Locally recurrent rectal cancer: improving radiation treatment

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Chapter 7

Postoperative complications following dose adaptation of Intraoperative Electron Beam Radiation Therapy (IOERT) for Locally Advanced or Recurrent Rectal Cancer

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Journal of Contemporary Brachytherapy. 2024 Apr; 16(2):85-94. doi: 10.5114/jcb.2024.139276.

ABSTRACT

Purpose: The benefit of intraoperative radiotherapy (IORT) in the treatment of locally advanced (LARC) or recurrent rectal cancer (LRRC) lies in its ability to provide a high radiation dose to a limited at-risk volume, thereby eliminating microscopic disease, whilst limiting toxicity concerns. A comparative study between high-dose-rate brachytherapy (IOBT) and intraoperative electron radiotherapy (IOERT) was performed, showing favourable LRFS after IOBT, possibly due to a higher surface dose that is inherent to the IOBT technique. The IOERT technique in CHE was adapted to increase the surface dose, aiming to improve local control. Postoperative complications due to an increased radiation dose remain of concern. This retrospective study compares complication rates before and after adapted IOERT dose.

Materials and methods: All patients undergoing surgery with IOERT for LARC or LRRC from September 2019 until July 2023 were selected. Patients selected until August 31, 2021, were included in the control cohort (n=108), from September 1, 2021, onwards were included in the intervention cohort (n=92). Perioperative and (major) postoperative complications were classified retrospectively; during admission, at 30 days and at 90 days.

Results: In LARC, a decrease in postoperative complications was seen (p=0.009). 19% of LARC patients experienced major postoperative surgical complications, i.e., Clavien-Dindo Grade 3b-5, regardless of treatment group. No difference in major 90-day complications was seen (p=0.142). In LRRC patients, use of induction chemotherapy dropped from 78% to 29% (p<0.001), complicating comparison. However, no difference in major postoperative complications was seen at 30 days (p=0.222) or 90 days (p=0.977) after surgery.

Conclusion: Increased surface dose of IOERT does not seem to lead to an increase in postoperative complications. Further research is needed to evaluate the efficacy of dose adaptation in IOERT to improve local oncological control rates. Routine evaluation of CTCAE scores in follow-up will help uncover possible long-term radiation-induced toxicity.

PURPOSE

In the field of rectal cancer, the risk of locoregional recurrence has been reduced by the introduction of Total Mesorectal Excision (TME) surgery, that has significantly improved locoregional control.[1–4] Neoadjuvant (chemo)radiotherapy has further reduced the chance of locoregional recurrence in patients with locally advanced rectal cancer (LARC).[5–8] Nevertheless, recurrences still occur and prove difficult to treat. In both primary and locally recurrent rectal cancer (LRRC), a microscopically radical (R0) resection margin has shown to be extremely important in improving local control.[4,7,9–11]

Intraoperative radiotherapy (IORT) can further improve local control in patients with locally advanced or recurrent rectal cancer (LARRC) by delivering a high dose of radiation to a limited at-risk volume, thus reducing excessive toxicity. By applying IORT to the at-risk resection margin, remaining microscopic disease may be treated intraoperatively.[12,13] IORT is mainly performed with electrons (IOERT), high-dose-rate (HDR) brachytherapy (IOBT), or low-kV X-rays (orthovoltage).

A recent article compared the results of IOERT versus IOBT for microscopically irradical (R1) resections in patients with LARRC.[14] An improvement in local recurrence-free survival (LRFS) was seen favouring IOBT. Not only does this suggest that IORT affects LRFS in general, but the difference in favour of IOBT raises the question of why this might be. Although many factors may have contributed, such as different patient populations, larger irradiated volumes, differences in operating times and various applicator types, one striking difference is the higher surface dose of IOBT compared to IOERT.[15] Since the surgical resection surface is the site where potential microscopic disease remains, it has been suggested that the different surface doses may have contributed strongly to the results. In a second article, the two techniques were compared and the IOERT technique was adapted to increase the surface dose to approximate that of IOBT (Figure 1).[16] First, a bolus of tissue equivalent Polymethyl methacrylate (PMMA) was added to the IOERT applicator exit to move the maximum dose to the tissue surface (Figure 2).The dose was then rescaled to increase the surface dose to approximate that of IOBT. The prescribed dose (10Gy) of the adjusted dose curve is still at 9mm, as in the original dose curve of IOERT. In this way, the dosimetric difference between IOERT and IOBT is reduced at the surface. One point of concern, however, is the potential additional toxicity caused by the higher surface dose. As described in Verrijssen et al, this was not expected, as the published literature on IOBT, which is characterized by a higher surface dose, does not show this increase in toxicity.[16] The present work aims to confirm this hypothesis.

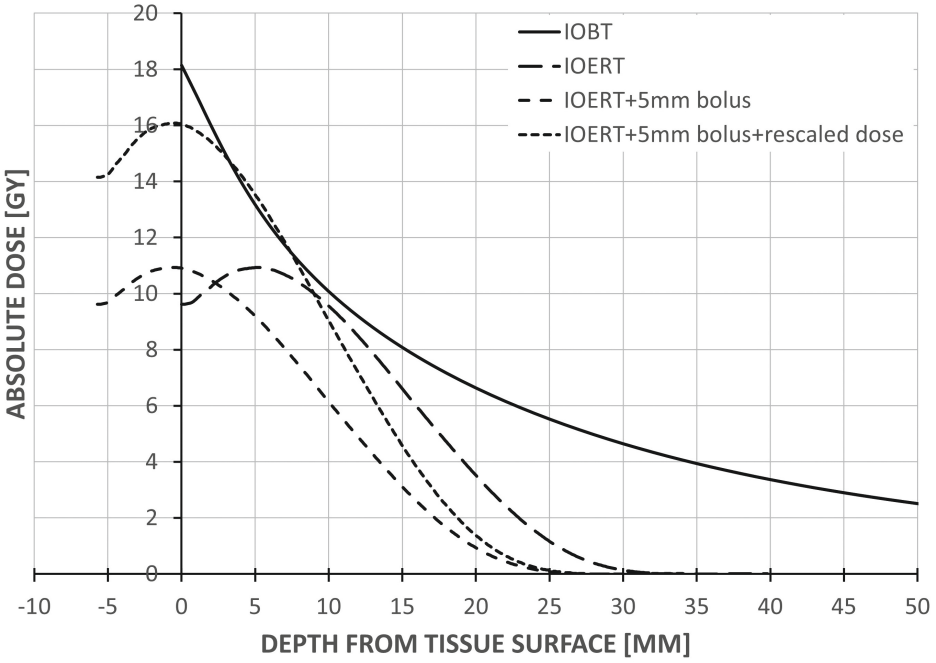

Figure 1. Graph showing the current situation for IOERT and IOBT in absolute dose at depth for IOBT (solid line) and IOERT (long dashed line). The short, dashed line illustrates the IOERT curve after applying a bolus, but before rescaling. The dotted line shows the IOERT curve with bolus and rescaling to deliver 10 Gy at 9 mm.

MATERIALS AND METHODS

Patient selection

All patients who underwent surgery in combination with IOERT for LARRC at Catharina Hospital Eindhoven (CHE) from September 1, 2019, to July 31, 2023, were selected. Patients treated until August 31, 2021, were included in the control cohort. Patients treated from September 1, 2021, onwards were included in the intervention cohort, after the adapted technique was introduced. Patients with a re-recurrence were excluded. Data of LRRC patients were extracted from a prospectively maintained database and were updated from electronic patient records as necessary. Data of LARC patients were retrieved from medical records. Information recorded consisted of baseline characteristics, neoadjuvant treatment, surgery, outcome, and follow-up. Follow-up was completed until August 29, 2023. The study was approved by the local medical ethics committee (nWMO-2022.130).

(Neoadjuvant) treatment

All patients received neoadjuvant (chemo)radiotherapy. For LARC, treatment regimens consisted of either short course radiotherapy (5x5Gy) or full course chemoradiotherapy (CRT) (25x2Gy), with concomitant capecitabine. LRRC patients received either full course CRT or chemo reirradiation (15x2Gy), with concomitant capecitabine. Selected LARRC patients received induction chemotherapy prior to (chemo)radiotherapy, which generally consisted of either 3-4 courses of CAPOX (capecitabine and oxaliplatin) or 4-6 courses of FOLFOX (5-FU, leucovorin and oxaliplatin).

Surgery was categorized as follows; abdominoperineal resection (APR); low anterior resection (LAR); total exenteration (TE) (consisting of a resection of the rectum, bladder, prostate and vesicles in male patients or ovaries, vagina, and uterus in female patients); and a tumour resection not otherwise specified (n.o.s.), i.e., tumour resection without formal bowel resection. All resections performed in addition to a formal bowel resection were documented separately (i.e., in the case of a TE, resections of the bladder, prostate and vesicles were also noted separately).

IOERT

A preliminary assessment of IOERT indication is performed for all patients undergoing either curative surgery or surgery in a palliative setting for maximal local control of LARRC. This is done during an expert multidisciplinary tumour board, consisting of at least an oncologic surgeon, a medical oncologist, a radiation oncologist and a radiologist, where staging at baseline and after neoadjuvant treatment is discussed. Perioperatively, the IOERT indication is reestablished by the surgeon and the radiation oncologist. In both instances, a clinical suspicion of either narrow or involved resection margins is considered an IOERT indication. Additional frozen sections of excised tissue can be used perioperatively to aid decision-making but are not required. The IOERT dose and irradiation site are also determined perioperatively, targeting the area at-risk for R1 resection. IOERT is administered via a Mobetron 2000 linear accelerator (IntraOp Medical, Sunnyvale California, USA), with energy of either 6, 9 or 12 MeV. Applicators with a diameter of five to ten centimetres can be used, with bevel angles of 0, 30 or 45 degrees. The dose rate is set at around 10 Gy/min. The IOERT dose previously depended on the depth of tissue considered at-risk for R1 resection, and was prescribed (at depth) at 10Gy, 12.5Gy or 14.4Gy to the 90% isodose surface. From September 1, 2021, onwards, all patients received a dose of 10Gy at the target depth, which corresponds to a dose between 15.5Gy and 16.5Gy at the tissue surface

(Figure 1).[16] The following IOERT variables are reported for each patient: Dose at target depth, dose at the surface (i.e., at 1mm tissue depth), and irradiated surface (cm^2).

Complications

Follow-up was performed according to the Dutch national guidelines for colorectal cancer.[17] Endpoints included all complications and readmissions within 30 days after surgery, as well as all major postoperative complications 90 days after surgery. Analyses were performed separately for LARC and LRRC. Perioperative and postoperative complications were retrospectively classified via the Clavien-Dindo classification.[18] The highest Clavien-Dindo grade was noted for each patient up to 30 days after surgery. Major postoperative complications (Clavien-Dindo grade 3b-5) were additionally classified at 90 days postoperatively. From September 1, 2021, adverse events were routinely assessed by the radiation oncologist, using the Common Terminology Criteria for Adverse Events Version 5.0 (CTCAE) at 3- and 12-months after IOERT.[19] These data were used to assess any long-term postoperative neuropathy. If not available, patient records were reviewed for evidence of peripheral neuropathy. No neuropathy was only classified as such if it was explicitly stated that no peripheral neuropathy was present.

Figure 2. Picture of the tissue-equivalent polymethyl methacrylate (PMMA) bolus attached to the IOERT applicator exit to move the maximum dose to the tissue surface.

Table 1. Baseline, tumour, and neoadjuvant treatment characteristics of patients with LARC and LRRC.

Patients with LARC		**Control n=54 (%)**	**Intervention n=47 (%)**	**Total n=101 (%)**	**p-value**
Gender	Male	35 (65)	28 (60)	63 (62)	0,588
	Female	19 (35)	19 (40)	38 (38)	
Age at diagnosis	Mean (SD)	62 (10,1)	60 (11,9)	61 (11,0)	0,180
T stage	T3	23 (43)	13 (28)	36 (36)	0,137
	T4	31 (57)	33 (72)	64 (64)	
N stage	N0	9 (17)	7 (15)	16 (16)	0,844
	N+	45 (83)	39 (85)	84 (84)	
M stage	M0	45 (83)	36 (77)	81 (80)	0.458
	M1	9 (17)	11 (23)	20 (20)	
MRF involved	Yes	44 (90)	39 (89)	83 (89)	0,857
Induction chemotherapy	No	30 (56)	19 (40)	49 (49)	0,129
	Yes	24 (44)	28 (60)	52 (52)	
Neoadjuvant RT	25x2Gy	47 (87)	41 (87)	88 (87)	0,722
	5x5Gy	6 (11)	4 (9)	10 (10)	
	Other	1 (2)	2 (4)	3 (3)	
Interval RT to surgery (weeks)	Median (IQR)	13 (12-15)	14 (12-18)	13 (12-16)	0,134
Patients with LRRC		**Control n=54 (%)**	**Intervention n=45 (%)**	**Total n=99 (%)**	**p-value**
Gender	Male	37 (69)	32 (71)	69 (70)	0,780
	Female	17 (32)	13 (29)	30 (30)	
Age at diagnosis	Mean (SD)	65 (9,0)	67 (8,5)	66 (8,8)	0,278
Multifocal recurrence	No	40 (76)	35 (78)	75 (77)	0,788
	Yes	13 (25)	10 (22)	23 (24)	
Induction chemotherapy	No	12 (22)	32 (71)	55 (44)	<0,001
	Yes	42 (78)	13 (29)	55 (56)	
Neoadjuvant RT	Full course	22 (41)	14 (31)	36 (36)	0,392
	Reirradiation	31 (57)	30 (67)	61 (62)	
	Other	1 (2)	1 (2)	2 (2)	
Metastases at diagnosis	No	48 (89)	43 (96)	91 (92)	0.286
	Yes	6 (11)	2 (4)	8 (8)	
Interval RT to surgery (weeks)	Median (IQR)	13 (11-14)	13 (11-14)	13 (11-14)	0,673

*MRF = mesorectal fascia, RT = radiation therapy. *Missing data were excluded from group comparisons **Due to rounding, not all percentages add up to 100%.*

Statistical analysis

Continuous data were expressed as a median (interquartile range (IQR)) or mean (standard deviation (SD)), as appropriate. Categorical data was presented as absolute numbers with percentages. Comparisons of continuous data were performed using independent T-tests, Wilcoxon sign rank test and Mann-Whitney U test, as appropriate. Comparisons of categorical data were performed using the Chi-Square test and Fisher-exact test, as appropriate. Two-sided p-values of <0.05 were considered statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 29.0, IBM Corp. Released 2022. Armonk, NY: IBM Corp.

RESULTS

Locally advanced rectal cancer

Between January 1, 2019, and July 31, 2023, 101 patients underwent surgery, of whom 54 (53%) were treated in the control group, and 47 (47%) in the (dose-escalated) intervention group. There were no significant differences in baseline characteristics, as summarized in Table 1. Surgeries performed were similar amongst treatment groups (p=0.248), as summarized in Table 2. Additional treatment characteristics of LARRC patients with metastatic disease can be found in the Supplementary Material. Overall, patients in the intervention group underwent fewer additional resections (13% vs 32%, p=0.025) than patients in the control group, with the exception that significantly more pelvic sidewall resections were performed in the intervention group (40% vs 19%, p=0.015). Of the 54 patients in the control cohort, 34 (63%) received 10Gy, 9 (17%) received 11.5Gy, 7 received 12.5Gy (13%) and 4 received 14.4Gy (7%), both at the surface and at depth. All patients in the intervention group received 10Gy at depth but obtained significantly higher IOERT dose at tissue surface (15.0Gy (n=1; 2%), 15.5Gy (n=20; 43%), 16.0Gy (n=26; 55%)), with a median of 16Gy (IQR 15.5-16) versus 10Gy (IQR 10-12) in the historical cohort (p<0.001). The irradiated surface was similar (p=0.13).

Table 3 shows comparisons of complications and readmissions for all patients. In LARC patients, the length of stay was shorter in the intervention group (7 days vs. 10 days, p=0.010). There were significantly fewer 30-day postoperative complications in the intervention group (80% vs. 55%, p=0.009), but the type of complications did not differ. Importantly, there was no increase in infectious gastrointestinal complications (p=0.267) or wound complications (p=0.748). Major postoperative complications were reported in

19% of patients, with no difference between treatment groups (20% vs 17%, p=0.761). There was no difference in complications at 90 days postoperatively (11% vs 23%, p=0.142), although data were missing in 24% of patients, mainly in the control group (30% vs 17%).

Locally recurrent rectal cancer

Between January 1, 2019, and July 31, 2023, 99 patients with LRRC underwent surgery, of which 45 (45%) were treated in the intervention group. The baseline characteristics of LRRC can be found in table 1. Primary tumour characteristics can be found in the supplementary material. No differences in baseline characteristics were observed. However, patients in the intervention cohort received significantly less induction chemotherapy (78% vs. 29%, p<0.001), but neoadjuvant CRT was similar (p=0.392).
Full details of the operation and IOERT are given in Table 2. Forty-nine percent of patients in the intervention group underwent a TE, compared to 19% in the control group (p=0.006). Significantly more bladder (53% vs 17%, p<0.001) and prostate resections (63% vs 27%, p=0.003) were performed in the intervention group, partly due to the higher number of TEs performed. Although the operations were more extensive, there was no difference in the duration of surgery (p=0.674).

Thirty-seven (67%) patients in the control group received 10Gy IOERT, 6 (11%) received 11.5Gy, 7 received 12.5Gy (13%) and 5 received 14.4Gy (9%), both at the surface and at the specification depth. The dose at depth was 10Gy for all patients in the intervention group, but the dose at the surface was significantly higher (15.5Gy (n=26; 58%), 16.0Gy (n=19; 42%)), with a median of 15.5Gy versus 10Gy (p<0.001). The irradiated surface was larger in the intervention group (40cm^2) than in the control group (28cm^2) (p=0.009). The overview of the applicator diameter and bevel used is presented in the Supplementary Material.

Postoperative complications were common but similar, occurring in 74% and 76% of patients, before and after dose adjustment, respectively (p=0.866). Major postoperative complications occurred in 18 patients before (33%) and in 11 patients after (24%) dose adjustment (p=0.624) at 30 days. There was no difference in the type of complications. No difference was found in major complications at 90 days (p=0.977), but data was missing in 32% and 22% of patients from the control and intervention group, respectively.

Table 2. Surgical and intraoperative radiation therapy characteristics of patients with LARC and LRRC.

		LARC				LRRC			
		Control n=54 (%)	**Intervention n=47 (%)**	**Total n=101 (%)**	**p-value**	**Control n=54 (%)**	**Intervention n=45 (%)**	**Total n=99 (%)**	**p-value**
Surgical procedure	LAR	18 (33)	23 (49)	41 (41)	0,248	9 (17)	3 (7)	12 (12)	0,006
	APR	29 (54)	18 (38)	47 (47)		18 (33)	14 (31)	32 (32)	
	Total exenteration	7 (13)	6 (13)	13 (13)		10 (19)	22 (49)	32 (32)	
	Resection N.O.S.	0 (0)	0 (0)	0 (0)		17 (32)	6 (13)	23 (23)	
Blood loss (litre)	Median (IQR)	1,4 (0,8-2,0)	0,9 (0,5-1,6)	1,1 (0,7-1,8)	0,062	2,0 (1,1-2,9)	2,5 (1,4-4,0)	2,2 (1,1-3,5)	0,069
Time surgery (hours)	Median (IQR)	4 (3-4)	4 (3-5)	4 (3-5)		5 (4-6)	5 (4-6)	5 (4-6)	0,674
Additional resection performed?	Yes	17 (32)	6 (13)	23 (23)	0,025	44 (82)	42 (93)	86 (87)	0,082
IOERT dose (Gy)	*Bladder*	7 (13)	6 (13)	13 (13)	0,990	9 (17)	24 (53)	33 (33)	<0,001
	Pelvic side wall	10 (19)	19 (40)	29 (29)	0,015	10 (19)	17 (38)	27 (27)	0,032
	Prostate	8 (23)	9 (32)	17 (27)	0,409	10 (27)	20 (63)	30 (44)	0,003
	Vesicles	15 (43)	17 (61)	32 (51)	0,159	18 (49)	22 (69)	40 (58)	0,092
At depth	Median (IQR)	10 (10-12)	10 (10-10)	10 (10-10)	<0,001	10 (10-12)	10 (10-10)	10 (10-13)	<0,001
At surface	Median (IQR)	10 (10-12)	16 (16-16)	14 (10-16)	<0,001	10 (10-12)	16 (16-16)	13 (10-16)	<0,001
Cumulative (EQD2)	Median (IQR)	n.a.	n.a.	n.a.	n.a.	78 (67-97)	94 (83-113)	94 (73-103)	0,002
Cumulative (EQD2 current tumour)	Median (IQR)	67 (67-71)	83 (83-85)	71 (67-83)	<0,001	53 (47-67)	65 (63-83)	63 (53-67)	<0,001
IOERT surface (cm2)	Median (IQR)	28 (28-40)	40 (28-40)	28 (28-40)	0,13	28 (28-40)	40 (28-40)	40 (28-40)	0,009

** Missing data were excluded from group comparisons.*

*** Due to rounding, not all percentages add up to 100%.*

**** Only men are included in group analysis of prostate and vesicle resections. No significant differences were reported in resections of the ureter, sacrum, lymph nodes, uterus, ovaries or vagina.*

Table 3. Group comparison of postoperative complications and readmission rates.

		LARC				LRRC			
		Control n=54 (%)	**Intervention n=47 (%)**	**Total n=101 (%)**	**p-value**	**Control n=54 (%)**	**Intervention n=45 (%)**	**Total n=99 (%)**	**p-value**
Admission (days)	Median (IQR)	10 (7-14)	7 (5-12)	9 (7-14)	0.010	11 (8-16)	11 (8-15)	11 (8-16)	0.894
Any complication (30d)	Any grade	43 (80)	26 (55)	69 (68)	0.009	40 (74)	34 (76)	74 (75)	0.866
Urogenital complications	Any grade	13 (24)	11 (23)	24 (24)	0.937	13 (24)	6 (13)	19 (19)	0.177
	Grade 1-2	13	10	23		11	5	16	
	Grade 3a-5	0	1	1		2	1	3	
Cardiopulmonary complications	Any grade	8 (15)	2 (4)	10 (10)	0.100	6 (11)	10 (22)	16 (16)	0.135
	Grade 1-2	7	2	9		5	8	13	
	Grade 3a-5	1	0	1		1	2	3	
Wound complications	Any grade	6 (11)	4 (9)	10 (10)	0.748	4 (7)	5 (11)	9 (9)	0.728
	Grade 1-2	1	0	1		2	4	6	
	Grade 3a-5	5	4	9		2	1	3	
Gastro-intestinal complications	Any grade	24 (44)	19 (40)	43 (43)	0.684	29 (54)	21 (47)	50 (51)	0.486
	Grade 1-2	13	12	25		15	15	30	
	Grade 3a-5	11	7	18		14	6	20	
GI: Ileus/Gastroparesis	Any grade	13 (24)	10 (21)	23 (23)	0.738	19 (35)	14 (31)	33 (33)	0.669
	Grade 1-2	11	8	19		14	12	26	
	Grade 3a-5	2	2	4		5	2	7	
GI: Infectious (including abscess)	Any grade	10 (19)	5 (11)	15 (15)	0.267	14 (26)	10 (22)	24 (24)	0.669
	Grade 1-2	2	2	4		4	5	9	
	Grade 3a-5	8	3	11		10	5	15	

Table 3. Continued

		LARC				LRRC			
		Control n=54 (%)	**Intervention n=47 (%)**	**Total n=101 (%)**	**p-value**	**Control n=54 (%)**	**Intervention n=45 (%)**	**Total n=99 (%)**	**p-value**
Other complications	Any grade	11 (20)	5 (11)	16 (16)	0.182	16 (30)	15 (33)	31 (31)	0.692
	Grade 1-2	10	4	14		11	8	19	
	Grade 3a-5	1	1	2		5	7	12	
Highest Clavien-Dindo (30d)	Grade 0-2	38 (70)	36 (77)	74 (73)	0.761	33 (61)	31 (69)	64 (65)	0.624
	Grade 3a	5 (9)	3 (6)	8 (8)		3 (6)	3 (7)	6 (6)	
	Grade 3b-5	11 (20)	8 (17)	19 (19)		18 (33)	11 (24)	29 (29)	
Readmission (30d)	Yes	4 (7)	5 (11)	9 (9)	0.730	15 (28)	6 (14)	21 (22)	0.101
Late major complications (31-90d) Grade 3b-5	No	4 (11)	9 (23)	13 (17)	0.142	14 (38)	12 (38)	26 (38)	0.977

** Missing data were excluded from group comparisons.*

*** Due to rounding, not all percentages add up to 100%.*

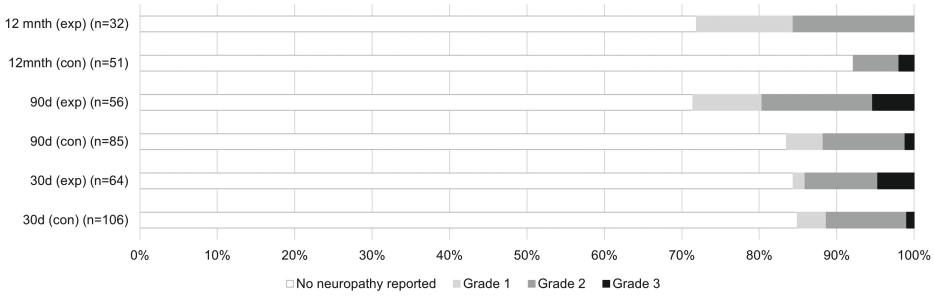

Figure 3. Physician-reported peripheral neuropathy relatively displayed. Missing data were excluded from analysis. Peripheral neuropathy was analysed for all patients, to account for the low number of events.

Peripheral neuropathy

Peripheral neuropathy was reported in 26 patients (15%) within 30 days and in 30 patients (21%) within 90 days of surgery, as shown in Table 4 and Figure 3. An increase in reported neuropathy was seen at 12 months postoperatively in the intervention group (28%), compared to the control group (8%) (p=0.019), but not at 30 or 90 days postoperatively. Data were missing in 15% at 30 days, in 30% at 90 days and in 59% at 12 months postoperatively. No CTCAE grade 4 or 5 neuropathy was observed. Operation reports were reviewed to investigate possible effects of surgery. In 12 patients (48%), neuropathy can be explained (in part) by the explicitly mentioned surgical resection of nerves or plexuses. Ten patients reported peripheral neuropathy at baseline that was due to chemotherapy or previous surgery. Peripheral neuropathy over time is shown in the Supplementary Material.

Table 4. Physician reported peripheral neuropathy.

Characteristic		Control n=108 (%)	Intervention n=92 (%)	Total n=200 (%)	p-value
Physician reported neuropathy	30 days (n=170)	16 (15)	10 (11)	26 (15)	0,379
	90 days (n=141)	14 (17)	16 (29)	30 (21)	0,258
	12 months (n=83)	4 (8)	9 (28)	13 (16)	0,019

DISCUSSION

This study suggests that increasing the IOERT surface dose in LARRC patients does not lead to an increase in postoperative complications. These results are in line with expectations expressed when the technique adaptation was introduced.[16] In Voogt et al., significantly more major complications occurred in LRRC patients treated with IOBT than with IOERT.[14]

These complications were presacral abscesses (26%), abdominal wound dehiscence with evisceration (8%), and intra-abdominal abscesses (6%). Several possible explanations have been mentioned, such as a larger irradiated area with IOBT, and a slower dose fall-off of IOBT, meaning that a larger volume of tissue receives a higher dose. Operating times are also generally longer as more time is required for applicator modulation and treatment planning. Another reason could be the higher surface dose of IOBT, with more heterogeneity within the surface dose and more hotspots. However, in this study, no increase in postoperative complications was observed despite an increase in the surface dose. This may indicate that the increased toxicity was caused by the other reasons mentioned.

In this study, there was a visible trend towards a larger irradiated area in the intervention group. However, the IOERT-irradiated volume was still smaller than that of IOBT. Previous studies have shown IOBT volumes are on average 2-3 times larger than IOERT with an upper limit exceeding 200 cm^2.[14,20–22] Therefore, the relatively small irradiated volume in IOERT may explain why no increase in complications was observed. An alternative hypothesis may be that although the surface dose was increased, the dose fall-off was steeper because of the dose build-up within the PMMA bolus (Figure 1). Moreover, the IOERT dose in the historical cohort was scaled up to 14.4 Gy to increase the surface dose; however, owing to the physical properties, this also leads to an increased dose beyond one centimetre depth. Therefore, with the PMMA bolus applied, theoretically, the dose at depth was less than that in the historical cohort.

Several factors complicated comparisons in this analysis. Due to the initiation of the PelvEx II trial in LRRC, the proportion of patients receiving induction chemotherapy decreased, as induction chemotherapy was standard of care for LRRC prior to the PelvEx II study in the CHE.[23] This may have decreased the perioperative morbidity, concealing the possible increase in toxicity due to IOERT. Although data on toxicity due to preoperative chemotherapy is lacking in LRRC, the RAPIDO trial in LARC patients saw no increase in postoperative complications after 6 cycles of CAPOX.[7] Moreover, in the current study, the proportion of patients treated with induction chemotherapy in LARC showed an increasing trend (44% versus 60%, p=0.129), in part due to the MEND-IT trial investigating the benefit of FOLFOXIRI induction chemotherapy in LARC.[24] Even so, in patients with LARC, no increase in toxicity was observed. Therefore, the confounding effect of induction chemotherapy on perioperative and postoperative complications may be minimal. Prospective data generated from both trials will provide more insight on induction chemotherapy-related complications.

The differences in surgical techniques further complicate the comparison. In patients with LARC, the proportion of LAR vs. APR vs. TE was consistent. In LRRC, resections were significantly more extensive in the intervention cohort, due to an increase in TEs (19% vs. 49%). This increase may be related to a cohort study comparing LRRC management between the Karolinska Institute (KAR) and CHE, revealing more R0 resections at KAR (76% R0 vs 61%), hypothesized to be due to more TEs (KAR 25% vs CHE 16%, p=0.02), with no difference in major complications (KAR 32% vs CHE 30%, p=0.742).[25] On the one hand, more extensive resections could lead to an increase in complications and length of surgery. On the other hand, a TE is an en-bloc resection, whereas operating more conservatively may result in additional partial resections, possibly leading to more tissue-healing complications. Nevertheless, no difference in complications was observed when stratifying for IOERT technique in either LARC or LRRC patients, despite varying operative management, supporting the idea that IOERT dose adaptation did not influence complications.

Peripheral neuropathy is an area of concern. The literature states that 3-23% of patients suffer from peripheral neuropathy due to extensive surgery and radiation within the pelvis.[26,27] Clinically, there seems to be underreporting of peripheral neuropathy, and it should be expected that this is also true in the current study. Although the data were limited, there was an increase in peripheral neuropathy in the intervention group at 12 months. However, shortly prior to introducing the dose-adaptation, a routine evaluation of peripheral neuropathy via CTCAE scoring at three months and one year postoperatively was introduced. Therefore, it is possible that the increase in peripheral neuropathy is merely due to improved reporting rather than due to the increased surface dose. Other factors influencing neuropathy are the surgery itself and chemotherapy.[28] As reported, neuropathy may also be explained by the performed surgery in several patients, as damage to the nerves or plexus within the pelvis was specifically mentioned in the surgical report. However, in reality, this percentage may be higher. When combining these factors, drawing conclusions, even on the extent of peripheral neuropathy, as well as the difference in neuropathy between IOERT techniques, is challenging. Standardized CTCAE scoring of peripheral neuropathies will help improve our understanding of this potentially invalidating toxicity following IOERT. Neuropathy should remain an area of caution, as it can lead to severe decrease in quality of life.[28–30]

One potential drawback of the new technique is the compromised view of the target volume due to the PMMA bolus attached at the applicator exit. Adequate inspection of the at-risk volume and the surrounding healthy tissue is necessary, with thorough multidisciplinary communication to deliver IOERT accurately and safely. Target volume reproducibility is also challenging and may impede future treatment planning or the understanding of IOERT-related complications. Intraoperative navigation may be able to provide a solution, by facilitating preoperative planning on MRI, intraoperative target volume definition and postoperative dose reconstruction.[31–34]

Ultimately, the goal is to improve the LRFS. In Voogt et al., a significantly higher LRFS was seen after IOBT versus IOERT.[14] There are many differences between IOERT and IOBT that may have influenced these results, such as the larger irradiated volumes or the flexible applicator in IOBT allowing for closer coverage of the at-risk area.[16] However, the fact remains that the at-risk area is generally at the tissue surface, at the resection margin Therefore, it was hypothesized that the higher surface dose for IOBT could have contributed largely to these results. Several papers, including that of Appelt et al., allude to a dose-response relationship for tumour regression in rectal cancer.[35] A higher surface dose could translate to a more effective eradication of the remaining microscopic disease. A longer follow-up is needed to evaluate oncological outcomes.

This study has several limitations. Due to the recent introduction of the new technique and the fact that patients are often referred to their own hospital after surgery, follow-up is often short, limiting conclusions. As follow-up data were mainly missing in the control group, there was a risk of bias and underreporting of complications in the control group, although there is no reason to believe that the missing data will significantly influence the results. The introduction of the PelvEx II trial, as well as a shift in the surgical approach, caused a significant difference in the characteristics of patients with LRRC. Nevertheless, it is unlikely that a clinically relevant, severe increase in toxicity due to IOERT dose adaptation would be missed because of the mentioned biases.
Although some conclusions can be drawn regarding the safety of dose adaptation, no conclusions can be drawn regarding oncological effects. A longer follow-up period in a larger cohort is necessary. Additionally, a larger cohort will be needed to draw conclusions on more subtle complications, such as peripheral neuropathy, which can be detrimental to quality of life, but are notoriously difficult to evaluate retrospectively. Standardized CTCAE scores during the follow-up will facilitate future toxicity comparisons. Future work

will also consist of analyses of oncological outcomes, especially of (in-field) LRFS, providing more information on the efficacy of dose adaption.

CONCLUSION

An increased surface dose of IOERT did not appear to increase postoperative complications. Further research is needed to evaluate the efficacy of dose adaptation of IOERT in improving the local oncological control rates. Routine evaluation of CTCAE scores during follow-up will help uncover possible long-term radiation-induced toxicities.

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SUPPLEMENTARY DATA OF CHAPTER 7

Table S1. Additional treatment characteristics of patients with distant metastases.

		LARC (n=20)	LRRC (n=8)
Group	Control	9 (45%)	6 (75%)
	Intervention	11 (55%)	2 (25%)
Diagnosis of metastases	Synchronous	20 (100%)	8 (100%)
Number of metastases	1	13 (65%)	4 (50%)
	2	3 (15%)	3 (38%)
	≥3	4 (20%)	1 (13%)
Intent of treatment	Curative*	18 (90%)	4 (50%)
	Palliative/not mentioned**	2 (10%)	4 (50%)
Location of metastases	Liver	11 (55%)	2 (25%)
	Lung	3 (15%)	5 (63%)
	Liver and Lung	1 (5%)	0 (0%)
	Supra-regional nodes	3 (15%)	0 (0%)
	Cerebral	1 (5%)	0 (0%)
	Peritoneal	1 (5%)	1 (13%)

** All patients treated with curative intent had oligometastatic disease. All metastases were treated radically, with SBRT and/or surgical resection and/or RFA.*

*** In two patients with LARC, intent of treatment was not explicitly mentioned and therefore scored palliatively. One patient presented with peritoneal metastases which were treated with HIPEC and IORT. One patient had a solitary cerebral metastasis for which a surgical resection was performed.*

*** In four patients with LRRC, intent of treatment was not explicitly mentioned and therefore scored palliatively. Two patients presented with lung metastases, that were treated with SBRT. One patient had peritoneal tumour depositions that were treated with HIPEC and IORT. One patient presented with a solitary liver metastasis, that was treated postoperatively at a referring hospital.*

Table S2. Primary tumour characteristics of patients presenting with LRRC.

Characteristic (LRRC)		Control n=54 (%)	Intervention n=45 (%)	Total n=99 (%)	p-value
Primary tumour					
Gender	Male	37 (69)	32 (71)	69 (70)	0,78
	Female	17 (32)	13 (29)	30 (30)	
T-stage	T0-2	4 (11)	9 (24)	13 (17)	0,128
	T3-T4	34 (90)	29 (76)	63 (83)	
N-stage	N0	14 (37)	16 (41)	30 (39)	0,707
	N1-2	24 (63)	23 (59)	47 (61)	
M-stage	M0	48 (91)	39 (89)	87 (89)	0,756
	M1	5 (9)	5 (11)	10 (10)	
Neoadjuvant treatment	None	23 (43)	15 (34)	38 (39)	0,365
	(C)RT	27 (50)	22 (50)	49 (50)	
	IC+CRT	4 (7)	7 (16)	11 (11)	
Neoadjuvant RT	Full-course CRT	22 (71)	16 (57)	38 (64)	0,508
If applicable	5x5Gy	8 (26)	10 (36)	18 (31)	
	Other	1 (2)	2 (7)	3 (5)	
Surgical procedure	LAR	34 (63)	28 (62)	62 (63)	0,814
	APR	15 (28)	14 (31)	29 (29)	
	Total exenteration	1 (2)	0 (0)	1 (1)	
	Other	4 (7)	3 (7)	7 (7)	
History of metastases?	No	40 (74)	39 (87)	79 (80)	0,106
	Yes	25 (26)	5 (11)	19 (19)	

Table S3. Surface area of IOERT determined by bevel and diameter.

Surface area IOERT (cm2)	Bevel (degrees)	Diameter (cm)	LARC		LRRC	
			Control n=54 (%)	Intervention n=47 (%)	Control n=54 (%)	Intervention n=45 (%)
27,8	**45**	**5**	30 (56)	22 (47)	25 (46)	11 (24)
40	**45**	**6**	15 (28)	21 (45)	18 (33)	26 (58)
54,4	**45**	**7**	3 (6)	3 (6)	4 (7)	7 (16)
22,7	**30**	**5**	3 (6)	0	3 (6)	1 (2)
40	**30**	**6**	3 (6)	0	2 (4)	0
54,4	**30**	**7**	0	0	1 (2)	0
19,6	**0**	**5**	0	0	1 (2)	0
28,3	**0**	**6**	0	0	0	0
38,5	**0**	**7**	0	1 (2)	0	0

**Due to rounding, not all percentages add up to 100%.*

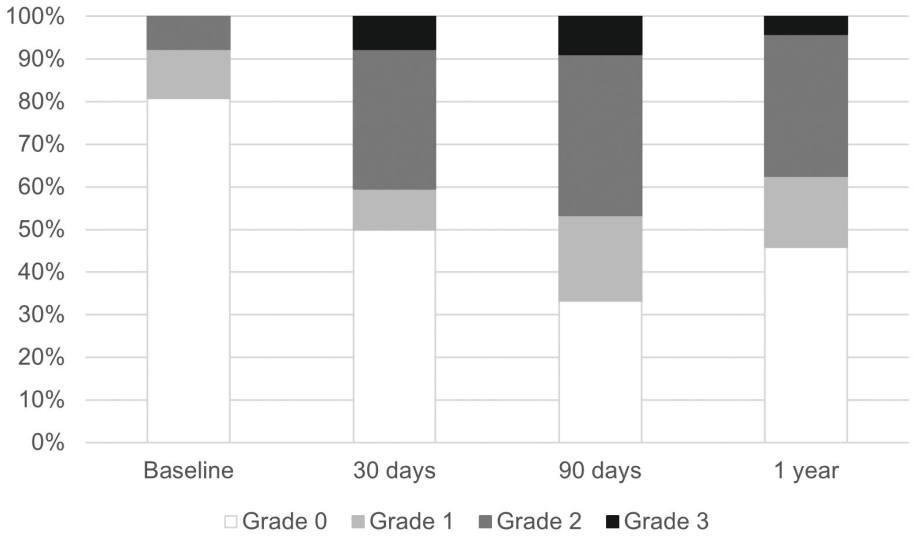

Figure S1. Peripheral neuropathy over time (n=52). Patients in whom no peripheral neuropathy was reported at any time point (n=148), were excluded. Missing data consisted of 0% at baseline, 0% at 30 days, 13% at 90 days, 54% at 12 months.