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Review Article

Intraoperative electron radiotherapy (IOERT) in colorectal cancer: Updated systematic review of techniques, oncological outcomes and complications

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A B S T R A C T

Background: Intra-operative electron radiotherapy (IOERT) directly delivers a large fraction of radiation to at-risk margins during surgery. However, the precise benefit of IOERT in patients with locally advanced and locally recurrent colorectal cancer (LACC/LRCC) is unclear. This study aimed to provide an updated summary of the current evidence available regarding IOERT as part of multi-modality treatment of LACC and LRCC.

Method: This systematic review update was prospectively registered on PROSPERO (CRD42023438184). An electronic literature search was carried out using Ovid (MEDLINE), EMBASE, Web of Science, and the Cochrane Library databases for studies from July 2011 to April 2024. The inclusion criteria were adult patients who received IOERT as part of multi-modal treatment for LACC or LRCC. The primary outcome was overall survival (OS), disease free survival (DFS) and local control (LC) at 5 years. Secondary outcomes included post-operative complications.

Results: 16 new studies were identified since the previous analysis, and included (study population 1912 patients) of which two were prospective. High heterogeneity prevented meta-analysis of outcomes except for 5-year OS which suggested a non-significant benefit favouring IOERT. Significant methodological concerns were identified making interpretations challenging, however patients with LACC or LRCC with an R1 resection margin showed a favourable 5-year OS (40 % and 18 % respectively) when compared to current evidence.

Conclusion: Although limited by a lack of appropriately conducted randomised evidence, IOERT-containing multi-modality treatment may improve oncological outcomes in LACC and LRCC patients with R1 resections.

1. Introduction

The aim of curative colorectal cancer surgery is to achieve a complete microscopic resection of the tumour by > 1 mm, known as R0 [1]. As both locally advanced and locally recurrent colorectal cancers (LACC and LRCC) are not bound by embryological anatomical borders, the completeness of their resections presents specific challenges to surgeons. Achieving an R0 resection in LACC but more so LRCC is complex as fibrosis is often indistinguishable from infiltrating tumour, with anatomical planes corrupted by previous surgery, sepsis, tumour regression or cancer therapies most notably external beam radiation therapy (EBRT). Despite advances in surgical techniques, the 5-year overall survival for LACC and LRCC remains poor at 52 % and 32 % respectively [2,3].

Intra-operative electron radiotherapy (IOERT), a type of intra-operative radiotherapy (IORT), is the direct application of a large fraction of radiation during an operative procedure [4]. IOERT is applied precisely at the site of the tumour bed with high recurrence risk whilst shielding adjacent radiosensitive structures. It is used as an adjunct as part of multi-modality therapy, including chemotherapy, EBRT, and surgery, in patients with LACC and LRCC.

The first pooled analysis of the effect of IORT, which included both

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IOERT and high dose-rate brachytherapy (HDR-IORT), on five-year oncological outcomes was published in 2013 [5]. The systematic review and meta-analysis included studies from 1965 to July 2011 and concluded that the addition of IORT to multi-modality treatment strategies improved local control (LC), disease-free survival (DFS) and overall survival (OS) in patients with LACC and LRCC, with tolerable associated morbidity. The study acknowledged the lack of randomised comparisons and that the utilisation of IORT was confined to a small number of cases by individual institutes, which had contributed to the heterogeneity of included studies. The study therefore made several recommendations for future studies to aid identification of patients who would benefit most from this treatment.

The purpose of this systematic review update is to provide a comprehensive summary of studies published since the last pooled analysis. This update focuses only on IOERT, to align with the recent interventional procedures guidance (IPG763) by the National Institute for Health and Care Excellence (NICE) on IOERT [6]. This systematic review update aimed to assess the impact of the application of IOERT on oncological outcomes (OS, DFS, LC, and IOERT in-field and out-of-field control), and the complications associated with IOERT, in patients with LACC and LRCC.

2. Methods

This systematic review was prospectively registered on PROSPERO (CRD42023438184) and is an update of a previous systematic review by Mirnezami and colleagues in 2011 [5]. The study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [7].

2.1. Search strategy and study inclusion

A systematic review was performed according to the preferred reporting items for systematic review and meta-analyses checklist (PRISMA). An electronic database search was carried out on June 8, 2023 using Ovid (MEDLINE), EMBASE, Web of Science, and the Cochrane Library databases (trials only) from July 2011 to June 2023. A re-run of the search was conducted prior to final analysis on April 4, 2024, covering the period between June 2023–April 2024. The search strategy can be seen in the Supplementary Material (Table S1). Only publications in the English language were included. Abstracts of publications identified by the above search strategy were retrieved and evaluated for study inclusion. Abstract and full texts of studies identified were retrieved and imported into Rayyan [8]. Each abstract was reviewed by at least two independent reviewers (AT, TM, or SL) who were blinded, and any disagreement was resolved by a third reviewer.

Studies that met the following inclusion criteria were included: 1) IOERT as part of multi-modal treatment involving surgical resection ± external beam radiotherapy (EBRT) ± chemotherapy ± immunotherapy for primary or recurrent colorectal cancer; 2) included adult patients (≥18 years) of any gender; 3) reported oncological outcomes (overall survival, disease-free survival, local or locoregional control, IOERT-in-field and out-of-field control), and or complications, specifically for the colorectal patient cohort. IOERT-in-field control was defined as local control specifically in the area to which IOERT was applied. IOERT out-of-field control was defined as local control in the area beyond the IOERT irradiation field. Complications were defined, as per the Clavien-Dindo classification, as any deviation from the normal post-operative course following surgery [9]. Complications focussed on long-term, wound, urological and anastomotic complications.

The types of studies included were randomized controlled trials, cohort studies, cross-sectional studies and case series reporting more than 10 IOERT cases. Comparative and non-comparative studies were included. Case reports were excluded. In the case of multiple studies reporting on the same patient cohort, the most recent publication with relevant outcome data best answering the study question was used. Due to known reported differences in oncological outcomes between LACC and LRCC, all analyses were carried out based upon these subgroups.

2.2. Quality assessment and data extraction

The methodological quality of included studies was assessed and graded by two independent reviewers (AT, MW) using the revised grading system of the Scottish Intercollegiate Guidelines Network (SIGN) [10]. Each study was given an overall quality rating of high quality, acceptable or unacceptable. In the event of disagreement, the opinion of a third reviewer (CW) was sought. As per the SIGN methodology checklists, any study graded as unacceptable was excluded from the review. The following data were extracted from each included study: first author, year of publication, study location, study type, study time-frame, population characteristics, number of subjects, cancer location (colon/rectum/both), primary or recurrent disease, pathological disease stage, IOERT radiation dosage, details of other treatment (chemotherapy/radiotherapy/immunotherapy), follow-up duration, incidence and details of complications, and oncological outcomes (OS, DFS, LC, IOERT in-field/out-of-field control). Data was extracted by two independent reviewers (AT, TM, MW). In cases of doubt or missing data, the author was contacted by reviewers to request for additional information.

2.3. Data analysis

For a comprehensive overview of the pooled effect of IOERT, a meta-analysis was planned combining data from the studies identified by this systematic review update (July 2011 onwards) with data from the previous systematic review by Mirnezami and colleagues (1965 to July 2011) [5]. The original systematic review and this update had the same inclusion criteria and search strategy, except the former included all types of IORT. As such, only studies from the previous review that included separate IOERT data were eligible for inclusion in the updated meta-analysis. Meta-analysis was conducted on the statistical software package R (version 4.4.0) using the 'metafor' package [11,12]. As per protocol, a meta-analysis was only performed if six or more studies reported the same outcome and if there was no evidence of heterogeneity ($I^2 < 40$ %). Fig. S1 shows a flowchart for how studies were assessed for eligibility in the meta-analysis, and the reasoning for whether or not a meta-analysis was carried out. A meta-analysis was performed for 5-year OS (Fig. S2). However, due to high heterogeneity ($I^2 > 40$ %), this is not presented in the main results. A meta-analysis was not performed for the other outcomes.

3. Results

3.1. Literature search

The database search identified 627 records, and 402 records remained after removal of duplicates. Following title and abstract screening, full texts were retrieved for 51 articles. Following detailed evaluation and risk of bias assessment, 16 newly identified studies were included in this systematic review update. No additional relevant papers were found after handsearching the reference lists of these studies. Fig. 1 shows the PRISMA flowchart for this systematic review update, and the reason for exclusions at each stage. An additional eleven studies met the inclusion criteria but were excluded [13–23]. Supplementary Table 2 shows the reasons for exclusion of these studies.

3.2. Description of newly identified studies

Of the 16 newly identified included studies, two were prospective [24,25], including one randomised controlled trial [25], and the remaining 14 were retrospective [26–39]. There were six comparative studies [25,29,31,32,36,39]. All studies were deemed 'acceptable' after

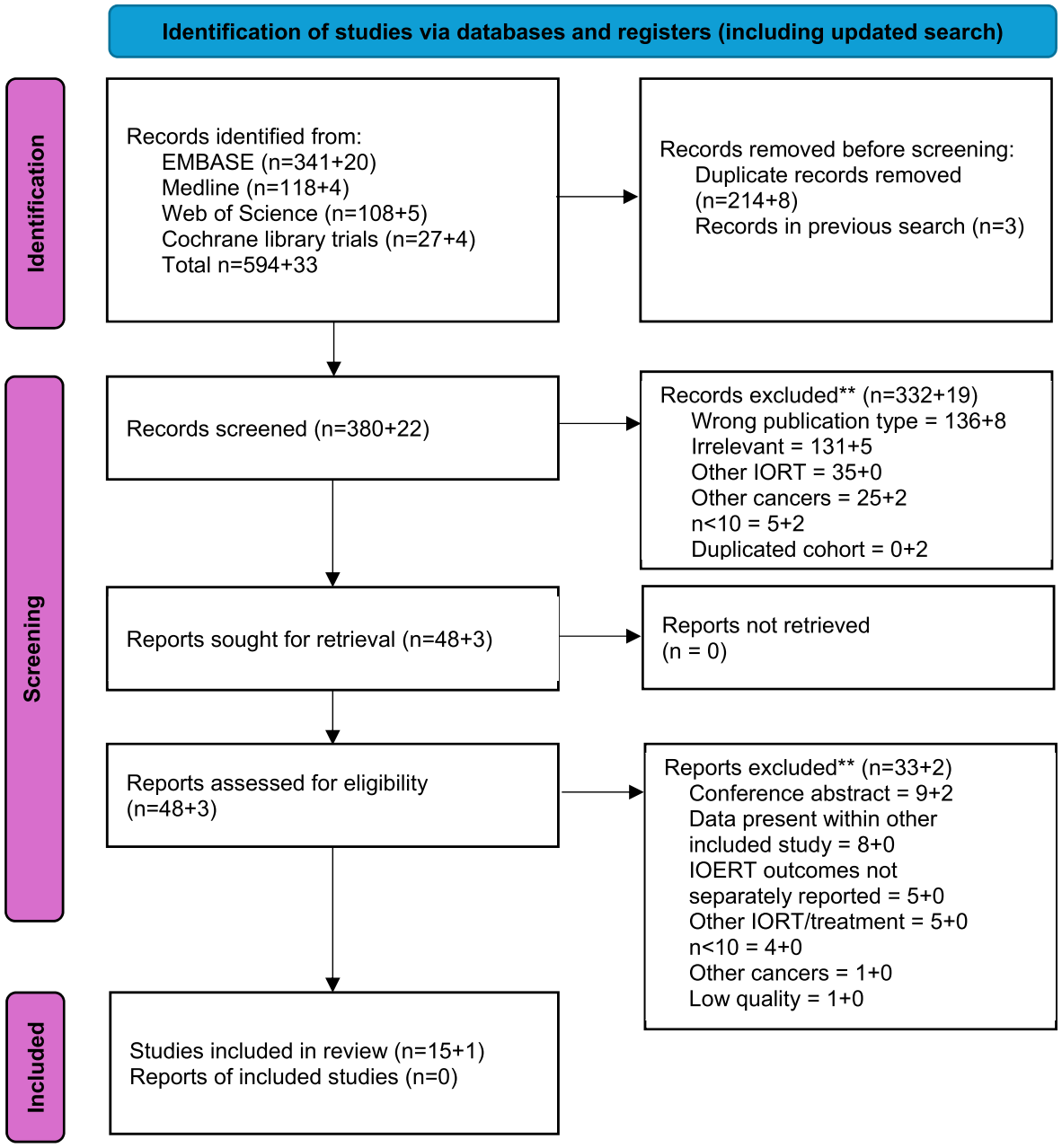

Fig. 1. – PRISMA diagram of the literature search, study selection, and inclusion (with reasons for exclusion).

risk of bias assessment using the SIGN checklist (Supplementary Table 3).

The indication for IOERT was LACC in 61.4 % (1174/1192), LRCC in 35.9 % (686/1192), and 2.7 % (52/1192) had LACC or LRCC but the outcomes were not reported separately. 99.9 % (1911/1912) underwent IOERT from the included studies. In one study, one patient out of twelve received HDR-IORT, however a decision was made to include this study, as the remaining patients all received IOERT [35].

The rationale for IOERT was explicitly stated in ten studies. This was "high-risk" or "at-risk" areas [31,32,38], margin status according to intraoperative frozen section [28,30], and "close" or "positive" or "narrow" margins [26,34,36,37]. In one study, IOERT was delivered to pelvic nerve plexuses following nerve-sparing TME with lateral lymph node dissection [25].

3.3. Oncological outcomes

3.3.1. Locally advanced colorectal cancer

3.3.1.1. Description of studies. Table 1 provides a summary of all eight newly identified studies reporting oncological outcomes for patients with LACC who underwent IOERT [24,25,30–34,36]. The disease staging was stated in all eight studies. These included patients with T4 disease [33], T3/T4 [31,32,36], majority T3 [24], T1-2 but majority of T3 [25]; and majority T2/T3 [30]. The remaining study consisted of patients with predominantly Stage II-IV disease [34]. With IOERT being a treatment modality for advanced margin threatening tumours, clearly this variety in T stages suggests that many patients in these studies would already be expected to have a clear resection margin, thereby negating any potential utility of IOERT.

The IOERT dosing strategy was outlined in all eight studies (overall range 10–20 Gy). One study used a fixed dose of 10 Gy [24]. Other

Table 1
– Studies reporting oncological outcomes following IOERT for locally advanced colorectal cancer.

Author, Year, Location	Comparative study	Study period	N (in IOERT group)	Cancer type	Clinical T stage	IOERT Dose (Gy)	Neo RT	Neo CT	Neo CRT	Adj RT	Adj CT	Adj CRT	Median follow-up (months)	Resection margin	5-year OS (%)	5-year DFS (%)	5-year LRC (%)
[36], Netherlands	Y	2000–2016	151	R	T1/2 2 T3 96 T4 52	10–12.5*	14	12	137	21 δ	–	–	–	R1 151	40	65 φ	–
[25], Japan	Y	2000–2017	38	R	T1/2 5 T3 31 T4 2	18-20*	–	–	–	0	15	0	69 (9.5–210)	R0 33 R1 5	71.5	–	–
[32], China	Y	1994–2007	71	R	T1/2 4 T3 39 T4 28	15**	0	0	0	0	0	71	78 (10–116.4)	R0 67 R1 4	74.6	69	89.7
[31], China	Y	1996–2007	45	R	T3 45	20***	0	0	0	0	45	0	72.9 (15.9–133.7)	R0 45	84	71	84
[24], Italy	N	2002–2005	39	R	T1/2 1 T3 38	10**	0	0	39	0	12	0	133 (26–158)	–	87	63.6	–
[34], USA	N	1999–2015	37	R	Stage I – 3 Stage II – 9 Stage III – 16 Stage IV - 8	11***	–	–	–	–	–	–	–	R0 28 R1/R2 9	19 (0–97) ϕ	–	–
[33], USA & Netherlands	N	1981–2010	417	R	T4 417	10-15*	79	–	325	27	71	–	52 (0–234)	R0 306 R1 111	56	55.1	–
[30], Spain	N	1995–2010	335	R	T2/3281 T4 54	12.5**	0	0	335	0	244	0	72.6 (4–205)	R0 323 R1 12	75	72	92

Y – Yes, N – No, R – Rectal, Neo RT – Neoadjuvant radiotherapy, Neo CT – Neoadjuvant chemotherapy, Neo CRT – Neoadjuvant chemoradiotherapy, Adj RT – Adjuvant radiotherapy, Adj CT – Adjuvant chemotherapy, Adj CRT – Adjuvant chemoradiotherapy, OS – Overall survival, DFS – Disease-free survival, LRC – Locoregional control. *range (no mean provided). **median. ***mean. ϕ median (range) of overall survival quoted. δ 21 patients had unspecified adjuvant therapy. φ 5-year local recurrence-free survival.

studies used a variable dosing strategy that depended on the target area and volume to be irradiated [36], the probability of residual disease [32], a combination of factors including EBRT total dose, size of IOERT applicator and intraoperative frozen section margin status [30], or the judgement of the surgeon and or radiation oncologist [31,34]. One study reported radiation fractions were increased in suspected cases of R2 resection compared to R0 or R1 margins [33].

Resection margin data was provided in all studies except one [24]. Only one study conducted an analysis of only patients with R1 disease [36]. The remainder had a combination of patients with majority R0 and some R1/R2 resections. No resection-specific analysis was carried out in these studies.

3.3.1.2. Comparative studies. During the study period, one randomised controlled trial conducted in Japan was identified. However this study randomised unselected T1-T4 rectal cancer patients to either IOERT and nerve-sparing TME with lateral lymph node dissection, or TME with lateral lymph node dissection with limited pelvic autonomic nerve preservation [25]. There were 38 patients in each group. Results showed no statistically significant difference in 5-year OS (OR 1.26, 95 % CI 0.52–3.05) or 5-year pelvic sidewall recurrence (OR 1.35, 95 % CI, 0.30–6.03) between the two groups. However, the trial was stopped early due to patients in the IOERT group having a significantly poorer distant metastasis-free survival (OR 2.55, 95 % CI 1.04–6.27) compared to the control. Although a randomised study, this study showed considerable limitations notably the recruitment of an unselected cohort of rectal cancer patients with up to 20 % of tumours being early stage and a negligible number in the T4 category, . These coupled with a small sample size recruited over a 17 year period during which many other aspects of care changed dramatically, as well as early trial termination, pose significant challenges to interpreting this study.

There were three non-randomised comparative studies [31,32,36]. A multi-centre cohort study in the Netherlands assessed oncological outcomes of patients who received HDR-IORT compared to IOERT in patients with an R1 resection of LACC and LRCC [36]. To date, this is the only study comparing these two treatment modalities. Of the LACC patients, there were 64 and 151 patients in the HDR-IORT and IOERT group respectively. On multivariable analysis, there was no statistically significant difference in 5-year OS between the two groups (47 % versus 40 %) (HR 1.10, 95 % CI 0.757–1.586). However, HDR-IORT was associated with significantly improved local recurrence-free survival compared to IOERT (79 % versus 65 %) (HR 0.50, 95 % CI 0.254–0.999) when accounting for pathological T stage, time between radiotherapy and surgery, and millimetres of resection margin.

The other two non-randomised comparative studies were both conducted in China [31,32]. Zhang and colleagues in 2015 compared the outcomes of patients with pT4N0/T1-4N + locally advanced rectal cancer treated with IOERT and adjuvant chemoradiotherapy compared to adjuvant chemoradiotherapy alone [32]. There were 71 patients in the IOERT group, and 77 in the non-IOERT group. The 5-year OS, DFS and LC between the two groups were favourable in the IOERT group (74.6 % vs 66.2 %, 69.0 % vs 58.5 %, and 89.7 % vs 79.2 % respectively). However, there was no statistically significant difference in these outcomes between the two groups. Over 93 % of patients in both groups had an R0 resection. Multivariable analysis of prognostic factors showed a trend of IOERT towards improvement of LC, though this was not statistically significant ($p = 0.079$). The other study conducted by the same authors was the same analysis but only included patients with T3N0M0 rectal cancer (these patients were excluded in Ref. [31,32]). Of the 45 patients who received IOERT compared to 46 who received adjuvant chemoradiotherapy alone, there was no statistically significant difference in 5-year OS, DFS, LC between the two groups (84 % vs 86 %, 71 % vs 73 %, 84 % vs 86 %).

3.3.1.3. Non-comparative studies. There were four non-comparative studies of patients with LACC who had IOERT. These consisted of patients with predominantly R0 resections, though no study reported oncological outcomes separately by resection margin. The largest was a multi-centre study combining data of two tertiary referral centres in the USA and Netherlands [33]. 417 patients were included. All patients had T4b rectal cancer and underwent multi-modality treatment including IOERT. The majority of patients underwent neoadjuvant treatment; 78 % had chemoradiotherapy, and 19 % had radiotherapy. 73 % had an R0 resection and 27 % had an R1/R2 resection. The 5-year OS and 5-year DFS was 56 % and 55 % respectively.

A large single-centre study conducted in Spain of 335 patients with T2-4 rectal cancer who underwent multi-modality treatment including IOERT and neoadjuvant chemoradiotherapy found a high 5-year OS, DFS and LRC of 75 %, 72 % and 92 % respectively [30]. This was the only study reporting in-field and out-of-field control for LACC patients. The 10-year IOERT in-field control and out-of-field control was 96 % and 96 % respectively. These results are likely to be partially explained by resection margin results, which showed that 96 % had an R0 resection.

An open-label phase I-II trial of 39 patients with locally advanced rectal cancer who received a trial of infusional 5-fluorouracil and gefitinib and neoadjuvant radiotherapy alongside IOERT found a 5-year OS and DFS of 87 % and 64 % respectively [24]. 97 % had T3 disease and 80 % had nodal disease, though no data on resection margin was reported. Finally, a single-centre study in the USA of 37 patients with LACC undergoing IOERT reported an OS of 19 months (range 0–97) [34]. 76 % had a resection margin of R0, and the remainder had R1/R2 resections.

3.3.2. Locally recurrent colorectal cancer

3.3.2.1. Description of studies. Table 2 provides a summary of all eight newly identified studies reporting oncological outcomes for patients with LRCC who underwent IOERT [26,28,34–39]. The dose of IOERT used was stated in all eight studies (range 9–20 Gy). Two studies did not provide data on resection margins [35,38]. With the exception of one study which conducted an analysis only on R1 patients [36], the majority of patients within each study had an R0 resection.

3.3.2.2. Comparative studies. A recent multi-centre non-randomised study using data from centres in USA and Japan compared patients with LRCC who received carbon-ion radiotherapy (CIRT) with or without surgery compared to IOERT-containing multi-modality treatment with neoadjuvant therapy [39]. There were 85 and 86 patients in the CIRT and IOERT group respectively. Resection margin in the IOERT group was R0 in 49 %, and R1/R2 in 51 %. Baseline characteristics of age and sex were similar between the two groups. The 5-year OS was 47 % in the CIRT group compared to 26 % in IOERT group, and this was significantly different (HR 0.5, 95 % CI 0.33–0.76).

The previously mentioned multi-centre cohort study in the Netherlands compared oncological outcomes of patients with an R1 resection of LRCC [36]. There were 46 patients in the HDR-IORT group and 112 in the IOERT group. On multivariable analysis, after adjusting for T and N stage, 5-year local recurrence-free survival (LRFS) was significantly higher in the HDR-IORT group (HR 0.57, 95 % CI 0.35–0.92). However, this was not reflected in the 5-year OS which was low in both cohorts (12 % vs 18 %, HR 1.17, 95 % CI 0.79–1.72). There were a few differences in baseline characteristics between the two groups which were not adjusted for in the LRFS multi-variate model, notably the interval between neoadjuvant therapy and surgery (13 % had a wait of <8 weeks in IOERT group compared to 39 % in the HDR-IORT group, $p < 0.01$) which may have skewed oncological results favourably towards the HDR-IORT group.

3.3.2.3. Non-comparative studies. Of the six non-comparative studies, the largest was a recent multi-centre study in USA by Ansell and

Table 2
– Studies reporting oncological outcomes following IOERT for locally recurrent colorectal cancer.

Author, Year, Location	Comparative study	Study period	N (in IOERT group)	Cancer type	IOERT Dose (Gy)	Neo RT	Neo CT	Neo CRT	Adj RT	Adj CT	Adj CRT	Follow up (months)	Resection margin	5-year OS (%)	5-year DFS (%)	5-year LC (%)
[39], USA & Japan	Y	2006–2019	86	R	15**	86	82	–	–	–	–	92.4	R0 42 R1 32 R2 12	25.7	–	–
[36], Netherlands	Y	2000–2016	112	R	10–12.5*	1	22	111	–	–	–	–	R1 112	18	19 φ	–
[38], USA	N	2008–2020	19	CR	15**	9	14	–	–	–	–	9.2 (1.2–61.2)	–	23 ϕ	–	–
[37], USA	N	2000–2015	267	R	10-20*	–	–	267	–	–	–	–	R0 94 IR1-R0 95 IR1-R1 78	IR0 52.8 ϕ IR1-R0 32.4 IR1-R1 34.8	IR0 36 ϕ IR1-R0 21.6 IR1-R1 21.6	–
[35], Brazil	N	2004–2015	12	CR	9-21*	–	–	–	–	–	–	97.2 (53–140)	–	58	–	23
[34], USA	N	1999–2015	19 14	R C	11***	–	–	–	–	–	–	–	R0 10, R1/R2 9 R0 11, R1/R2 3	43 (5–166) ϕ 36 (3–165)	–	–
[28], Spain	N	1995–2011	60	R	12.5**	–	–	19	9	30	–	36 (2–189)	R0 38 R1 22	43	37	44
[26], Germany	N	1991–2006	97	R	10-20*	6	–	40	0	33	8	33 (1–187)	R0 36 R1 32 R2 29	30	–	41

Y – Yes, N – No, R – Rectal, CR – Colorectal, C – Colon, Neo RT – Neoadjuvant radiotherapy, Neo CT – Neoadjuvant chemotherapy, Neo CRT – Neoadjuvant chemoradiotherapy, Adj RT – Adjuvant radiotherapy, Adj CT – Adjuvant chemotherapy, Adj CRT – Adjuvant chemoradiotherapy, OS – Overall survival, DFS – Disease free survival, LC – Local control. *range no mean. **median, ***mean. ϕ median OS quoted. φ 5-year local recurrence-free survival.

colleagues in 2022 and was the only study reporting oncological outcomes based on resection margins [37]. This comprised 267 patients with locally recurrent rectal cancer who underwent IOERT-containing multi-modality treatment and had intra-operative frozen section analysis during surgery. This involved the operating surgeon presenting the resected specimen in real-time to a histopathologist who would then carry out a histological assessment of the margins to identify the resection status. The report would be delivered back to the surgical team in around 30–45 min, who would then decide whether to carry out re-resection in cases of an R1 resection. As such, the cohort was stratified into three groups; initial R0 (IR0), initial R1 converted to R0 after re-resection (IR1-R0), and initial R1 that remained R1 after re-resection (IR1-R1). There were 94 (35 %) in the initial R0 group, 95 (36 %) in the IR1-R0, and 78 (29 %) in IR1-R1. Regarding oncological outcomes, the OS was 4.4 years in IR0, 2.7 years in IR1-R0, and 2.9 years in IR1-R1. When comparing IR1-R0 to IR0, and IR1-R1 to IR0, OS was significantly reduced (RR 0.7 [0.5–0.9] and RR 0.6 [0.4–0.9] respectively). However, there was no statistically significant difference in OS noted comparing IR1-R0 to IR1-R1 (RR 0.9 [0.7–1.3]). Similar results were also noted for DFS.

The remaining non-comparative studies were derived from single centres. The largest was a study in Germany investigating oncological outcomes for 97 patients with LRCC undergoing curative intent surgery and IOERT [26]. Just under half of patients underwent additional neoadjuvant chemoradiotherapy, and resection margin was R0 in 37 %, R1 in 33 %, and R2 in 30.0 %. 5-year OS and LC was 30 % and 41 % respectively. In a study by Calvo and colleagues of 60 patients with LRCC undergoing IOERT-containing treatment, the 5-year OS, DFS and LRC was 43 %, 37 %, and 44 % respectively [28]. Just under two-thirds of this cohort had an R0 resection and the remaining had an R1 resection.

Two studies investigated the use of IOERT for recurrent pelvic malignancies more broadly [35,38]. Information on resection margin was not present in either study. Coelho et al. investigated oncological outcomes of patients undergoing IOERT and found that for the 12 patients in the colorectal group, 5-year OS and LRC was 58 % and 23 % respectively [35]. Of 19 patients with recurrent colorectal cancer with para-aortic lymph node recurrences in the study by Hall and colleagues, the median OS was 23 months [38]. Finally, a single-centre study in the USA which included 19 and 14 patients with locally recurrent rectal and colon cancer undergoing IOERT reported an OS of 43 months (range 5–166) and 36 months (3–165) respectively [34]. The resection margin was R1/R2 in 47 % and 21 % in the rectal and colon cancer groups respectively.

3.4. Complications

Table 3 shows a summary of complications attributable to IOERT-containing treatment regimes. The overall complication rate ranged between 26 and 59 % [26,27,36]. Post-operative mortality ranged between 1 and 5% [26,28,29,34,36].

Commonly reported complications included those related to the wound e.g. surgical site infection [27,29], wound dehiscence [38], and healing disturbance [26,38]. Gastrointestinal complications included abscess or collection [25–27,29,34], anastomotic leak [25,27,29], and diarrhoea [31,32,38]. Fistula was reported at a rate of 2–7% [14,26,28,29,34]. Urological complications included ureteral obstruction/-stricture/stenosis [26,34,38], persistent urinary retention [26], urinary leakage [26,34], urinary tract lesions [27], and hydronephrosis [34]. Neurological complications included peripheral neuropathy in 0–8% [25,26,28,31] and paraesthesia in 5 % [34]. Of note, Roeder and colleagues found that neuropathy was present in 11 % of patients receiving an IOERT dose of ≥15 Gy compared to 6 % of patients with less than 15 Gy, though this difference was not statistically significant [26].

There were four studies providing comparative data on complications associated with IOERT compared to standard care [25,29,31,32].

Table 3
– Studies reporting complications following IOERT for locally advanced and locally recurrent colorectal cancer.

Author, Year, Location	Cancer type	N (in IOERT group)	IOERT Dose (Gy)	Overall complications (n)	Short-term complications (n)	Long-term complications (n)
[39], USA & Japan	LRR	86	15**	–	–	Genitourinary (11) φ ϕ Gastrointestinal (7) φ ϕ
[38], USA μ	LRCR	19	15**	–	Wound/infectious (dehiscence, delay healing, abscess) (4) Diarrhoea (2)	Lower extremity oedema (2) Foot drop due to recurrence (1) Ureteral obstruction due to recurrence (1)
[36], Netherlands	LAR	151	10–12.5*	45 θ	In-hospital mortality (2)	-
[36], Netherlands	LRR	112	10–12.5*	29 θ	In-hospital mortality (4)	-
[25], Japan	LAR	38	18-20*	–	Anastomotic leak (7/24) Abscess (7) Small bowel obstruction (5)	-
[24], Italy	LAR	39	10**	–	–	Genitourinary (14) φ ϕ Gastrointestinal (4) φ ϕ General (2) φ ϕ
[34], USA δ	LAR/LRC/LRR	77	11***	53/29 ω	Abscess (12) Ileus (10) Urinary tract infection (10) Urinary retention (8) Acute blood loss anaemia (7) Urine leak (5) Wound (surgical site infection) (4) Small bowel obstruction (4) Readmission within 30 days (19) In-hospital mortality (1)	Small bowel obstruction (14) Back/pelvis/sacral pain (5) Leg pain or paraesthesia (4) Pelvic sacral insufficiency or microfracture (3) Ureteral stricture (3) Urinary incontinence (2) Urinary retention (1) Erectile dysfunction (1) Deep vein thrombosis (1) Perineal hernia (1) Vesicocutaneous fistula with abscess (1)
[32], China	LAR	71	15**	–	Mucositis of anal verge (17) Leukopenia (11) Diarrhoea (5)	Hydronephrosis (5) Incomplete intestinal obstruction (3)
[31], China	LAR	45	15-25*	–	Diarrhoea (2)	Peripheral neuropathy (2)
[29], Germany	LAR/LRR	52	10-20*	–	Wound (surgical site infection) (8) Presacral abscess (5) Bladder dysfunction (4) Anastomotic leakage* (4/35) Reoperation (2) Stenosis (2) Sexual dysfunction (1) Burst abdomen (1) Fistula (1) In-hospital mortality (2)	–
[30], Spain	LAR	335	10-15*	102/34 ψ	Skin (41) ϕ Bowel (34) ϕ Rectal (18) ϕ Bladder (4) ϕ	Gastrointestinal (19) φ Genitourinary (8) φ Neurologic (2) φ
[28], Spain	LRR	60	12.5**	25/12 ψ	Wound (5) ϕ Peripheral neuropathy (5) ϕ Fistula (4) ϕ Soft tissue abscess (1) ϕ Peri-operative mortality (3) ϕ	Neurologic (6) ϕ Gastrointestinal (4) ϕ
[27], Italy	LAR	41	10**	17	Wound (surgical site infection) (6) Anastomotic leak (3) Anastomotic bleeding (2) Intra-abdominal collection (1)	Urinary tract lesions (1)
[26], Germany	LRR	97	10-20*	57	Wound (healing disturbance) (19) Abscess or fistula (16) Transient urinary retention (9) Neuropathy (8) Haemorrhage (6) Ileus (3) Delayed gastrointestinal passage (3) Persistent urinary retention (3) Ureteral stenosis (3) Anal stenosis (2) Perineal hernia (1) Sphincter insufficiency (1) Urinary leakage (1) Compartment syndrome (1) Reoperation (22) 90-day mortality (3)	-

LRR – Locally recurrent rectal, LRCR – Locally recurrent colorectal, LAR – Locally advanced rectal, LRC – Locally recurrent colon. * range (no mean or median provided). **median. ***mean. φ late toxicity. μ complications reported as part of the wider cohort of 26 patients with recurrrent pelvic malignancies of which 19 had LRCR. ϕ grade 3 or greater toxicity. δ cohort included two patients with primary appendiceal cancer. ω short-term complications/long-term complications. ψ grade 3 or greater acute toxicity/chronic toxicity. θ Clavien-Dindo grade III-V complications.

The only randomised trial demonstrated no statistically significant difference in the incidence of anastomotic breakdown, intra-pelvic abscess, and small bowel obstruction between the IOERT and control group, although the incidence of anastomotic breakdown was higher but not statistically significant (29 % versus 13 %) [25]. Similar findings were noted by Zhang and colleagues in 2014 and 2015 when assessing the incidence of diarrhoea, leukopenia and mucositis of the anal verge in an IOERT group compared to patients receiving EBRT and surgery [31,32]. The remaining study found no statistically significant difference in all complications observed (Table 3), including mortality, between an IOERT group and those who only received surgery with or without neoadjuvant chemoradiotherapy, though the incidence of surgical site infection was noted to be slightly higher (15 % versus 9 %) [29].

4. Discussion

The rationale for IOERT in LACC and LRCC is to deliver targeted radiotherapy to at-risk or narrow margins during surgery, particularly where the dose of EBRT is limited due to the potential of toxicity to adjacent viscera. The previous systematic review by Mirnezami and colleagues, which included studies between 1965 and July 2011, found that the addition of IORT (including both IOERT and HDR-IORT) to conventional multi-modality treatment in patients with LACC and LRCC was associated with improved oncological outcomes including 5-year LC, DFS and OS, and a similar profile of post-operative complications [5]. The authors noted the limitations, most notably the heterogeneity of included studies, the lack of randomised comparative data, and limited analysis on patients specifically with R1 resection margins.

This systematic review update focussed on studies only including IOERT that were published after the review (July 2011) by Mirnezami and colleagues. The majority of data came from single-centre retrospective cohort studies. The studies were heterogeneous, due to differences in IOERT dosing strategy, the definitions of LACC, resection margins, and treatment protocols used. Furthermore, the multi-modality control arm of included comparative studies varied, ranging from neoadjuvant therapy to HDR-IORT to more novel carbon ion radiotherapy. This was the likely reason for the high heterogeneity observed in the meta-analysis for 5-year OS that was carried out (see Fig. S2).

The findings from this review suggest that the addition of IOERT may not result in improved oncological outcomes in patients with LACC and LRCC with R0 resection margins. For example regarding LACC, the only randomised controlled trial which assessed oncological outcomes of IOERT with nerve-sparing TME compared to TME with limited pelvic autonomic nerve preservation, demonstrated patients in the IOERT group had no significant difference in 5-year OS or pelvic sidewall recurrence compared to the latter. The majority (87 %) of patients in this trial had an R0 resection. Nevertheless, concerns regarding the utility of this study for evaluating IOERT are significant. These include the fact that this was a single centre study aiming to determine utility of complete pelvic autonomic nerve preservation in T1-T4 rectal cancer patients (up to 20 % were T1/T2; and only 2 % were T4), and the study failed to recruit over a 17-year period during which a variety of other treatments changed significantly. In addition, the long period of recruitment for such a common grouping of rectal cancer raises concern regarding patient selection. Similarly, two non-randomised studies comparing outcomes of IOERT-containing treatment to adjuvant chemoradiotherapy and surgery demonstrated no significant difference in 5-year OS, DFS and LC in LACC patients, although results were favourable towards the IOERT group (75 % vs 66 %, 69 % vs 59 %, and 90 % vs 79 %). Over 93 % of patients in both studies had R0 resections. Regarding LRCC, of the only study that stratified by R0 resection, the median OS of patients was 53 months, which compares similarly to the timeframe reported in the literature (19–66 months) [40].

In their previous review, Mirnezami and colleagues suggested that patients with R1 resections, who typically have unfavourable prognoses, may be most likely to derive oncological benefit from the application of IOERT [5]. Achieving an R0 resection is surgically challenging in LACC and more so in LRCC as post-operative fibrosis is often indistinguishable from infiltrating tumour and anatomical planes are corrupted from previous surgery, sepsis, or radiotherapy. In this study, the rate of R1/R2 resection was as high as 27 % in patients with LACC and 51 % in LRCC. A recent multi-centre study by the PelvEx Collaborative showed that the rate of R1 resection in patients with LACC and LRCC was 14 % and 26 % respectively [41]. This represents a significant group of patients in whom an R0 resection is not achieved. The findings from this review suggest that the addition of IOERT may confer an oncological benefit for this group of patients. Moreover, the distance from the circumferential margin is a robust predictor of local disease recurrence. A margin of <2 mm is associated with a higher local recurrence risk compared with patients having a >2 mm margin [42,43]. However recently Koh and colleagues have examined the significance of margin status in locally recurrent rectal cancers with a microscopically clear margin being most predictive of enhanced overall survival, with margins up to >0.5 mm offering a local recurrence benefit but not a survival benefit [44].

For example, the only study that analysed solely R1 resections found a 5-year OS of 40 % and 18 % in LACC and LRCC patients having IOERT multi-modality treatment respectively. This is a higher rate compared to that reported of R1 patients receiving standard care without IOERT. For example, a multi-centre study of 896 patients undergoing multi-visceral resection for primary locally advanced rectal cancer found a 5-year OS of 21 % for those with R1 resection [45]. Moreover, a single-centre study of 902 patients with primary colorectal cancer found an R1/R2-specific 5-year OS of 35 % [46]. Similarly, a systematic review in 2016 that pooled the results of 550 patients with LRCC found a 5-year OS of 11.4 % in patients who had an R1 resection [40]. The only other LRCC study that stratified between resection margins in this review found that the median survival in patients with R1 resection was 32 months. This compares slightly favourably to the literature in cases of R1 resection, with a reported rate of 20–30 months [40]. Although there are likely a number of factors such as patient selection and differing treatment protocols that may explain this discrepancy as well as the inherent limitation of non-randomised and retrospective cohort studies, this finding parallels the results of the previous review by Mirnezami and colleagues, suggesting a potential use for the application of IOERT where an R1 resection is anticipated.

In an unanticipated finding, the only randomised trial in this study showed that IOERT was associated with significantly lower distant metastasis-free survival compared to the control group, resulting in the trial being stopped early [25]. One explanation for this finding as suggested by the authors was that the concurrent radiation may temporarily disrupt or suppress the host immune system, leading to increased cancer cell migration and invasion, and that similar findings were noted in a randomised trial assessing the efficacy of IORT in pancreatic cancer [47]. However, this finding may also be a consequence of the IOERT group receiving less radical surgery in an attempt to preserve pelvic autonomic nerve function. The same trial showed no significant differences in other oncological outcomes such as OS and pelvic sidewall recurrence, and the rate of R0 resection was lower in the IOERT group compared to the control (although this was not statistically significant). As such, this may in turn have directly affected the development of metastatic disease. To date this surprising finding has not been replicated in any of the other studies on patients receiving IOERT reviewed in this or our previous manuscript.

Of note, two non-randomised comparative studies in this review compared IOERT to other forms of novel radiation therapy. Voogt and colleagues found that local recurrence-free survival was higher in the group receiving HDR-IORT compared to IOERT in patients with LACC and LRCC. Although this finding is confined within the remits of a non-randomised analysis, one potential explanation may have been that the dose of IOERT in this study was relatively low (10–12.5 Gy) when compared to the other LACC studies in this review (10–20 Gy range). The only randomised trial in this review, which contained patients with

predominantly R0 resections, used a much higher dose of 18–20 Gy. In another study, Jeans and colleagues found that the 5-year OS in patients with LRCC was significantly higher in the cohort receiving carbon-ion radiotherapy compared to IOERT. However, this study found no differences in other oncological outcomes namely pelvic recurrence, distant metastases and disease progression. As such, the authors noted this may have been secondary to differences in patient health and comorbidities, details of which were not available in the study. The median size of the tumour in the IOERT-containing group was also found to be larger (5 cm vs 2.9 cm) which may have in part contributed to the higher proportion of R1/R2 resections, worsening prognosis. Interestingly, immediate re-resection to R0 for confirmed R1 resection on intraoperative frozen section analysis resulted in inferior oncological outcomes to those patients who had a confirmed R0 on initial resection, suggesting that the resection margin and IOERT may not be the only factors involved in determining oncological outcomes. It is plausible that tumour dissemination in obtaining an R1 margin may incur a sufficiently negative outcome to mitigate for any advantage conferred by the extra radiotherapy boost.

Finally, this study paralleled the findings by Mirnezami and colleagues with regards to complications. Although there was heterogeneity in which complications were reported as well as the dose of IOERT used, the comparative studies showed no significant difference in total, wound, urological and anastomotic complications from IOERT. An absolute increase in anastomotic breakdown and wound infection was noted, though this was not statistically significant. Of note, one study found a dose-dependent relationship with the IOERT dose and the development of neuropathy, which poses further questions as to the optimal dose required to potentially improve oncological outcomes whilst limiting post-operative complications.

This review is subject to several limitations. Most of the studies were retrospective in nature, except for two prospective studies, and were typically from single institutions. IOERT is typically delivered in specialised centres with a high caseload and as such, outcomes may also be dependent on the experience of the surgical team. With the exception of one randomised controlled trial, all other comparative studies consisted of non-randomised cohorts. Furthermore, almost all these studies included another novel form of therapy (for example HDR-IORT or carbon-ion radiotherapy) as the comparator, making it difficult to infer the additional benefit derived from IOERT when compared to 'standard' treatment, and some centres used HDR brachytherapy in addition to IOERT with an improved LRFS and but no significant benefit in OS. Furthermore, the heterogeneity of included studies, for example in their definition of LACC and LRCC, IOERT dosing strategy (range of 10–12.5 Gy up to 18–20Gy depending upon the centre), disease staging, patient selection, and treatment protocol makes it challenging to generalise the results to a wider population. The exact timing of surgery and the size of the tumour is also likely to affect treatment outcomes. Importantly, the time period of some studies spanned over two decades, which is likely to mean treatment strategies, including the availability of new surgical techniques and changes in chemoradiotherapy regimes, changed over the time course of the study. IOERT was delivered as part of a multimodality treatment regime which means any observed oncological benefit within an IOERT group cannot be put down solely due to the addition of IOERT. Much of the data also came from large expert tertiary centres which may not be generalisable to a wider population. Importantly, there was a lack of resection margin specific data, making pathological reporting and its consistency with a clear common language, the most critical items of information needed for evaluating any potential benefit of IOERT, making it difficult to appreciate the specific setting in which IOERT is most likely to be useful.

This systematic review update, alongside the previous review, suggests that the application of IOERT in patients with LACC and LRCC may be beneficial within the setting of an R1 or a "close" R0 resection margin. Given the complexity of operating in LACC and LRCC, and the results from this study that showed that up to half of patients had an R1 resection despite being done in large specialist centres, this suggests that IOERT may confer an additional oncological benefit in this important subgroup of patients. However, it also highlights the limitations of the current data and demonstrates the need for further randomised evidence, a consistent pathological reporting language and a robust systematic pathological approach to limit reporting inaccuracies. ELECTRA is an ongoing double-blinded feasibility study (ISRCTN48105173) of IOERT in patients with LACC and LRCC, aiming to determine the acceptability and feasibility of recruiting, randomising and delivering IOERT in a randomised controlled trial setting as preparatory work for a future late phase RCT [48,49]. Results from this body of work will help to address the unknowns associated with this novel intervention.

5. Conclusions

Although the field is limited by a lack of randomised controlled trial evidence, the use of IOERT-containing multi-modality treatment may improve oncological outcomes in patients with LACC and LRCC, with R1 resection margins.

5.1. Critical view

Despite advances in surgical techniques, the oncological outcomes for patients with LACC and LRCC remain poor. This systematic review update, alongside the original review, provides to date the most comprehensive overview of the impact of IOERT on oncological outcomes in this group of patients (1965–April 2024). The findings from this work suggests that the addition of IOERT to multi-modality treatment may confer an oncological benefit in patients with positive resection margins whilst demonstrating a similar profile of complications to standard therapy. Given the inherent challenges of obtaining a complete tumour-negative resection in this group of patients, and that the use of EBRT is limited due to the potential toxicity to adjacent viscera that have previously been irradiated, this suggests IOERT may be an important tool to be added to multi-modality therapy in patients with LACC and LRCC. This review also highlights the limitations of the current evidence (the need for further randomised trial evidence) and poses further research questions regarding dosing strategies to derive oncological benefit versus minimising complications, and the exact population in whom IOERT delivery would be most beneficial. We believe this work adds to the literature, and will enable both clinicians and researchers to better understand the current evidence regarding IOERT in this complex group of patients.

CRediT authorship contribution statement

Abhinav Tiwari: Data acquisition, Quality control of data and algorithms, Data analysis and interpretation, Statistical analysis, Manuscript preparation. **Sheah Lin Lee:** Data acquisition, Data analysis and interpretation, Writing – review & editing. **Tom MacCabe:** Data acquisition, Data analysis and interpretation, Writing – review & editing. **Michal Woyton:** Data acquisition. **Charles T. West:** Writing – review & editing. **Rohan Micklethwaite:** Data acquisition, Writing – review & editing. **Hideaki Yano:** Writing – review & editing. **Malcolm A. West:** Study concepts, Study design, Writing – review & editing. **Alex H. Mirnezami:** Study concepts, Study design, Writing – review & editing.

Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2025.109724.

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