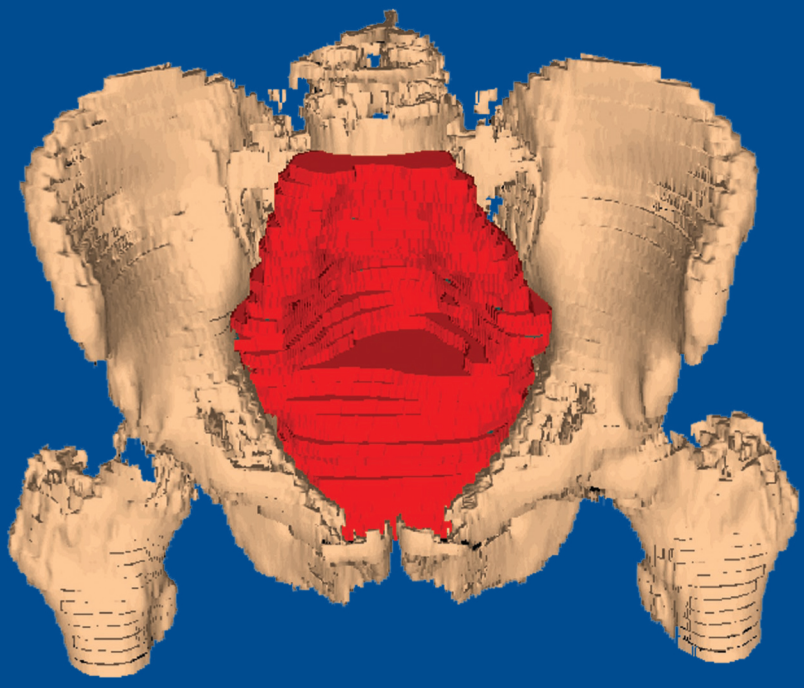
THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY TECHNIQUES FOR RECTAL CANCER



Joost Nuyttens

THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY TECHNIQUES FOR RECTAL CANCER

Drie-dimensionele conformele radiotherapietechnieken voor de behandeling van rectumkanker

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Cover: The three-dimensional shape of the clinical target volume for rectal cancer (anterior-superior view).

Erasmus Universiteit Rotterdam

THREE-DIMENSIONAL CONFORMAL RADIATION THERAPY TECHNIQUES FOR RECTAL CANCER

Drie-dimensionele conformele radiotherapietechnieken voor de behandeling van rectumkanker

Proefschrift

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Aan Karolien
Florien
Mijn ouders

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Chapter 1

Introduction.

Introduction

The third most common malignancy in the Netherlands is colorectal cancer. Rectal cancer affects every year around 2000 new patients. The highest incidence is found at an age above 70 years, and in men (sex ratio: 1.48).

In Europe, the treatment of preference for locally advanced rectal cancer is surgery and preoperative radiotherapy. The addition of concurrent chemotherapy is currently investigated. However, these combined modality treatments induce side effects.
Diarrhea is the major side effect of (neo-)adjuvant radiation therapy for rectal cancer [3, 15]. An overview of acute and late severe bowel toxicity is given in tables 1.1-1.3.

The relationship between the volume of small bowel irradiated and the development of diarrhea is well recognised [10, 13, 21]. In the seventies, large parallel opposed fields (APPA) were used [11]. They produced hotspots in areas which usually included large and small bowel and played a causative role in the toxicity profile of these patients. Exclusion of the small bowel from the pelvis in order to improve the tolerance to therapy has been the subject of a considerable number of research efforts. First, the use of a three- or four-field beam arrangement with an abdominal wall compression device (belly board) and bladder distension was investigated [9, 17, 26]. An APPA-field set up with a patient in supine position resulted in an irradiation of 620 cm^3 bowel. In contrast, a 4-field technique with a patient in prone position reduced the irradiated bowel volume to 145 cm^3 [10].

The implementation of image guided conformal radiotherapy is a another way to reduce the amount of (small) bowel in the irradiation volume. Conformal radiotherapy using three-dimensional (3-D) treatment planning allows for more precise delivery of the irradiation and, therefore, better sparing of the surrounding critical normal tissues can be assumed. It also allows for higher doses compared to conventional radiotherapy. This technique has been widely used in prostate cancer. The contouring of the clinical target volume and the organs at risk (mainly rectum) combined with a dedicated 3-D treatment planning did result in dose escalation studies without increasing severe late complications

[29]. Chapter 2 reports low acute toxicity after dedicated 3-D conformal treatment planning in prostate cancer.

Despite the good results of 3-dimensional conformal treatment planning in prostate cancer, this technique has not routinely been used for rectal cancer because of the lack of accurate data regarding the motion of the organs at risk and the clinical target volume (CTV). Chapter 3 describes the position and motion of the small bowel inside the pelvis in pre- and postoperative patients with rectal cancer and tries to explain why less bowel toxicity is seen in preoperative patients. The shape and motion of the clinical target volume for rectal cancer is presented in Chapter 4. This information is mandatory to treat a patient with 3-D conformal radiotherapy. However, due to the complex shape of the CTV, the gain of 3-D conformal radiotherapy was in fact little and therefore, the intensity modulated radiotherapy was introduced.
With intensity modulated radiotherapy, we are able to create a more homogeneous dose inside the CTV and to reduce the dose to the surrounding critical organs. Chapter 5 presents the reduction of small bowel exposure with intensity modulated radiotherapy planning compared to conventional treatment planning.

Finally, another conformal radiotherapy technique is intraoperative brachytherapy (IOBT). This technique was developed to treat fixed or tethered rectal cancer that often invades the adjacent organs or pelvic wall. It involves the delivery of a single large radiation dose to residual tumour or to the tumour bed of a resected tumour at the time of surgery, while adjacent organs at risk like bowel can either be shielded or moved outside the treatment field. The intraoperative brachytherapy uses a remotely controlled high-dose-rate (HDR) afterloader. The afterloader contains a small Iridium-192 point source mounted at the end of a steel wire. This source is transported under computer control into hollow afterloading catheters (stepping source technique). For IOBT, these catheters are embedded in a custom made silicon template. After tumour resection, an appropriately sized and shaped silicon template is placed on the residual tumour or on the tumour bed and secured into place. The dose is usually prescribed at 1 cm depth and according to the protocol, a dose of 10 Gy is to be delivered in these cases. The treatment time is either determined through individual planning after localisation of the IOBT geometry or using

preplanned atlases [12, 18]. The technique of intraoperative high-dose-rate brachytherapy is illustrated in Chapter 6 and chapter 7 presents the results of the first analysis of 39 patients.

Chapter 8 summarises the results and general conclusions of this thesis.

Table 1.1. Overview of acute severe bowel toxicity in randomised preoperative chemoradiotherapy trials

author	number of patients	treatment RT + SU	CT+RT+SU	SU+RT+CT	total dose (Gy)
Boulis-Wasif [4]	245	33	33	x	2.3 Gy x 15
Hyams [15]	116	x	39	23	45 / 50.4
Sauer [25]	805	x	13	12	50.4
Bosset [3]	798	17	34	x	45 Gy
Mean		25	30	23	

SU: surgery; RT: radiotherapy; CT: chemotherapy

Table 1.2. Overview of acute severe bowel toxicity in preoperative chemoradiotherapy trials

author	number of patients	percentage of toxicity	total dose (Gy)	type of chemotherapy
Mehta [19]	32	28	45 / 50.4	5-FU + CPT-11
Kim [16]	45	4	45 / 50.4	Capecitabine
Rodel [24]	26	54	50.4	Capecitabine & oxaliplatin
Videtic [28]	29	3.4	48.5 / 60	5-FU
De La Torre [6]	35	22	45 / 60 - 65	UFT
Minsky [20]	20	17	46.8 / 50.4	5FU
Mohiuddin [22]	33	15	45 / 60	5FU
Dunst [7]	36	3	50.4	Capecitabine
Reerink [23]	43	11	50 / 60	5FU + LV
Mean		21		

Table 1.3: overview of late severe bowel toxicity in pre- and postoperative randomised (chemo)radiotherapy trials

study	number of patients	Su alone	RT+ SU	SU+ RT	technique	upper field border	dose (Gy)
Swedish rectal cancer [5]	1168	10	30	x	3- or 4-field	L5	25
Uppsala [8]	471	6	5	11	3-Field	mid L4	25
Stockholm I [14]	572	7	11	x	APPA	L2	25
Stockholm II [14]	455	8	9	x	4-field	mid L4	25
MRC III [1]	469	17	x	20	APPA	18x15 cm	40
France [2]	172	0	20	x	4-field	L4-L5	46
Rotterdam [27]	172	x	x	2	3- or 4-field	L5-S1	50

SU: surgery; RT: radiotherapy

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Chapter 2

Dose-volume relationship for acute side effects during high dose conformal radiotherapy for prostate cancer.

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Dose–volume relationship for acute side effects during high dose conformal radiotherapy for prostate cancer

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Abstract

Purpose: To determine acute and late complications for bladder and rectum and to determine dose–volume correlations.

Methods and materials: Sixty-four patients received definitive treatment for prostate cancer between January 1995 and December 1998 using conformal three-dimensional radiotherapy. Doses ranged from 72 to 80 Gy. The acute and late side effects were gathered retrospectively, and graded according to Radiotherapy and Oncology Group criteria (RTOG). The patients were divided into two groups: ≤72 Gy (Group A) and ≥76 Gy (Group B) and had a mean follow-up of 32 and 22 months, respectively.

Results: No grades 3–4 acute, urinary or rectal toxicity was reported. Acute grade 2 rectal complications were seen in 10 and 18% of the patients in Groups A and B, respectively. They were observed at a mean dose of 38 Gy. Acute grade 2 urinary symptoms were 33 and 47% for Groups A and B, respectively. They were seen at a mean dose of 43 Gy. Acute rectal symptoms were dose–volume related. Patients without diarrhea had a mean rectal volume receiving a dose of 70 Gy or more of 8.5 cm^3. However, patients with RTOG 2 diarrhea had a volume of 16.5 cm^3 ($P = 0.042$). No dose–volume relationship for acute bladder symptoms or late complications were seen. Grades 1–2 late rectal and bladder complications were seen in 11 and 8% of the patients, respectively. None required hospital admission or transfusion.

Conclusion: Radiotherapy to the prostate can be given at 80 Gy. No grades 3–4 acute, urinary or rectal toxicity was reported. Acute rectal symptoms are dose–volume related.

Keywords: Complications; Radiotherapy; Prostate cancer; Dose–volume relationship

1. Introduction

The dose of radiation that can be given is usually limited by the need to restrict the number and severity of side effects. Conformal radiotherapy using three-dimensional (3D) treatment planning allows for more precise delivery of treatment, more sparing of the surrounding normal tissues and may allow higher doses compared to conventional radiotherapy [21]. We initiated a conformal therapy prostate cancer protocol in 1995, and have carefully escalated dose. Current treatment doses range from 72 Gy and beyond 80 Gy, with excellent outcome and without major complications [5,7,14,16,27]. Several articles report that the treatment with conformal radiotherapy produces fewer side effects than conventional radiotherapy or surgery [12,21,26]. Late side effects are 'dose-limiting', since they are generally permanent and may be progressive in severity. They have been studied more often [1,2,6,18,19,23,24] and gastro-intestinal (GI) and genito-urinary (GU) side effects are seen mostly during the first 24 months of follow-up. Late GU side effects occur at a mean time of 22 months, while late rectal bleeding is seen at a mean time of 14 months [18] or a median time of 17 or 18 months [6,23]. With doses up to 66 Gy, acute grades 1 and 2 rectal complications occur in 63 and 19% of the patients, respectively [9]. When higher doses are used, the acute side effects are not well known. We initiated a conformal therapy program at MUSC in the beginning of 1995 and have escalated doses slowly from 72 to 80 Gy. From this group, we analyzed the incidence of acute side effects, the dose at what they occur, and the associated volumes. Because we have a short follow-up for late complications, we report the preliminary late complications.

2. Methods and materials

We initiated a retrospective study of all prostate cancer patients treated with conformal therapy, with follow-up

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Table 1
Dose (Gy) to the PTV

Dose escalation	Prognosis	P + 1 cm M	P + V + 1 cm M	P + 1 cm M	P + 0.5 cm M	Total dose
No	Favourable	50		22		72
	Unfavourable		50	26		76
Yes	Favourable	50		26		76
	Unfavourable		50	20	10	80

P, prostate; V, seminal vesicles; M, margin.

greater than 6 months. Sixty-four patients with prostate cancer were treated with curative intent at the Medical University of South Carolina between January 1995 and December 1998. Patients with T4, metastatic and recurrent tumors after prostatectomy were excluded. The majority of the patients were treated with the same technique. These patients were treated with five fields: two lateral, one anterior, and two posterior oblique fields. Initially, a dose of 72 or 76 Gy was given depending on prognostic factors (stage, PSA and Gleason score). Because all treatments have been well tolerated with minimal toxicity, the dose was escalated to 76 and 80 Gy. The delivered dose to the planning target volume (PTV) for each group is shown in Table 1. An extra margin from the PTV to the block was taken to get at least the 95% isodose line around the PTV. Treatment was given 5 days a week in 2 Gy per fraction. We outlined the PTV, rectum and bladder on computed CT scan images taken every 3 mm. The caudal border of the rectum was set at 9 mm cranial from the most caudal part of the anus. The cranial border of the rectum was set at the rectosigmoid flexure. Bladder and rectal volumes were derived from dose–volume histograms.

For assessment of early or late radiation side effects, bladder and bowel toxic effects were scored by use of the standard Radiotherapy and Oncology Group (RTOG) criteria [3]. Diarrhea is defined as frequent loose bowel movements without associated rectal irritation (tenesmus). Tenesmus is defined as rectal irritation or urgency. Cystitis is defined as irritative bladder symptoms such as frequency and dysuria. The grades are as follows: Grade 0 = no symptoms; grade 1 = minor symptoms requiring no treatment; grade 2 = symptoms that respond to simple outpatient management and do not affect lifestyle (performance status); grade 3 = distressing symptoms that affect lifestyle and may necessitate hospital admission for diagnosis or minor surgical intervention (e.g. uretral dilation); grade 4 = major surgical intervention (e.g. laparotomy, colostomy, cystectomy or long stay in hospital; grade 5 = fatal complications. Grades 1 and 2 rectal bleeding is defined as incidental and intermittent bleeding, not requiring admission to the hospital or a blood transfusion, respectively. Grade 3 rectal bleeding is defined as bleeding which requires admission to the hospital or a blood transfusion. RTOG data were gathered retrospectively. Impotence was not scored because many patients received hormonal treatment during and after the radiotherapy for at least 1 year. Statistics were done with *t*-test. The patients were seen every 3 months for the first 2 years and every 6 months thereafter. Late complications were scored if the patient had a follow-up longer than 7 months. Ten patients were lost to follow-up or had a follow-up shorter than 200 days. The mean follow-up of the remaining 54 patients was 27 months. The patients were divided into two groups: ≤72 Gy (Group A) and ≥76 Gy (Group B). Groups A and B had a mean follow-up of 32 months (10–49 months) and 22 months (7–43 months), respectively. The patients were always seen on the same day of the week, however, on request of the patient, they could be seen on another day too. The side effects were written on a follow-up sheet in the chart with dose and time at which they occurred. Prescribed medication, reason of prescription as well as the generic name and dose of prescribed drug or examinations were registered too.

3. Results

3.1. Acute complications

Sixty-four patients were treated, 30 to a dose of 72 Gy, 15

Table 2
Patient characteristics

	≤ 72 Gy	≥ 76 Gy
Number of patients	30	34
Mean age (years)	68	69
Stage		
T1a	0	1
T1b	1	0
T1c	8	4
T2a	10	9
T2b	6	4
T2c	4	7
T3	1	9
Gleason score		
2 to 3	2	0
4 to 7	27	28
8 to 10	1	6
PSA		
<10	22	12
>10	8	22

Table 3
Percentage of acute rectal side effects with corresponding grade

Dose (Gy)	Grade	Tenesmus (%)	Diarrhea (%)	Total (%)
≤72	Grade 0	93	87	80
	Grade 1	7	3	10
	Grade 2	0	10	10
≥76	Grade 0	85	79	73
	Grade 1	12	6	9
	Grade 2	3	15	18

to a dose of 76 Gy and 19 to a dose of 80 Gy. Baseline characteristics of the two groups are shown in Table 2. No patients experienced a grade 3 or greater complication. Therefore, we investigated the minor grades 1 and 2 complications. Acute rectal side effects were seen in 20 and 27% of the patients in Groups A and B, respectively (Table 3). Grades 1 and 2 side effects in Group A were seen in 10% of the patients. For Group B 9% had grade 1 side effects and 18% had grade 2 side effects. Grade 2 diarrhea was only seen in 10 and 15% for Groups A and B, respectively. These symptoms were seen at a mean dose of 43 Gy for Group A and 35 Gy for Group B (Table 4). These patients usually reported first a mild diarrhea, not requiring medication at a mean dose of 39 and 32 Gy for Groups A and B, respectively. No acute rectal grade 3 or 4 toxicity was seen.

Minor acute urinary side effects were seen in 63 and 71% of the patients in Groups A and B, respectively (Table 5). There were 30% grade 1 and 33% grade 2 side effects in Group A. For Group B, 24% had grade 1 side effects and 47% had grade 2 side effects. Grade 2 dysuria was seen in 30% of the patients in Group A and in 24% of Group B. Medication was prescribed at a mean dose of 46 and 42 Gy for Groups A and B, respectively (Table 6). Seven percent of Group A and 35% of Group B patients had grade 2 frequency. At a mean dose of 29 Gy for Group A and at 46 Gy for Group B, medication was prescribed. In both groups, only grade 1 urgency was seen. It occurred in 3 and 6% of the patients in Groups A and B, respectively.

3.2. Irradiated volumes

The calculated rectal volumes for the acute rectal symptoms were of the same magnitude for the low doses but diverted for greater doses (Table 7). Patients without symptoms had a mean rectal volume of 26 cm^3 receiving 40 Gy or more. The mean rectal volume for RTOGs 1 and 2 were 34 and 32 cm^3, respectively. However, at a rectal dose of 70 Gy or more, the difference between these groups was much more different. In the RTOG 0 group the mean rectal volume was 8.3 cm^3: for RTOG 1 this was 14.6 cm^3 and for RTOGs 2 this was 15 cm^3. When the RTOGs 1 and 2 complications were combined, the irradiated volume was 14.8 cm^3 and significantly different when compared with RTOG 0 ($P = 0.034$). The same trend was seen when we looked at the patients with acute diarrhea. Patients without diarrhea had a mean rectal volume receiving 70 Gy or more of 8.5 cm^3. However, patients with RTOG 2 diarrhea had a mean rectal volume of 16.5 cm^3 ($P = 0.042$). With rectal doses of 75 Gy or more, patients with no diarrhea had a mean volume of 3.9 cm^3. For the same dose level, RTOG 2 patients had a mean volume of 10.9 cm^3 ($P = 0.049$). The percentage of irradiated rectum showed similar results which are shown in Table 8.

Table 4
Mean dose at first appearance of acute rectal side effects

Dose (Gy)	Grade	Tenesmus (Gy)	Diarrhea (Gy)	Total (Gy)
≤72	Grade 1 (symptoms)	34	20	29
	Grade 2 (symptoms)	0	39	39
	Grade 3 (medication)	0	43	43
≥76	Grade 1 (symptoms)	43	57	47
	Grade 2 (symptoms)	32	32	32
	Grade 3 (medication)	32	36	35

Table 5
Percentage of acute bladder side effects with corresponding grade

Dose (Gy)	Grade	Frequency (%)	Urgency (%)	Dysuria (%)	Total (%)
≤72	Grade 0	90	97	40	37
	Grade 1	3	3	30	30
	Grade 2	7	0	30	33
≥76	Grade 0	34	94	55	29
	Grade 1	21	6	21	24
	Grade 2	35	0	24	47

The dysuria and frequency were not dose–volume related. Larger irradiated bladder volumes per dose level were found within the RTOG 0 group compared with the RTOGs 1 and 2 groups. When patients were grouped according to RTOG bladder symptoms, no correlation in side effects, dose and volumes were found (Table 9).

3.3. Late complications

No grade 3 or 4 late rectal or bladder symptoms were seen. Four patients (7%) had late grade 1 rectal toxicity. Two patients complained of temporary mild diarrhea that resolved without medication. Occult fecal blood was found in two other patients for a short period, which resolved spontaneously, and sigmoidoscopy was not required. Two patients (4%) had grade 2 toxicity due to rectal bleeding but sigmoidoscopy could not find a cause. Four other patients had red blood loss per anus and underwent sigmoidoscopy: one patient was diagnosed with rectal cancer, another with polyps and diverticulosis, and two patients with hemorrhoids. Hospital admissions or blood transfusions were never required.

Grade 1 late urinary complications were found in two patients (4%): one patient complained of temporary dysuria

Table 6
Mean dose at first appearance of acute bladder side effects

Dose (Gy)	Grade	Frequency (Gy)	Urgency (Gy)	Dysuria (Gy)	Total (Gy)
≤72	Grade 1 (symptoms)	36	22	37	35
	Grade 2 (symptoms)	29	/	38	36
	Grade 2 (medication)	29	/	46	43
	Grade 1 (symptoms)	50	68	45	50
≥76	Grade 2 (symptoms)	36	/	28	33
	Grade 2 (medication)	42	/	41	42

and haematuria, another complained of urgency and frequency. Two patients (4%) had grade 2 side effects: one complained of moderate urgency and frequency and required medication, the other developed dripping of urine. A fifth patient complained also of frequency but urine analysis showed an infection.

No correlation between dose–volumes and late side effects could be found.

4. Discussion

4.1. Rectal volume

Rectal volumes are reported in mean cm^3 as well as in percentage of rectal volume. We think that absolute volumes are of more value than percentage, because absolute volumes do not account for inter- and intrapatient variations in the rectal definition. The transition of the sigmoid to the rectum is a surgical definition and cannot be seen on CT scan. For this reason, we chose to draw the rectum from the last sigmoid flexure (rectosigmoid flexure) until 9 mm from the anus. We only used one treatment planning CT scan a day. This results in an estimation of the real rectal volume because the rectal volume changes day by day and decreases over time. A filled rectum will have an overestimation of the irradiated rectal volume, an empty rectum an underestimation [10]. Some authors give a suppository to the patients just before the treatment to empty the rectum. However, the advantage of this has not been shown. The use of the rectum wall volume is described too, because there is less variation in volume due to the rectal filling [10]. However, a different rectum wall thickness has been used according to the rectal filling, but also a constant thickness has been assumed [10,25].

4.2. Acute rectal complications

We have demonstrated that relatively high doses can be given without acute grade 3 or 4 toxicity during the treatment. Despite the high doses delivered, the patients had only minor grade 1 or 2 complications. Even with doses up to 80 Gy only 3 of the 19 patients had acute grade 2 rectal side effects. More side effects were seen in Group B. When the high dose volumes per group were compared, a greater mean irradiated rectal volume was found for the RTOG 2 scores then for the RTOG 0 scores. When Group B was compared with Group A, the irradiated rectal volumes were greater in Group B. So the higher the dose, the more the volume was treated and the more side effects were reported.

By using the absolute volumes we found that a mean rectal volume of 11 cm^3 receiving a dose of 75 Gy or more can cause diarrhea-requiring medication. However, some patients had a larger volume than this and had no symptoms. This can be explained by an overestimation of the rectal volume due to rectal filling during the treatment planning CT scan or by interpatient sensitivity differences. Storey et al. [20] and Pollack et al. [15] found no dose–volume correlation for the proportional volumes treated to 60 Gy or greater and no difference in the incidence of acute rectal symptoms when treated to 70 or 78 Gy. The fact that

Table 7
Mean irradiated rectal volumes (cm^3 and SD) with associated RTOG score or acute symptom (diarrhea) and associated dose

	Dose (Gy)	RTOG 0		RTOG 2		RTOG 1 + 2	
		cm^3	SD	cm^3	SD	cm^3	SD
RTOG	60	15	9	21	22	21	20
	70	8	7	15	20	15*	16
	75	4	6	10	20	8	16
Acute diarrhea	60	15	9	23	23	22	20
	70	9	7	17*	21	15	19
	75	4	6	11*	21	10	18

* Significantly different when compared with RTOG 0 ($P < 0.05$).

Table 8
Mean percentage of irradiated rectal volume (% and SD) with associated RTOG score or acute symptom (diarrhea) and associated dose

	Dose (Gy)	RTOG 0		RTOG 2		RTOG 1 + 2	
		%	SD	%	SD	%	SD
RTOG	60	18	10	26*	17	25*	15
	70	10	9	18*	16	17*	14
	75	5	8	10	17	7	14
Acute diarrhea	60	18	9	28*	18	24	16
	70	10	8	20*	17	17*	15
	75	5	8	12	18	10	15

* Significantly different when compared with RTOG 0 ($P < 0.05$).

Table 9
Mean irradiated bladder volumes (cm^3) with associated RTOG score for dysuria and dose

	Dose (Gy)	RTOG 0	RTOG 1	RTOG 2	RTOG 1 + 2
Dysuria	60	30	22	25	24
	70	19	12	16	15
	75	9	5	9	7

both groups were first treated by using a four-field box technique to a dose of 46 Gy can have caused this result. This corresponds with our findings that grade 2 side effects are reported at a mean dose of 35–43 Gy for Groups A and B, respectively. Leibel et al. [11], who used almost the same beam directions as we did, found the same acute rectal symptom incidence for the whole study: 14%. He also did not find grade 3 or 4 acute rectal symptoms. Shu et al. [19] treated 44 patients to a dose of 82 Gy with 3D conformal and intensity modulated radiotherapy. He reported acute GI symptoms in 34% of the patients. However, 32% of the patients received whole pelvis treatment that significantly increased the incidence of acute toxicity.

4.3. Late rectal complications

Despite the high doses that were delivered to the prostate, late side effects in this study are low. However, with a longer follow-up this may still increase, because the mean follow-up for Groups A and B was 32 and 22 months, respectively. Late GU side effects occur at a mean time of 22 months, while late rectal bleeding is seen at a mean time of 14 months [18] or at a median time of 17 or 18 months [6,23]. Considering these data, the late toxicity of our patients probably will increase more in Group B than A. On the other hand, the low late toxicity can be explained by the low irradiated rectal volumes. Dearnaley et al. [4] reports 37% late rectal RTOG 1 side effects for the patients treated with conformal radiotherapy, which is higher than this series despite much lower doses. In his conventional group, 56% of the patients had late rectal RTOG 1 side effects. The RTOG 77-06 study [13] reported bowel toxicity caused by doses up to 70 Gy such as diarrhea (15%), proctitis (11%), rectal stricture (9%), rectal bleeding (20%) and rectal ulcer (2%) when they were treated with a pelvis field and boost to the prostate. Sandler et al. [17] found a 3% risk of a grade 3 or 4 complication at 3 years. Two-third of his patients received a pelvic field with a maximal dose of 71 Gy. Teshima et al. [23] found a 3 year actuarial rate of grade 2 rectal bleeding of 11% in patients who received $<$73 Gy and 22% in those who received 73 Gy with conformal radiotherapy. With our doses up to 80 Gy no rectal ulcers or rectal strictures were diagnosed. This provides evidence that the volume of irradiated tissue is an important determinant of toxicity. Wachter et al. [24] found an average volume of 26% at a dose of 66 Gy to cause late rectal side effects. Storey et al. [20] reported a significant increase in late rectal complications when more than 25% of the rectum received 70 Gy or more. Hartford et al. [6] reported rectal bleeding if 70% of the anterior rectal wall received 60 Cobalt Gray Equivalent. We were not able to demonstrate a dose–volume effect for patients with late rectal side effects versus no side effects, probably due to the low incidence of late complications. However, both Schultheiss et al. [18] and Jackson et al. [8] were able to find dose–volume relationship for late rectal bleeding. Boersma et al. [1] found severe rectal bleeding in patients where more than 40 and 30% of the rectal wall volume received at least 65 and 70 Gy, respectively.

4.4. Acute bladder complications

No grade 3 or 4 acute bladder toxicity was reported. Grade 2 acute urinary symptoms were seen in 33 and 47% for Groups A and B, respectively. The results of the low dose group are in the same range as Leibel et al. [11] reported. He found a grade 1 incidence of 44% and grade 2 incidence of 25%, probably because his doses were varying from 65 to 75 Gy. Koper et al. [9] found a lower grade 2 toxicity (16%), probably due to the lower dose (66 Gy). Although, he reported a great difference in irradiated bladder volume between the conventional and conformal group, no correlation was found. RTOG scores were split up into frequency and dysuria but these toxicities were not bladder volume dependent. Also Leibel et al. [11] did not find a toxicity volume correlation. The lack of this correlation can be explained by the inflammation of the prostatic urethra or by bladder volume variation. Lebesque et al. [10] found an intrapatient bladder volume variation of 33% and a bladder wall volume variation of 17% and concludes that the bladder wall volume is the only relatively constant volume during treatment. Nocturia was not scored because many patients had this symptom before the start of the treatment. Grade 2 urinary symptoms were reported at a dose of 28–42 Gy, but most of the patients refused medication at that time, but requested the medication 1 or 2 weeks later. This explains why the medication was prescribed at a higher dose when compared with the RTOG 1 symptoms.

4.5. Late bladder complications

Only four patients of the 54 (7%) can be classified as having some minor late bladder symptoms. This number can increase due to our short follow-up. One patient complained of dripping but he was more than 70 years old. Since incontinence is age related and more frequent in patients older than 65 years, it is not clear that incontinence is treatment related [22]. Urinary symptoms were not related to dose or the volume of irradiated bladder. Dearnaley et al. [4] found no significant difference in late grade 1 or higher urinary side effects with conformal versus conventional treatment and Pollack et al. [15] did not find a correlation between volume and toxicity. This suggests that

urinary symptoms are most likely related to urethritis and not to bladder irradiation.

In summary, with a mean follow-up of 27 months, we have seen no grade 3 or 4 acute or late urinary or rectal toxicity with doses as high as 80 Gy. We have demonstrated a dose–volume relationship with grade 2 acute rectal side effects, which were seen in 10 and 18% of the patients in Groups A and B. They were observed at a mean dose of 38 Gy. Acute grade 2 urinary symptoms were 33 and 47% for Groups A and B, respectively, and were seen at a mean dose of 43 Gy. No dose–volume relationship for bladder symptoms was seen. Minor late rectal and bladder side effects were seen in ten of the patients but none of these required admissions to the hospital or blood transfusions. No correlations between dose–volumes and late side effects could be found.

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Chapter 3

The position and volume of the small bowel during adjuvant radiation therapy for rectal cancer.

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THE POSITION AND VOLUME OF THE SMALL BOWEL DURING ADJUVANT RADIATION THERAPY FOR RECTAL CANCER

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Purpose: The rate of small bowel toxicity from adjuvant pelvic radiation therapy (RT) for rectal cancer has been reported to be lower for patients treated preoperatively (Preop). This was probably due to a lesser volume of irradiated small bowel; however, studies of postoperative treatment reported that patients with an abdominoperineal resection (APR), who likely have the largest volume of small bowel in the pelvis, had less acute and chronic toxicity than those with a low anterior resection (LAR). In this study, three-dimensional treatment planning techniques were used to characterize the position and volume of small bowel in the pelvis and compare these to repeat studies obtained during the typical 5-week course of treatment to attempt to explain the above observations.

Methods and Materials: Treatment planning CT scans were obtained in 30 patients with rectal cancer (10 Preop, 10 LAR, 10 APR), including 12 patients with weekly CT scans during RT (65 scans). The position of the small bowel was measured by the distance to the nearest small bowel from the bones of the posterior pelvis and by the volume of small bowel within four anatomically defined regions of the pelvis. The motion of the small bowel was expressed as the standard deviation of the small bowel position measured with both the distance and the volume in the 12 patients with repeat studies.

Results: Contrast-containing small bowel was found an average 2.9 cm more anterior than small bowel without contrast below the sacral promontory. The position of the small bowel in Preop patients was significantly more anterior ($p \leq 0.01$) with less volume ($p \leq 0.04$) in the pelvis than postoperatively treated patients. The small bowel was also more anterior for patients with an LAR vs. APR ($p \leq 0.03$) but with similar volume in all pelvic regions. Small bowel motion, expressed as the standard deviation of the distance from the bones of the posterior pelvis to the closest small bowel, was 2.9 cm, 1.4 cm, and 0.2 cm for the Preop, LAR, and APR group, respectively. The LAR group had a considerable degree of motion in the posterior pelvis. Increased bladder volume was associated with reduced small bowel volumes, although this benefit decreased during treatment.

Conclusion: Because treatment planning CT scans can detect small bowel that does not contain contrast, they may be more accurate than the traditional small bowel series. The Preop patients had significantly less pelvic small bowel supporting the clinical observation of better tolerance to therapy. The higher small bowel toxicity reported for LAR vs. APR patients may be explained by the greater variability of both the position and volume of the small bowel in the posterior pelvis for LAR patients. This finding suggests that a single planning study may not be accurate for the block design used for boost treatment of LAR patients. Bladder-filling techniques were useful for Preop and LAR but not APR patients, and decreased in benefit over time. This study suggested that treatment planning CT scans were more useful than a small bowel series and that more than one treatment planning CT may be obtained in any patient receiving > 45 Gy for rectal cancer. However, further research will be necessary to determine the optimal timing and total number of repeat studies.

Small bowel, Radiotherapy, Toxicity, Rectal cancer, Motion.

INTRODUCTION

Diarrhea is a common side effect of adjuvant radiation therapy (RT) combined with chemotherapy for carcinoma of the rectum (1–5). In a prospective four-arm randomized trial of adjuvant postoperative chemoradiotherapy, acute severe diarrhea occurred in 15–39% of subjects and partially accounted for the approximately 20% of patients that failed to complete therapy (4). If failing to receive the complete treatment decreases the efficacy of therapy, then reducing the rate of acute diarrhea may lead to an overall improvement in therapeutic outcome. Preoperative radio-

chemotherapy has been associated with a lower incidence of Grade 3+ diarrhea than postoperative RT (3, 6–10), presumably due to an absence of fixed bowel loops within the pelvis (8). This proposed mechanism was supported by studies in rectal cancer and gynecologic cancers that have found fixed small bowel in 29% and 65% of patients, respectively (11, 12). The presence of a fixed bowel loop would have two consequences. First, it would ensure that the fixed portion of small bowel received all of the radiation dose, in contrast to mobile small bowel, which may move outside of the irradiated volume. Second, a fixed portion may tether the small bowel within the pelvis, which could lead to an increase in the total volume of small bowel irradiated. The only study that compared the volume of small bowel irradiated between preoperative and postoperative RT found a significant difference, suggesting that this hypothesis was correct (8).

The relationship between the volume of small bowel irradiated and the development of diarrhea is well recognized (8, 13, 14) but was not well quantified until recently (15). Nevertheless, exclusion of the small bowel from the pelvis to improve the tolerance to therapy has been the subject of a considerable number of research efforts. These have ranged from surgical techniques, such as omental slings, pelvic mesh, and tissue expanders, to radiation techniques, such as a prone cradle with a depressed area for small bowel exclusion ("belly board"), bladder distension, and multifield arrangements (16, 17). In fact, the use of preoperative treatment could be viewed as another method to exclude the small bowel from the pelvis. The success of these maneuvers has typically been determined using a small bowel series at the time of simulation, although three-dimensional treatment planning has been used to demonstrate the superiority of a "belly board" (17–19).

Recommendations for treatment planning for adjuvant pelvic RT have included a single small bowel study (16). However, the small bowel is a mobile structure and, other than at the root of the mesentery and any surgically adherent areas, would be expected to change in position during the course of treatment. One section of small bowel is essentially indistinguishable from another and, short of surgically marking segments, the only method available to assess motion would be to compare the position and volume of small bowel within the pelvis over time. There are three reports that have addressed the variability of the position of the small bowel during a course of RT. All three calculated the volume of small bowel using the outline of the contrast seen with a small bowel series, and the variability was judged using a single repeat small bowel series during RT. One study found that the benefit of bladder filling was lost midway through therapy in 18 people receiving RT for rectal cancer (11). The other two reports included patients with other pelvic malignancies and differed in their conclusions. One report studied 50 individuals and found that there was an average increase in small bowel volume by 20% after 45–50 Gy but did not supply further data (13). The other studied 12 patients, 4 of whom had rectal cancer, and found no alteration in small bowel mobility after 39.6–46 Gy (20).

The study reported here used treatment planning computed tomographic (CT) scans with oral contrast to measure the position and the volume of the pelvic small bowel. This method is inherently more accurate than the traditional small bowel series and offers the possibility of volumetric studies. We hypothesized that individuals treated with preoperative RT would have a different position and volume of the small bowel than those treated with postoperative RT. A number of the individuals also had CT scans in the treatment position obtained on a weekly basis. These studies were used to determine the possible range of motion by the small bowel and the impact of the bladder and colon on the small bowel position.

METHODS AND MATERIALS

The treatment planning CT scans were reviewed for 30 consecutive patients with rectal cancer. All scans were obtained using a helical CT scanner with a 0.5 cm slice thickness and included a minimum visualization of the entire treated volume of the pelvis. The postoperative group consisted of 10 patients with abdominoperineal resections (APR) and 10 with low anterior resections (LAR). Nine patients were treated with preoperative RT (Preop). One patient was treated with postoperative pelvic RT after a wide local excision (WLE) of a T2 low rectal primary tumor. Because this patient had no intraabdominal surgery, he was included with the preoperative RT group for purposes of analysis. Oral contrast was given between 1½ and 2 h (11) before the treatment planning CT scan in 29 patients. All were placed prone on a vacuum bag cradle with a depressed area for small bowel exclusion but rigid foam beneath the pubis and the chest. Patients were given full bladder instructions before the treatment planning CT scan.

On each CT slice, distances were measured from the anterior border of L5 and the sacrum to the closest small bowel in the midline and 2 cm to both the left and right of the midline (Fig. 1). These distances were obtained for both any small bowel and for contrast-containing small bowel. Measurements of the most caudal position of the small bowel were also obtained in the cranial-caudal dimension. Student's *t* test was used to compare the characteristics of small bowel position between and within the three groups (APR, LAR, and Preop).

Volumetric measurements were obtained by dividing the pelvis into four regions based, in part, on a typical treatment field (Fig. 2). The superior border of the suprapelvic region was the top of L5. The anterior border of the suprapelvic and anterior midpelvic region was placed 5 cm anterior to the sacral promontory with the posterior border at the sacral promontory. The sacral promontory also was the border between the anterior and central midpelvic regions. The border between the central midpelvic and the posterior midpelvic regions was halfway between the sacral promontory and the sacrum. The posterior border of the posterior

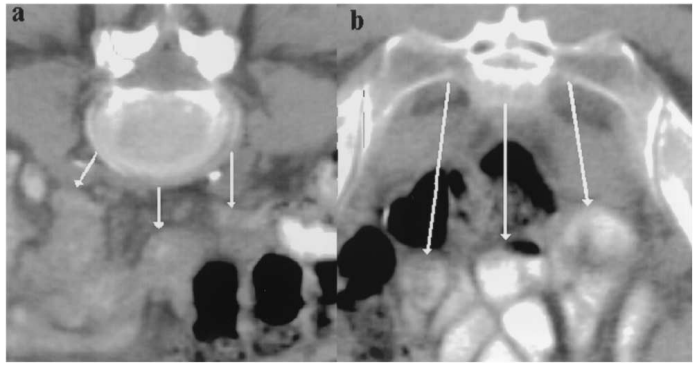

Fig. 1. Two examples of the distance measurement performed from the posterior bones of the pelvis at L5 (a) and the midsacrum (b).

midpelvic region was the posterior sacrum. The inferior border of the midpelvic regions was 1 cm above the symphysis pubis. Mean volume differences in each of the four regions between the different surgical groups were compared using Student's *t* test.

Twelve of the patients (2 APR, 6 LAR, 3 Preop, and 1 WLE) also had weekly CT scans in the treatment position with small bowel contrast. There were 4–7 CT scans per patient (median of 5) depending on the length of treatment and patient cooperation. The scans were registered using the bones of the pelvis, and the organs of interest were outlined on each CT slice by a single physician (J.J.N.), allowing a subjective comparison of studies within the same patient by overlaying digitally reconstructed radiographs. Objective motion of the small bowel was calculated using both the distance to small bowel from the posterior bones and the volume of small bowel within each defined region of the pelvis. The distance to the nearest small bowel on each CT slice was subtracted from the mean distance for the individual patient and the standard deviation (SD) was calculated. Motion was also expressed using the volumetric data by subtracting the volume per region on each weekly CT scan from the mean volume for each patient and determining the SD from these data. The coefficient of variance was calculated by dividing the SD by the mean.

The relationship of bladder filling to small bowel position was examined using both the distance measurement and volume measurements. First, the height of the small bowel within the pelvis was measured as the most inferior position of the small bowel. This measurement was compared to the normalized bladder volume to examine if any relationship existed between the small bowel position and the bladder volume. The small bowel height was also recorded in relationship to the bladder volume as a function of treatment time. Second, the volume was used to examine for correlations between the bladder volume and small bowel volume within the defined regions.

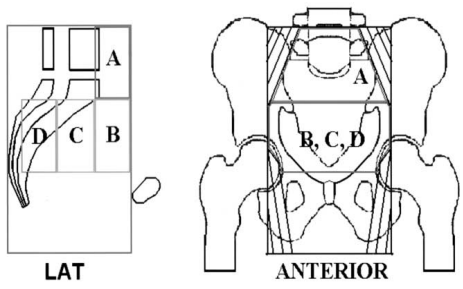

Fig. 2. Division of the pelvis into the separate regions, referred to as the suprapelvis (A), anterior midpelvis (B), central midpelvis (C), and posterior midpelvis (D).

RESULTS

Small bowel visualization

Incomplete visualization of the small bowel was found in 17 of the 29 patients with small bowel contrast for the initial treatment planning CT (Fig. 3). Below the sacral promontory, the most posterior portion of contrast-containing small bowel was an average of 2.9 cm more anterior to the noncontrast-containing small bowel. Above the sacral promontory, the average distance was 1.5 cm, again with noncontrasted small bowel more posterior. In 8 patients, the most inferior CT slice did not contain small bowel contrast, leading to an average cranial-caudal mismatch of 1.8 cm. For the remainder of this analysis, the entire small bowel was used without regard to contrast.

Small bowel position

Measurement of the distance from the posterior bones of the pelvis to the closest portion of small bowel found significant differences in the position of the small bowel inferior to the sacral promontory among the three patient groups (Fig. 4). From the sacral promontory until 5 cm

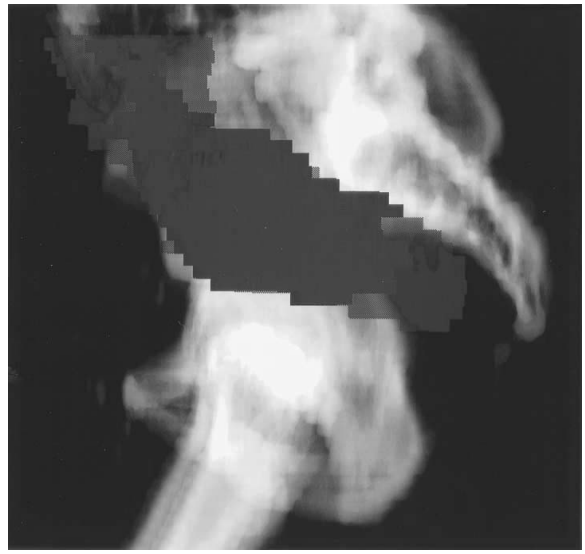

Fig. 3. A digitally reconstructed radiograph showing the position of opacified (purple) vs. all small bowel (blue).

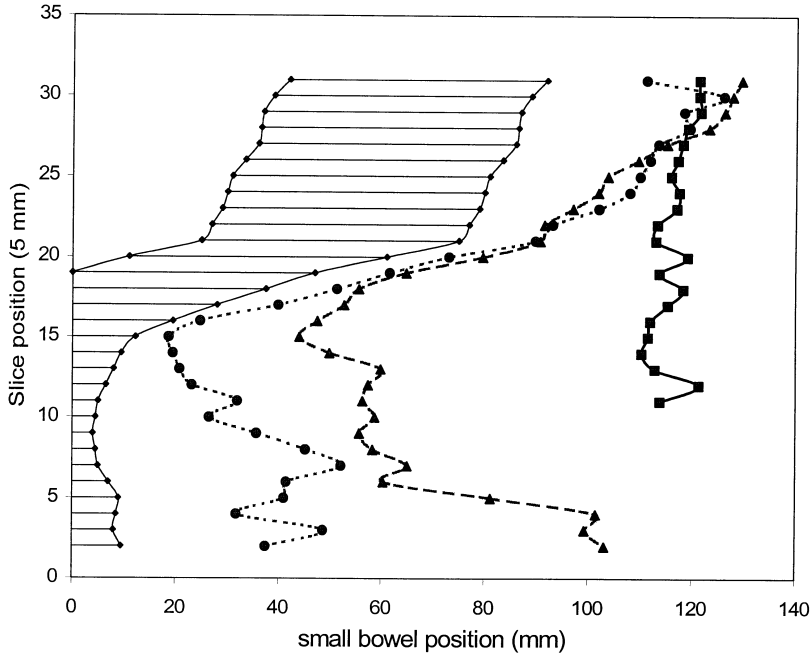

Fig. 4. The mean distance from the posterior bones of the pelvis (diamond symbols) to the closest small bowel in the midline for low anterior resection (triangles), abdominoperineal resection (circles), and preoperative (squares) patients. The sacral promontory was placed at slice position 22 for all measurements.

Table 1. The frequency (%) of small bowel at the designated level

	cm inferior to the sacral promontory					
Surgery	0	2	4	6	8	10
Preop	70	60	40	10	10	0
LAR	100	100	90	80	40	20
APR	100	100	100	90	60	10

Abbreviations: Preop = patients receiving preoperative RT; LAR = low anterior resection; APR = abdominoperineal resection.

inferior to the promontory, midline measurements were significantly different ($p \leq 0.01$) between the Preop and both the APR and LAR groups. The APR and LAR groups were also significantly different from each other ($p \leq 0.03$) for most of the distance inferior to the promontory (except between 6 and 7.5 cm inferior to the promontory). On the right side of the pelvis, the distance to small bowel was significantly different between APR vs. Preop patients ($p \leq 0.01$), inferior to the sacral promontory and vs. LAR patients from 1.5 to 7 cm inferior to the sacral promontory ($p \leq 0.02$). Differences between the LAR and Preop patients were only found caudally from 2.5 cm inferior to the sacral promontory ($p \leq 0.01$). The distance to small bowel on the left was significantly different for APR and LAR vs. Preop ($p \leq 0.04$).

The observation of any small bowel within the pelvis was markedly different between the different surgical groups (Table 1). In 6 of 10 APR patients, the small bowel was found at 8 cm inferior to the promontory, compared to only 1 of 10 Preop patients.

Volumetric analysis found no difference in small bowel volume in the suprapelvic region (Table 2). In the anterior midpelvic region, the mean volume of small bowel for both the APR and LAR group was nearly equal, although only the LAR group was significantly different from the Preop group ($p = 0.03$). Together, the postoperative patients (APR plus LAR) had a significantly larger volume of small bowel in the anterior midpelvis than the Preop group ($p = 0.02$). The APR group had significantly more small bowel in both the central ($p = 0.002$) and posterior midpelvis ($p = 0.02$) than the Preop group. In fact, all of the APR patients had small bowel in the posterior midpelvis, whereas no small bowel was found in this region in any of the Preop group.

Table 2. The position of the small bowel within the pelvis, expressed as the mean volume (cm^3) of small bowel per region as defined in Figure 2

Region within the pelvis	Mean volume (cm^3)			
	APR	LAR	APR + LAR	Preop
Suprapelvis	43	40	41	37
Anterior midpelvis	149	159*	157*	46*
Central midpelvis	74*	50	56*	4*
Posterior midpelvis	14*	6	8	0*

* p-value < 0.05 for Preop versus APR, LAR, or APR + LAR group.

Small bowel motion

Comparison of the digitally reconstructed radiographs found considerable differences in the position of the small bowel during a course of treatment (Fig. 5). The Preop group had the largest degree of motion in the anterior to posterior dimension. At 5 cm inferior to the sacral promontory, the average standard deviation was 2.7 cm, 1.4 cm, and 0.2 cm for the Preop, LAR, and APR groups, respectively (Table 3). The LAR group also had a considerable amount of motion, with an average SD of up to 3.1 cm at 8 cm inferior to the sacral promontory. The smallest degree of motion was found below the sacral promontory in the APR group, which suggested fixation against the sacrum. The average standard deviations of the movement to the left and right of the midline were similar (data not shown). In the craniocaudal dimension the average SD was 1.6 cm, 1.1 cm, and 0.8 cm for the Preop, LAR, and APR groups, respectively.

Volumetric analysis found that the average standard deviation of the small bowel volume in the anterior midpelvis was similar for all three patient groups (Table 4). However, because the Preop group had less overall small bowel, the coefficient of variance for the preoperative patients was three times higher than for the postoperative patients. Overall, the highest coefficient of variance was found in the posterior midpelvis for the LAR group (350%) and in the central midpelvis for the Preop group (225%), suggesting that any single measurement of the small bowel position, such as the traditional small bowel series for treatment planning, has a large probability of inaccuracy in these regions.

Bladder volume vs. small bowel

There was a relationship found between the most inferior small bowel position in the cranial-caudal dimension on each CT scan and the bladder volume, with a correlation coefficient of 0.59 ($p = 0.0005$) and 0.7 ($p = 0.0003$) for LAR and Preop groups, respectively (Fig. 6). No correlation was found for the APR group ($r = 0.11$, $p = 0.7$). There was a trend toward reduced bladder volumes with a more inferior position of the small bowel during the last 3 weeks of treatment (Fig. 7). There was no correlation between the bladder volume and the position of the small bowel in the anterior to posterior dimension.

The mean volume of the bladder in the anterior midpelvic region was 84 cm^3 for APR and LAR patients and 95 cm^3 for the Preop patients. In the central midpelvis, the bladder volume was 25 cm^3 for the APR group, 8 cm^3 for the LAR group, and 5 cm^3 for the Preop group, but without a significant difference. In the anterior midpelvic region, the bladder volume and small bowel volume were correlated ($r = 0.53$, $p < 0.0001$), and a full bladder reduced the small bowel volume by 64%. This relationship was present for

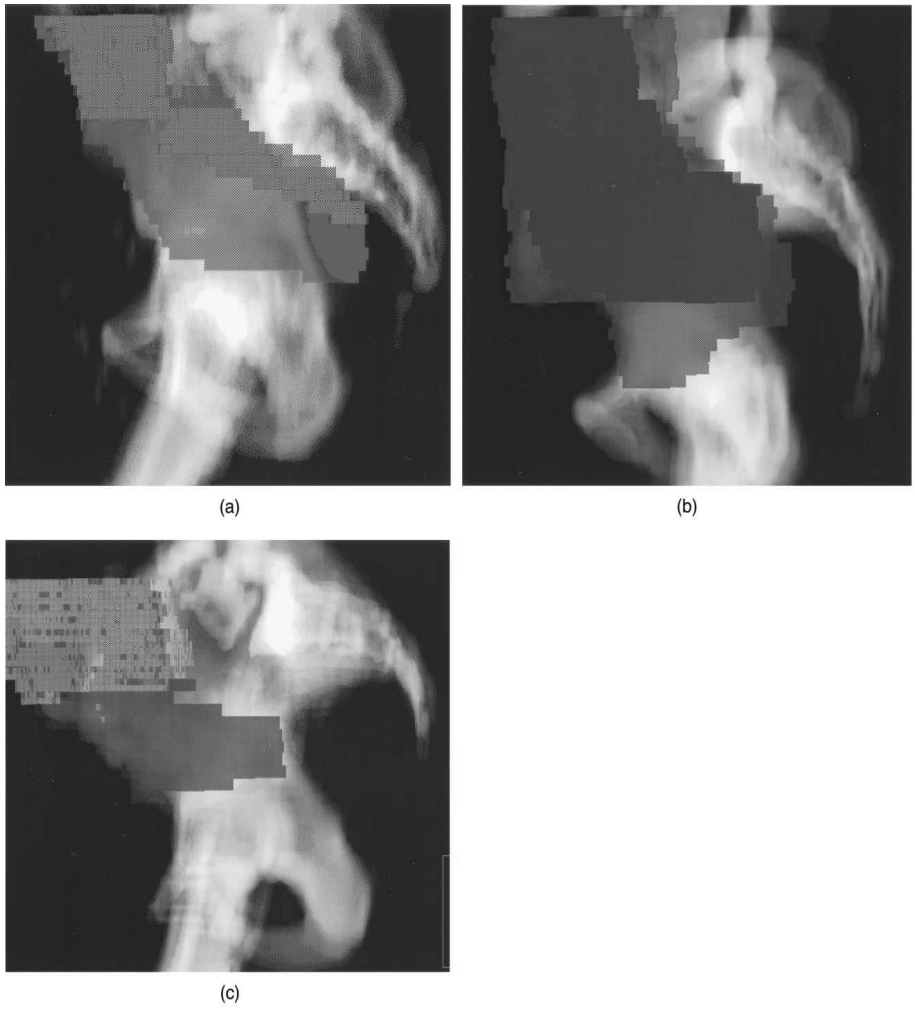

Fig. 5. Digitally reconstructed radiographs showing the maximum and minimum position of the small bowel observed during a course of adjuvant pelvic RT. (a) A patient with an abdominoperineal resection, with the maximum position shown in green, the minimum in red, and overlap shown as a combination of the two colors. (b) A patient with a low anterior resection, with the maximum position shown in blue, the minimum in red, and the overlap in purple. (c) A patient receiving preoperative treatment, with the maximum shown in blue, the minimum in yellow, and overlap in tan.

both the LAR group ($r = 0.58$, $p = 0.0005$; 48% small bowel reduction) and the Preop group ($r = 0.59$, $p = 0.01$; 140% small bowel reduction). In the central midpelvic region there was a good correlation ($r = 0.57$; $p = 0.001$) between the small bowel volume and the volume of the bladder plus the colon. When the bladder and colon were fully present, there was a 130% reduction in small bowel volume. There was no correlation between the bladder volume in the anterior midpelvis and the small bowel volume in the suprapelvis ($r = 0.01$; $p = 0.9$), suggesting that a full bladder does not push the small bowel into this region.

DISCUSSION

It is impossible to directly compare the traditional small bowel series to a treatment planning CT, as the contrast requirements are different for each of the two studies. Although the CT scan could be performed first followed by administration of additional oral contrast for the small bowel series, the time delay required to allow the extra full-strength barium to reach the small bowel would introduce a potential source of variation. In this study, there was no variation due to time as the position of opacified bowel

Table 3. Motion of the small bowel for 12 patients with weekly treatment planning CT scans during treatment*

Inferior to sacral promontory	Average standard deviation (cm)		
	APR	LAR	Preop
0 cm	1	1.1	1.5
2.5 cm	0.2	1	1.6
5.0 cm	0.2	1.4	2.7
7.5 cm	0.1	2.4	N/A

* The average standard deviation (cm) of the distance in the midline from the posterior bones of the pelvis to the small bowel is shown for each of the surgical groups of patients. Distances are shown at a specified distance inferior to the sacral promontory.

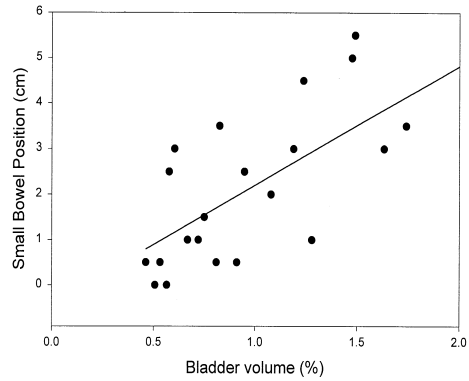

Fig. 6. The craniocaudal small bowel position vs. bladder volume in preoperatively treated patients.

on the CT scan was used to mimic the traditional small bowel series. Unopacified small bowel was found in over 50% of the CT scans, with an average distance from opacified small bowel of over 1.5 cm. This difference was most likely due to incomplete filling of the ileum despite the administration of oral contrast at the recommended 1½ to 2 h before the study (11). Because the ileum may be the target organ for acute radiation enteritis (21, 22), inaccurate visualization is especially concerning, and suggests that the added expense of treatment planning CT scans was well justified.

As hypothesized, the position of the small bowel in the pelvis was significantly more anterior and superior in the preoperative group. Significant differences were also found in the volumetric analysis, providing objective evidence that the preoperatively treated patients had less small bowel irradiated than postoperatively treated patients. This finding is in general agreement with a report that found a mean 462 cm^3 of small bowel irradiated in postoperatively treated patients compared to 212 cm^3 in preoperatively treated patients (8). However, in contrast to that report, we found a considerably smaller volume irradiated in both groups, with a mean of 262 cm^3 and 87 cm^3 for postoperative and preoperative patients, respectively. Part of this difference could have been due to minor disagreements in the field design at the anterior and superior border but the bulk of the difference was probably due to the method used for measurement. In our study, the small bowel was outlined on each CT slice and three-dimensional treatment planning was used. The other study used the outline of the opacified small bowel seen on orthogonal simulation films, which would tend to overestimate the volume of small bowel. Regardless of the differences between studies, this study provided more evidence that preoperative treatment irradiates a significantly less volume of small bowel than postoperative treatment.

Despite the common perception that preoperative treatment is better tolerated, there is no current randomized evidence of reduced Grade 3+ diarrhea. The only published randomized study of preoperative RT to 45–50 Gy vs. postoperative RT found that the Grade 3+ diarrhea rate was 39% for preoperative treatment and 23% for postoperative treatment (2). This finding was considerably different from multiple single-arm, single-institution studies of preoperative RT to 45–50 Gy, that have reported severe diarrhea rates of only 1–14% (3, 6, 7, 9, 10). A number of possible reasons exist for the difference between the randomized and nonrandomized studies, including the radiation therapy field design, beam arrangement, and chemotherapy agents used. However, we believe that the discrepancy probably was due to the different toxicity grading scales used. These definitions have ranged in precision from the absolute number (6, 7, 23) or an increase in the number of bowel movements in 24 h (24), to a subjective judgment that the toxicity was "severe," "life-threatening," or "intolerable requiring ther-

Table 4. The motion of the small bowel within the pelvis, as expressed by the average standard deviation of the volume of small bowel per region as defined in Figure 2 and the coefficient of variation

Region within the pelvis	Standard deviation/Coefficient of variation			
	APR	LAR	APR + LAR	Preop
Suprapelvis	6/14	12/30	11/27	12/32
Anterior midpelvis	38/25	28/23	30/19	34/74
Central midpelvis	20/27	22/44	21/38	9/225*
Posterior midpelvis	4/29	21/350*	14/175*	0/0

* Coefficient of variation was greater than 100%.

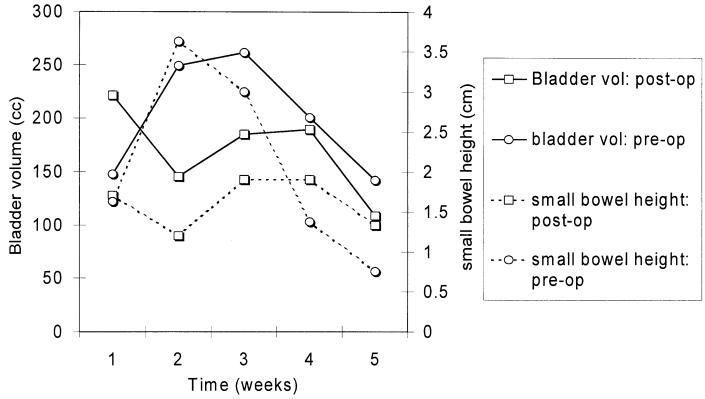

Fig. 7. The bladder volume and lowest small bowel position over time for Preop and Postop patients.

apy" (1, 9, 10, 25). Thus, a preoperative patient with pretreatment diarrhea due to the tumor itself could be assigned a high maximum toxicity grade in a study using the absolute number of bowel movements per day but a low grade in a study using an increase in the number of bowel movements per day. Indeed, the authors of the randomized preoperative vs. postoperative treatment study believed that pretreatment diarrhea due to the unresected tumor was probably the explanation for the discrepancy between the preoperative and postoperative diarrhea rates found in the trial (2). This question could be answered simply by obtaining pretreatment symptoms, or comparing the weekly diarrhea assessment to the timing of the RT, as patients with diarrhea due to the tumor would be expected to exhibit a high diarrhea grade at the start of treatment. The perception of improved tolerance to preoperative treatment may be genuine, but not measurable using toxicity scales that fail to account for baseline function.

In fact, all of the toxicity grading scales for diarrhea can be criticized. Scales that measure the maximum number of stools in one day ignore the baseline bowel function and overemphasize the single 24-h evaluation. Most ignore the reversibility of symptoms with medications or diet modification. Those depending on "severe" or "life-threatening" toxicity require a subjective decision on the part of the treating physician, which is more difficult to define in a multi-institutional setting. The current Common Toxicity Criteria defines Grade 3 diarrhea as an increase of greater than or equal to 7 stools per day, or incontinence, or the need for parenteral support (26). Although this scale can account for pretreatment diarrhea, it ignores the reversibility of symptoms with antidiarrheal medications and diet modification, and focuses on the single worst day of treatment without regard to the length of time that symptoms are present. With this definition, a patient experiencing nine bowel movements in 24 h compared to the usual two bowel movements would have Grade 3 toxicity even if symptoms completely resolved by the following day using antidiarrheal medications and diet modification, and the remainder of treatment was accomplished without difficulty.

Between the two postoperative groups, APR patients had a significantly more posterior small bowel position but with only minor differences in volume in the pelvic region compared to the LAR patients. Other studies have also found no difference in the volume of small bowel irradiated between these two patient groups (27). This would suggest that tolerance to treatment would be equal or, if anything, worse for the APR group given the relationship between the volume irradiated and the development of acute small bowel toxicity (15). However, the clinical evidence disagrees with this prediction, finding that the rate of severe diarrhea was actually worse for the LAR group (5). In a review of 96 patients treated with adjuvant postoperative RT and chemotherapy on a multi-institutional study, the rate of Grade 3+ diarrhea was 30% vs. 13% for LAR and APR patients, respectively (5). One explanation for this apparent disagreement is that measurements of stool frequency were less accurate after an APR, as the stool is collected in the stoma bag. However, the risk of chronic bowel injury has also been reported to be higher in LAR patients (28), and given that chronic bowel injury is a more objective endpoint, this evidence suggests that a real difference exists between these patient groups.

Although our study included only 2 patients with an APR and 5 with a LAR, some observations may help to explain the greater toxicity in LAR patients. The distance measurements suggested fixation of the small bowel in the posterior pelvis for the APR group, with a standard deviation of only 1 mm at 7.5 cm below the sacral promontory, compared to 3.1 cm for the LAR group at the same point. The volume measurements within the posterior pelvis found that APR patients had 14 cc of small bowel with a 4 cc standard deviation whereas LAR patients had 6 cc of small bowel but a 21 cc standard deviation. Together, these data suggested that a single small bowel study obtained for treatment planning may be accurate for APR patients, but would fail

to completely define the overall possible position of the small bowel in the LAR group. Thus, the block design for any boost beyond 45 Gy was probably more accurate for APR than LAR patients, and LAR patients may have inadvertently received a dose to the small bowel higher than that intended. Further investigation including a larger number of patients will be necessary, but these results suggest that repeat treatment planning CT scans may be reasonable in any patient in whom the planned dose of RT exceeds 45 Gy. It does not, however, provide enough information regarding the timing or total number of any repeat studies.

Bladder-filling techniques were helpful for both preoperative and LAR patients, but not for those with an APR. This benefit was most evident in the anterior pelvic region, which was the region with the largest volume of small bowel in all groups. Although not usually within a treatment volume, this region would be expected to receive exit dose from a posterior to anterior treatment field. Given that small bowel toxicity was shown to be primarily dependent on the volume of small bowel receiving over 15 Gy (15), reducing the volume of the small bowel in the anterior region may have an impact on the tolerance to therapy. However, there was some evidence that this benefit was lost over time, in agreement with another study (11). The explanation for this was not obvious. It was possible that patients were experiencing bladder, small bowel, or rectal irritation with increased frequency and had difficulty performing the full bladder instructions. However, it is also possible that the treated subjects simply became less attentive to the full bladder instructions, despite weekly reminders.

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Chapter 4

The variability of the clinical target volume for rectal cancer due to internal organ motion during adjuvant treatment.

Nuyttens JJ, Robertson JM, Yan D, Martinez A.

Int J Radiat Oncol Biol Phys 2002; 53: 497-503.

THE VARIABILITY OF THE CLINICAL TARGET VOLUME FOR RECTAL CANCER DUE TO INTERNAL ORGAN MOTION DURING ADJUVANT TREATMENT

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Purpose: This study defined the clinical target volume (CTV) for the adjuvant treatment of rectal cancer and applied this definition to multiple CT scans obtained during the typical 5-week course of treatment to measure the modification to the CTV due to internal organ motion that would be needed to define the planning target volume (PTV).

Methods and Materials: Ten patients with rectal cancer had weekly treatment planning CT scans during adjuvant radiation therapy. All patients were given oral contrast, placed prone on a rigid foam cradle with a depressed area for small bowel exclusion, and instructed to have a full bladder. The CT scans were registered according to the bones of the pelvis, and the CTV was outlined on each CT slice. Movement of the CTV in all dimensions was measured. The CT scan with the lowest and highest bladder volume for each patient was used to calculate the CTV movement due to bladder filling.

Results: The largest difference in the CTV occurred 10 cm caudal to the anus, with a standard deviation of 1 cm. Bladder filling displaced the anterior border of the CTV an average of 7 mm over a cranial to caudal length of 2.5 cm. Other borders of the CTV were based on muscle, bone, or major blood vessels and were stable.

Conclusion: Modification of the CTV to design a PTV can be unequal, with the largest change at the anterior border of the inferior pelvis.

Rectal cancer, CTV, Organ motion.

INTRODUCTION

One of the primary side effects of adjuvant radiation therapy (RT) for rectal cancer is acute radiation enteritis (1–6). In a randomized study of postoperative RT with chemotherapy, 15% to 39% of subjects developed acute Grade 3+ diarrhea, and 11 of the 24 treatment-related deaths were due to gastrointestinal causes (4). Although the coadministration of chemotherapy has a great effect on the risk of diarrhea, the relationship between the volume of small bowel irradiated and the risk of acute radiation enteritis is well known (7–9). In fact, a recent study using three-dimensional treatment planning tools found that the development of acute radiation enteritis was highly correlated with the dose and volume of small bowel irradiation (10). A number of efforts using surgical and radiation therapy techniques have attempted to reduce this risk by reducing the volume of small bowel irradiated (11–13).

The rate of diarrhea with postoperative RT has provided some of the rationale for the administration of preoperative RT. Studies using the outline of the small bowel on simulation films have shown that RT given preoperatively irradiated considerably less small bowel than postoperative (7), suggesting that the surgery led to tethering or fixation of the small bowel within the posterior pelvis. Multiple single-institution studies of preoperative RT with chemotherapy have supported this concept, with considerably lower rates of diarrhea (14–16). However, randomized trials of preoperative RT found acute severe diarrhea in 33–39% of subjects (2, 17, 18), which was probably partly related to the presence of the primary tumor.

Intensity-modulated radiation therapy (IMRT) is a promising method for reduction in the volume of small bowel irradiated. In a preliminary treatment planning study, the absolute volume of small bowel irradiated to ≥95% of the prescription dose was reduced by 11 to 185 cm^3 (19). Although these findings were very encouraging, before routine clinical use a number of issues related to internal organ motion needed to be resolved. This included characterization of the position and motion of the small bowel, which is the primary dose-limiting structure (20).

The target volume can also be variable due to internal

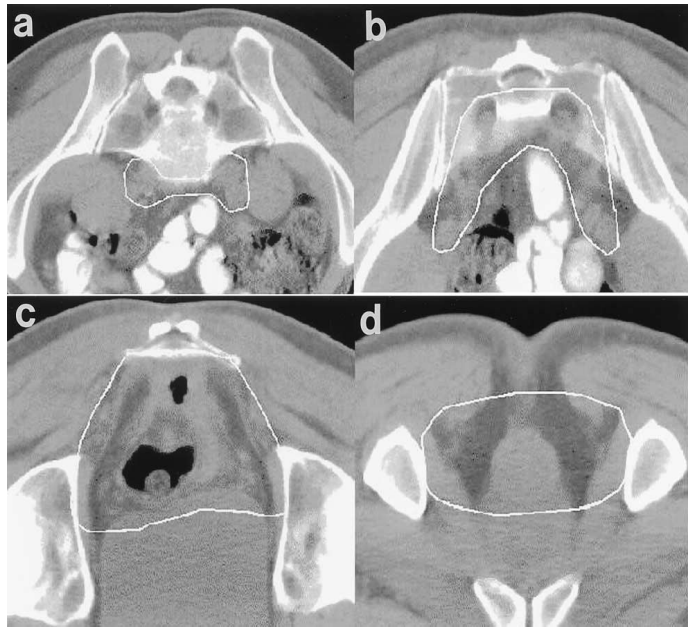

Fig. 1. The shape of the CTV at the superior pelvis (a), upper mid-pelvis (b), lower mid-pelvis (c), and inferior pelvis (d).

organ motion. Traditional definitions of the target volume may have been anatomically based, but they were always expressed according to the bones of the pelvis. Therefore, to study motion of the target volume a formal definition of the clinical target volume (CTV) using computed tomography (CT)-based anatomy was required. This was then compared on multiple CT scans obtained during treatment. Because the rectum and bladder can influence the position of the CTV, the motion of these structures vs. the position of the CTV was also measured.

METHODS AND MATERIALS

Ten patients (7 male, 3 female) with rectal cancer had CT scans of the abdomen and pelvis obtained for planning and once a week during treatment (55 CT scans total). Six patients received radiotherapy after a low anterior resection (LAR), 1 after wide local excision (WLE), and 3 patients were treated preoperatively (Preop). All patients were given oral contrast 1½ to 2 h before CT scanning, placed prone on a rigid foam cradle with a cut-out area for small bowel exclusion, and instructed to have a full bladder. After alignment of the bony pelvis, organs at risk and the CTV were contoured by the same physician (J.J.N.) and reviewed by another (J.M.R.). Volumes of the regions of interest were derived from the Pinnacle 4.2 planning system.

The conventional 3-field treatment plan was made by using the traditional guidelines (4, 11, 21). The superior border was placed at the middle of the L5 vertebral body. The inferior border was placed at least 5 cm below the anastomosis for the LAR patients, and 5 cm below the tumor or 1 cm below the anus for the Preop and WLE patients. The posterior border was placed 1.5 to 2 cm posterior to the anterior border of the sacrum. The anterior border of the field was placed 2 to 3 cm anterior from the sacral promontory. For the lateral fields, a femoral block was designed to block the half of the femur (21).

The CTV was defined as the rectum and perirectal tissues plus the regional lymphatics (Fig. 1). In the cranial-caudal dimension, contours of the target structures began at the inferior edge of L5 and ended at least 4 cm below the anastomosis for the LAR patients, and 4 cm below the tumor or below the anus for the Preop and WLE patients. With corrections for the planning target volume (PTV) and penumbra, these superior and inferior borders approximated the conventional field. Because the lymphatics follow vascular structures, the distal common and internal iliac arteries and veins were included plus a 3- to 5-mm margin, depending on the presence of bowel or bone. The posterior border of the perirectal tissues was defined by the posterior edge of the sacral foramina or the most anterior portion of the gluteus maximus. The lateral border was the ileum, piriformis, and obturator internus muscles. The anterior border was defined by the internal iliac vessels, sigmoid colon,

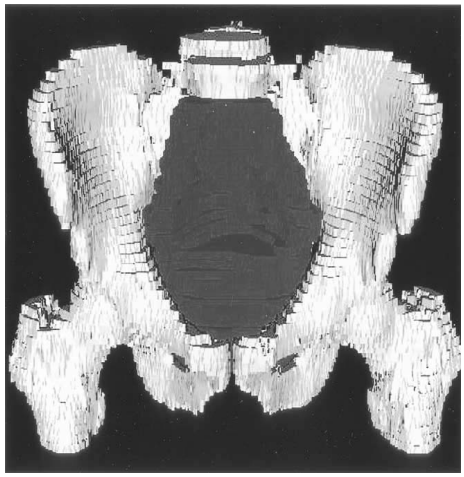

Fig. 2. The three-dimensional shape of the CTV (anterior-superior view).

bladder, vagina, prostate, and small bowel. The small bowel was always excluded as much as possible; however, if it was adjacent to the sacrum, then the anterior border of the CTV was set at least 5 mm ventral to the sacral wall. The colon of LAR patients was included 2 cm cranial to the anastomosis. In Pre-op patients, the rectum was included 3 cm cranial to the tumor. The resulting three-dimensional definition of the CTV had a complex shape with an anteriorly oriented concavity superior to an inferior cone (Fig. 2).

After registration of the CT scans according to the bones of the pelvis, the individual contoured CTVs were compared. The variability of the anterior border of the CTV was obtained by measuring the distance from the midline of the anterior border of L5/sacrum to the most anterior margin of each CTV (Fig. 3). Motion of the CTV was calculated for the individual patient by subtracting the distance of the anterior margin of the CTV from its mean position on each CT slice. This allowed calculation of the standard deviation of all movement. Movement of the rectum in the anterior and posterior dimension was measured using an identical method. The positions of the left and right lateral margins of the rectum were measured from the medial edge of the bones of the pelvis or the lateral edge of the gluteal muscle on each slice. This distance was then used to calculate the rectal motion as was done for the CTV movement. To allow comparison of the movement of the CTV or rectum between patients, the CT slice that encompassed the anus was set as the zero slice. Cranial-caudal motion of the anastomosis was measured as the movement of the most cranial and most caudal staples.

To examine the maximal influence of bladder filling, the CT scan with lowest and highest bladder volume of each patient was reviewed. The anterior to posterior difference in distance of the two CTVs was measured, as well as the length of the difference in the cranial-caudal dimension. The volume difference between the two CTVs was calculated.

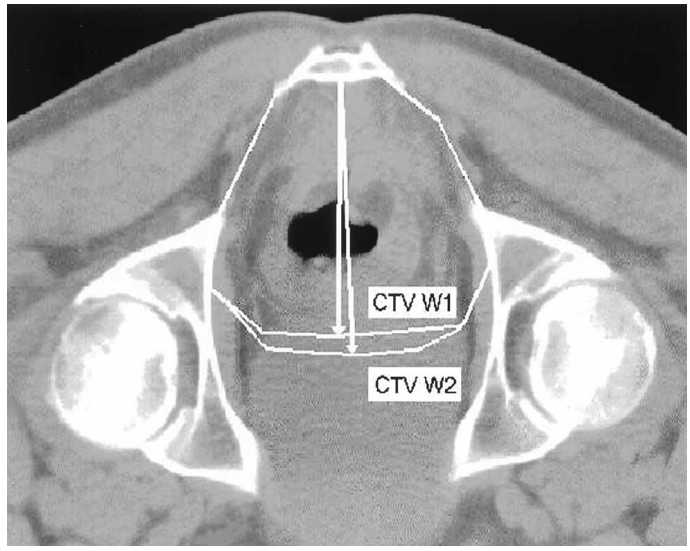

Fig. 3. Measurement of the anterior border of the CTV. CTV W1 = clinical target volume of the first CT scan taken during the first week of treatment. CTV W2 = clinical target volume of the second CT scan taken during the second week of treatment.

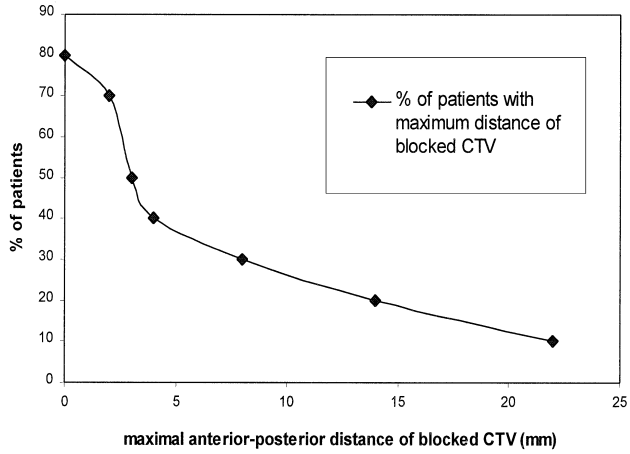

Fig. 4. Cumulative percent of patients with maximum distance of blocked CTV (anterior-posterior direction).

RESULTS

The CTV vs. the conventional 3-field volume

The femoral block used in the lateral conventional treatment fields shielded a portion of the CTV at least once in 7 of the 10 individuals. These 7 individuals had a total of 40 scans, of which 16 were found with shielding of the CTV. In 1 patient, a portion of the CTV was blocked in all of the scans. In the cranial-caudal dimension, the CTV was blocked over an average distance of 2.3 cm. In 3 patients, the CTV was shielded by at least 8 mm in the anterior-posterior dimension (Fig. 4).

CTV motion

Differences in the CTV appeared to be dependent on the location within the pelvis. In the superior pelvis, where the CTV was primarily defined by the common and internal iliac blood vessels, the anterior border varied according to the position of the small bowel. Displacement of the anterior border of the CTV was only observed between the left and right common or internal iliac vessels. This was related to the variability of the small bowel, due to the decision to place the anterior border at least 0.5 cm from sacral wall or major blood vessels and to include a certain amount of small bowel if the small bowel was adjacent to these structures. In the inferior pelvis, the standard deviation (SD) varied from 3 to 10 mm due to the position of the bladder, prostate, vagina, or rectum. At the anus, the SD of the anterior CTV position had a value of 3 to 4 mm, which increased to 4 to 6 mm at 5.5 cm above the anus, and to 10 mm 9 cm above the anus (Fig. 5).

The increase of the SD at 5.5 cm above the anus corresponded with the average position of the bladder floor, which was 5.1 cm above the anus, and was caused by the bladder filling. The bladder displaced the anterior margin with an average of 7 mm posteriorly and over an averaged cranio-caudal length of 2.5 cm. The averaged added volume associated with an empty bladder was 18 cm^3. The highest CTV volume difference between a full and empty bladder was 51 cm^3. Bladder filling had no effect on the CTV in 2 patients. They were both female LAR patients.

There was no motion observed of the posterior or lateral borders. This was expected given the registration according to the bones of the pelvis and the anticipated stability of the muscles and major blood vessels.

Rectal motion

The motion of the anterior rectal border was very similar with the motion of the anterior border of the CTV (Fig. 5). Thus, it was possible that the rectum may move outside the anterior margin of the CTV if this border was drawn too close to the rectum. The lateral margins of the rectum also

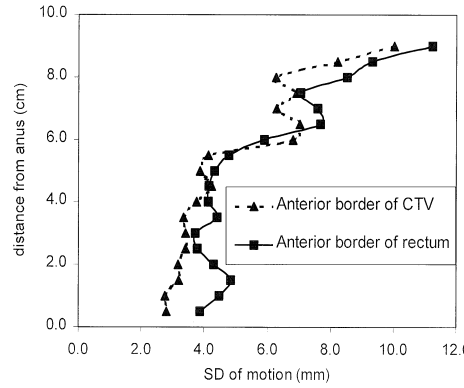

Fig. 5. The standard deviation of motion of the anterior border of the CTV and rectum (1 standard deviation).

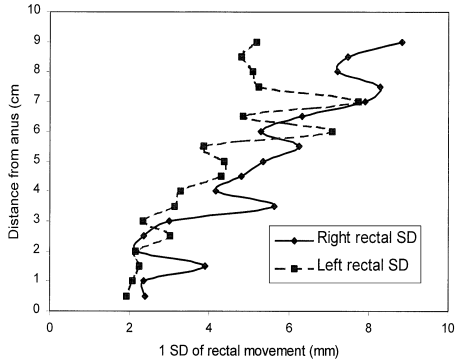

Fig. 6. Lateral and posterior movement of the rectum (1 standard deviation).

moved to a similar degree; however, because the distance from rectum to the CTV was much larger in this dimension, the motion was inconsequential (Fig. 6). The posterior margin of the rectum was also observed to move, with a SD of 4, 7, and 2 mm at the anus, and 4.5 cm and 9 cm cranial from the anus, respectively. Motion of the surgical clips placed at the anastomosis was studied in 5 patients, with the largest cranial and caudal movements of 1 and 1.5 cm for 4 of the 5 patients, respectively.

DISCUSSION

Traditional treatment planning efforts for rectal cancer used the bone landmarks of the pelvis and radiopaque soft tissue markers to design the irradiated volume. With the development of three-dimensional treatment planning, however, a much more strict definition of the CTV was required. Even though this was more involved, the target volume definitions were fundamentally the same, and included the anastomosis, the mesorectal soft tissues, and the lymphatic drainage pattern.

The risk of recurrence at the anastomosis has been shown in multiple studies of the patterns of failure after a low anterior resection, finding recurrent disease at the anastomosis in 67% to 80% of all patients with a pelvic recurrence (22, 23). The mesorectum has also been found to be at risk, as pathologic examinations of the specimen obtained from a total mesorectal excision have found an incidence of mesorectal tumor deposits in approximately 40% of patients with a pathologic T3 tumor (24). The designation of the CTV used in this study included the entire mesorectum with generous borders, typically extending to the nearest bone or muscle of the pelvis. The pelvic wall was always included, as a review of 49 sites of local recurrence in 34 patients found the pelvic wall to be involved in 24 (25). Perhaps the most uncertain border of the CTV was along the mobilized colon immediately proximal to the anastomosis, where we excluded any large bowel that was more than 2 cm superior to the surgical clips of the anastomosis. Given the surgical technique, it was believed to be unlikely that any mesorectum existed anterior to the mobilized colon in this region, although if any were present then it would have been excluded from the CTV. Remnants of mesorectum lateral and posterior to the mobilized colon would have been included as part of the presacral and vascular volumes in this region.

The distal border of the CTV was defined based on studies of the pathologic distribution of disease as well as reviews of the patterns of failure. Multiple pathologic studies of the surgical specimens have found no evidence of cancer more than 4 cm distal to the primary tumor (26–28). Clinical studies rarely have included the distance of a recurrence distal to the anastomosis (23, 29), although one report found that 4 of the 46 recurrences were found 3 cm distal to the anastomosis (22).

The definition of the CTV was also determined by the lymphatic drainage of the rectum (30). Recurrences in lymph nodes have often been found, with 90% of involved lymph nodes located in the pelvis (31). The best measurement of lymphatic involvement may be obtained from labor-intensive pathologic studies that use the clearing method, which has been reported to identify normal lymph nodes smaller than 4 mm and metastatic lymph nodes that would not have been identified using the conventional manual method. With the clearing method, investigators found an average of over 70 lymph nodes per specimen in 182 patients with rectal cancer. In 70 patients with rectal tumors below the peritoneal reflection, the incidence of any nodal metastasis was 62.9% for the perirectal lymph nodes, which included the superior rectal and middle rectal arteries inside the pelvic plexus, 12.9% for the lymph nodes along the middle rectal artery outside the pelvic plexus and the internal iliac artery, and 5.7% for lymph nodes along the common iliac and obturator arteries (32). Even though the middle rectal and presacral vessels were not routinely individually identified on the treatment planning CT scan, the CTV in the inferior pelvis was broadly defined and would have been expected to always include those structures, as shown in Fig. 1c. The internal iliac, obturator, presacral, and distal common iliac vessels were always identified and were outlined on the treatment planning CT scan with a margin, as shown in Figs. 1a and 1b. The presacrum was entirely included in the CTV.

Although the major blood vessels can be readily identified on the treatment planning CT scan, there was little information in the literature to specify the radial distance from a blood vessel within which unenlarged lymph nodes lie. Using reports of conventional lymphangiography (33, 34), we decided to place the border of the CTV at least 3 to 5 mm radial to the internal iliac, obturator, and common iliac vessels, and at least 5 mm anterior to the sacrum. This specific issue did not need to be addressed for traditional treatment planning, but has become much more important with three-dimensional treatment planning and especially IMRT, and will need to be resolved for rectal cancer as well

as any site that involves adjuvant nodal irradiation along blood vessels.

This study found that the femoral block routinely used in the lateral fields of a conventional treatment plan frequently shielded a portion of the CTV, which was due to internal organ motion occurring during the course of treatment. This was not surprising, given that studies of the prostate have demonstrated that a considerable degree of motion was possible (35). The shielded area was located at the level of the bladder, prostate, uterus, vagina, or near the anastomosis. Although the size of the area was relatively small, approximately 2.5 × 1 cm, the adjustments applied to the CTV to form a PTV would have greatly increased the size of the untreated volume. Irradiation of this particular location may be especially important, as the Minnesota reoperation series found that nearly one-half of the tumor bed failures occurred along the posterior prostate and bladder in men or the rectovaginal septum in women (36). Traditional simulation methods may be adequate for women, as a radiopaque marker can be placed in the vagina, although there have been no studies of the effect of rigid marker on the resting position of the vagina. In addition, before the study reported here, there has been no examination of the position of the vagina during the typical 5½-week course of therapy. In men, delineation of this region would require a Foley catheter, which is not done routinely. This problem may be addressed by simply reducing the size of the femoral block or deleting it entirely. This study, however, suggested that the best solution was to use three-dimensional treatment planning, as it provides a much greater degree of confidence in the anatomic detail, and to add extra margin anteriorly in this location.

Motion of the CTV was not equal in all dimensions. The posterior and lateral borders and the anterior border in the superior pelvis were all very stable, as would be expected given that these borders were determined by the bone, muscle, and major blood vessels. The greatest degree of motion of the CTV was observed near the anterior structures of the inferior pelvis and was most likely to have been due to bladder filling. The rectum also exhibited variability in position with a SD that was slightly higher than that of the CTV definition.

Modifications to the CTV to account for internal organ motion when constructing a PTV do not need to be equal in all dimensions. In all areas other than near the bladder and prostate or the uterus and vagina, only a minimal increase in size would be necessary. However, at the anterior border of the inferior pelvis the modification will need to be larger than the 1 cm SD to ensure coverage of the target volume during the course of adjuvant treatment in all patients. Rather than just applying the modification as a class solution, another possible approach would be to obtain multiple treatment planning CT scans for each patient and individualize the PTV. In fact, studies using this approach, also known as adaptive radiation therapy, are currently in progress for prostate cancer (37). Either way, this modification would probably have only a minimal effect on the use of intensity-modulated radiation therapy, as there is no small bowel in this location.

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Chapter 5

The influence of small bowel motion on both a conventional three-field and intensity modulated radiation therapy (imrt) for rectal cancer.

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Cancer/Radiothérapie submitted.

Abstract

Purpose: To investigate the reduction of irradiated small bowel volume with IMRT planning in rectal cancer and to asses the variability of the irradiated small bowel in the conventional planning as in the IMRT planning by obtaining weekly CT scans.

Methods and Materials: Twelve patients with rectal cancer had treatment planning CT scans of the pelvis with small bowel contrast obtained for planning and once a week during treatment (65 CT scans total). The scans were registered using the bony structures. The clinical target volume, small bowel, large bowel and bladder were outlined on each slice. The first CT scan was used for IMRT planning (IMPlan) and conventional three-field planning (ConPlan), which were then applied to the CT scans obtained during therapy.

Results: The median value among patients of the mean volume over a patient's scan of small bowel irradiated ≥95% was 112 cm^3 (Standard Deviation (SD): 31 cm^3) for the ConPlan and 42 cm^3 (SD: 17 cm^3) for the IMPlan. The median total bladder volume was 148 cm^3 (SD: 130 cm^3). There was a good correlation between the volume of irradiated small bowel and the bladder volume for IMPlan with <50 cm^3 irradiated small bowel and ConPlan with <150 cm^3 ($p=0.002$).

Conclusion: The use of IMRT led to a potentially clinically meaningful reduction in the volume of small bowel irradiated, even when accounting for small bowel motion. A full bladder was of greatest benefit in individuals with the smallest volume of small bowel in the treatment field.

Résumé

Objectif: Investigation de la réduction du volume irradié des intestins grêles par l'application de la radiothérapie conformationnelle avec modulation d'intensité (RMCI) pour le traitement du cancer du rectum, comparée avec le traitement conventionel et estimation des variations du volume irradié dans les deux cas.

Patients et méthodes: Pour douze cas de cancer du rectum, un scan CT du pelvis avec contraste intestinal a été fait avant le traitement, ainsi qu'un scan toutes les semaines pendant le traitement (65 scans au total). Les scans ont été alignés en utilisant les structures osseuses. Le volume cible, les intestins grêles, les gros intestins et la vessie ont été délineés dans toutes les coupes. Le premier scan a été utilisé pour faire un plan RMCI

et un plan conventiel de trois champs. Ces plans ont été ensuite calculés pour les scans obtenus pendant le traitement.

Résultats: La médiale du volume d'intestins grêles irradiés pour moins que 95% est 112 cm^3 (déviation standard (DS): 31 cm^3) pour le plan conventionel et 42 cm^3 (DS: 17 cm^3) pour le plan RMCI. La médiale du volume de la vessie est 148 cm^3 (DS: 130 cm^3). Il y a une bonne corrélation entre le volume de la vessie et le volume d'intestins grêles irradiés moins de 50 cm^3 pour le plan RMCI en moins de 150 cm^3 pour le plan conventionel (p=0.002).

Conclusion: L'utilisation de la RMCI devrait conduire à une réduction substantielle du volume d'intestins grêles irradiés, même en tenant compte du mouvement intestinal. Une vessie pleine a été grandement bénéfique aux malades avec un petit volume d'intestins grêles irradiés.

INTRODUCTION

Acute diarrhea has been reported to be a frequent side effect of adjuvant combined radiation therapy (RT) and chemotherapy for rectal cancer. Postoperative treatment has a reported 20 to 35% rate of grade 3 + diarrhea in randomised trials [18, 26]. Preoperative RT with chemotherapy has been widely perceived as less toxic, however, severe diarrhea rates of 12 to 39% have been reported in randomised studies [15, 24].

The relationship between the volume of irradiated small bowel and the development of acute small bowel toxicity has been well recognised. In the seventies, large parallel opposed fields (APPA) were used [12]. They produced hotspots in areas that usually included large and small bowel and played a causative role in the toxicity profile of these patients. Exclusion of the small bowel from the pelvis in order to improve the tolerance to therapy has been the subject of a considerable number of research efforts. The first one was the use of a three- or four-field beam arrangement with an abdominal wall compression device (belly board) and bladder distension [10, 12, 16]. An APPA-field set up with a patient in supine position resulted in an irradiation of 620 cm^3 bowel. In contrast, a 4-field technique with a patient in prone position reduced the irradiated bowel volume to 145 cm^3 [11].

Other methods to reduce the amount of small bowel inside the radiation field were surgical techniques, such as omental slings, pelvic mesh and tissue expanders [23].

Intensity Modulated Radiation Therapy (IMRT) also offers the potential for reducing the volume of irradiated small bowel [22]. However, the small bowel is a mobile structure. In a study using three-dimensional treatment planning tools, the distance from the sacrum to the small bowel at 5 cm caudal to the sacral promontory varied with a standard deviation of 2.7 cm, 1.4 cm, and 0.2 cm for preoperative patients, and patients with low anterior resections (LAR) and abdominoperineal resections, respectively [20]. The coefficient of variation of the volume of small bowel exceeded 100% in the posterior midpelvis for LAR and all postoperative patients and in the central midpelvis for preoperative patients suggesting that any single study of the small bowel position could be inaccurate in these areas.

Because of the variation in small bowel position and volume observed in the previous work, we assessed the variability of small bowel volume for an IMRT plan in 12 patients who had weekly treatment planning CT scans obtained during routine adjuvant pelvic RT. In order to bring this information into perspective, we used the identical methods to assess the variability for a conventional three-field plan. We also investigated the role of bladder filling on the volume of irradiated small bowel.

METHODS AND MATERIALS

Twelve patients with rectal cancer had treatment planning CT scans of the pelvis obtained for planning and once a week during treatment (65 CT scans total). Eleven patients had T3 or N+ rectal cancer by transrectal ultrasound or pathologic examination and included 2 patients treated after an abdominoperineal resection (APR), 6 after low anterior resection (LAR), and treated 3 preoperatively (Preop). One individual was treated adjuvantly after a wide local excision (WLE) for a T2 tumour. Because this person had no intraabdominal surgery, he was included with the preoperative group for the purposes of analysis. There were 4 females and 8 males. All patients were given oral contrast between 1 ½ to 2 hours before the CT scan [7] and placed prone on a vacuum bag cradle with a depressed area for small bowel exclusion but rigid foam beneath the pubis and the chest. Patients were instructed to have a full bladder for the simulation and reminded of the importance of bladder distension during weekly on-treatment visits. The weekly CT scan during treatment was made after the radiotherapy treatment and the patients were instructed only to urinate after CT scan was made.

There were 4 to 7 CT scans per patient (median of 5) depending on the number of weeks that the patient was receiving treatment and patient co-operation. All CT scans were obtained using a helical CT scanner with a 5-mm slice interval and included a minimum visualization of the entire treated volume of the pelvis. The scans were registered manually using the bones of the pelvis and the small bowel, large bowel and bladder were outlined on each CT slice by a single physician (J.J.N.) and verified by a second physician (J.M.R.).

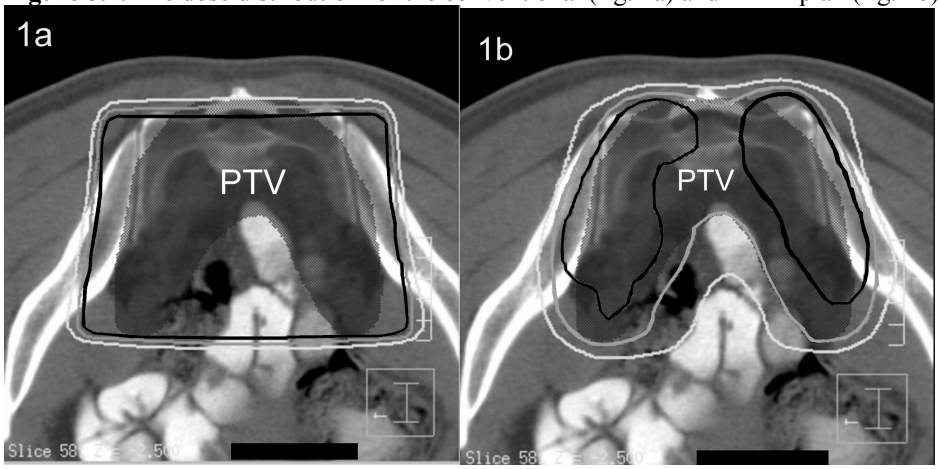
The first treatment planning CT scan was used to generate two separate treatment plans. One plan used a conventional plan 3-field arrangement with the treatment borders, dose and inhomogeneity requirements as per the Southwest Oncology Group guidelines for protocol 9304. This plan placed the superior treatment border at mid-L5, the anterior border 3 cm anterior to the sacral promontory, the posterior border was placed 2 cm posterior to the anterior border of the sacrum and the inferior border was 1.5 cm inferior to the perineal scar in APR patients and at least 5 cm inferior to the anastomosis or tumour in LAR and Preop patients, respectively. The prescription was calculated with the isocenter at 100% and a dose inhomogeneity of no more than 105%.

Each patient also had an IMRT plan calculated, with the clinical target volume (CTV) designed to include the rectum, perirectal tissues and regional lymphatics according to the standard field definitions and the patterns of failure [12, 21]. In the cranial-caudal dimension, contours of the target structures began at the inferior edge of L5 and ended at least 4 cm below the anastomosis for the LAR patients, and 4 cm below the tumour or below the anus for the preop and WLE patients. With corrections for the planning target volume and penumbra, these cranial and caudal borders approximated the conventional field. Because the lymphatics follow vascular structures, the distal common and internal iliac arteries and veins were included plus a 3 to 5 mm margin, depending on the presence of bowel or bone. The posterior border of the perirectal tissues was defined by the posterior edge of the sacral foramina or the most anterior portion of the gluteus maximus. The lateral border was the ileum, piriformis, and obturator internus muscles. The anterior border was defined by the internal iliac vessels, sigmoid colon, bladder, vagina, prostate and small bowel. The small bowel was always excluded as much as possible, however, if it was adjacent to the sacrum, then the anterior border of the CTV was set at least 5 mm ventral to the sacral wall. The colon of LAR patients was included

2 cm cranial to the anastomosis. In Pre-op patients, the rectum was included 3 cm cranial to the tumour. The resulting three-dimensional definition of the CTV had a complex shape with an anteriorly oriented concavity superior to an inferior cone [21].

The planning target volume (PTV) equalled the CTV plus 3 mm margin. The IMRT plan consisted of 5 equispaced beams for all patients. The constraints to the PTV were set to encompass it within the 95% isodose line while delivering 100% to the isocenter, using the Konrad system (MRC, Heidelberg, Germany) for inverse treatment planning. A maximum dose of 110% was allowed as this only occurred within the CTV. For the small bowel, a maximum dose of 95% of the prescribed dose or less was allowed and the small bowel volume/dose at $V(D_k\%)$, with $D_k = 40, 60, 80$ were minimized. The dose distribution of both plans is shown in figure 5.1. Both the conventional and the IMRT plan were then applied to the weekly CT images.

Figure 5.1. The dose distribution for the conventional (fig. 1a) and IMRT plan (fig. 1b).



Grey surface: PTV; black line: 100%; grey line: 95%; white line: 80%

Total bladder or total small bowel volumes were derived from the three-dimensional treatment planning system. The total small bowel volume was equal to the amount of small bowel located caudally to the superior edge of L5 and was contoured for each patient from the same slice for all of the CT scans. Small bowel and colon volumes inside the 95% or 90% isodose line were derived from the dose volume histograms. To compare mean values, the t-test was used. The patient-specific variation of the irradiated bowel volume inside the 95% isodose line was calculated using the standard deviation of

the irradiated bowel volume of each patient normalized to the corresponding mean. To diminish large variations in the anatomy between the patients, each small bowel volume of one patient was divided by the mean volume for that patient with a percentage value as result (e.g.: 100 % or 1 equals the mean volume). The same was done for colon and bladder volumes (e.g.: 0.5 results in an almost empty bladder, 1 equals the mean volume and 2 results in a full bladder). These percentage numbers were used in the correlation analysis with linear regression. To view a volume difference over time, all small bowel and bladder volumes of every week were summed and averaged from all patients and a correlation was calculated.

RESULTS

Conventional treatment, IMRT and small bowel motion

The mean small bowel volume within the 95% isodose line for conventional treatment was 180 cm^3, 160 cm^3, and 69 cm^3 for APR, LAR and Preop patients, respectively (Table 5.1).

Table 5.1. The mean small bowel volume inside the 95% isodose line per patient with standard deviation, for conventional treatment and Intensity Modulated Radiation Therapy (IMRT) planning.

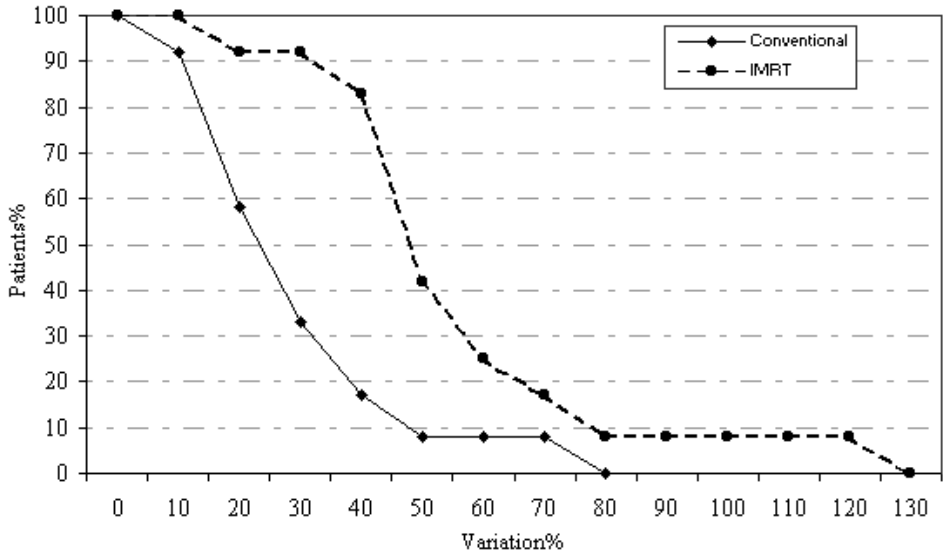
Surgical Procedure	Conventional planning			IMRT planning		
	Mean small bowel volume (cc)	Small bowel shift (SD) cc	% of mean	Mean small bowel volume (cc)	Small bowel shift (SD) cc	% of mean
APR	154	69	45	50	15	30
APR	206	15	7	69	10	14
LAR	87	12	14	12	5	42
LAR	110	15	14	34	17	50
LAR	247	28	11	81	36	44
LAR	96	31	34	22	12	55
LAR	110	60	55	53	45	85
LAR	308	50	16	120	67	56
WLE	124	47	38	42	25	59
Pre-op	34	10	29	3	2	67
Pre-op	112	50	45	36	22	61
Pre-op	5	4	80	8	11	137

SD = standard deviation; APR = abdominoperineal resection; LAR = low anterior resection; WLE = wide local excision; Pre-op = preoperative chemoradiation;

The average of the individual standard deviations of the small bowel volume for both the postoperative and preoperative groups were similar, with 32 cm^3 and 28 cm^3,

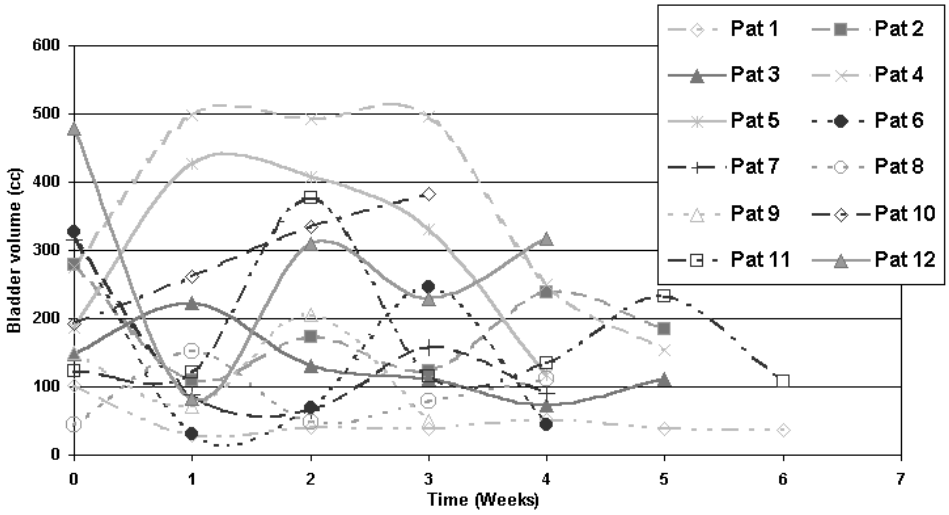
respectively. With the IMRT treatment plan, the mean volumes were considerably smaller than the conventional plan with 59 cm^3, 54 cm^3 and 22 cm^3 for APR, LAR and Preop patients, respectively. This represented a volume reduction of 67%, 69% and 41% compared to the conventional plan. In absolute terms, 11 of the 12 patients experienced a reduction in irradiated small bowel volume by a median of 76 cm^3 (range 31 to 188 cm^3). The only patient who failed to benefit had an irradiated mean small bowel volume of only 5 cm^3 with the conventional beam arrangement. The median standard deviation of irradiated small bowel volume was 31 cm^3 (range 4 to 69 cm^3, mean 33 cm^3) for the conventional plan compared to a median of 17 cm^3 (range 2 to 67 cm^3, mean 23 cm^3) for IMRT.

Figure 5.2. Distribution of patient-specific variation, percentage relative to the mean, of small bowel volume irradiated by at least 95% isodose.



The relative patient-specific variation for small bowel volume irradiated by ≥95% of the prescription dose was much larger for IMRT (mean 58%) than for the conventional treatment (mean 32%) (Figure 5.2), due to the reduced overall volume irradiated with the IMRT plan. For almost all the patients there is 30% higher relative variation of small bowel with IMRT than with the conventional plan.

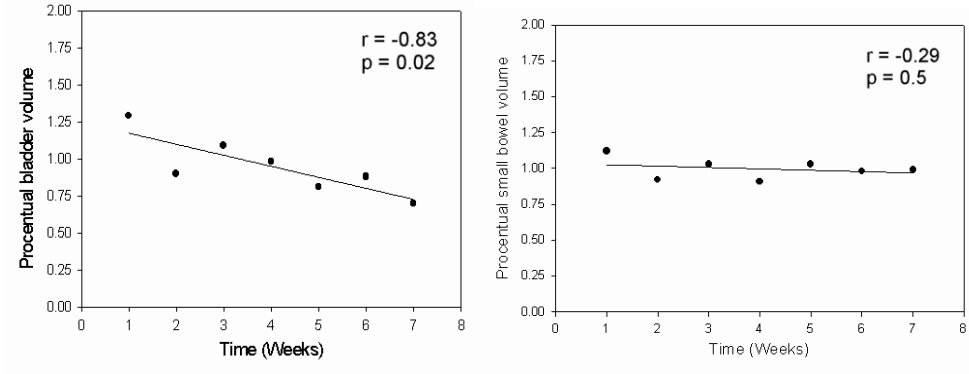
Figure 5.3. Individual bladder volume over time for all patients.



Bladder volume and small bowel volume trends

The median bladder volume was 148 cm^3 (range 29 to 499 cm^3). Despite personal instructions at the time of consultation, simulation and weekly during therapy, there was a considerable amount of variation observed in absolute bladder volume over time (Figure 5.3). When the bladder volume and the total small bowel volume within the pelvis were normalized to the mean, there was a reduction in bladder volume over time, while the total small bowel volume was almost constant (Figure 5.4). There was a trend toward an increased volume of irradiated small bowel (14 cm^3; p = 0.04) over time for the IMRT treatment but a 15 cm^3 decrease for the conventional treatment.

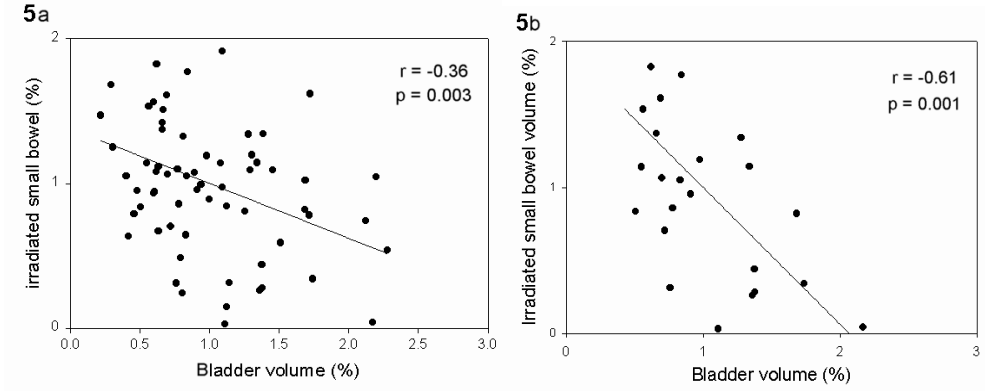
Figure 5.4. The mean bladder and small bowel volume over time.



Correlations

Correlations between the volume of irradiated small bowel inside the 90% isodose line and the bladder volume for both the IMRT plan ($r = -0.36$, $p = 0.003$) and the conventional plan ($r = -0.37$, $p = 0.002$) were calculated. A full bladder reduced the volume of irradiated small bowel by 72% for the IMRT plan and by 50% for the conventional plan. The benefit of having a full bladder was greatest for Preop patients, with a reduction of 190% ($r=-0.61$, $p=0.001$) for the IMRT plan and 130% ($r=-0.69$, $p=0.0002$) for the conventional plan (Figure 5.5). There was no correlation for APR patients.

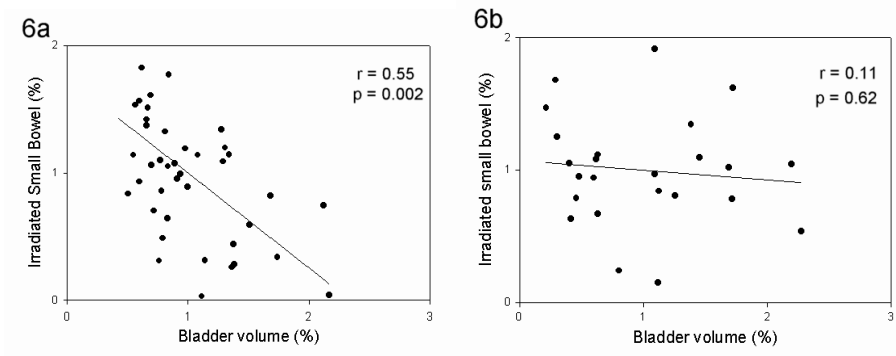
Figure 5.5. Correlation between small bowel and bladder for all patients treated with IMRT (fig. 5a) and for preoperatively treated patients with IMRT treatment (fig. 5b).



A good correlation between small bowel and bladder volumes was found for IMRT patients with less than 50 cm^3 inside the 95% isodose line ($r=0.55$, $p=0.002$). Patients with > 50 cm^3 exhibited no relationship between bladder and small bowel volumes ($r=0.11$, $p=0.62$) (Figure 5.6). For the conventional plan, a similar result was found if the patients were divided into more or less than 150 cm^3 small bowel inside the 95% isodose line. In this case, however, bladder distension was associated with a reduction in irradiated small bowel by 90% compared to the 150% achieved for the IMRT plan in patients with less than 50 cm^3 of small bowel.

No correlation between irradiated small bowel and colon was found, for all patients or for any subgroup.

Figure 5.6. Correlation between small bowel and bladder for patients with less (fig. 6a) or more than 50 cm^3 (fig. 6b) irradiated small bowel with the IMRT treatment.



DISCUSSION

Acute severe bowel toxicity is still a problem as reported by randomised chemoradiotherapy trials (Table 5.2) and ranges from 13 to 39% (mean 30%). Late severe bowel toxicity is seen in 2 to 30% of the patients, treated with pre- or postoperative radiotherapy in randomised trials (Table 5.3).

Table 5.2. Overview of acute severe bowel toxicity in pre-operative randomised chemoradiotherapy trials

	number of patients	RT+ SU	CT+RT +SU	SU+RT +CT	technique	upper field border	dose (Gy)
EORTC 72-76 [6]	245	33	33	x	APPA	L2	34.5
NSABP R-03 [15]	116	x	39	23	4-field	L5/S1	45 / 50.4
CAO/ARO/AIO-94 [24]	805	x	13	12	3- or 4-field	L5/S1	50.4
EORTC 22921 [5]	798	17	34	x	3- or 4-field	S2-S3	45

SU: surgery; RT: radiotherapy; CT: chemotherapy

Although acute and late bowel toxicity is reported by these and many other authors, dose-volume thresholds have not been reported. Only a few authors reported dose-volume correlations by using the outline of the small bowel contrast on orthogonal simulation films to calculate the volume of irradiated small bowel. In a study of 150 patients with six different primary tumour types, including 51 with rectal cancer, a statistically significant association was found between the volume of small bowel in the high dose portion of the pelvis and the development of acute diarrhea. The volume of small bowel was on average of 116 cm^3 for patients with grade 1 diarrhea to 342 cm^3 for those with grade 2 diarrhea

[11]. In contrast with these results, Shanahan *et al.* reported a grade 2 diarrhea in 24% of the patients with an average irradiated small bowel volume of 102 cm^3[25].

Table 5.3: Overview of late severe bowel toxicity in pre- and postoperative randomised (chemo)radiotherapy trials

	Number of patients	Su alone	RT+ SU	SU+ RT	Technique	Upper field border	Dose (Gy)
Swedish rectal cancer [8]	1168	10	30	x	3- or 4-field	L5	25
Uppsala [9]	471	6	5	11	3-Field	mid L4	25
Stockholm I [14]	572	7	11	x	APPA	L2	25
Stockholm II [14]	455	8	9	x	4-field	mid L4	25
MRC III [1]	469	17	x	20	APPA	18x15 cm	40
France [3]	172	0	20	x	4-field	L4-L5	46
Rotterdam [27]	172	x	x	2	3- or 4-field	L5-S1	50

SU: surgery; RT: radiotherapy

Another study described a grade 2 diarrhea in 31% and 71% of the patients with an average irradiated small bowel volume of 23 cm^3 and 241 cm^3, respectively [13]. The addition of chemotherapy complicates the dose-volume correlation even more: Minsky *et al*. reported in his chemoradiotherapy trial a grade 3+ toxicity with an average of 374 cm^3 irradiated small bowel, compared to a grade 0-2 toxicity with an average of 176 cm^3 [19]. Considering the above mentioned acute dose-volume correlations, the quantification of these relationships is not consistent. Possible reasons for this inconstancy are the inclusion of non-rectal tumours, different treatment techniques (APPA vs. 3- or 4-field), and the inconsistency in small bowel volume measurements due to the method employed, as only the outline of the small bowel position was used, not the actual organ volume.

Only Baglan *et al*. used treatment planning CT scans in patients treated with pre- or postoperative chemoradiotherapy and found grade 3+ acute diarrhea at a dose of 40 Gy with an average small bowel volume of 216 cm^3, compared to a grade 0-2 toxicity with 78 cm^3. They also reported for grade 3+ toxicity a dose-volume threshold: 125 cm^3 small bowel at a dose of 40 Gy [4].

With the conventional treatment, 5 of the 12 patients had 125 cm^3 or more irradiated small bowel. The IMRT planning for these patients reduced the volume of small bowel substantially. However, a reduction of acute bowel toxicity will have to be proven in clinical research.The answer to the question if IMRT will result in a reduction of the late side effects is even more difficult, because the available data are even more inconsistent:

Gallagher e*t al*. reported chronic diarrhea grade 1 and 2 with an average volume of 158 cm^3 and 473 cm^3 irradiated small bowel, respectively [11]. Letchert *et al*. described that chronic diarrhea was seen in 31% and 42% of the patients with an average volume of 77 cm^3 and 328 cm^3 irradiated small bowel [17].

When the effect of the mobility of the small bowel was included in the analysis, this study found that IMRT for rectal cancer reduced the mean volume of small bowel irradiated to $\geq$ 95% by approximately one-third of the volume irradiated using a conventional three-field arrangement. In absolute terms, motion of the small bowel had approximately the same effect for both IMRT and conventional fields, although the relative effect was much higher for IMRT due to the lower total volume of small bowel irradiated.

In agreement with other studies [11, 12, 20], voluntary bladder distension was associated with a smaller volume of irradiated small bowel. Previous studies, however, measured this benefit only once or twice during treatment, using the outline of small bowel contrast on simulation films and included very few people with rectal cancer [2, 7]. In our previous work using three-dimensional treatment planning tools and multiple assessment times, a significant relationship was found between the volume of the bladder and the height of the small bowel in the cranial-caudal dimension and reduced small bowel volume in the anterior mid-pelvis for the LAR and preoperative patients, but not for APR patients [20]. There was a trend towards reduced bladder volumes in the last 2 weeks of treatment, which may have reflected either patient inattentiveness or increased difficulty maintaining a full bladder if increased stool frequency was present.

The dosimetric consequences of bladder distension over the course of treatment were examined in this study. Correlation of the normalized bladder volume to the normalized small bowel volume revealed a definite relationship that was strongest for patients with less than 50 cm^3 and 150 cm^3 irradiated small bowel for the IMRT and conventional plans, respectively. Considering that patients with less than 125 cm^3 of irradiated small bowel had no evidence of acute small bowel toxicity in an analysis using three-dimensional treatment planning of conventionally treated subjects [4], it could be concluded that voluntary bladder distension was of greatest benefit in those patients who needed it the least.

CONCLUSION

With IMRT, the amount of irradiated small bowel was reduced to one third of the small bowel volume in the conventional field, but was not beneficial to all patients. The variation of small bowel volume irradiated by ≥ 95% of the prescription dose during treatment was on average 32% for the conventional treatment and 58% for the IMRT. Despite good instructions, the patients were not able to maintain a full bladder during treatment. There was a good correlation between the volume of irradiated small bowel and the bladder volume for the IMRT plan with < 50 cm^3 irradiated small bowel and the conventional plan with < 150 cm^3. Further clinical research will have to point out if IMRT will result in a reduction of acute bowel toxicity for a selected group of patients.

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Chapter 6

Intraoperative HDR brachytherapy for rectal cancer using a Flexible Intraoperative Template: standard plans versus individual planning.

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Intraoperative HDR brachytherapy for rectal cancer using a flexible intraoperative template: standard plans versus individual planning

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Abstract

HDR intraoperative brachytherapy (IOBT) is applied to locally advanced rectal tumors using a 5 mm thick flexible intraoperative template (FIT). To reduce the procedure time, treatment planning is performed using standard plans that neglect the curvature of the FIT. We have calculated the individual treatment plan, based on the real geometry of the FIT, and the dose at clips placed during surgery. A mean treatment dose of 9.55 ± 0.21 Gy was found for the individual plan, compared to the prescribed 10 Gy ($P < 0.0001$). The mean central dose was 10.03 ± 0.10 Gy in the standard plan and 9.20 ± 0.32 Gy in the individual plan ($P < 0.0001$). The mean dose at the corners of the FIT was 10.3 Gy in the standard plan and ranged between 10.3 and 10.5 Gy in the individual plan. In 63% of the clips, the dose was larger than 15.0 Gy, which is equivalent to a gap between the FIT and the target smaller than 5 mm. In 18% of the clips, the dose was smaller than 13.0 Gy indicating that locally the gap was larger than 5 mm. Clinical practice will have to prove if these small dose deviations influence the clinical outcome.

Keywords: Brachytherapy; High dose rate; Rectal cancer; Treatment planning

1. Introduction

High dose rate (HDR) intraoperative brachytherapy (IOBT) is a treatment modality in radiation therapy used as an adjuvant to surgery for locally advanced cancers [5]. It involves the delivery of a single large radiation dose to residual (microscopic) tumor at the time of surgery with a remotely controlled HDR afterloader. For IOBT, the source is transported into catheters embedded in a surface applicator. After tumor resection an appropriately sized and shaped (custom-made) applicator is placed on the residual (microscopic) tumor and secured into place. Adjacent organs can be either shielded or retracted away from the treatment area. The irradiation time is determined either through individual planning after simulation of the IOBT geometry [15] or using preplanned atlases [3,13].

In 1994 an Integrated Brachytherapy Unit (IBU) (Nucletron, The Netherlands), i.e. a shielded operating room equipped with an HDR afterloader (microSelectron HDR, Nucletron, The Netherlands) and a dedicated brachytherapy localizer (Nucletron, The Netherlands), was established at the Erasmus MC-Daniel den Hoed Cancer Center [8]. This set-up enables integration of the entire brachytherapy procedure, i.e. implantation, implant reconstruction, dose planning and irradiation in a single session. The IBU is an ideal and economic environment both for (fractionated) HDR brachytherapy [9,10] as well as for IOBT.

In our institution, IOBT is used as part of a multimodality treatment for locally advanced primary or recurrent rectal tumors since 1997 using a flexible intraoperative template (FIT). To reduce the total procedure time, treatment planning during IOBT is performed using standard geometries, i.e. flat templates neglecting the curvature of the FIT, present in the treatment planning system. For each patient an individual treatment plan is calculated after finishing the procedure. The individual treatment plan is based on reconstruction of the FIT geometry and clip locations

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from isocentric films and importing the actual dwell times. The purpose of this paper is to discuss the feasibility of our technique for IOBT of rectal tumors. The question is raised whether the dose reduction towards the treated area, caused by the curvature of the FIT, can be neglected. For this reason, the individual treatment plans and the standard plans were compared in terms of dose at the prescribed depth from the surface of the FIT. IOBT applicators are always presented as blankets enclosing every irregularity. However, with catheters in place, the flexibility of the applicator is reduced and small irregularities are not covered. Even after pressing gauze dressings into the pelvis, the applicator could reshape, and a gap between the applicator and the target surface can occur. The only way to define the dose at the surface retrospectively was to determine the dose at the clips, enabling calculation of the gap between the FIT and the target surface at the clip areas.

2. Materials and methods

IOBT is applied to locally advanced primary or recurrent rectal tumors using a FIT. The FIT is a 5 mm thick flexible silicon template containing parallel catheters spaced 1 cm apart (Fig. 1). The shape of the FIT can be rectangular or corners can be cut off to conform to the target area. During surgery the size and shape of the FIT are determined by the surgeon and radiation oncologist. The shape, in combination with the catheter positions, is overlaid on a paper template which is used as input for the treatment planning system (Plato BPS, Nucletron, The Netherlands). Treatment planning is performed using standard geometries, i.e. flat templates neglecting the curvature of the FIT, present in the treatment planning system. Active dwell positions are chosen according to the size and shape of the actual FIT as present on the paper template. The dose is specified at the reference depth (usually 10 mm from the surface of the FIT, which is equal to 12.5 mm from the center of the catheters). For each active dwell position, a dose point is placed on a line perpendicular to the FIT at the reference depth.

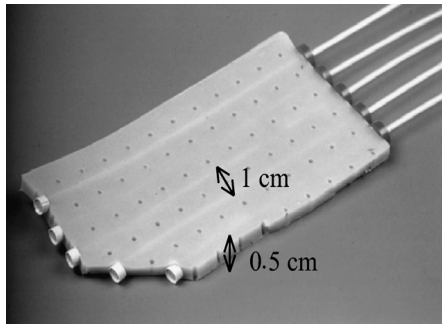

Fig. 1. The flexible intraoperative template (FIT); indicated are the catheter spacing of 1 cm and the FIT thickness of 0.5 cm.

The dwell times are optimized such that the dose in the dose points is as homogeneous as possible using the 'optimization on dose points on distance' algorithm as implemented in Plato BPS (Nucletron, The Netherlands) [16]. The reference dose is defined as the average dose in the dose points and is in the case of rectal cancer 10.0 Gy. The procedure with standard plans is chosen to eliminate the time-consuming catheter reconstruction. Before the irradiation is started, the irradiation time is checked by an independent manual calculation [14]. During treatment planning, isocentric reconstruction films are made using the dedicated brachytherapy localizer [8]. Reconstruction of the actual FIT geometry, using these films, is performed after the IOBT procedure is finished. The individual treatment plan is calculated by importing the dwell times from the standard treatment plan in the reconstructed FIT geometry. The actually delivered dose, i.e. the treatment dose, is defined as the average dose in dose points, placed on a line perpendicular to the reconstructed FIT at the prescribed depth. This dose is expected to be less than 10.0 Gy due to the anatomy of the pelvis.

For evaluation of the procedure, the treatment dose, as calculated in the individual plan, was compared to the prescribed dose of 10.0 Gy. Also, a comparison of the dose in a selection of five dose points, located at the prescribed depth in both the standard plan and the individual plan, was made. One dose point was chosen centrally in the target area and four on each corner, i.e. located at the outermost catheters at the third dwell position (10 mm from the edge) (Fig. 2).

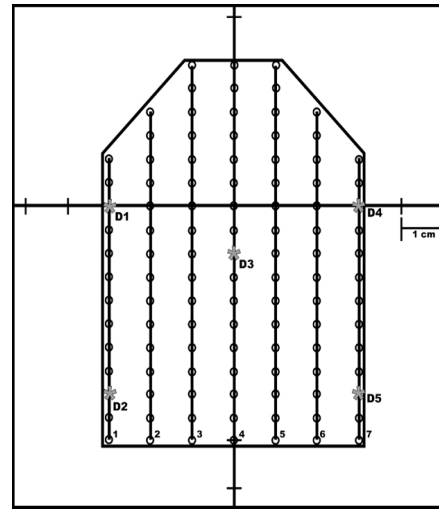

Fig. 2. Example of a (flat) FIT geometry (a rectangle with two corners cut off), consisting of seven catheters spaced 1 cm apart with active dwell positions spaced 5 mm apart. ∗, the position of the five dose points (D1, D2, D3, D4, D5) used for evaluation.

During surgery, clips were placed at the tissue surface to delineate the target area. The position of the clips was reconstructed from the reconstruction films. The calculated dose in the clip locations in the individual treatment plan is representative for the local dose at the target surface and was used as a measure of the gap between the FIT surface and the target. This way the depth in tissue covered by the reference dose can be determined. A FIT containing seven catheters of 6 cm each was considered. The central plane of this FIT, i.e. the plane perpendicular to the catheters and located at the center of the catheters ($y = 0$ mm), is drawn in Fig. 3A. Three trajectories are indicated, i.e. at the center of the FIT ($x = 0$ mm), in between catheters 5 and 6 ($x = 15$ mm) and at the edge of the FIT ($x = 30$ mm). For each of these trajectories a depth dose curve, i.e. the dose along the z-axis, is printed in Fig. 3B. A fourth trajectory is calculated at $x = 0$ mm and $y = 25$ mm (5 mm from the edge of the FIT, i.e. through the second dwell position in catheter 4). The dose is plotted as a function of the distance from the centers of the catheters which are located at $z = 0$ mm. The distance between the clips (located at the tissue surface) and the center of the catheters would be 2.5 mm in case of a perfect fit between the FIT and the target. This corresponds with a dose ranging between 17.5 and 42.5 Gy, strongly depending on the location along the FIT (Fig. 3B). In case of a 5 mm gap between the FIT and the target, the clips would be at 7.5 mm from the center of the catheters. The dose at the clip locations will then vary between 13.0 and 15.0 Gy. In the latter case, the actually delivered dose will be located at 5 mm depth in tissue as the dose was prescribed at 10 mm from the FIT surface.

3. Results and discussion

Thirty-nine patients were included in the analysis. The number of catheters used was on average 8.4 (range 5–14), corresponding to an average of 146.3 dwell positions (range 49–341). The number of clips placed in each patient varied between 0 and 7, mean 3.5. The reference depth was 10 mm from the FIT surface in 37 cases. In two cases a combination of two reference depths, i.e. 5 mm and 10 mm, was used. The average air kerma strength of the HDR source was 29 300 cGy h^{-1} cm^2 (range 16 000–46 300 cGy h^{-1} cm^2) resulting in an average irradiation time of 26 min 28 s (range 9 min 5 s–66 min 2 s). When recalculating the irradiation time using a newly installed HDR source (with a source strength of approximately 40 840 cGy h^{-1} cm^2) an average irradiation time of 17 min 8 s (range 8 min 42 s–32 min 14 s) was found depending on the size of the FIT.

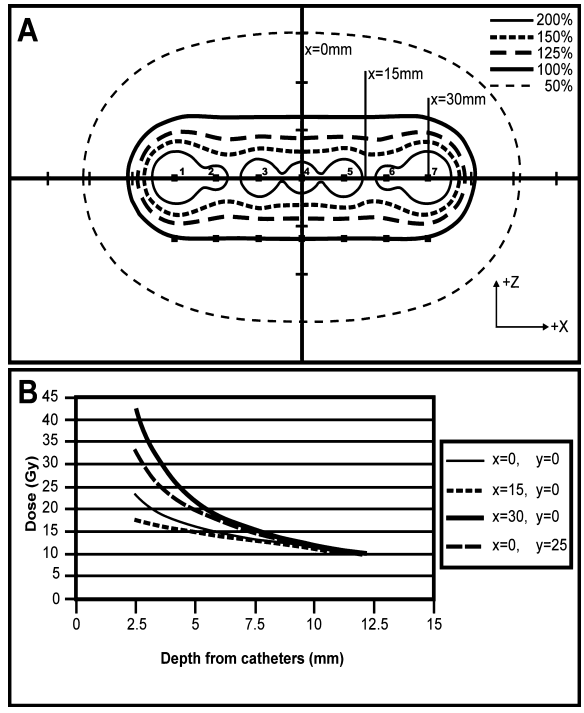

Fig. 3. (A) A plane through the center ($y = 0$ mm) of a FIT containing seven catheters of 6 cm each, with the 200, 150, 125, 100 and 50% isodose lines shown. (B) The depth dose curves along the z-axis for the FIT geometry shown in (A).

When looking at the total procedure time, other factors have to be taken into account too, e.g. preparation of the radiation oncologist, adjustment and positioning of the FIT, treatment planning, preparation for the irradiation, check cable run and removal of the FIT. In literature, wide ranges are found for total irradiation times and procedure times in similar IOBT studies [4,13]. We estimate that the time needed for treatment planning could be reduced by about 45 min when using standard plans.

In four patients, the standard plan was only available because it was not possible to make (isocentric) reconstruction films. For two patients the standard plan was not available as the individual treatment plan was calculated during the application. One patient was excluded from the evaluation because he was treated at two separate sites using a single standard plan. Therefore, the standard plan could be compared to the individual plan in 32 patients. An average treatment dose of 9.55 ± 0.21 Gy was found for the individual treatment plan while the reference dose in the corresponding standard plan was always 10.0 Gy ($P < 0.0001$). The dose in the individual plan was lower than in the standard plan due to the curvature of the FIT and because the dose was prescribed at the convex side of the FIT. The average central dose, i.e. the dose in dose point D3, was 10.03 ± 0.10 Gy in the standard plan and 9.20 ± 0.32 Gy in the individual plan ($P < 0.0001$). In the standard plan, the average dose in the dose points at the corners of the FIT, i.e. D1, D2, D4 and D5, was 10.3 Gy (Fig. 4). The variation of the dose in these points was small as a result of the dwell time optimization. In the individual plan the average dose in these points varied between 10.3 and 10.5 Gy (Fig. 4). In other studies using preplanned dosimetry atlases [1–4,6,11–13], no information is provided on the actual dose delivered at the reference depth. This dose will deviate from the prescribed dose due to the curvature of the applicator. Harrison et al. [3] have investigated the effect of applicator curvature in order to make an extensive atlas of both planar and moderately curved applicators. Kneschaurek et al. [7] also investigated this effect. However, they use equal dwell times and prescribe the dose in the center of the target at the applicator surface. Clinically they do not account for the applicator curvature as the effect is negligible when prescribing at the applicator surface.

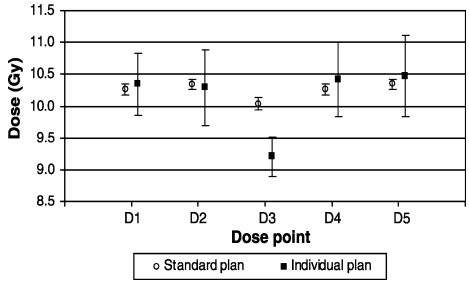

Fig. 4. Dose in dose points D1–D5 averaged over all patients for both the standard plan and the individual plan. For the location of dose points D1–D5 see Fig. 2. Indicated is the average dose for each dose point and the SD.

On a total of 134 clips implanted, 113 clips were located perpendicular under the FIT. In 20 clips (18%) a dose lower than 13.0 Gy was found, indicating a gap of 5 mm or more between these clips and the FIT surface (Fig. 3). Therefore, the reference dose was located at less than 5 mm depth in tissue. For 71 out of 113 clips, the calculated dose was larger than 15.0 Gy which is equivalent to a gap smaller than 5 mm, meaning that locally a dose of 10.0 Gy was delivered to at least 5 mm depth in tissue (Fig. 3). In 22 clips (19%) a dose between 13.0 and 15.0 Gy was calculated. In this case the conclusion on gaps depends on the location of the clip along the FIT (Fig. 3). Unfortunately this evaluation does not give us the dose in the center of the target, i.e. the area most at risk, because the clips were positioned at the edge of the close or positive resection margins. Therefore, we recommend that extra clips should be placed in the center of the target. In that case the same evaluation method could give information on the gap between the target and the FIT surface and thus the depth of the treatment isodose in tissue right in the area most at risk. In general in IOBT literature, information is given on a prescribed dose and a reference depth as a distance from the surface of the applicator [1–4, 6,11–13]. However, the gap between the applicator and the tissue surface determines the actual reference depth in tissue. Due to the curvature of the target area it is not realistic to assume that this gap will always be negligible. The actual dose in tissue should be presented, e.g. by analysing the dose in clips placed centrally at the target surface. Clinical practice will have to prove if the small dose deviations caused by neglecting the FIT curvature in the standard plans and by potential gaps between the FIT and the target influence the clinical outcome.

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Chapter 7

High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer.

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HIGH-DOSE-RATE INTRAOPERATIVE RADIOTHERAPY FOR CLOSE OR POSITIVE MARGINS IN PATIENTS WITH LOCALLY ADVANCED OR RECURRENT RECTAL CANCER

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Purpose: A high-dose-rate intraoperative radiotherapy (HDR-IORT) technique for rectum cancer was developed and the technique, local failure, and survival were analyzed.

Methods and Materials: After the exclusion of metastatic patients, 37 patients were treated with external beam RT, surgery, and HDR-IORT between 1997 and 2000. Primary locally advanced rectum cancer was found in 18 patients and recurrent disease in 19. HDR-IORT was only administered if the resection margins were ≤2 mm. The flexible intraoperative template is a 5-mm-thick pad with 1-cm-spaced parallel catheters. Clips were placed during surgery to define the target area. A dose of 10 Gy was prescribed at a 1 cm depth from the template surface and calculated using standard plans. After treatment, the dose at the clips was calculated using the reconstructed template geometry and the actual treatment dwell times. The median follow-up of surviving patients was 3 years. No patients were lost to follow-up.

Results: Overall, 12 patients (32%) had local recurrence, 5 (14%) of which were in the HDR-IORT field. The 3-year local failure rate for primary tumors and recurrent tumors was 19% and 52%, respectively ($p = 0.0042$). The 3-year local failure rate was 37% for negative margins and 26% for positive margins ($p = 0.51$). A high mean dose at the clip (17.3 Gy) was found. The overall survival was significantly different for primary vs. recurrent tumors, stage, and grade.

Conclusion: Because of the HDR technique, a high dose at the clips was found, with good local control. More out-of-field than in-field failures were seen. The local failure rate was significantly different for primary vs. recurrent disease.

Rectal cancer, Intraoperative radiotherapy, Brachytherapy, Local recurrence.

INTRODUCTION

Primary locally advanced and recurrent rectum tumors are a heterogeneous group of tumors, that include intrapelvic tethered rectum tumors, fixed tumors, enlarged nodes, and metastatic disease.

The risk of developing local recurrence after treatment of a primary tumor increases with increased stage. Treatment of early-stage rectal cancer with preoperative radiotherapy (RT) and total mesorectal excision resulted in a recurrence-free rate of 94% for Stage II and 85% for Stage III tumors (1). More advanced rectal tumors treated with postoperative RT and chemotherapy resulted in a recurrence-free rate of 73% for low-risk patients (T1–T2N+ or T3N0) and 48% for high-risk patients (T3N+ or T4, any N) (2).

Survival after recurrence depends on stage and treatment and this results in a 3-year survival rate varying from 0% to 60% (3–5). The cause of death in these patients is often systemic disease. However, a mortality rate of 16–44% owing to local failure has been reported (6, 7). Fixed or tethered rectum tumors often invade the adjacent organs or pelvic wall and result in an even worse local control and survival. To treat these latter tumors, intraoperative RT (IORT) was developed, because the conventional doses and techniques were insufficient or would lead to a greater incidence of radiation complications.

Two techniques have been in use: intraoperative electron beam radiotherapy (IOERT) and high-dose-rate brachytherapy (HDR-IORT). The advantages of IOERT are the treatment depth to >1 cm with a choice of electron energies and quick delivery of the radiation (<10 min). The flexible template in HDR brachytherapy can treat all surfaces; how-

ever, the treatment times and total procedure times are longer. The steep dose gradient between the target surface and the reference depth is another advantage, because the highest dose is at the area at risk. However, it also limits the use of intraoperative brachytherapy to target depths <0.5–1 cm. Because of these differences, the treatment indications can be different and the results of these two techniques are not completely comparable. IOERT is the most frequently used technique. At least 14 cancer centers (5, 7–19) have reported their results with IOERT, and only 3 have reported their results with HDR-IORT (4, 20, 21).

These three cancer centers used a 1-cm-thick pad as a template and often prescribed a dose of 15 Gy at the surface or at 0.5 cm depth from the pad. We changed this technique to create a high dose at the surface and a steep dose gradient. We developed a 0.5-cm-thick pad and prescribed a dose of 10 Gy at 1 cm depth from the pad surface. In 1997, the HDR-IORT program was started at the Erasmus Medical Center–Daniel Den Hoed Cancer Center. The HDR-IORT was only performed if the resection margins on frozen section analysis were ≤2 mm. Thirty-nine patients with locally advanced primary or locally recurrent rectum cancer had close or positive margins on frozen section analysis and were treated during surgery with HDR-IORT. All patients received preoperative external beam RT (EBRT) to the tumor and pelvis. To evaluate our alternative HDR-IORT technique, an analysis of the local failures was made with regard to the location of the local recurrence.

Table 1. Patient characteristics

	Total	Primary	Recurrent
Patients (*n*)	37	18 (49)	19 (51)
Median follow-up of surviving patients (y)	3.0	2.8	3.3
Stage (*n*)			
T3N0	20 (54)	12 (66)	8 (42)
T4N0	12 (32)	3 (16)	9 (47)
T1-4N1	5 (14)	3 (16)	2 (11)
Margin (*n*)			
Negative	19 (51)	11 (61)	8 (42)
Positive	18 (49)	7 (39)	11 (58)
Gender (*n*)			
Male	25 (70)	12 (66)	13 (74)
Female	12 (30)	6 (34)	6 (26)
Differentiation grade (*n*)			
1	3 (8)	3 (17)	0 (0)
2	29 (78)	14 (78)	15 (79)
3	4 (11)	0 (0)	4 (21)
Unknown	1 (3)	1 (6)	0 (0)
Resection (*n*)			
LAR	1 (3)	0 (0)	1 (5)
APR	21 (57)	15 (83)	6 (31)
ASR	15 (40)	3 (17)	12 (63)
Age (y)			
0–49	9 (24)	6 (33)	3 (16)
50–69	18 (49)	8 (44)	10 (53)
70–79	10 (27)	4 (22)	6 (31)

Abbreviations: LAR = lower anterior resection; APR = abdominoperineal resection; ASR = abdominosacral resection.
Numbers in parentheses are percentages.

METHODS AND MATERIALS

EBRT and surgery

Between 1997 and 2000, 97 patients with locally advanced primary or recurrent rectum tumors were treated with EBRT. After preoperative screening (CT scan of thorax, abdomen, and pelvis), 23 patients were not eligible for surgery because of poor performance status, inoperable tumors, or distant metastases. Of the 74 patients, 39 had close or positive resection margins and were treated with HDR-IORT. During resection, 2 patients were diagnosed with metastasis and were excluded from this analysis. Of the remaining 37 patients, 18 had primary locally advanced rectum cancer and 19 had recurrence. All patients had adenocarcinoma. The patient characteristics are shown in Table 1. Five patients received 25 Gy preoperative EBRT in five fractions and 31 patients received 50 Gy in 25 fractions. One patient with recurrent cancer was previously treated with 50.4 Gy and received for the second RT session an EBRT dose of 30.6 Gy in 1.8-Gy fractions. EBRT was delivered by either a three-field technique, using one posterior and two lateral portals or a four-field box technique. The pelvic field borders were defined as follows: the lateral borders extended 1.5 cm lateral of the bony pelvis, with the cranial border the promontory (L5-S1), and the caudal border was at least below the foramina obturatoria to 2 cm under the anus, depending on the tumor position. The dorsal border encompassed the sacrum, and the anterior border was chosen in such a way that the tumor region was widely covered. None of the patients received pre- or postoperative chemotherapy. Some patients were treated with chemotherapy, if metastases were diagnosed during follow-up. For each patient, the selected type of surgery was based on the fixation and location of the tumor. One low anterior resection, 21 abdominoperineal, and 15 abdominosacral resections were performed. Forty organs or adjacent structures were completely or partially resected (Table 2). The median follow-up of the surviving patients was 2.8 years for the patients with primary tumors and 3.3 years for those with recurrence. No patients were lost to follow-up.

Intraoperative RT

The flexible intraoperative template (FIT) developed at our department is a 5-mm-thick pad made of flexible silicon with

Table 2. Resection of organs

Resection	No (*n*)	Yes (*n*)	Partially (*n*)
Bladder	28	7	2
Prostate	13	7	5
Posterior vaginal wall	5	7	0
Uterus with adnex	8	4	0
Small bowel	33	0	4
Sacrum	22	0	15
Psoas	33	0	4

Table 3. Place of FIT in the pelvis

Place of FIT	*n*
Posterior pelvic wall	1
Posterior and left lateral pelvic wall	8
Posterior and right lateral pelvic wall	9
Posterior, left and right lateral pelvic wall	2
Posterior, left and right lateral, and anterior pelvic wall	0
Anterior pelvic wall	6
Anterior and left lateral pelvic wall	0
Anterior and right lateral pelvic wall	1
Anterior, left and right pelvic wall	4
Left lateral pelvic wall	2
Right lateral pelvic wall	4

Abbreviation: FIT = flexible intraoperative template.

1-cm-spaced parallel source guide tubes running through the center of the template. Before positioning the FIT, three to four surgical clips were placed generously around the target surface. The size and shape of the FIT were then adjusted to the target surface. The FIT, in combination with the catheter positions, was overlaid on a paper template. The paper template was used as input for the treatment planning system (Plato BPS, versions 13.3 and 13.7, Nucletron, The Netherlands). After positioning, the FIT was pressed against the area at risk by filling the pelvis with gauze pads. This was done to avoid the bolus effect from blood and/or surgical fluid during IORT and to push critical organs away from the FIT. Two orthogonal radiographs were taken to see whether the target surface (clips) was encompassed by the applicator. Treatment planning was performed using the standard geometries present in the treatment planning system. A dose of 10 Gy was delivered, usually at 1 cm depth from the applicator surface. The prescription depth was altered to a combination of 0.5 and 1 cm for 1 patient and for another patient to 1 and 2 cm. After treatment, the dose at the clips was calculated using the reconstructed template geometry and the actual treatment times. IORT was only administered if resection margins to the tumor were ≤2 mm, which was judged on frozen section analysis. In the final pathology report, positive margins were found in 18 patients and negative margins in 19 patients. Of these 19 patients, 4 had a resection margin <1 mm. Profuse bleeding or hemodynamic instability during surgery occurred in 7 patients. For these 7 patients, clips were not placed and/or orthogonal radiographs were not taken to reduce the operation time. In total, 129 clips were placed; 112 clips were apparently positioned directly under the FIT and 17 just at the edge of the FIT. The posterior and/or right pelvic walls were most frequently treated with the FIT (Table 3). On average, 8 tubes with a FIT surface of 69 cm^3 were used. The mean radiation time was 27 min (Table 4).

Table 4. IORT characteristics

Characteristic	Median (range)	Mean	SD
Catheters (*n*)	7 (5–14)	8	2.7
FIT surface (cm^2)	60 (24–161)	69	35
Radiation time (min)	21 (10–66)	27	14
Clips (*n*)	4 (2–7)	4	1.1

Abbreviations: IORT = intraoperative radiotherapy; FIT = flexible intraoperative template.

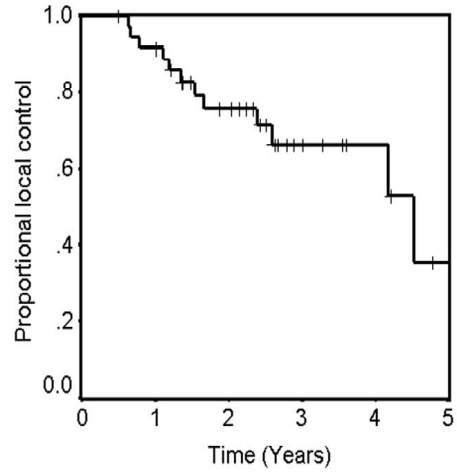

Fig. 1. Overall time to local recurrence.

Definitions and statistical analysis

A local recurrence was defined as tumor regrowth within the EBRT field, and an IORT in-field recurrence was defined as a recurrence completely or partially within the IORT field, as seen on CT or MRI. Local recurrence and distant metastasis were scored until patient death and censored thereafter. Local control and survival curves were calculated using the actuarial Kaplan-Meier method. Comparisons for survival were made using the log–rank test. For other comparisons, the Kruskal-Wallis test was used.

RESULTS

Local control

Twelve patients (33%) developed local recurrence, five recurrences were in the IORT field and seven were out-of-field. One IORT in-field failure (1 of 18 patients; 6%) was seen in the primary locally advanced group and four (4 of 19 patients; 21%) in the recurrence group. Three IORT in-field failures were diagnosed in patients with positive resection margins. The median time to local recurrence was 4.5 years (Fig. 1). The 3-year actuarial failure rate for primary and recurrent tumors was 19% and 52%, respectively ($p = 0.042$, Fig. 2a). For patients with an abdominoperineal resection, the mean time to local failure was 4.2 years; for those with an abdominosacral resection, it was 2.8 years ($p = 0.043$, Fig. 2b). The 3-year local failure rate was 37% for those with negative margins and 26% for those with positive margins ($p = 0.51$, Fig. 2c).

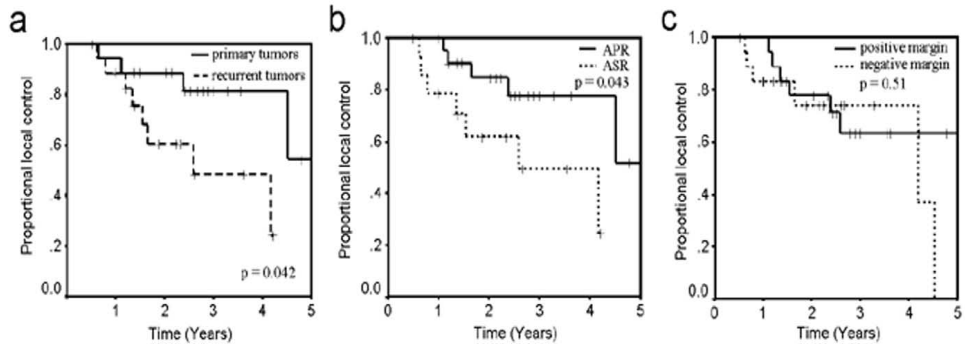

Fig. 2. Time to local recurrence for (a) primary/recurrent tumor, (b) resection type, and (c) resection margin. APR = abdominoperineal resection; ASR = abdominosacral resection.

Out-of-field failures were seen earlier than in-field failures (median time 16 vs. 31 months, $p = 0.077$).

Eight of the 12 local failures were located in the posterior pelvis (Fig. 3). The median distance of the out-of-field recurrence to the area treated with the FIT was 2 cm (range 1–5). Four recurrences were found growing in the sacrum or sacral foramina.

IORT technique

The mean dose to all clips was 15.79 Gy. The mean dose to the 112 clips under the FIT and 17 clips at the edge was 17.27 and 6.05 Gy, respectively. Of the 112 clips, 20 received a dose <13 Gy. A dose <10 Gy was calculated in 4 of these 20. Patients with and without an in-field recurrence had a mean clip dose of 18.00 Gy (range 12.39–24.42) and 17.21 Gy (range 7.15–42.64). Patients with an in-field recurrence had a mean FIT of 82 cm^2 compared with 67 cm^2 for the rest of the patients ($p = 0.63$). No relationship between the size of the FIT, number of resected organs, or topography of local recurrences was found.

Complications

At the start of EBRT, 57% of the patients complained of pain, 32% of irregular stools, 27% of intrapelvic discomfort, and 5% of urinary problems. Postoperatively, many complications were diagnosed, including a delay in wound healing in 46%, abscesses in 16%, leakage at the anastomosis site in 5%, and fistulas in 8%. Plexopathy was found in 14% of the patients. Only 3 patients had late complications: one had chronic diarrhea (Radiation Therapy Oncology Group [RTOG] Grade 1), another had chronic pain in the pelvis (RTOG Grade 2), and the last had radiating pain to the lower extremities (RTOG Grade 2). Sacral necrosis was not found.

Overall survival

The actuarial 5-year survival rate was 38%, with a median survival of 2.8 years (Fig. 4). The 3-year overall survival rate for patients with primary and recurrent tumors was 61% and 34%, respectively (Fig. 5a), and this difference was statistically significant ($p = 0.016$). Two patients

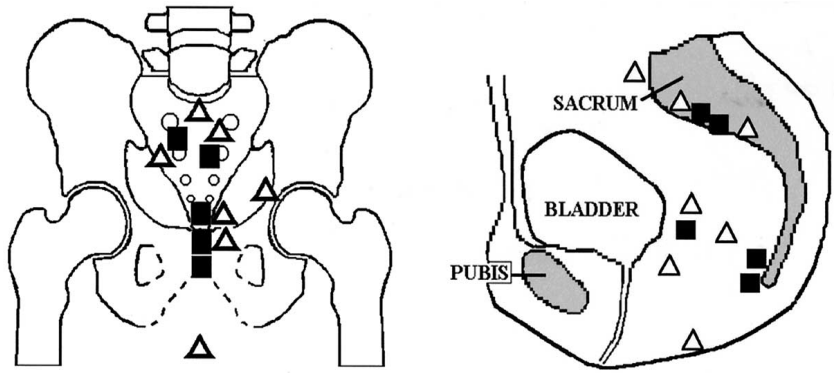

Fig. 3. Place (centrum) of recurrence after IORT. Triangles indicate out-of-field IORT recurrence; squares indicate in-field IORT recurrence.

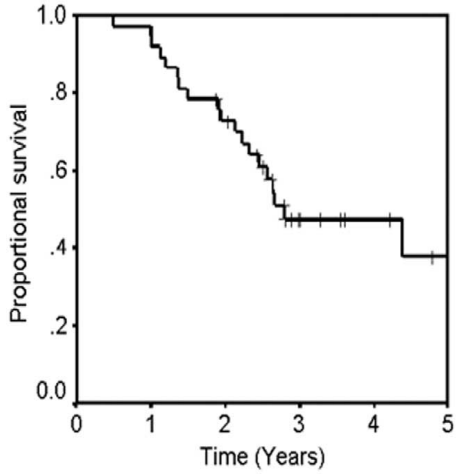

Fig. 4. Overall survival.

(5%) died of local disease and 17 (46%) of metastases. Of these 17 patients, 4 died of peritonitis carcinomatosa. Seventeen patients were still alive, 13 without disease, at last follow-up. The overall survival was significantly different according to stage ($p = 0.0016$) and grade ($p = 0.0012$; (Fig. 5b,c). Patients <50 years had a median survival of 2.2 years compared with 4.4 years for patients >50 ($p = 0.31$).

Distant metastases were found in 18 patients. Several patients had metastasis in >1 organ: 5 patients had metastasis in the liver, 8 in the lung, 4 in the peritoneum, and 7 in other locations. No patients with liver metastasis were rescued by surgery. Metastases were found in 44% and 53% of the patients with primary and recurrent tumors, respectively. The metastasis-free survival was not significantly different between primary and recurrent tumors ($p = 0.45$).

DISCUSSION

The use of IORT for rectal cancer has been reported by at least 17 cancer centers; however, only 3 of these 17 used HDR-IORT. Two centers (4, 22) used a 1-cm-thick pad (HAM applicator) and usually prescribed a dose of 15 Gy at 0.5 cm from the pad surface. The third center also developed a 1-cm-thick pad, but prescribed a dose of 15 Gy to the surface (23). Our technique is different, with the use of a 0.5-cm-thick pad and a prescribed dose of 10 Gy to 1 cm from the pad surface. The advantages of this thinner pad are the increased flexibility and higher surface dose. In combination with dwell time optimization, doses up to 40 Gy to the clips were found at the corners of the template, as verified by the clip doses. According to the dosimetric characteristics of our technique, a clip dose of ≥13 Gy indicated a gap between the FIT and area of risk of <5 mm or a well-positioned template at the clip. An adequate dose at the clip was found in 82%. Although the thinner template is more flexible, we still found a gap of ≥5 mm between the FIT surface and the clips in 18%. However, we only found a dose <10 Gy in 3.5% of the clips, so we may assume that our technique was well carried out. The cause of the in-field failures was not found. No dose difference in patients with and without in-field failures was found.

Although high doses were applied to the surface, only 3 patients complained of late toxicity. Two patients reported chronic radiating pain and one chronic diarrhea. The postoperative toxicity of the integral treatment was high, as reported by many authors (4, 7, 10, 20, 24, 25). Many patients underwent extended resection combined with preoperative RT. It was often difficult to assign a particular complication as being a result of surgery or RT. Huber *et al.* (21) found a significant greater complication rate in patients treated with HDR-IORT, Hashiguchi *et al.* (7) described a trend, and Noyes *et al.* (26) found no difference in their combined analysis of 220 patients.

Five of the 12 local recurrences were IORT in-field recurrences. Because more out-of-field failures were found than in-field failures, it can be assumed that IORT is an effective treatment. However, a randomized trial is needed to confirm this. Nine studies (7, 8, 10, 11, 19–21, 24) also reported the site of recurrence. For primary tumors and recurrent tumors, 17% and 49% of the local failures were in

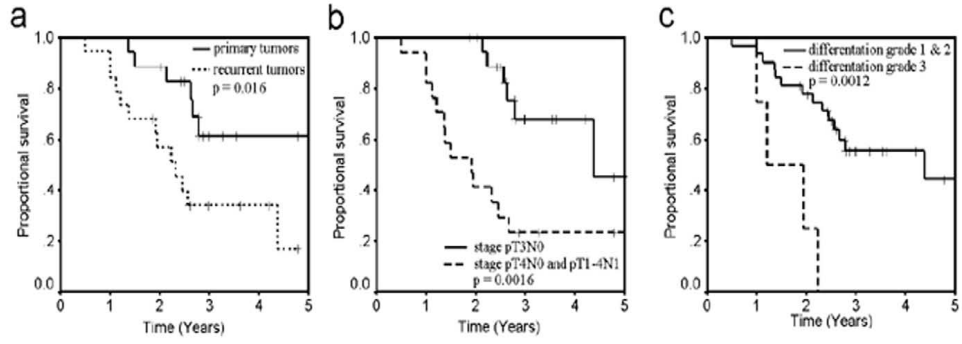

Fig. 5. Survival according to (a) primary/recurrent tumor, (b) stage, and (c) grade.

Table 5. Number of in-field failures according to author and technique

Tumor	Author	In-field failure	Total failures	%	Technique
Primary	Huber *et al.* (21)	0	3	0	HDR-IORT
	Gunderson *et al.* (11)	1	8	13	IOERT
	Calvo *et al.* (18)	1	3	30	IOERT
	Present study	1	4	25	HDR-IORT
	Total	3	18	17	
Recurrent	Bussieres *et al.* (8)	9	21	50	IOERT
	Pezner *et al.* (19)	8	13	43	IOERT
	Haddock *et al.* (24)	12	18	62	IOERT
	Eble *et al.* (10)	4	9	67	IOERT
	Hashiguchi *et al.* (7)	1	9	44	IOERT
	Nag *et al.* (20)	7	14	11	HDR-IORT
	Present study	4	8	50	HDR-IORT
	Total	45	92	49	

Abbreviations: HDR-IORT = high-dose-rate intraoperative radiotherapy; IOERT = intraoperative electron radiotherapy.

field, respectively (Table 5). Because out-of-field failures were more frequent than in-field failures, the question is raised of how the occurrence of these out-of-field failures can be reduced. Our out-of-field failures were within 5 cm of the IORT area and could be included by extending the FIT. However, four local failures were located in the sacrum or sacral foramina. HDR-IORT probably could not have prevented these local failures, because they were situated close to the nerves. The question arises whether higher doses or larger FITs could have prevented the other recurrences, without increasing the toxicity.

As opposed to other reports, we did not find that close or positive margins resulted in differences in the local recurrence rate ($p = 0.51$). Many authors (4, 8, 11, 14, 22, 27) have reported a statistically significant difference in the local failure rate according to the resection margin. However, they usually compared negative margins with microscopically positive margins or gross total resection margins and not close margins (<2 mm) with positive margins. Extended resections, such as abdominosacral resections and total and partial organ resections, were often performed. Patients who underwent abdominosacral resection had a significantly different greater local failure rate than did patients with abdominoperineal resection ($p = 0.043$). This can be explained by the larger amount of disease or more aggressive character of the tumor when abdominosacral resections were necessary.

Of our patients, 33% had local failure. For primary locally advanced tumors, the 3-year local failure rate was 19%. Other authors found a comparable 3-year local failure rate of 16% and 23% (1, 2). Harrison *et al.* (27) reported a 2-year local failure rate of 19%. Recurrent tumors had a 3-year local failure rate of 52%. The reported 3-year local failure rate varies between 53% and 79% (4, 6, 8, 19, 22). A statistically significant difference ($p = 0.042$) in the time to local failure between the primary and recurrent tumors was found, but has not been previously reported.

Patients with primary tumors survived longer than patients with recurrence ($p = 0.016$). The 2-, 3-, and 5-year overall survival rate for patients with primary tumors was 89%, 61%, and 61%, respectively. Harrison *et al.* (27) reported a 2-year survival rate of 69%, and other authors (11, 14, 21) reported a 3- and 5-year survival rate of 55% and 45%, respectively. In this study, patients with recurrent tumors had a 3-year overall survival rate of 34%. Most authors (4, 5, 7, 8, 22) reported a 3-year survival rate of 30–50%; however, other authors (10, 24) found a 3-year survival rate of 12% and 64%. Patients with pathologic proven positive nodes, T4 tumors, or Grade 3 differentiation had a statistically significant lower survival. Complete or partial resection (4–7, 10, 11, 22, 27), the use of IORT plus EBRT (4, 22), concomitant chemoradiotherapy (11), and larger irradiated target areas (20) were found to be other significant prognostic factors by other authors.

CONCLUSION

The HDR-IORT technique for rectal cancer resulted in a high local control rate. Because of the calculation of the dose to the clips, we can conclude that our technique was well carried out. The local failure rate for those with positive margins compared with those with close margins did not differ. Because IORT out-of-field recurrences were common, a greater EBRT dose, a larger FIT area, or the addition of concurrent chemotherapy may be of benefit for these patients. Patients with primary tumors had significantly greater local control and survival than did patients with recurrent tumors. Other prognostic factors for survival were stage and differentiation grade.

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Chapter 8

Summary, general conclusions and future perspectives.

Summary

Diarrhea is the major side effect of (neo-)adjuvant radiation therapy for rectal cancer. Although pre-operative radiotherapy diminished the bowel toxicity, it is still a clinical problem. Conformal radiotherapy techniques can be used to reduce the bowel toxicity. Dedicated 3-D conformal radiotherapy planning for prostate cancer resulted in a low acute toxicity (chapter two). Sixty-four patients received definitive treatment for prostate cancer and were conformal treated with 72 to 80 Gy. No grade 3-4 acute, urinary or rectal toxicity was reported. Acute grade 2 rectal complications were seen in 10% of the patients treated to ≤72 Gy and in 18% of the patients treated to ≥76 Gy. Acute rectal symptoms were dose-volume related: patients without diarrhea had a mean rectal volume receiving a dose of 70 Gy or more of 8.5 cm^3, however, patients with RTOG 2 diarrhea had a volume of 16.5 cm^3 ($p=0.042$). Only 10% of the patients had grade 1-2 late rectal and bladder complications. These results demonstrate that rectal and bladder toxicity is low after dedicated 3-dimensional conformal treatment planning. Accurate knowledge of internal organ motion of the main organ at risk (small bowel) and clinical target volume (CTV) for rectal cancer is mandatory.

Chapter three describes the amount and movement of small bowel inside the pelvis in pre-operative and postoperative patients with rectal cancer. The position of any volume of small bowel in preoperatively treated patients was significantly more anterior ($p\leq0.01$) with less volume ($p\leq0.04$) in the pelvis than in postoperatively treated patients. This anatomical difference explains why the preoperatively irradiated patients in 2 randomised studies (Uppsala, CAO/ARO/AIO-94) had less toxicity compared to the postoperative patients. Blocking all or a part of the small bowel inside the radiation fields without knowing the CTV definition could lead to inappropriate treatment (i.e. geographical miss).

In chapter 4, the internal motion of the CTV is calculated to create the planning target volume (PTV). Movement of the CTV in all dimensions was measured. The largest difference in the CTV occurred 10 cm cranial from the anus, (standard deviation of 1 cm). Bladder filling displaced the anterior border of the CTV with 7 mm on average. Other borders of the CTV were based on muscle, bone, or major blood vessels and were stable. Modification of the CTV in order to design a PTV can be unequal. This CTV was also

compared with the conventional 3-field technique and as a consequence of this analysis, we suggested to omit the block positioned on the half of the femur because it can shield a part of the CTV.

The reduction of irradiated small bowel volume was investigated with intensity modulated conformal planning (chapter 5) compared to 3-D conformal planning. The 3-D conformal planning is not capable to conform the dose around the CTV with sharp gradients because the CTV has a large complex shape. IMRT divides each beam into numerous small (pencil) beams, and with these (pencil) beams intensity maps are created that result in a homogeneous conformal irradiated PTV and CTV with sharp gradients towards the organs at risk. For the conventional planning, the mean volume small bowel irradiated $\geq$ 95% was 112 cm^3 and for the IMRT plan 42 cm^3. The amount of motion for the irradiated small bowel was much larger for the IMRT planning than for the conventional treatment plan. The use of IMRT can lead to a clinically meaningful reduction in the volume of small bowel irradiated. However, we are in need of clinical results that will prove this hypothesis (evidence based medicine).

High-dose-rate intraoperative brachytherapy is another conformal radiotherapy technique and is described in chapter 6. It is a simple and adequate technique for locally advanced rectal tumors because small bowel and bladder can easily be pulled away from the target. To define the target area, clips are placed during the surgery and a 5-mm-thick flexible intraoperative template (FIT) with 1-cm spaced parallel catheters is used to cover the target area. To reduce the procedure time, treatment planning is performed using standard plans that neglect the curvature of the FIT. We calculated the individual treatment plan, based on the real geometry of the FIT, and the dose at clips placed during surgery. A mean treatment dose of 9.55 $\pm$ 0.21 Gy was actually found for the individual plan, instead of the prescribed 10 Gy ($p<0.0001$) at 1 cm. The largest deviation was found in the centre of the FIT. In 18% of the clips, the dose was smaller than 13.0 Gy indicating that locally the gap was larger than 5 mm. The rest of the clips received a dose higher than 13 Gy. These results indicate that our technique satisfies our quality assurance requirements.

Chapter 7 reports the local failure rate, site of local recurrence and survival rate of patients treated with the high-dose-rate intraoperative (HDR-IORT) technique for rectal cancer. After exclusion of metastatic patients, 37 patients with primary locally advanced rectum cancer or recurrent disease were treated with external beam radiotherapy, surgery and

HDR-IORT. HDR-IORT was only administered if resection margins were ≤ 2 mm. A dose of 10 Gy was prescribed at 1 cm depth from the template surface and calculated using standard plans. The median follow up of surviving patients was 3 years. Overall, 12 patients (32%) had a local recurrence, five (14%) were HDR-IORT in-field. The local failure rate for recurrent tumors was significantly poorer than for primary tumors. The 3-year local failure rate was 37% for negative margins and 26% for positive margins (p=0.51). The overall survival was significantly different for primary/recurrent tumors, stage and grade. In summary, HDR-IORT can be considered as an effective treatment. Reasonable control rates can be obtained in the relatively poor subset of patients (with irradical resection margins). Also testifying to this, more out-field than in-field failures were seen and no difference in local failure rate in patients with positive or negative resection margins was found.

General conclusion and future perspectives

Diarrhea in the treatment of locally advanced rectal cancer is still a problem. Three-dimensional conformal treatment planning for prostate cancer enabled us to increase the dose without increasing the toxicity. Pre-operatively treated patients have less small bowel in the pelvis and have for that reason less toxicity. With the calculated movement of the CTV, we are able to define a non-uniform PTV that can be irradiated using 3-D conformal radiotherapy techniques. However, as to be expected by the complex shape of the PTV for rectal cancer, the gain with 3-D conformal radiotherapy for rectal cancer is small. With IMRT, we are better able to shape the radiotherapy dose to the PTV and less radiation dose is to be received by the small bowel. Clinical results will have to prove if the toxicity profile of patients treated with IMRT is in fact different, i.e. lower. Intraoperative radiotherapy (IORT) is another technique to give a high dose to the target, while the organs at risk are spared to a large extent. With this technique, patients with positive resection margins had an equal local failure rate as the patients with close resection margins and also more out-field failures than in-field failures were seen. These results indicate that IORT is an effective therapy. Unfortunately, no randomised results are available. A multi-institutional randomised trial allow for a better answer to this question.

Samenvatting, conclusie en toekomstperspectieven

Samenvatting

Diarree is de voornaamste complicatie van de neo-adjuvante radiotherapeutische behandeling van rectumkanker (hoofdstuk 1). Alhoewel pre-operative radiotherapie de darmtoxiciteit vermindert, is het nog steeds een klinisch probleem. Conformele radiotherapietechnieken kunnen gebruikt worden om de darmtoxiciteit te verminderen. Toegewijde drie-dimensionele conformele radiotherapieplanning voor de behandeling van prostaatkanker resulteerde in een lage darmtoxiciteit (hoofdstuk 2). Vierenzestig patiënten met prostaatkanker werden behandeld met conformele radiotherapie tot een totale dosis van 72 tot 80 Gy. Geen acute graad 3 of 4 blaas- of rectumtoxiciteit werd vastgesteld. Acute graad 2 rectumcomplicaties werden gezien in 10% van de patiënten behandeld tot een dosis van ≤72 Gy en in 18% van de patiënten behandeld tot ≥76 Gy. Acute rectumklachten waren dosis-volume gerelateerd: patiënten zonder diarree hadden een gemiddeld rectumvolume van 8.5 cm^3 dat een dosis van 70 Gy of meer kreeg. Patiënten met een RTOG graad 2 diarree hadden een gemiddeld rectumvolume van 16.5 cm^3 ($p=0.042$). Late graad 1-2 blaas- en rectumcomplicaties werden geregistreerd in 10% van de patiënten. Deze resultaten tonen aan dat de blaas- en rectumtoxiciteit laag is na toegewijde drie-dimensionele conformele radiotherapieplanning.

Nauwkeurige kennis van de beweging van het voornaamste risico-orgaan (dunne darm) en het klinische doelvolume (CTV) bij rectumkanker zijn noodzakelijk om drie-dimensionele conformele radiotherapieplanning voor rectumkanker toe te passen.

Hoofdstuk 3 beschrijft het volume en de beweging van de dunne darm in het bekken bij pre- en postoperatieve patiënten met rectumkanker. De dunne darmen van pre-operatief bestraalde patiënten lagen in het bekken significant meer anterior ($p\leq0.01$) met minder volume ($p\leq0.04$) in vergelijking met postoperatief behandelde patiënten. Dit anatomische verschil verklaart waarom 2 gerandomiseerde studies (Upsalla, CAO/ARO/AIO-94) minder toxiciteit bij pre-operatief geïrradiëerde patiënten aantoonden in vergelijking met postoperatief geïrradiëerde patiënten. Het compleet of gedeeltelijk afschermen van de dunne darmen met blokken kan wel de toxiciteit verminderen, maar kan ook leiden tot een onefficiënte behandeling door het niet bestralen van een deel van het doelvolume, indien het klinische doelvolume (CTV) en zijn beweging ervan niet gekend zijn. In hoofdstuk 4 wordt de interne beweging van het CTV berekend om dan met die kennis een

planningsdoelvolume (PTV) te creëren. Beweging van het CTV werd in alle richtingen gemeten. De grootste beweging van het CTV kwam 10 cm craniaal van de anus voor (standaarddeviatie: 1 cm). Blaasvulling verschoof de anterieure grens van het CTV met gemiddeld 7 mm. Andere grenzen van het CTV worden bepaald door spier, bot of grote bloedvaten en vertonen geen beweging. Aanpassingen om van het CTV een PTV te maken, kunnen dus in verschillende richtingen met een ongelijke uitbreiding gebeuren. Het CTV werd ook vergeleken met het doelvolume van de conventionele 3-velden techniek. Concluderend uit dit onderzoek raden wij aan om een blok geplaatst op de helft van de femur weg te laten omdat dit het CTV kan afschermen. Hierdoor ontstaat er een onefficiënte behandeling.

De volumereductie van bestraalde dunne darmen werd onderzocht met intensiteitsgemoduleerde radiotherapie (IMRT) en vergeleken met de conventionele 3-velden techniek (hoofdstuk 5). IMRT deelt elke bestralingsbundel op in talrijke kleine (potlood) bundels en met deze (potlood) bundels worden intensiteitsmappen gecreëerd die resulteren in een homogene conformele bestraling van het CTV en PTV, met scherpe gradiënten naar de risico-organen. Met de conventionele planning was het volume dunne darm, bestraald $\geq$ 95%, 112 cm^3 en voor de IMRT planning 42 cm^3. De beweging van het volume bestraalde dunne darm was veel groter voor IMRT dan voor conventionele planning. Het gebruik van IMRT kan leiden tot een klinisch relevante vermindering van het volume bestraalde dunne darm. We hebben evenwel klinische studies nodig om deze hypothese te bevestigen.

Intra-operatieve HDR brachytherapie is een andere techniek in de conformele radiotherapie en is beschreven in hoofdstuk 6. Het is een eenvoudige en adequate techniek voor lokaal gevorderde rectumtumoren omdat tijdens de operatie de darmen en de blaas gemakkelijk van het doelvolume kunnen weggehouden worden. Om het doelvolume te kunnen aflijnen werden er tijdens de operatie nietjes geplaatst. Een 5-mm dik en buigzaam matje met parallelle holle buisjes werd op het doelvolume gelegd. In de holle buisjes kwam een radioactieve bron die via de computer gestuurd werd. Om de proceduretijd te verminderen, werd de planning gemaakt via een standaardplan dat geen rekening hield met de kromming van het matje. Op basis van de reële geometrie van het matje werd een nieuwe planning gemaakt en werd de dosis in de nietjes berekend. Een gemiddelde dosis van 9.55 $\pm$ 0.21 Gy werd gevonden met de nieuwe planning in plaats van de

voorgeschreven dosis van 10 Gy op 1cm ($p<0.0001$). De grootste afwijking werd gevonden in het centrum van het matje. In 18% van de nietjes was de dosis kleiner dan 13 Gy, wijzend op een minder goed aangedrukt matje. De overige nietjes kregen een dosis hoger dan 13 Gy. Deze resultaten tonen aan dat de techniek voldoet aan onze kwaliteitseisen.

Hoofdstuk 7 beschrijft het locale falen, de plaats van het locale falen en de overleving van patiënten met rectumkanker die behandeld zijn met intra-operatieve brachytherapie. Na exclusie van de gemetastaseerde patiënten, werden 37 patiënten met een primaire locaal gevorderde rectumtumor of met een locaal recidief behandeld met externe radiotherapie, chirurgie en intra-operatieve brachytherapie. Intra-operatieve brachytherapie werd alleen toegepast indien de resectiemarge ≤ 2 mm was. Een dosis van 10 Gy werd voorgeschreven op een diepte van 1 cm, berekend vanaf het oppervlak van het matje en gebruik makend van standaardplannen. De mediane opvolgperiode was 3 jaar. Twaalf patiënten (32%) ontwikkelden een locaal recidief, dat bij 5 patiënten (14%) gelegen was in het intra-operatieve bestralingsveld. Het locale falen kwam significant meer voor bij patiënten met een locaal recidief dan bij patiënten met een primaire tumor. De kans op een locaal recidief na 3 jaar was 37% voor patiënten met een negatief snijvlak en 26% voor patiënten met een positief snijvlak ($p=0.51$). De overleving was significant verschillend voor primaire/recidieverende tumoren, tumor stadium en graad. Buiten het intra-operatieve bestralingsveld werden meer locale recidieven gevonden dan in het intra-operatieve bestralingsveld. Ook werd geen verschil in het locale falen gevonden tussen patiënten met positieve en negatieve snijvlakken. Dus goede locale controle met intra-operatieve brachytherapie kan behaald worden in een kleine groep van patiënten met slechte prognose.

Conclusie en toekomstperspectieven

Diarree in de behandeling van lokaal gevorderd rectumkanker is nog steeds een probleem. Drie-dimensionele conformele radiotherapieplanning voor prostaatkanker stelt ons in staat om de radiotherapiedosis te verhogen zonder de toxiciteit te verhogen. Pre-operatief behandelde patiënten hebben minder dunne darmen in het bekken en daardoor minder toxiciteit. Met de berekende beweging van het klinisch doelvolume zijn we in staat om een planningsvolume te maken met ongelijke marges. Dit planningsvolume kan op zijn beurt gebruikt worden in de drie-dimensionele conformele radiotherapie. Door de ingewikkelde vorm van het planningsvolume was de winst met de drie-dimensionele conformele radiotherapieplanning echter gering en werd intensiteitsgemoduleerde radiotherapie toegepast. Met intensiteitsgemoduleerde radiotherapie zijn we beter in staat om de radiotherapiedosis te richten op het PTV en minder op de darmen. Klinische resultaten zullen in de toekomst moeten bewijzen dat de neveneffecten met een intensiteitsgemoduleerde radiotherapiebehandeling minder voorkomen. Intra-operatieve radiotherapie is een andere techniek om een hoge dosis op het doelvolume te geven zonder de risico-organen te bestralen. Met deze techniek hadden patiënten met een positief snijvlak in vergelijking met patiënten met een negatief snijvlak een gelijk aantal locale recidieven en werden meer locale recidieven buiten het intra-operatieve bestralingsveld geconstateerd dan in het bestralingsveld. Deze resultaten wijzen erop dat intra-operatieve radiotherapie een effectieve techniek is, alhoewel er geen gerandomiseerde studies bestaan. Een gerandomiseerde studie lopende in meerdere kankercentra zou een beter antwoord geven op deze vraag.

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Curriculum vitae

Joost Nuyttens werd geboren op 16 oktober 1969 te Kortrijk (België). In juni 1987 behaalde hij het getuigschrift Hoger Algemeen Secundair Onderwijs / Latijn Wetenschappen aan het Sint-Amands college te Kortrijk.

In 1987 startte hij de studie diergeneeskundige aan de Universiteit Gent. Hij behaalde het diploma van dierenarts in 1993 en kreeg de VDV-prijs (Vlaamse Dierenartsen Vereniging) voor het eindwerk: Morfologische studie van de musculatuur van het derde ooglid bij de kat. In 1990 startte hij de studie geneeskunde aan de Universiteit Gent en behaalde in 1996 het diploma van arts.

Aansluitend startte hij de opleiding tot radiotherapeut op de afdeling radiotherapie van het Universitair Ziekenhuis Gent onder leiding van Prof. Dr. W. De Neve. Om de opleiding in de Verenigde Staten van Amerika verder te kunnen zetten werden de ECFMG (The Educational Commission for Foreign Medical Graduates) diplomas Step I en II behaald in 1997.

De opleiding tot radiotherapeut werd van september 1998 tot en met augustus 1999 verder gezet op de afdeling radiotherapie van de Medical University of South Carolina (MUSC) onder leiding van Prof. Dr. A.T. Turrisi, III. De abstract en presentatie "The pregnant patient treated with radiotherapy: 2 cases and a review of the literature for the biological effects" werd op het jaarlijkse Radiological Society of North America (RSNA) congres te Chicago bekroond door de Research Trainee Prize of the RSNA.

Van september 1999 tot en met juli 2000 werd de opleiding radiotherapie voortgezet op de afdeling radiotherapie van het William Beaumont Ziekenhuis te Detroit onder leiding van Dr. A. Martinez.

Daarna werd de opleiding radiotherapie beëindigd op de afdeling radiotherapie van het Universitair Ziekenhuis Gent in juli 2001.

Sinds september 2001 is hij werkzaam als radiotherapeut-oncoloog in het Erasmus MC - Daniel den Hoed Oncologisch Centrum.

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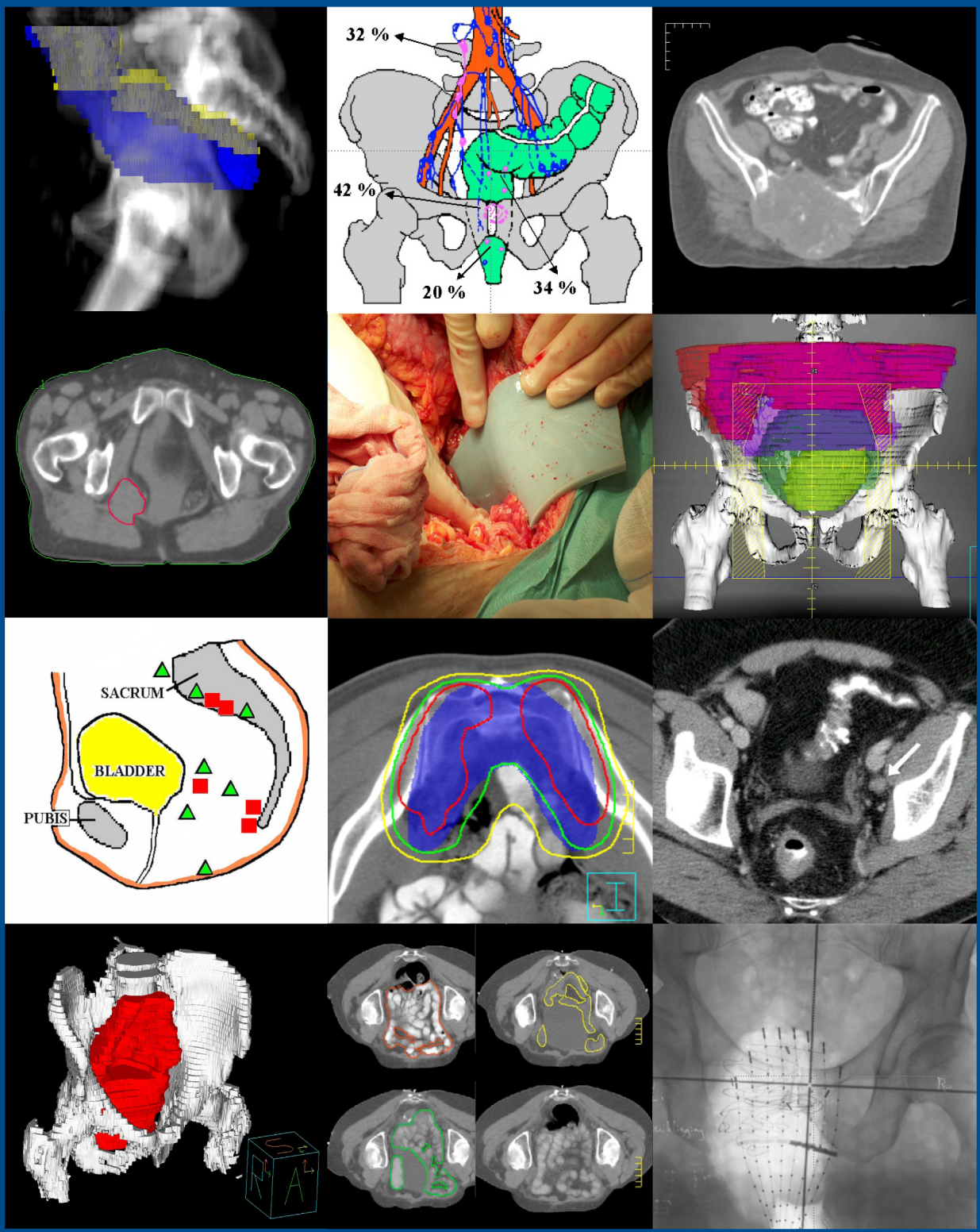
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