



Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres

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Abstract

Objective: Aim of this study is analysing the pooled results of Intra-Operative Electron beam Radiotherapy (IOERT) containing multimodality treatment of locally recurrent rectal cancer (LRRC) of two major treatment centres.

Methods and materials: Five hundred sixty five patients with LRRC who underwent multimodality-treatment up to 2010 were studied. The preferred treatment was preoperative chemo-radiotherapy, surgery and IOERT. In uni- and multivariate analyses risk factors for local re-recurrence, distant metastasis free survival, relapse free survival, cancer-specific survival and overall survival were studied.

Results: Two hundred fifty one patients (44%) underwent a radical (R0) resection. In patients who had no preoperative treatment the R0 resection rate was 26%, and this was 43% and 50% for patients who respectively received preoperative re-(chemo)-irradiation or full-course radiotherapy ($p < 0.0001$). After uni- and multivariate analysis it was found that all oncologic parameters were influenced by preoperative treatment and radicality of the resection. Patients who were re-irradiated had a similar outcome compared to patients, who were radiotherapy naive and could undergo full-course treatment, except the chance of local re-recurrence was higher for re-irradiated patients. Waiting-time between preoperative radiotherapy and IOERT was inversely correlated with the chance of local re-recurrence, and positively correlated with the chance of a R0 resection.

Conclusions: R0 resection is the most important factor influencing oncologic parameters in treatment of LRRC. Preoperative (chemo)-radiotherapy increases the chance of achieving radical resections and improves oncologic outcomes. Short waiting-times between preoperative treatment and IOERT improves the effectiveness of IOERT to reduce the chance of a local re-recurrence.

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Introduction

Since the introduction of total mesorectal excision (TME) in the treatment of primary rectal cancer the local recurrence rate has decreased.¹ This effect may also be partially attributable to neoadjuvant and adjuvant therapy.²

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As a result of these improvements locally recurrent rectal cancer (LRRC) has become a relatively rare disease. The 5 year local recurrence rate in rectal cancer has decreased from 20–40% to 4–8%.²

Treatment of locally recurrent rectal carcinoma represents an important clinical challenge, with significant morbidity and a poor prognosis.^{3,4} In the treatment of LRRC the general idea has gradually shifted from non-intervention or palliative (chemo)radiation to more aggressive multimodal treatment approaches combined with intended radical surgery, especially in those cases without metastatic disease.^{5–13} With this shift the prognosis also changed, from a median survival of 8 months to a reported 5 year overall survival ranging from 30 to 39%.^{1,9}

The best results of surgery for LRRC can be realized after full course preoperative radiotherapy. However in more and more primary rectal cancer patients, preoperative (chemo) radiation is used to achieve downsizing of the tumour and facilitate surgical resection.^{5,14,15} In patients who had radiotherapy for their primary rectal cancer, dose tolerance of normal tissue limits the dose of subsequent external beam radiotherapy (EBRT) that can be delivered safely. To overcome this problem intra-operative radiation therapy (IORT) with either electrons (IOERT) or high-dose-rate brachytherapy (HDR-IORT) can provide a solution.^{9–14,16–20} With IORT a boost of radiotherapy can be delivered, after maximal surgical resection, to the area of narrow or positive resection margins. Dose limiting surrounding structures can be removed or shielded from the IORT boost. IORT has become an integral part of multimodality treatment of LRRC at a number of institutions worldwide.^{9–14,16–20} The addition of concurrent chemotherapy to the neoadjuvant EBRT has improved local control, time to treatment failure, and cancer-specific survival compared with radiotherapy alone in a phase III Norwegian trial for unresectable rectal cancer.¹⁵

Two tertiary referral centres for LRRC practicing IOERT-containing multimodality treatment, the Mayo Clinic in Rochester (USA) and the Catharina Hospital in Eindhoven (The Netherlands), pooled their data to analyse the patient and treatment factors influencing local recurrence (LR), distant metastasis free survival (DMF), relapse free survival (RFS) cancer-specific survival (CSS) and overall survival (OS) in uni- and multivariate analyses.

Methods and materials

The Mayo Clinic institutional review board and the Catharina Hospital review board approved this study.

Patients

The Mayo Clinic Rochester (MAYO) started their IOERT program in 1981 and since then has been a worldwide leader in treating patients with locally advanced primary and recurrent rectal carcinomas (LARC,

LRRC).^{9,16,18,21,22} The Catharina Hospital Eindhoven (CHE) started applying IOERT in treating patients with LARC and LRRC in 1994 in a program based on the Mayo program and in the beginning advised by specialists from the Mayo Clinic.^{10,20} Both centres have collected the data prospectively in a database. In both centres all patients referred and considered for treatment are discussed in a multidisciplinary setting.

The data of patients with locally recurrent rectal carcinomas of the Catharina Hospital Eindhoven (CHE) and the Mayo Clinic Rochester (MAYO) have been pooled from the beginning of their IOERT-program until the end of 2010 to allow for a sufficient follow-up. Patients with recurrent rectal cancer and without preoperative distant metastases were selected, including only patients in whom the surgical intent was a gross total resection. This left 565 patients for analyses. Mean follow up time for surviving patients was 40 months (range 1–240). The median number of months between primary surgery and surgery for the recurrence was 38 months (range 3–235).

Treatment

In [Table 1](#) the similarities and differences between the institutions are shown. Patients at MAYO were younger (60.8 vs 62.8 years) but had a similar follow-up. Most patients received preoperative radiotherapy: 256 (45.5%) as re-irradiation and 249 (44.2%) as full course, only 58 (10.3%) had no preoperative treatment. In the MAYO cohort, 49 patients (8.7%) received adjuvant chemotherapy and 28 patients (5.0%) postoperative (chemo) radiotherapy compared to no postoperative treatments in the CHE. Treatment methods have been described in detail in prior manuscripts from both institutions and will only be summarized here.^{9,10,17,18,20}

The preoperative radiotherapy dose was typically in the range of 45–54 Gy in fractions from 1.8 to 2.0 Gy in previously un-irradiated patients. If the patients received radiotherapy for the primary tumour they were usually re-irradiated with a median dose of 30 Gy (MAYO range, 5–39.6 Gy). A majority of the patients received preoperative radiotherapy (n = 505, re-irradiation or a full-course of radiotherapy), combined with 5-FU based chemotherapy in 424 patients.

Surgery with IOERT was performed after a mean waiting period of 41 days from completion of neoadjuvant therapy. At MAYO the waiting time was significantly shorter than at the CHE ([Table 1](#)), with shorter intervals of 0.1–3 weeks generally used in re-irradiated patients and an interval of 3–6 weeks in patients receiving full dose preoperative (chemo) radiation. Of the 256 re-irradiated patients at CHE and MAYO, 63.6% had their resection and IORT within 4 weeks after finishing the preoperative treatment, compared to 15.8% of the 249 patients who underwent full-course preoperative treatment (p < 0.0001). IOERT was delivered as an electron boost during open

Table 1
Patient characteristics of the Mayo Clinic Rochester and the Catharina Hospital Eindhoven.

| Characteristic | All N = 565 | CHE N = 207 | MAYO N = 358 | p-Value |
|---|---------------------|---------------------|---------------------|--------------------|
| Mean age, yrs (range) | 61.5 ± 11.0 (21–87) | 62.8 ± 9.9 (39–87) | 60.8 ± 13.7 (21–87) | 0.029 |
| Mean FU, mo (range) | 44.8 ± 42.6 (1–240) | 48.4 ± 43.7 (1–227) | 42.6 ± 41.8 (1–240) | 0.120 |
| Gender | | | | 0.190 |
| Male | 346 (61%) | 123 (59) | 223 (62) | |
| Female | 219 (39%) | 84 (41) | 135 (38) | |
| Preop Rx | | | | 0.455 |
| None | 58 (10.3%) | 23 (11.1) | 35 (9.8) | |
| Re (chemo)RT | 256 (45.5%) | 87 (42.0) | 169 (47.5) | |
| Full course (Chemo)RT | 249 (44.2%) | 97 (46.9) | 134 (42.7) | |
| Waiting time between end of preoperative radiotherapy and IORT | | | | < 0.0001 |
| 0.1–2 weeks | 138 (28.5%) | 1 (0.6) | 137 (43.8) | |
| 2.1–4 weeks | 53 (10.9%) | 4 (2.3) | 49 (15.7) | |
| 4.1–6 weeks | 92 (19.0%) | 10 (5.8) | 82 (26.2) | |
| 6.1–8 weeks | 74 (15.3%) | 49 (28.5) | 25 (8.0) | |
| 8.1–10 weeks | 56 (11.5%) | 47 (27.3) | 9 (2.9) | |
| 10.1–12 weeks | 40 (8.2%) | 36 (20.9) | 4 (1.3) | |
| >12 weeks | 32 (6.6%) | 25 (14.5) | 7 (2.2) | |
| Total | 485 (100%) | 172 (100) | 313 (100) | |
| Postoperative Chemotherapy | | | | < 0.0001 |
| No | 516 (91.3%) | 207 (100) | 309 (86.3) | |
| Yes | 49 (8.7%) | 0 | 49 (13.7) | |
| Postoperative external beam radiotherapy | | | | < 0.0001 |
| No | 537 (95.0%) | 207 (100) | 330 (92.2) | |
| Yes | 28 (5.0%) | 0 | 28 (7.8) | |

Yr = year, Preop Rx = preoperative treatment, ChemoRT = chemoradiotherapy.

Waiting time = interval from end of preoperative therapy to surgery.

Postop = postoperative, Chemo = chemotherapy.

surgery, following maximal resection. Both centres have a dedicated linear accelerator in the operating theatre. The IOERT dose and energy was comparable and was typically in the range of 10–17.5 Gy, the energies ranged from 8 to 12 MEV and the most commonly used bevelled applicator was 6 cm in diameter. The dose of IOERT was determined peri-operatively based on frozen section pathological examination and the dose of EBRT that had been given preoperatively or was planned postoperatively. For patients in who 45–54 Gy fractionated EBRT was feasible or given, the IOERT dose was typically 10–12.5 Gy for patients with R0 or R1 resection and 15–20 Gy following R2 resection. In re-treatment patients where EBRT is restricted to approximately 30 Gy, the IOERT dose was typically 15–20 Gy.

Statistical analysis

Statistical analysis was performed using SPSS package (SPSS 19.0 for Windows; SPSS Inc, Chicago, IL). *t*-tests and chi-square tests were used to compare individual variables. Local re-recurrence (LR) rate, distant metastases (DM) rate, cancer-specific survival (CSS) and overall survival (OS) were estimated using the Kaplan–Meier method. CSS was defined as the time between rectal cancer surgery and death caused by rectal cancer. Differences were assessed using the Log–Rank test. *p*-Values were two-sided

and considered statistically significant at a value of 0.05 or less. For determination of risk factors, first univariate analyses were performed by analysing the effect of the covariates in a univariate Cox regression, stratifying for treatment center. Then, covariates with trend-significant effects (*p*-value < 0.10) were selected for multivariate analysis, stratifying for treatment centers, using stepwise Cox proportional hazards regression modelling. Both forward and backward stepwise regression was used and a two-sided *p*-value of less than 0.05 was considered significant.

Results

IOERT

Of all patients 12 (2.1%) did not receive IOERT. The reasons for not administering IOERT were massive blood loss resulting in packing the abdomen with gauzes, and comorbidity of the patient.

Radicality of the resection

Overall, 251 patients of the 565 patients (44%) underwent a radical R0 resection. The main factors related to radicality of resection were preoperative treatment and waiting time from the end of preoperative therapy to surgical resection with IOERT (Table 2). In the group of

Table 2
Influence of patient and preoperative parameters on radicality of resection.

| Characteristic | Resection | | | | Uni-variate p-value | Multi-variate (R0 vs R1/R2) |
|-----------------------|---------------|---------------|---------------|------------------|------------------------|--------------------------------|
| | R0 No. (%) | R1 No. (%) | R2 No. (%) | Total No. (%) | | |
| Age | | | | | 0.044 | 0.108 |
| ≤69 yrs | 180 (41.9) | 146 (34.0) | 104 (24.2) | 430 (100) | | |
| ≥70 | 71 (52.6) | 43 (31.9) | 21 (15.6) | 135 (100) | | |
| Gender | | | | | 0.408 | |
| Male | 147 (42.5) | 117 (33.8) | 82 (23.7) | 346 (100) | | |
| Female | 104 (47.5) | 72 (32.9) | 43 (19.6) | 219 (100) | | |
| Preop Rx | | | | | < 0.0001 | 0.169 |
| None | 15 (25.9) | 20 (34.5) | 23 (39.7) | 58 (100) | | |
| Re (chemo)RT | 110 (43.0) | 100 (39.1) | 46 (18.0) | 256 (100) | | |
| Full course (chemo)RT | 125 (50.2) | 68 (27.3) | 56 (22.5) | 249 (100) | | |
| Waiting time | | | | | 0.007 | < 0.0001 |
| 0.1–2 weeks | 54 (39.1) | 58 (42.0) | 26 (18.8) | 138 (100) | | |
| 2.1–4 weeks | 26 (49.1) | 15 (28.3) | 12 (22.6) | 53 (100) | | |
| 4.1–6 weeks | 33 (35.9) | 31 (33.7) | 28 (30.4) | 92 (100) | | |
| 6.1–8 weeks | 37 (50.0) | 23 (31.1) | 14 (18.9) | 74 (100) | | |
| 8.1–10 weeks | 33 (58.9) | 14 (25.0) | 9 (16.1) | 56 (100) | | |
| 10.1–12 weeks | 26 (65.0) | 13 (32.5) | 1 (2.5) | 40 (100) | | |
| >12 weeks | 17 (53.1) | 7 (21.9) | 8 (25.0) | 32 (100) | | |

* For multivariate analyses, the most significant cut-off point of 7 weeks was used.

Yr = year, Preop Rx = preoperative treatment, EBRT = external beam irradiation.

ChemoRT = chemoradiotherapy, Waiting time = interval from end of preoperative therapy to surgery.

patients who had no preoperative treatment the R0 resection rate was only 26%, while this was between 43.0% and 50.2% in the patients who received preoperative re-(chemo-) irradiation of full course (chemo-) radiotherapy respectively ($p < 0.0001$, univariate). Waiting time was positively correlated with the chance of achieving a R0 resection. Multivariate regression analysis demonstrated that waiting time was the only significant variable for radicality of resection ($p = 0.007$) (Table 2 and Fig. 1). Radicality was the most robust parameter for oncological

outcome both in univariate and multivariate analysis, p values were < 0.0001 for LR, OS, MFS, RFS and CSS (Appendices 1–5).

Local re-recurrence

One hundred and eighty one patients developed a local re-recurrence (45.3% 5-year LR rate). After uni- and multi-variate analysis (Appendix 1) the risk factors associated with local re-recurrence were preoperative treatment,

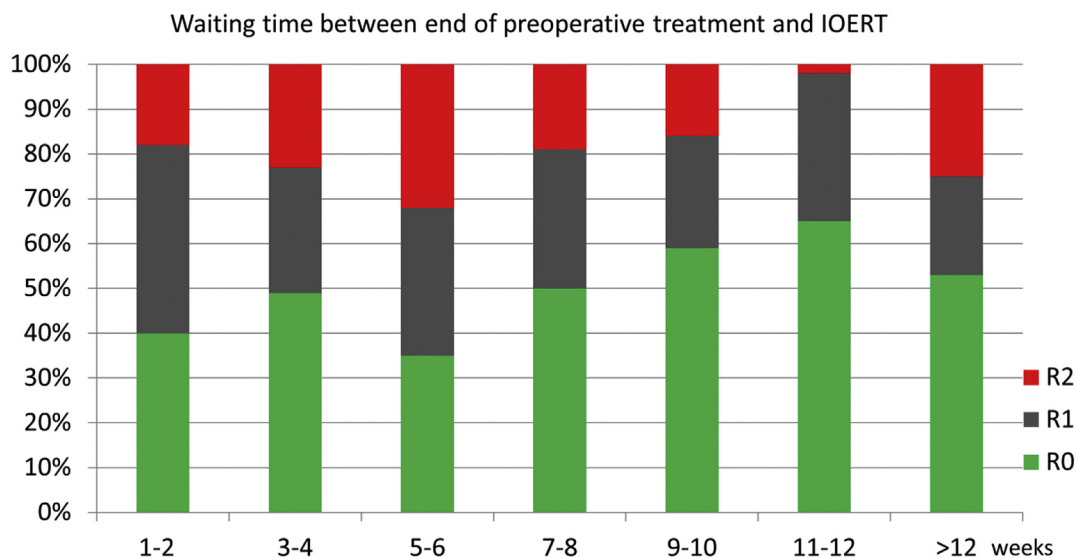


Figure 1. Influence of waiting time (from end of preoperative therapy to surgery with IOERT) and radicality of resection. Longer waiting times result in more R0 resections.

waiting time and radicality of the resection. After full course preoperative CRT, 3 and 5-year local re-recurrence rates were 27% and 38%, which was significantly better ($p = 0.008$, univariate) than after no preoperative therapy (50%, 59%) and re-irradiation (46%, 52%).

Short waiting times after preoperative radiotherapy significantly reduced the chance of developing a re-recurrence (Figs. 2 and 3) especially in R1 resected patients ($p = 0.007$). Fig. 2 shows 5-year local recurrence rates after different waiting times in R0, R1 and R2 resected patients. The most significant cut-off point was found at 7 weeks after modelling for all possible cut-off points. Fig. 3 shows that the three year local re-recurrence rate of R1 resected and R0 resected seem to be similar after shoreter waiting times.

Radicality was the strongest prognostic variable for the development of a re-recurrence ($p < 0.0001$). Three and

5-year local re-recurrence rates for R0, R1 and R2 resections were: R0 – 22%, 28%; R1 – 53%, 64%; R2 – 48%, 61% (Fig. 4 shows the survival curves for radicality of resection and oncological outcome).

Distant metastases and relapse free survival

The three and five year distant metastases free survival (DMFS) was 50% and 43%. Both after univariate analysis and multivariate analysis, preoperative treatment (Fig. 5), radicality of the resection (Fig. 4) and postoperative radiotherapy were significant variables (Appendix 1). The group who received postoperative instead of preoperative (chemo) radiotherapy was small and had the poorest DMFS (3-yr: 25%; 5-yr: 15%). Adjuvant postoperative chemotherapy had no beneficial effect, but numbers again were small.

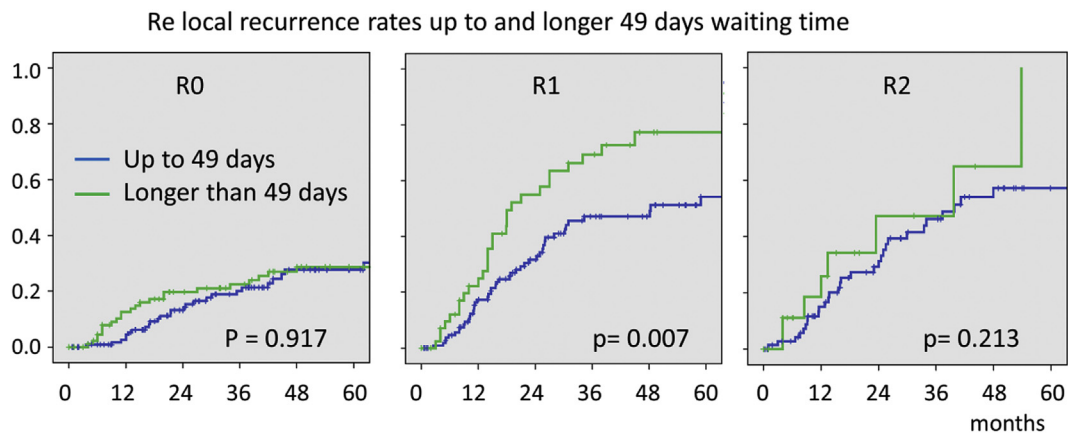


Figure 2. Influence of waiting time and radicality of resection (from end of preoperative therapy to surgery with IORT) on local re-recurrence rates.

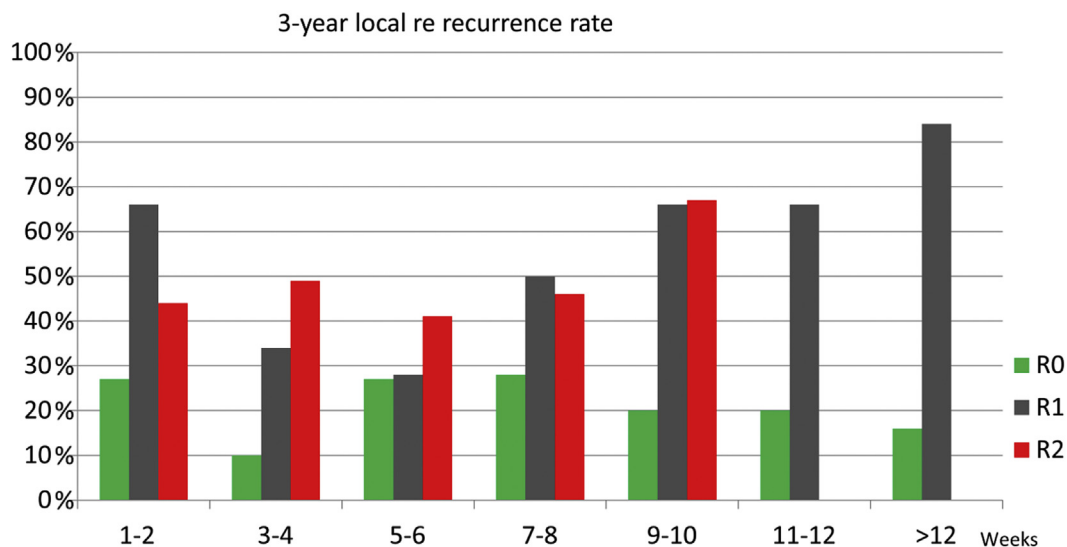


Figure 3. Three year local re-recurrence rates in relation to waiting time and radicality of resection. Note the low re-local recurrence rates in R1 resected patients after waiting times between 3 and 6 weeks.

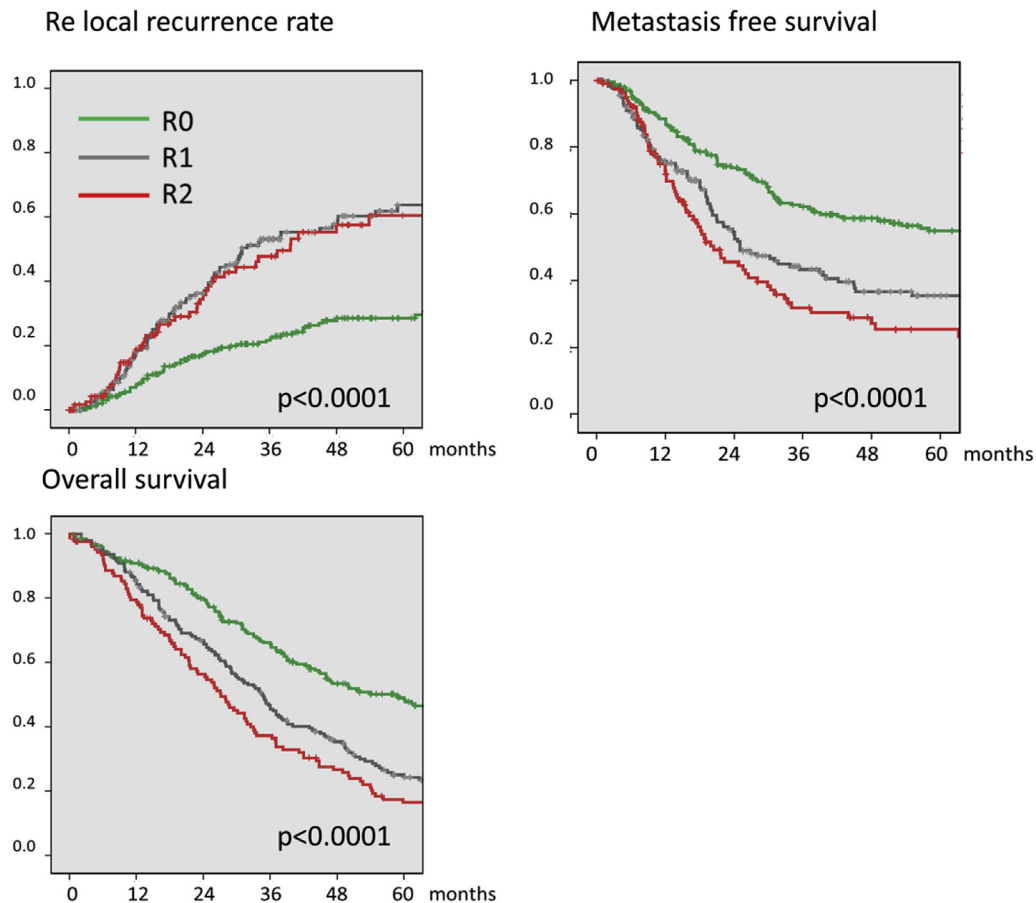


Figure 4. Kaplan–Meier survival curves for local re-recurrence rates, metastasis free survival and overall survival, showing the effect of radicality of resection. All curves were highly significant different from each other, except for the local re-recurrence curves of R1 and R2 resections.

Relapse free survival was affected by preoperative treatment ($p = 0.002$, univariate) and radicality of resection ($p < 0.0001$) (Appendix 3). The significant factors after multivariate analysis included full dose preoperative chemoradiation ($p = 0.035$) and radicality of resection ($p < 0.0001$).

Cancer-specific survival

The three and five year CSS were 62% and 41%. The factors associated with CSS after uni-variate analysis were radicality of the surgery ($p < 0.0001$), preoperative treatment ($p = 0.002$) and postoperative radiotherapy ($p < 0.0001$, poorer outcome). On multi-variate analysis, a trend in preoperative treatment ($p = 0.073$) reached statistical significance for full dose CRT ($p = 0.022$), and a significant effect of radicality of resection persisted ($p < 0.0001$) (Appendix 4).

Overall survival

The three and five year overall survival (OS) was 52% and 33% respectively. Preoperative treatment ($p = 0.001$), radicality of resection ($p < 0.0001$) and postoperative

radiotherapy ($p = 0.003$, poorer outcome) had an impact on overall survival. After multivariate analysis both preoperative treatment (0.046; best with full dose CRT [$p = 0.013$]) and radicality of resection ($p < 0.0001$) remained significant. Three and five year OS by extent of resection were: R0 – 66%, 48%; R1 – 47%, 25%; R2 – 37%, 17%. For preoperative treatment, 3 and 5 year OS were: none – 33%, 20%; low-dose re-treatment – 54%, 31%; full dose CRT – 57%, 37% (Appendix 5).

Discussion

In this pooled analysis the results of multimodality treatment of a large cohort of patients treated for LRRC is presented. With pooling of data a possible bias is introduced. Therefore, before starting this analysis treatment protocols and patient data of both centres were compared, and a specialist trained at the CHE visited the Mayo Clinic to observe treatment of patients. It was concluded that the treatment delivered in both groups of patients was relatively comparable. Other limitations of the analysis include changes in treatment protocol over time, especially with regard to patients who had received prior pelvic irradiation.

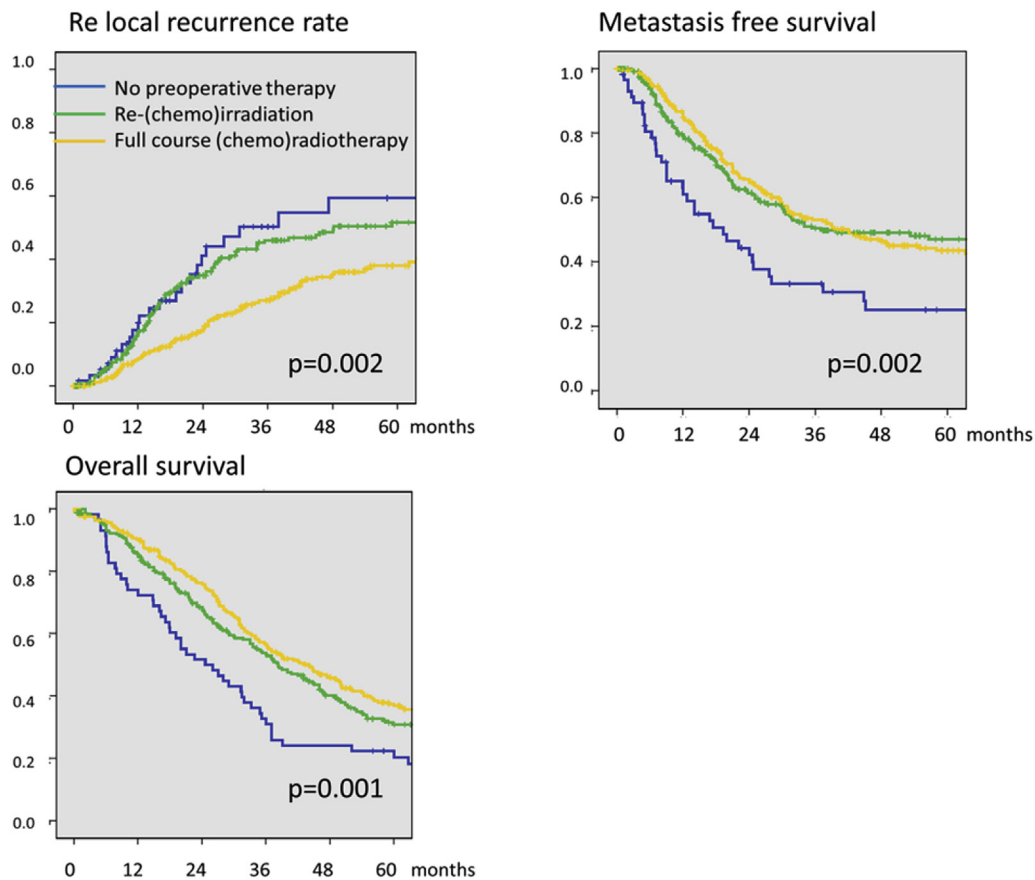


Figure 5. Type of preoperative treatment vs. oncologic outcomes — patients with re-irradiation had similar outcomes than patients after full course of radio-chemotherapy (except for re-local-recurrence rates). In contrast patients without preoperative treatment had poorest outcomes.

The only significant difference in the treatment approach at the two institutions was the variation in waiting time after completion of neoadjuvant treatment to surgical resection/IOERT. At MAYO the waiting time was 6 weeks or less in 86% of patients vs. 9% of patients at CHE. The MAYO preferred waiting time of 3–6 weeks after full dose preoperative EBRT or chemoradiation was based on the desire to get an additive effect of the EBRT and IOERT components of treatment, by reducing the duration of irradiation, in an attempt to maximize local control of disease. The usual waiting time of ≥ 6 weeks at CHE was driven by the desire to get maximum tumour shrinkage from the pre-operative therapy and potentially increase the rate of R0 resection.

Treatment of LRRC requires a multimodality approach, in which neoadjuvant chemoradiation, extensive resection and possible IOERT are combined.^{5–13,17,18,20} Treating patients with a local recurrence after treatment for primary rectal cancer or locally advanced rectal cancer is especially challenging. Due to prior surgery, anatomical boundaries are distorted and previously irradiated patients may have developed fibrosis in the area of the recurrence.

Re-irradiation for local recurrence

In previously irradiated patients it has been shown that patients with recurrent rectal cancer can be safely re-irradiated with acceptable complication rates. Mohiuddin and co-workers evaluated long-term results of re-irradiation in a group of 103 patients with recurrent rectal cancer whose primary cancer was treated with a median dose of 50.4 Gy.²³ Re-irradiation doses ranged from 15 to 49.2 Gy (median 34.8 Gy). Treatment breaks or early termination of treatment was necessary in 15% of patients and late complications occurred in 21.4%. The authors concluded that in patients with recurrent rectal carcinoma, high doses of re-irradiation can be delivered with acceptable risks without prohibitive long-term side effects. Valentinini et al. addressed the same subject in a study in which 59 previously irradiated patients were treated with EBRT for a rectal cancer recurrence.⁵ The median EBRT dose for the primary tumour was 50.4 Gy, and 30 Gy in the re-irradiation scheme. Re-irradiation was tolerated with Grade 3 toxicity of 5.1% or lower, leading to the conclusion that neoadjuvant chemoradiation can be applied with a low risk of acute toxicity and acceptable incidence of late

complications. Bosman et al. recently evaluated the subject of re-irradiation in 135 patients treated for LRRC and concluded that re-irradiation (with concomitant chemotherapy) has few side-effects and complements radical resection of recurrent rectal cancer.²⁴ Bosman et al. evaluated the subject of re-irradiation in 135 patients treated for LRRC and concluded that re-irradiation (with concomitant chemotherapy) has few side-effects and complements radical resection of recurrent rectal cancer.²⁴

In the current IOERT pooled analysis, which includes the largest series of re-irradiated patients, survival outcomes for re-irradiated patients were similar to those of patients who underwent full course preoperative treatment (Fig. 3). In the MAYO cohort, however, early patients who presented with local recurrence and had prior pelvis irradiation did not receive any preoperative (chemo) radiation prior to resection/IOERT. MAYO investigators cautiously initiated low-dose preoperative re-irradiation starting with 10 Gy/5 fractions/1 week and sequentially escalated the preoperative EBRT dose to 25.2–30.6 Gy in 1.8 Gy fractions plus concurrent 5FU in most previously irradiated patients.^{9,18}

Role of IORT

Even when patients can be re-irradiated, the dose tolerance of normal tissue limits the dose of EBRT. A solution to overcome this problem is IORT with either electrons (IOERT) or HDR-brachytherapy. The advantage of IOERT is that a boost of radiation can be delivered to an area at risk while the dose limiting surrounding structures can be removed or shielded from the radiation field. The combination of EBRT and IOERT can deliver a tumouricidal dose equivalent to 62–90 Gy, dependent on the dose of both EBRT and IOERT that are delivered.^{9,25}

It is difficult to establish the contribution of IOERT in the improved results LRRC treatment, since there are no randomized trials comparing treatment of such patients with or without IOERT. However, Suzuki et al. evaluated treatment outcomes in a Mayo Rochester series of 106 LRRC patients with R1 or R2 resection of whom 42 received IOERT in their treatment regimen (41 of 42 also received EBRT; ≥ 45 Gy in 38).²⁶ None of the 106 patients had evidence of extra-pelvic involvement. Significant improvement was found in both 3 year local control and overall survival (LC: 60% vs 7%; OS: 43 vs 18%) and 5 year OS (19% vs 7%, $p = 0.0006$) in favour of patients receiving IOERT. In the 95 patients with R2 resection, there was an advantage in both 3-yr OS (44% vs 15%) and local control (LC = 60% vs 7%) for IOERT vs non-IOERT patients. For those who presented with pain, similar differences were seen in IOERT vs non-IOERT patients (3-yr OS: 43 vs 19%; 3-yr LC 55 vs 8%). In view of the small number of R1 patients, such comparisons were not feasible.

Valentini et al. also reported a probable improvement in outcomes with the use of IOERT in a series of 47 patients

with LRRC.²⁷ All patients received preoperative chemotherapy, 21 had radical resection and 11 had IOERT at the time of resection. IOERT patients had improved 5-year local control (79% vs 32%) and trends for improved 5-yr OS (41% vs 22%).

There is debate with regard to whether or which LRRC patients with R0 resection will benefit from the addition of IOERT to the treatment scheme, as noted in the systematic review and meta-analysis of IORT outcomes in colorectal cancer by Mirnezami et al.²⁸ While the meta-analysis of outcomes for locally recurrent cancer showed a significant effect with IORT for both local control (pooled odds ratio of 0.22; $p = 0.03$) and 5-yr OS (HR = 0.51; $p = 0.009$) patients with R0, R1 and R2 resection were included in the analyses.²⁸ In the MAYO IOERT analysis by Haddock et al. of 607 patients with locally recurrent colorectal cancer, 5-yr OS in 226 patients with R0 resection was 46% and 5-yr LC was 72% (vs 68% with both R1 and R2 resection).⁹ In a prior MAYO LRRC analysis by Suzuki et al. of 65 patients with R0 resection, in which only 3 patients had IOERT, 5-y OS was 34% and 5-yr LC was 53%.²⁶

With primary rectal or colorectal cancer, several series, have reported improved local control with IOERT as a component of treatment after an R0 resection of T4 cancers.^{19,22,29} In a Massachusetts General Hospital series, 95 patients with T4 rectal cancer received preoperative (chemo)irradiation followed by complete resection; 40 had an IOERT boost and 55 did not due to either favourable tumour response or IOERT was not technically feasible.²⁹ Local control was better with IOERT in both responders (100% vs 84%) and non-responders (88% vs 73%). Accordingly, the authors recommended that IORT should be delivered, if technically feasible, independent of the extent of tumour downstaging after preoperative treatment.

In a recent Memorial Sloan Kettering HDR-IORT analysis by Terezakis et al., 212 patients with locally recurrent colorectal cancer had HDR-IORT after R0 or R1 resection (HDR-IORT not feasible after R2 resection).³⁰ Preoperative treatment was chemoradiation in previously un-irradiated patients, and chemotherapy alone if prior EBRT. Outcomes were similar to IOERT series with 5-yr LC of 71%, 65% and 49% for negative ($n = 96$), close (2 mm or less; $n = 41$) or positive R1 resection margins ($n = 72$) and 5-yr OS of 57%, 49% and 25% respectively.

Local recurrence

Factors that influence local recurrence have been identified previously. For primary rectal cancers, these factors include a more advanced T category of disease, more involved lymph nodes, lymphovascular invasion, poor differentiation, extramural venous invasion and an abdominoperineal resection.^{1,2,6}

In the current LRRC IORT pooled analysis, irradical resection (R1 or R2) was of significant influence on the rate of subsequent local re-recurrence, with a 5 year rate

of 61% and 64% vs. 28% after R0 resection ($p < 0.0001$), an observation that has been confirmed by other studies with fewer patients.^{6,8,31} The radicality of resection was influenced by neoadjuvant therapy, with an R0 resection rate of only 26% in patients who had no preoperative treatment vs. 43% and 50% in those who received preoperative treatment ($p < 0.0001$).

The current analysis found a differential effect on the prevention of subsequent local recurrences depending on the length of waiting time from completion of preoperative therapy to surgery and IOERT. Waiting times of 7 weeks or less significantly reduced the rate of subsequent local relapse, especially in R1 resected patients ($p < 0.007$). This finding seems to suggest implicitly that waiting time and biological effectiveness are related. From a radiobiological perspective, the finding is logical: the shorter the waiting time, the lower the chance for repopulation of cancer cells in the previously irradiated tumour. Accordingly, shorter waiting times improve the additive anti-tumour effects of the pre-operative and intra-operative components of irradiation. The optimal window for surgical resection/IOERT seems to be between 2 and 7 weeks following completion of preoperative therapy.

The current study also demonstrates that longer waiting times after preoperative (chemo) radiation for LRRC lead to an increase of radical R0 resections. Longer waiting times may result in more effective downstaging and down-sizing of the tumour, which might help the surgeon achieve a radical resection, which has also been suggested in primary rectal cancer series evaluating preoperative radiation/chemoradiation.³² The findings in the current study, however, present an interesting challenge to the surgeon and radiation oncologist, since shorter waiting times more effectively control local re-recurrence than longer waiting times, especially in R1 resected patients.

A different outcome was found in a Korean study by Lim et al. which was performed to evaluate the optimal waiting time to surgery following preoperative chemoradiation (CRT) to 50.4 Gy for LARC with resection 4–8 weeks later. There was no difference in pathologic or surgical outcomes in patients who had surgery 28–41 d after CRT vs. 42–56 days (T-category downstaging – 47.5 vs 44.4%; complete response – 13.8 vs 15.0%; sphincter preservation – 83.9 vs 82%) and both groups had similar local-recurrence free survival ($p = 0.1165$).³³

In the current pooled analysis, the optimal windows for longer waiting times and possibly more R0 resections, and shorter waiting times to reduce local re-recurrences especially in R1 resected patients show an important overlap, which has clinical consequences for the planning and management of locally recurrent rectal cancer patients. Significant downstaging can be observed 4–6 weeks after full-dose concurrent chemoradiation, as shown by Lim et al.³³ and the effect of IOERT on the reduction on local re-recurrences in the current LRRC pooled analysis is still present up to 7 weeks. From this it follows, the optimal

window for maximal surgical resection and IOERT is around 5–7 weeks after finishing full course preoperative treatment.

With lower dose preoperative re-irradiation/chemoradiation, however, significant downstaging cannot be expected routinely. Accordingly, shorter waiting times from the end of preoperative therapy and surgery/IOERT are indicated in order to achieve a stronger additive effect of preoperative and intraoperative irradiation.^{9,34}

Relapse and survival factors

The most important factors for improving both disease relapse and survival in the treatment of patients with LRRC, in the current IORT pooled analysis, were preoperative therapy and a radical R0 resection. On univariate analysis, preoperative therapy and R0 resection decreased both local ($p = 0.002$, $p < 0.0001$; [Appendix 1](#)) and distant relapse ($p = 0.001$, $p < 0.0001$; [Appendix 2](#)) and improved RFS ($p = 0.002$, $p < 0.0001$; [Appendix 3](#)), CSS ($p = 0.002$, $p < 0.0001$) and OS ($p = 0.001$, $p < 0.0001$).

On multi-variate analysis, R0 resection continued to have a major impact on local and distant relapse, RFS, CSS and OS ($p < 0.0001$ for each) and preoperative therapy (vs no preoperative therapy) had an impact on both local recurrence ($p = 0.008$) and OS ($p = 0.046$). Full-dose preoperative CRT had a significant impact on RFS ($p = 0.035$), CSS ($p = 0.022$) and OS ($p = 0.013$).

Conclusions

The aim of this study was to analyse the pooled data of two major treatment centres using IOERT as a component of treatment for a large cohort of 565 patients with locally recurrent rectal cancer. These data confirm that radicality of the resection and full dose preoperative chemoradiation or re-(chemo-) irradiation are important factors influencing disease relapse and survival. A new finding is the importance of shorter waiting times for the radiobiological effect of IOERT, which may become an important issue in the management of these patients and which may result in better prevention of subsequent local re-recurrences even in R1 resected patients.

Author contribution

Fabian A. Holman contributed to conception and design, to acquisition of data, to analysis and interpretation of data, to drafting the article and to revising it critically for important intellectual content, and gave final approval of the version to be published.

Sietske J. Bosman contributed to conception and design, to analysis and interpretation of data and to revising it critically for important intellectual content, and gave final approval of the version to be published.

Michael G. Haddock contributed to conception and design, to analysis and interpretation of data, to acquisition of data and to revising it critically for important intellectual content, and gave final approval of the version to be published.

Leonard L. Gunderson contributed to analysis and interpretation of data and to revising it critically for important intellectual content, and gave final approval of the version to be published.

Miranda Kusters contributed to conception and design, to analysis and interpretation of data and to revising it critically for important intellectual content, and gave final approval of the version to be published.

Grard A.P. Nieuwenhuijzen contributed to analysis and interpretation of data and to revising it critically for important intellectual content, and gave final approval of the version to be published.

Hetty A. van den Berg contributed to acquisition of data and revising the article critically for important intellectual content, and gave final approval of the version to be published.

Heidi Nelson contributed to acquisition of data and revising the article critically for important intellectual content, and gave final approval of the version to be published.

Harm J.T. Rutten contributed to conception and design, to acquisition of data, to analysis and interpretation of data, to drafting the article and to revising it critically for important intellectual content, and gave final approval of the version to be published.

Conflicts of interest

None declared.

Source of funding

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejso.2016.08.015>.

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