Clinical selection strategy for and evaluation of intra-operative brachytherapy in patients with locally advanced and recurrent rectal cancer

Dijkstra, Esmée A; Mul, Véronique E M; Hemmer, Patrick H J; Havenga, Klaas; Hospers, Geke A P; Kats-Ugurlu, Gursah; Beukema, Jannet C; Berveling, Maaike J; Moumni, Mostafa El; Muijs, Christina T

Published in:
Radiotherapy and Oncology

DOI:
10.1016/j.radonc.2021.03.010

Publication date:
2021

Radiotherapy and Oncology 159 (2021) 91–97

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Clinical selection strategy for and evaluation of intra-operative brachytherapy in patients with locally advanced and recurrent rectal cancer

Esmée A. Dijkstra [a], Véronique E.M. Mul [b], Patrick H.J. Hemmer [c], Klaas Havenga [c], Geke A.P. Hospers [a], Gursah Kats-Ugurlu [d], Jannet C. Beukema [b], Maaike J. Berveling [b], Mostafa El Moumni [c], Christina T. Muijs [b], Boudewijn van Etten [c,*]

[a] University of Groningen, University Medical Centre Groningen, Department of Medical Oncology, the Netherlands; [b] University of Groningen, University Medical Centre Groningen, Department of Radiation Oncology, the Netherlands; [c] University of Groningen, University Medical Centre Groningen, Department of Surgery, the Netherlands; [d] University of Groningen, University Medical Centre Groningen, Department of Pathology and Medical Biology, the Netherlands

ARTICLE INFO

Article history:
Received 4 November 2020
Received in revised form 5 March 2021
Accepted 8 March 2021
Available online 17 March 2021

Keywords:
Rectal neoplasms
Neoadjuvant therapy
Brachytherapy
Radiation oncology
Patient selection
Adverse effects

ABSTRACT

Background and purpose: A radical resection of locally advanced rectal cancer (LARC) or recurrent rectal cancer (RRC) can be challenging. In case of increased risk of an R1 resection, intra-operative brachytherapy (IOBT) can be applied. We evaluated the clinical selection strategy for IOBT.
Materials and methods: Between February 2007 and May 2018, 132 LARC/RRC patients who were scheduled for surgery with IOBT standby, were evaluated. By intra-operative inspection of the resection margin and MR imaging, it was determined whether a resection was presumed to be radical. Frozen sections were taken on indication. In case of a suspected R1 resection, IOBT (1 × 10 Gy) was applied. Histopathologic evaluation, treatment and toxicity data were collected from medical records.
Results: Tumour was resected in 122 patients. IOBT was given in 42 patients of whom 54.8% (n = 23) had a histopathologically proven R1 resection. Of the 76 IOBT-omitted R0 resected patients, 17.1% (n = 13) had a histopathologically proven R1 resection. In 4 IOBT-omitted patients, a clinical R1/2 resection was seen. In total, correct clinical judgement occurred in 72.6% (n = 88) of patients. In LARC, 58.3% (n = 14) of patients were overtreated (R0, with IOBT) and 10.9% (n = 5) were undertreated (R1, without IOBT). In RRC, 26.5% (n = 9) of patients were undertreated.
Conclusion: In total, correct clinical judgement occurred in 72.6% (n = 88). However, in 26.5% (n = 9) RRC patients, IOBT was unjustifiedly omitted. IOBT is accompanied by comparable and acceptable toxicity. Therefore, we recommend IOBT to all RRC patients at risk of an R1 resection as their salvage treatment.

In the treatment of locally advanced rectal cancer (LARC) and recurrent rectal cancer (RRC), radiotherapy with concurrent chemotherapy followed by delayed surgery results in increased local control (LC) [1–4]. By this multimodality treatment downstaging occurs, which leads to a higher radical (R0) resection rate, resulting in a more favourable prognosis [5–11]. However, a radical resection may still be challenging [5,6,9,11–17].

Since local recurrence is associated with a poor quality of life and severe morbidity [18], it is important to maximise local control. Therefore, intra-operative brachytherapy (IOBT) can be used to give extra local therapy as resection margins may still be at risk of undetectable residual disease (R1) [19,20]. In literature however, there is yet no consensus if the addition of IOBT results in improved LC, overall survival (OS) and disease-free survival (DFS) in LARC and RRC patients [21,22]. A retrospective study demonstrated improved LC, OS and DFS after intraoperative radiotherapy (IORT) whereas two randomised trials failed to confirm these advantages of IORT [22–24].

During IOBT, dose-limiting organs such as the small bowel are kept out of the irradiation field, to decrease local toxicity [22,25]. In this way, the irradiation dose can be raised while optimising the balance between the local anti-tumour effects and toxicity. However, IOBT can be accompanied by severe side effects, such as bleeding and neuropathy [5,20,26]. Also, there is no consensus on the indication of IOBT/IORT. In some studies, all patients received IOBT/IORT, while in others the decision making was based on preoperative examinations, on microscopic or macroscopic

* Corresponding author at: Hanzeplein 1, P.O. Box 30.001, 9700 RB Groningen, the Netherlands.
E-mail address: b.van.etten@umcg.nl (B. van Etten).

https://doi.org/10.1016/j.radonc.2021.03.010
0167-8140/

remaining tumour (in which the definition of free resection margin differed) or on frozen sections [11,13,21].

The potential complication risks of additional IOBT should be weighed against the potential clinical benefits. Therefore, in our study IOBT was performed if an irradical (R1) resection was suspected based on the judgement of the surgeon and radiation oncologist. The primary aim of this study is to evaluate the accuracy of this clinical selection strategy for IOBT, and the secondary objective is to assess its toxicity.

Materials and methods

Between February 2007 and May 2018, 132 patients with adenocarcinoma of the rectum were evaluated and scheduled for resection with IOBT standby. Our institutional ethical review committee approved this analysis (METc number: 2019/069).

Staging was performed using endoscopy with biopsies, CT-scan of thorax/abdomen and (DW-)MRI-scan. Treatment policy was discussed in a multidisciplinary rectal cancer expert board. If patients were radiotherapy naïve, they received 50.0–50.4 Gy (2.0–1.8 Gy/fraction daily) using a 3- or 4-field technique. Previously irradiated patients were re-irradiated with 30.0–30.6 Gy (2.0–1.8 Gy/fraction daily) using a 3- or 4-field technique [27]. Target volume for irradiation and re-irradiation was the tumour and suspected lymph nodes with margin, combined with the following lymph node regions: internal iliac regions, obturatorius regions, mesorectum and presacral area. Radiotherapy in LARC and RRC patients was usually combined with twice-daily capecitabine 825 mg/m^2. In case of distant metastasis, patients were treated according to the M1-regimen (5x5 Gy daily followed by six cycles of CAPOX-B) [28]. Patients were restaged approximately six weeks after neoadjuvant treatment and scheduled for surgery 8–12 weeks after completion of the neoadjuvant therapy. Low anterior resection (LAR), (extra levator) abdominoperineal resection (APR), anterior-, posterior- or total exenteration were performed. In some cases, the distal sacrum was resected.

IOBT was standby during the resection if inadequate resection margins were expected. During surgery, the surgeon, in collaboration with the radiation oncologist, determined the radicality of the resection by means of observation and palpation of the resection margin combined with information obtained from the preoperative MRI. In case of a clinically (expected) R1 resection, IOBT was performed. In case of an R0 or R2 resection, multiple irradical resection planes or a hemodynamically unstable patient, IOBT was omitted. Frozen sections were not mandatory.

Our IOBT procedure largely corresponds to the procedure described by Deurloo et al. [29]. In preparation of the IOBT procedure, library plans were prepared, which are optimized at the reference depth of the complete target area except for the dwell positions at the angular points. During surgery, the size of the irradical resection was determined, into which the flexible intraoperative template (FIT) was placed. A FIT is a 5 mm thick flexible silicone template which contains parallel catheters spaced 1 cm apart. The FIT could be cut into the desired geometry. Because of the flexibility of the FIT, the FIT could be placed in the most optimal position in which the FIT is well aligned with the target volume. To define the target area, the FIT was placed at the tissue surface area, which was marked by clips. The treatment plans were selected from the library and a dose of 10 Gy was specified at the reference depth at 1 cm from the surface of the FIT. The total duration of the intraoperative irradiation was 10–20 minutes. Appendix A demonstrated the adjustment and placement of the FIT. The specimen was fixed for 24 hours in formalin. The radicality of the resection was defined according to guidelines; R0: free surgical margins (>1mm), R1: microscopically involved margins ($\leq$1mm) and R2: macroscopically involved margins [30].

Acute side-effects, within 30 days after surgery, and late side-effects, within 90 days after surgery, were retrospectively classified according to Clavien-Dindo [31] and the Common Terminology Criteria for Adverse Events version 5 [32], based on the reports of the treated physician.

Statistics

Proportions were compared with chi-square tests and continuous parameters, depending on the distribution of the data, with *T*-test or Mann-Whitney *U* test. All tests were two-tailed, and *p*-values $\leq$ 0.05 were considered statistically significant. The positive predictive value (PPV) was calculated as the number of R1/2 resections at histopathological evaluation divided by the number of clinically suspected R1/2 resections during surgery. Sensitivity was calculated as the number of R1 frozen sections divided by the number of R1 resections at histopathological evaluation. Patients were followed-up until five years after surgery. Median follow-up was calculated from the date of surgery until censoring. The overall survival was calculated from the date of surgery until the last follow-up or death using the Kaplan-Meier method. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, New York, USA). The overall survival figure was conducted by R version 4.0.2.

Results

In total, 132 patients were scheduled for surgery with IOBT standby. Patients' characteristics are shown in Table 1. IOBT was performed in 42 patients. The IOBT-performed group (n = 42) consisted of 24 LARC, and 18 RRC patients and the IOBT-omitted group (n = 90) of 46 LARC and 44 RRC patients including ten patients by whom the tumour was not resected (Appendix B). Of the patients with recurrent rectal cancer, 12 patients had actually recurrent sigmoid carcinoma located at the colorectal anastomosis in the pelvis.

Of the LARC patients (n = 70), 84.3% received 50.0/50.4 Gy (n = 59). In 96.6% of patients concomitant chemotherapy was given (n = 57). Concomitant chemotherapy was omitted in two patients (3.4%) because of thrombopenia (n = 1) and respiratory infection (n = 1). In one patient (1.4%), chemoradiotherapy was prematurely stopped because of extreme anxiety regarding the treatment which did not resolve by medication. Nine patients (12.9%) received 5x5 Gy radiotherapy, of which six patients (66.7%) were treated according to the M1-regimen. One patient (1.4%) was treated with 30.6 Gy and concomitant capecitabine because of prior radiotherapy for a bladder tumour. Of the RRC patients (n = 62), 58.1% (n = 36) were re-irradiated with a total dose of 30.0/30.6 Gy and 97.2% (n = 35) of them also received concomitant chemotherapy. In total, 24 radiotherapy naïve RRC patients (38.7%) received long-course radiotherapy, and 95.8% (n = 23) received concomitant chemotherapy. Concomitant chemotherapy was omitted because of gastrointestinal toxicity during chemotherapy for the primary tumour (n = 2). In total, two patients (3.2%) were treated with 5x5 Gy, of which one patient according to the M1 regimen.

The median interval between last neoadjuvant therapy and surgery for LARC was 13 weeks (interquartile range (IQR) 10–17 weeks) and for RRC 12 weeks (IQR 9–15 weeks). All LARC patients (n = 70) and 90.3% of the RRC patients (n = 56) underwent surgery (Appendix B). Reasons to omit surgery were: tumour progression with no curative options (n = 4) and patient refusal (n = 2). During the resection, four RRC cases were irresectable and therefore not eligible for IOBT, leaving 122 patients in the analysis (Appendix B). In 42 patients IOBT was given during the resection.

Table 1
Patient and preoperative treatment characteristics.

	IOBT performed (n = 42)				IOBT omitted (n = 90)			
	LARC (n = 24)		RRC (n = 18)		LARC (n = 46)		RRC (n = 44)	
Gender								
Male	18	(75.0)	13	(72.2)	27	(58.7)	24	(54.5)
Female	6	(25.0)	5	(27.8)	19	(41.3)	20	(45.5)
Age in years (mean, range)								
	62	[33–79]	60	[41–72]	63	[35–83]	67	[36–80]
Histology tumour								
Adenocarcinoma	24	(100.0)	14	(77.8)	46	(100.0)	27	(61.4)
Neuroendocrine	0	(0.0)	1	(5.6)	0	(0.0)	1	(2.3)
Mucinous	0	(0.0)	0	(0.0)	0	(0.0)	1	(2.3)
Unknown	0	(0.0)	3	(16.7)	0	(0.0)	15	(34.1)
cT- and N-stage								
cT3N0	2	(8.3)	10	(55.6)	1	(7.7)	17	(38.6)
cT3N+	6	(25.0)	1	(5.6)	18	(39.1)	8	(18.2)
cT4N0	4	(16.7)	5	(27.8)	5	(10.9)	12	(27.3)
cT4N+	12	(50.0)	2	(11.1)	22	(47.8)	7	(15.9)
cM-stage								
cM0	22	(91.7)	14	(77.8)	42	(91.3)	34	(77.3)
cM1	2	(8.3)	4	(22.2)	4	(8.7)	10	(22.7)
Location cM-stage								
Liver	1	(50.0)	0	(0.0)	4	(57.1)	6	(60.0)
Pulmonary	0	(0.0)	3	(75.0)	2	(28.6)	1	(10.0)
Lymphatic	1	(50.0)	0	(0.0)	1	(14.3)	2	(20.0)
Peritoneum	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)
Oligometastasis[a]	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)

Data is presented as n (%).
IOBT intra-operative brachytherapy; *LARC* locally advanced rectal cancer; *RRC* recurrent rectal cancer.
[a] symphysis pubis.

The location of IOBT was lateral pelvic sidewall in 54.8% (n = 23) and pre-sacral in 45.2% (n = 19) of patients (table 2). An APR was significantly more often performed in IOBT-omitted patients.

Histopathological characteristics are listed in Table 2, Figs. 1A and 1B. In total, 34.4% (n = 42) patients received IOBT. Of these patients, IOBT was given in 41 (97,6%) because of clinical suspicion of an R1 resection, in the other patient who underwent IOBT the resection was clinically judged as R0; however, the frozen section showed an R1 resection. In the final histopathological evaluation 23 (54.8%) R1 and 19 (45.2%) R0 resections were found. In total, overtreatment with IOBT occurred in 19 patients; 14 out of 24 (58.3%) LARC and 5 out of 18 (27.8%) RRC patients. In the remaining 80 patients (65.6%), IOBT was omitted. In 76 patients (95.0%), an R0 resection was suspected during surgery. At histopathological evaluation, 63 resections (82.9%) were R0 and 13 resections (17.1%) were R1. Because of a negative frozen section, three times (3.8%) IOBT was omitted while an R1 resection was suspected. Once (1.3%), an R2 resection was accomplished. In conclusion, undertreatment occurred in 5 out of 46 (10.9%) LARC patients and 9 out of 34 (26.5%) RRC patients.

In the total patient group (n = 122), the PPV of the clinical evaluation was 53.3%. In case of LARC and RRC, the PPV was 44.4% and 66.7%, respectively. Frozen sections were taken in 44 patients (36.1%) and were accomplished with a low sensitivity of 61.1%. The sensitivity and specificity of frozen sections in LARC patients (n = 18) was 40.0% and 76.9% and in RRC patients (n = 26) 69.2% and 91.6%, respectively.

One patient (0.8%) died within 30 days. This patient died of acute pulmonary haemorrhage 15 days after surgery with unknown origin as cause of death. No grade IV toxicity occurred. Although not significant, acute pain grade I-II occurred numerically twice as often in patients who underwent IOBT (p = 0.06). In total, 4.8% and 2.5% of the acute pain grade I-II were neuropathic in the IOBT-performed and IOBT-omitted group, respectively (p = 0.51). Although also not significant, acute gastrointestinal toxicity grade III was more reported by patients in whom IOBT was omitted (p = 0.029). In conclusion, there were no significant differences in acute and late toxicity between these groups (Table 3).

The median follow-up was 35.3 months (interquartile range 19.6–51.8). Regardless of radicality, the overall survival three years after surgery was 80.2% in the IOBT-omitted LARC and RRC patients (n = 80) and 68.6% in the IOBT-performed LARC and RRC patients (n = 42) (p = 0.007) (Appendix C).

Discussion

This is the first study which evaluates the clinical selection strategy for IOBT in LARC and RRC patients. This study demonstrates that in the vast majority (89.1%) of LARC patients, the judgement of the surgeon in collaboration with the radiation oncologist to omit IOBT was correct. However, in RRC, the clinical judgment on the radicality of the resection was correct in only 69.2% of patients. An R1 resection was diagnosed in 26.5% of IOBT-omitted patients. Overall, 17.5% of the total group of patients with IOBT standby were undertreated (IOBT-omitted in R1 resection).

In our study, only patients with a clinically suspected R1 resection received IOBT. We demonstrated corresponding PPVs of 53.3%, 44.4% and 66.7% in the total patient group, LARC and RRC patients, respectively. A high PPV indicates that when a tumour was clinically predicted as R1/2, this was usually true. To the best of our knowledge, no other studies are determining PPV of the clinical selection strategy. Comparable to our research, there are two other studies in which not all patients received IOBT [11,13]. In these studies, R0 based on frozen section analysis was used for decision-making. However, frozen sections can provide false negative diagnosis and are time-consuming [33,34]. In the current study, we sampled for frozen sections in 36.1% of cases and reached a low sensitivity of 61.1%. In RRC patients frozen sections were taken more often (in 61.1% and 44.1% in the IOBT-performed and IOBT-omitted, respectively). This suggests that the resection in

Table 2
Surgical and pathology characteristics.

	IOBT performed (n = 42)				IOBT omitted IOBT omitted (n = 80)			
	LARC (n = 24)		RRC (n = 18)		LARC (n = 46)		RRC (n = 34)	
Type of resection								
LAR	6	(25.0)	2	(11.1)	16	(34.8)	4	(11.8)
APR	8	(33.3)	3	(16.7)	22	(47.8)	14	(41.2)
Anterior exenteration	1	(4.2)	3	(16.7)	2	(4.3)	0	(0.0)
Posterior exenteration	0	(0.0)	0	(0.0)	0	(0.0)	3	(8.8)
Total exenteration	9	(37.5)	5	(27.8)	6	(13.0)	7	(20.6)
Local excision	0	(0.0)	5	(27.8)	0	(0.0)	6	(17.6)
Location IOBT								
Sacral	13	(54.2)	6	(33.3)				
Pelvic bone	11	(45.8)	12	(66.7)				
IOBT planes								
1 plane	22	(91.7)	18	(100.0)				
2 planes	2	(8.3)	0	(0.0)				
Radicality of surgery (clinical judgement)								
R0 (>1 mm)	0	(0.0)	1	(5.6)	43	(93.5)	33	(97.1)
R1 (≤1 mm)	24	(100.0)	17	(94.4)	2	(4.3)	1	(2.9)
R2 (irradical)	0	(0.0)	0	(0.0)	1	(2.2)	0	(0.0)
Radicality of frozen section								
R0 (>1 mm)	4	(16.7)	1	(5.6)	9	(19.6)	15	(44.1)
R1 (≤1 mm)	5	(20.8)	10	(55.6)	0	(0.0)	0	(0.0)
R2 (irradical)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
No frozen section taken	15	(62.5)	7	(38.9)	37	(80.4)	19	(55.9)
Radicality of pathology								
R0 (>1 mm)	14	(58.3)	5	(27.8)	40	(87.0)	25	(73.5)
R1 (≤1 mm)	10	(41.7)	13	(72.2)	5	(10.9)	*9	(26.5)
R2 (irradical)	0	(0.0)	0	(0.0)	1	(2.2)	0	(0.0)
Overall judgement								
Correct judgement	10	(41.7)	13	(27.8)	40	(87.0)	25	(73.5)
Overtreatment[a]	14	(58.3)	5	(72.2)	-	–		
Undertreatment[b]	–		–		5	(10.9)	9	(26.5)

Data is presented as n (%).
IOBT intra-operative brachytherapy; *LARC* locally advanced rectal cancer; *RRC* recurrent rectal cancer; *R0* clear resection margins; *R1* ≤ 1 mm resection margin between 0 and 1 mm; *R2* macroscopic residual tumour.
*One patient was haemodynamically unstable during surgery; therefore it was not possible to perform IOBT.
[a] IOBT performed and at histopathological evaluation R0
[b] IOBT omitted and at histopathological evaluation R1

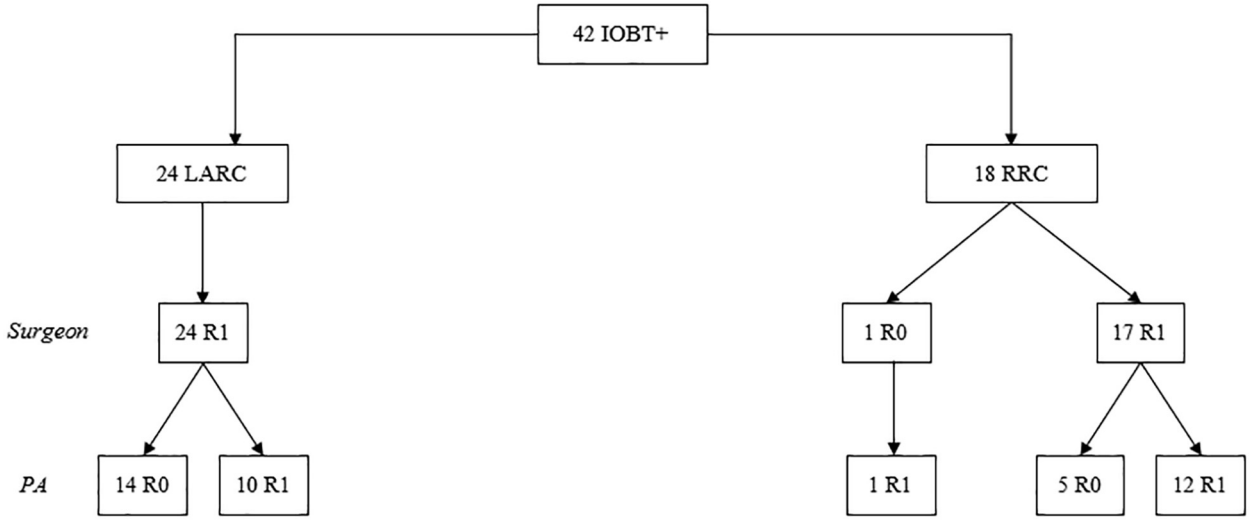

Fig. 1A. Surgical and histopathological resection margin of IOBT performed patients.

RRC patients is more difficult to judge for radicality, and then a frozen section could be useful. However, accurate clinical judgement of resection margin for frozen section analysis is usually hampered by fibrosis after previous resection or previous preoperative radiotherapy [35]. Because of this, the more aggressive biological behaviour of RRC and most importantly, the resection which is beyond normal anatomic surgical planes, could result in a higher risk of positive resection margins (R1) [36–38]. However, the specificity of a frozen section was only 50% in LARC patients in which an R0 resection was obtained and IOBT was performed (n = 9), respectively (data not shown). Besides, the sensitivity and specifity of all LARC patients in which a frozen section was takan was 40.0%

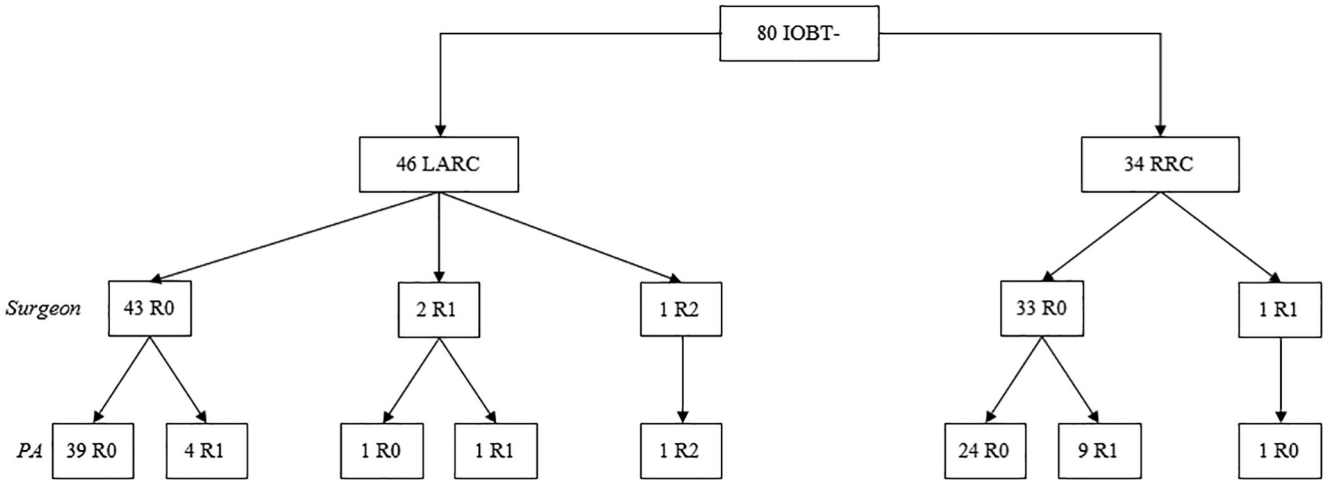

Fig. 1B. Surgical and histopathological resection margin of IOBT omitted patients in patients with a resected tumour only.

Table 3
Acute and late toxicity.

	IOBT performed (n = 42)		IOBT omitted (n = 80)		p-value
Acute toxicity Grade 1-2[a]					
Gastrointestinal	4	(9.5)	14	(17.5)	0.24
Infections	10	(23.8)	13	(16.3)	0.31
Nervous system	3	(7.1)	8	(10.0)	0.60
Pain	13	(31.0)	13	(16.3)	0.06
Sexual	1	(2.4)	0	(0.0)	0.17
Urinary	12	(28.6)	25	(31.3)	0.76
Vascular	2	(4.8)	1	(1.3)	0.23
Wound dehiscence	9	(21.4)	11	(13.8)	0.28
Acute toxicity Grade 3-4[a, +]					
Gastrointestinal	1	(2.4)	9	(11.3)	0.09
Infections	3	(7.1)	3	(3.8)	0.41
Wound	3	(7.1)	2	(2.5)	0.22
Late toxicity Grade 1-2[b]					
Infections	0	(0.0)	1	(1.3)	0.47
Pain	2	(4.8)	2	(2.5)	0.97
Wound	1	(2.4)	2	(2.5)	0.97
Late toxicity Grade 3-4[b, +]					
Gastrointestinal	1	(2.4)	3	(3.8)	0.69
Infections	1	(2.4)	0	(0.0)	0.17
Vascular	1	(2.4)	0	(0.0)	0.17

IOBT intra-operative brachytherapy.
[a]according to Clavien Dindo.
[b]according to Common Terminology of Criteria for Adverse Events version 5.
[+]no grade 4 toxicity occurred.

and 76.9%, whereas the sensitivity and specifity was 69.2% and 91.6% in RRC patients respectively. In addition, in only 47.7% of all LARC patients who received IOBT (n = 24) because of an R1 resection, were also scored as an R1 resection at histopathological evaluation. Therefore, frozen sections should be omitted in LARC patients.

Although not significant, acute pain grade I-II was reported twice as often in patients who underwent IOBT reported (p = 0.06). This may be explained by the fact that an extensive resection was performed in this patient group. Furthermore, acute nervous system toxicity grade I-II was comparable between the groups and occurred in 7.1% and 10.0% in the IOBT-perfomed and IOBT-omitted group, respectively. Neuropathy is a serious toxicity [20]. In our study, nervous system toxicity and neuropathic pain occurred only as grade 1–2 (in total: 11.9% (n = 5) in IOBT-performed and 12.5% (n = 10) in IOBT-omitted patients). Haddock et al. demonstrated comparable grade 1–2 neuropathy symptoms of 12.4% of patients [20]. However, Haddock et al. used IORT instead of IOBT, which is known for its homogeneous target and greater depth dose [39]. It seems that most acute pain grade I-II was related to the extension of the resection and that this was comparable between the groups (23.8% vs. 13.8% in the IOBT-performed and IOBT-omitted group, respectively (p = 0.16), data not shown). Since postoperative morbidity (grade $\geq$ 3) is most often related to the extent of the resection [40], it could be expected that IOBT dependent complications might occure more than 90 days after surgery.

Acute gastrointestinal toxicity grade III was numerically more reported by IOBT-omitted patients (p = 0.09). All acute gastrointestinal toxicity, accept for anastomotic leakage, occurred in patients who underwent an APR. The extensiveness of an APR is probably associated with an increased risk of systemic inflammatory response which may result in hypotension and therefore more gastrointestinal toxicity. Possibly the small numbers contributes to the numerical difference in gastrointestinal toxicity. Without clear explanation, anastomotic leakage occurred in 14.7% of the patients who underwent a LAR or anterior exenteration (data not shown). The radiotherapy target volume in both groups was tumour with

margin, the mesorectal area and presacral and internal iliac lymph node region. So target volume, and therefore organs at risk, does not explain the numerical difference in gastrointestinal toxicity.

We demonstrated a three-year overall survival of 68.6% and 80.2% in IOBT-performed and IOBT-omitted patients, respectively. Since IOBT-omitted patients lived significantly longer, this suggests that the clinical selection strategy went well. However, the patient groups in our study are small and heterogeneous. Besides, in 14 patients (17.5%) in who IOBT was omitted an R1 resection was found at histopathological evaluation. So conclusions must be drawn with caution. Besides, two randomised trials failed to demonstrate a survival benefit of IOBT-performed patients as well [22,23].

There are some limitations of the current study. IOBT is not often performed in the Netherlands, therefore the numbers are small. Besides, the patient population is heterogeneous. The CTCAE scoring system is used retrospectively, which could have resulted in underestimation of the toxicity. However, we believe that the number of retrospectively scored toxicity is accurate, since toxicity was asked at every follow-up moment. Though, toxicity results should be interpreted with cautions.

In our study patients received 1x10 Gy IOBT only in case an irradical resection was suspected. However, the accurate selection of an expected irradical resection margins was difficult, resulting in undertreatment (R1 resection and IOBT-omitted) in 17.5% (14/80) of the patients. In the current study, the use of frozen sections did not seem to improve the accuracy. Promising devices and methods to improve detection of R1 marigins per-operatively could be the use of bevacizumab-800CW by back-table and intra-operative fluorescence-guided imaging, computer navigation-assisted surgery or diffuse reflectance spectroscopy [41,42].

Conclusions

We demonstrated that correct clinical judgement to perform IOBT occurred in 41.7% of LARC patients and 72.2% of RRC patients. In IOBT-omitted patients, a correct clinical judgement was accomplished in 87.0% of LARC and 73.5% of RRC patients. Since only 10.9% of the LARC patients were undertreated, we can conclude that the clinical selection strategy in LARC patients went well in the vast majority of patients. However, 26.5% of RRC patients were undertreated (IOBT-omitted and R1 resection at histopathology). Moreover, patients who received IOBT had acceptable toxicity and comparable toxicity to patients who did not receive IOBT. Based on the current results, we recommend performing IOBT in all RRC patients at risk of an R1 resection since in RRC it is often their salvage treatment, and IOBT is accompanied by acceptable toxicity. For RRC patients who are at risk of an R1 resection we advise to referre this patient to a hospital which is able to perform IOBT.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like to thank all referral hospitals (Appendix D) for their contribution to follow-up data.

Sources of support

None

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.03.010.

References

[1] Bosset J-F, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355(11):1114–23. https://doi.org/10.1056/NEJMoa060829.
[2] Gérard J-P, Conroy T, Bonnetain F, Bouché O, Chapet O, Closon-Dejardin M-T, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24 (28):4620–5. https://doi.org/10.1200/JCO.2006.06.7629.
[3] Braendengen M, Tveit K, Berglund A, Birkemeyer E, Frykholm G, Påhlman L, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. J Clin Oncol 2008;26:3687–94. https://doi.org/10.1200/JCO.2007.15.3858.A.
[4] Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351(17):1731–40. https://doi.org/10.1056/NEJMoa040694.
[5] Dresen RC, Gosens MJ, Martijn H, Nieuwenhuijzen GA, Creemers G-J, Daniels-Gooszen AW, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol 2008;15(7):1937–47. https://doi.org/10.1245/s10434-008-9896-z.
[6] Holman FA, Bosman SJ, Haddock MG, Gunderson LL, Kusters M, Nieuwenhuijzen GAP, et al. Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres. Eur J Surg Oncol 2017;43(1):107–17. https://doi.org/10.1016/j.ejso.2016.08.015.
[7] Mohiuddin M, marks GM, Lingareddy V, Marks J. Curative surgical resection following reirradiation for recurrent rectal cancer. Int J Radiat Oncol Biol Phys 1997;39(3):643–9.
[8] Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. J Clin Oncol 2007;25(8):971–7. https://doi.org/10.1200/JCO.2006.10.0255.
[9] Kusters M, Holman FA, Martijn H, Nieuwenhuijzen GA, Creemers G-J, Daniels-Gooszen AW, et al. Patterns of local recurrence in locally advanced rectal cancer after intra-operative radiotherapy containing multimodality treatment. Radiother Oncol 2009;92(2):221–5. https://doi.org/10.1016/j.radonc.2009.03.002.
[10] Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers G-J, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. Br J Surg 2014;101(10):1280–9. https://doi.org/10.1002/bjs.2014.101.issue-1010.1002/bjs.9569.
[11] Hahnloser D, Nelson H, Gunderson LL, Hassan I, Haddock MG, O'Connell MJ, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. Ann Surg 2003;237(4):502–8. https://doi.org/10.1097/01.SLA.0000059972.90598.5F.
[12] M. Vermaas F.T.J. Ferenschild J.J.M.E. Nuyttens A.W.K.S. Marinelli T. Wiggers J. R.M.M. van der Sijp et al. Preoperative radiotherapy improves outcome in recurrent rectal cancer 48 5 2005 918 928 10.1007/s10350-004-0891-6.
[13] Wiig JN, Tveit KM, Poulsen JP, Olsen DR, Giercksky K-E. Preoperative irradiation and surgery for recurrent rectal cancer. Will intraoperative radiotherapy (IORT) be of additional benefit? A prospective study. Radiother Oncol 2002;62(2):207–13. https://doi.org/10.1016/S0167-8140(01)00486-8.
[14] Bosman SJ, Vermeer TA, Dudink RL, de Hingh IHJT, Nieuwenhuijzen GAP, Rutten HJT. Abdominosacral resection: Long-term outcome in 86 patients with locally advanced or locally recurrent rectal cancer. Eur J Surg Oncol 2014;40 (6):699–705. https://doi.org/10.1016/j.ejso.2014.02.233.
[15] Holman FA, Haddock MG, Gunderson LL, Kusters M, Nieuwenhuijzen GAP, van den Berg HA, et al. Results of intraoperative electron beam radiotherapy containing multimodality treatment for locally unresectable T4 rectal cancer: a pooled analysis of the Mayo Clinic Rochester and Catharina Hospital Eindhoven. J Gastrointest Oncol 2016;7(6):903–16.
[16] F.T.J. Ferenschild M. Vermaas J.J.M.E. Nuyttens W.J. Graveland A.W.K.S. Marinelli J.R. van der Sijp et al. Value of intraoperative radiotherapy in locally advanced rectal cancer 49 9 2006 1257 1265 10.1007/s10350-006-0651-x.
[17] Roeder F, Treiber M, Oertel S, Dinkel J, Timke C, Funk A, et al. Patterns of failure and cocal control after intraoperative electron boost radiotherapy to the presacral space in combination with total mesorectal excision in patients with locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2007;67:1381–8. https://doi.org/10.1016/j.ijrobp.2006.11.039.
[18] Glyn T, Frizelle F. Quality of life outcomes in patients undergoing surgery for locally recurrent rectal cancer. Semin Colon Rectal Surg 2020;31(3):100767. https://doi.org/10.1016/j.scrs.2020.100767.
[19] Abdelfatah E, Page A, Sacks J, Pierorazio P, Bivalacqua T, Efron J, et al. Postoperative complications following intraoperative radiotherapy in abdominopelvic malignancy: A single institution analysis of 113 consecutive patients. J Surg Oncol 2017;115(7):883–90. https://doi.org/10.1002/jso.24597.
[20] Haddock MG, Miller RC, Nelson H, Pemberton JH, Dozois EJ, Alberts SR, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys 2011;79 (1):143–50. https://doi.org/10.1016/j.ijrobp.2009.10.046.

[21] Wiig JN, Giercksky K-E, Tveit KM. Intraoperative radiotherapy for locally advanced or locally recurrent rectal cancer: Does it work at all?. Acta Oncol (Madr) 2014;53(7):865–76. https://doi.org/10.3109/0284186X.2014.895037.
[22] Dubois J-B, Bussieres E, Richaud P, Rouanet P, Becouarn Y, Mathoulin-Pélissier S, et al. Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. Radiother Oncol 2011;98(3):298–303. https://doi.org/10.1016/j.radonc.2011.01.017.
[23] Masaki T, Takayama M, Matsuoka H, Abe N, Ueki H, Sugiyama M, et al. Intraoperative radiotherapy for oncological and function-preserving surgery in patients with advanced lower rectal cancer. Langenbeck's Arch Surg 2008;393 (2):173–80. https://doi.org/10.1007/s00423-007-0260-8.
[24] Mannaerts GHH, Rutten HJT, Martijn H, Hanssens PEJ, Wiggers T. Comparison of intraoperative radiation therapy-containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer. Dis Colon Rectum 2001;44:1749–58. https://doi.org/10.1007/bf02234450.
[25] Mannaerts GHH, Rutten HJT, Martijn H, Hanssens PEJ, Wiggers T. Effects on functional outcome after IORT-containing multimodality treatment for locally advanced primary and locally recurrent rectal cancer. Int J Radiat Oncol Biol Phys 2002;54(4):1082–8. https://doi.org/10.1016/S0360-3016(02)03012-2.
[26] Alektiar KM, Zelefsky MJ, Paty PB, Guillem J, Saltz LB, Cohen AM, et al. High-dose-rate intraoperative brachytherapy for recurrent colorectal cancer. Int J Radiat Oncol 2000;48(1):219–26. https://doi.org/10.1016/S0360-3016(00)00634-9.
[27] Roels S, Duthoy W, Haustermans K, Penninckx F, Vandecaveye V, Boterberg T, et al. Definition and delineation of the clinical target volume for rectal cancer. Int J Radiat Oncol Biol Phys 2006;65(4):1129–42. https://doi.org/10.1016/j.ijrobp.2006.02.050.
[28] van Dijk TH, Tamas K, Beukema JC, Beets GL, Gelderblom AJ, de Jong KP, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. Ann Oncol 2013;24(7):1762–9. https://doi.org/10.1093/annonc/mdt124.
[29] Kolkman-Deurloo I-K, Nuyttens JJ, Hanssens PEJ, Levendag PC. Intraoperative HDR brachytherapy for rectal cancer using a flexible intraoperative template: Standard plans versus individual planning. Radiother Oncol 2004;70(1):75–9. https://doi.org/10.1016/j.radonc.2003.10.010.
[30] Wittekind C, Compton C, Quirke P, Nagtegaal I, Merkel S, Hermanek P, et al. A uniform residual tumor (R) classification: Integration of the R classification and the circumferential margin status. Cancer 2009;115(15):3483–8. https://doi.org/10.1002/cncr.v115:1510.1002/cncr.24320.
[31] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: A new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205–13. https://doi.org/10.1097/01.sla.0000133083.54934.ae.
[32] Cancer Therapy Evaluation Program. Common terminology criteria for adverse events v5.0. Common Terminol Criteria Advers Events v30 2017. https://doi.org/10.1080/00140139.2010.489653.
[33] Santana RP, Morais NS, Samary YRS, Bezerra ALR, Takano DM. Evaluation of the accuracy of frozen section in different anatomical sites. J Bras Patol e Med Lab 2018;54:319–24. https://doi.org/10.5935/1676-2444.20180053.
[34] Kos M, Krušlin B, Čupić H, Belicza M. Time consuming and decision making process in frozen section surgical pathology service. Acta Clin Croat 2005;44:197–201.
[35] Starzewski JJ, Pająk JT, Pawełczyk I, Lange D, Gołka D, Brzezińska M, et al. The radiation-induced changes in rectal mucosa: Hyperfractionated vs. hypofractionated preoperative radiation for rectal cancer. Int J Radiat Oncol Biol Phys 2006;64(3):717–24. https://doi.org/10.1016/j.ijrobp.2005.08.009.
[36] Bhangu A, Ali SM, Darzi A, Brown G, Tekkis PP. Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer. Color Dis 2012;14:1457–66. https://doi.org/10.1111/j.1463-1318.2012.03005.x.
[37] Cyr DP, Zih FSW, Wells BJ, Swett-Cosentino J, Burkes RL, Brierley JD, et al. Long-term outcomes following salvage surgery for locally recurrent rectal cancer: A 15-year follow-up study. Eur J Surg Oncol 2020;46(6):1131–7. https://doi.org/10.1016/j.ejso.2020.02.032.
[38] Alberda WJ, Verhoef C, Schipper MEI, Nuyttens JJ, Rothbarth J, De Wilt JHW, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. Dis Colon Rectum 2015;58:677–85. https://doi.org/10.1097/DCR.0000000000000388.
[39] Calvo FA, Meirino RM, Orecchia R. Intraoperative radiation therapy first part: rationale and techniques. Crit Rev Oncol Hematol 2006;59(2):106–15. https://doi.org/10.1016/j.critrevonc.2005.11.004.
[40] Hyngstrom JR, Tzeng C-W, Beddar S, Das P, Krishnan S, Delclos ME, et al. Intraoperative radiation therapy for locally advanced primary and recurrent colorectal cancer: ten-year institutional experience. J Surg Oncol 2014;109 (7):652–8. https://doi.org/10.1002/jso.23570.
[41] de Jongh SJ, Tjalma JJJ, Koller M, Linssen MD, Vonk J, Dobosz M, et al. Back-table fluorescence-guided imaging for circumferential resection margin evaluation using bevacizumab-800CW in patients with locally advanced rectal cancer. J Nucl Med 2020;61(5):655–61. https://doi.org/10.2967/jnumed.119.232355.
[42] Baltussen EJM, Brouwer de Koning SG, Sanders J, Aalbers AGJ, Kok NFM, Beets GL, et al. Tissue diagnosis during colorectal cancer surgery using optical sensing: An in vivo study. J Transl Med 2019;17(1). https://doi.org/10.1186/s12967-019-2083-0.