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Intraoperative radiotherapy (IORT) reduces local recurrence rates in patients with microscopically involved circumferential resection margins after resection of locally advanced rectal cancer

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Abstract

Purpose

Intraoperative radiotherapy (IORT) is advocated by some for patients with locally advanced rectal cancer (LARC) who have involved or narrow circumferential resection margins (CRM) after rectal surgery. This study evaluates the potentially beneficial effect of IORT on local control.

Methods

All surgically treated patients with LARC treated in a tertiary referral center between 1996 and 2012 were analyzed retrospectively. The outcome of patients treated with IORT with a clear but narrow CRM (≤2mm) or a microscopically involved CRM was compared to patients who were not treated with IORT.

Results

A total of 409 patients underwent resection of LARC and 95 patients (23%) had a CRM ≤2mm. Four patients were excluded from further analysis due to a macroscopically involved resection margin. In 43 patients with clear but narrow CRMs, there was no difference in the cumulative 5-year local recurrence-free survival of patients treated with (n=21) or without IORT (n=22) (70 vs. 79%,p=0.63). In 48 patients with a microscopically involved CRM, there was a significant difference in the cumulative 5-year local recurrence-free survival in favor of the patients treated with IORT (n=31) compared to patients treated without IORT (n=17) (84 vs. 41%,p=0.01). Multivariable analysis confirmed that IORT was independently associated with a decreased local recurrence rate (HR 0.24, 0.07–0.86). There was no significant difference in complication rate of patients treated with or without IORT (65% vs. 52%,p=0.18)

Conclusion

The current study suggests that IORT reduces local recurrence rates in patients with LARC with a microscopically involved CRM.

Introduction

Local control is an important goal of the surgical treatment of rectal cancer. Local recurrences are usually accompanied by severe pain and poor quality of life.[1] One of the most important predictive factors for local recurrence is the circumferential resection margin (CRM).[2] The recognition of an involved CRM as one of the main causes of local recurrences has led to the introduction of total mesorectal excision (TME), resulting in less involved margins and consequently less local recurrences. A further decrease of CRM-involvement was caused by introducing neoadjuvant (chemo-)radiotherapy. Unfortunately, despite using neoadjuvant (chemo-)radiotherapy followed by TME, CRM-involvement is still reported in 17–20% of the patients with locally advanced rectal cancer (LARC) and results in local recurrence rates of 55–62% in these patients.[3,4]

Several institutes worldwide have integrated intraoperative radiotherapy (IORT) to the multimodality approach of LARC to improve outcome. IORT refers to the delivery of a boost of radiation at the time of surgery. One single IORT dose results in a two to three times higher biological equivalent than the same dose given by conventional fractionation.[5] The rationale behind IORT is that this extra radiation boost, if preceded by neoadjuvant radiotherapy, may be able to eradicate microscopic remnants after an incomplete resection. In addition to patients with microscopically involved CRMs, IORT may also be beneficial in patients with a clear but narrow CRM (≤2mm), because these patients are also known to have a higher risk of local recurrence.[6]

In the literature, the results of the effect of IORT on local control in patients with LARC are contradictory. Some retrospective studies reported a beneficial effect [7-11], but others, including a recently published randomized controlled trial, did not find any beneficial effect.[12-14] However, these studies report on patients that in the majority of cases had radical resections and some describe both LARC and locally recurrent rectal cancer patients. Comparative studies focusing on LARC with involved or clear but narrow CRMs specifically are lacking. The aim of the current study is to evaluate whether IORT after neoadjuvant radiotherapy decreases the local recurrence rate in patients with LARC with a microscopically involved CRM or a clear but narrow CRM after TME.

Patients and methods

Between 1996 and August 2012, all patients undergoing curative TME for LARC in the Erasmus Cancer institute, a tertiary referral center for T4 colorectal cancer for the southwest region of The Netherlands, were entered in a database. LARC was defined as large T3 or T4 rectal tumors with clinical suspicion of narrow or involved CRMs with or

without potentially malignant lymph nodes, or rectal tumors with potentially malignant lymph nodes outside the TME plane.

Based on the final pathology report, all patients with a CRM equal or less than 2 mm were retrospectively analyzed. These patients were divided into two groups; a group with resections with a clear, but narrow CRM (≤2mm) and a group with a microscopically involved CRM. In these groups, we compared the local recurrence-free survival and overall survival of the patients who were treated with and without IORT.

Neoadjuvant (chemo-)radiotherapy

All patients received preoperative (chemo-)radiotherapy, either as a short course (25Gy) delivered in 5 fractions or as a long course (44,6–50Gy) delivered in 19-25 fractions. From 2006 onwards, patients received chemoradiotherapy with capecitabine administered orally at a dose of 825 mg/m^2 twice a day during radiotherapy days as reported previously.[15] Before 2006, no patient received concomitant chemotherapy. Radiotherapy was administered by a three-field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy. The lateral pelvic borders were defined as 1.5cm lateral of the bony pelvis, the cranial border was the promontory, and the caudal border was below the foramina obturatoria to 2cm under the anus, depending on tumor position.

Surgery, intraoperative radiotherapy and adjuvant treatment

Surgical strategy was planned preoperatively in a multidisciplinary tumor board. TME was performed in all patients and multivisceral 'beyond TME' resections were performed in those with tumor ingrowth into surrounding structures. Patients in whom a CRM ≤2mm was expected were planned in an operation theatre with IORT facilities. During surgery, CRM status was evaluated on frozen sections. When the CRM was ≤2mm, IORT was applied to the resection area involved. Patients in whom a CRM >2mm was expected were planned in an operation theatre without IORT facilities and no standard frozen sections of the specimen were taken.

IORT was delivered by high dose rate (HDR) brachytherapy. The area where the resection margin was considered to be at risk was marked with surgical clips. IORT was administered to this area by a flexible intraoperative template (FIT), which was described previously.[16] a 5mm-thick pad made of flexible silicon with 1cm-spaced parallel source guide tubes running through the center of the template. The size and shape of the FIT were adjusted by surgeon and radiation oncologist. Thereafter, it was placed on the target surface. Treatment planning was performed using the standard geometries present in the treatment planning system. A dose of 10Gy was delivered, usually at 1cm depth from the applicator surface. Peri-operative morbidity was divided into surgical and non-

surgical morbidity and was graded according to the Dindo-Clavien classification.[17] Our treatment protocol for LARC does not include adjuvant chemotherapy or postoperative radiotherapy. Nevertheless, some patients received adjuvant chemotherapy or underwent postoperative radiotherapy.

Follow up

Patients visited the outpatient clinic every 3 months during the first two years. Thereafter, patients were examined biannually. The first two years CEA determination was performed every 3 months and thoracic and abdominal imaging biannually. After 2 years of follow up, CEA determination was performed biannually and thoracic and abdominal imaging yearly. Patients were usually discharged from further follow up after 5 years. During follow up, a local recurrence was established by symptoms, CEA increase or imaging. All suspected recurrences were confirmed by CT or MR imaging. Biopsies were attempted routinely.

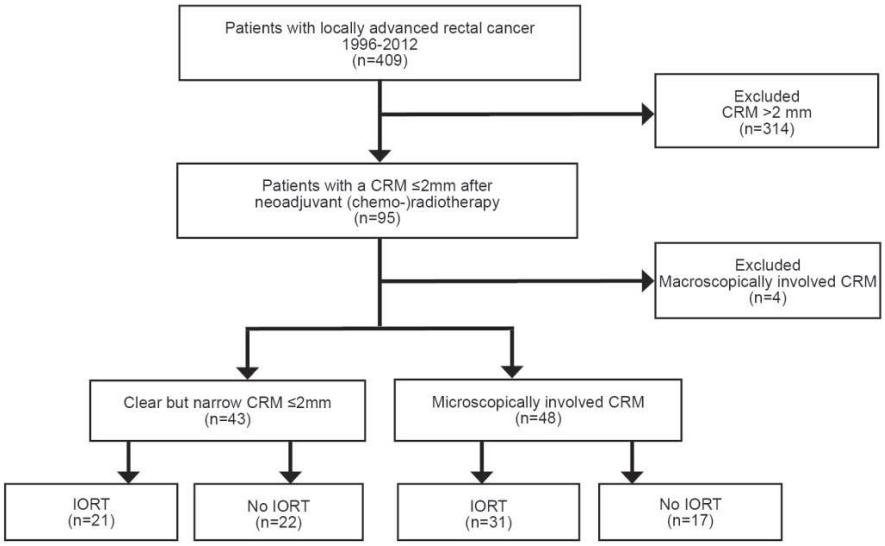
Statistical analysis

Statistical analysis was carried out using SPSS (version 20.0.0). Data was reported as median (interquartile range). Categorical data was reported as count (percentage). The Chi-square, Fisher's exact and Mann-Whitney U test were used for comparison of both groups as appropriate. Univariate local recurrence-free survival and overall survival analyses were carried out by means of Kaplan–Meier curves and log rank tests. Univariate and multivariable analyses by Cox hazard regression models were performed to determine the prognostic value of covariates.

Results

A total of 409 patients underwent TME surgery for LARC between 1996 and August 2012. Neoadjuvant (chemo-)radiotherapy was administered to 399 patients. Of these patients, 95 patients had a CRM ≤2mm on final pathology report. Forty-three patients had a clear but narrow CRM ≤2mm and 48 patients had a microscopically involved CRM. Four patients underwent a macroscopic irradical resection and were not included in this study. *(Fig. I)*

Figure I. Study flowchart of all patients



Resections with a clear but narrow CRM (≤2mm)

Patient and tumor characteristics of the patients with radical resections with a clear but narrow CRM ≤2mm are depicted in *table I*. Twenty-one patients were treated with IORT (49%), whereas 22 patients (51%) did not receive IORT. The main reasons for not administering IORT was preoperative understaging (n=14). In these patients, perioperative frozen sections were not performed and IORT was not considered. The other cause for omitting IORT was a false-negative result of the perioperative frozen sections, while the CRM proved to be ≤2mm on final pathology report (n=8).

Surgery, perioperative results and adjuvant treatment

The interval between ending radiotherapy and surgery was 9 (interquartile range, 7–12) weeks for the patients treated with IORT and 8 weeks (interquartile range, 7–11) for the patients treated without IORT (p=0.91). There were no differences in the surgical procedures and TNM stage *(table II).* Operation time was significantly longer and there was significantly more blood loss in patients treated with IORT. One patient treated with IORT received adjuvant chemotherapy compared to 2 patients who were not treated with IORT.

Local recurrence-free survival and overall survival

The median follow up was 38 (interquartile range, 15-66) months for patients treated with IORT and 39 (interquartile range, 11–73) months for patients treated without IORT. The estimated 3- and 5-year local recurrence-free survival of the 21 patients treated with

Table I. patients and tumor characteristics

	Clear but narrow CRM ≤2 mm			Resections with a microscopically involved CRM		
	Non IORT (%)	**IORT (%)**	**p-value**	**Non IORT (%)**	**IORT (%)**	**p-value**
Total	22	21		17	31	
Gender						
Male	15 (68)	18 (86)	-	11 (65)	23 (74)	-
Female	7 (32)	3 (14)	0.28*	6 (35)	8 (26)	0.73**
Age ∓	59 (17–76)	66 (43–76)	0.08***	56 (23–75)	61 (18–77)	0.84***
Neoadjuvant treatment						
Short course RTx	1 (5)	1 (4)	-	3 (18)	2 (6)	-
Long course RTx	9 (41)	12 (50)	-	9 (53)	13 (42)	-
Chemoradiotherapy	12 (55)	8 (33)	0.55**	5 (21)	16 (52)	0.24**
Tumor localization						
≤ 5 cm	12 (55)	11 (52)	-	9 (53)	16 (52)	-
> 6 cm	10 (45)	10 (48)	0.69**	8 (47)	15 (48)	0.93**
Clinical tumor stage						
T3	13 (59)	6 (29)	-	8 (47)	10 (32)	-
T4	9 (31)	15 (71)	0.04	9 (53)	21 (68)	0.31
Clinical nodal stage						
N0	10 (46)	13 (62)	-	7 (41)	13 (42)	-
N+	12 (54)	12 (38)	0.65	10 (59)	18 (58)	0.96

*CRM, Circumferential resection margin, IORT, intra-operative radiotherapy ∓, Years (interquartile range); RTx, Radiotherapy, CTx, Chemotherapy; * using Fisher's exact test; **, Using χ^2; ***, using Mann-Whitney U test*

IORT was 82% and 70% respectively. This did not significantly differ from the 3- and 5-year local recurrence-free survival of 79% and 79% respectively of patients treated without IORT (p=0.63) (*figure IA)*. Further univariate analysis for local recurrence-free survival is outlined in *table III*. Five-year overall survival did not differ significantly between patients treated with or without IORT (63 vs. 81%,p=0.28). The only independent prognostic factor for overall survival was synchronous metastatic disease (HR 5.18, CI95%: 1.27–21.2).

Resections with a microscopically involved CRM

Patient and tumor characteristics of 48 patients with a microscopically involved CRM are depicted in *table I*. IORT was administered to 31 patients (65%), whereas 17 patients (35%) did not receive IORT. In 12 patients the reasons for not administering IORT was preoperative understaging, whereas 5 patients had false-negative frozen section results. In patients not treated with IORT, stage IV disease was more common than in patients treated with IORT (52 vs. 13%,p=0.01).

Table II. Surgical, pathological results and adjuvant therapy

	Clear but narrow CRM ≤2 mm			Resections with a microscopically involved CRM		
	Non IORT (%)	**IORT (%)**	**p-value**	**Non IORT (%)**	**IORT (%)**	**p-value**
Total	22	21		17	31	
Surgical procedure						
LAR	8 (40)	4 (19)	-	6 (35)	4 (13)	-
APR	6 (27)	9 (43)	-	6 (35)	14 (45)	-
Intersphinteric	1 (5)	1 (5)	-	0	1 (3)	-
Posterior exenteration	5 (23)	3 (14)	-	3 (9)	5 (16)	-
Total exenteration	2 (9)	4 (19)	-	2 (6)	4 (13)	-
Abdominoperineal sacral	0	0	0.55**	0	3 (10)	0.40**
Operation time (minutes) ∓	317 (145–672)	481 (258–662)	0.003***	293 (220–343)	495 (433–580)	<0.001***
Blood loss (milliliters) ∓	1650 (200– 12.500)	3.300 (300 –20.000)	0.016***	1750 (790–3290)	3000 (1700–5350)	0.10***
Tumor stage						
T3	16 (72)	17 (81)	-	9 (52)	11 (35)	-
T4	6 (28)	4 (19)	0.72*	8 (48)	20 (65)	0.40**
Nodal stage						
N0	10 (45)	11 (52)	-	7 (41)	19 (61)	-
N+	12 (55)	10 (48)	0.65**	10 (59)	12 (39)	0.18**
Distant metastases	4 (18)	3 (15)	1.00*	9 (52)	4 (13)	0.01*
Pulmonary	0	0	-	1 (5)	1 (3)	-
Liver	4 (18)	3 (15)	-	8 (47)	3 (10)	-
Adjuvant therapy						
Chemotherapy	1 (5)	2 (10)	-	1 (6)	0	-
Radiotherapy	0	0	-	2 (12)	0	-

*CRM, Circumferential resection margin, IORT, Intra-operative radiotherapy; LAR, Low anterior resection; APR, Abdominoperineal resection ∓,Interquartile range; *, Using Fisher's exact test; **, Using χ^2; ***, Using Mann Whitney U test*

Surgery, perioperative results and adjuvant treatment

The interval between ending radiotherapy and surgery was 8 (interquartile range, 6–11) weeks for the patients treated with IORT and 7 (interquartile range, 6–9) weeks for the patients treated without IORT (p=0.18). Surgical procedures were similar in both groups *(table II).* Operation time was significantly longer in the IORT group. Two patients treated without IORT received an adjuvant radiation boost of 20–30Gy and one patient received adjuvant chemotherapy. No patients treated with IORT received adjuvant therapy.

Local recurrence-free survival and overall survival

The median follow up was 23 (interquartile range, 11–46) months for patients treated with IORT and 12 (interquartile range, 6–22) months for patients treated without IORT. Of the patients treated with IORT, 4 patients developed a local recurrence, whereas 14

Table III. Univariate analysis of local recurrence-free survival and overall survival of resections with a clear but narrow CRM ≤2mm

		Local recurrence-free survival			Overall survival	
		Number of patients	**Hazard ratio local recurrence (95%CI)**	**P-value**	**Hazard ratio overall survival (95%CI)**	**P-value**
Gender						
	Male	33	1		1	
	Female	10	2.50 (0.56 – 11.21)	0.23	1.55 (0.39 – 6.22)	0.63
Neo-adjuvant Treatment						
	RTx (25-50Gy)	23	1		1	
	CTxRTx (50Gy)	20	0.21 (0.09 – 11.09)	0.23	0.48 (0.10 – 2.35)	0.37
Period of surgery						
	1996-2004	18	1		1	
	2005-2012	25	0.26 (0.20 – 1.39)	0.18	0.92 (0.24 – 3.50)	0.91
Surgical resection						
	LAR	15	1		1	
	APR	28	3.05 (0.36 – 25.41)	0.27	1.81 (0.38 – 8.70)	0.52
Tumor stage						
	T3	32	1		1	
	T4	11	1.75 (0.34 –- 9.12)	0.51	2.12 (0.53 – 8.53)	0.66
Nodal stage						
	N-	21	1		1	
	N+	22	0.96 (0.19 – 4.72)	0.96	0.63 (0.14 - 2.81)	0.54
CRM						
	>0 and ≤1 mm	14	1		1	
	>1 and ≤2 mm	29	0.77 (0.18 – 3.56)	0.67	2.16 (0.45 – 10.42)	0.32
Metastatic disease						
	No	36	1		1	
	Yes	7	1.54 (0.18 – 13.14)	0.69	5.18 (1.27 – 21.22)	0.02
Tumor differentiation grade						
	Well and moderate	36	1		1	
	Poor	7	1.11 (0.13 - 9.58)	0.92	2.00 (0.40 – 9.98)	0.40
Vasoinvasion						
	No	32	1		1	
	Yes	11	1.77 (0.32 – 9.56)	0.51	1.70 (0.32 – 9.16)	0.53
Tumor localization						
	≤ 5 cm	25	1		1	
	> 6 cm	18	2.13 (0.42 – 10.75)	0.36	0.79 (0.15 – 4.06)	0.77
IORT						
	No	22	1		1	
	Yes	21	1.44 (0.32 – 6.47)	0.63	2.10 (0.53 – 8.42)	0.29

CRM, Circumferential resection margin; RTx, Radiotherapy; CTxRTx, Chemoradiotherapy; LAR, Low *anterior resection; APR,* Abdominoperineal *resection; IORT, Intraoperative radiotherapy*

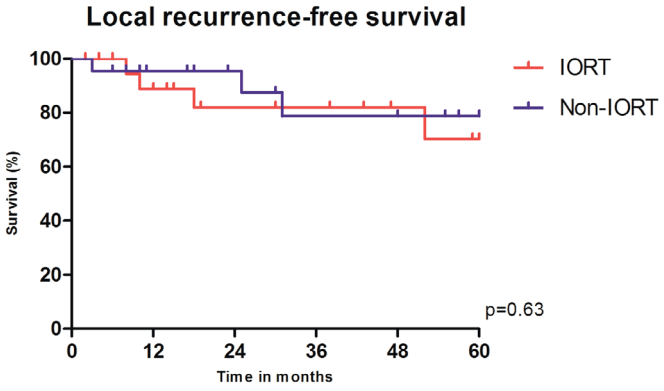
Table IV. Univariate local recurrence free survival and overall survival of resections with a microscopically involved CRM

	Local recurrence-free survival			Overall survival	
	Number of patients	**Hazard ratio local recurrence (95%CI)**	**P-value**	**Hazard ratio overall survival (95%CI)**	**P-value**
Gender					
Male	34	1		1	
Female	14	2.82 (0.86 – 9.26)	0.09	0.86 (0.38 – 1.95)	0.72
Neo-adjuvant Treatment					
RTx (25-50Gy)	27	1		1	
CTxRTx (50Gy)	21	0.51 (0.14 – 1.93)	0.32	0.46 (0.19 – 1.13)	0.08
Period of surgery					
1996-2004	21	1		1	
2005-2012	27	1.05 (0.32-3.45)	0.94	0.76 (0.37 – 1.58)	0.47
Surgical resection					
LAR	14	1		1	
APR	34	0.46 (0.14 – 1.52)	0.20	1.2 (0.53 – 2.72)	0.66
Tumor stage					
T3	20	1		1	
T4	28	0.63 (0.19 – 2.09)	0.45	1.82 (0.80 – 3.73)	0.17
Nodal stage					
N0	26	1		1	
N+	22	1.32 (0.36 – 5.01)	0.66	1.1 (0.49 – 2.41)	0.82
Metastatic disease					
No	35	1		1	
Yes	13	2.86 (0.86 – 9.27)	0.10	1.98 (0.92 – 4.28)	0.08
Tumor differentiation grade					
Well and moderate	37	1		1	
Poor	11	4.88 (1.46 – 15.12)	0.004	1.65 (0.75 – 3.6)	0.21
Vasoinvasion					
No	35	1		1	
Yes	13	1.09 (0.27 – 4.36)	0.90	1.1 (0.49 – 2.53)	0.80
Tumor localization					
≤ 5 cm	25	1		1	
> 6 cm	23	1.67 (0.45 – 6.21)	0.45	1.25 (0.56 – 2.78)	0.56
IORT					
No	17	1		1	
Yes	31	0.23 (0.07– 0.81)	0.016	0.39 0.19– 0.81)	0.01

CRM, Circumferential resection margin; RTx, Radiotherapy; CTxRTx, Chemoradiotherapy; LAR, Low anterior resection; APR, Abdominoperineal resection; IORT, Intraoperative radiotherapy

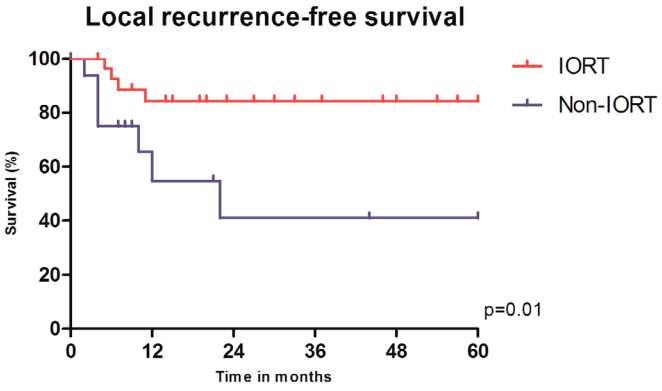
patients died without developing a local recurrence. Of the patients treated without IORT, 7 patients developed a local recurrence, whereas 7 patients died without developing a local recurrence. This resulted in significant difference in 5-year local recurrence-free survival in favor of the patients treated with IORT (84% vs. 41%,p=0.01). This is shown in *figure IB*. When 2 two patients who received a post-operative radiotherapy boost were excluded, the difference in 5-year local recurrence-free survival was more pronounced (84% vs. 33%, p=0.004). Further univariate analysis is depicted in *table IV*.

Figure IA: local recurrence-free survival of patients with clear but narrow CRMs (≤2mm)



Patients at risk						
IORT	21	16	12	11	8	5
Non-IORT	22	17	14	10	9	6

Figure IB: Local recurrence-free survival of patients with microscopically involved CRMs



Patients at risk						
IORT	31	21	15	11	8	5
Non-IORT	17	7	4	3	2	2

Multivariable analysis confirmed that IORT (HR 0.24, 95%CI: 0.07–0.86) and poor tumor differentiation (HR 4.82, 95%CI: 1.46–15.94) were independently associated with local recurrence-free survival. There was also a significant difference in 5-year overall survival in favor of the patients treated with IORT (41 vs. 13%,p=0.008). Further univariate analysis demonstrated that IORT was the only significant prognostic factor for overall survival (HR 0.39, CI95%: 0.19–0.81) *(table IV)*.

Perioperative morbidity and mortality of all patients

The perioperative morbidity and mortality is outlined in *table V.* In 52 patients treated with IORT, 38 complications occurred in 34 patients (65%). In 39 patients treated without IORT, 23 complications occurred in 20 patients (52%). There was no significant difference in number of patients with complications (p=0.18), nor in grade of complications between patients treated with or without IORT. A relaparotomy was performed in 2 patients (4%) treated with IORT compared to 1 patient (3%) not treated with IORT.

Table V. Peri-operative morbidity and mortality of all patients

	Non IORT (%)	IORT (%)	p-value
Total	39	52	
Peri-operative morbidity			
Surgical			
Abdominal/perineal wound infections	9 (23)	18 (31)	0.14*
Presacral abscess	5 (13)	3 (6)	0.28**
Relaparotomy	1 (3)	2 (4)	1.00**
Anastomotic leakage †	1 (3)	1 (2)	-
Wound dehiscence	0	1 (2)	-
Non-surgical			
Pneumonia/atelectasis	4 (10)	8 (15)	0.76**
Cardiac	1 (3)	2 (6)	1.00**
Urinary tract infection	3 (8)	5 (8)	1.00**
Grading of complications (Dindo-Clavien)			
Grade ≥2	10 (25)	17 (33)	0.16**
Grade ≥3	6 (15)	8 (15)	1.00**
Grade ≥4	1 (3)	1 (2)	1.00*
Mortality			
In hospital mortality	1 (3)	0	-

*IORT, Intraoperative radiotherapy; †, Only in patients with an anastomosis without a diverting Ileostoma; *, using Fischer's exact; **, using χ^2*

Discussion

The current study suggests that IORT reduces the local recurrence rate in patients with a microscopically involved CRM after neoadjuvant radiotherapy for LARC. This study did not find evidence that IORT reduces local recurrence rates in patients with a clear but narrow CRM (≤2mm). The complication rate is not increased in patients treated with IORT.

Patients with a microscopically involved CRM who were treated with IORT had a significantly improved 5-year local recurrence-free survival of 84% compared to 41% for the patients who were treated without IORT. This suggests that administering IORT can eradicate microscopic remnants after incomplete resections and thus improve local control.

The reduction of the local recurrence rate by IORT contradicts the results of a recently published randomized controlled trial, which demonstrated no beneficial effect of IORT after neoadjuvant radiotherapy.[12] However, that study included mostly patients with radical resections, thus providing evidence that standard administration of IORT in patients with a radical resection is not beneficial. This is in line with our finding that IORT had no beneficial effect on patients with radical resections with a clear but narrow CRM. Although the recurrence rate in these patients is increased, the recurrence rate is not as high as in patients with involved resection margins. Consequently, many more patients would be required to confirm a beneficial effect of IORT in this specific patient group; neither the randomized controlled trial, nor our study can answer this question

The literature is scarce on the effect of IORT in relation with the resection margin status and in particular in patients with R1-resections of LARC. In patients with a microscopically involved CRM, local recurrence rates of 41-100% are reported after neoadjuvant radiotherapy without administering IORT.[3,4,18,19] One comparative study demonstrated that IORT improved 5-year local control in patients with a microscopically involved CRM.[20] Non-comparative studies reported 5-year local control rates after IORT for LARC of 55-77% in patients with an involved CRM.[9,21-23] These rates are relative low compared to our 5-year local recurrence-free survival of 84%, which may be explained by the fact that we excluded patients with macroscopically involved margins. Others demonstrated that IORT did not result in a similar increase in local control after IORT for macroscopically involved resection margins as in patients with microscopically involved resection margins.[9,11,14] This suggest that IORT may be less or uneffective in patients with macroscopic involved resection margins.

Preoperative understaging and false-negative frozen section evaluation resulted in the omission of IORT in patients with involved or narrow margins. However, the erroneous omission of IORT made it possible for us to make a unique comparison of patients treated with or without IORT, which was impossible in other studies from centers that apply IORT routinely in LARC patients. Our false-negative rate of CRM-involvement on preoperative

imaging and on frozen sections seems high, but one should keep in mind that only patients with a CRM ≤2mm were selected. The overall false-negative CRM-involvement rate of 409 surgically treated patients was 6% (24/409) which is in line with a 5% false-negative rate of CRM-involvement in the Mercury trial.[24] The 7% (13/196) false-negative rate of frozen sections was slightly higher and was probably caused by sampling error. Still, this latter finding has led us to change our protocol. Currently, patients in whom we judge the risk of sampling error to be high are treated with IORT regardless of frozen section results.

Although the operation time was longer and the estimated blood loss was higher in patients who were treated with IORT, there was no significant difference in complication rate between patients who were treated with or without IORT. Administering an extra dose of radiotherapy could contribute to an increased toxicity or a higher complication rate. However, administering radiotherapy intraoperatively provides the ability to treat a specific area at risk under direct visual control with the possibility to shield surrounding structures from radiation. Previous studies from other institutes confirmed that administering IORT is safe and feasible and does not result in a higher complication rate.[10,12] Our overall complication rate of 65% in patients treated with IORT is higher compared to other institutes, reporting complications rates of 15-35%.[12,20,25] This difference may be explained by the fact that we included patients with more advanced tumors (≤2mm) and patients undergoing multivisceral resections (33%).

Due to the retrospective nature of this analysis, this study has drawbacks. Different neoadjuvant radiotherapy regimes were used in this study. Although the nature of the neoadjuvant treatment did not differ significantly, more patients who had microscopically involved CRMs treated with IORT had received neoadjuvant chemoradiotherapy. This is caused by the fact that chemoradiotherapy was introduced in 2006 and IORT was applied with an increasing frequency after 2006. Several randomized controlled trials demonstrated that adding chemotherapy during radiotherapy reduces the local recurrence rate.[26] However, these results were mainly based on radical resections. Furthermore, it could be hypothesized that patients with an involved CRM after chemoradiotherapy may have an even more aggressive tumor behavior, because this group consists of poor responders. This assumption is supported by the study of Nagtegaal et al.[2] Patients with an involved CRM after (chemo-)neoadjuvant radiotherapy had a higher chance on local recurrence than patients with a involved CRM who were treated without neoadjuvant (chemo-)radiotherapy.

Another remarkable finding was that in the group of patients who did not receive IORT for a microscopically involved CRM, significantly more patients had stage IV disease. Patients with stage IV disease were generally referred to our hospital for metastatic surgery and not for LARC specifically. Stage IV patients with involved CRMs on pathological staging were understaged preoperatively. On the other hand, patients

with a compromised CRM on preoperative clinical staging were specifically referred for IORT to our hospital, whereas the patients who were understaged preoperatively underwent surgery in other hospitals. This may explain the higher number of patients with understaged rectal cancer in the group of patients with stage IV disease. Stage IV disease was not the reason for omitting IORT; all patients were planned for a curative resection by a 'liver first' approach, synchronous resection of rectum and metastases or resection of the metastases in later stage.[27]

The presence of metastatic disease explains the shorter length of follow up in patients with an involved CRM not treated with IORT. Regardless of this shorter follow up time, patients who were not treated with IORT had a higher local recurrence rate compared to patients treated with IORT, who were followed longer. Nevertheless, metastasized disease may indicate more aggressive tumor behavior, which may also be associated with a higher local recurrence rate, even though the presence of synchronous metastases was not a significant risk factor for local recurrence in the univariate analysis. The difference in stage IV patients makes it inappropriate to draw any conclusions about the effect of IORT on overall survival, despite a significant difference between patients treated with or without IORT, because distant metastases are the most important prognostic factor for overall survival.

Several studies advocated a randomized controlled trial for definitive evidence of the effect of IORT in patients with incomplete resections. The accrual of a sufficient number of patients for such a trial would be challenging. This is illustrated by the small number of patients treated with an involved CRM over a long period of time in a high volume center in the current study. Furthermore, it is questionable whether not administering IORT in patients with involved margins may be considered acceptable in institutes currently performing IORT. Nevertheless, this study is the result of a retrospective analysis and therefore all known drawbacks of retrospective studies apply.

In conclusion, IORT does not have a benefit for patients who undergo radical resections of rectal cancer. However, our results suggest that IORT reduces the local recurrence rate in patients with microscopically involved CRMs. Patients who are at risk for a microscopically involved CRM should undergo surgery in centers with IORT facilities.

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