META-ANALYSIS

The role of intraoperative radiotherapy in advanced rectal cancer: a meta-analysis

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Abstract

Aim: Patients with locally advanced and locally recurrent rectal cancer (LARC/LRRC) experience higher rates of local recurrence (LR) and poorer overall survival than patients with primary rectal cancer restricted to the mesorectum despite improved neoadjuvant treatment regimens and radical surgical procedures. Intraoperative radiotherapy (IORT) has been suggested as an adjunctive tool in the surgical management of these challenging cases. However, clear evidence regarding the oncological benefit of IORT is sparse. The aim of this review was to update this evidence in the era of standardized neoadjuvant radiotherapy administration.

Method: A systematic review of patients who received IORT as part of multimodal treatment for advanced rectal cancer from 2000 to 2020 and an analysis of IORT and surgery/external beam radiotherapy (EBRT) groups was performed. The primary endpoint was the rate of LR between the two groups.

Results: Seven papers met the predefined criteria. LR was reduced by the addition of IORT when compared with the surgery/EBRT alone group (14.7% vs. 21.4%; OR 0.55, 95% CI 0.27–1.14; \(p = 0.11\)). There was no increase in reported genitourinary morbidity, wound issues, pelvic collections or anastomotic leak in those patients who received IORT. Notably, there was no survival difference between the two groups.

Conclusion: The addition of IORT to current treatment strategies in the management of patients with LARC/LRRC is associated with a lower rate of locoregional recurrence without increased morbidity. However, this marks a highly selective group of patients, with heterogeneity regarding indications, prior neoadjuvant treatments and/or IORT dosing.

KEYWORDS
intra-operative radiotherapy, locally advanced rectal cancer, locally recurrent rectal cancer, surgical outcomes

INTRODUCTION

Locally advanced and locally recurrent rectal cancers (LARC/LRRC) represent two distinct clinical entities, yet they pose the single greatest challenge to colorectal surgeons, namely obtaining a negative resection margin in the presence of complex, advanced disease. Neoadjuvant radiotherapy can facilitate downstaging of advanced tumours, and improved local control is well documented [1–4]. Unfortunately, a proportion of patients will have threatened margins making a complete resection (R0) difficult. Where rectal
cancer is incompletely resected, patients experience high rates of local failure, distant metastasis and mortality [5,6].

Intraoperative radiotherapy (IORT) has been proposed as a means to improve outcomes in patients where margins are threatened. Intraoperative administration enables the operator to more accurately target the area(s) of maximum concern with optimal timing and with an increased radiosensitivity brought about by high tissue oxygen tension in the context of surgical intervention [7,8]. With respect to rectal cancer, it can minimize toxicity to bladder, ureter, prostate, vagina and uterus, while also facilitating protection of the small bowel [9], the main dose-limiting factor when administered as external beam radiotherapy (EBRT). Doses greater than 50 Gy, the usual maximum dose permitted in long-course neoadjuvant EBRT, are associated with undesirable effects such as ulceration and stricture [10]. IORT can therefore facilitate dose escalation to the biological equivalent of two to three times that which can be administered as EBRT [11]. When used in conjunction with EBRT, it can help identify candidates who may benefit from selective local treatment intensification [9], and there is evidence of efficacy in the ability of radiotherapy to control microscopic residual disease [12] and reduce local recurrence (LR) in a dose–response manner [13].

However, despite evidence of a trend towards a reduction in locoregional relapse, there are concerns about unacceptably high rates of distant progression, a lack of survival benefit and potential for cumulative toxicity [14], particularly in patients who have been previously irradiated [15]. Furthermore, this toxicity has been shown to be proportional to the administered dose and can lead to symptoms which are chronic and difficult to treat [14,16,17]. This review aimed to assess the potential role of IORT in LARC/LRRC in the context of modern neoadjuvant chemoradiotherapy regimens.

METHOD

A systematic review was performed with reference to the Cochrane Handbook for Systematic Reviews [18] and according to the guidelines and recommendations from the preferred reporting items for systematic reviews and meta-analyses checklist (PRISMA) [19]. Institutional review board approval was not required.

Search strategy

An electronic search for relevant publications was performed using PubMed, Embase, Ovid and the Cochrane collaboration database for research published between 1 January 2000 and 1 January 2020. Searches of trial databases and 'grey literature' were also performed, with no relevant results. The following search headings were used: 'intraoperative radiotherapy' and 'rectal cancer'. All titles were screened initially, and appropriate abstracts were reviewed. The reference sections of each of the relevant publications and Google Scholar were also screened for other applicable publications. The last search date was 30 November 2020.

Inclusion criteria

To be included in the meta-analysis, the studies had to meet the following criteria: (a) report on patients with histologically confirmed advanced rectal cancer (LARC/LRRC); (b) report on patients having IORT; (c) be directly comparable in terms of local control between a group receiving IORT and a surgery/EBRT only group; (d) report on the outcomes of interest; (e) report on series of >10 patients; (f) have a clear research methodology; (g) be published on or after 1 January 2000.

Exclusion criteria

Studies were excluded from the analysis if: (a) they did not specify that these patients had LARC or LRRC; (b) they did not report outcomes following IORT; (c) they reported on series of <10 patients; (d) they reported on national or pooled databases; (e) the methodology was not clearly reported; (f) the data were overlapping.

Data extraction

Two reviewers (MPF, MF) independently reviewed the literature according to the above predefined strategy and criteria. Each reviewer extracted the following data variables: title and reference details (first author, journal, year, country), study population characteristics (number in the study, gender and age), disease characteristics and treatment specifics (LARC or LRRC, use of neoadjuvant chemoradiotherapy, type of surgical resection, histopathological outcomes and postoperative outcome data (morbidity, mortality, survival). All data were recorded independently by both literature reviewers in separate databases and were compared at the end of the reviewing process to limit selection bias. The databases were also reviewed by a third person (MK). Duplicates were removed and any disparities were clarified.

Outcomes of interest

A number of primary and secondary outcomes were used in the meta-analysis to compare the addition of IORT in the multimodality treatment of LARC/LRRC.

The primary outcome was the locoregional recurrence rate. Secondary outcomes were morbidity outcomes – radiation-specific (ureteral stenosis, neuropathy/plexopathy, sacral osteonecrosis) and nonspecific (wound infection, pelvic abscess, anastomotic leak etc) – and survival outcomes.

Statistical analysis

Statistical analysis was performed using Revman Statistical Software (v.5, Copenhagen, Denmark). Binary outcome data were reported as
odd ratios (ORs), and 95% confidence intervals (95% CIs) were estimated using the Mantel–Haenszel method. For continuous data, mean differences and 95% CIs were estimated using inverse variance weighting. Outcome measures [mean + standard deviation (SD) and median + interquartile range] were recorded. If needed, outcome variables (mean and SD) were estimated from the median and range using the formula described by Hozo et al [20]. Heterogeneity was assessed by the $I^2$ statistics, with >50% being considered as considerable heterogeneity. Statistical significance was attributed to $p$-values <0.05. The quality score rating was determined for each nonrandomized publication and recorded. The risk of bias in the included studies was assessed by one of the authors (MF) and verified by a second (MK). Risk of bias of nonrandomized studies was assessed using the ROBINS-I tool [21], whereas the ROB-2 tool was used for randomized trials [22].

RESULTS

Eligible studies

A total of 543 articles were initially identified using the aforementioned search strategy. On full text screening, seven publications that met the inclusion criteria were included in the meta-analysis [23–29]; Tables 1 and 2). All studies were directly comparable in terms of oncological and morbidity outcomes between cohorts of patients with LARC or LRRC who had and had not received IORT. These studies were published from 2000 onwards to reflect changes in contemporary management strategies from those with LARC/LRRC. On review of the extracted data, there was 100% agreement between the two reviewers (MF, MPF).

Demographics

Analysis was performed on 833 patients; of these 422 underwent IORT as part of multimodality treatment for LARC/LRRC and were compared with 411 patients who did not undergo IORT. Men made up 68.5% of the participants. A higher proportion of patients in the IORT group were male (71.5%) compared with the surgery/EBRT group (65.2%). In the IORT group 362 patients underwent the procedure for LARC and 60 for LRRC. Similarly, the majority of the surgery/EBRT group were treated for LARC (n = 367) rather than LRRC (n = 44).

Treatment modalities

In terms of neoadjuvant treatment, more patients in the IORT group received neoadjuvant radiotherapy than those in the surgery/EBRT group (78.7% vs. 58.2%), with 85 in the IORT group undergoing concurrent neoadjuvant chemotherapy compared with 61 in the surgery/EBRT group. In one study, all patients in both the IORT group (n = 71) and the EBRT only group (n = 77) received adjuvant chemoradiation [29]. A further 79 patients (18.7%) in the IORT group received adjuvant chemotherapy compared with 54 patients (13.1%) in the surgery/EBRT group.

IORT was administered to 422 patients in the included studies. In six of the seven studies, IORT was administered to the area where the resection margin was considered to be most ‘at risk’, i.e. where it was fixed to the sacrum or pelvic sidewall or where microscopic or macroscopic positive margins were encountered. The remaining study delivered IORT to the pelvic autonomic nerve plexuses bilaterally following nerve-preserving surgery [24]. Doses ranged from

**TABLE 1** Baseline characteristics

| Author | Study size | Study period | Age (years) | Gender (M/F) | LARC/LRRC |
|--------|------------|--------------|-------------|--------------|------------|
| Wiig [23] | 80 IORT, 88 non-IORT | 1990 onwardsa | IORT 64 (34–80), non-IORT 68 (39–83) | IORT 49/31, non-IORT 45/43 | IORT 20/60; non-IORT 44/44 |
| Masaki [24] | 19 IORT, 22 non-IORT | 2000–2007 | N/S | IORT 14/5, non-IORT 15/7 | All LARC (≥T3 or ≥N1 and M0) |
| Dubois [25] | 72 IORT, 68 non-IORT | 1993–2001 | IORT 62.5 (36–79), non-IORT 64.5 (42–80) | IORT 56/16, non-IORT 48/19 | All LARC (≥T3 or ≥N1 and M0) |
| Valentini [26] | 29 IORT, 44 non-IORT | 1991–2006 | 63 (22–86) | N/S | All LARC (T4) |
| Sadahiro [27] | 99 IORT, 68 non-IORT | 1991–2001 | IORT 60 (±10), Non-IORT, 61 (±13) | IORT 80/19, non-IORT 47/21 | All LARC (≥T3, Nx and M0) |
| Alberda [28] | 52 IORT, 39 non-IORT | 1996–2012 | N/S | IORT 41/11, non-IORT 26/13 | All LARC (≥T3 and Nx) |
| Zhang [29] | 71 IORT, 77 non-IORT | 1994–2007 | IORT 58 (35–73), non-IORT 63 (35–71) | IORT 41/30, non-IORT 55/22 | All LARC (T4N0 or Tx and ≥N1) |

Abbreviations: EBRT, external beam radiotherapy; F, female; IORT, intraoperative radiotherapy; LARC, locally advanced rectal cancer; LRRC, locally recurrent rectal cancer; M, male; NCRT, neoadjuvant chemoradiotherapy; NRT, neoadjuvant radiotherapy; N/S, not specified; Tx, treatment; Nx, Any nodal status.

Age Values given as median (range).

*aNot specified but study published in 2001.
10 to 25 Gy. One study reported on the length of time taken to carry out the IORT procedure, which ranged from 15 to 60 min with a mean of 28.3 min.

**Surgical procedures**

Five studies reported in detail on the type of surgical resections that were performed. Low anterior resection (LAR) was the most commonly performed procedure, with 43.5% in the IORT group and 53.7% in the non-IORT group undergoing LAR. Abdominoperineal resection (APR) was the next most common, at 36.6% and 25.9% of the IORT and non-IORT cohorts respectively. Exenterative procedures were performed in 16 patients in the IORT group and 12 in the non-IORT group. In one of the studies, all patients underwent bilateral lateral lymph node dissection. Three sacral resections were carried out, all in the IORT group.

**Surgical outcomes**

The resection margins (R status) were reported separately for the IORT and surgery/EBRT groups in four of the included studies (Tables 3 and 4). Patients in the surgery/EBRT group were more likely to have undergone an R0 resection (75.5%) compared with the IORT group (64.2%). A greater proportion of the patients in the IORT group underwent an R1 resection compared with the control group (29.3% vs. 14.2%). More patients in the surgery/EBRT group, however, underwent an R2 resection (10.3% vs. 6.5%).

**Locoregional recurrence**

All studies reported on the rates of LR between the IORT and surgery/EBRT groups. The rate of LR was lower in the IORT group than in the surgery/EBRT group (14.7% vs. 21.4%) (OR 0.55, 95% CI 0.27–1.14; p = 0.11). This result was not statistically significant (Figure 1).

**Morbidity**

With regard to radiation-specific morbidity, there was no reported clinically significant neuropathy or ureteral stenosis reported in either group. One study reported five episodes of incomplete intestinal obstruction, three in the IORT group and two in the EBRT only group. That study also reported 13 documented episodes of hydronephrosis in 148 subjects, five out of 71 in the IORT group and eight out of 77 in the surgery/EBRT only group. However, eight of those 13 patients had documented concomitant disease recurrence. There was one reported occurrence of a partial sacral osteonecrosis with painful sequelae in the IORT group in a patient who had local control at 13 years of follow-up [29]. IORT was not shown to be associated with higher rates of wound infection, pelvic abscess, anastomotic leak or need for surgical reintervention than the surgery/EBRT group (Figures 2–5). Where expressed as an overall percentage of

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**TABLE 2** Treatment modalities

| Author      | Neoadjuvant Tx | IORT dose (Gy) | Adjuvant chemo. |
|-------------|----------------|----------------|-----------------|
| Wiig [23]   | Yes (all EBRT 46 Gy) | 15–20          | None           |
| Masaki [24] | No             | 18–20          | IORT 7/19, non-IORT 9/22 |
| Dubois [25] | Yes (all EBRT 40 Gy) | 15–18*         | IORT 18/72, non-IORT 13/68 |
| Valentini [26] | Yes (all NCRT) | 10–15         | N/S            |
| Sadahiro [27] | Yes (IORT 67 NRT only and 32 NCRT; non-IORT none) | 15–25       | IORT 52/99, non-IORT 30/68 |
| Alberda [28] | Yes (IORT 24 NCRT, 28 NRT; non-IORT 17 NCRT, 22 NRT) | 10           | IORT 2/52, non-IORT 2/39 |
| Zhang [29]   | No             | 10–20          | IORT 71/71, non-IORT 77/77 |

**Abbreviations**: EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy; NCRT, neoadjuvant chemoradiotherapy; NRT, neoadjuvant radiotherapy; N/S, not specified; Tx, treatment.

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**TABLE 3** Outcomes – intraoperative radiotherapy cohort

| Study      | Resection status | Local recurrence | Overall survival |
|------------|------------------|------------------|-----------------|
| Wiig [23]  | R0 32, R1 33, R2 15 | 39/80           | 35%             |
| Masaki [24] | N/R              | 1/19             | N/R             |
| Dubois [25] | N/R              | 6/72             | 88*             |
| Valentini [26] | R0 29         | 0/29             | N/S             |
| Sadahiro [27] | N/R          | 2/99             | 79%             |
| Alberda [28] | R0 21, R1 31 | 4/52             | 63%             |
| Zhang [29]  | R0 67, R1 4     | 10/71            | 74.6%           |

**Abbreviation**: N/R, not reported.
patients who experienced a complication, 36.3% of the IORT group had one or more complications compared with 28.6% in the surgery/EBRT group.

**Survival outcomes**

Four patients (0.9%) in the surgery/EBRT group were reported as suffering 30-day mortality within the present meta-analysis. The causes were listed as follows: two from postoperative pneumonia, one pulmonary embolus and one from a cardiac complication on day 10. One death (0.2%) in the IORT group was attributed to acute cardiac failure. Valentini et al. reported one other death within 30 days but did not specify which group the patient was in [26]. Where reported, the 5-year overall survival in the IORT group ranged from 35% to 79%. The overall survival in the surgery/EBRT group ranged from 35% to 81%.

**TABLE 4  Outcomes – surgery ± external beam radiotherapy cohort**

| Study       | Resection | Local recurrence | Overall survival |
|-------------|-----------|------------------|------------------|
| Wiig [23]   | R0 48, R1 14, R2 26 | 39/88             | 35%              |
| Masaki [24] | N/R       | 1/22             | N/R              |
| Dubois [25] | N/R       | 4/68             | 106⁴           |
| Valentini [26] | R0 49      | 7/49             | N/S              |
| Sadahiro [27] | N/R       | 11/68            | 58%              |
| Alberda [28] | R0 22, R1 17 | 7/39             | 81%              |
| Zhang [29]  | R0 72, R1 5 | 19/77            | 66.2%            |

Abbreviations: N/R, Not reported; N/S, Not specified between treatment groups.

⁴Survival given as median in months.

**DISCUSSION**

This systematic review and meta-analysis sought to update the evidence with regard to the role of IORT in the management of rectal cancer. It was observed that the addition of IORT is associated with a lower rate of LR but it has no significant impact on overall survival. However, much of the early promise for the benefit of IORT in the management of rectal cancer was derived from small, single-centre case series in patients who were treated before the broad utilization of neoadjuvant radiotherapy [1,2]. Furthermore, many of the data on IORT pre-date the introduction of standardized total mesorectal excision [30]. In the modern era, ongoing interest in IORT is derived from highly specialized surgical oncologists who have a longstanding investment and experience in delivering IORT. Therefore, these results may not necessarily be applicable to rectal cancer patients treated according to current standards of care.

On the other hand, it is well documented that the greatest prognostic factor for overall survival for patients who undergo radical surgery for LARC/LRRC is the achievement of a negative (R0) resection margin [31–34]. Conversely, R1 resections are associated with local failure rates as high as 45% [35]. Therefore, any intervention which may improve local disease control should be considered, as these patients will not only suffer from high rates of local relapse and a subsequently poorer overall prognosis [36] but the majority will also experience debilitating symptoms and a reduced quality of life (QOL) [37,38].

The results from our meta-analysis suggest that there is an improvement in local control with the addition of IORT and that it comes with no increase in morbidity. However, these results must be interpreted with caution. Unfortunately, due to a paucity of data in the individual studies it is unclear why patients were chosen to undergo IORT and it was not possible to analyse the effect of IORT in subgroups of patients who underwent an R0 compared to an R1 resection, nor was it possible to distinguish between primary and recurrent cases. As expected, patients in the surgery/EBRT group...
were more likely to have undergone an R0 resection than the IORT group (75.5% vs. 64.2%). However, a much greater proportion of the IORT cohort received neoadjuvant radiotherapy than the surgery/EBRT group (78.7% vs. 58.2%). Additionally, 79 (18.7%) patients in the IORT group received adjuvant chemotherapy compared with 54 (13.1%) in the surgery/EBRT group. The reduction in LR with neoadjuvant radiotherapy is incontrovertible [2], and one European pooled analysis showed a 6.5% reduction in the rate of local relapse in patients who received adjuvant chemotherapy [39]. In conjunction, these discrepancies between the two groups in terms of multimodality treatment may confound the small difference in LR observed between the two groups.

Advanced rectal cancer is challenging to treat due to the narrow confines of the bony pelvis and involvement of adjacent organs [40].

| Study or Subgroup | IORT Events | Surgery +/- EBRT Events | Odds Ratio M-H, Random, 95% CI |
|------------------|-------------|-------------------------|-----------------------------|
| Alberda 2014     | 18          | 9                       | 1.76 [0.69, 4.51]           |
| Dubois 2011      | 7           | 8                       | 0.81 [0.28, 2.36]           |
| Sadahiro 2004    | 23          | 8                       | 2.27 [0.95, 5.43]           |
| Wiig 2000        | 2           | 8                       | 0.26 [0.05, 1.25]           |
| **Total (95% CI)** | **303**    | **263**                  | **1.13 [0.50, 2.54]**       |

**FIGURE 2** Wound infections (EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy; M-H, Mantel–Haenszel)

| Study or Subgroup | IORT Events | Surgery +/- EBRT Events | Odds Ratio M-H, Random, 95% CI |
|------------------|-------------|-------------------------|-----------------------------|
| Alberda 2014     | 3           | 5                       | 0.42 [0.09, 1.86]           |
| Masaki 2008      | 4           | 3                       | 1.69 [0.33, 8.73]           |
| Wiig 2000        | 17          | 17                      | 1.13 [0.53, 2.39]           |
| **Total (95% CI)** | **151**    | **149**                  | **1.01 [0.54, 1.87]**       |

**FIGURE 3** Pelvic abscess (EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy; M-H, Mantel–Haenszel)

| Study or Subgroup | IORT Events | Surgery +/- EBRT Events | Odds Ratio M-H, Random, 95% CI |
|------------------|-------------|-------------------------|-----------------------------|
| Alberda 2014     | 1           | 1                       | 0.75 [0.05, 12.30]          |
| Dubois 2011      | 6           | 3                       | 1.97 [0.47, 8.21]           |
| Masaki 2008      | 3           | 2                       | 1.83 [0.25, 13.47]          |
| Sadahiro 2004    | 6           | 3                       | 1.40 [0.34, 5.79]           |
| Wiig 2000        | 3           | 8                       | 0.39 [0.10, 1.52]           |
| **Total (95% CI)** | **315**    | **276**                  | **1.06 [0.51, 2.18]**       |

**FIGURE 4** Anastomotic leak (EBRT, external beam radiotherapy; IORT, intraoperative radiotherapy; M-H, Mantel–Haenszel)
Now, with significant improvements in the perioperative care, surgical techniques and improved survival, there has been an increased focus and emphasis on improving patient QOL and survivorship [41]. This is particularly relevant in the context of LARC/LRRC, where positive surgical margins are inherently more likely to affect QOL [37]. Despite this increased focus, questions remain as to the impact that individual treatment strategies have on QOL [42]. With respect to IORT and rectal cancer, neuropathy and urinary obstruction would be the most significant outcomes of concern [17]. Of note, no clinically relevant neuropathy was reported in any of the 833 patients included in this study, nor was there any reported impact on sexual function. As mentioned above, there were 13 patients who had hydronephrosis on long-term follow-up, but eight of these had concomitant disease recurrence and they did not occur more frequently in the IORT group. However, this may be explained by the retrospective nature of some of the included studies, a relatively short duration of follow-up or the fact that the studies were not designed to detect long-term complications.

Heterogeneity in the application of IORT is another factor which limits the interpretation of our findings. Dosing regimens differed quite significantly, ranging from one study where all patients received 10 Gy to another where one-fifth of the cohort were administered a dose of 25 Gy. The study by Wilg et al. [23] was the only one to have a predetermined dosing schedule for R0/R1 and R2 resections, respectively, and it was also the only study which set out the indications for IORT. This raises the question as to why many of the patients in one cohort received IORT, given the relatively high rates of complete resection (64.2%). Ultimately, concerns surrounding excess morbidity and overtreatment will persist given the inability to delineate a specific group who would benefit from the addition of IORT. More evidence is needed to suggest exactly which patients should receive IORT and, where indicated, what protocol should be adhered to.

## CONCLUSION

The addition of IORT to standardized regimens in the management of LARC/LRRC is associated with a lower rate of locoregional recurrence without increased morbidity. However, heterogeneity in patient selection (prior treatments) and dosing practices remains unclear.

## CONFLICT OF INTEREST

All authors declare no conflict of interest.

## FUNDING STATEMENT

No internal or external funding was provided.

## AUTHOR CONTRIBUTIONS

All authors have seen, edited and approved the final version of this paper.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in Appendix S1 of this article.

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SUPPORTING INFORMATION
Additional Supporting Information may be found online in the Supporting Information section.

How to cite this article: Fahy MR, Kelly ME, Power Foley M, Nugent TS, Shields CJ, Winter DC. The role of intraoperative radiotherapy in advanced rectal cancer: a meta-analysis. Colorectal Dis. 2021:00:1–9. https://doi.org/10.1111/codir.15698