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The Prevention of Radiation-induced Small Bowel Complications

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Moderate dose pelvic radiotherapy is associated with a 5% severe complication risk related to the small bowel. Strictures and/or fistulation can occur many years after treatment. These complications are difficult to treat, and surgical treatment (excision, bypass) bears a significant morbidity risk. The risk of chronic diarrhoea or malabsorption may increase to 40%, depending on the irradiated small bowel volume. Late small bowel complications are generally irreversible due to vascular aetiology. Prevention of these complications can be achieved by limiting the volume of small bowel treated. Consequences for radiotherapeutic techniques in treatment for rectal cancer are multiple beam set-up, customised blocking based on visualisation of the small bowel in the treatment position, and the use of a special open table-top device that results in a small bowel shift from the treatment field.

Key words: radiation enteritis, small bowel complications
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INTRODUCTION

RADIOTHERAPY INDUCES early and late effects in the gastrointestinal tract. In the pelvis, the small bowel is the most radiosensitive and, therefore, dose-limiting organ. Acute symptoms, consisting of diarrhoea and abdominal cramps, occur in the majority of patients treated with a fractionated course of pelvic radiotherapy. These symptoms are generally transient and respond to medication. Late small bowel symptoms usually occur in the first year, but latency periods up to 7 years after therapy are reported [1]. These complications are often irreversible and difficult to treat. In reporting complications, different grading systems are used, as can be noted in recent publications [2–4]. Aiming at using a 'common language', the Radiation Therapy Oncology Group (RTOG) (U.S.A.) and European Organization of Research and Treatment of Cancer (EORTC) have developed a classification that is mainly based on the impact of symptoms on the patient's performance status and type of treatment required (Table 1). There is no common agreement on how to account for reversibility or correctibility of symptoms. Pedersen and colleagues have shown that reporting frequencies rather than actuarial rates can underestimate the risk of late morbidity, especially in patients with a poor prognosis [3]. In their analysis of 442 patients treated for cervical cancer, the 5-year actuarial estimate of both severe small bowel and rectosigmoid complications was almost double the 5-year frequency (7 and 13% and 17 and 28%, respectively.

Small bowel obstructions requiring surgery occur in 5% of patients treated to a dose of 45–50 Gy in 5 weeks [1, 2, 5]. Beyond this dose, the (crude) incidence of obstruction can rise to 37% [6]. The risk of chronic diarrhoea has been reported to vary with volume and can rise to 40% (actuarial 5-year estimate) [4]. The main factors predisposing to late radiation-induced small bowel complications are total dose and dose per fraction, volume of irradiated small bowel, the use of single-field treatment daily, chemotherapy, and previous abdominal surgery [1, 2, 4–7]. Several patient-related factors indicating vascular comorbidity (age, diabetes, hypertension) that are potentially predictive for increasing the risk of late intestinal injury, have failed to be of significant importance [1, 5]. This could be due to a spectrum of severity that exists for these conditions. The

Table 1. RTOG and EORTC late radiation morbidity scoring systems

General principles	
RTOG late radiation morbidity scoring system	
Grade 1	Minor symptoms requiring no treatment
Grade 2	Symptoms responding to simple outpatient management
Grade 3	Distressing symptoms altering performance status, hospitalisation for diagnosis or minor surgical intervention may be required
Grade 4	Major surgical intervention (laparotomy, colostomy) or prolonged hospitalisation required
Grade 5	Fatal complications
RTOG/EORTC late radiation morbidity scoring for small intestine	
Grade 1	Mild diarrhoea or cramping, bowel movement up to five times daily
Grade 2	Moderate diarrhoea and colic, bowel movement more than five times daily
Grade 3	Obstruction or bleeding requiring surgery
Grade 4	Necrosis, perforation, fistula
Grade 5	Death related to small bowel morbidity

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aim of the present paper is to discuss the factors that might be influenced to prevent small bowel complications.

PATHOGENESIS OF RADIATION-INDUCED SMALL BOWEL INJURY

While early effects reflect epithelial stem cell injury [8], the critical radiation lesion for chronic injury is progressive vascular disease resulting in endarteritis [9–11]. The clinical effects of radiation on the small bowel are mainly related to malabsorption due to mucosal gut depletion, and changes in gastrointestinal motility. Diarrhoea and abdominal cramps occur in both acute and late phase, and in the late phase, small bowel obstruction and formation of fistulas may be related to slowly evolving vascular injury that causes fibrosis of the bowel wall. Histological features of early and late chronic radiation enteritis are well documented: both in the early and late phase of diarrhoea, denudation of the mucosal layer is observed with ulceration and microabscesses [8, 11]. In the late post-treatment phase, these features are accompanied by vascular changes, such as microthrombi in small and large arteries and hyalinisation of vessels with focal infarctions [10, 11]. Barium sulphate perfusion studies, performed in patients who underwent resection of a bowel segment for radiation-induced bowel stricture, have shown a decrease in perfusion on stricture localisations that extend throughout the bowel wall [12].

FUNCTIONAL STUDIES

Measurements of radiation-induced small bowel dysfunction have focused on abnormalities in gastrointestinal absorption and motility [13–16]. Currently, no specific functional test is available, and prospective studies are lacking. Diarrhoea is mainly caused by bile acid malabsorption in the terminal ileum [15], but may also be caused by intraluminal bacterial overgrowth resulting from small bowel strictures. To differentiate these two potential mechanisms, currently a sensitive bile acid absorption test, measuring the retention of synthetic Selenium-75-containing bile acids (75-SeHCAT) is combined with a test for colonisation, such as one of the available breath tests [13, 14, 16]. This combination is especially helpful in determining possible therapeutic management, such as administration of cholestyramine or antibiotics. In a recent retrospective study, Yeoh and associates investigated gastrointestinal function in 30 randomly selected patients treated for cervical carcinoma, and compared results with those of 18 healthy controls [16]. Measurements consisted of assessment of symptoms, absorption studies (bile acids, vitamin B12, lactose and dietary fat), gastrointestinal transit time (gastric emptying, small intestinal transit and whole gut transit), and intestinal permeability (urinary excretion of [Cr^{51}]EDTA, lactulose and rhamnose). All but 1 patient had at least one abnormal test. Gastrointestinal symptom score was significantly higher, and absorption of all of the compounds mentioned significantly lower in patients, whereas patients demonstrated significantly shorter gastric emptying and small intestinal transit time. The authors suggest that measurement of bile acid malabsorption might be the 'most sensitive' test for radiation enteritis because it was abnormal in 50% of patients. An interesting observation was the significant relationship found between bile acid absorption and whole gut transit in both patients and controls. It is suggested that radiation-induced altered motility can contribute to malabsorption of bile acids. This is supported by the clinical observation of improved or normalised 75-SeHCAT retention after delaying bowel motility with loperamide in patients with chronic diarrhoea after irradiation [17]. In a prospective study on the effect of pelvic radiotherapy (with or without hyperthermia) on intestinal permeability, a significant rise in EDTA/mannitol ratio in the urine was observed after completion of therapy [18]. In enteropathic diseases, the permeability of large molecular weight (MW) molecules ([^{51}Cr]EDTA) is decreased, while absorption of low MW probes (mannitol) is increased. In conclusion, intestinal dysfunction is demonstrated in patients treated with pelvic radiotherapy, but the available functional tests lack a high specificity or sensitivity. The diagnosis is mainly based on clinical symptoms, becoming apparent mostly in an advanced stage.

PREVENTION OF SMALL BOWEL INJURY

The volume effect: clinical impact of reduction of the small bowel volume in the treatment field

Because of the relative posterior location of the target volume in rectal cancer patients, lateral treatment portals can spare a portion of anteriorly located small bowel and bladder. The visualisation of small bowel by barium contrast enables optimal sparing by the use of customised individual lead blocks [19].

Recently, it has become clear that efforts to reduce the volume of small bowel treated result in less gastrointestinal side-effects [1, 2, 6]. Gallagher has studied the volume, distribution and mobility of opacified small bowel by fluoroscopy and orthogonal radiographs in 150 patients who received pelvic radiotherapy in a prospective study [2]. The mean small bowel volume in the treatment field, as estimated by orthogonal radiographs, varied from 50 cm^3 using a four-field technique in prone position with abdominal wall compression and bladder distension, to 1 010 cm^3 in patients who were treated with a two-field technique in the supine position after abdominoperineal resection. Both acute and late gastrointestinal side-effects correlated with pelvic small bowel volume, and type of surgery performed. A small bowel shift in prone position has been observed in patients treated on a special open table-top device (belly board) [1]. With the use of the device, less small bowel in the pelvis was observed, resulting in an obstruction rate of only 3% in 31 patients.

Quantification of the volume effect

The significance of quantifying the correlation between dose, volume and late complications is related to technical developments in radiation treatment technique. Optimisation of techniques using modern three-dimensional radiation treatment planning systems ultimately aims at dose escalations to improve local tumour control, by sparing the maximum volume of normal tissue (conformal therapy). These developments in technique precede the clinical knowledge on expected complications using dose–volume histograms. A problem especially related to the small bowel is its mobility, so only an estimation of the volume present during a 5-week-fractionated course is possible [20]. So far, data on quantification of the small bowel volume in conformal therapy and the correlation with side-effects has been only published for acute toxicity by Tait and colleagues [21]. They conclude that less small bowel was irradiated at a high dose in patients treated with pelvic conformal therapy, as compared to conventional treatment. However, assessment of the impact of volume on acute bowel symptoms proved to be complex because, in the acute phase, the contribution of different parts of the bowel (rectum, small bowel) to a particular symptom is often unclear.

Recently, two studies have been performed to investigate quantitative aspects of the volume effect regarding late small

bowel complications in conventional radiotherapy [5, 7]. The aim of the first study was to determine the quantitative correlation between irradiated small bowel volume and severe small bowel complications in patients treated for several pelvic and abdominal malignancies, including rectal cancer [6]. A method was developed to estimate small bowel volumes in the high-dose region using computed tomography (CT) scans in the treatment position. In a retrospective study of 111 patients, irradiated after surgery for rectal cancer to a dose of 45–50 Gy in 5 weeks, extended antero-posterior postero-anterior opposite pelvic treatment (upper level L2, mean small bowel volume 790 cm^3) resulted in a 37% severe complication rate (obstruction requiring surgery). For a three-field technique treatment limited to the pelvis (mean small bowel volume (SBV) 165 cm^3), this complication rate was only 6%. These data were combined with literature data on small bowel obstructions, occurring after several pelvic or abdominal treatments to different dose levels. For these typical treatment fields (bladder and endometrium cancer, non-Hodgkin's lymphoma), small bowel volumes were estimated accordingly. The data were fitted to the dose–complication relationship using the maximum likelihood method, and the volume was taken into account by a power law. This resulted in the determination of a volume exponent of 0.26 ± 0.05. In practical terms, this means that by doubling the irradiated volume, a decrease in dose of 17% is necessary for the same complication rate. The study also indicated that a higher incidence of small bowel complications was observed after rectal surgery than other types of surgery (e.g. staging laparotomy), which could possibly be explained by the development of more adhesions.

A second study was performed to validate this volume exponent and to study the volume effect for all symptomatic small bowel complications [4]. For this purpose, small bowel volumes in the high-dose (50 Gy) region were measured using orthogonal barium films for 203 patients participating in a multicentre European protocol on postoperative radiotherapy for rectal carcinoma. The dose prescription according to the protocol was 50 Gy in 2-Gy fractions. The target volume encompassed the posterior pelvis up to the promontorium, and a four-field (box) technique was recommended. A large variation of small bowel volumes was observed with a mean of 231 cm^3 (0–975 cm^3). Ninety per cent of patients were evaluable for late complications with a median follow-up period of 36 months (range 2–98). The 5-year actuarial rates of small bowel obstruction and chronic diarrhoea were 11 and 41%, respectively. No significant correlation was found between the incidence of obstruction and pelvic small bowel volume. The 5-year estimate of chronic diarrhoea varied from 31% in patients with volumes below 77 cm^3 to 42% in patients with volumes over 328 cm^3 (Figure 1). Reviewing the literature, the available data on small bowel obstruction and estimated irradiated volume indicate that the volume effect for obstruction is present only when a large volume (800 cm^3) is treated. Intra-abdominal surgery seems to be a specific risk factor associated with obstruction, since in series of patients who are treated with extended field radiotherapy for prostate or cervical cancer (no intra-abdominal surgical procedures), the incidence of obstruction is less than 4% [4]. We conclude that the data from both studies indicate a difference in the volume effect for the symptoms diarrhoea and obstruction. These differences could reflect differences in target substructures of the small bowel involved in radiation enteritis. Stenosis and obstruction could develop by injuries to the outer fibromuscular structure or peritoneal layer. This effect probably increases

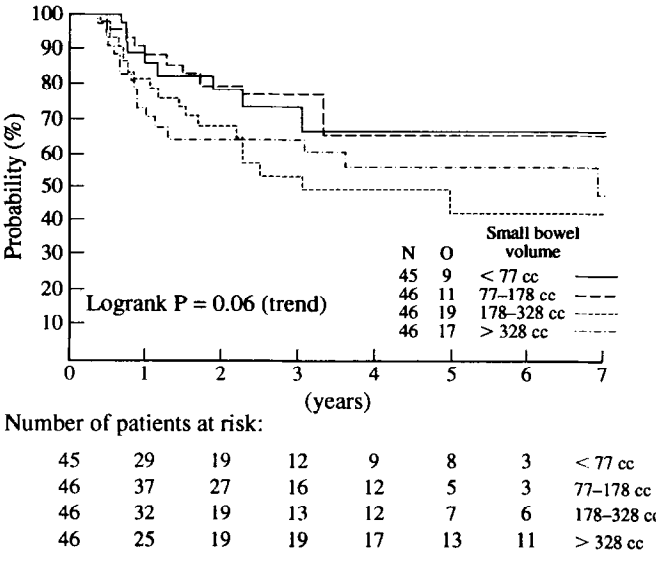

Figure 1. Actuarial estimate of chronic diarrhoea (more than three bowel movements daily) in patients treated with pelvic postoperative radiotherapy for rectal cancer, according to irradiated small bowel volume [4].

when radiation is combined with surgery. Diarrhoea and malabsorption is caused by depletion of mucosal layer by a direct cytotoxic effect or secondary to decreased vascular supply.

Surgical efforts to exclude small bowel from the pelvis

Many surgical techniques have been used to exclude the small bowel from the pelvis, including the creation of a pelvic diaphragm with peritoneal flaps, and implantation of absorbable meshes, silicon prostheses or pelvic tissue expanders. The disadvantages of these measures are the sensation of abdominal discomfort and the morbidity related to the surgical procedures. In a volumetric analysis, Herbert and associates demonstrated the beneficial effect of the placement of a removable tissue expander [22]. In 14 patients who had a tissue expander inserted, the mean small bowel volume receiving the full dose was 25 cm^3 compared with 239 cm^3 in 63 patients who did not. Diarrhoea requiring medication was observed in 31 versus 71% of these patients, respectively. Further analysis of both surgical and radiation-related chronic morbidity in patients with tissue expanders is needed to determine the advantages of such devices.

Elemental diets

It has been suggested that elemental diets (ED), referring to products containing nutrients in their simple form, taken during radiotherapy, may decrease early radiation enteritis. The basis for the protective effect that has been studied mainly in animals is probably due to a reduction in pancreaticobiliary secretions. This decreases the initial noxious effect on injured mucosa, thus contributing to keeping the glycocalyx membrane intact and maintaining the absorption capacity [23]. McArdle and associates studied the effect of elemental diet in patients who were given 5×4 Gy prior to cystectomy for bladder carcinoma. The diet was started 3 days before and continued for 4 days during radiotherapy. The ED patients had a better nitrogen balance pre- and postoperatively compared to historical controls, suffered less abdominal cramps and diarrhoea, and biopsy specimens of the ileal mucosa were normal, with maintenance of the brush border enzyme activity [24]. Since ED are often unpalatable, they are mainly administered by nasogastric tube. No prospective study

on possible beneficial effects of ED on chronic complications has been published thus far. Acute reactions are generally manageable with medication, thus leaving the role of "preventive" ED uncertain.

Preventive medication

Recently, a placebo-controlled study has shown a decrease in both early and late radiation enteritis symptoms in patients who received orally sucralphate during pelvic radiotherapy, compared to controls [25]. These symptoms refer to both diarrhoea and proctitis, defaecation incontinence, and loss of blood and mucus due to rectal mucosa damage. Sucralphate is a basic aluminium salt of the sulphated disaccharide sucrose. It is an effective drug in the treatment of gastric ulceration by formation of a viscous coagulum, providing protection against bile and enzyme effects for several hours after ingestion. Pharmacological actions of sucralphate on gastric mucosa involve adsorption of pepsin and bile acids, stimulation of mucus and bicarbonate secretion, increase in mucosal blood flow and protection of microvessels. A benefit of phophylactic sucralphate, with respect to chemo- or radiotherapy-induced mucositis, has been observed in patients treated for head and neck cancer. We are currently investigating the effect of sucralphate on late bowel symptoms in a placebo-controlled study in patients who have pelvic radiotherapy.

TREATMENT OF RADIATION-INDUCED SMALL BOWEL COMPLICATIONS

Conservative treatment

Acute diarrhoea occurring in the majority of patients undergoing pelvic or abdominal radiotherapy is mostly self-limiting and can be successfully treated by loperamide. In approximately 10%, symptoms require interruption of treatment. ED or bowel rest and parenteral nutrition might reduce acute symptoms, but use is restricted to the minority of patients having severe and uncontrollable symptoms.

Chronic symptoms caused by small bowel injuries can vary from malabsorption of varying degrees to mechanical bowel dysfunction by strictures. This diversity of symptoms requires different treatment approaches, and radiological studies combined with the available malabsorption studies can be helpful in interpreting these symptoms. In the patient presenting with diarrhoea, tests on ileal malabsorption, as described above, can be useful in separating bile malabsorption from bacterial overgrowth, which can influence treatment. However, no randomised studies have demonstrated the benefit of any conservative intervention. Antispasmodics, antibiotics, cholestyramine and acetylsalicylate have been reported to be successful in symptom management, as have low-fat diets. Supplements of vitamin B12, vitamins A and D and/or iron might be needed in conditions of ileal dysfunction, fat malabsorption or bacterial overgrowth. It is clear that, especially dietary measurements, require patient compliance to be effective and can greatly influence quality of life.

Surgical management

Surgical management of radiation enteritis is complicated for several reasons. The extent of bowel involvement can easily be underestimated and ideally, lesions should be widely excised with two ends of non-involved bowel used for the anastomosis; multiple sites can be involved and synchronous or metachronous rectosigmoid lesions can occur; and the patient might be in a poor nutritional condition.

Small bowel lesions mostly occur in the ileum. Ileal injury by itself proved to be a poor prognostic factor in a retrospective series of 57 patients studied, who required surgical intervention for any radiation-induced bowel injury [26]. Forty-four per cent of patients with isolated ileal lesions died due to radiation enteritis, and patients with ileal lesions often had other lesions. Surgery for any type of radiation-induced bowel injury is associated with a serious high complication rate (such as anastomotic leakage) (30%) and perioperative mortality. Furthermore, approximately 40% of patients may need second or even third procedures for more injuries since vascular-induced injury progresses in time [26].

CONCLUSION

Chronic radiation enteritis is a serious clinical problem because of its progressive nature and difficult management. Decreasing the volume of the small bowel in the treatment field is clearly an important objective in pelvic treatment techniques, decreasing the risk of radiation-induced chronic diarrhoea. However, the volume effect for severe complications (strictures, fistulation) is less clear, and so far no quantitative data support the routine application of doses above 50 Gy to a small intestinal volume without exceeding an acceptable severe complication risk. Because of the mobility of the small bowel, interpretation of dose–volume parameters will be difficult. Therefore, the decision to give high doses necessary to eradicate macroscopic tumour volumes should be based on careful individual treatment planning, with exclusion of the small bowel from the radiation fields. To achieve this, radiotherapeutic measurements available include a multiple field set-up, and the use of a "belly board", with the patient in prone position and treatment with full bladder, especially in posterior pelvic target localisations. Visualisation of the small bowel in the treatment position is important to enable adequate customised blocking in all treatment fields. Surgical displacement of the small bowel should be considered if cure requires a high (>50 Gy) dose. Until the dream of 'selective' protective agents against vascular radiation injury comes true, prevention of small bowel complications is a matter of dose, fractionation and treatment technique.

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