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ESTRO/ACROP IORT recommendations for intraoperative radiation therapy in primary locally advanced rectal cancer

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ABSTRACT

Summary: Carcinoma of the rectum is a heterogeneous disease. The clinical spectrum identifies a subset of patients with locally advanced tumours that are close to or involve adjoining structures, such as the sacrum, pelvic sidewalls, prostate or bladder. Within this group of patients categorized as "locally advanced", there is also variability in the extent of disease with no uniform definition of resectability. A practice-oriented definition of a locally advanced tumour is a tumour that cannot be resected without leaving microscopic or gross residual disease at the resection site. Since these patients do poorly with surgery alone, irradiation and chemotherapy have been added to improve the outcome. Intraoperative irradiation (IORT) is a component of local treatment intensification with favourable results in this subgroup of patients.

International guidelines (National Comprehensive Cancer Network (NCCN) guidelines) currently recommend the use of IORT for rectal cancer resectable with very close or positive margins, especially for T4 and recurrent cancers.

We report the ESTRO-ACROP (European Society for Radiotherapy and Oncology - Advisory Committee on Radiation Oncology Practice) recommendations for performing IORT in primary locally advanced rectal cancer.

Contents

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1. Introduction

The available evidence favours the use of neoadjuvant chemoradiation to maximize local control in cT3–4 and N+ rectal cancer disease stages. Meta-analysis considering preoperative or postoperative radiotherapy alone versus chemoradiation strategies has shown significant improvement in local control through the use of preoperative chemoradiation [35]. Surgery is the decisive component in curing rectal cancer and achieving local control, but even where expert-proven total mesorectal excision (TME) has been performed, the local recurrence rate for surgery alone is up to 21% in unselected tumour stages [1]. In pelvic lymph node metastatic patients, local recurrence of over 33% has been reported after unilateral lymph node dissection and 14% after bilateral lymph node dissection [2]. TME surgery and neoadjuvant chemoradiation are standards in contemporary practice.

After surgery alone, performed using accredited best practices, the results describe [1] a local recurrence rate based on T stage (T3, 12.2%; T4, 21.4%), N status (N+, 16%; N-, 3.6%), and circumferential margin involvement (yes, 20%; no, 6.2%). This general pattern of local relapse can be further analysed in terms of topographic distribution within the pelvic anatomy. After total mesorectal excision (TME), the presacral subsite is the predominantly involved pelvic area, accounting for 3.6% of all recurrences and 32% of observed local recurrences. Other identified sites of recurrences are lateral (18%), anterior (18%), anastomosis (24%) and perineum (5%).

The potential origin of local recurrence after rectal cancer treatment in the presacral space has been studied by Kusters and coworkers [3]. It can be hypothesized that mobilizing the rectum causes lymph fluid and tumour cells left behind after TME to flow into the lateral lymphatic system. The fluid then leaks due to gravity and is collected in the presacral seroma.

The anatomical involvement of recurrences after adjuvant or neoadjuvant radiotherapy alone or chemoradiation describes an estimated 5-year locoregional control of 91% [4]. The MD Anderson study (554 patients, from 1989 to 2001) reports 36 patients with locoregional recurrence at 43 sites: 28 (65%) were in-field, 7 (16%) marginal, and 8 (19%) out-field radiotherapy recurrences. The total rate of presacral in-field recurrences was 41%, and the low pelvic region was predominant for both preoperative (60%) and postoperative (43%) irradiation. N1–2 disease status was predictive of in-field locoregional recurrence in multivariate analysis, while T4, downstaging, and pN status were significant in univariate evaluation. Recent analysis have identified initial enlarged pelvic nodal disease by MRI assessment as a significant adverse factor for local control using conventional multimodal treatment [5,6].

In this guideline/publication, the ESTRO Task Force reports recommendations for performing IORT in primary locally advanced rectal cancer (LARC). These recommendations aim to define clinical indications, patient-selection criteria and technical aspects in a multidisciplinary setting in order to standardize treatment modalities across centres already using IORT and to help institutions that intend to start IORT programmes for primary LARC.

2. Evidence review and update

We performed a retrospective review of the literature between 1995 and 2017, recording treatment strategies, disease characteristics and clinical results obtained with multimodal treatment including an intraoperative irradiation component. Table 1 contains data evaluated in 21 reports (2,843 patients analysed) in resected primary LARC [7–27]. In 2013, Mirnezami et al. [28] published a systemic review and meta-analysis evaluating IORT in the treatment of LARC; those authors concluded that IORT may improve oncological outcome in such patients.

3. Pre-treatment investigations

3.1. Patient selection for IORT

Patients diagnosed with LARC are eligible to be re-evaluated and discussed by a multidisciplinary tumour board (MTB) for multimodal treatment strategies including exploratory laparotomy and IORT.

Table 2 shows patient selection for IORT: disease, treatment sequence and radiation dose recommendations.

Studies required for candidate selection include the following:

- Pathology of adenocarcinoma
- History and physical examination
- ASA score (CPEX cardiopulmonary exercise testing, optional)
- Conventional blood test
- CEA
- Multidetector computed tomography
- MRI
- Endoscopic ultrasonography
- Chest CT

Potential supportive actions to be considered preoperatively:

- Self-expanding stent
- colostomy

Table 1
Clinical results in primary locally advanced rectal cancer: 3 decades review (2.659 patients).

Author (year)/study period	Median follow-up	# patients	Stage	Treatment			Surgery	5 year LC	5 yearDFS/OS
				RT	CT	IORT			
Nakfoor et al[7] (1998) 1978–1996	41 months	73	T_3T_4	Pre45-50.4 Gy	5FU	10–12.5 Gy 12.5–20 Gyelectrons	R0 45 (62%) R + 28 (38%)	89%65%	63% OS32% OS
Weinstein et al[8] 1995 1987-1992	36 months	11	T_3T_4NxM0	Pre 45 Gy	5FU	R0 10 Gy R1 15 Gy R2 20 Gy electrons	R0 9R + 2	100%	OS 67%(3 year)
Azinovic et al[9] (2011)	n.s.	59	T_3T_4	Pre 46 GyPost 13 Gy	5FU	10–15 Gy electrons	R0	1, 4, 93%	77% OS, 52% OS
Sole et al[10], (2014), 1995–2010	72.6 months	335	cT_{3-4} 93%, cN + 69%	Pre, 45–50.4 Gy	Tegafur, Induction (62%), Folfox 4, Adjuvant 73%	10–15 Gy electrons	R0 323, R1 12	Infield 3,3%, 92% LRC (5–10 year)	75% OS, 62% OS, (10 year)
Krempien et al[11], (2006), 1991–2003,	61 months	210	II-III-IV	Pre 88, Post 122, Median 41.4 Gy	Pre 88, Post 122, 5 FU 93%	8–18 Gy, (median 10 Gy) electrons	R0 192, R1/2 18	93%, 91% (10 year), 98% inside IOERT field (5 year)	69% OS, 51%, (10 year), 66% DFS
Kusters et al[12], (2010), Up to 2005	56 months	605	T_3 71%, T_4 29%	Pre 45–50 Gy	5 FU 64%, Postop CT 42%	10–12.5 Gy electrons	R0 89%, R1 11%	88%	67% OS
Harrison et al[13], (1998), 11/92–12/96	17.5 months	22	Primary unresectable	Pre 50 Gy	5FU-LV	10–20 Gy, brachytherapy	R0, R+	81% (2 year), R0 92% (2 year), R1 38% (2 year)	69% DFS, (2 year), R0 77% DFS (2 year), R1 38% DFS (2 year)
Nuyttens et al[14], (2004), 1997–2000	36 months	18	LARC	Pre/post	none,	10 Gy, brachytherapy	Margins $\leq$ 2 mm	19% (3 year)	R0 37% OS, R + 26% OS
Gunderson et al[15], (1997), 1982–1993	minimum follow-up of 18 months	22	LARC	Pre 50 Gy	5 FU	8–20 Gy (median 12.5 Gy), electrons	R0 83%	75%, 92% (crude LC rate in R0)	64% OS
Dubois et al[16], (2011), 1993–2001	60.1 months	72	$_cT_3$ 89%, $_cN$ + 33%, $_cN0$ 64%	Pre 40 Gy	Adjuvant 25%	15 Gy, electrons	n.s.	92%	70% OS
Roeder et al[17], (2007), 1991–2004, ,	59 months	243	T_3T_4	41.4 Gy, 88 pre, 122 post	88 pre	Median 10 Gy, R0 10 Gy, R1 12 Gy, R2 15 Gy, electrons	R0 224, R1/2 19	92%, Infield ~~R~~ 97% LC	n.s.,
Kusters et al[18], (2009), 1994–2006	n.s.	290	LARC	pre 45–50.4 Gy, 86 pre	204 pre, 39 post	, R0 10 Gy, R1 12.5 Gy, R2 15–17.5 Gy, electrons	R0, R+	87%, 47% of LR outside IORT field.	Median follow-up time for, surviving patients 45 months
Zhang et al[19], (2015), n.s.	78 months	71	$_pT_4N_0/_pT_{1-4}N_+$	45–50 Gy, N + post	5FU + CDDP + oxali, 4–6 < years	10–20 Gy, electrons,	R0 67 (94.4%), R1 4 (5.6%)	90%	75% OS, 69% DFS
Mathis et al[20], (2008), 09/1981–02/2007,	n.s.	106	Unresectable, LARC, (Colon)	45–55 Gy	5 FU	7.5 – 25 Gy, Median 12.5 Gy electrons,	R0, R2	86%, (40 colon)	49% OS,
Sadahiro et al[21], (2004), 1991–2001,	67 months	99	$T_{3-4}N_XM_0$	20 Gy	UFT	15–25 Gy, electrons	98%	98%	79%
Alberda et al[22], (2014), 1996–2012	n.s.	31	LARC	45–50 Gy, (some patients 25 Gy in 5 fractions)	n.s.	10 Gy brachytherapy	R0 $\leq$ 2 mm, R1	84%	n.s.
Valentini et al[23], (2009), 1991–2006	31 months	100	T_4M_0	45–55 Gy	5 FU	10–15 Gy, electrons	R0 78%,	100%, R0 90%	59% OS, R0 68% OS, R1-R2 22% OS
Brady et al[24], (2017), 1999–2015	n.s.	37	LARC	50 Gy	5 FU	9–12 Gy, electrons	R + 24%,	84%, 5.4% infield	mean OS, 47 months
Zhang et al[25], (2014), 1996–2007	72.9 months	45	$_pT_3N_0M_0$	none	Adjuvant, 5FU, CDDP, Oxali, LV	15–25 Gy, electrons	TME (95%)	84%	84% OS, 71% DFS
Holman et al[26], (2016), 1981–2010,	52 months	417	T_4	45–54 Gy, 78% pre	5 FU, Adjuvant 19%	R0, R1 10–12.5 Gy, R2 > 15 Gy electrons	R0 73%	81% LC,	56% OS, (all patients), 64% OS (R0), 55% DFS
Calvo et al[27], (2015), 1/00–12/13	62 months	54	cT4NxM0	50 Gy	Tegafur, Neo FOLFOX-4x2 (77%), Adjuvant (73%)	10–20 Gy, electrons	R0 83%	77%	75% OS, 67% DFS

LARC: locally advanced rectal cancer, LC: local control, OS: overall survival, DFS: disease-free survival, R0: negative resection margins; R1: microscopic positive resection margins; R2: gross residual tumor, n.s.: not stated.

Table 2
Patient selection for IORT: disease, treatment sequence and radiation dose recommendations.

Disease status	
Clinical setting	primary locally advanced rectal cancer
Indications	Potentially Resectable
Stage	T3-T4
Treatment	
Preoperative chemo/RT followed by resection + IOERT boost	
Radiotherapy dose	
IORT boost	10 to 12.5 Gy for negative resection margins (R0) 12.5 to 15 Gy for microscopic positive resection margins (R1) 15 to 20 Gy for macroscopic or gross residual tumor (R2)
External Beam Radiation Therapy (EBRT)	45–50 Gy (in 25–28 fractions)

Additional studies in high risk patients to be considered as clinically indicated:

- PET-CT
- Laparoscopy

A significant proportion of unresectable or locally advanced patients will be recommended for neoadjuvant strategies (including a preoperative chemoradiation component) and should be restaged before laparotomy in terms of performance status, imaging and CEA evolution.

3.2. Pre-treatment clinical staging imaging

The clinical stage of patients is assessed by means of abdominal and pelvic computed tomography (CT) and magnetic resonance imaging (MRI), to verify the eventual loss of the fat plane interphase towards critical organs or structures, hence the inability to perform an upfront R0 resection is likely to be unfeasible. In addition, patients undergo routine laboratory tests and chest CT and endoscopic ultrasound to evaluate the depth of invasion.

3.3. External beam radiotherapy

Patients with primary LARC who are candidates for intensive local strategies including EBRT, IORT, with or without induction systemic chemotherapy, have been treated and reported on over the last 4 decades [29,30]. Fluopyrimidin-sensitized full-dose preoperative EBRT using multiple-field techniques, including 3D conformal or (rotational) intensity-modulated irradiation (3D CRT, IMRT, VMAT, Helical Tomotherapy), have been used based on institutional protocols and technological availability. Extended pelvic fields to 45 Gy in 25 fractions over 5 weeks, with optional boost fields to tumour plus 2–2.5 cm, are carried out to reach total doses of 50.4–54 Gy. If external iliac nodes are at risk due to tumour adherence or fixation to anterior structures (bladder, prostate, cervix, uterus), IMRT in combination with image-guided radiotherapy (IGRT) can be useful in decreasing small-bowel volumes [32].

4. Surgical procedures

4.1. Surgical factors

Following a course of preoperative chemoirradiation, surgical exploration is undertaken in a variable interval range (institutional practice) 4–12 weeks later. The delay allows ongoing tumour downsizing after preoperative treatment, as well as the resolution of treatment-induced acute side effects. Accurate preoperative staging is important because IORT primarily benefits those patients who can undergo a total tumour resection. Ideal patients are those with a high Karnofsky score, who are willing to undergo major surgery that may include stoma creation and possible pelvic exenteration. There should be no distant metastases to liver, lungs or peritoneum, and no enlarged lymph nodes in the para-aortic or groin area. A well-defined oligometastatic status may be reconsidered if radical pelvic surgery is attempted. Invasion of pelvic nerves or the sciatic notch (i.e. no sciatica or sacral/buttock pain) or evidence of tumour invading or wrapped around the iliac vessels or ureters are unfavourable features. In order to assess the extent of the tumour, preoperative evaluation ordinarily includes an abdominal and rectal exam, sigmoidoscopy and/or colonoscopy, abdominal, pelvic and chest computed tomography (CT) or MRI. Ultrasound-guided endoscopy adds relevant information to the evaluation in terms of nodal and mural extension, and the PET-CT scan provides information on nodal involvement and distant metastatic disease. If there is any question of involvement of the urologic system, an intravenous urogram or MRI, urology consultations and cystoscopy may be required. If a colostomy is possible, preoperative evaluation by an enterosomal therapist should be considered. Surgery is usually best carried out via a midline incision that allows extension as necessary and permits multiple stomas. Laparoscopic approach is an alternative option [31]. Adhesiolysis and abdomen evaluation for liver and peritoneal metastases is mandatory. If metastases that are not resectable with curative intent are found (i.e. solitary liver metastasis), intraoperative irradiation is not performed and treatment ends with palliative resection (or only EBRT). If no metastases are evident or are limited and can be resected to effect a cure, the patient undergoes abdominoperineal resection, low anterior resection or pelvic exenteration, depending upon the extent and location of the tumour. En bloc wide resection is the best option: total resection of the tumour is desirable, but if that cannot be done, debulking is recommended. Haemostasis after resection is important because pooled blood covering the tumour bed may decrease the IORT dose at depth (bolus effect). If an anastomosis is to be performed, it is completed after the delivery of IORT. To minimize the likelihood of complications, it is preferable to mobilize the left colon completely and use unirradiated bowel (descending colon) for the proximal end of the anastomosis.

4.2. IORT factors

The decision to treat with IORT is based on the surgical findings, margin status assesment and pretreatment physical examination and imaging studies, and is an intraoperative collaborative judgment made by the surgeon and the radiation oncologist. It is crucial to define the area at highest risk for subsequent local relapse to determine the optimal position for the IORT field. Margins of resection are determined by frozen-section pathologic analysis of the surgical specimen and sometimes the tumour bed.

5. IORT procedure: post resection

5.1. IORT: Treatment methods and techniques

IORT for primary LARC has predominantly been delivered with megavoltage electrons produced by a medical linear accelerator. Brachytherapy or orthovoltage data do not currently allow for equivalent scientific analysis or recommendations. As such, the term IOERT will be used in the remainder of the report to separate high energy electron-based IORT form other forms of IORT. A bolus

should be used depending on electron beam energy to ensure adequate surface dose. Accumulation of intra surgical fluid could influence radiation penetration in an unpredictable way and should be avoided. The electron beam energy and dose of IORT are determined by the resection status and geometry of the treated field. Shielding parts inside the tumoure bed is not recommended due to the dosimetric uncertainties introduced by such action. Instead, temporal displacement by mechanical distraction should be considered as best option to avoid irradiation of dose-sensitive structures at risk. Surgical clips can help to define the dominant area at risk selected for irradiation. Surgical retractors for the displacement of remaining uninvolved movable structures such as rectal stump, bladder, prostate, uterus, vagina, small bowel, descending colon and ureters are most helpful for properly exposing the radiation target (presacral area or posterior pelvic space) and for expediting positioning of the IORT applicator. Displacement of normal tissue should be carefully documented using iconographic documentation of the final pre- and post-intraoperative irradiation assemblage.

6. Radiation target definition

Conditions for considering IOERT boost: tumour adherence after preoperative chemoirradiation; inadequate soft-tissue radial margins (close < 1 cm) and high risk for relapse, including N+ status or adherence to initial staging. Patients with gross residual cancer, with microscopically positive margins or with close (<2–5 mm) radial soft-tissue margins are candidates for IOERT. The tumour bed can be marked with sutures to facilitate later positioning and direct the IOERT applicator, which is selected according to the location and size of the area to be irradiated. The internal diameters of circular applicators of selection in the pelvic space typically range from 4 to 10 cm. Applicator size is selected to allow full coverage of the high-risk area, which is generally on the presacrum or pelvic sidewall. Usually, the largest applicator that will fit into the area is preferred. The shape is chosen so that the geometry fits the specific situation of tumour versus normal tissue, which can be difficult if the high-risk area is located in an anatomically confined region such as the pelvis. Most have bevelled ends of 15° or 30°, enabling good apposition of the applicator to slope surfaces in the pelvis in order to maximize dose homogeneity. It is important that the applicator is placed so that the tumour or tumour bed is fully covered, sensitive normal tissue is not included in the beam and there is no fluid build-up in the treatment area. The applicator not only directs the electron beam accurately to the high-risk area, but also serves to move sensitive normal tissue out of the way, especially the small bowel and ureter. Visceral retraction and packing are also usually necessary. If a distal rectal stump remains for later anastomosis, it should also be excluded from the IOERT field by retraction with the applicator and packing or with the use of lead sheets, which can be cut out to block sensitive normal tissue that cannot be removed from the path of the beam. During treatment, suction catheters are positioned to minimize fluid build-up within the applicator. Most IOERT treatments in rectal cancer are given via a transabdominal approach, since the area of concern is usually the posterior presacrum or posterolateral pelvic sidewall. A perineal port is occasionally used after abdominoperineal resection to treat ~~a~~ very low-lying tumour involving the coccyx or distal presacrum, distal pelvic sidewall or portions of the prostate, and base of the bladder when an exenteration is not performed. After the IOERT applicator has been positioned, it is docked to the linear accelerator and the IOERT is delivered. To guarantee the sterile field throughout the procedure, before irradiation, sterile drapes should cover the surgical bed and the part of the collimator inside and near the surgical bed.

Doses of radiation delivered intraoperatively are in the range of 10–20 Gy with lower doses being given for minimal residual disease (narrow or microscopically positive margins) and higher doses for gross residual disease after maximal resection. For patients undergoing complete resection with negative but narrow margins (R0), the IOERT dose is usually 10–12.5 Gy, whereas for patients undergoing subtotal resection with microscopically positive margins (R1), it is 12.5–15 Gy. For patients with macroscopic or gross residual disease after resection (R2), 17.5–20 Gy is recommended. Electron energies used are 6–15 MeV, depending on the thickness of the residual tumour. The prescribed dose is specified at the 90% isodose.

The whole process can be summarized as follows:

1. Definition of radiation target: tumour bed assessment; surgical margin status (inspection of the surgical field and the posterior aspect of the surgical specimen).
2. Normal uninvolved tissue to be excluded (mobilized out) from the IOERT radiation volume: rectal remnant (if present); intrapelvic organs uninvolved (bladder, prostate, uterus, vagina, ovaries); distal colon; small bowel; ureters.
3. Normal tissue at risk to be included in the radiation target volume: presacral area; vascular and lymphatic structures (iliac regions).

The further considerations necessary for IORT using electron beam technology are:

1. Applicator selection: IOERT applicator adaptation (Fig. 1) to the post-surgical bed at risk in terms of:

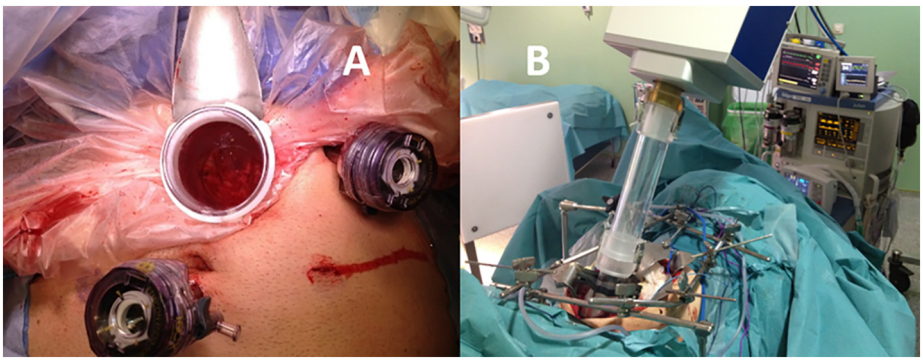

Fig. 1. An IORT electron procedure view: A. Laparoscopic anterior-resection procedure: the retractor is asureing the exclusion of the rectal remant fron the IOERT field encompassing the presacral space. B. Open IOERT procedure: the multiple retractors exclude normal uninvolved organs and tissues (ureters, centro-pelvic organs, small bowell, etc.) from the target pelvic area.

a. Size (diameter): able to encompass the presacral space or lateral pelvic walls at risk (the largest able to fit inside the pelvic cavity). The availability of diameters of between 4 and 10 cm is a safe range for applicator sizes.
b. Bevel angle: bevelled ends of between 30° and 45° are recommended to appropriately encompass the surgical bed with residual disease or at risk of recurrence and to adapt to the anatomical configuration of the presacral region in the pelvic cavity. The same criteria apply in the case of predominantly lateral pelvic wall involvement.

2. Electron energy selection: 90% isodose should encompass in depth the presacral tissue content with a safety dosimetric margin (0.1–0.5 cm). Fluid stability is key for appropriate energy selection. This depth can be estimated by real-time intraoperative measurements, together with data obtained from the preoperative CT scan. Meticulous haemostasis and intra-pelvic surgical fluid management are relevant for electron energy selection. In the event of fluid instability at the radiation target, a higher electron energy level selection is an alternative. When bone tissue is part of the target volume a higher electron energy could be selected. If the surface dose of the chosen applicator is<90%, bolus with an appropriate thickness should be applied.
3. Dose selection (single fraction boost component): resection specimens at low risk after favourable dissection procedure doses of 10 to 12.5 Gy are recommended. Recommended doses for a specimen with a close margin or margin with suspected/-confirmed cancer range from 12.5 to 15 Gy. After laborious vascular and/or soft-tissue dissection with suspected residual cancer, 15 to 20 Gy should be considered.
4. In the case of multiple IOERT target volumes, overlapping of the corresponding irradiation volumes should be avoided, as significant hot and/or cold spots are likely.
5. In vivo dosimetry is strongly recommended as a quality-assurance procedure.

7. Treatment delivery

Prior to dose delivery, the appropriate physical and dosimetrical parameters (electron energy, applicator size, length and bevel angle, monitor units, bolus choice, use of additional shielding inside the irradiated area) should be checked by a medical physicist as well as by the physician (radiation oncologist) in a four-eyes principle. Usually, a medical physicist or a Radiation Therapist (RTT) aligns the gantry to the applicator for docking and enters the data in the control console. During irradiation (approximately 1–2 min, depending on dose and dose rate), all personnel must be evacuated from operation room except the patient for radiation protection purposes. Patients should be carefully monitored by videocamera during irradiation and vital parameters should be monitored and be visible outside the operating room. In the event of an emergency, irradiation should be stopped immediately and nurses, anaesthesiologists and surgeons should be prepared to enter the operating room at any time immediately after cessation of irradiation.

8. Dose prescription

For tumours resected without identifiable residual gross tumour, doses in the range of 10.0–12.5 Gy are applied, depending on the extent of suspected residual microscopic malignant disease or high-risk area for recurrence in the presacral space, lateral pelvic walls or a combination of targets. For close margin with suspected/confirmed cancer, the recommended dose may range from 12.5 to 15 Gy. For gross residual or unresected tumours, doses of 15–20 Gy have been employed. A library of predefined isodose curve distribution for a range of IORT applicator diameters, bevelled end shapes and electron beam energies has to be available for intraoperative consultation. These dose values should be prescribed at the 90% isodose curve. A medical physicist should be involved pre- or intra-operatively in the choice of bolus or corrections for special situations (e.g. residual air gap, additional shielding, bone tissue density correction).

9. Applicator removal

After treatment has been completed, special attention should be paid to removal of the applicator in order to avoid any trauma to surrounding tissues and possible bleeding. In the event of bleeding during the irradiation time, it is advisable to aspirate the blood first in order to clearly visualize the end of the collimator in contact with the patient's tissues and allow for a safe manoeuvre. Removal of the applicator may be performed by the surgeon or by the radiation oncologist with the assistance of a nurse.

10. Recording and reporting

Clinical and dosimetry forms should be filled out with all relevant patient, tumour and treatment parameters. Clinical data should include demographics, performance status, symptoms and serum tests, including CEA, comorbidities and Charlson comorbidities index. Tumour-related data should include imaging studies, biopsy report, clinical and pathological stage, grading and possible biomolecular studies. Treatment data should include neoadjuvant treatments, the surgical report and the main characteristics of the IOERT procedure, including collimator diameter, bevel angle, bolus, beam energy, dose prescription and duration of the procedure. As mentioned before, in vivo dosimetry is strongly recommended as a quality-assurance procedure. Radiation target contents should be described: organs and structures included in the IOERT radiation beam. Radiation protection of normal uninvolved tissues: description of temporary mobilization or intrafield customized protection (in particular, rectal stump and ureters).

Preoperative MRI and CT scans can be obtained to identify the primary tumour, regional lymph nodes and critical organs in order to design a provisional treatment plan. No fully reliable treatment planning systems currently exist for intraoperative irradiation; however, the availability of preoperative images may help with identifying anatomical structures to guide the positioning of the applicator. Whenever obtained, all these imaging data should be included in the patient's final documentation. Photographs of final applicator positioning and surface anatomy in the IOERT target are recommended.

Intraoperative ultrasound can also be helpful in some cases to verify residual tumour thickness in depth and the location of critical structures, such as ureters and major vessels.

The final documentation of the IOERT procedure should also include the surgical notes and the anaesthesiology report.

Table 3 reports the parameters for the IOERT electron beam procedure in primary locally advanced rectal cancer.

11. Recommendation on patient care

11.1. Care during the course of IOERT

The sterile field should be guaranteed throughout the IOERT procedure. Before irradiation, sterile drapes should cover the surgical field and the part of the collimator inside and near the surgical bed. Patients should be carefully monitored by videocamera during irradiation and vital parameters should be monitored and be visi-

Table 3
Parameters for IORT electron beam procedure in primary locally advanced rectal cancer.

IORT Parameters	
Target volumen description	- Tumour residue (R0, R1, R2) - Normal tissues exposed - Normal tissues protected/mobilized - Special conditions: ■ Vascular manipulation ■ Others
IORT factors	- Applicator size /diameter ■ Bevelled end (degrees) - Electron energy ■ Isodose prescription - Total dose - Number of fields ■ Report every parameter for every field ■ Overlapping (yes / no) ■ Field–within-a-field (description) - Protections - Fluid stability - Time of beam on - Gantry angulation - In vivo dosimetry (system/site measured)
Integrated pre-IORT treatment factors	- Surgery: type of resection (R0, R1, R2) ■ Quality of Total Mesorectal Excision (TME) - Preoperative ■ Chemoradiation (CRT) (short vs long course) ■ Induction chemotherapy + CRT (short vs long course) - Postoperative ■ CRT ■ CRT + adjuvant chemotherapy

ble outside the operating room. In the event of an emergency, irradiation should be stopped immediately and nurses, anaesthesiologists and surgeons should be prepared to enter the operating room at any time immediately after cessation of irradiation.

11.2. Post-treatment patient care and follow-up

Patients treated with IOERT for LARC require thorough care. All vital and clinical parameters should be monitored in the days following the procedure, and special attention should be paid to blood tests, including renal and liver functions, bowel movements and onset of new symptoms and signs.

After the IOERT procedure combined with surgical resection, the patient may receive further treatment, including postoperative adjuvant systemic treatment. Therefore, the follow-up schedule starts after treatment completion and usually does not substantially differ from that of locally advanced rectal cancer treated without IOERT. During imaging studies, special attention should be paid to any tissue potentially included in the IOERT volume such as sacrum, rectal remnant and ureters.

12. Treatment tolerance and adverse effects

IOERT dose-sensitive structures in the pelvic anatomy include peripheral nerves, ureters, bladder, small intestine, rectal stump, ovaries, urethra and vagina. The uterus and prostate are considered relatively resistant to escalated doses, including IOERT boost. Neuropathy is dose dependent: 3% for 12 Gy boost and 23% for 15 Gy boost. Ureter dysfunction is reported in 56% of ureters included in the IOERT field (any dose) and in < 15% of ureters not included (15).

Late-onset adverse events described in the updated results included small-bowel obstruction in 14% of patients, wound infection/breakdown in 9%, fistula with abscess in 8%, bladder dysfunction in 7%, sexual dysfunction in 6%, enteritis/proctitis in 3%, and abdominopelvic abscess in 3% (20).

13. Conclusions and future directions

The treatment of locally advanced or clinical stage T4 primary rectal cancer has evolved over the past 30 years. The current international consensus recognizes the value of preoperative strategies with chemoradiation and the potential of IOERT boost in cT4 patients (NCCN, ESMO guidelines). Progress in surgical methodology can incorporate an IORT component, which is feasible in laparoscopic approaches [31].

It is of methodological scientific interest to randomly compare standard treatment ± IORT, but such trials did not accrue well in the United States or Europe and were closed. Alternatively, feasible trials may focus on standardizing optimized local treatment of EBRT, resection and IOERT or HDR-IORT, optimal chemotherapy/targeted agents/immunotherapy during and after EBRT, and the presence or absence of dose modifiers during IORT.

1. IOERT is a feasible, tolerable, and efficient radiation-boosting technique that can be explored in tailored treatment for primary LARC patients.
2. Recommendations for guiding tailoring of IOERT in primary disease in terms of promoting local tumour control include the following:
   - The unfavourable nature of nodal and margin positivity together with no downstaging effects. IOERT is an alternative for further dose-escalation and target volume redesign to improve local control under these conditions.
   - The tendency of T4 stage to recur in anterior pelvic structures, although IOERT has also been reported to promote high local control rates in this disease category.
   - The excellent local results obtained in more favourable disease risk factors, which might make it advisable to reconsider the need for radiation treatment intensification and implement strategies with short-course preoperative pelvic irradiation including an IOERT component [33,34]
   - The use of adjuvant chemotherapy should be recommended after IOERT treatment in patients with proven adverse local features.
3. In-vivo-dosimetry and intra-operative imaging could improve the accuracy, reproducibility and documentation and provide data for evaluation and tailoring of IOERT
4. Tailored IOERT may be further defined by establishing correlations between biological equivalent dose (BED) calculations, topographic patterns of recurrence, and prognostic features for local effects. This information is not currently available. It will open the clinical scope for using single-dose IOERT alone, with field-within-a-field dosimetric modulations, and in combination with systemic therapy in the oligometastatic model. An individualized approach is recommended for the minority of patients with clinical or radiological local disease progression during preoperative pelvic irradiation component.

Disclosures

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