

Original Article

Portuguese Program of Intraoperative Radiotherapy in the Management of Locally Advanced and Recurrent Rectal Cancer: A 10-Year Single-Centre Experience

Programa Português de Radioterapia Intraoperatória no Tratamento do Cancro Retal Localmente Avançado e Recorrente: Experiência de 10 Anos num Único Centro

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ABSTRACT

Introduction: Intraoperative radiotherapy (IORT) delivers focused dose escalation to high-risk areas during rectal cancer surgery. Its precise contribution to locally advanced (LARC) and locally recurrent rectal cancer (LRRC) remains debated, with no randomized trial demonstrating a survival benefit. We report a 10-year experience of the Portuguese national IORT program at IPO-Porto, contextualized within the current evidence base.

Methods: Single-centre retrospective cohort study (January 2010–December 2020). We included 271 patients with LARC (cT3 CRM+, cT4, M0) receiving neoadjuvant chemoradiotherapy, radical surgery, and IORT, and 59 patients with LRRC (M0) treated with surgery and IORT. Primary endpoints: disease-specific survival (DSS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS).

Results: The 5-year DSS was 63.2% for primary LARC and 36.9% for LRRC ($p<0.001$). The 5-year LRFS was 87.6% for primary and 72.4% for recurrences ($p=0.007$). Local disease reappearance within the IORT field occurred in 8.8% of primary and 20.3% of recurrent cases. Clavien-Dindo grade $\geq$ III complications occurred in 20.2%. Clavien-Dindo grade V (mortality) occurred in 0.7% of cases. Intraoperative frozen-section margin status correlated with IORT dose selection and influenced locoregional outcomes. In multivariate analysis, downstaging (HR 0.18; $p<0.001$) and R1 resection (HR 2.62; $p<0.001$) were independent predictors of DSS in primary LARC. R0 resection and adjuvant chemotherapy were strongly associated with improved local control and survival.

Conclusion: IORT is safe and effective as a locoregional dose-escalation tool for LARC and LRRC. Outcomes are comparable to the best international benchmarks. R0 resection remains the dominant prognostic factor. The future combination of IORT with total neoadjuvant therapy warrants prospective evaluation.

Keywords: Neoadjuvant Therapy; Neoplasm Recurrence, Local; Rectal Neoplasms/radiotherapy; Rectal Neoplasms/surgery

RESUMO

Introdução: A radioterapia intraoperatória (RIO) permite a escalada de dose de radioterapia em áreas de alto risco de recidiva durante a cirurgia do cancro do reto. A dimensão da contribuição da RIO no cancro do reto localmente avançado (CRLA) e no cancro do reto localmente recidivado (CRLR) permanece em debate, sem que qualquer ensaio randomizado tenha demonstrado benefício na sobrevivência. Neste trabalho apresentamos a experiência de 10 anos do programa nacional de RIO no IPO-Porto, com a respetiva contextualização da evidência científica atual.

Métodos: Estudo retrospectivo de coorte, unicêntrico (janeiro de 2010 – dezembro de 2020). Foram incluídos 271 doentes com CRLA (cT3 CRM+, cT4, M0) submetidos a quimiorradioterapia neoadjuvante, cirurgia radical e RIO, e 59 doentes com CRLR (M0) tratados com cirurgia e RIO. Os objetivos principais analisados foram a sobrevivência específica de doença (SED), sobrevivência livre de recidiva local (SLRL) e sobrevivência livre de metástases à distância (SLMD).

Resultados: A SED aos 5 anos foi de 63,2% no CRLA primário e de 36,9% no CRLR ($p<0,001$). A SLRL aos 5 anos foi de 87,6% nas doenças primárias e de 72,4% nas recidivas ($p=0,007$). O reaparecimento local da doença no local da RIO ocorreu em 8,8% dos casos primários e em 20,3% dos casos com recorrência. Complicações Clavien-Dindo grau $\geq$ III ocorreram em 20,2% dos doentes. Clavien-Dindo grau V (mortalidade) ocorreu em 0,7% dos casos. O estado das margens avaliado por exame extemporâneo intraoperatório correlacionou-se com a seleção da dose de RIO e influenciou os resultados locorregionais. Na análise multivariada, a redução do estágio da doença (HR 0,18; $p<0,001$) e a ressecção R1 (HR 2,62; $p<0,001$) foram preditores independentes da SED no CRLA primário. A ressecção R0 e a quimioterapia adjuvante estão significativamente associadas a um melhor controlo local e a melhor sobrevivência.

Conclusão: A RIO é segura e eficaz como instrumento de escalada da dose, em contexto locorregional, no CRLA e CRLR. Os resultados são semelhantes aos melhores parâmetros de referência internacionais. A ressecção R0 mantém-se como o principal fator prognóstico. A futura combinação da RIO com a terapia neoadjuvante total justifica a realização de uma avaliação prospetiva em ensaio clínico.

Palavras-chave: Neoplasias Retais/cirurgia; Neoplasias Retais/radioterapia; Recidiva Local de Neoplasia; Terapia Neoadjuvante.

INTRODUCTION

Rectal cancer accounts for approximately 30% of all colorectal cancers and represents one of the most challenging gastrointestinal malignancies, particularly when presenting as locally advanced or recurrent disease.^{1,2} Locally advanced rectal cancer (LARC), defined as cT3 with circumferential resection margin (CRM) involvement or cT4 disease without distant metastases, carries a significant risk of locoregional failure despite modern multimodal therapy.³ Locally recurrent rectal cancer (LRRc) is associated with 5-year overall survival rates below 30% in most series and requires complex salvage strategies.^{4,5}

The standard treatment for LARC involves neoadjuvant chemoradiotherapy (CTRT) followed by radical surgery with total mesorectal excision (TME) and optional adjuvant chemotherapy. This approach achieves local recurrence rates of 5%–10% in centres of excellence, but outcomes worsen substantially with positive margins or locally recurrent disease.^{6,7} Achieving an R0 resection remains the principal determinant of long-term survival.⁸

Intraoperative radiotherapy (IORT), specifically intraoperative electron radiotherapy (IORT), is a technique that delivers a single high-dose fraction of radiation directly to the tumor bed or residual risk areas at the time of surgery. It exploits the ability to retract or shield vulnerable organs, thereby allowing dose escalation beyond the limits imposed by conventional external beam radiotherapy (EBRT).^{9,10} The ESTRO/ACROP guidelines (2020) recommend IORT as a component of multimodal treatment for carefully selected patients with LARC (T4 or threatened CRM) or LRRc, particularly when margins are close or positive.^{11,12}

Despite its logical radiobiological rationale, the evidence base for IORT remains predominantly retrospective. No randomized trial has demonstrated a statistically significant improvement in overall survival.^{13,14} A French multi-institutional randomized phase III trial found no benefit of adding 18 Gy IORT in predominantly T3 favourable tumors.¹⁵ A recent meta-analysis (Fahy *et al*, 2021¹³) and a systematic review with meta-analysis (Amarnath, 2023¹⁶) suggest improved local control (OR ~0.55) but no definitive survival advantage. A large propensity-matched National Cancer Database (NCDB) analysis showed a numerically higher but non-significant 5-year OS with IORT (58.4% vs 54.9%) for margin-positive T3–T4 disease.¹⁷ The benefit of IORT thus appears to reside primarily in locoregional control, making careful patient selection and technical excellence essential.

The Instituto Português de Oncologia do Porto (IPO-Porto) is a tertiary oncological reference centre managing approximately 10 000 new patients per year and around 400 new cases of rectal cancer, serving as the national reference for complex rectal cancer. Its IORT program was launched in January 2010, representing the first IORT program within the Portuguese National Health Service (SNS), initially using a fixed linear accelerator. We report 10-year outcomes of this program, integrate findings with the current international evidence, and identify unresolved questions for future research.

METHODS

STUDY DESIGN AND PATIENT POPULATION

Single-centre retrospective cohort study at IPO-Porto (January 2010–December 2020). The study population comprised two groups: (1) Primary LARC: 271 patients with histologically confirmed rectal adenocarcinoma staged cT3 CRM+ or cT4 without distant metastases (M0); (2) LRRc: 59 patients with locally recurrent rectal cancer (M0). Unresectable distant metastases or performance status incompatible with major pelvic surgery were excluded. The IPO-Porto Ethics Committee approved the study, and it was conducted in accordance with the Declaration of Helsinki.

MULTIDISCIPLINARY TEAM AND STAGING

A dedicated multidisciplinary team (surgical oncologists, radiation oncologists, medical oncologists, radiologists) evaluated all patients. Staging workup included pelvic magnetic resonance imaging (MRI), computed tomography (CT) chest/abdomen/pelvis, and endorectal ultrasound when appropriate. Clinical staging followed AJCC/UICC 8th edition criteria.

TREATMENT PROTOCOL

Primary LARC: Neoadjuvant long-course CTRT (45.0–50.4 Gy in 25–28 fractions with concurrent fluoropyrimidine), followed after a median 8.9-week interval by radical surgery (TME) and IORT, then adjuvant chemotherapy in eligible patients.

LRRc: Re-irradiation (low dose with chemotherapy, 30.0 Gy/15 fractions) in patients with prior pelvic radiotherapy; standard long-course CTRT in previously non-irradiated patients; followed by composite resection/exenteration and IORT.

When technically possible, IORT doses were stratified by intraoperative frozen-section margin status: R0 resection 10.0–12.5 Gy; R1 resection 12.5–15.0 Gy; R2 resection 15.0–20.0 Gy. This risk-adapted dosing approach is consistent with ESTRO/ACROP IORT guidelines.^{11,12}

IORT TECHNIQUE

IORT was delivered using a Varian linear accelerator (fixed, in a dedicated bunker) from 2010 to 2020. Electron energies of 6, 9, 12, and 15 MeV were available; 9 MeV was most commonly used (77.9%). Applicator cones (diameter 5–10 cm; bevel 0°, 15°, 30°, 45°) were selected intraoperatively to match the target volume geometry. We routinely performed in vivo dosimetry with Gafchromic EBT3 films.^{18,19} Mean treatment time was 18.6 minutes.

ENDPOINTS AND STATISTICAL ANALYSIS

Categorical variables were summarized as frequencies and percentages, whereas continuous variables were summarized as means and standard deviations.

The primary endpoints were disease-specific survival (DSS), local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS). DSS was defined as the time from the date of IORT to death from rectal cancer or the date of last follow-up. LRFS was defined as the time from the date of IORT to local recurrence or last follow-up, whichever occurred first. DMFS was defined as the time from the date of IORT to the occurrence of distant metastasis or last follow-up, whichever occurred first.

Secondary endpoints: surgical morbidity (Clavien-Dindo classification), local disease reappearance within the IORT field, frozen-section margin status correlation with IORT dosing, and identification of independent prognostic factors. Kaplan-Meier curves were used for survival estimation; groups were compared by log-rank test. Multivariate analysis used Cox proportional hazards regression (variables with *p*<0.1 in univariate were included). Statistical significance: *p*<0.05. Analyses were performed with R v4.1.0.

RESULTS

PATIENT AND TREATMENT CHARACTERISTICS

A total of 330 patients were included. The mean age was 59.0 years (SD 11.6 years), and 220 patients (66.7%) were male. The mean follow-up was 39.6 months (SD 29.8). Full characteristics are in Table 1.

SURGICAL COMPLICATIONS

Complications occurred in 50.7% of patients. Clavien-Dindo grade III–IV adverse events occurred in 20.2% (n=57), with pelvic abscess or anastomotic complications accounting for 41.4% of severe events, followed by fistula/ureter stenosis (17.2%), perineal wound dehiscence (17.2%), neuropathy (13.8%), and other causes (10.0%). Mortality (Clavien-Dindo grade V) was 0.7% (n=2). The 30-day surgical complication

Table 1. Tumour and treatment characteristics (n=330)

Characteristic	n	%
Primary tumour	271	82.1
cT3 CRM+	111	40.2
cT4	106	38.4
Local recurrence	59	17.9
Recurrence: anastomotic site	24	40.7
Recurrence: pre-sacral	15	25.4
Neoadjuvant chemoradiotherapy (primary)	250	90.6
Pre-op RT dose ≥45 Gy	239	89.2
Abdominoperineal resection (APR)	109	39.5
Low anterior resection (LAR)	71	25.7
Extended surgery	65	23.6
Pelvic exenteration	31	11.2
pT0–T2 (pathological downstaging)	41	14.9
pT3	135	48.9
R0 surgical margin	202	73.2
R1 surgical margin	71	25.7
R2 surgical margin	3	1.1
Adjuvant chemotherapy	176	63.8
Median hospital stay, days (range)	12 (2–173)	–

Table 2. IORT technical parameters

Parameter	Most frequent value	n / %
IORT dose	10.0 Gy	153 (55.4%)
IORT dose	12.5 Gy	70 (25.4%)
IORT dose	15.0 Gy	47 (17.0%)
Electron energy	9.0 MeV	215 (77.9%)
Application site	Pre-sacral region	230 (83.3%)
Mean treatment time	18.6 minutes	–

rate was 33.3%. These morbidity figures are consistent with published series for complex pelvic surgery including IORT.^{9,13,17,20} Importantly, sepsis/infectious complications were independently associated with significantly worse DSS (*p*<0.0001), as were urinary complications (*p*=0.009) and haemorrhagic complications (*p*=0.022). Perineal dehiscence and anastomotic leak did not significantly affect DSS.

LOCAL DISEASE REAPPEARANCE WITHIN THE IORT FIELD

Only when there were doubts about the resection margins in oncological terms (R0) and when it was technically feasible,

Table 3. Postoperative complications by Clavien-Dindo grade

Grade	Description	n	%
Grade 0	No complications	163	49.3
Grade I	Minor deviation, no intervention	32	9.7
Grade II	Pharmacological treatment required	66	20.1
Grade III	Surgical/endoscopic/radiological intervention	62	18.8
Grade IV	Life-threatening, ICU required	5	1.4
Grade V	Death	2	0.7

intraoperative assessment of surgical margins by frozen section was performed and guided the selection of the IORT dose according to the risk-adapted protocol described above. In the primary tumour group (n=271), local disease reappeared within the irradiated field in 8.8% (n=19). Among

R0 sections, the rate was 8.1%; among R1 resections, 11.5%. In the LRRC group (n=59), field reappearance occurred in 20.3% (n=11). In cases that recurred, the previous surgery had incomplete mesorectal excision, which was associated with 100% local reappearance versus 0% when the mesorectal resection was complete ($p<0.001$); in 91.7% of surgical field recurrences, patients had not received preoperative radiotherapy.

SURVIVAL OUTCOMES

Kaplan-Meier survival analyses are summarized in Tables 4 and 5. All comparisons by log-rank test.

MULTIVARIATE ANALYSIS

Table 6 presents the Cox proportional hazards regression results for both groups.

Table 4. Disease-Specific Survival (DSS)

Comparison	Group	n	5-yr DSS (95%CI)	p-value
Tumor type	Primary LARC	271	63.2% (55.3–72.2)	$p<0.001$
	LRRC	59	36.9% (25.3–53.7)	(log-rank)
Margin status	R0	202	67.9% (60.0–76.8)	$p<0.001$
	R1	71	26.0% (16.4–41.4)	(log-rank)
Adjuvant CT	Yes	176	64.1% (55.2–74.4)	$p<0.001$
	No	100	43.6% (33.7–56.3)	(log-rank)

Table 5. Local Recurrence-Free Survival (LRFS) and Distant Metastasis-Free Survival (DMFS)

Endpoint	Group	5-year Rate (95%CI)	p-value
LRFS	Primary LARC	87.6% (81.9–93.6)	$p=0.007$
	LRRC	72.4% (59.4–88.2)	(vs primary)
DMFS	Primary LARC	64.7% (56.8–73.6)	$p=0.05$
	LRRC	55.0% (41.3–73.2)	(vs primary)

Table 6. Multivariate analysis – Disease-Specific Survival

Group	Variable	Category	n	HR	95%CI	p-value
Primary LARC	Downstaging	No (ref)	98	1.00	–	–
		Yes	110	0.18	0.09–0.36	<0.001
	Pathologic Margin	R0 (ref)	156	1.00	–	–
		R1	52	2.62	1.52–4.52	<0.001
	Adjuvant CT	No (ref)	67	1.00	–	–
		Yes	141	0.92	0.70–1.22	0.568 (NS)
LRRC	Pathologic Margin	R0 (ref)	37	1.00	–	–
		R1	19	2.77	1.34–5.70	0.006
	Downstaging	No (ref)	39	1.00	–	–
		Yes	17	0.47	0.17–1.28	0.137 (NS)

DISCUSSION
OVERVIEW

This study reports the largest published Portuguese single-centre IORT series for rectal cancer, spanning 330 patients and 10 years. Because primary LARC and LRRC differ in natural history, tissue environment, prior treatment exposure and the determinants of outcome, the two groups are discussed separately below. The multivariate profiles summarised in Fig. 1 support this separation: pathological margin status carried an almost identical prognostic weight in both settings (HR 2.62 and 2.77), whereas the effect of tumour downstaging was strong and significant only in primary disease.

PRIMARY LOCALLY ADVANCED RECTAL CANCER
ONCOLOGICAL OUTCOMES IN CONTEXT

Our 5-year DSS of 63.2% for primary LARC and 5-year LRFS of 87.6% compare favourably with the major international benchmarks. The European pooled analysis by Kusters *et al* (n=605, 4 major IORT centres) reported a 5-year OS of 67.1% and a local recurrence rate of 12.0% for LARC treated with multimodal therapy including IORT.²¹ A large American retrospective series by Zhang *et al* reported a 5-year OS of 64% and local control of 82%.²² Our results are congruent with these datasets, validating the quality and oncological standards of the IPO-Porto program.

The meta-analysis by Mirnezami *et al* (n=3003, 29 studies) concluded that IORT improved oncological outcomes in

advanced and recurrent colorectal cancer despite methodological heterogeneity.²³ The more recent meta-analysis by Liu *et al* (2021) specifically demonstrated that IORT's principal benefit is in 5-year local control (pooled OR 3.07; $p<0.001$ in observational studies; OR 1.37, $p=0.249$ in RCTs), with no statistically significant improvement in 5-year overall survival or disease-free survival.¹⁴ Our LRFS data reinforce this: IORT in combination with neoadjuvant CTRT and radical surgery produces excellent local control, consistent with IORT's biological role as a locoregional intensification tool.

RO RESECTION IN PRIMARY DISEASE

In primary LARC, R1 versus R0 resection conferred a hazard ratio of 2.62 for DSS ($p<0.001$), a finding replicated across virtually all published IORT series and meta-analyses.^{8,9,13,17} IORT should therefore be conceptualized as a complement to, not a substitute for, radical surgery. As the ESTRO/ACROP guidelines state, IORT is indicated for T4 tumours with threatened CRM or R1 resections as a local intensification measure, not as a mechanism to compensate for inadequate surgical radicality.¹¹

The NCDB propensity-matched analysis by Erkaya *et al* (2025) specifically examined margin-positive (R1) T3–T4 rectal cancer and found that IORT was associated with improved local recurrence-free survival in this subset, supporting its targeted use in high-risk margin situations.¹⁷ A prior NCDB analysis by Khan *et al* (2022) in patients treated with

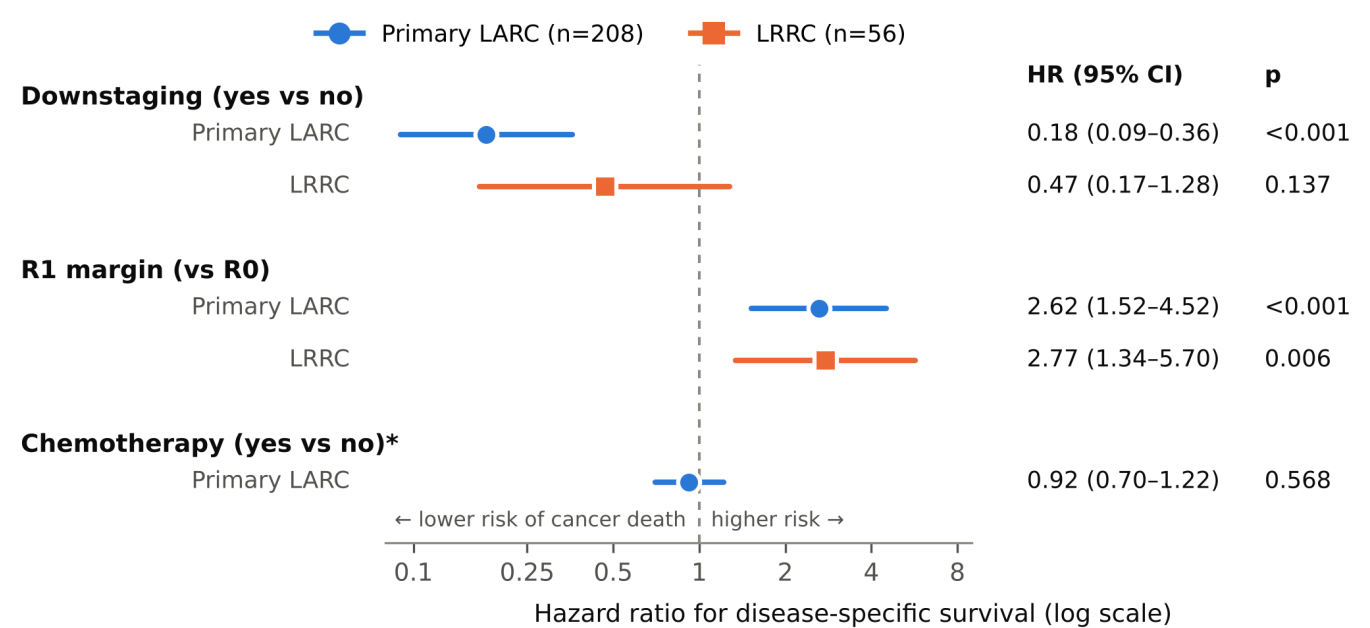


Figure 1. Independent predictors of disease-specific survival in primary LARC and LRRC (Cox multivariate model, Table 6). Points are hazard ratios with 95% confidence intervals on a logarithmic scale; values to the left of 1 indicate lower risk of death from rectal cancer. *Chemotherapy variable as reported in Table 6, modelled for the primary group only.

short-course radiotherapy-based TNT found a numerically higher but non-significant 5-year OS with IORT (58.4% vs 54.9%), suggesting that the survival impact may become clearer in prospective settings with controlled comparators.²⁴

DOWNSTAGING: SUBGROUP ANALYSIS AND ALIGNMENT WITH TOTAL NEOADJUVANT THERAPY

Pathological downstaging after neoadjuvant CRT was the strongest independent favourable predictor of DSS in primary LARC (HR 0.18; 95% CI 0.09–0.36; $p < 0.001$), corresponding to an 82% relative reduction in the hazard of cancer-specific death after adjustment for margin status and chemotherapy (Fig. 1). Its magnitude exceeded that of margin status itself: expressed on the same scale, the protective effect of downstaging ($1/0.18 \approx 5.6$ -fold) was roughly twice the adverse effect of an R1 resection (2.62-fold), and even the least favourable bound of its confidence interval (0.36) indicates a substantial survival advantage. Downstaging was observed in 110 of the 208 patients (52.9%) entering the multivariate model, yet only 41 patients (14.9%) reached pT0–T2, indicating that in the long-course CRT era most responses were partial T-category shifts rather than deep responses.

This gradient has two implications. First, response to neoadjuvant therapy behaves as an *in vivo* marker of tumour biology: tumours that regress after CRT are also those

least likely to have disseminated. Second, it identifies non-responders as the subgroup with the greatest unmet need, in whom both the local risk at surgery and the systemic risk remain high. These are the patients in whom intraoperative dose escalation is most likely to be needed, and whose outcome IORT alone cannot be expected to rescue.

Total neoadjuvant therapy (TNT) acts on exactly this axis (Fig. 2). In RAPIDO, short-course radiotherapy followed by consolidation chemotherapy doubled the pathological complete response (pCR) rate (28% vs 14%) and reduced 3-year distant metastases (20.0% vs 26.8%; HR 0.69; $p = 0.005$).²⁵ In PRODIGE 23, induction mFOLFIRINOX before CRT increased the pCR rate from 12.1% to 27.8% and improved 3-year disease-free survival (76% vs 69%) and metastasis-free survival (79% vs 72%).²⁶ If the strong prognostic weight of downstaging in our cohort reflects a causal contribution of tumour response, deepening response with TNT would be expected to translate into survival gains of the kind observed in these trials. Our data also provide an institutional baseline under long-course CRT (52.9% downstaging; 14.9% pT0–T2) against which a TNT-based programme can be measured.

Fig. 2 also shows why TNT does not make IORT redundant. In our primary cohort, distant failure at 5 years (35.3%) was almost three times more frequent than local failure (12.4%), so the main residual risk after IORT-containing treatment is

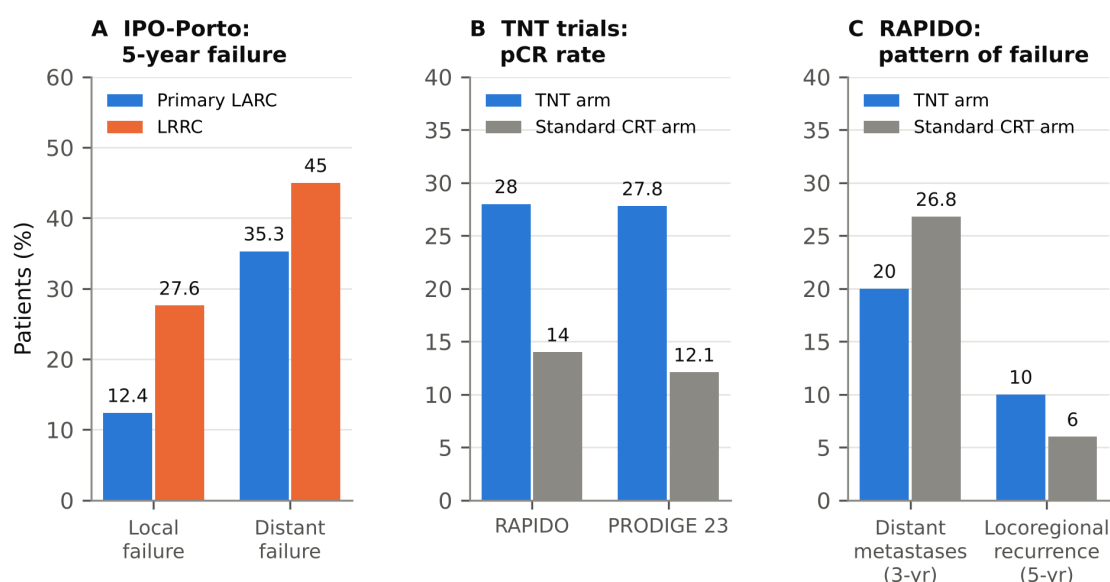


Figure 2. Aligning the IPO-Porto failure pattern with the evidence for total neoadjuvant therapy. (A) Five-year local and distant failure in this cohort, estimated as 1 – Kaplan–Meier LRFS and DMFS (Table 5). (B) Pathological complete response in the TNT and standard chemoradiotherapy arms of RAPIDO²⁵ and PRODIGE 23.²⁶ (C) Three-year distant metastases and 5-year locoregional recurrence in RAPIDO.^{25,27} Trial data are shown for context and are not directly comparable with this retrospective cohort.

systemic—the target of TNT. Conversely, the 5-year update of RAPIDO showed a higher locoregional recurrence rate with the TNT strategy than with standard CTRT (10% vs 6%; $p=0.027$), with a breached mesorectum more frequent among the patients who recurred.²⁷ TNT therefore improves systemic control at the cost of a measurable local signal, which is precisely the risk IORT is designed to address. The two strategies are complementary: TNT for the systemic component and for downstaging, IORT for the residual locoregional risk in patients with threatened or involved margins after response assessment. This hypothesis forms the scientific basis for a prospective IORT+TNT trial planned at IPO-Porto, comparing long-course CTRT versus short-course radiotherapy plus consolidation chemotherapy (FOLFOX/CAPOX or FOLFIRINOX) followed by surgery with IORT in T3 CRM+, T4 and LRRC patients.

SURGICAL MORBIDITY AS A CRITICAL DECISION FACTOR: THE LOSS OF ADJUVANT CHEMOTHERAPY

In this series, morbidity was not only a safety outcome but a determinant of oncological outcome. Clavien-Dindo grade III–IV complications occurred in 20.2% of patients, reflecting the complexity of the procedures (exenteration 11.2%, extended resection 23.6%) and within the 15%–25% reported for comparable IORT populations.^{9,13,20} Meta-analyses have not identified statistically significant increases in total complications, anastomotic leaks or urological complications attributable to IORT *per se*,^{13,23} although several series report more wound infections and pelvic abscesses in IORT-treated patients, consistent with our experience.^{11,17,20} Dose-limiting peripheral neurotoxicity at IORT doses ≥ 15 Gy accounted for 13.8% of severe events, concordant with published tolerance thresholds.⁹

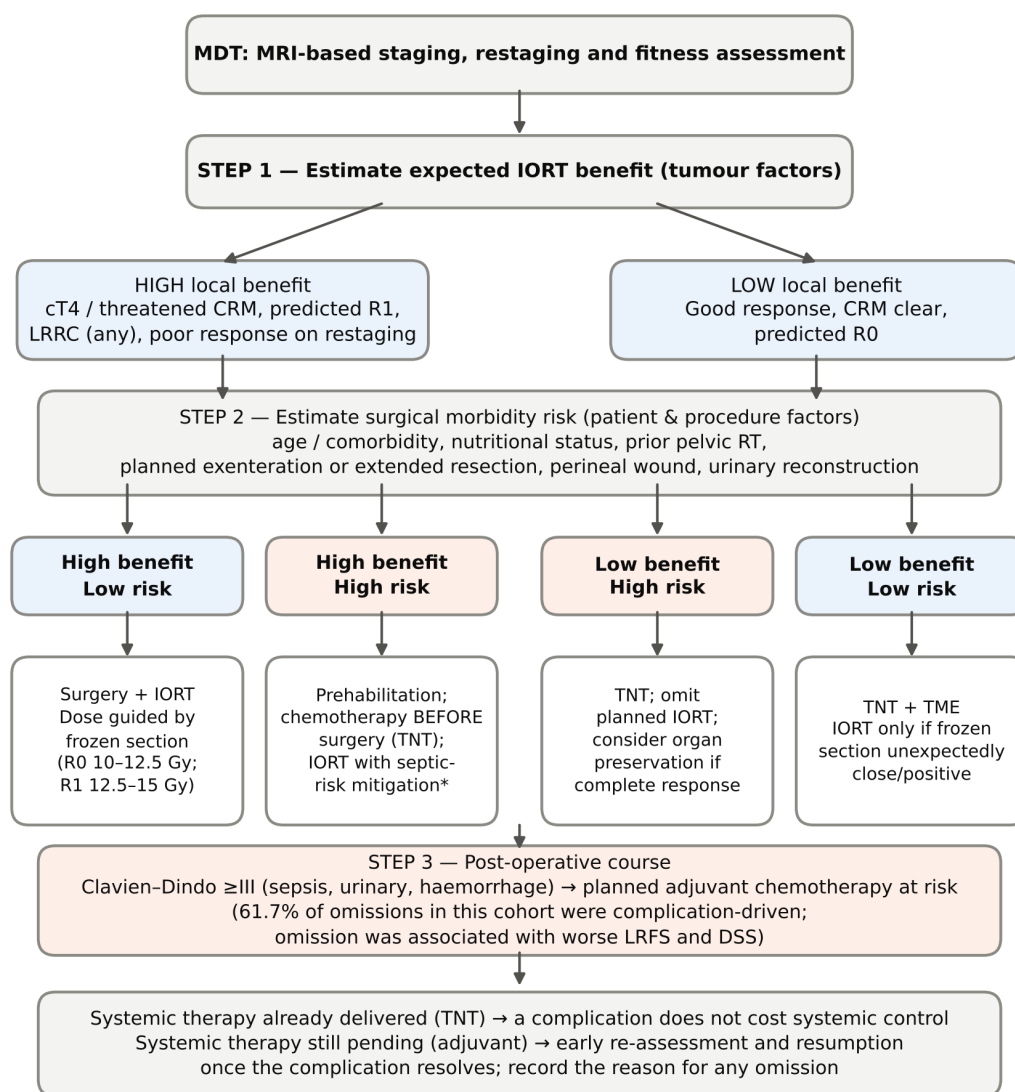
Three findings link morbidity to oncological failure. First, septic ($p<0.0001$), urinary ($p=0.009$) and haemorrhagic ($p=0.022$) complications were each associated with significantly worse DSS, whereas perineal dehiscence and anastomotic leak were not. Second, 61.7% of the patients who did not receive planned adjuvant chemotherapy were prevented from doing so by surgical complications. Third, patients who did not receive adjuvant chemotherapy had a lower 5-year DSS (43.6% vs 64.1%; $p<0.001$) and a shorter time to local recurrence ($p=0.021$). Adjuvant chemotherapy did not retain independent significance for DSS in multivariate analysis (HR 0.92; $p=0.568$), consistent with the Kusters pooled analysis, in which adjuvant chemotherapy after IORT-containing treatment prevented local recurrence rather than distant metastases,²¹ and suggesting that much of its univariate

effect reflects which patients were well enough to receive it. When systemic therapy follows surgery, a severe complication does not merely delay recovery: it frequently removes the systemic component of treatment altogether.

We therefore propose that surgical morbidity risk be weighed explicitly against the expected local benefit of IORT before surgery, using a three-step risk–benefit framework (Fig. 3). Step 1 estimates the expected IORT benefit from tumour factors (cT4 or threatened CRM, predicted R1 resection, poor response on restaging, recurrent disease). Step 2 estimates morbidity risk from patient and procedural factors (comorbidity and nutritional status, prior pelvic radiotherapy, planned exenteration or extended resection, perineal wound and urinary reconstruction). Where expected benefit is high and risk acceptable, surgery with IORT dosed by frozen-section margin status is appropriate. Where both benefit and risk are high, the central recommendation is to deliver systemic chemotherapy before surgery—a TNT sequence—so that a postoperative complication can no longer cost the patient systemic treatment, combined with prehabilitation and septic-risk mitigation (perineal flap or negative-pressure wound therapy, nutritional optimisation, ureteric protection). Randomised data support this sequencing: in the GCR-3 trial, induction chemotherapy achieved better compliance and lower acute toxicity than the same regimen given adjuvantly.²⁸ Where benefit is low and risk high, IORT should not be planned, and TNT with consideration of organ preservation in complete responders is preferable; where both are low, TNT and TME are standard, with IORT reserved for an unexpectedly close or positive frozen section. Step 3 addresses the postoperative course: any Clavien-Dindo grade $\geq$ III event should trigger early multidisciplinary review of pending systemic therapy and systematic recording of the reason for any omission. This framework is derived from a retrospective cohort and is hypothesis-generating; it requires prospective validation, and its components are being incorporated into the planned IORT+TNT protocol.

LOCALLY RECURRENT RECTAL CANCER A DISTINCT BIOLOGICAL AND SURGICAL ENTITY

LRRC is not simply a later stage of the same disease. Recurrence develops in an operated and frequently irradiated pelvis in which anatomical planes are lost, fibrosis and reduced vascularity create a hypoxic and less radiosensitive environment, and tumour tends to spread along fascial planes, nerves and pelvic sidewall structures rather than as a contained mass.^{4,10,12} Prior pelvic radiotherapy limits the external-beam dose that can be safely re-delivered, making intraoperative dose escalation one of the few means



* Septic-risk mitigation: perineal flap or negative-pressure wound therapy, nutritional optimisation, ureteric protection. Proposed framework derived from the IPO-Porto cohort (2010–2020); hypothesis-generating — requires prospective validation.

Figure 3. Proposed risk–benefit algorithm integrating expected IORT benefit, surgical morbidity risk and the risk of losing adjuvant chemotherapy. Derived from the IPO-Porto cohort (2010–2020); hypothesis-generating and requires prospective validation. CRM, circumferential resection margin; LRRC, locally recurrent rectal cancer; LRFS, local recurrence-free survival; DSS, disease-specific survival; MDT, multidisciplinary team; RT, radiotherapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

of delivering a biologically effective dose to the surface at highest risk.¹² These features explain why the determinants of outcome in LRRC differ from those in primary disease.

Our 5-year DSS of 36.9% and 5-year LRFS of 72.4% in LRRC compare well with the pooled analysis by Holman *et al* (n=565), in which radicality of resection and full-dose preoperative (chemo)irradiation were the dominant prognostic factors.²⁹ Distant failure was also more frequent than in primary disease (5-year DMFS 55.0% vs 64.7%; Fig. 2A), consistent with the more advanced biological stage of recurrent disease.

MARGIN STATUS, NOT TUMOUR RESPONSE, DRIVES OUTCOME

In LRRC, R1 resection was the only independent predictor of DSS (HR 2.77; 95% CI 1.34–5.70; $p=0.006$), whereas downstaging did not reach significance (HR 0.47; 95% CI 0.17–1.28; $p=0.137$; Fig. 1). The point estimate suggests a possible benefit of response, but the wide interval and the small number of downstaged patients (n=17) preclude firm conclusions. Biologically, this pattern is expected: reduced re-irradiation doses and a hypoxic, fibrotic tumour bed make deep responses less likely, so that the extent of surgical clearance becomes the decisive variable. The Beyond TME

consensus identifies R0 resection as the most important predictor of prognosis and supports extended resection beyond TME planes when required to achieve it.³⁰ The downstaging-driven TNT paradigm therefore cannot be transferred directly to LRRC; the priority remains an R0 resection, with IORT intensifying the dose at the surface where clearance is narrowest.

PATTERN OF IN-FIELD REAPPEARANCE

Local reappearance within the IORT field was more than twice as frequent in LRRC as in primary disease (20.3% vs 8.8%). All in-field reappearances in the recurrence group occurred in patients whose index operation had an incomplete mesorectal excision, with none after a complete mesorectal excision. This suggests that the quality of the initial operation shapes the biology of the recurrence itself: recurrences arising after incomplete index surgery appear more infiltrative and more difficult to control, even with salvage surgery and IORT. It reinforces that the most effective strategy against LRRC remains its prevention through high-quality primary TME and appropriate neoadjuvant treatment.

MORBIDITY IN RECURRENT DISEASE

The risk–benefit balance of Fig. 3 is weighted differently in LRRC. Expected local benefit is high almost by definition, because re-irradiation dose is limited and margins are frequently narrow; morbidity risk is also higher, owing to re-operative fields, exenterative procedures and previously irradiated tissue. In this setting IORT is rarely the component to omit; instead, morbidity risk should guide the choice of technique and reconstruction. Voogt *et al* found that HDR-IORT achieved better local recurrence-free survival than IORT after R1 resection, but with more major complications in LRRC,³¹ illustrating that dose intensification and morbidity must be balanced individually in recurrent disease.

TECHNICAL CONTRIBUTIONS AND DOSIMETRIC QUALITY

The IPO-Porto physics group has made substantive contributions to the international IORT literature: dosimetric characterization of pelvic IORT using Gafchromic EBT3 films,¹⁸ effects of irradiation surface geometry and shielding on dose distributions,¹⁹ *in vivo* dosimetry during pelvic IORT,³² and confirmation that TachoSil hemostatic patches do not compromise target irradiation.³³ These publications collectively establish a rigorous dosimetric quality assurance framework specific to pelvic IORT.

A key technical challenge in IORT is that clinical dose distributions frequently differ from reference beam data

used for prescription, particularly when irradiation surfaces are curved or angled.³² The systematic use of Gafchromic *in vivo* dosimetry throughout our series allowed real-time verification of delivered dose, contributing to treatment consistency. Future mobile IORT platforms with integrated 3D dose calculation, such as those recently described for recurrent rectal cancer,³⁴ will enable prospective dosimetric optimization and may further improve local control and reduce toxicity by refining applicator positioning and dose homogeneity.

LIMITATIONS

This study has several limitations, namely: Retrospective, non-randomized design: The absence of a concurrent non-IORT control group limits causal inference. Observed survival differences may reflect selection bias favouring patients referred for IORT (fitter, more complete staging, higher-volume centre effect). Heterogeneous patient population: The cohort includes both primary LARC and LRRC, with different natural histories, prior treatment exposures, and surgical complexities. Although analysed separately, comparisons must be interpreted cautiously. Evolving treatment protocols: The 10-year study period (2010–2020) spans substantial changes in rectal cancer management, including wider adoption of MRI-based staging, more selective use of adjuvant chemotherapy, and the emergence of TNT. These secular trends may confound temporal comparisons. Incomplete follow-up: The median follow-up of 39.6 months may be insufficient to capture late local recurrences and long-term survival events. Ten-year outcomes are not yet available for the full cohort. Single-centre experience: Results reflect the expertise of a high-volume national reference centre with dedicated IORT infrastructure and trained multidisciplinary teams. Outcomes may not be reproducible in lower-volume or less-specialized settings. Quality-of-life data: No prospective quality-of-life assessment was included in the retrospective phase, a recognized gap in the IORT literature that the planned prospective trial will address.

UNRESOLVED QUESTIONS AND FUTURE DIRECTIONS

Despite decades of institutional experience and accumulating literature, several fundamental questions about IORT for rectal cancer remain unresolved:

DOES IORT IMPROVE OVERALL SURVIVAL?

No randomized trial has demonstrated a statistically significant survival benefit from IORT in rectal cancer. Meta-analyses confirm local control benefit but not survival advantage.^{13,14,16}

The French RCT (Dubois *et al*, 2011) found no benefit, though it included predominantly T3 tumours with relatively favourable biology.¹⁵ A properly powered, contemporary RCT stratified by tumour stage and resection margin would be needed to definitively answer this question.

WHAT IS THE OPTIMAL INTEGRATION WITH TOTAL NEOADJUVANT THERAPY?

As TNT becomes the preferred neoadjuvant strategy for LARC,^{25,26} its interaction with IORT is undefined. The proposed IORT+TNT trial at IPO-Porto addresses this directly. Key questions include: Does TNT-induced downstaging reduce the need for IORT dose escalation in R0 cases? Does TNT's systemic benefit make IORT's local control benefit relatively more clinically meaningful? What is the optimal sequencing and chemotherapy backbone (FOLFOX versus CAPOX versus FOLFIRINOX)?

HOW DOES IORT COMPARE WITH OTHER DOSE-ESCALATION STRATEGIES?

Contact X-ray brachytherapy and HDR-IORT represent alternative dose-escalation modalities. The comparison between IORT and HDR-IORT is particularly relevant: Voogt *et al* (2021) found similar overall survival but better local recurrence-free survival with HDR-IORT for R1 resections, at the cost of more major complications in LRRC.³¹ Head-to-head prospective comparisons are lacking.

CAN 3D DOSIMETRIC IORT IMPROVE OUTCOMES?

The introduction of mobile IORT with real-time 3D dose calculation addresses a longstanding limitation of the technique: the inability to verify actual dose distribution to the intended target.³⁴ Clinical dose distributions in pelvic IORT frequently differ from reference beam data used for prescription.³² Whether improved dosimetric precision translates into better local control or reduced toxicity is

an open hypothesis that future prospective programs are uniquely positioned to investigate.

WHAT IS THE IMPACT OF IORT ON QUALITY OF LIFE?

Prospective quality-of-life data from IORT-treated rectal cancer patients are virtually absent from the literature. Given the complex pelvic surgery required and the potential for neurovascular injury from high-dose IORT, characterizing functional outcomes (bowel, bladder, sexual, and pain domains) is essential for informed consent and patient selection. The planned IPO-Porto prospective trial incorporates quality-of-life as a co-primary endpoint.

CONCLUSION

In this 10-year IPO-Porto experience, IORT was feasible and provided durable locoregional control in selected patients with locally advanced and recurrent rectal cancer. R0 resection remains the key determinant of outcome, confirming that IORT should complement, rather than replace, optimal radical surgery. Its main role is locoregional dose escalation in patients at high risk of local failure, particularly those with T4 disease, threatened or involved margins, and locally recurrent tumors. Although no overall survival benefit can currently be established, these results support IORT as a valuable component of a multidisciplinary, risk-adapted treatment strategy.

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ETHICAL DISCLOSURES

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Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of patient data.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2024).

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CONTRIBUTORSHIP STATEMENT

Study design and data collection: JPS, OS, DG, and LLS were responsible for the conception and design of the study and for data collection and curation.

Statistical analysis and review: PLS and LLS performed and critically reviewed the statistical analyses, including Kaplan-Meier survival estimation, log-rank testing, and Cox proportional hazards regression.

Manuscript writing and critical revision: All authors contributed to the drafting and critical revision of the manuscript for important intellectual content.

Final approval: All authors have read and approved the final version of the manuscript.

DECLARAÇÃO DE CONTRIBUIÇÃO

Desenho do estudo e recolha de dados: JPS, OS, DG e LLS foram responsáveis pela conceção e desenho do estudo, bem como pela recolha e curadoria dos dados.

Análise estatística e revisão: PLS e LLS realizaram e reviram criticamente as análises estatísticas, incluindo a estimativa de sobrevivência de Kaplan-Meier, o teste de log-rank e a regressão de riscos proporcionais de Cox.

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REFERENCES

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2022. *CA Cancer J Clin.* 2022;72:7-33. doi:10.3322/caac.21708
2. Benson AB, Venook AP, Al-Hawary MM, Azad N, Chen YJ, Ciombor KK, et al. Rectal Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2022;20:1139-67. doi:10.6004/jnccn.2022.0051
3. Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg.* 2007;246:693-701. doi:10.1097/SLA.0b013e318156e4f8
4. Hahnloser D, Nelson H, Gunderson LL, Hassan I, Haddock MG, O'Connell MJ, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. *Ann Surg.* 2003;237:502-8. doi:10.1097/01.SLA.0000059438.89967.6C
5. Glimelius B, Tiret E, Cervantes A, Arnold D; ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2013;24 Suppl 6:vi81-88. <https://doi.org/10.1093/annonc/mdt240>
6. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol.* 2011;12:575-82. doi:10.1016/S1470-2045(11)70097-3
7. Nagtegaal ID, Marijnen CA, Kranenbarg EK, van de Velde CJ, van Krieken JH. Pathology Review Committee. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one millimeter but two millimeters is the limit. *Am J Surg Pathol.* 2002;26:350-7. doi:10.1097/00000478-200203000-00010
8. Wibe A, Møller B, Norstein J, Carlsen E, Wiig JN, Heald RJ, et al. A national strategic change in treatment policy for rectal cancer—implementation of total mesorectal excision as routine treatment in Norway. *Dis Colon Rectum.* 2002;45:857-66. doi:10.1007/s10350-004-6299-5
9. Haddock MG. Intraoperative radiation therapy for colon and rectal cancers: a clinical review. *Radiat Oncol.* 2017;12:11. doi:10.1186/s13014-016-0752-1
10. Gunderson LL, Willett CG, Calvo FA, Harrison LB, eds. Intraoperative Irradiation: Techniques and Results. 2nd ed. Totowa: Humana Press; 2011.
11. Calvo FA, Sole CV, Rutten H, Poortmans P, Asencio JM, Serrano J, et al. ESTRO/ACROP IORT recommendations for intraoperative radiation therapy in primary locally advanced rectal cancer. *Clin Transl Radiat Oncol.* 2020;25:29-36. doi:10.1016/j.ctro.2020.09.001
12. Calvo FA, Sole CV, Rutten H, Dries WJ, Lozano MA, Cambeiro M, et al. ESTRO/ACROP IORT recommendations for intraoperative



radiation therapy in locally recurrent rectal cancer. *Clin Transl Radiat Oncol.* 2020;24:41-48. doi:10.1016/j.ctro.2020.06.007

13. Fahy M, Kelly M, Power-Foley M, Nugent TS, Shields CJ, Winter DC. The role of intraoperative radiotherapy in advanced rectal cancer: a meta-analysis. *Colorectal Dis.* 2021;23:3145-55. doi:10.1111/codi.15698
14. Liu B, Ge L, Wang J, Chen YQ, Ma SX, Ma PL, et al. Efficacy and safety of intraoperative radiotherapy in rectal cancer: A systematic review and meta-analysis. *World J Gastrointest Oncol.* 2021;13:69-86. doi:10.4251/wjgo.v13.i1.69
15. Dubois JB, Bussières E, Richaud P, Rouanet P, Becouarn Y, Mathoulin-Pélissier S, et al. Intra-operative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. *Radiother Oncol.* 2011;98:298-303. doi:10.1016/j.radonc.2011.01.017
16. Amarnath S. The role of intraoperative radiotherapy treatment of locally advanced rectal cancer. *Clin Colon Rectal Surg.* 2023;37:239-47. doi:10.1055/s-0043-1770718
17. Erkaya M, Karahan S, Oruc M, Amarnath SR, Miller JA, Alipouriani A, et al. The Impact of Intraoperative Radiotherapy on Margin Positive Locally Advanced Rectal Cancer: A Propensity-Matched Analysis of The National Cancer Database. *J Surg Oncol.* 2025;132:1257-65. doi:10.1002/jso.70102.
18. Costa F, Sarmiento S, Sousa O. Assessment of clinically relevant dose distributions in pelvic IORT using Gafchromic EBT3 films. *Phys Med.* 2015;31:692-701. doi:10.1016/j.ejmp.2015.05.014
19. Esposito A, Sakellaris T, Limede P, Costa F, Cunha LT, Dias AG, et al. Effects of shielding on pelvic and abdominal IORT dose distributions. *Phys Med.* 2016;32:1257-65. doi:10.1016/j.ejmp.2016.09.009
20. Klink CD, Binnebösel M, Holy R, Neumann UP, Junge K. Influence of intraoperative radiotherapy (IORT) on perioperative outcome after surgical resection of rectal cancer. *World J Surg.* 2014;38:992-6. doi:10.1007/s00268-013-2313-1
21. Kusters M, Valentini V, Calvo FA, Krempien R, Nieuwenhuijzen GA, Martijn H, et al. Results of European pooled analysis of IORT-containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastases. *Ann Oncol.* 2010;21:1279-84. doi:10.1093/annonc/mdp501
22. Zhang Q, Tey J, Yang Z, Li P, Peng L, Fu S, et al. Adjuvant chemoradiation plus intraoperative radiotherapy versus adjuvant chemoradiation alone in patients with locally advanced rectal cancer. *Am J Clin Oncol.* 2015;38:11-6. doi:10.1097/COC.0b013e3182868ce0
23. Mirnezami R, Chang GJ, Das P, Chandrakumaran K, Tekkis P, Darzi A, et al. Intraoperative radiotherapy in colorectal cancer: systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol.* 2013;22:22-35. doi:10.1016/j.suronc.2012.11.001
24. Khan Z, Rooney M, Das P, Ludmir EB, Koay EJ, Smith GL, et al. Intraoperative Radiation After Pelvic Short Course Radiation-Based Total Neoadjuvant Therapy for Patients With Rectal Adenocarcinoma at High Risk for Local Recurrence. *Clin Colorectal Cancer.* 2022;21:204-11. doi:10.1016/j.clcc.2022.01.002.
25. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CA, Putter H, Kranenbarg EM, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22:29-42. doi:10.1016/S1470-2045(20)30555-6
26. Conroy T, Bosset JF, Etienne PL, Rio E, François É, Mesgouez-Nebout N, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2021;22:702-15. doi:10.1016/S1470-2045(21)00079-6
27. Dijkstra EA, Nilsson PJ, Hospers GA, Bahadoer RR, Meershoek-Klein Kranenbarg E, Roodvoets AG, et al. Locoregional failure during and after short-course radiotherapy followed by chemotherapy and surgery compared with long-course chemoradiotherapy and surgery: a 5-year follow-up of the RAPIDO trial. *Ann Surg.* 2023;278:e766-72. doi:10.1097/SLA.0000000000005799
28. Fernández-Martos C, Pericay C, Aparicio J, Salud A, Safont M, Massuti B, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo Cancer de Recto 3 study. *J Clin Oncol.* 2010;28:859-65. doi:10.1200/JCO.2009.25.8541
29. Holman FA, Bosman SJ, Haddock MG, Gunderson LL, Kusters M, Nieuwenhuijzen GA, et al. Results of a pooled analysis of IORT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres. *Eur J Surg Oncol.* 2017;43:107-17. doi:10.1016/j.ejso.2016.06.003
30. Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg.* 2013;100:1009-14. doi:10.1002/bjs.9192
31. Voogt EL, Van Rees JM, Hagemans JA, Rothbarth J, Nieuwenhuijzen GA, Cnossen JS, et al. Intraoperative electron beam radiotherapy (IORT) versus high-dose-rate intraoperative brachytherapy (HDR-IORT) in patients with an R1 resection for locally advanced or locally recurrent rectal cancer. *Int J Radiat Oncol Biol Phys.* 2021;111:753-62. doi:10.1016/j.ijrobp.2021.02.006
32. Costa F, Sarmiento S, Gomes D, Magalhães H, Arrais R, Moreira G, et al. In vivo dosimetry using Gafchromic films during pelvic intraoperative electron radiation therapy (IORT). *Br J Radiol.* 2016;89:20160193. doi:10.1259/bjr.20160193.
33. Sarmiento S, Costa F, Pereira A, Lencart J, Dias A, Cunha L, et al. Attenuation measurements show that the presence of a TachoSil surgical patch will not compromise target irradiation in intra-operative electron radiation therapy or high-dose-rate brachytherapy. *Radiat Oncol.* 2015;10:7. doi:10.1186/s13014-014-0316-1
34. Roeder F, Fastner G, Fussl C, Sedlmayer F, Stana M, Berchtold J, et al. First clinical application of image-guided intraoperative electron radiation therapy with real-time intraoperative dose calculation in recurrent rectal cancer: technical procedure. *Radiat Oncol.* 2023;18:80. doi:10.1186/s13014-023-02374-6