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Original article

Patterns of local recurrence in locally advanced rectal cancer after intra-operative radiotherapy containing multimodality treatment

Miranda Kusters [a,b], Fabian A. Holman [b], Hendrik Martijn [c], Grard A. Nieuwenhuijzen [b], Geert-Jan Creemers [d], Alette W. Daniels-Gooszen [e], Hetty A. van den Berg [c], Adriaan J. van den Brule [f], Cornelis J.H. van de Velde [a], Harm J.T. Rutten [b,*]

[a] Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Surgery, Catharina Hospital, Eindhoven, The Netherlands
[c] Department of Radiotherapy, Catharina Hospital, Eindhoven, The Netherlands
[d] Department of Oncology, Catharina Hospital, Eindhoven, The Netherlands
[e] Department of Radiology, Catharina Hospital, Eindhoven, The Netherlands
[f] Laboratory for Pathology, Catharina Hospital, Eindhoven, The Netherlands

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ABSTRACT

Background and purpose: The purpose of this study is to analyze the patterns of local recurrence (LR) after intra-operative radiotherapy (IORT) containing multimodality treatment of locally advanced rectal carcinoma (LARC).

Methods and materials: Two hundred and ninety patients with LARC who underwent multimodality treatment between 1994 and 2006 were studied. For patients who developed LR, the subsite was classified into presacral, postero-lateral, lateral, anterior, anastomotic or perineal. Patient and treatment characteristics were related to subsite of LR.

Results: After 5 years, 34 patients (13.2%) developed LR. The most prominent subsite of LR was the presacral subsite. 47% of the local recurrences occurred outside the IORT field. Most recurrences developed when IORT was given dorsally, while least occurred when IORT was given ventrally. Especially after dorsal IORT a high amount of infield recurrences were observed (6 of 8; 75%). In multi-variate analysis tumor distance of more than 5 cm from the anal verge and a positive circumferential margin were associated with presacral local recurrence.

Conclusions: Multimodality treatment is effective in the prevention of local recurrence in LARC. IORT application to the area most at risk is feasible and seems effective in the prevention of local recurrence. Dorsal tumor location results in unfavourable oncologic results.

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In the treatment of locally advanced rectal carcinoma (LARC) a long course of neoadjuvant (chemo)radiotherapy is currently considered the best regimen in order to achieve downstaging for a subsequent radical resection [1–3]. Still, local recurrence rates vary between 6% and 33%, depending on tumor stage and type of treatment [1–3]. Intra-operative radiotherapy (IORT) administered as a boost after preoperative external beam radiotherapy (EBRT), is feasible in the multimodality treatment of LARC without increased tissue toxicity [4–6]. Historical studies suggest that IORT may improve local control and survival [4,7,8], probably by sterilizing microscopic residual tumor particles in a specific area. Most institutions using IORT-containing multimodality treatment regimens, deliver the boost to the presacral space, because this is the area considered most at risk [8] and because other areas are difficult to cover with the applicator [9]. In two studies reporting on patterns of local recurrence after IORT, 59–67% of the local relapse showed to develop outside the presacral IORT radiation field [8,9].

The purpose of this study is to analyze the patterns of local recurrence in the patients operated in the Catharina Hospital, a national referral center for the treatment of LARC. In this clinic IORT-containing multimodality treatment is used since 1994, with the delivery of the boost to the area mostly considered at risk on the basis of radiological and intra-operative findings. The main question of this study is whether this approach leads to less outfield local recurrences. Furthermore, the risk factors for local recurrence, distant metastases and cancer-specific death were analyzed.

* Corresponding author. Address: Department of Surgery, Catharina Hospital Eindhoven, Postbox 1350, 5602 ZA Eindhoven, The Netherlands.
E-mail address: harm.rutten@cze.nl (H.J.T. Rutten).

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Methods and materials

Patients and treatment

From 1994 to 2006, 364 patients with primary locally advanced rectal carcinoma (LARC) were referred to the Catharina Hospital for multimodality treatment. Locally advanced rectal carcinoma was defined as a tumor infiltrating through the mesorectal fascia (clinical T4 stage) or within proximity of less than 2 mm (clinical T3+ stage) on CT or MRI. The treatment consisted of neoadjuvant (chemo)radiotherapy, extended surgery and intra-operative radiotherapy (IORT) to the area most at risk for residual tumor. Details on this strategy have been described before [4,10,11]. In the preoperative work-up or at the resection laparotomy distant metastases were found in 74 patients. These patients were excluded from this study, leaving 290 patients for analyses. Median follow-up time for surviving patients was 45 months (range 15–157).

The preoperative EBRT dose was typically in the range of 45–50.4 Gy in fractions of 1.8 Gy. The IORT dose was typically in range from 10 to 17.5 Gy. The energies ranged from 8 to 12 MEV. The most used diameter of the applicator was 6 cm. Forty-eight of these patients did not receive IORT: because of massive blood loss during the operation (2 patients), 44 patients had no area at risk after resection and two patients were expected to have too much morbidity from IORT.

Over the years the neoadjuvant and adjuvant treatment schemes have changed within the institute. In the first years only a long course of neoadjuvant radiotherapy was given and since 1999 chemotherapy was added to the radiotherapy scheme. Adjuvant chemotherapy was gradually accepted, but a substantial number of patients had no adjuvant treatment.

Definitions

As mentioned before, clinical T-stage was assessed on preoperative CT or MRI. Because CT is not considered accurate in the assessment of clinical N-stage and not all patients underwent MR imaging, clinical N-stage was not reported in this study. Lymph node positivity was defined as positive lymph nodes in the pathologic specimen. Point reduction was defined as the difference in T-stage in the clinical and the pathological assessment. Any downstaging was defined as a point reduction of 1 or greater. A complete remission was achieved when no tumor cells were found in the pathologic specimen (Stage 0).

Radicality of the resection was defined as follows: a R0 resection had free surgical margins, a R1 resection had focally microscopically involved margins, and a R2 resection was defined as more than 1 cm^2 involved margins. A R+ resection was defined as a R1 or R2 resection.

Methods

As the Catharina Hospital is a national referral center for patients with LARC, data on the primary tumor were retrieved from the referring hospitals. After LARC treatment most patients returned to their initial hospital for follow-up. By contacting these hospitals, follow-up data could be completed in all patients.

Patients with a local recurrence (LR), defined as any rectal cancer recurrence in the small pelvis, were identified. LR was diagnosed clinically, radiologically or histologically. When patients had developed local recurrence, available images at the time of discovery of the LR were retrieved.

Examining the images and data, the location of the recurrence was classified into one of the following subsites: (1) Presacral: predominantly midline, in contact with the sacral bone, (2) Posterolateral: laterally located, near to or invading the piriform muscle, in contact with the sacral bone, (3) Lateral: laterally located, in association with anterior organs or along the iliac vessels or in the obturator lymph node compartment, (4) Anterior: predominantly midline, involving bladder, uterus, vagina, seminal vesicles or prostate, (5) Anastomotic: midline, after low anterior resection, low Hartmann procedure or local excision, at the staple line, (6) Perineal: midline, perineum or anal sphincter complex with surrounding perianal and ischiorectal space.

Consequently, the site of local relapse was related to the target site of IORT. If there was partial or complete overlap between the IORT-site and the LR-site, the local recurrence was considered infield. When there was no overlap, the local recurrence site was defined as outfield.

Statistical analysis

Statistical analysis was performed using SPSS package (SPSS 16.0 for Windows; SPSS Inc, Chicago, IL). T-tests and chi-square tests were used to compare individual variables. Cancer-specific survival was defined as the time between surgery and death caused by cancer. Survival was estimated using the Kaplan–Meier method. Differences were assessed using the Log-Rank test. p-values were two-sided and considered statistically significant at a value of 0.05 or less. For LR, cumulative incidences were calculated accounting for death as competing risk [12]. Similarly, cumulative incidences were calculated for subsite of LR, with death and other types of LR as competing risks, and for cancer-specific survival, with death due to other causes as competing risk. Multi-variate analyses of local recurrence and overall survival were performed by first testing the effect of covariates in a uni-variate Cox regression. Covariates with trend-significant effects (p-value < 0.10) were then selected for multi-variate Cox regression. The following variables were studied for local recurrence rate, metastasis free survival and cancer-specific survival: age, gender, tumor distance from anal verge, clinical T-stage, preoperative (chemo)radiotherapy, type of surgery, any downstaging, N-stage, margin involvement and postoperative chemotherapy.

Results

Patient, treatment and pathologic characteristics

Patient, treatment and pathologic characteristics are listed in Tables 1 and 2. Neoadjuvant treatment was not significantly dependent on clinical T-stage ($p = 0.44$). Downstaging occurred in 39% of the patients after preoperative radiotherapy and in 61% after chemoradiotherapy ($p < 0.001$). A complete remission was observed in 3% and 13% after radiotherapy and chemoradiotherapy, respectively ($p = 0.02$). Adjuvant chemotherapy had no correlation with postoperative stage ($p = 0.19$), nor margin positivity ($p = 0.39$).

Patterns of local recurrence

After 5 years 34 of the 290 patients developed local recurrence (13.2%). Five-year local recurrence rate was 7.6% after R0 resections, compared to 37.9% after R+ resections ($p < 0.001$). Table 3 shows the patterns of local recurrence in all patients and in only R0 patients. The most prominent site of local recurrence was the presacral subsite (five-year local recurrence rate 5.1%). Selecting only R0 patients, presacral local recurrences were still the most common local recurrence types.

Thirty two of the 34 local recurrences occurred after IORT. Seventeen of these 32 (53%) were located in the IORT field; 15 were

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Table 1
Patient and treatment characteristics.

	No. of patients (n = 290)
Median age, years (range)	63 (36–86)
Gender	
Male	179 (62)
Female	111 (38)
Tumor distance from anal verge	
5 cm or less	154 (53)
More than 5 cm	136 (47)
Clinical T-stage	
T3+	113 (39)
T4	177 (61)
Preoperative (chemo)radiotherapy	
Only radiotherapy	86 (30)
Chemoradiotherapy	204 (70)
Type of surgery	
Low anterior resection	132 (45)
Abdominoperineal resection	138 (48)
Abdominotranssacral resection	12 (4)
Exenteration	8 (3)
Dose of IORT (Gy)	
0	48 (17)
10 (R0)	217 (74)
12.5 (R1)	14 (5)
15 (R2)	9 (3)
17.5 (R2)	2 (1)
Target of IORT	
None	48 (17)
Ventral	45 (16)
Ventrolateral	13 (4)
Lateral	89 (31)
Dorsolateral	51 (18)
Dorsal	40 (13)
Unknown	4 (1)
Postoperative chemotherapy	
No	251 (87)
Yes	39 (13)

Table 2
Pathologic characteristics.

	No. of patients (n = 290)
Postoperative TNM stage	
Complete remission	27 (9)
I	18 (6)
II	145 (50)
III	100 (45)
Point reduction in T-stage	
−1	11 (4)
0	120 (41)
1	120 (41)
2	7 (3)
3	20 (7)
4	12 (4)
Radicality	
R0	247 (85)
R1	37 (13)
R2	6 (2)

Point reduction is the reduction in T-stage (−1 is growth from T3 to T4 stage).

outside it (47%). Patterns of local recurrence stratified for IORT target are listed in Table 4. Most recurrences developed when IORT was given dorsally, while least occurred when IORT was given ventrally. The percentages of R0/R+ resections between the IORT target locations were not significantly different (p = 0.20). Especially after dorsal IORT a high amount of infield recurrences were observed (six of eight; 75%). After lateral IORT, around 64% of the recurrences were outside the radiation field, of which 57% (four of seven) presacral.

Table 3
Patterns of local recurrence.

	All patients (n = 290)	Only R0 patients (n = 247)
Presacral	14 (5.1)	8 (3.6)
Posterolateral	5 (1.8)	1 (0.4)
Lateral	3 (1.1)	2 (0.8)
Anterior	7 (2.5)	4 (1.6)
Anastomotic	2 (0.7)	1 (0.4)
Perineal	3 (1.0)	2 (0.8)
Total	34 (13.2)	18 (7.6)

Values in parentheses are the five-year local recurrence rates with competing risk analysis.

Uni- and multi-variate analyses

Analyzing the risk factors for local recurrence, lymph node positivity, margin positivity and no downstaging resulted in a p-value of less than 0.10 in uni-variate analysis. In multi-variate analysis only margin positivity resulted in a significant association with local recurrence. For presacral local recurrence specifically, a tumor distance of more than 5 cm from the anal verge and circumferential margin positivity were both significant in uni- and multi-variate analyses (Tables 5 and 6).

Five-year distant metastases rate was 35.1%; 30.4% in R0 resections and 65.3% in R+ resections ($p < 0.001$). For metastases free survival, neoadjuvant radiotherapy, margin positivity, lymph node positivity and no downstaging were significant in uni-variate analysis and only margin positivity in multi-variate analysis.

Cancer-specific survival was 66.7% after 5 years. In R0 resections it was 73.0%, compared to 30.9% in R+ resections ($p < 0.001$). Cancer-specific survival was reduced by neoadjuvant radiotherapy, lymph node positivity, margin positivity, no downstaging and no adjuvant chemotherapy in uni-variate analysis. In multi-variate analysis lymph node positivity and margin involvement influenced survival significantly.

Discussion

The purpose of this study was to evaluate the results of multimodality treatment in 290 patients with locally advanced rectal carcinoma at the Catharina Hospital. Five-year local recurrence rate was 13.2% and cancer-specific survival was 67.7%. This compares favourably to other studies with IORT-containing multimodality treatment [7,13,14], taking into account that as much as 61% of the tumors were preoperatively staged T4 carcinomas.

This study confirms that radicality of the resection is by far the most important factor influencing local control, distant metastases rate and cancer-specific death in multi-variate analyses. In a previous study of the first 201 patients in this series margin involvement was 21% [11], higher than the 15% in the current study. This is probably attributable to the increased use of chemoradiotherapy instead of radiotherapy, resulting in downstaging in 61% of the tumors. Further, increased experience of the multidisciplinary team might have resulted in improved treatment planning, based on pre- and intra-operative evaluation of the tumor extent. Thus, for optimal treatment of LARC the use of preoperative chemoradiation and surgery in high-volume centers specialized in multidisciplinary treatment of LARC is essential.

The most prominent site of local recurrence was the presacral subsite; about 40% of all local recurrences. This is in accordance with several studies in low stage and advanced rectal disease [9,15,16]. The genesis of the presacral local recurrence is puzzling. Several hypotheses can be made speculating its origin. The first hypothesis is that positive margins cause tumor spill, which develops into presacral local recurrence through force of gravity [17].

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Table 4
Patterns of local recurrence stratified for IORT target.

IORT target	LRR	Infield	*Presacral*	*Postero-lateral*	*Lateral*	*Anterior*	*Anasto-motic*	*Perineal*	Total[a]
Ventral	5.6	1 (50)	1 (50)	0	0	X	0	0	2/45
Ventrolateral	8.3	0	1 (10)	0	X	0	0	0	1/13
Lateral	13.6	4 (36)	4 (36)	X	X	2 (18)	1 (9)	0	11/89
Dorsolateral	21.6	6 (60)	X	X	0	2 (20)	0	2 (20)	10/51
Dorsal	25.1	6 (75)	X	X	0	1 (13)	1 (13)	0	8/40

Values in parentheses are percentages of the numbers of local recurrences per target category.
LRR = five-year local recurrence rate per IORT target category.
X = infield.
[a] Number of local recurrences/number of patients having received IORT per target category.

Table 5
Univariate-variate analysis on risk of presacral local recurrence.

	Hazard ratio	95% CI	*p*
Age category			0.896
<55 years	1.00		
55–62 years	0.60	0.13–2.67	
63–69 years	0.63	0.14–2.82	
>70 years	0.83	0.19–3.70	
Gender			0.569
Male	1.00		
Female	0.71	0.22–2.31	
Tumor distance from anal verge			0.045
5 cm or less	1.00		
More than 5 cm	3.74	1.03–13.60	
Clinical T-stage			0.470
T3+	1.00		
T4	1.54	0.48–5.02	
Preoperative (chemo)radiotherapy			0.755
Only radiotherapy	1.00		
Chemoradiotherapy	0.83	0.26–2.70	
Type of surgery			0.315
Non-sphincter-saving	1.00		
Sphincter-saving	1.78	0.58–5.43	
Any downstaging			0.210
No	1.00		
Yes	0.49	0.16–1.50	
N-stage			0.612
N0	1.00		
N+	1.34	0.44–4.09	
Circumferential margin			0.001
Negative	1.00		
Positive	6.91	2.31–20.69	
Postoperative chemotherapy			0.340
No	1.00		
Yes	0.04	0.00–30.73	

Table 6
Multivariate-variate analysis on risk of presacral local recurrence.

	Hazard ratio	95% CI	*p*
Tumor distance from anal verge			0.037
5 cm or less	1.00		
More than 5 cm	3.96	1.09–14.40	
Circumferential margin			<0.001
Negative	1.00		
Positive	7.28	2.43–21.84	

In the TME trial 75% of the presacral local recurrences occurred after abdominoperineal resection (APR) surgery and 29% of the APR-specimens had positive margins. Also in the current study margin positivity was associated with presacral local recurrence, making this theory very plausible. Second, as after exclusion of margin positive patients presacral local recurrence is still prominent, somehow tumor cells must have been left behind despite negative margins. One could hypothesize that in transit tumor cells in the lateral lymph flow routes leak back into the surgical volume, as it was shown that Japanese patients had more local recurrences when the lateral lymph nodes on one side in the pelvis were left behind, than when a bilateral lymph node dissection was performed [18]. This would explain why presacral local recurrence is more common in advanced disease than in limited disease (Ref: Kusters et al., Patterns of local recurrence in the Dutch TME trial: bad tumor or bad surgery?), as lateral spread occurs mostly in high stage tumors. Further, since presacral recurrences develop despite dorsal IORT makes postoperative migration of tumor cells to the presacral subsite more plausible. Controversial in this theory is that tumor height of 5 cm or more is associated with a higher incidence of presacral local recurrence, as lateral spread is mainly associated with low tumor location [19]. Further studies have to be conducted to elucidate the mechanisms of presacral local recurrence genesis.

Relating the patterns of local recurrence to the IORT target, 47% of the local recurrences developed outside the IORT field. This is less than that in the few studies reporting on this subject, in which the boost of IORT was given only on the presacral area [8,9]. Consequently it might be suggested that an IORT-boost specifically to the area at risk is more effective in the prevention of local recurrence, possibly because the area that causes tumor spill is sterilized. Delivery of IORT to any specific area is technically very feasible. Normally, it can be delivered through an abdominal access. However, the ventral area can be irradiated more adequately transperineally.

An interesting finding is that the more dorsally the IORT is applied, the higher the local recurrence rates are. IORT target is inherent to the side to which the primary tumor extends to or through the mesorectal fascia. Consequently, dorsal tumor extension leads to more local relapse than ventral extension, while margin involvement is not significantly different. Further, dorsal tumor extension is very therapy resistant, as 75% of the recurrences are infield. Slight improvements in local recurrence rates could possibly be made if in ventrolateral or lateral tumor location also the presacral area would be irradiated, as this is site of relapse in 57–100% of the outfield recurrences. We however expect that this makes no difference, because this boost on the presacral area cannot influence tumor cells that migrate postoperatively.

Finally, as the development of metastases in 35% of the patients is still a major problem, more widespread use of preoperative chemoradiotherapy and postoperative chemotherapy is advisable. Further, as cancer-specific survival is significantly affected by lymph node positivity and lymph nodes have shown not to be essentially affected by the treatment [11], more aggressive treatment variants for lymph node positive patients have to be explored.

In conclusion, multimodality treatment is effective in the prevention of local recurrence in the management of LARC and obtaining a free circumferential margin is the most important factor for good oncologic results. IORT application to the area most at risk

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is feasible and seems more effective in the prevention of local recurrence than IORT application to the dorsal area.

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