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Clinical overview: adjuvant therapy of gastrointestinal cancer

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Abstract Adjuvant therapy has been tested widely in the treatment of cancers of the stomach, pancreas, and large bowel. In the USA, the use of postoperative chemoradiation in stomach cancer is considered a standard of care after the publication of the Intergroup Study 0116 in September 2001. This study demonstrated significant benefit in overall and disease-free survival for patients receiving postoperative treatment with fluorouracil (5-FU)/leucovorin chemotherapy and radiation after gastric resection. Adjuvant chemotherapy is not considered to be of significant benefit, and such therapy for patients with resected gastric cancer is investigational. There is interest in the use of neoadjuvant chemotherapy strategies as preoperative treatment followed by surgical resection. This approach has been tested in a randomized study of over 500 patients carried out by the Medical Research Council in the UK. This study demonstrated that patients receiving preoperative and postoperative epirubicin, cisplatin, 5-FU (ECF) chemotherapy, had a downstaging of tumor size, an increase in rates of curative resection, and an increase in disease-free but not overall survival. With pancreatic cancer, there is a controversy over postoperative chemoradiation after pancreatic resection. A recently completed Intergroup Study compared gemcitabine to 5-FU chemotherapy given before and after radiation in resected pancreatic cancer. Over 500 patients have been accrued to this study, which recently closed. In Western Europe, the results of a large clinical trial (ESPAC) have suggested that chemoradiation is not beneficial in patients with resected pancreatic cancer. In large bowel cancer, 5-FU-based adjuvant chemotherapy regimens are superior to surgery alone, particularly in node-positive patients. The use of newer combinations including 5-FU/leucovorin plus irinotecan and 5-FU/leucovorin plus oxaliplatin are also of interest as chemotherapy in resected colon cancer patients. The recent publication of the MOSAIC trial demonstrated that 5-FU/leucovorin/oxaliplatin (FOLFOX 4) improves progression-free survival in node-positive patients over 5-FU/leucovorin alone. The results of studies of 5-FU/leucovorin and irinotecan both in Europe (PETACC) and the USA (IFL vs 5-FU/leucovorin) are awaited with interest. Another area of interest in resected colon cancer is the use of molecular genetic monitoring to assess the likelihood of patient relapse. The data over the past several years have demonstrated that patients whose tumors do not have deletion of the deleted in colon cancer (DCC) gene on chromosome 18 have an improved outcome. Recent data are available with tumors that demonstrate microsatellite instability (MSI). Such tumors represent about 15% of all colon cancers and have an improved outcome when compared to those not expressing MSI, and may not benefit from adjuvant chemotherapy.

Keywords Gastric · Colonic · Pancreatic · Adjuvant chemotherapy

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Introduction

The adjuvant therapy for gastrointestinal cancer has been extensively explored over the past 30 years. The current status of such therapies is evaluated in this review.

Gastric adenocarcinoma

The primary curative treatment of gastric carcinoma and distal esophageal cancer is surgical resection [5, 17, 26].

In stomach cancer potentially resectable for cure (stages 0–IV M0), the surgical aim should be to perform a tumor resection entailing at least a partial gastrectomy with an *en bloc* dissection of lymphatic tissue. For at least 20 years there has been an international debate regarding the most appropriate surgical procedures to use in cases of potentially curable gastric carcinoma [17, 26]. The point at issue is whether extensive *en bloc* lymph node dissection along with complete resection of the primary stomach tumor improves survival. The extent of resection is defined using the designation of D0, D1, and D2:

D0 Incomplete resection of N1 nodes

D1 Complete resection of N1 nodes

D2 Complete resection of N1 + N2 nodes.

If a surgeon resects in an *en bloc* fashion, all of the tumor plus the N1 lymph nodes, a D1 dissection has been performed. If the N2 nodes are resected, this is termed a D2 dissection. If N1 nodes are not taken, a D0 procedure has been performed. The D2 dissection as a norm for gastric cancer surgery was developed from surgical practice in Japan. Japanese surgeons have reported superior results with the D2 surgical resection in gastric cancer for a number of years [17]. Small phase III comparisons of D1 and D2 dissections have been completed in South Africa and Hong Kong [23]. These studies were underpowered (fewer than 30 patients per arm) and showed no survival benefit for D2 nodal dissection.

In the Netherlands, a much larger phase III study including 711 evaluable patients also tested D2 vs D1 dissection [5]. This study also demonstrated that the D2 dissection does not improve overall survival and is associated with a higher operative morbidity and mortality. This study is also of interest because it provides data for assessing the effect of extended lymph node dissection on staging accuracy. Bunt et al. have reported that patients undergoing D2 dissections have significantly more accurate surgical pathological staging than patients undergoing D1 dissections [6]. The Dutch investigators asked their pathologists to evaluate staging of patients on-study who had undergone D2 resections. These pathologic specimens were first evaluated as if only D1 resection (removal of N1 nodes only) had been performed and a pathologic stage was applied. Subsequently the whole specimen, including the N2 nodes was evaluated and the actual pathologic stage was defined (Table 1). This study demonstrated that a D1 dissection, when compared to a D2 dissection, understages 60–75% of patients (Table 1). For clinical scientists evaluating the effect of postoperative systemic therapy in gastric cancer, it is important to understand that less than D2 dissections result in a significant risk of understaging.

Irrespective of the surgical procedure used for the treatment of gastric cancer, the effectiveness of surgical resection is poor. When survival of node-positive patients is examined after gastric resection in the USA, overall survival is at best 30% [12, 19]. The reason patients die is the development of symptomatic metastatic disease arising from unresected microscopic metastases present at the time of surgical resection. Because of the high risk of relapse after gastric resection, there has been a great deal of interest in strategies to prevent relapse and improve survival for patients with stomach cancer. The major approaches that have been explored fall into the categories of preoperative or neoadjuvant approaches and postoperative or adjuvant therapy strategies.

Adjuvant therapy approaches

Adjuvant therapy of gastric cancer using systemic therapy alone or as part of combined modality therapy with curative intent has also been widely tested within the past three decades. Adjuvant cytotoxic chemotherapy alone has been of minimal benefit. A meta-analysis by Hermans et al. demonstrated no conclusive value for adjuvant chemotherapy [12]. Another meta-analysis by Earle and Maroun showed borderline statistically significant, but clinically insignificant, survival improvement from the use of adjuvant chemotherapy [9]. In the USA, a clinical trial testing fluorouracil (5-FU), doxorubicin, and mitomycin (FAM) chemotherapy in a cooperative group (Southwest Oncology Group) also did not demonstrate any benefit for adjuvant chemotherapy [19]. In this study, 191 patients were randomized to either 1 year of FAM following surgery or surgery alone. There was no benefit for chemotherapy and the survival curves of treated and control patients were overlapping. The overall survival at 5 years demonstrated in the study was approximately 35% for both surgery alone, and for surgery followed by FAM chemotherapy. At present adjuvant chemotherapy should be considered investigational. Newer regimens

Table 1 Gastric cancer. Stage migration: D1 compared to D2 gastrectomies (data from Bunt et al. [6])

D1 TMN		D2 TMN				% Change
Stage	No. of patients	Stage II	Stage IIIA	Stage IIIB	Stage IV	
II	48	30	18			38
IIIA	49		19	29	1	61
IIIB	24			6	18	75

such as epirubicin, cisplatin, and 5-FU (ECF) and docetaxel, cisplatin, and 5-FU (DCF) have not been tested as pure adjuvant therapy in patients with resected gastric cancer.

One of the important therapeutic findings in gastric cancer over the past 15 years has been that, in patients with known residual disease, the combination of radiation therapy plus fluorinated pyrimidine (5-FU) used as a radiation sensitizer could result in the complete control (apparent cure) of small amounts of residual or recurrent stomach cancer [10]. This use of combined modality radiation and chemotherapy has also been demonstrated to be efficacious in esophageal cancer [13], resulting in a prolonged disease-free survival (DFS) for patients without the need for surgical resection. Because of the demonstrated benefit for combined radiation and fluorinated pyrimidine in patients with known residual gastric and esophageal carcinoma, a US Intergroup Study was initiated in the early 1990s to test whether the combination of 5-FU/leucovorin plus radiation therapy after surgical resection would be of value to patients with resected gastric carcinoma (SWOG9008/INT0116) (Fig. 1). A total of 603 patients were enrolled in this study in 7 years of accrual. The study was first reported in the spring of 2000 and updated in September 2001 [20]. This study included 281 eligible patients receiving 5-FU/leucovorin/radiation and 275 eligible patients in the observation arm. Of patients in both arms, 85% had node-positive carcinoma (stage IIIA, IIIB, or IV). The types of surgery performed in this study were carefully analyzed. Results demonstrated that the standard of care in the USA does not include extended lymph node dissections. Dissections $<$D1 (only partial removal of the N1 nodes) were carried out in 54% of patients, and only 10% of patients were treated with D2 dissection.

Combined modality therapy as delivered in SWOG9008/INT0116 was well tolerated [20]. Although 41% of patients experienced grade III and 32% experienced grade IV toxicities (mainly hematologic toxicity), only three patients (1%) died as a result of treatment. It is important to review carefully and verify radiation treatment planning to deliver this combined modality therapy safely and effectively. When SWOG9008/INT0116 radiation treatment plans were reviewed before initiation of therapy, 34% were found to have major deviations. Two-thirds of these deviations would have resulted in under-treatment of patients, while one-third had the potential for delivering severely toxic radiation.

Disease-free and overall survival were significantly improved by combined modality 5-FU/leucovorin/radiation therapy. Median time to relapse was 30 months in the treatment arm vs 19 months in the control arm ($P < 0.0001$; two-sided P value). Overall survival was also improved with a median survival of 35 months in the treatment arm vs 28 months in the control arm ($P = 0.01$; two-sided P value). Although there was a suggestion that local relapse (defined as relapse within the residual stomach) was decreased by combined modality therapy, this was not statistically significant. While it is possible that further follow-up may modify some of the clinical results of SWOG9008/INT0116, the significant improvements in disease-free and overall survival obtained with acceptable toxicity have made combined modality radiation chemotherapy a standard of care in patients with resected gastric cancer.

Neoadjuvant therapy

Until recently, neoadjuvant treatment, which typically employs chemotherapy and/or radiation therapy, before attempts at surgical resection of gastric cancer, has been tested only in nonrandomized phase II studies. Clinical investigators at Memorial Sloan Kettering in New York [4] and the University of Southern California [7] have reported results using this therapeutic approach. Both of these groups used a treatment plan entailing the use of systemic preoperative chemotherapy along with postresection intraperitoneal chemotherapy, a strategy designed to prevent relapse in the peritoneal cavity. Intraperitoneal chemotherapy is a rational approach since the peritoneal cavity is a common site of recurrence for gastric cancer.

An example of aggressive neoadjuvant therapy is the 1997 report by Crookes et al. at the University of Southern California [7]. In this study, 59 patients received combined modality therapy consisting of continuous infusion 5-FU with weekly leucovorin and cisplatin. This was followed by surgical resection of the primary gastric tumor. Postoperatively resected patients

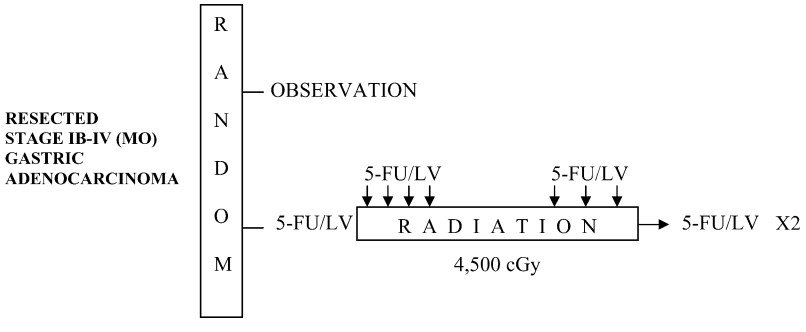

Fig. 1 Schema for SWOG 9008/INT 0116. Patients with resected stage IB-IV (MO) were randomly allocated to either observation or postoperative chemoirradiation (see reference 20) (*5-FU* 5-fluorouracil, *LV* leucovorin)

received two cycles of intraperitoneal 5-fluro2-deoxyuridine and cisplatin. This study demonstrated that 56 of 59 (95%) patients receiving neoadjuvant therapy were able to undergo surgical resection. Forty patients (71%) underwent resections with curative intent. Only 9 of 40 patients (23%) who had curative resection developed recurrent carcinoma. The median time of follow-up at the time of this report exceeded 45 months. The observed relapse rate in well-designed prospective studies after gastric cancer resection is in the range of 60–70% [12, 19]. The 23% relapse rate in the University of Southern California study with a median follow-up of almost 4 years is an impressive phase II result. However, the only definitive means to test neoadjuvant therapy is in phase III prospective clinical trials.

In the spring of 2003, the results of the first well-powered phase III neoadjuvant chemotherapy study were presented at an American Society of Clinical Oncology meeting [2]. This clinical trial conducted by the British Medical Research Council (MRC) randomly allocated 503 patients with potentially resectable gastric cancer to either preoperative and postoperative ECF [24] chemotherapy versus surgery alone. The results of this study, called the MAGIC trial, demonstrated statistically significant improvement in DFS (medians 12 months vs 18 months; $P = 0.002$, log rank). There was an increased rate of overall survival which, however, did not reach statistical significance (medians 18 months vs 22 months; $P = 0.063$, log rank). There were no excesses in surgical complication rates for patients receiving neoadjuvant therapy versus those receiving surgery only. There were two other important results of the MAGIC study. First, the curative resection rate appeared to be increased by neoadjuvant therapy. Surgeons were asked to assess whether a curative ''RO'' resection had been performed at the time of surgery. Operating surgeons estimated that 69% of patients receiving surgery only were curatively resected versus 79% of patients receiving neoadjuvant therapy ($P = 0.018$) (Table 2). There also was a significant (Table 2) downstaging of T stage (surgery only T4 64%, neoadjuvant therapy T4 49%; $P = 0.011$). The results of the MAGIC study demonstrated that there are some benefits for neoadjuvant chemotherapy. However, it is not yet clear how neoadjuvant therapy may be incorporated into the multimodality therapy of localized gastric cancer.

Table 2 Gastric cancer. MAGIC trial treatment results: effects of neoadjuvant therapy on curative resection and downstaging of tumors (data from Allum et al. [2]) (*ECF* epirubicin/cisplatin/5-FU)

	ECF	Surgery alone
No. of patients having surgery	212 (85%)	232 (92%)
Median time to surgery (days)	99	14
Proportion of curative resections (%)	79*	69
Proportion T_3/T_4 tumor (%)	49**	64

*$P = 0.018$, **$P = 0.011$

The question may fairly be asked: how do the results of neoadjuvant therapy in the MRC MAGIC study [2] compare to the results of INT0116 [20]? It is helpful to compare patient characteristics in the two studies (Table 3). There were similar numbers of patients in both studies (> 500) and an equal frequency of T3/T4 tumors (approximately 65%). The frequency of nodal metastases was greater in INT0116 (85%) than in MAGIC (72%). Poor-prognosis patients with more than four nodes involved with tumor were more common in INT0116 (43%) than in MAGIC (27%). In general, it appears that the INT0116 patients were at higher risk for recurrence than MAGIC patients. Although it is not possible directly to compare outcomes between the two studies using tests of statistical significance, it is possible to compare general outcomes. The patients receiving surgery only did better in INT0116 (52% 2-year survival) than those receiving surgery only in the MAGIC study (40% 2-year survival). The treatment arms also demonstrated better 2-year survival outcomes for INT0116 (58%) compared to MAGIC (48%). It is important to emphasize that these general comparisons would need to be confirmed in prospective studies before any conclusions on relative efficacy can be drawn. However, since it was demonstrated in MAGIC that tumors were downstaged and resectability increased, both highly desirable results, and that INT0116 demonstrated that postoperative chemoradiation increased disease-free and overall survival, one could argue that new studies should evaluate neoadjuvant therapy combined with postoperative chemoradiation. Such studies would require phase II pilot clinical trials to carefully assess patient tolerance of aggressive pre- and postoperative therapy. Combining neoadjuvant and postoperative chemoradiation may well result in further improvements in the outcome of patients with resectable gastric cancer.

Future prospects

What future approaches will be used in attempting to improve the survival of patients with stomach cancer? The results of SWOG9008/INT0116 demonstrate that for the population of gastric cancer patients undergoing gastrectomy in the US, postoperative chemoradiation improves survival, and future clinical trials, to be

Table 3 Gastric cancer. Patient characteristics of INT0116 and MAGIC trials (data from Macdonald et al. [20] and Allum et al. [2], respectively)

	INT0116	MAGIC
No. of patients	554	503
T_3/T_4 (%)	68	64 (surgery only)
Nodes (–) (%)	15	28
Nodes (+) (%)	85	72
Nodes >4 (%)	43	27

considered successful, must show outcomes equal or superior to the treatment arm of SWOG9008/INT0116. The about to be activated National Intergroup adjuvant therapy study (Fig. 2) will test ECF chemotherapy before and after chemoradiation compared to a standard arm which is essentially the same as the treatment arm of SWOG9008/INT0116. Although chemoradiation may be considered a standard of care, it may well be that future cytotoxic chemotherapy regimens may be proven to be of value as adjuvant therapy without radiation. Another strategy of interest resulting from the recent evidence of benefit from neoadjuvant chemotherapy would be to combine neoadjuvant chemotherapy with postoperative chemoradiation. Newer approaches to cancer management, including antiangiogenesis strategies and growth factor receptor inhibition with either monoclonal antibodies [25] or small-molecule inhibitors of epithelial growth factor receptor (EGFR) activity [3] may be of value.

Clinical trials need to be mounted to critically evaluate adjuvant and neoadjuvant therapy strategies in gastric cancer. Patients identified preoperatively should be candidates for phase III trials testing neoadjuvant therapy followed by surgery vs surgery alone. The specific neoadjuvant treatment programs could use chemotherapy, chemotherapy plus radiation, as well as perhaps newer targeted therapies such as EGFR inhibition. In patients identified postoperatively, a phase III trial using a SWOG9008/INT0116 chemoradiation arm as a standard control vs newer chemotherapy (ECF) plus irradiation opened in 2003 (Fig. 2). In the future, new studies built upon the chemoradiation theme will likely test targeted therapies (EGFR antagonists, antiangiogenesis agents, etc.) with and without chemotherapy given with postoperative radiation therapy.

Pancreatic cancer

Adenocarcinoma of the pancreas is a highly lethal disease occurring in approximately 30,000 patients per year in the USA and resulting in death in at least 95% of these patients [14]. The standard therapy with curative intent is resection of the pancreas. However, only 15% of all patients are resectable for cure and a mere 15% of these patients will be long-term survivors [14]. Adjuvant therapy of pancreatic cancer has been relatively infrequently studied because of the paucity of patients eligible for phase III trials. During the past 25 years in the USA, efforts have been made to study postoperative chemoradiation after curative resection. In the 1980s, a phase III study of postoperative chemoradiation versus surgery alone was carried out by the Gastrointestinal Tumor Study Group (GITSG) (Fig. 3) [16]. This trial included only 42 patients and showed a significant survival benefit at 2 years (42% vs 18%; $P < 0.03$) for 5-FU plus 4000 cGy radiation [16]. Following the results of this phase III study along with phase II results demonstrating approximately the same survival outcomes [11], postoperative chemoradiation has been accepted in the USA as a standard of care. Most recently, a phase III United States Intergroup Study (Fig. 4) to test whether gemcitabine pre- and postchemoradiation is superior to the 5-FU/radiation arm of the GITSG study has completed accrual. Over 500 patients have been enrolled in this-well powered phase III trial, but the only question being addressed in this study is the value of gemcitabine

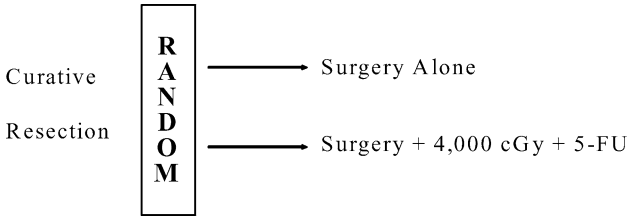

Fig. 3 Schema for pancreatic cancer adjuvant therapy conducted by the Gastrointestinal Tumor Study Group (see reference 11) (*5-FU* 5-fluorouracil)

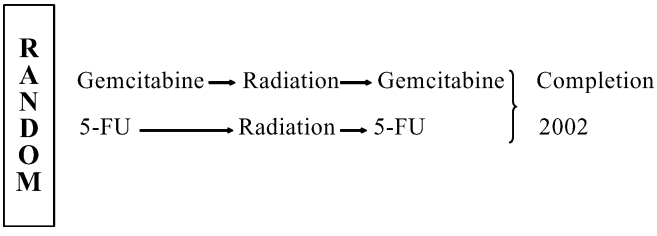

Fig. 4 Schema for the US Intergroup Study of adjuvant chemoradiation in pancreatic cancer (*5-FU* 5-fluorouracil)

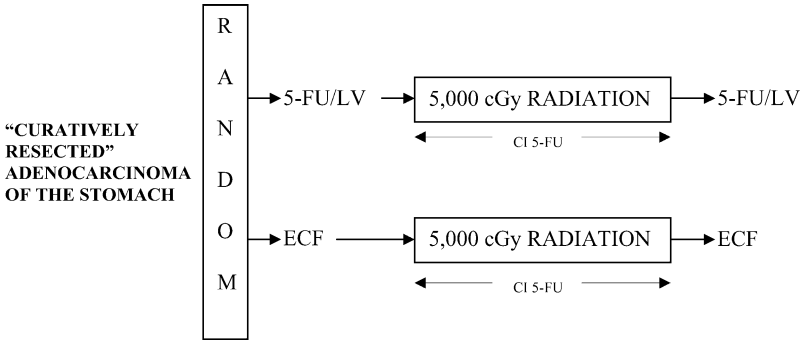

Fig. 2 Schema for US Intergroup postoperative adjuvant therapy study (*5-FU* 5-fluorouracil, *LV* leucovorin, *ECF* epirubicin/cisplatin/5-FU, *CI* continuous infusion)

versus 5-FU as pre- and postchemoradiation treatment; the value of chemoradiation itself is not being tested in this study.

In Europe, there has not been widespread acceptance of postoperative chemoradiation as a standard of care for resected pancreatic cancer. In 2001, the results of a large phase III study (ESPAC trial) with a somewhat complex design were reported [21]. This clinical trial had patients randomly allocated to surgery alone, chemoradiation, or chemotherapy alone. Because of its complex design, the study's results have been felt difficult to interpret by some [1]. The results have, however, been interpreted (Table 4) as showing no benefit for chemoradiation and possible benefit for cytotoxic chemotherapy alone. In Europe, the standard of care is not postoperative chemoradiation and it is felt that surgery-alone control arms are appropriate for phase III trials.

Large-bowel cancer

The use of adjuvant chemotherapy in the management of resected large-bowel cancer is a standard of care particularly for patients at high risk for relapse (stage III and stage II with obstruction or perforation of the bowel at the site of the tumor) [18]. The standard approach until 2003 was to use 5-FU plus leucovorin (folinic acid) in a wide variety of doses and schedules as postoperative adjuvant chemotherapy. The expected improvement in overall 5-year survival and cure rate with 5-FU/leucovorin is approximately 15% better than that obtained with surgery alone.

Recently data from a phase III trial demonstrating an improvement to the 5-FU/leucovorin results have been reported [8]. This study, designated the "MOSAIC" trial, tested an infusional 5-FU/leucovorin regimen with and without the platinum analogue oxaliplatin, and demonstrated superior DFS for the oxaliplatin regimen at a median follow-up of 3 years. In this well-designed phase III study, 2270 patients with resected stage II and III colon cancer were enrolled. There was an improvement in DFS for those with stage III disease for the oxaliplatin regimen compared to 5-FU/leucovorin (68% vs 58%), which was statistically significant for patients with stage III disease ($P < 0.05$). There were differences in DFS in those with stage II disease favoring the oxaliplatin regimen (85% vs 80%), but these were not statistically significant ($P > 0.05$). Many clinicians now accept 5-FU/leucovorin/oxaliplatin as a standard of care for patients with resected colon cancer with lymph node metastases. There are, however, a number of pending phase III studies testing irinotecan plus 5-FU/leucovorin regimens, the results of which are expected to be reported in 2004. These studies may provide clinicians with acceptable irinotecan combinations to use as adjuvant therapy in patients with resected colon cancer.

Study of the molecular genetics of large-bowel cancer has been of great interest in the past decade [15, 22, 27]. There is no doubt that carcinogenesis in the large bowel results from the accumulation of mutations in a combination of protooncogenes and tumor suppressor genes (Table 5). There are now data that these molecular genetic abnormalities seen in colon cancers may bear upon both the overall prognosis of resected colon cancer and also upon the efficacy of adjuvant therapy in this disease. In 1994, Jen et al. [15] studied the effect of deletions of the long arm (18q) of chromosome 18 upon outcome in resected colon cancer. It has been established that 18q deletion can result in the loss of a known tumor suppressor gene on the long arm of the chromosome. This gene is termed the deleted in colon cancer (DCC) gene. In 145 patients in whom adjuvant chemotherapy was not administered, Jen et al. demonstrated that in those with stage II disease with a normal chromosome 18, the 5-year survival was 93%. In patients with 18q deletions, the survival was 54% ($P = 0.008$). Likewise, Watanabe et al. found similar results in patients receiving adjuvant chemotherapy [27]. The 5-year survival for patients with 18q deletion was 50% versus 74% for those with a normal chromosome 18 ($P = 0.006$). Watanabe et al. also

Table 4 Pancreatic cancer. ESPAC 541 eligible patients (data from Neoptolemos et al. [21])

	Median survival (months)	*P* value
Chemoradiation	15.5	
No chemoradiation	16.1	0.24
Chemotherapy	19.7	
No chemotherapy	14.0	0.005

Table 5 Genes altered in colon cancers

Gene	Chromosome	Tumors with mutations (%)	Class	Action
"FCC"	2	About 15	?	Maintains DNA replication accuracy
K-Ras	12	About 50	Oncogene	Intracellular signaling molecule
Cyclins	Various	4	Oncogene	Helps regulate cell cycle
Neu/HER2	17	2	Oncogene	Growth factor receptor
Myc	8	2	Oncogene	Regulates gene activity
APC	5	> 70	Tumor suppression	Unknown
DCC	18	> 70	Tumor suppression	Cell adhesion molecule
P53	17	> 70	Tumor suppression	Regulates gene activity

Table 6 Microsatellite instability (MSI). Colon cancer survival: adjuvant chemotherapy (data from Ribic et al. [22])

	No. of patients	5-year disease-free survival (%)	*P* value
MSI low			
Adjuvant	230	70	
No adjuvant	245	59	0.01
MSI high			
Adjuvant	53	69	
No adjuvant	42	83	0.11

noted in 319 patients analyzed that 155 (49%) had 18q deletions, suggesting that this abnormality could be expected to be present in roughly 50% of patients.

In July 2003, an important communication evaluating the effect of microsatellite instability (MSI) upon the prognosis for resected colon cancer and upon the prediction of the effect of adjuvant chemotherapy on outcome in resected large-bowel cancer was published [22]. MSI refers to a finding of an increased frequency of variability of microsatellite nucleotide repeats in the DNA of colon cancers. MSI is high in approximately 15% of patients with large-bowel cancers and the patients may have differences both in prognosis and in outcome following adjuvant chemotherapy when compared to the 85% of patients demonstrating low levels of MSI [22]. Ribic et al. [22] studied outcome results from phase III adjuvant chemotherapy studies in which a total of 570 patients were randomly allocated to adjuvant chemotherapy after resection or resection alone (Table 6). In the majority of patients with low-frequency MSI tumors, the 5-year DFS was significantly improved by adjuvant chemotherapy ($P = 0.01$). In the patients with high-frequency MSI tumors, there was no benefit for adjuvant therapy when compared to no adjuvant therapy (69% vs 83%; $P = 0.11$). These results suggest, but do not confirm, that adjuvant therapy may have a negative effect on the outcome in patients with high-frequency MSI.

In the future, MSI and DCC status will be important factors to evaluate when choosing colon cancer patients who are to receive adjuvant therapy. Clinical trials currently in the planning process will prospectively assess whether patients with normal chromosome 18 and/or high-frequency MSI tumors benefit from adjuvant chemotherapy or conversely do not need such therapy, since they have a high likelihood of being cured by surgery alone. Interfacing tumor molecular genetic prognostic and predictive factors with the treatment decisions will clearly be of increasing importance in oncology.

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