Interventional procedure overview of intraoperative electron beam radiotherapy for locally advanced and locally recurrent colorectal cancer

Contents

Table 1 Abbreviations

Abbreviation	Definition
CI	Confidence interval
EBRT	External beam radiotherapy
HDR-brachytherapy	High dose rate-brachytherapy
HR	Hazard ratio
IOERT	Intraoperative electron beam radiotherapy
IORT	Intraoperative radiotherapy
LARC	Locally advanced rectal cancer
LRFS	Local recurrence-free survival
LRRC	Locally recurrent rectal cancer
NR	No response
OR	Odds ratio
OS	Overall survival
RCT	Randomised controlled trial

Indications and current treatment

Colorectal cancer is a common cancer. It typically occurs in people older than 50, with the risk increasing with age. About 5% to 20% of people with colorectal cancer have locally advanced disease, in which the cancer has invaded nearby tissues. After primary resection to remove the tumour, it returns in the same place in about 5% to 20% of people.

There are various treatments for colorectal cancer, including resection, chemotherapy and radiotherapy. Treatment choice depends on the type of cancer, location and staging. The radicality of resection is the most important prognostic factor for survival. Resection is referred to as:

- R0, when there are clear margins around the tumour
- R1, when there are microscopically involved margins
- R2, when there are macroscopically involved margins or gross residual disease.

What the procedure involves

The procedure is done during surgery for locally advanced or locally recurrent colorectal cancer. Once the tumour is resected, the patient is positioned to receive a megavoltage electron dose from a linear accelerator. Either the operating theatre is equipped with a stationary linear accelerator, the patient is transferred to a dedicated room, or a mobile linear accelerator is brought into the theatre. Radiation-sensitive organs surrounding the tumour site can be displaced or shielded from the IOERT field. A single large fraction of radiation (typically 10 Gy to 20 Gy) is then delivered via an applicator directly to the tumour bed. The aim is to improve local control and increase survival rates.

There are several techniques for delivering IORT, including IOERT, HDR-brachytherapy and orthovoltage. This overview is a summary of the evidence for IOERT and is not an assessment of HDR-brachytherapy or orthovoltage techniques.

Outcome measures

The main outcomes included recurrence (local and distant), OS, cancer-specific survival (time from treatment until death from cancer) and disease-free survival (time from treatment until cancer recurs or death).

Evidence summary

Population and studies description

This overview is based on 3,144 patients from 2 systematic reviews and meta-analyses, 4 case series and 1 cohort study. However, both systematic reviews included studies that used HDR-brachytherapy. Additionally, there may have been significant overlap in patient populations of the case series because of studies being done in similar institutions over similar time periods.

This is a rapid review of the literature, and a flow chart of the complete selection process is shown in figure 1. This overview presents 7 studies as the key evidence in table 2 and table 3, and lists 48 other relevant studies in table 5.

The 2 systematic reviews and meta-analyses of comparative studies considered 7 studies and 15 studies, respectively. There were 2 RCTs (a third RCT was incorrectly reported in 1 of the systematic reviews) reported in the systematic reviews. All other studies were observational and typically retrospective.

Recruitment periods of the key evidence studies began in 1978 (1 study included in Liu, 2021). Follow-up periods, when reported, ranged from 25.5 months to 80.0 months.

The studies included in the systematic reviews were done in various locations, including several countries in Europe, the US, China and Japan. Of the other key evidence studies, 1 was done in the US, 2 were done in the US and The Netherlands, 1 was done in The Netherlands, and 1 was done in Germany, Italy, Spain, and The Netherlands.

Most studies included people with rectal cancer and only Haddock (2011) included patients with colon and rectal cancer. Most patients in the Fahy (2021) systematic review had locally advanced rectal cancer; a breakdown between LARC and LRRC was not reported in the Liu (2021) systematic review. Of the other studies, 2 included people with locally recurrent colorectal or rectal cancer, and 2 included people with locally advanced rectal cancer. One study specified that patients were only included in the analysis if they had an R1 resection (Voogt, 2021). Table 2 presents the study details.

Figure 1 Flow chart of study selection

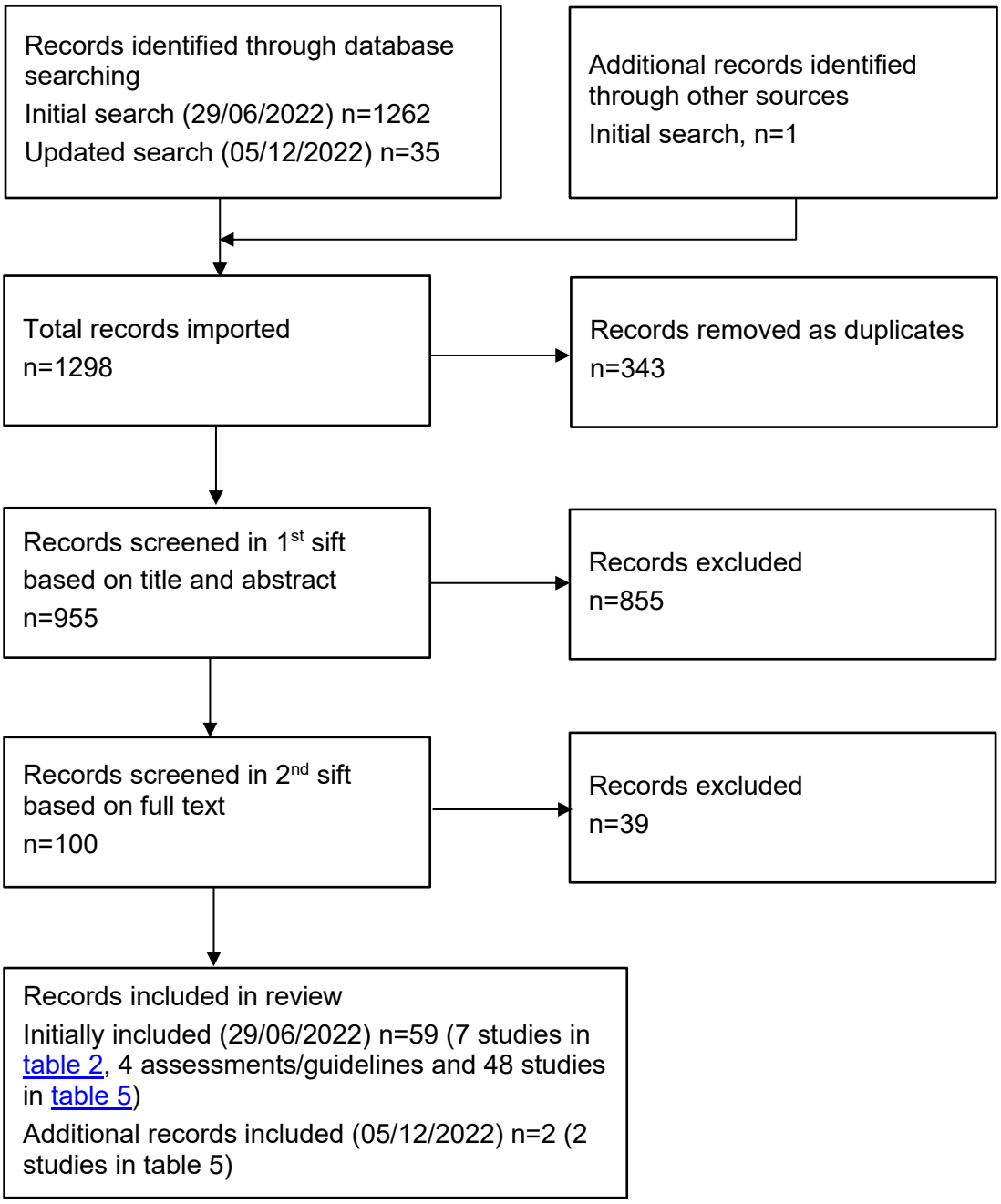

Table 2 Study details

Study no.	First author, date country	Studies/Patients (male:female)	Age	Study design	Inclusion criteria	Intervention	Follow up
1	Fahy 2021 Various	7 studies (6 IOERT; 1 HDR-brachytherapy) including 2 RCTs n=422 IORT n=411 surgery or EBRT	Median ages ranged from 58 to 64	Systematic review and meta-analysis	Confirmed LARC or LRRC; people who had IORT; comparison in terms of local control between a group receiving IORT and a surgery/EBRT only group; outcomes of locoregional recurrence rate or morbidity, more than 10 patients; clear research methodology; published on or after 1 January 2000.	6 studies used IOERT, 1 study used HDR-brachytherapy; comparator was surgery/EBRT Dose of IORT ranged from 10 Gy to 25 Gy	NR
2	Liu 2021 Various	15 studies (12 IOERT, 3 HDR-brachytherapy) including 3 RCTs n=687 IORT n=773 surgery/EBRT	Mean ages ranged from 58 to 66	Systematic review and meta-analysis	Studies that compared IORT and surgery/EBRT treatment for people with rectal cancer; at least 20 patients.	12 studies IOERT, 3 studies HDR-brachytherapy; comparator was surgery/EBRT Dose of IORT ranged from 10 Gy to 25 Gy	Study means ranged from 25.5 months to 80.0 months

3	Voogt 2021 The Netherlands	n=373 (total LARC and LRRC) n=263 IOERT n=110 HDR-brachytherapy 255 male;118 female	278 were younger than 70; 95 were older than 70	Retrospective cohort study; prospectively collected data	Consecutive patients with LARC or LRRC who had an R1 resection after undergoing intentionally curative surgery in which IORT was delivered by either IOERT or HDR-brachytherapy.	IOERT Comparator was HDR-brachytherapy Dose was typically 10 Gy to 12.5 Gy	NR
4	Haddock 2011 US	n=607 369 male:238 female	Median 62	Retrospective case series; prospectively collected data	Patients with recurrent colorectal cancer who had IOERT and surgical resection.	IOERT Median dose was 15 Gy	Median for survivors 44 months
5	Holman 2017 US/The Netherlands	n=565 346 male:219 female	Mean 61.5	Retrospective case series; prospectively collected data	Recurrent rectal cancer and without preoperative distant metastases, including only patients in whom the surgical intent was a gross total resection.	IOERT Dose was typically 10 Gy to 12.5 Gy for R0 or R1 resections and 15 Gy to 20 Gy after R2 resection	Mean for survivors 40 months

6	Holman 2016 US/The Netherlands	n=417 248 male;169 female	Mean 59.2	Retrospective case series; prospectively collected data	Primary locally advanced (T4b) rectal cancer without preoperative distant metastases, locally unresectable for cure at initial presentation.	IOERT Dose was typically 10 Gy to 12.5 Gy for R0 or R1 resections and 15 Gy or higher after R2 resection	Mean 52 months
7	Kusters 2010 Germany, Italy, Spain, The Netherlands	n=605 389 male;216 female	Mean 62	Retrospective case series; prospectively collected data	Locally advanced rectal cancer without preoperative distant metastases.	IOERT Dose was typically 10 Gy to 12.5 Gy	Mean 62 months

Table 3 Study outcomes

First author, date, study design	Efficacy outcomes	Safety outcomes
Fahy 2021 Systematic review and meta-analysis	**Locoregional recurrence** Meta-analysis of 7 studies: no statistically significant difference between IORT and surgery/EBRT, OR 0.55, 95% CI 0.27 to 1.14; p=0.11. IORT: 14.7% Surgery/EBRT: 21.4%	**Wound infections** Meta-analysis of 4 studies: no statistically significant difference between IORT and surgery/EBRT, OR 1.13, 95% CI 0.50 to 2.54, p=0.76 **Pelvic abscess** Meta-analysis of 3 studies: no statistically significant difference between IORT and surgery/EBRT, OR 1.01, 95% CI 0.54 to 1.87, p=0.99 **Anastomotic leak** Meta-analysis of 5 studies: no significant difference between IORT and surgery/EBRT, OR 1.06, 95% CI 0.51 to 2.18, p=0.88 **Reintervention rate** Meta-analysis of 3 studies: no statistically significant difference between IORT and surgery/EBRT, OR 1.13, 95% CI 0.43 to 2.98, p=0.80

Liu 2021 Systematic review and meta-analysis	**5-year OS** Meta-analysis of 9 studies: no statistically significant difference between IORT and surgery/EBRT, HR 0.80, 95% CI 0.60 to 1.06; p=0.189 **5-year disease-free survival** Meta-analysis of 6 studies: no statistically significant difference between IORT and surgery/EBRT, HR 0.94, 95% CI 0.73 to 1.22; p=0.650 **5-year local control** Meta-analysis of 14 studies: statistically significantly better with IORT than surgery/EBRT, OR 3.07, 95% CI 1.66 to 5.66; p=0.000 RCTs: No statistically significant difference between treatments: OR 1.37, 95% CI 0.35 to 5.35; p=0.655 Observational studies: statistically significantly better with IORT than surgery/EBRT: OR 3.45, 95% CI 1.54 to 7.73, p=0.000)	**Abscess** Meta-analysis of 6 studies: no statistically significant difference between IORT and surgery/EBRT, OR 1.10, 95% CI 0.67 to 1.80, p=0.833 **Fistulae** Meta-analysis of 3 studies: no statistically significant difference between IORT and surgery/EBRT, OR 0.79, 95% CI 0.33 to 1.89; p=0.600 **Wound complications** Meta-analysis of 8 studies: no statistically significant difference between IORT and surgery/EBRT, OR 1.02, 95% CI 0.52 to 2.02, p=0.948 **Anastomotic leakage** Meta-analysis of 7 studies: no statistically significant difference between IORT and surgery/EBRT, OR 1.09, 95% CI 0.59 to 2.02; p=0.775 **Neurogenic bladder dysfunction** Meta-analysis of 3 studies: no statistically significant difference between IORT and surgery/EBRT, OR 0.69, 95% CI 0.31 to 1.55; p=0.369

Voogt 2021 Cohort study	**<u>LARC (IOERT n=151; HDR-brachytherapy n=64)</u>** **OS** There was no statistically significant difference in OS between treatments (p=0.989) HDR-brachytherapy 3-year OS: 61% HDR-brachytherapy 5-year OS: 47% IOERT 3-year OS: 58% IOERT 5-year OS: 40% Significant prognostic factors were age, time between radiation therapy and surgery, pathologic tumour and lymph node stage, and resection margin. **Local recurrence-free survival** There was no statistically significant difference in local recurrence-free survival between treatments (p=0.103). HDR-brachytherapy 3-year LRFS: 82% HDR-brachytherapy 5-year LRFS: 79% IOERT 3-year LRFS: 71% IOERT 5-year LRFS: 65% However, in multivariate analysis, treatment modality was borderline statistically significantly associated with local recurrence-free survival: HR 0.504, 95% CI 0.254 to 0.999, p=0.050. Other significant prognostic factors included time between radiation therapy and surgery, pathological tumour stage, and resection margin. **<u>LRRC (IOERT n=112; HDR-brachytherapy n=46)</u>** **OS**	**<u>LARC (IOERT n=151; HDR-brachytherapy n=64; data available for 91% of patients)</u>** **Death** No statistically significant difference in in-hospital mortality between the treatments (p=0.546): HDR-brachytherapy: 0% IOERT: 1% **Major complications** No statistically significant difference in major complications (Clavien-Dindo grade 3 or higher) between the treatments (p=0.665): HDR-brachytherapy: 27% IOERT: 30% Most common major complications were: Presacral abscess (27%) Bleeding (11%) Abdominal wound dehiscence with evisceration (11%) Intra-abdominal abscess (9%) Perineal wound necrosis (5%) Leakage of the ureter or bladder reconstruction (5%) Anastomotic leakage (5%) Ureter stenosis (5%) **<u>LRRC (IOERT n=112; HDR-brachytherapy n=46; data available for 99% of patients)</u>** **Death**

First author, date, study design	Efficacy outcomes	Safety outcomes
	There was no statistically significant difference in OS between treatments (p=0.747) HDR-brachytherapy 3-year OS: 39% HDR-brachytherapy 5-year OS: 12% IOERT 3-year OS: 44% IOERT 5-year OS: 18% Significant prognostic factors were age and pathologic lymph node stage. **Local recurrence-free survival** There was no statistically significant difference in local recurrence-free survival between treatments (p=0.139). HDR-brachytherapy 3-year LRFS: 38% HDR-brachytherapy 5-year LRFS: 34% IOERT 3-year LRFS: 29% IOERT 5-year LRFS: 19% However, in multivariate analysis, treatment modality was statistically significantly associated with local recurrence-free survival: HR 0.567, 95% CI 0.349 to 0.920, p=0.021. Other significant prognostic factors included pathological tumour and lymph node stage.	No statistically significant difference in in-hospital mortality between the treatments (p>0.999): HDR-brachytherapy: 2% IOERT: 4% **Major complications** Statistically significantly more major complications (Clavien-Dindo grade 3 or higher) with HDR-brachytherapy than IOERT (p=0.017): HDR-brachytherapy: 46% IOERT: 26% Most common major complications were: Presacral abscess (26%) Leakage of the ureter or bladder reconstruction (12%) Abdominal wound dehiscence with evisceration (8%) Intra-abdominal abscess (6%)

First author, date, study design	Efficacy outcomes	Safety outcomes
Haddock 2011 Case series	**OS** 5-year OS: 30% 10-year OS: 16% Significant prognostic factors were treatment era (better survival for more recently treated patients), no prior chemotherapy, and radicality of the resection (R0 better than R1 better than R2). **Disease relapse** 5-year central relapse (within the IOERT field): 14% 5-year local relapse: 28% 5-year distant relapse: 53% Significant prognostic factors were previous irradiation (previously irradiated patients were more likely to relapse) and radicality of resection (R0 resection better than R1/2)	There were 621 treatment-related complications that affected 302 patients. Of those, 302 complications were considered severe or greater. **Deaths** 6 patients (less than 1%) died without relapse of treatment-related complications, and none had been previously irradiated. One patient died from uncontrolled bleeding from the colostomy, 6 weeks after IOERT, n=1. Five additional patients died 3 months to 22 months after surgery for small-bowel obstruction, small-bowel perforation, or complications arising after surgical correction of the bowel complication. **IOERT-related severe complications** Wound infection, abscess, fistula, n=42 (7%) Gastrointestinal tract fistula or obstruction, n=7 (1%) Ureteral obstruction, n=18 (3%) Neuropathy, n=18 (3%)

First author, date, study design	Efficacy outcomes	Safety outcomes
Holman 2017 Case series	**Local re-recurrence** 5-year local re-recurrence: 45.3% Significant prognostic factors were preoperative treatment, waiting time between preoperative treatment and surgery, and radicality of the resection. **Distant metastases-free survival** 3-year distant metastases-free survival: 50% 5-year distant metastases-free survival: 43% Significant prognostic factors were preoperative treatment, radicality of the resection, postoperative radiotherapy. **Cancer-specific survival** 3-year cancer-specific survival: 62% 5-year cancer-specific survival: 41% Significant prognostic factors were preoperative treatment and radicality of the resection. **OS** 3-year OS: 52% 5-year OS: 33% Significant prognostic factors were preoperative treatment and radicality of the resection.	Not reported.

First author, date, study design	Efficacy outcomes	Safety outcomes
Holman 2016 Case series	**Local recurrence** 5-year local recurrence: 19.3% Significant prognostic factors were time between preoperative treatment and surgery, and radicality of resection. **Distant metastases-free survival** 5-year distant metastases-free survival: 64% Significant prognostic factor was radicality of the resection. **Cancer-specific survival** 5-year cancer-specific survival: 64.6% Significant prognostic factor was radicality of the resection. **Relapse-free survival** 5-year relapse-free survival: 55.1% Significant prognostic factor was radicality of the resection. **OS** 3-year OS: 73% 5-year OS: 56% Significant prognostic factors were radicality of the resection and age.	Not reported.

First author, date, study design	Efficacy outcomes	Safety outcomes
Kusters, 2010 Case series	**Local recurrence** 5-year local recurrence rate: 12% Significant prognostic factors were no downstaging, lymph node positivity, margin involvement and no adjuvant chemotherapy. **Distant recurrence** 5-year distant metastases recurrence: 29.2% Significant prognostic factors were male gender, preoperatively staged T4 disease, no downstaging, lymph node positivity and margin involvement. **Cancer-specific survival** 5-year cancer-specific survival: 73.5% Significant prognostic factors were male gender, lymph node positivity and margin involvement. **OS** 5-year OS: 67.1% Significant prognostic factors were older than 70 years, male gender, no downstaging, lymph node positivity, margin involvement and no adjuvant chemotherapy.	Not reported.

Procedure technique

In the 2 systematic reviews and meta-analyses, there were 1 study and 3 studies that used HDR-brachytherapy, respectively (Fahy 2021; Liu 2021). All other studies used IOERT. The devices used to deliver IOERT were not well described. The IOERT dose was typically 10 Gy to 12.5 Gy, with some studies permitting higher doses.

Efficacy

Local recurrence or control outcomes

Seven studies reported local recurrence or local control.

The 2 systematic reviews and meta-analyses reported different findings. In the Fahy (2021) meta-analysis of 7 studies, there was no statistically significant difference between IORT and surgery/EBRT in locoregional recurrence rates, OR 0.55 (95% CI 0.27 to 1.14, p=0.11).

In the Liu (2021) meta-analysis of 14 studies, 5-year local control was statistically significantly better with IORT than surgery/EBRT, OR 3.07 (95% CI 1.66 to 5.66, p=0.000, Liu 2021). When analysing results by study design, this difference was observed in observational studies (OR 3.38; 95% CI 1.73 to 6.57, p=0.000), but not RCTs (OR 1.37; 95% CI 0.35 to 5.35, p=0.655).

The cohort study of IOERT compared with HDR-brachytherapy in people who had an R1 resection found that, after multivariate analysis, people who had IOERT were less likely to experience local recurrence-free survival than people who had HDR-brachytherapy. In people with LARC, in multivariate analysis, LRFS was borderline statistically significantly worse with IOERT (HR 0.504; 95% CI 0.254 to 0.999, p=0.050). Similar findings were reported in LRRC, when in multivariate analysis, LRFS was statistically significantly worse with IOERT (HR 0.567; 95% CI 0.349 to 0.920, p=0.021; Voogt 2021).

Two case series reported outcomes for recurrent colorectal cancer or LRRC. In one, 5-year central relapse (within the IOERT field) was 14% and 5-year local relapse was 28.0% (Haddock 2011). In the other, 5-year local re-recurrence was 45.3% (Holman 2017). The common prognostic factor reported by both studies was radicality of the resection.

Two case series reported outcomes for LARC. Five-year local recurrence ranged from 12.0% (Kusters 2010) to 19.3% (Holman 2016). The common prognostic factor reported by both studies was radicality of the resection.

OS

Six studies reported OS.

In a meta-analysis of 9 studies, Liu (2021) found no statistically significant difference in OS between IORT and surgery/EBRT (HR 0.80; 95% CI 0.60 to 1.06, p=0.189; Liu 2021).

The cohort study of IOERT compared to HDR-brachytherapy in people who had an R1 resection reported that there was no statistically significant difference in OS between people who had IOERT and people who had HDR-brachytherapy (LARC, p=0.989; LRRC, p=0.747; Voogt 2021).

Two case series reported outcomes for recurrent colorectal cancer or LRRC. Five-year OS ranged from 30% (Haddock 2011) to 33% (Holman 2017). Haddock (2011) reported 10-year OS of 16%. Common prognostic factors reported by both studies were radicality of the resection and preoperative treatment. Haddock (2011) additionally reported that patients treated after 1997 had better OS.

Two case series reported outcomes for LARC. Five-year OS ranged from 56.0% (Holman 2016) to 67.1% (Kusters 2010). Common prognostic factors reported by both studies were radicality of the resection and age.

Disease-free survival

One study reported disease-free survival.

In a meta-analysis of 6 studies, Liu (2021) found no statistically significant difference between IORT and surgery/EBRT (HR 0.94; 95% CI 0.73 to 1.22, p=0.503; Liu 2021).

Cancer-specific survival

Three studies reported cancer-specific survival.

One case series reported outcomes for LRRC. Five-year cancer-specific survival was 41% (Holman 2017). Prognostic factors were preoperative treatment and radicality of the resection.

Two case series reported outcomes for LARC. Five-year cancer-specific survival ranged from 64.6% (Holman 2016) to 73.5% (Kusters 2010). The common prognostic factor reported by both studies was radicality of the resection.

Distant metastases

Four studies reported distant metastases outcomes.

Two case series reported outcomes for recurrent colorectal cancer or LRRC. In one study, 5-year distant relapse was 53% (Haddock 2011). In the other study, 5-year distant metastases-free survival was 43% (Holman 2017). Common prognostic factors reported by both studies were preoperative treatment and radicality of the resection.

Two case series reported outcomes for LARC. Five-year distant metastases-free survival was 64.6% in Holman (2016) Five-year distant metastases recurrence was 29.2% in Kusters (2010). The common prognostic factor reported by both studies was radicality of the resection.

Safety

Death

One case series reported that for people with recurrent colorectal cancer, 6 patients (less than 1%) died of treatment-related complications without relapse of disease. One death was due to bleeding from the colostomy, and 5 deaths were due to complications arising after surgical correction bowel complications (Haddock 2011).

One cohort study reported that in people with LARC, there was no statistically significant difference in in-hospital mortality between IOERT and HDR-brachytherapy (HDR-brachytherapy 0%; IOERT 1%; p=0.546). Similarly, in people with LRRC, there was no statistically significant difference in in-hospital mortality between the treatments (HDR-brachytherapy 2%; IOERT 4%, p>0.999; Voogt 2021).

Severe complications

One cohort study reported that in people with LRRC, there were statistically significantly more major complications (Clavien-Dindo grade 3 or higher) with HDR-brachytherapy than IOERT (HDR-brachytherapy 46%; IOERT 26%, p=0.017; Voogt 2021). No statistically significant difference was observed in people with LARC (p=0.546).

One case series reported that in people with recurrent colorectal cancer, there were 302 complications considered severe or greater (Haddock 2011).

Reintervention rate

One meta-analysis compared the reintervention rate between IORT and surgery/EBRT. In the Fahy (2021) meta-analysis of 3 studies, there was no statistically significant difference in reintervention rate between IORT and surgery/EBRT (OR 1.13; 95% CI 0.43 to 2.98, p=0.80).

Specific complications

Wound complications/infections

Two studies compared wound complications or infections between IORT and surgery/EBRT. In the Fahy (2021) meta-analysis of 4 studies there was no statistically significant difference in wound infections between IORT and surgery/EBRT (OR 1.13; 95% CI 0.50 to 2.54, p=0.76). Similarly, in the Liu (2021) meta-analysis of 8 studies, there was no statistically significant difference in wound complications between IORT and surgery/EBRT (OR 1.02; 95% CI 0.52 to 2.02, p=0.948).

In the Voogt (2021) cohort study, abdominal wound dehiscence with evisceration was reported in 11% and 8% of people with LARC and LRRC, respectively, and perineal wound necrosis was reported in 5% of people with LARC. It was not clear how many were observed in people who had IOERT compared against people who had HDR-brachytherapy.

In the Haddock (2011) case series, 7% of people had a wound infection, abscess or fistula that was classified as severe.

Abscess

Two meta-analyses compared abscess or pelvic abscess between IORT and surgery/EBRT. In the Fahy (2021) meta-analysis of 3 studies, there was no statistically significant difference in pelvic abscess rates between IORT and surgery/EBRT (OR 1.01; 95% CI 0.54 to 1.87, p=0.99). Similarly, in the Liu (2021) meta-analysis of 6 studies, there was no statistically significant difference in abscess rates between IORT and surgery/EBRT (OR 1.10; 95% CI 0.67 to 1.80, p=0.833).

In the Voogt (2021) cohort study, presacral abscess was reported in 27% and 26% of people with LARC and LRRC, respectively, and intra-abdominal abscess

was reported in 9% and 6%, respectively. It was not clear how many were observed in people who had IOERT compared against people who had HDR-brachytherapy.

Anastomotic leak

Two meta-analyses compared anastomotic leak between IORT and surgery/EBRT. In the Fahy (2021) meta-analysis of 5 studies, there was no significant difference in anastomotic leak between IORT and surgery/EBRT (OR 1.06; 95% CI 0.51 to 2.18, p=0.88). Similarly, in the Liu (2021) meta-analysis of 7 studies, there was no statistically significant difference in anastomotic leak between IORT and surgery/EBRT (OR 1.09; 95% CI 0.59 to 2.02, p=0.775).

In the Voogt (2021) cohort study, anastomotic leakage was reported in 5% of people with LARC. It was not clear how many were observed in people who had IOERT compared against people who had HDR-brachytherapy.

Fistulae

One meta-analysis compared fistulae between IORT and surgery/EBRT. In the Liu (2021) meta-analysis of 3 studies, there was no statistically significant difference in fistulae between IORT and surgery/EBRT (OR 0.79; 95% CI 0.33 to 1.89, p=0.600).

In the Haddock (2011) case series, 1% of people had a gastrointestinal tract fistula or obstruction that was classified as severe.

Neurogenic bladder dysfunction

One meta-analysis compared neurogenic bladder dysfunction between IORT and surgery/EBRT. In the Liu (2021) meta-analysis of 3 studies, there was no statistically significant difference between IORT and surgery/EBRT (OR 0.69; 95% CI 0.31 to 1.55, p=0.369).

Neuropathy

In the Haddock (2011) case series, 3% of people had neuropathy that was classified as severe.

Bladder complications

In the Voogt (2021) cohort study, ureter stenosis was reported in 5% of people with LARC. Leakage of the ureter or bladder reconstruction was reported in 5% and 12% of people with LARC and LRRC, respectively. It was not clear how many were observed in people who had IOERT compared with people who had HDR-brachytherapy.

In the Haddock (2011) case series, 3% of people had ureteral obstruction that was classified as severe.

Bleeding

In the Voogt (2021) cohort study, bleeding was reported in 11% of people with LARC. It was not clear how many were observed in people who had IOERT compared with people who had HDR-brachytherapy.

Anecdotal and theoretical adverse events

Expert advice was sought from consultants who have been nominated or ratified by their professional society or royal college. They were asked if they knew of any other adverse events for this procedure that they had heard about (anecdotal), which were not reported in the literature. They were also asked if they thought there were other adverse events that might occur, even if they have never happened (theoretical). For this procedure, the professional experts did not list any anecdotal or theoretical adverse events.

Five professional expert questionnaires for this procedure were submitted. Full details of what the professional experts said about the procedure is in the specialist advice questionnaires.

Validity and generalisability

Seven studies were included in the key evidence summary, including 2 systematic reviews and meta-analyses, 1 cohort study, and 4 case series. Research was done in various countries in Europe and worldwide, though there were no UK studies included in the key evidence.

Both systematic reviews contained comparative studies only.

Fahy (2021) included 2 RCTs. Liu (2021) incorrectly reported that 3 RCTs were included: Masaki (2008) should have been treated as an interim analysis of Masaki (2020). Both RCTs (Dubois 2011 and Masaki 2020) were small (fewer than 75 patients per arm). The other studies included in Fahy (2021) and Liu (2021) were observational.

The systematic reviews reported conflicting results: Fahy (2021) found no statistically significant difference in locoregional recurrence between IOERT and surgery/EBRT. Liu (2021) found statistically significantly better local control with IOERT than surgery/EBRT. However, this difference was driven by results from observational studies; a separate analysis of RCTs found no difference.

The authors cite a lack of data concerning the radicality of resection and heterogeneity in patient selection and dosing as potentially confounding factors.

In the other comparative study included (Voogt 2021), IOERT was associated with statistically significantly worse outcomes than HDR-brachytherapy, after an R1 resection. However, IOERT was associated with statistically significantly fewer severe complications. The authors conclude that further research is required to refine the IOERT procedure.

Given that IOERT is typically used as part of multimodality treatment that may include preoperative (chemo)radiotherapy, resection, IOERT, and postoperative

(chemo)radiotherapy, it is difficult to assess the efficacy of IOERT in the non-comparative case series.

The case series show that the most important factor associated with efficacy is the radicality of resection, with R0 resections associated with the best survival and recurrence outcomes.

The multimodality nature of treatment, and the effect size of resection radicality, may mask the true efficacy of IOERT. Both meta-analyses suggest IOERT efficacy, but the authors note that further research is needed to fully understand this.

Most patients had LARC or LRRC; there was very limited data on IOERT for colon cancer (all from Haddock 2011).

The follow-up periods, when reported, ranged from 25 months to 80 months.

The authors report no industry funding nor conflicts of interest.

Existing assessments of this procedure

In 2022, the National Comprehensive Cancer Network (NCCN) published clinical practice guidelines on rectal cancer. The guidelines recommend that:

- ‘Intraoperative radiation therapy (IORT), if available, may be considered for very close or positive margins after resection, as an additional boost, especially for patients with T4 or recurrent cancers.’

In 2020, the European Society for Radiotherapy and Oncology/Advisory Committee for Radiation Oncology Practice (ESTRO/ACROP) published recommendations for primary locally advanced (Calvo 2020a) and locally recurrent (Calvo 2020b) rectal cancer. The recommendations were published to

define clinical indications, patient selection criteria and technical aspects of IORT. The publication notes that:

- 'IORT for LARC/LRRC has predominantly been delivered with megavoltage electrons produced by a medical linear accelerator (IOERT). There are not sufficient scientific data to support the use of brachytherapy or orthovoltage delivery systems for IORT.'

In 2019, the American Brachytherapy Society published a consensus statement on IORT for several types of cancer (Tom 2019). For colorectal cancers, the recommendations were:

- 'IORT can be considered at the time of surgical resection of locally advanced or recurrent colorectal cancer in cases with concern for a positive margin, particularly when pelvic EBRT has already been delivered. A dose of 15 Gy in a single treatment to 5 mm depth in tissue using IORT-HDR has been used. However, doses less than or equal to 12.5 Gy in a single fraction should be used to reduce the risk of neuropathy when IOERT is used.'

Related NICE guidance

NICE guidelines

- NICE guideline on colorectal cancer.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Professional societies

- The Royal College of Radiologists

- Association of Surgeons of Great Britain and Ireland
- The Association of Coloproctology of Great Britain and Ireland
- BASO – The Association for Cancer Surgery

Company engagement

NICE asked companies who manufacture a device potentially relevant to this procedure for information on it. NICE received 1 completed submission. This was considered by the interventional procedures team and any relevant points have been taken into consideration when preparing this overview.

References

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3. Voogt ELK, van Rees JM, Hagemans JAW et al. (2021) Intraoperative Electron Beam Radiation Therapy (IOERT) Versus High-Dose-Rate Intraoperative Brachytherapy (HDR-IORT) in Patients With an R1 Resection for Locally Advanced or Locally Recurrent Rectal Cancer. International journal of radiation oncology, biology, physics 110(4):1032-43.
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6. Holman FA, Haddock MG, Gunderson LL et al. (2016) Results of intraoperative electron beam radiotherapy containing multimodality treatment for locally unresectable T4 rectal cancer: A pooled analysis of the Mayo Clinic Rochester and Catharina Hospital Eindhoven. Journal of Gastrointestinal Oncology 7(6):903-16.
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8. National Comprehensive Cancer Network (2022) NCCN Guidelines Version 1.2022: Rectal Cancer.
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10. Calvo FA, Sole CV, Rutten HJ et al. (2020b) ESTRO/ACROP IORT recommendations for intraoperative radiation therapy in locally recurrent rectal cancer. Clinical and Translational Radiation Oncology 24:41-8.
11. Tom MC, Joshi N, Vicini F et al. (2019) The American Brachytherapy Society consensus statement on intraoperative radiation therapy. Brachytherapy 18(3):242-257.

Methods

NICE identified studies and reviews relevant to intraoperative electron beam radiotherapy for locally advanced and locally recurrent colorectal cancer from the medical literature. The following databases were searched between the date they started to 29 June 2022: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following inclusion criteria were applied to the abstracts identified by the literature search.

- Publication type: clinical studies were included with emphasis on identifying good quality studies. Abstracts were excluded if they did not report clinical outcomes. Reviews, editorials, and laboratory or animal studies, were also excluded and so were conference abstracts, because of the difficulty of appraising study methodology, unless they reported specific adverse events that not available in the published literature.
- Patients with locally advanced or locally recurrent colorectal cancer.
- Intervention or test: intraoperative electron beam radiotherapy.
- Outcome: articles were retrieved if the abstract contained information relevant to the safety, efficacy or both.

If selection criteria could not be determined from the abstracts the full paper was retrieved.

Potentially relevant studies not included in the main evidence summary are listed in the section on other relevant studies.

Find out more about how NICE selects the evidence for the committee.

Table 4 literature search strategy

Databases	Date searched	Version/files
MEDLINE (Ovid)	05/12/2022	1946 to December 02, 2022
MEDLINE In-Process (Ovid)	05/12/2022	1946 to December 02, 2022
MEDLINE Epubs ahead of print (Ovid)	05/12/2022	December 02, 2022
EMBASE (Ovid)	05/12/2022	1974 to 2022 December 02
EMBASE Conference (Ovid)	05/12/2022	1974 to 2022 December 02
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	05/12/2022	Issue 11 of 12, November 2022
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	05/12/2022	Issue 11 of 12, November 2022
International health technology assessments database (INAHTA)	05/12/2022	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

MEDLINE search strategy

The MEDLINE search strategy was translated for use in the other sources.

1 exp Colorectal Neoplasms/
2 ((Colon* or rect* or Bowel* or colorect*) adj4 (cancer* or neoplasm* or lesion* or tumour* or tumor* or malignan* or carcinoma* or adenocarcinoma*)).tw.
3 or/1-2
4 (IOERT or IORT).tw.
5 ((Intraoperat* or intra operat or intra-operat*) adj4 radiat* therap*).tw.
6 electron beam therap*.tw.
7 ((electron* or beam*) adj4 linear adj4 accelerator*).tw.
8 or/4-7
9 3 and 8
10 Mobetron.tw.
11 LIAC.tw.
12 NOVAC.tw.
13 10 or 11 or 12
14 9 or 13
15 Animals/ not Humans/
16 14 not 15

Other relevant studies

Other potentially relevant studies to the IP overview that were not included in the main evidence summary (tables 2 and 3) are listed in table 5. Studies with fewer than 50 patients were not included in the table.

Table 5 Additional studies identified

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Ansell J, Perry WRG, Mathis KL et al. (2021) Re-resection of Microscopically Positive Margins Found on Intra-Operative Frozen Section Analysis Does Not Result in a Survival Benefit in Patients Undergoing Surgery and Intraoperative Radiation Therapy for Locally Recurrent Rectal Cancer. Diseases of the colon and rectum	Cohort study n=267 Follow up=5 years	Re-resection of microscopically positive margins to obtain R0 status does not appear to provide a significant survival advantage or prevent local re-recurrence in patients undergoing surgery and intraoperative radiation therapy for locally recurrent rectal cancer.	Studies with more people or longer follow up included.
Azinovic I, Calvo FA, Santos M et al. (1997) Intense local therapy in primary rectal cancer: multi-institutional results with preoperative chemoradiation therapy plus IORT. Spanish Group of IORT. Frontiers of radiation therapy and oncology 31:196-9	Case series n=76 Follow up=24 months	Intense local therapy including preoperative chemoradiation therapy, surgery and IORT is feasible, acceptably tolerated and able to induce a high local control rate (no recurrence detected in the IORT-boosted region).	Studies with more people or longer follow up included.
Brady JT, Crawshaw BP, Murrell B, et al. (2017) Influence of intraoperative radiation therapy on locally advanced and recurrent colorectal tumors: A 16-year experience. American journal of surgery 213(3):586-589	Case series n=77	IORT resulted in low local failure rates and should be considered for patients with locally advanced or recurrent colorectal cancers.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Bussieres E, Dubois JB, Demange L et al. (1997). IORT: a randomized trial in primary rectal cancer by the French group of IORT. Frontiers of radiation therapy and oncology 31:217-220	RCT n=30	The performance of randomised trials is needed to demonstrate the possible benefit of IORT on the local control in cancer. Rectal cancer is one of the locations which can benefit from a radiation booster, considering the dramatic aspects of local failure.	Earlier publication of Dubois, 2011.
Bussieres E, Gilly FN, Rouanet P, et al. (1996) Recurrences of rectal cancers: results of a multimodal approach with intraoperative radiation therapy. French Group of IORT. Intraoperative Radiation Therapy. International journal of radiation oncology, biology, physics 34(1):49-56	Case series n=73 Follow up=37 months	Intraoperative radiation therapy is a complementary treatment for recurrences of rectal cancer. It provides encouraging results, particularly in some selected situations, when patients have not previously been treated with external radiation therapy. Further studies of multimodal treatments are necessary.	Studies with more people or longer follow up included.
Calvo FA, Gomez-Espi M, Diaz-Gonzalez JA, et al. (2002) Intraoperative presacral electron boost following preoperative chemoradiation in T3-4Nx rectal cancer: initial local effects and clinical outcome analysis. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 62(2):201-206	Case series n=100 Follow up=23 months	IOERT electron boost to the presacral region is feasible to integrate systematically in the intensive combined treatment of locally advanced rectal cancer, including neoadjuvant chemoradiation segment.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Calvo FA, Serrano J, Cambeiro MA et al. (2022) Intra-operative electron radiation therapy: an update of the evidence collected in 40 years to search for models for electron-FLASH studies. Cancers 14: 3693	Review n=4,320 with rectal focus (19,148 total) Median Follow up= up to 78 months	Clinical outcomes following IOeRT doses in the range of 10 Gy to 25 Gy (with or without external beam fractionated radiation therapy) show a wide range of local control from 40% to 100% depending upon cancer site, histology, stage and treatment intensity.	Review, including different cancer sites.
Calvo FA, Serrano J, Sole C et al. (2022) Clinical feasibility of combining intraoperative electron radiation therapy with minimally invasive surgery: a potential for electron-FLASH clinical development. Clinical and Translational Oncology https://doi.org/10.1007/s12094-022-02955-z	Case series n=125 Median follow up= 59.5 months	Minimally invasive and robotic-assisted surgery is feasible to combine with intraoperative electron radiation therapy and offers a new model explored with electron-FLASH beams.	Studies with more people or longer follow up included.
Calvo FA, Sole CV, Alvarez de Sierra P, et al. (2013) Prognostic impact of external beam radiation therapy in patients treated with and without extended surgery and intraoperative electrons for locally recurrent rectal cancer: 16-year experience in a single institution. International journal of radiation oncology, biology, physics. 86(5):892-900	Case series n=60 Follow up=36 months	Present results suggest that a significant group of patients with LRRC may benefit from EBRT treatment integrated with extended surgery and IOERT.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Calvo FA, Sole CV, Serrano J et al. (2013) Post-chemoradiation laparoscopic resection and intraoperative electron-beam radiation boost in locally advanced rectal cancer: long-term outcomes. Journal of cancer research and clinical oncology 139(11):1825-33	Case series n=125 Follow up=59.5 months	Postchemoradiation laparoscopically assisted IOERT is feasible, with an acceptable risk of postoperative complications, shorter hospital stay, and similar long-term outcomes when compared to the open surgery approach.	Studies with more people or longer follow up included.
Cantero-Munoz P, Urien MA, Ruano-Ravina A (2011). Efficacy and safety of intraoperative radiotherapy in colorectal cancer: a systematic review. Cancer letters 306(2):121-133	Systematic review n=15 studies	Adding IORT to conventional treatment reduces the incidence of local recurrences within the radiation area over 10%. IORT is a safe technique as it does not increase toxicity associated with conventional treatment.	More recent systematic reviews included.
Diaz-Gonzalez JA, Calvo FA, Cortes J, et al. (2006) Prognostic factors for disease-free survival in patients with T3-4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. International journal of radiation oncology, biology, physics 64(4):1122-1128	Case series n=115	Females with an intense pathologic response (pT(mic) residue) to preoperative chemoradiotherapy have an excellent 3-year disease-free survival.	Studies with more people and more relevant outcomes included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Dresen RC, Gosens MJ, Martijn H, et al. (2008) Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Annals of surgical oncology 15(7):1937-1947	Case series n=147 Follow up=34 months	Radical resection is the most significant predictor of improved survival in patients with LRRC. Neoadjuvant radio (chemo-) therapy is the best option in order to realise a radical resection. Re-irradiation is feasible in patients who already received irradiation as part of the primary rectal cancer treatment.	Studies with more people or longer follow up included.
Dubois J-B, Bussieres E, Richaud P et al. (2011) Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology 98(3): 298-303	RCT n=73 Follow up=61.2 months	Although this randomised study did not demonstrate any significant improvement in local control and disease-free survival in rectal cancer patients treated with preoperative radiation therapy receiving IORT or not, it confirmed the technical feasibility and the necessity for evaluating IORT for rectal carcinoma in further clinical studies.	Included in the Fahy 2021 and Liu 2021 systematic reviews.
Eble MJ, Lehnert T, Herfarth C, Wannenmacher M (1998). Intraoperative radiotherapy as adjuvant treatment for stage II/III rectal carcinoma. Recent results in cancer research Fortschritte der Krebsforschung Progres dans les recherches sur le cancer 146:152-160	Case series n=63	Moderate-dose IORT and EBRT is safe, considering related late toxicities. It is an effective local treatment approach, resulting in an encouraging local control rate.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Eble MJ, Lehnert T, Herfarth C, Wannenmacher M (1997). IORT as adjuvant treatment in primary rectal carcinomas: multi-modality treatment. Frontiers of radiation therapy and oncology 31:200-203	Case series n=104 Follow up=30.6 months	IORT seems to be ideal for this purpose. Compared with a historical control the risk of small-bowel obstruction was markedly reduced in our series (7 versus 0%) while local control is excellent.	Studies with more people or longer follow up included.
Elashwah A, Alsuhaibani A, Alzahrani A, et al. (2022) The Use of Intraoperative Radiation Therapy (IORT) in Multimodality Management of Cancer Patients: a Single Institution Experience. Journal of Gastrointestinal Cancer	Case series n=188	The data presented discusses using of IORT treatment for different malignant tumours as a part of multimodality treatment. IORT seems safe and feasible; however, a longer follow-up period is needed for proper evaluation and to define the role of IORT in a tailored multimodality approach.	Studies with more people or longer follow up included.
Gunderson LL, Martin JK, Beart RW, et al. (1998) Intraoperative and external beam irradiation for locally advanced colorectal cancer. Annals of surgery. 207(1):52-60	Case series n=51	The incidence of distant metastases is high in patients with recurrence, but subsequent peritoneal failures are infrequent. Acute and chronic tolerance have been acceptable, but peripheral nerve appears to be a dose-limiting structure. Randomised trials are needed to determine whether potential gains with IORT are real.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Gunderson LL, Nelson H, Martenson JA, et al. (1997) Locally advanced primary colorectal cancer: intraoperative electron and external beam irradiation +/- 5-FU. International journal of radiation oncology, biology, physics. 37(3):601-614	Case series n=61 Follow up=more than 18 months	Both OS and disease control appear to be improved with the addition of IOERT to standard treatment. More routine use of systemic therapy is indicated as a component of IOERT-containing treatment regimens because the incidence of distant metastases was 50% of patients at risk.	Studies with more people or longer follow up included.
Gunderson LL, Nelson H, Martenson JA, et al. (1996) Intraoperative electron and external beam irradiation with or without 5-fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. Diseases of the colon and rectum 39(12):1379-1395	Case series n=123	Even with locally recurrent lesions, the aggressive multimodality approaches including IOERT have resulted in improved local control and long-term survival rates of 20% versus an expected 5% with conventional techniques.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Haddock MG, Gunderson LL, Nelson H, et al. (2001) Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. International journal of radiation oncology, biology, physics 49(5):1267-1274	Case series n=51 Follow up=21 months	Long-term local control can be obtained in a substantial proportion of patients with aggressive combined modality therapy, but long-term survival is poor due to the high rate of distant metastasis. Re-irradiation with EBRT in addition to IOERT appears to improve local control. Strategies to improve survival in these poor-risk patients may include the more routine use of conventional systemic chemotherapy or the addition of novel systemic therapies.	Studies with more people or longer follow up included.
Ishikura S, Ogino T, Ono M, et al. (1999) Preliminary results of pelvic autonomic nerve-preserving surgery combined with intraoperative and postoperative radiation therapy for patients with low rectal cancer. Japanese journal of clinical oncology. 29(9):429-433	Case series n=50 Follow up=41 months	The preliminary results showed good local control rate for patients with stage 1 to 2 tumours. For patients with stage 3 tumours, the local control rate was unsatisfactory, but nerve sparing was not the cause of local recurrence. Further investigation of function-preserving surgery without decreasing curability is needed.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Kienle P, Abend F, Dueck M et al. (2006) Influence of intraoperative and postoperative radiotherapy on functional outcome in patients undergoing standard and deep anterior resection for rectal cancer. Diseases of the colon and rectum 49(5):557-567	Cohort study n=63 with IOERT	Patients with anterior resection for rectal cancer who undergo full-dose radiotherapy have significantly more impairment of anorectal function than patients without radiotherapy. Patients who were only exposed to intraoperative radiotherapy showed moderate impairment of continence function, suggesting that the influence of radiotherapy on anal function may be dose-dependent and application-dependent.	Studies with more people or longer follow up included.
Klink CD, Binnebosel M, Holy R et al. (2014). Influence of intraoperative radiotherapy (IORT) on perioperative outcome after surgical resection of rectal cancer. World journal of surgery. 38(4):992-996	Cohort study n=52	Intraoperative radiotherapy appears to be a safe treatment option in patients with locally advanced or recurrent rectal cancer with acceptable complication rates. The effect on local recurrence rate has to be estimated in long-term follow up.	Included in the Liu 2021 systematic review.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Krempien R, Roeder F, Oertel S, et al. (2006) Long-term results of intraoperative presacral electron boost radiotherapy (IOERT) in combination with total mesorectal excision (TME) and chemoradiation in patients with locally advanced rectal cancer. International journal of radiation oncology, biology, physics 66(4):1143-1151	Case series n=210 Follow up=61 months	Multimodality treatment with TME and IOERT boost in combination with moderate dose pre- or postoperative chemoradiotherapy is feasible and results in excellent long-term local control rates in patients with intermediate to high-risk locally advanced rectal cancer.	Studies with more people or longer follow up included.
Kusters M, Holman FA, Martijn H, et al. (2009) Patterns of local recurrence in locally advanced rectal cancer after intra-operative radiotherapy containing multimodality treatment. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology 92(2):221-225	Case series n=299	Multimodality treatment is effective in the prevention of local recurrence in LARC. IORT application to the area most at risk is feasible and seems effective in the prevention of local recurrence. Dorsal tumour location results in unfavourable oncologic results.	Studies with more people or longer follow up included.
Llaguna OH, Calvo BF, Stitzenberg KB, et al. (2011) Utilization of interventional radiology in the postoperative management of patients after surgery for locally advanced and recurrent rectal cancer. The American surgeon 77(8):1086-1090	Case series n=66	Surgery for locally advanced primary rectal cancer and locally recurrent rectal cancer is associated with significant morbidity but low mortality. Interventional radiologic procedures play a significant role in the postoperative management of these patients and may decrease the need for reoperation.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Mannaerts GHH, Rutten HJT, Martijn H, et al. (2002). Effects on functional outcome after IORT-containing multimodality treatment for locally advanced primary and locally recurrent rectal cancer. International journal of radiation oncology, biology, physics 54(4):1082-1088	Case series n=97 Follow up=14 months	As a result of multimodality treatment, most of these patients have to deal with long-term physical morbidity, the need for help with daily care, and considerable social impairment. These consequences must be weighed against the chance of cure if the patient is treated and the disability eventually caused by uncontrolled tumour progression if the patient is not treated. These potential drawbacks should be discussed with the patient preoperatively and taken into account when designing a treatment strategy.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Masaki T, Matsuoka H, Kishiki T et al. (2020) Intraoperative radiotherapy for resectable advanced lower rectal cancer-final results of a randomized controlled trial (UMIN000021353). Langenbeck's archives of surgery 405(3):247-54	RCT n=38 Follow up=69 months	With the aid of IORT, complete pelvic autonomic nerve preservation can be done without increase of pelvic sidewall recurrence; however, IORT may increase the incidence of distant metastases. Therefore, IORT cannot be recommended as a standard therapy to compensate less radical resection for advanced lower rectal cancer.	Included in the Fahy 2021 and Liu 2021 systematic reviews.
Mathis KL, Nelson H, Pemberton JH (2008). Unresectable colorectal cancer can be cured with multimodality therapy. Annals of surgery 248(4):592-598	Case series n=146 Follow up=3.7 years	Aggressive multimodality therapy for locally unresectable primary colorectal cancer results in excellent local disease control and a 5-year disease-free and OS rate of 43% and 52% respectively with no operative mortality and acceptable perioperative morbidities.	Studies with more people or longer follow up included.
Mirnezami R, Chang GJ, Das P, et al. (2013) Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. Surgical oncology. 22(1):22-35	Systematic review and meta-analysis	Despite methodological weaknesses in the studies evaluated, our results suggest that IORT may improve oncological outcomes in advanced and recurrent colorectal cancer.	More recent systematic reviews included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Nakfoor BM, Willett CG, Shellito PC, et al. (1998). The impact of 5-fluorouracil and intraoperative electron beam radiation therapy on the outcome of patients with locally advanced primary rectal and rectosigmoid cancer. Annals of surgery 228(2):194-200	Case series n=145 Follow up=53 months	Treatment strategies using 5-fluorouracil during irradiation and IOERT for patients with locally advanced rectal cancer are beneficial and well tolerated.	Studies with more people or longer follow up included.
Nordkamp S, Voogt ELK, van Zoggel DMGI, et al. (2022) Locally recurrent rectal cancer: oncological outcomes with different treatment strategies in two tertiary referral units. The British journal of surgery 109(7):623-631	Cohort study n=377 Follow up=36 months	In radiotherapy-naive patients, neoadjuvant full-course chemoradiation confers the best oncological outcome. However, neoadjuvant therapy does not diminish the need for extended radical surgery to increase R0 resection rates.	Studies with more people or longer follow up included.
Noyes RD, Weiss SM, Krall JM et al. (1992) Surgical complications of intraoperative radiation therapy: the Radiation Therapy Oncology Group experience. Journal of surgical oncology 50(4):209-15	Cohort study n=129	his large multi-institutional experience in patients with advanced malignancy demonstrates that patients receiving IORT do not have a higher surgical complication rate than those not receiving IORT. Long-term survival data await the implementation of Phase III trials in advanced intraabdominal malignancy.	Complications assessed in the Fahy 2021 and Liu 2021 systematic reviews.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Pacelli F, Sanchez AM, Covino M, et al. (2013) Improved outcomes for rectal cancer in the era of preoperative chemoradiation and tailored mesorectal excision: a series of 338 consecutive cases. The American surgeon 79(2):151-161	Case series n=338 Follow up=59 months	The extent of mesorectal excision should be tailored depending on tumour location and the use of neoadjuvant chemotherapy, combined with IORT in advanced middle and low rectal cancer, leading to remarkable tumour downstaging with excellent prognosis in responding patients.	Studies with more people or longer follow up included.
Potemin S, Kubler J, Uvarov I, et al. (2020) Intraoperative radiotherapy as an immediate adjuvant treatment of rectal cancer due to limited access to external-beam radiotherapy. Radiation oncology (London, England) 15(1):11.	Cohort study n=172 Follow up=23 months	IORT is a valuable option for patients with locally advanced rectal cancer in the absence of access to EBRT.	Studies with more people or longer follow up included.
Roeder F, Goetz JM, Habl G, et al. (2012) Intraoperative Electron Radiation Therapy (IOERT) in the management of locally recurrent rectal cancer. BMC cancer 12:592	Case series n=54 Follow up=51 months	Long-term OS and local control can be achieved in a substantial proportion of patients with recurrent rectal cancer using a multimodality IOERT-containing approach, especially in case of clear margins. Local control and OS remain limited in patients with incomplete resection. Preoperative re-irradiation and adjuvant chemotherapy may be considered to improve outcome.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Roeder F, Treiber M, Oertel S et al. (2007) Patterns of failure and local control after intraoperative electron boost radiotherapy to the presacral space in combination with total mesorectal excision in patients with locally advanced rectal cancer. International journal of radiation oncology, biology, physics 67(5);1381-8	Case series n=243 Follow up=59 months	Intraoperative electron beam radiotherapy as part of a multimodal treatment approach including TME is a highly effective regimen to prevent local failure. The presacral space remains the site of highest risk for local failure, but IOERT can decrease the percentage of relapses in this area.	Studies with more people or longer follow up included.
Rutten HJ, Mannaerts GH, Martijn H, Wiggers T. (2000) Intraoperative radiotherapy for locally recurrent rectal cancer in The Netherlands. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 26suppla:16-20	Case series n=62	Total dose of irradiation and completeness of resection were significantly correlated to a better prognosis.	Studies with more people or longer follow up included.
Sadahiro S, Suzuki T, Ishikawa K, et al. (2004) Preoperative radio/chemo-radiotherapy in combination with intraoperative radiotherapy for T3-4Nx rectal cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology 30(7):750-8	Cohort study n=99 Follow up=67 months	The combined preoperative radio/chemoradiotherapy and IORT for clinical T3-4Nx rectal cancer significantly reduces local recurrence and improves prognosis. Combination of preoperative radiotherapy and oral chemotherapy improves the feasibility of sphincter-preservation.	Included in the Fahy 2021 and Liu 2021 systematic reviews.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Sadahiro S, Suzuki T, Ishikawa K, et al. (2001) Intraoperative radiation therapy for curatively resected rectal cancer. Diseases of the colon and rectum 44(11):1689-1695	Case series n=78	In patients with adenocarcinoma of the middle or lower third of the rectum, intraoperative radiotherapy to the entire dissected surface of the pelvis reduced local recurrence in Stage II and Stage III patients and improved survival in Stage II patients.	Likely overlap with Sadahiro, 2004.
Sofo L, Ratto C, Doglietto GB, et al. (1996) Intraoperative radiation therapy in integrated treatment of rectal cancers. Results of phase II study. Diseases of the colon and rectum 39(12):1396-1403	Case series n=68 Follow up=28.3 and 25.9 months	Results of this study suggest that multimodal treatment (including IORT) in rectal cancer is safe, has no significant increase of mortality and morbidity, and also shows a trend for local improvement. A longer term follow up and larger numbers of patients could demonstrate the therapeutic efficacy of IORT in rectal cancer.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Sole CV, Calvo FA, Serrano J et al. (2014) Post-chemoradiation intraoperative electron-beam radiation therapy boost in resected locally advanced rectal cancer: long-term results focused on topographic pattern of locoregional relapse. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology 112(1):52-8	Case series n=335 Follow up=72.6 months	Overall results after multimodality treatment of LARC are promising. Classification of risk factors for LRRC has contributed to propose a prognostic index that could allow us to guide risk-adapted tailored treatment.	Studies with more people or longer follow up included.
Tepper JE, Wood WC, Cohen AM. (1989) Treatment of locally advanced rectal cancer with external beam radiation, surgical resection, and intraoperative radiation therapy. International journal of radiation oncology, biology, physics 16(6):1437-1444	Case series n=60	The local control and survival results in the primary tumours appear favourable compared with other series in the literature and suggest benefit to the use of IORT. For patients treated for local recurrence, local control and long-term survival can be obtained, but the results are not as encouraging as for the primary tumours.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Tveit KM, Wiig JN, Olsen DR, et al. (1997) Combined modality treatment including intraoperative radiotherapy in locally advanced and recurrent rectal cancer. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology 44(3):277-82	Case series n=115 Follow up=up to 60 months	The combined modality treatment with preoperative external radiotherapy and extensive pelvic surgery with IORT is sufficiently promising to start a randomised trial on the clinical value of IORT as a boost treatment in the multidisciplinary approach to this disease.	Studies with more people or longer follow up included.
Valentini V, Coco C, Rizzo G, et al. (2009) Outcomes of clinical T4M0 extra-peritoneal rectal cancer treated with preoperative radiochemotherapy and surgery: a prospective evaluation of a single institutional experience. Surgery 145(5):486-494	Cohort study n=100 Follow up=31 months	A multimodal approach enabled us to obtain a 5-year OS of about 60%. IORT increased local control. The role of adjuvant chemotherapy needs to be further investigated.	Included in the Fahy 2021 and Liu 2021 systematic reviews.
Valentini V, Rosetto ME, Fares C (1998) Radiotherapy and local control in rectal cancer. Rays 23(3):580-585	Case series n=71 Follow up=6 years	The incidence of metastases was 35% in the patients with local recurrence and 16% in those with local control. The difference in survival was highly significant in patients with local control as compared with those with local recurrence: at 5 years 87% and 32% respectively. Patients with local control showed a lower incidence of metastasis and a better survival.	Studies with more people or longer follow up included.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Wiig JN, Poulsen JP, Tveit KM et al. (2000) Intra-operative irradiation (IORT) for primary advanced and recurrent rectal cancer. a need for randomised studies. European journal of cancer (Oxford, England : 1990) 36(7):868-874	Cohort study n=80 Follow up=22 months	IORT did not seem to influence the local recurrence rate when R0 and R1 resections were analysed separately or in a multivariate analysis. The IORT and surgery/EBRT groups were not identical with regard to type of cancer and R-stage. Still the lack of an identifiable impact of IORT suggests that there is a need for randomised studies of the IORT effect.	Included in the Fahy 2021 systematic review.
Wiig JN, Tveit KM, Poulsen JP, et al. (2002). Preoperative irradiation and surgery for recurrent rectal cancer. Will intraoperative radiotherapy (IORT) be of additional benefit? A prospective study. Radiotherapy and oncology: journal of the European Society for Therapeutic Radiology and Oncology 62(2):207-213	Cohort study n=59	Macroscopic removal of the recurrence improves survival. Whether R0- is better than R1-resections is not clear. The effect of IORT is not a major one. IORT need be evaluated in randomised controlled trials.	Included in the Liu 2021 systematic review.

Article	Number of patients and follow up	Direction of conclusions	Reason study was not included in main evidence summary
Zhang Q, Tey J, Yang Z, et al. (2015) Adjuvant chemoradiation plus intraoperative radiotherapy versus adjuvant chemoradiation alone in patients with locally advanced rectal cancer. American journal of clinical oncology 38(1):11-16	Cohort study n=71 Follow up=72.3 months	For patients with locally advanced rectal cancer, higher radiation dose may contribute to the improvement of both LC and disease-free survival, without significantly increasing the incidence of acute and long-term complications compared with adjuvant chemoradiotherapy alone.	Included in the Fahy 2021 systematic review.