volume–outcome relationship for esophagectomy can be defined (Fig. 1).

The Patient

At the center of this paradigm is the patient whose outcome is dependent on the skills and resources surround him. However, the patient's own health and risk factors

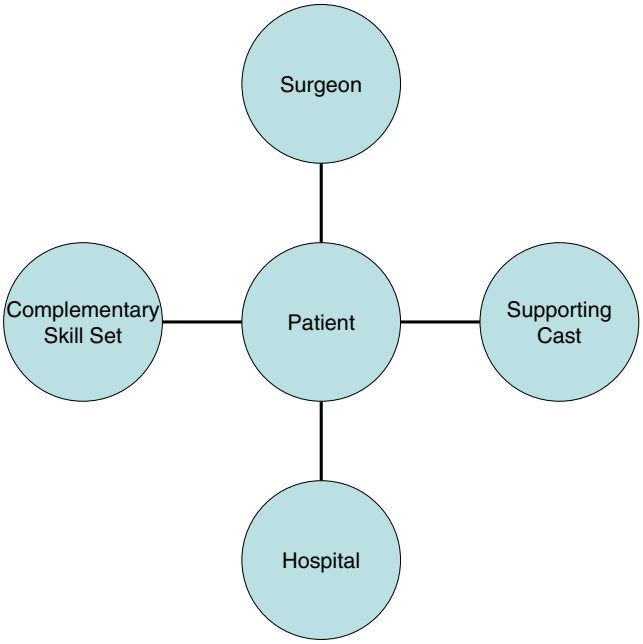

Figure 1 The paradigm for volume–outcome relationships in esophagectomy.

potentially can play a role in outcome. Intuitively, the patient's co-morbidities should influence outcome, but there is a lack of supporting evidence for this fact. Rodgers et al.[7] showed that individual patient factors had a greater influence on mortality than volume, but their identified factors race, female gender, and peripheral vascular disease were seemingly unlikely to influence outcome compared to the expected cardiopulmonary diseases. This is further supported by Begg and colleagues[9] who used the SEER database to show a volume–outcome relationship that was not influenced by case mix or patient factors. Some of these results are most likely because of selection bias in the surgical series, where the healthier candidates are able to undergo a major operation, whereas patients with significant co-morbidities are not offered surgery as part of their care.

The Surgeon

Specific surgical skills are obtained during the long resident training process. Intuitively, more sub-specialized training in areas such as general thoracic surgery or dedicated esophageal training should lead to better trained surgeons with greater exposure, experience, and skills compared to general surgical training. Dimick et al.[10] analyzed 1,946 patients undergoing esophagectomy using national Medicare data. When analyzed by surgeon training (thoracic vs. general surgery), mortality rates were lower for thoracic surgeons. However, when surgeon and hospital volume were accounted for, the influence of training was less important than the hospital and surgeon volume.

Although no study has been completed for surgeons who sought additional training in esophageal fellowship programs, there is no reason to believe that this outcome would be any different when comparing general surgery versus esophageal fellowship. It may be plausible that outcomes from surgeons who have completed either an esophageal fellowship or both thoracic and esophageal fellowships may have even better outcomes than thoracic surgeons since the volume of esophagectomy in many training centers is limited. Until recently, thoracic residents were required to complete only four esophagectomies to become board certified; whereas a minimum of 20 esophagectomies is required today. Based on these minimum requirements, some of the smaller training programs in the USA are going to have difficulty meeting those minimum requirements.[11]

Complementary Skill Set

The benefits within an esophageal fellowship surround the complementary skills acquired by the trainee in endoscopy, management of benign esophageal disease, Barrett's esophagus, advanced endoscopic therapies, and minimally invasive approaches. Furthermore, knowledge and experience with the regional anatomy, problem solving around complex foregut problems, and the added case volume may be beneficial. There has been no published study examining the impact of complementary skills on the outcome of esophagectomy, but Allareddy et al.[12] analyzed data from the Nationwide Inpatient Sample of the Healthcare Cost and Utilization Project from 2000–2003. They examined the impact of complex cardiovascular procedures on foregut procedures (esophagectomy and pancreatectomy) and vice versa. They concluded that higher volumes in non-related areas do not influence patient outcome and that benefits are only derived from the specific procedure or "family of procedures" affecting the same organ system. For esophageal surgeons, that family of procedures or complementary skill set includes procedures such as laparoscopic Nissen fundoplication, Heller myotomy, diaphragmatic hernia repair, Roux-en-Y gastric bypass, and the various types of esophagectomy.

The Hospital

As an extension of the complementary skills concept for surgeons, hospitals, too, can have similar skill sets. Hospitals have long been categorized into community hospitals or academic/teaching hospitals, and a subset of teaching hospitals have thoracic training programs and

some have only general surgery programs. Meguid et al.[13] examined over 4,000 esophagectomies performed at hospitals with thoracic and general surgery residencies, hospitals with general surgery residencies, and hospitals without training programs. In-hospital mortality was reduced in all teaching hospitals, but the lowest mortality was seen in hospitals with thoracic surgery training programs.

In a similar study, Birkmeyer et al. used Medicare data from 51 National Cancer Institute designated hospitals and 51 control hospitals to evaluate cancer surgery on six procedures: esophagectomy, pancreatectomy, colectomy, lung resection, gastrectomy, and cystectomy.[14] Only cystectomy and pancreatectomy failed to show that NCI-designated hospitals had lower mortality rates. Interestingly, survival rates did not differ between NCI and non-NCI centers of patients surviving surgery. However, Wenner et al.[15] analyzed 5-year survival rates in German hospitals performing less than 5, 5–15, and greater than 15 esophagectomies. Survival rates were 17%, 19%, and 22%, respectively, with a statistical difference between the low- and high-volume hospitals.

The Supporting Cast

The supporting cast of health care professionals that impact the outcome of a patient undergoing esophagectomy includes nearly every medical specialty and every allied health professional. Since the surgeon's skill accounts for around 45% of the patient's outcome,[2] that leaves the majority of the outcome heavily dependant on these professionals. The greatest impact is usually felt when patients develop complications arising from surgery. Dimick et al.,[16] using data from hospitals in Maryland, compared the postoperative complications of esophagectomy patients in high- and low-volume hospitals. They concluded that renal failure, pulmonary complications, sepsis, and re-intubation were significantly higher in low-volume hospitals. Patti et al.,[17] using 1,500 discharges from the state of California, showed similar findings. Hospitals performing fewer than 30 esophagectomies had a complication rate of 16.4% compared to hospitals performing greater than 30 esophagectomies where the complication rate was 4.8%.

Pulmonary complications, even in high-volume hospitals, represent the most common complication and include re-intubation, aspiration, pneumonia, and respiratory failure.[18] The best treatment for this constellation of pulmonary complications is prevention, which begins with epidural analgesia. Cense et al.[19] showed that the presence of a functioning epidural reduced the incidence of pneumonia, re-intubation, ICU days, and hospital mortality. The expertise of a qualified anesthesia group experienced in thoracic epidural analgesia and a sophisticated pain service are paramount to have a functioning epidural. The presence of adequate pain control can ameliorate the stress response as well as facilitate early mobilization of the patient, chest physical therapy, deep breathing, and coughing exercises by allied health professionals.

Although much of the impact on patient outcome is a result of care provided by clinicians postoperatively, the diagnostic services at a given hospital can also play an enormous role in the quality of care. Pre-therapy esophageal cancer staging is dependent upon radiologic images from CT, PET, and EUS. Van Vliet et al. analyzed 573 cases of esophageal cancer undergoing preoperative staging in The Netherlands. Low-volume regional centers found true positive lymph node metastasis in 8% and true positive distant metastasis in 7% compared to high-volume referral centers that had detection rates of 16% and 20%, respectively. This translated into 72 of 573 or 13% of patients having one or more metastases detected at a referral center. They concluded that, in part, this detection rate was directly attributable to the experience of the radiologist. Missed detection can lead to under staging followed by aggressive treatment when the patient is palliative or overstaging followed by aggressive trimodality therapy when surgery alone would have yielded similar survival rates.

Perspectives of a Young Surgeon

The Leapfrog Group (www.leapfroggroup.org) has determined that 13 esophagectomies defines a high-volume center, but the threshold for determining a high-volume center ranges from 6 to 50.[7,20] Metzger et al.,[20] performed a meta-analysis of eight papers to assess the threshold for a high-volume center. After calculating the area under the curve, they determined that a minimum of 20 esophagectomies needed to be performed per institution to result in lower mortality. At this threshold, the sensitivity was 86%, specificity 96%, and an odds ratio of 0.43.

However, which is the correct threshold? It is doubtful that any one methodology that is used to determine a threshold value is more correct than another. Meguid et al.[21] developed a statistical model using over 3,000 patients to determine the threshold for high volume. In this series, the mean number of esophagectomies was four per year. They concluded that a threshold of 10 was the best model but went on to conclude that there were very few differences between the other threshold levels they studied and suggested that volume alone was insufficient at defining a center of excellence.

When I completed surgical training (general surgery, thoracic surgery, and esophageal fellowship), I joined a

general thoracic surgery practice that historically performed an average of ten esophagectomies per year. They were the only group performing this procedure at the hospital. In my first full year in practice, we performed 11 esophagectomies. This has grown to 23 in year 2 and now to 26 esophagectomies in year 3 for the group and the hospital. There were two mortalities (3.5%). What have I learned?

I believe that esophagectomy is the paradigm for volume–outcome relationships. In my first ten esophagectomies, I relied on my thoracic and esophageal fellowship training and drew upon my experiences with benign esophageal disease and thoracic surgery (complementary skills). It also helped to have senior partners with extensive esophageal training and mentors only a quick phone call away. This kept our mortality rate 0 in the first year. We looked back at our mistakes and thought about the ways to improve. Many of the challenges were not in the technical aspects of performing the surgery but in the postoperative care and managing complications.

The success of the supporting cast depends on the surgeon to be open with direct communication about the perioperative and postoperative care. Our anesthesiologists were facile at the thoracic epidural for fifth interspace thoracotomy or the lumbar epidural for obstetrical analgesia but did not appreciate the difference with a seventh interspace thoracotomy, long midline laparotomy, and neck incision used for en bloc esophagectomy. The nursing staff, respiratory therapists, nutritionists, and physical therapists were also inexperienced with this degree of surgery and the nuances of esophagectomy—postural drainage and chest physical therapy cannot be done with the patient in Trendelenberg. This meant multiple meetings and allied health professional in-service sessions were required to achieve the anticipated patient outcomes while building an esophageal center of excellence.

Once we completed the education of our supporting cast and centralized the postoperative care in one ICU and one ward, our complication rate decreased, but more importantly, when one occurred, all team members knew how to successfully manage the complication. As our volume has grown, we have been able to maintain a low in-hospital and 30-day mortality rate. However, even though volume has risen and mortality has remained low, there is more to achieving low mortality than volume alone. There is a lot of time spent educating and communicating with other consultants and allied health professionals to achieve these outcomes.

Conclusions

Esophagectomy is the ideal paradigm to examine the volume–outcome relationship because it is a complex procedure that is uncommonly performed with potential for significant complications and detriments to survival. Both the surgeon and the hospital are the central figures in this relationship, but they are not the only participants or factors necessary to achieve better outcomes. The patient's co-morbidities, surgeon's training, complementary skill set, and supporting cast all have significant influences on the overall outcome. Young surgeons, who are well trained, can perform esophagectomy with low mortality while their volume increases within this paradigm.

References

1. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N Engl J Med 2002;346(15):1128–1137.
2. Birkmeyer JD, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. N Engl J Med 2003;349(22):2117–2127.
3. Luft HS, Bunker JP, Enthoven AC. Should operations be regionalized? The empirical relation between surgical volume and mortality. N Engl J Med 1979;301(25):1364–1369.
4. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. Ann Intern Med 2002;137(6):511–520.
5. Chang AC, Birkmeyer JD. The volume–performance relationship in esophagectomy. Thorac Surg Clin 2006;16(1):87–94.
6. Urschel JD. Esophagectomy volume and operative mortality. J Gastrointest Surg 1998;2(5):492.
7. Rodgers M, Jobe BA, O'Rourke RW, Sheppard B, Diggs B, Hunter JG. Case volume as a predictor of inpatient mortality after esophagectomy. Arch Surg 2007;142(9):829–839.
8. Khuri SF. Quality, advocacy, healthcare policy, and the surgeon. Ann Thorac Surg 2002;74(3):641–649.
9. Begg CB, Cramer LD, Hoskins WJ, Brennan MF. Impact of hospital volume on operative mortality for major cancer surgery. Jama 1998;280(20):1747–1751.
10. Dimick JB, Goodney PP, Orringer MB, Birkmeyer JD. Specialty training and mortality after esophageal cancer resection. Ann Thorac Surg 2005;80(1):282–286.
11. Evans J. Resident Caseload Increase Seen in Positive Light. Thoracic Surg News 2008;1:4.
12. Allareddy V, Konety BR. Specificity of procedure volume and in-hospital mortality association. Ann Surg 2007;246(1):135–139.
13. Meguid RA, Weiss ES, Cattaneo SM, Sussman MS, Brock MV, Yang SC. Decreased operative mortality for esophageal cancer resections at hospitals with thoracic surgery training programs: Should esophagectomies only be performed by thoracic surgeons? In: American Association for Thoracic Surgery, 2008, San Diego, CA, p. 90.
14. Birkmeyer NJ, Goodney PP, Stukel TA, Hillner BE, Birkmeyer JD. Do cancer centers designated by the National Cancer Institute have better surgical outcomes? Cancer 2005;103(3):435–441.
15. Wenner J, Zilling T, Bladstrom A, Alvegard T. Influence of surgical volume on hospital mortality for cancer of the esophagus and gastric cardia: A national survey in Sweden 1987–96. In: European Surgical Association 10th Annual Meeting, 2003, Paris, France, p. 36–37.
16. Dimick JB, Pronovost PJ, Cowan JA, Lipsett PA. Surgical volume and quality of care for esophageal resection: do high-volume

hospitals have fewer complications? Ann Thorac Surg 2003;75 (2):337–341.
17. Patti MG, Corvera CU, Glasgow RE, Way LW. A hospital's annual rate of esophagectomy influences the operative mortality rate. J Gastrointest Surg 1998;2(2):186–192.
18. Law S, Wong KH, Kwok KF, Chu KM, Wong J. Predictive factors for postoperative pulmonary complications and mortality after esophagectomy for cancer. Ann Surg 2004;240 (5):791–800.
19. Cense HA, Lagarde SM, de Jong K, et al. Association of no epidural analgesia with postoperative morbidity and mortality after transthoracic esophageal cancer resection. J Am Coll Surg 2006;202(3):395–400.
20. Metzger R, Bollschweiler E, Vallbohmer D, Maish M, DeMeester TR, Holscher AH. High volume centers for esophagectomy: what is the number needed to achieve low postoperative mortality? Dis Esophagus 2004;17(4):310–314.
21. Meguid RA, Weiss ES, Chang DC, Brock MV, Yang SC. The effect of volume on esophageal cancer resections: What constitutes acceptable resection volumes for centers of excellence? In: American Association of Thoracic Surgery, 2007, Washington, DC, p. 170.

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Initial Experience with New Intraluminal Devices for GERD Barrett's Esophagus and Obesity

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Abstract
Background Transoral intraluminal surgery is less painful. However, endoscopic antireflux procedures have been unsuccessful, endoscopic foregut mucosal excision procedures are often difficult to perform, and endoscopic intraluminal suturing is both imprecise and too shallow. We have endeavored to correct these deficiencies and report here new devices for GERD, obesity, and Barrett's mucosal excision.
Method A retrospective review of ex vivo and in vivo animal experiments using sharp blade mucosal excision for esophageal and gastric mucosa and a suturing device with transverse needles designed to full thickness penetrate the gastric wall were completed. A total of 338 excisions were performed in 134 ex vivo tissue experiments and in 119 in vivo attempts. Suture needle testing was performed in ex vivo human stomachs and porcine stomachs and in in vivo canine and baboon stomachs.
Results One excision perforation (0.9%) occurred in a live animal. Satisfactory mucosal excision depth for the Barrett's device was reproducible. Progressive suture actuation reliability improved from 83% during ex vivo testing to 96.7% in in vivo experiments.
Conclusion The results demonstrate feasibility, reliability, and safety for gastric and esophageal mucosal excision. Suturing reliability improved and further studies will be performed to finalize the instrument designs, the operative techniques, and the other device applications.

Keywords Mucosa · GERD · Barrett's esophagus · Obesity · Endoscopy · Excision

Introduction

Laparoscopy, a surgical milestone within the past two decades has irreversibly changed the surgical paradigm. In combination with sophisticated engineering and advanced endoscopic techniques, surgeons are now able to perform more complex endoluminal procedures. At Creighton University, we have focused on transoral procedures for Barrett's mucosa, gastroesophageal reflux disease (GERD), and obesity. The unique excision technique and suture management used is also applicable for post gastric bypass pouch and outlet reduction, gastric sleeve revision, esophageal perforation closure, and colon polyp excision.

The endoscopic techniques published to date for GERD can be categorized in three major groups. Techniques applying radiofrequency to the lower esophageal sphincter,[1] approaches injecting or implanting biopolymers at the GEJ,[2,3] and devices that perform endoluminal sewing or plicating at the gastro esophageal junction.[4–8] However, none of these devices/techniques have become the standard of care.[9]

Based on the excellent weight loss results observed with restrictive procedures such as adjustable gastric banding, a transoral endoscopic outpatient intraluminal restrictive

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procedure that could be effectively revised after several years is expected to be appealing to patients and surgeons alike. Investigations of intraluminal restrictive techniques for obesity are ongoing but durability of effect is in question.[10,11]

Numerous mucosal ablation and excision methods for Barrett's esophagus have been devised; ablation techniques include photodynamic therapy, ultrasonic ablation, Argon beam coagulation, radiofrequency ablation, cryotherapy ablation, and bipolar electrocoagulation.[12–15] The primary excision technique is endoscopic mucosal resection (EMR) which is limited by cautery margins, specimen disorientation, and small size. Both EMR and the ablation methods are designed to remove the Barrett's epithelium and to treat either high-grade dysplasia or early noninvasive adenocarcinoma.

Mucosal excision has been shown to be relatively safe with a bleeding rate of 8% and a perforation rate of less than 1%.[16] However, this form of therapy often provides a piece meal removal of the tissue, or cancer if present, and the tissue specimens cannot be oriented for pathologic inspection; thus, accurate lateral margins are unattainable. More importantly, the technique is time consuming and difficult to perform. A device that would reliably, rapidly, and safely remove mucosa and muscularis mucosa with a low incidence of complication would be attractive.

Durability of effect for endoluminal GERD and obesity procedures is lacking, and our intention is to create sufficient scar formation to prevent tissue separation over time. The main focus of our initial laboratory work was feasibility, safety, quality, and reliability of mucosal excision and suture needle actuation. Here, we report the results of this effort and a new device for Barrett's mucosal excision.

Methods

Testing was performed in ex vivo porcine, canine, baboon, and human tissue.

A dilator-shaped device (SafeStitch Medical Inc.) was used to perform excision and suture placement (Fig. 1). The 60 F flexible instrument has a distal integrated excision and suture capsule, while a standard small caliber transnasal endoscope introduced through the device shaft is used for direct visualization. The 5-cm long rigid distal capsule contains the excision blade, vertical anchor needles for tissue holding and Adrenalin injection, and two circular needles each connected to a separate 2.0 Prolene suture running through the device (Figs. 2 and 3). Two sets of two full-thickness sutures and a mucosal excision down to the level of the muscularis propria on the anterior and the posterior stomach wall are used for each stage of the

Figure 1 The 60 F dilator-shaped endoluminal gastroplasty device.

gastroplasty. After correct positioning of the device with the endoscope in retroflexion, the gastric wall is pulled into the trough with 500 mm/Hg negative pressure. The two three-quarter-circle needles are actuated to rotate 360° through the captured tissue. The tissue is then injected with 5 cm^3 of 1:200,000 adrenalin solution to create tissue swelling for hemostasis and a safe cut in the correct gastric wall layer (Fig. 4). The second suture excision cycle is performed by advancing the device into the correct position and repeating the sequence. The sutures are then tied and cut with a flexible endoscopic device resulting in a full-thickness stomach wall apposition. The vertical gastroplasty line is approximately 6 cm long and a result of three subsequent overlapping stages forming the neo-esophagus with pouch and restrictive outlet (Fig. 5). Attention was paid to excision and excision overlap safety and reliability for both the one stage GERD gastroplasty and the three-stage obesity gastroplasty line.

Esophageal mucosal resection using a new flexible endoscopic device (SafeStitch Medical Inc.) was performed. Preliminary ex vivo studies were carried out with porcine, canine baboon, and human esophagi. These experiments allowed us to determine the correct excision technique and device characteristics necessary for consistent strip endoscopic mucosal resection.

The instrument consists of a flexible shaft (Fig. 6) with an integrated distal excision capsule. A standard small

Figure 2 5 cm long rigid distal excision and suture capsule with transnasal endoscope in a retroflexed position. The guillotine excision blade is half way advanced and visible within the excision trough.

caliber transnasal endoscope is introduced into the device for visual orientation (Figs. 7 and 8). The excision capsule is 5 cm long and is rigid (Fig. 9). The device is mounted on the endoscope, and the rounded distal flexible tip allows safe introduction of the device through the oropharynx. The resection window is 2.8 cm long, 1.3 cm wide, and 0.4 cm deep and is positioned by endoscopic visualization. After device positioning the endoscope is retracted into the device shaft. Two suction channels pull the mucosa into the capsule and vertical anchor needles help fix the tissue in position. To assure the correct cutting depth and hemostasis a 1:200,000 Adrenaline solution is injected with a longitudinal injection needle placed above the bottom of the trough (Fig. 9). The injectate further separates the muscularis mucosa from the muscularis propria thus increasing the "target space." The multifunctional device handle provides longitudinal-injection-needle placement with

Figure 3 Capsule with flexible transition that allows introduction through the oro- and hypopharynx.

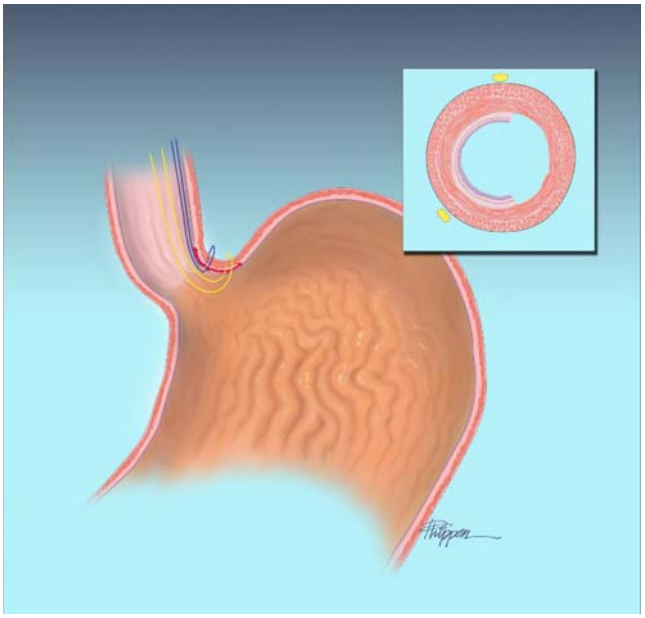

Figure 4 Step 1 gastroplasty for GERD at GEJ with excision pattern including 180° of the distal esophagus.

simultaneous controlled injection. The desired cutting depth through the first third of the submucosa assures complete removal of Barrett's mucosa and submucosal glands while decreasing the potential for stricture formation. A guillotine blade resects the mucosa (Fig. 9). Mucosal excision is performed with a single proximal-to-distal pushing movement of the blade. After the mucosectomy is complete, the device is removed from the esophagus with the specimen within the capsule. The specimen can be easily orientated for the pathologist and sent for histological analysis.

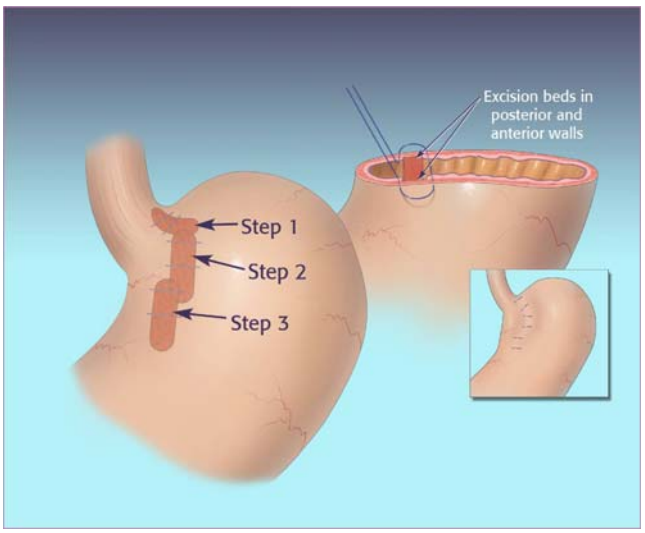

Figure 5 Schematic description of a three-step vertical gastroplasty with excision overlap and full-thickness sutures placement.

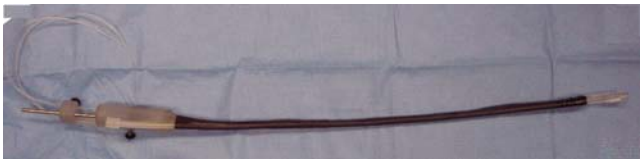

Figure 6 Barrett's excision device with flexible shaft, excision capsule, and multifunctional handle.

Results

Gastric mucosal excisions were most often within the submucosal layer and in-vivo testing submucosal excision depth was present in 98% of specimens. Only successful tissue injection with subsequent tissue swelling ensures a safe overlap excision. In ex vivo experiments focusing on excision overlap we provoked full-wall excision (n=6). As a result, we modified the injection needle positions to achieve more reliable submucosal injection when partially overlapping previously excised areas. The new injection needle positions allowed consistent fluid bolster application and successful excision overlap in 99.1% of in vivo experiments. In the latest gastroplasty excision and suture device, suture needle actuation reliability increased from 83% in ex vivo experiments to 96.7% during in vivo procedures.

The first nonsurvival canine and porcine esophageal mucosa excision experiments were promising in terms of safety. The device could be introduced without trauma in both canine and porcine models, and six mucosal excisions were performed without bleeding. Easy 1-mm target cautery mark localization and accurate capsule placement was proven. No perforations occurred and none of the in vivo esophagi, after removal, showed evidence of excision penetration to the muscularis propria level.

Figure 7 A transnasal endoscope is advanced through the tip of the device and retroflexed within the stomach for proper device positioning.

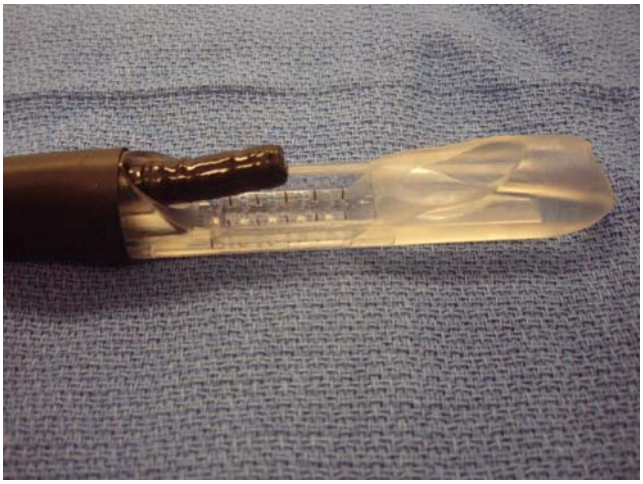

Figure 8 The antegrade position provides visualization of the distended target area.

Discussion

Laboratory results have demonstrated gastric and esophageal mucosal excision feasibility and safety. Intraluminal gastric automated suture placement reliability was established but further device revisions are needed for both excision and suturing before proceeding to human trials.

The appeal of an outpatient transoral endoscopic obesity procedure has led to multiple investigations of endoscopic treatments. Deviere and Moreno have published pilot human studies using a transoral device to create a vertical gastroplasty.[10,11] The device named transoral gastroplasty (Satiety, Palo Alto, CA) contains a stapler body with two jaws and a septum with retraction wire to orient the stomach tissue for capture and stapling. Suction pulls tissue from the anterior and posterior walls of the stomach into the device and the stapler is closed and fired. Three rows of 11

Figure 9 The 5-cm long rigid excision capsule with vertical anchor needles, suction ports, guillotine excision blade, and a longitudinal injection needle.

titanium staples create a transmural staple line connecting the anterior and posterior stomach. The continuity of the gastroplasty line, especially at the proximal aspect of the neo-esophagus, is a requirement as a single gap will increase emptying, resulting in the loss of the pouch and volume restriction. This complication was seen by Deviere et al. as staple line gaps were visible endoscopically or on barium swallow in 13 of 21 patients (~62%).[11]

Maish et al. compared the depth of invasion accuracy of endoscopic ultrasound (EUS) using a 7.5- and a 12-MHz probe and EMR findings in surgically resected esophageal specimens.[17] Ultrasound and EMR findings concurred in only one of seven patients. In two patients, the EUS understaged the tumor depth, and in two patients, the EUS overstaged the depth of invasion. In their study, the accuracy of EUS to determine intramucosal from submucosal tumor invasion was 20%. Final pathologic examination confirmed that the EMR specimen had accurately determined the depth of tumor invasion in all seven lesions. Two patients had complete removal of a visible cancer by EMR, but after resection, an additional adenocarcinoma was found within the Barrett's segment that had not been previously detected. One of these patients had a 16-cm segment of Barrett's mucosa, but the other had a short tongue of Barrett's mucosa.[17] These findings demonstrate the importance of clean excision margins and widespread excision. Occult esophageal adenocarcinoma biopsy error rates in patients with previous diagnosed high-grade dysplasia or adenocarcinoma are as high as 43%.[18]

The largest endoscopic resection study for high-grade intraepithelial neoplasia and mucosal adenocarcinoma achieved a complete response in 96.6% of 349 patients and a mean follow-up of 63.6±23.1 months. The technique used was the "suck-and-cut" technique with a ligation device or cap.[19] Confirmatory studies are needed.

Endoscopic mucosal resection is an important staging and therapeutic tool for a select group of patients with Barrett's esophagus. However, current limitations of EMR include lateral and depth margin coagulation artifacts, absence of specimen orientation, and small specimen size.

Further device modifications would make endoscopic mucosal resection of colonic lesions possible. Many colon polyps are sessile,[20] and a snare EMR technique is being used. A cold blade device with mucosal injection and a big resection window would provide accurate histologic margins and avoid piecemeal resections. Access to the transverse and right colon will require design changes. Bleeding is always a concern with mucosal excision but immediate Adrenaline solution injection or cautery is possible with the current mucosal excision device.

Additional procedures amenable to the devices described are post-gastric bypass pouch and outlet reduction. Both conditions are becoming more common as more gastric bypass operations are performed. Mucosal excision with full-thickness suturing is more likely to succeed than the other endoscopic techniques being currently employed. Tissue stretching can be altered by significant scar formation. Macrophages, the precursors of fibroblasts which make collagen, come from the blood stream, and the blood supply of the stomach is excellent throughout. Stimulation of this pathway and prevention of re-epithelialization after mucosal excision is necessary.

Finally, esophageal perforations are being successfully managed with stents and fibrin glue but occasional mediastinal leakage continues. Immediate full-thickness suture placement in the transverse plane for a longitudinal tear could be advantageous. Currently available suturing devices for the esophagus place sutures longitudinally. The suture mucosal excision device will be modified to a suture-only approach and would be applicable for esophageal, gastric, and colonic perforations.

Conclusion

The GERD and obesity gastroplasty device described is the only transoral device that addresses two pathologies using one device and similar operative technique. The reported results demonstrate feasibility, reliability, and safety of this approach. The Barrett's device is the first automated mucosal excision system that also has proven reliable in obtaining correct depth mucosal specimens. Further studies for both devices will be performed to finalize design and operative techniques.

References

1. Wolfsen HC, Richards WO. The Stretta procedure for the treatment of GERD: a registry of 558 patients. J Laparoendosc Adv Surg Tech A 2002;12:395–402.
2. Devière J, Costamagna G, Neuhaus H, et al. Nonresorbable copolymer implantation for gastroesophageal reflux disease: a randomized sham-controlled multicenter trial. Gastroenterology 2005;128:532–540.
3. Cicala M, Gabbrielli A, Emerenziani S, et al. Effect of endoscopic augmentation of the lower oesophageal sphincter (Gatekeeper reflux repair system) on intraoesophageal dynamic characteristics of acid reflux. Gut 2005;54:183–186.
4. Schwartz MP, Wellink H, Gooszen HG, et al. Endoscopic gastroplication for the treatment of gastro-oesophageal reflux disease: a randomised, sham-controlled trial. Gut 2007;56:20–28.
5. Schilling D, Kiesslich R, Galle PR, et al. Endoluminal therapy of GERD with a new endoscopic suturing device. Gastrointest Endosc 2005;62:37–43.
6. Rothstein R, Filipi C, Caca K, et al. Endoscopic full-thickness plication for the treatment of gastroesophageal reflux disease: A randomized, sham-controlled trial. Gastroenterology 2006;131:704–712.

7. Cadière GB, Rajan A, Germay O, et al. Endoluminal fundoplication by a transoral device for the treatment of GERD: A feasibility study. Surg Endosc 2008;22:333–342.
8. Jobe BA, O'Rourke RW, McMahon BP, et al. Transoral endoscopic fundoplication in the treatment of gastroesophageal reflux disease: the anatomic and physiologic basis for reconstruction of the esophagogastric junction using a novel device. Ann Surg 2008;248:69–76.
9. Rothstein RI. Endoscopic therapy of gastroesophageal reflux disease: outcomes of the randomized-controlled trials done to date. J Clin Gastroenterol 2008;42:594–602.
10. Moreno C, Closset J, Dugardeyn S, et al. Transoral gastroplasty is safe, feasible, and induces significant weight loss in morbidly obese patients: results of the second human pilot study. Endoscopy 2008;40:406–413.
11. Devière J, Ojeda Valdes G, Cuevas Herrera L, et al. Safety, feasibility and weight loss after transoral gastroplasty: First human multicenter study. Surg Endosc 2008;22:589–598.
12. Overholt BF, Panjehpour M, Haydek JM. Photodynamic therapy for Barrett's esophagus: follow up in 100 patients. Gastrointest Endosc 1999;49:1–7.
13. Morino M, Rebecchi F, Giaccone C, et al. Endoscopic ablation of Barrett's esophagus using argon plasma coagulation (APC) following surgical laparoscopic fundoplication. Surg Endosc 2003;17:539–542.
14. Bowers SP, Mattear SG, Waring PJ, et al. KTP laser ablation of Barrett's esophagus after anti-reflux surgery results in long-term loss of intestinal metaplasia. Surg Endosc 2003;17:49–54.
15. Montes CG, Brandalise NA, Deliza R, et al. Antireflux surgery followed by bipolar electrocoagulation in the treatment of Barrett's esophagus. Gastrointest Endosc 1999;50:173–177.
16. Ell C, May A, Pech O, et al. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). Gastrointest Endosc 2007;65:3–10.
17. Maish MS, DeMeester SR. Endoscopic mucosal resection as a staging technique to determine the depth of invasion of esophageal adenocarcinoma. Ann Thorac Surg 2004;78:1777–1782.
18. Nigro JJ, Hagen JA, DeMeester TR, et al. Occult esophageal adenocarcinoma: extent of disease and implications for effective therapy. Ann Surg 1999;230:433–438.
19. Pech O, Behrens A, May AD, et al. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. Gut 2008;57(9):1200–1206.
20. Waye JD. Advanced polypectomy. Endosc Clin N Am 2005;15 (4):733–756.

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DEMEESTER FESTSCHRIFT

Future Applications of Flexible Endoscopy in Esophageal Surgery

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Abstract
Introduction Flexible endoscopy has long played a role in esophageal surgery, and procedures like perforation closure, stenting of occluding malignancies, antireflux procedures, and removal of Barretts are increasingly replacing open and laparoscopic procedures. We present early results of a series of acute animal experiments studying the feasibility of using flexible endoscopes for complex esophageal surgery such as Heller myotomy and esophagectomy.
Methods A total of six animals and one human cadaver have been operated on in a series of three protocols. The first study involves extraluminal flexible endoscopy through a cervical incision. The esophagus is dissected to the phrenoesophageal junction and a Heller myotomy performed. The second study involves labeling specific mediastinal node areas using EUS and transesophageal tattooing. Transcervical access is once again obtained, and wide esophageal dissection is performed; sequential identification of the marked nodes is performed. The final study involves full thoracic esophageal mobilization and laparoscopic gastric mobilization for an esophagogastrectomy.
Results Heller myotomy in five animals was performed via flexible endoscopy. Total operative time was 49 min with mean time for myotomy being 22 min. One animal had hemodynamic compromise from over insufflating the mediastinum with air. The second study involved three animals and one human cadaver. An average of four nodes was marked by EUS, and there was 100% success in identifying all nodes with flexible medistinoscopy. Operative times had a mean of 187 min (147–227) for the animal model and 198 min for the cadaver model.
Conclusion There is a move to increase the role of flexible endoscopy in GI surgery. This is facilitated by the introduction of novel scopes and instrumentation designed for NOTES. We outline early favorable results from animal studies looking at the use of flexible endoscopy as a surgical tool for Heller myotomy and esophagectomy.

Keywords NOTES · Endoscopy · Flexible endoscope · Endoluminal surgery · Natural orifice · Esophagus · Esophagectomy · Barretts

Introduction

Of all the evolutionary trends in GI surgery over the last several decades, perhaps none has been as intriguing and far-reaching as the move to “minimally invasive” or “less invasive” surgery. In the past, little thought was given to patient comfort, quality of life, or patient preference. Instead, all efforts were directed towards effective disease treatment, minimization of iatrogenic and infectious complications, and patient survival. This changed with the paradigm shifting introduction of video laparoscopy in the late 1980s. Seemingly almost overnight, surgeons became aware of the negative physiologic effects of large access incisions, the advantage of the magnification and precision offered by video technology, and the marketability of a

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patient friendly approach. Laparoscopic surgery has almost uniformly been a surgical triumph. There has been, however, a largely ignored aspect of GI surgery that has also parlayed the public's demand for less invasive surgery into a phenomenal growth—this time at the expense of traditional surgery—which is the development and evolution of interventional flexible endoscopy. Initially only a diagnostic tool, flexible endoscopy has slowly increased its "interventional" or "surgical" capabilities to the point where it has largely replaced a number of once common open or laparoscopic procedures (Table 1). While the growth of flexible endoscopic surgery is undoubtedly good for patient care, it has, and will continue to, erode the surgeon's role in care of many GI diseases unless surgeons adopt flexible endoscopic approaches.

The introduction of the concept of natural orifice translumenal endoscopic surgery (NOTES) in 2004 offers opportunity for further replacement of traditional surgeries with flexible endoscopic procedures.[1] Table 2 lists NOTES procedures that have been described in the literature either as laboratory experiments or clinical studies. Table 2 also indicates that esophageal surgery is not immune to this movement from laparoscopy to flexible endoscopy. We present an outline of our current laboratory projects investigating the role of advanced flexible endoscopy in esophageal surgery and discuss other experiments described in the literature as well as technology developments that will further enable flexible endoscopic esophageal surgery.

Methods

All studies involving animals had protocols approved by the IACUC of our institution. Our current research is a series of acute feasibility studies looking at the utility of flexible endoscopes in the performance of esophageal surgery for benign and malignant disease. This multiphase study is supported by grants from the Natural Orifice Surgery Consortium for Assessment and Research group, Society of American Gastrointestinal and Endoscopic Surgeons, and the European Association of Endoscopic Surgery. Study one is the efficacy of transcervical mediastinoscopy for esophageal dissection—and Heller myotomy. Study 2 is the use of concomitant EUS and paraesophageal endoscopy for sentinel node identification and resection as well as wide esophageal and node dissection. Study 3 is the combination of endoluminal endoscopy, laparoscopy, and flexible endoscopic dissection for total esophagectomy.

Surgical Technique

Study 1 Pigs (35–40 kg) are anesthetized, with monitoring lines inserted, and they are positioned supine. A single-lumen endotracheal tube is used. A single-channel endoscope (GIF XP160, Olympus, Tokyo, Japan) is placed per-os and positioned within the mid-esophagus. A 2-cm transverse cervical incision is created, and the esophagus is identified. Blunt dissection is used to gain entrance into the superior mediastinum. A dual-channel therapeutic flexible endoscope (GIF 2T160, Olympus, Tokyo, Japan) is inserted through the cervicotomy into the upper mediastinum, and the mediastinum is insufflated with as little CO_2 pressure as necessary. Two different dissection planes have been established: the first is the juxta-esophageal plane and the other is the true mediastinal plane (trachea, pericardium, aorta, and pleura). The paraesophageal dissection seeks to expose the entire esophagus down to the attachment of the phreno-esophageal ligament (Fig. 1). Once completed, a distal esophageal myotomy is performed using endoscopic scissors, an endoscopic Maryland forceps, and an endoscopic monopolar articulating hook knife (all three; NOTES Toolbox, Ethicon Endo Surgery, Cinnicinati, OH). Figure 2 The myotomy is started 4 to 5 cm above the GEJ and extended onto the stomach 1.5 to 2 cm. Completion is assessed by concomitant endoluminal endoscopy.

Table 1 Open and Laparoscopic GI Surgeries Substantially Impacted by Flexible Endoscopic Alternatives

Disease	Traditional surgery	Laparoscopic/thoracoscopic surgery	Flexible endoscopic surgery
Common duct stones	−	+	+++
Zenkers diverticulum	−	+	++
Barretts ± high grade dysplasia	+	+	++
Early mucosal cancer esophagus/stomach	−	+	++
GI bleeding	−	−	+++
Feeding tubes	−	−	+++
Pancreatic pseudocyst	−	+	++
Periampulary tumors	+	−	++

− rarely if ever done, + sometimes done, ++ often done, +++ always done this way

Table 2 NOTES Procedures Reported in Experiments or Clinical

Procedure	Natural orifice approach	Laboratory experiment	Clinical
Appendectomy	Transgastric	+	+
	Transvaginal	+	+
	Transrectal	+	+?
Cholecystectomy	Transgastric	+	+
	Transvaginal	+	+
Exploratory peritneoscopy ± liver bx	Transgastric	+	+
	Transvaginal	+	
Oopherectomy	Transgastric	+	
	Transvaginal	+	+
Tubal ligation	Transgastric	+	
	Transvaginal	+	+
Heller myotomy	Transesophageal	+	+?
Inguinal hernia repair	Transgastric	+	
Ventral hernia repair	Transgastric transvaginal	+	
		+	+
Distal pancreatectomy	Transgastric transvaginal	+	
		+	
PEG salvage	Transgastric		+
Left colectomy	Transrectaltransvaginal	+	
		+	
Right colectomy	Transgastric transrectal	+	
		+	
Atrial ventricular ablation for a-fib	Transesophageal	+	
Thoracoscopy/lung bx	Transesophageal	+	
	Transgastric	+	
Nephrectomy	Transvaginal	+	+
Adrenalectomy	Transvaginal	+	
Splenectomy	Transgastric	+	
Mediastinoscopy	Transesophageal	+	
Sleeve gastrectomy	Transvaginal	+	+
Gastrojejunostomy	Transgastric	+	

The second experiment using the same access and model involves endoscopic and balloon dissection of the mediastinal plane. The goal is to dissect oncologic planes widely around the esophagus and to identify as many mediastinal lymph nodes as possible. The procedure starts as above with the exception that a linear EUS scope is used at the beginning to pre-identify mediastinal node groups and to mark them by injecting marking ink with a 25-gauge EUS needle. Cervical access is obtained and the esophagus identified. For this phase, dissection is started inside the thoracic inlet way from the esophagus. Through the scope balloon dissectors, hook cautery and dissecting forceps are used to dissect along the right pleura, the trachea, the aorta, and the pericardium. Attempts are made to identify all the previously tattooed nodes and node-bearing areas (Fig. 3). Following exploration, a standard thoracotomy is performed to look for missed nodes and to identify any injuries (Fig. 4).

The planed third phase of our research will extend the dissection described above to completely mobilize the thoracic esophagus. Standard laparoscopic access will then be used to mobilize the stomach and make a stapled gastric conduit as has been previously described.[2] The cervical esophagus will then be transected and the specimen removed. The flexible scope and a grasper will be used to pull the gastric conduit up through the mediastinum where a standard cervical anastomosis can be performed.

Results

To date, only phases 1 and 2 of the experimental studies have been carried out with a total of eight animals and one human cadaver. In all eight animals, mediastinal access was easily obtained and a para-esophageal plane found. Dissection was easily performed with blunt dissection, cautery,

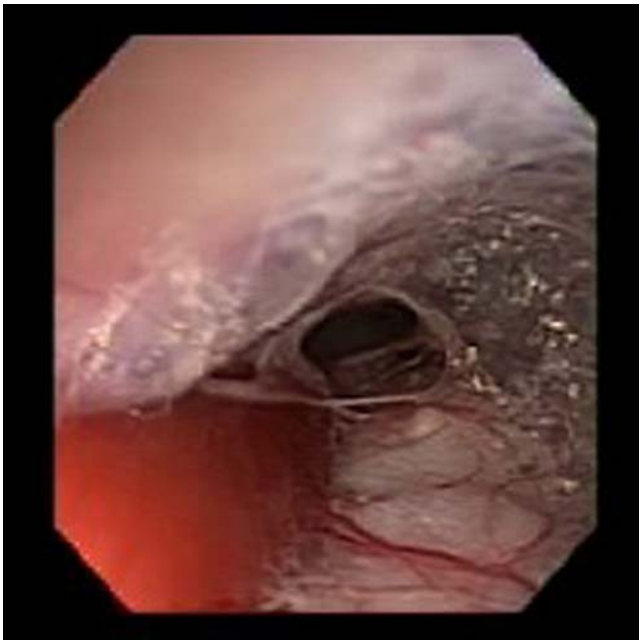

Figure 1 The endoscopic view of the dissected esophagus following CO_2 mediastinal insufflation and balloon dissection.

and with endoscopic balloons. Controlled low pressure CO_2 insufflation through the scope greatly facilitated identification and development of the para-esophageal plane. For the porcine model, the mean dissection time from scope insertion to identifying the phrenoesophageal ligament or crura was 27 min (56–17). Slight bleeding (<5 ml) was encountered in one animal, coming from the subcarinal area when the wrong plane was initially chosen. Control was obtained with a flexible 3.7 mm, bipolar forceps (NOTES Toolbox, Ethicon Endo Surgery, Cincinnati, OH). No injury occurred to the esophagus or vagus nerves. The Heller myotomy was performed in five animals in an average of 22 min (8–35). Total length was 5 cm (4–6) and was confirmed to be adequate by endoluminal endoscopic visualization. Because of the peculiarities of the porcine gastro-esophageal junction, it was not possible to measure the extent of the gastric myotomy, but the distal extent of the myotomy was more difficult and took the majority of the dissection time. In three animals, the gastric myotomy was carried through the phrenoesophageal membrane and well on to the intraperitoneal stomach. There were no injuries to the mucosa or bleeding encountered, but one animal suffered severe tachycardia and hypotension from a presumed tension pneumomediastinum. Chest tubes placed bilaterally did not show evidence of pneumothorax. The pig was killed immediately following the endoscopic dissection. Necropsy revealed no obscure bleeding or trauma from the endoscopic dissection, but signs of previous pericarditis were evident which may have predisposed this animal to hemodynamic problems. This animal was also done with air insufflation which is less well tolerated than CO_2.

In the second experiment, three animals have been performed. An average of four nodes was tattooed by EUS. Wide mediastinal dissection was much more time-consuming than the juxta-esophageal dissection above. Total procedure time (scope insertion to final identification of the phreno-esophageal junction and identification of all marked node areas) was 187 min (147–227). All tattooed node areas were identified in all animals (100%). Blood loss was minimal (4 ml [0–8]).

To date, one fresh frozen human cadaver has been done. Both a mediastinal dissection and Heller were performed without difficulty. Total dissection time was 198 min. The Heller myotomy was accomplished in 33 min without perforation. Node dissection was successful for both the para-esophageal nodes and for the subcarinal node packet.

Discussion

We describe a current course of research efforts looking at utilizing flexible endoscopes for complex esophageal surgery. Although these investigations are only in their

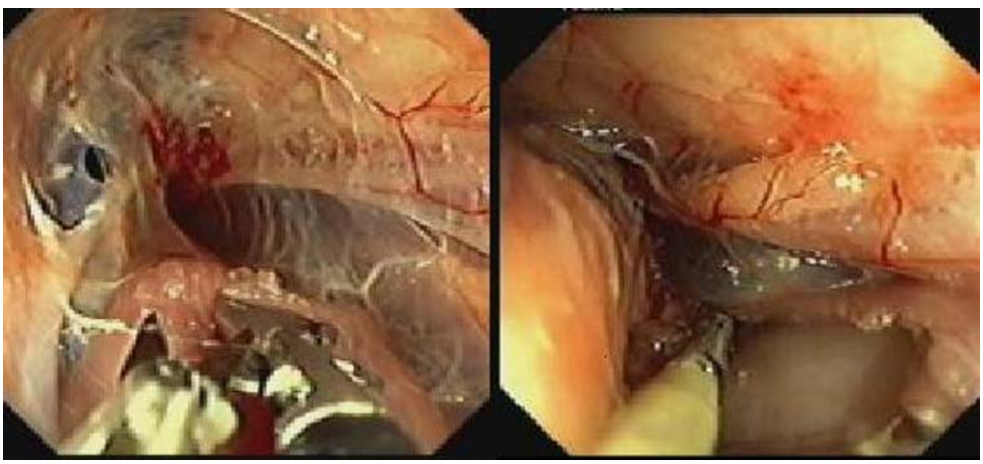

Figure 2 Endoscopic Heller myotomy with endoscopic Maryland dissector and scissors.

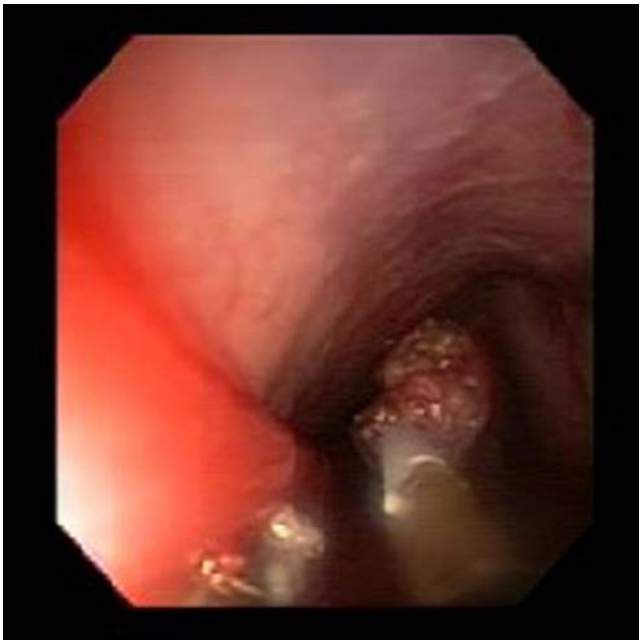

Figure 3 Endoscopic identification and resection of marked mediastinal lymph nodes.

preliminary stages—looking only at feasibility in acute models—they have demonstrated several things to date:

- Positive pressure CO_2 mediastinoscopy is tolerated to a limited extent in the pig model but is a dramatic aid in creation and dissection of tissue planes in the mediastinum. Air insufflation, on the other hand, resulted in severe cardiopulmonary derangement in the one animal it was used for.
- The juxta-esophageal plane of dissection is readily created and provides a complete view of the entire thoracic esophagus down to the insertion of the phreno-esophageal ligament (where dissection then becomes much more difficult). This exposure, and the currently

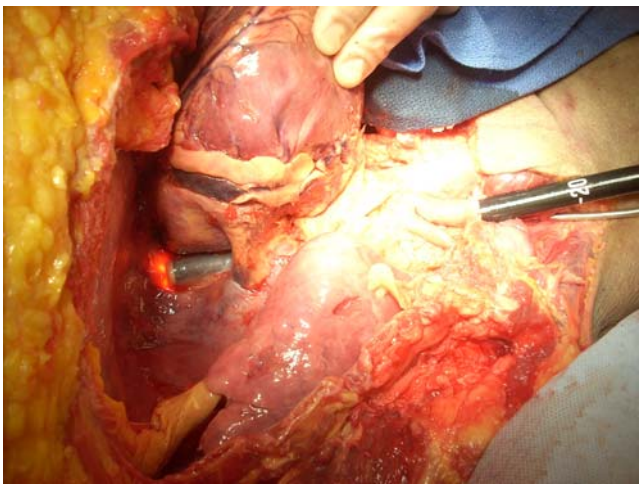

Figure 4 Thoracotomy with endoscope in situ to assess node harvest.

Figure 5 Prototype bipolar coagulation tool (Ethicon Endosurgical, Blue Ash, OH) which can coapt vessels as large as 5 mm.

Figure 6 Flexible endoscopic instruments (4 mm) which match the function of laparoscopic tools.

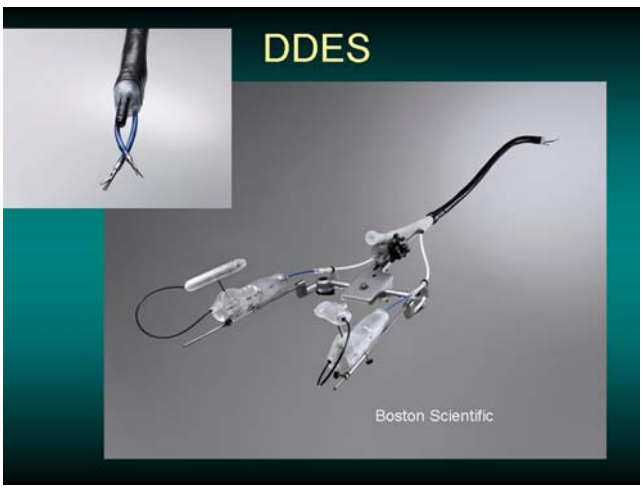

Figure 7 New generation of flexible endoscope with ergonomic articulating instruments having 6 *df* ay their tips. This replicates the laparoscopic paradigm with a camera person and two handed dissection by the surgeon.

available endoscopic instrumentation, is more than adequate to perform a Heller myotomy. Other authors have, in fact, described flexible endoscopic Heller myotomy. First described by Pasricha et al. in 2007, they described a different technique of creating an endoluminal mucosal incision, dissecting a submucosal flap distally with the endoscope and then dividing the circular muscle.[3] The mucosal flap was then closed with endoscopic clips.[4] Obvious surgical concerns would be the integrity of the endoluminal closure and completeness of the myotomy; both because of only dividing the circular muscle layer as well as difficulty identifying the distal extent of the myotomy. Nonetheless, the authors reported success in four survival animals with good manometric ablation of the LES. Perretta et al. have also recently reported a similar technique with the addition of an endoluminal fundoplication with the Esophyx device (Endogastric Solutions, Seattle, WA).[5] There have been, in fact, unpublished reports of human cases being done with this technique.[6] We believe that our approach may have some advantages insofar as it provides a more standard visualization, divides all muscle layers, and does not breach the esophagus, but this remains to be proven in comparative studies. Transesophageal flexible endoscopy has been done for other procedures as well. Fitscher-Ravens has described transesophageal lymph node harvest, and others have described a transesophageal flexible endoscopic approach for atrial ablations for atrial fibrillation.[7,8]

- A wider "en bloc" dissection as would be used in an oncological esophagectomy seems also possible although much more labor-intensive. Intraoperative EUS is invaluable in this model to maintain orientation and identify large vascular structures. EUS use is, however, restricted by the introduction of CO_2 gas into the tissue planes which obliterates subsequent ultrasonic views. Flexible endoscopic instrumentation is currently inadequate for extensive resection use, but several technologies now in development will perhaps make this a clinical reality. These needed tools include: hemostatic devices (Fig. 5), standard "laparoscopic like" tools (Fig. 6), and a new generation of flexible therapeutic endoscopes that offer triangulation, more instrument degrees of freedom and better ergonomics (Fig. 7).[9]

Conclusion

Flexible endoscopic approaches have, and will continue to, replace open and laparoscopic surgeries on the foregut. Our preliminary studies have shown that it is feasible to perform complex interventional mediastinoscopy and excisional esophageal surgery in the animal model. The literature corroborates our experience with reports of human procedures including NOTES Heller myotomy and transesophageal node resection. With future technology developments, it may be feasible to even perform esophagectomy and reconstruction using flexible endoscopes.

References

1. Kalloo AN, Singh VK, Jagannath SB, Niiyama H, Hill SL, Vaughn CA, Magee CA, Kantsevoy SV. Flexible transgastric peritoneoscopy: a novel approach to diagnostic and therapeutic interventions in the peritoneal cavity. Gastrointest Endosc. 2004;60(1):114–117. doi:10.1016/S0016-5107(04)01309-4.
2. Swanstrom LL. Thoracoscopic/laparoscopic esophagectomy. In Jones DB, Maithel SK, Schneider BE, eds. Atlas of minimally invasive surgery. Woodbury: Cine-Med, Inc., 2006, pp 496–523.
3. Pasricha PJ, Hawari R, Ahmed I, Chen J, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Gostout CJ. Submucosal endoscopic esophageal myotomy: a novel experimental approach for the treatment of achalasia. Endoscopy 2007;39(9):761–764. doi:10.1055/s-2007-966764.
4. Sumiyama K, Gostout CJ, Rajan E, Bakken TA, Knipschield MA. Transesophageal mediastinoscopy by submucosal endoscopy with mucosal flap safety valve technique. Gastrointest Endosc 2007;65 (4):679–683. doi:10.1016/j.gie.2006.10.017.
5. Perretta S, Allemann P, Dallemagne B, Marescaux J. Natural Orifice Transluminal Endoscopic Surgery (N.O.T.E.S.) for neoplasia of the chest and mediastinum. Surg Oncol 2009;18(2):177–180.
6. WebSurg. www.Websurg.com; 2008
7. Fritscher-Ravens A, Patel K, Ghanbari A, Kahle E, von Herbay A, Fritscher T, Niemann H, Koehler P. Natural orifice transluminal endoscopic surgery (NOTES) in the mediastinum: long-term survival animal experiments in transesophageal access, including minor surgical procedures. Endoscopy 2007;39(10):870–875. doi:10.1055/s-2007-966907.
8. Sumiyama K, Gostout CJ, Rajan E, Bakken TA, Knipschield MA, Chung S, Cotton PB, Hawes RH, Kalloo AN, Kantsevoy SV, Pasricha PJ. Pilot study of transesophageal endoscopic epicardial coagulation by submucosal endoscopy with the mucosal flap safety valve technique (with videos). Gastrointest Endosc 2008;67:496–523.
9. Spaun GO, Zheng B, Swanstrom LL. A multitasking platform for NOTES; a bench top comparison of a new device for flexible endoscopic surgery and standard dual channel endoscope. Surg Endosc. 2009; in press. doi:10.1007/s00464-009-0476-5.