Radiotherapy and Oncology 149 (2020) 150–157

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

ESTRO IORT Task Force/ACROP recommendations for intraoperative radiation therapy with electrons (IOERT) in breast cancer

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ARTICLE INFO

Article history:
Received 30 April 2020
Accepted 30 April 2020
Available online 13 May 2020

Keywords:
Breast cancer
Accelerated partial breast irradiation
Intraoperative radiation therapy
Electron beam
Single dose radiotherapy

ABSTRACT

The aim of this review is to provide a comprehensive overview of the role of intraoperative radiation therapy with electrons (IOERT) in breast conserving therapy (BCT), both as partial breast irradiation (PBI) as well as anticipated boost ("IOERT-Boost"). For both applications, the criteria for patient selection, technical details/requirements, physical aspects and outcome data are presented.

IOERT as PBI: The largest evidence comes from Italian studies, especially the ELIOT randomized trial. Investigators showed that the rate of in-breast relapses (IBR) in the IOERT group was significantly greater than with whole breast irradiation (WBI), even when within the pre-specified equivalence margin. Tumour sizes >2 cm, involved axillary nodes, Grade 3 and triple negative molecular subtypes emerged as statistically significant predictors of IBR. For patients at low risk for in-breast recurrence (ASTRO/ESTRO recommendations), full dose IOERT was isoeffective with standard WBI. Hence, several national guidelines now include this treatment strategy as one of the standard techniques for PBI in carefully selected patients.

IOERT Boost: The largest evidence for boost IOERT preceding WBI comes from pooled analyses performed by the European Group of the International Society of Intraoperative Radiation Therapy (ISIORT Europe), where single boost doses (mostly around 10 Gy) preceded whole-breast irradiation (WBI) with 50 Gy (conventional fractionation). At median follow-up periods up to ten years, local recurrence rates around 1% were observed for low risk tumours. Higher local relapse rates were described for grade 3 tumours, triple negative breast cancer as well as for patients treated after primary systemic therapy for locally advanced tumours. Even in this settings, long-term (>5y) local tumour control rates beyond 95% were achieved. These encouraging results are interpreted as being attributable to utmost precision in dose delivery (by avoiding a "geographic and/or temporal miss"), and the possible radiobiological superiority of a single high dose fraction, compared to the conventionally fractionated boost.

IOERT also showed favourable results in terms of cosmetic outcome, assumedly thanks to the small treated volumes combined with complete skin sparing.

Introduction

In breast conserving treatment (BCT), radiation therapy following breast-conserving surgery (BCS) is performed as whole breast irradiation (WBI) or, increasingly, as accelerated partial breast irradiation (APBI), targeting the tissue surrounding the original tumour site (tumour bed) in selected patients with low local recurrence risks [1].

Increasing doses to the tumour bed have shown to reduce local recurrence rates, supporting the introduction of tumour bed boosts. Therefore, additional (boost) doses of 10–16 Gy are routinely applied with external electrons, photons, or interstitial brachytherapy.

Early experiences with the use of intraoperative radiation therapy (IORT) were published in the late nineties [2]. The rational for

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https://doi.org/10.1016/j.radonc.2020.04.059
0167-8140/

IORT, compared to other APBI techniques was to avoid geographic as well as temporal misses [3], reduced treated volumes with skin sparing potentially contributing to better cosmetic outcome, and shortening the overall treatment time. Moreover, during the last decade there has been growing evidence that IORT might exploit increased anti-tumour effects due to higher single dose during surgery [4–6]. Taking into account these findings, IORT has been investigated for both APBI and tumour bed boost.

Following the introduction of mobile linear accelerators, IORT for breast cancer became increasingly popular in Europe during the last two decades. In 2014, Krengli et al. published a survey on the use of IORT across Europe among 31 radiation oncology centres. Data on more than 7.196 patients were available for various tumours, including 5.659 with breast cancer [7] in which single dose IORT for APBI was delivered in 33% of cases and boost followed by WBI in 66%. In 95.4% of cases, IORT was performed with electrons (IOERT) and in 4.6% with 50 kV X-rays. Single-doses APBI was administered in the range of 18 Gy (8%)–21 Gy (71.1%) and as a boost between 8 and 12 Gy.

This paper aims to provide an overview on intraoperative radiation therapy with electrons (IOERT). Emphasis is placed on available trials, clinical outcome in terms of local control (LC) and overall survival (OS), as well as criteria for patient selection. Furthermore, technical and physical aspects are described, to help understand and consider IOERT a possible treatment option in daily practice. For possible applications of IORT with 50-kV orthovoltage X-rays, we refer to the recommended national UK guidelines [8].

IOERT as accelerated partial breast irradiation (APBI): "Full dose IOERT

Evidence: systematic review (Table 1)

IOERT as sole radiation therapy for early breast cancer (BC) has been investigated since 1999 through phase I and II studies assessing the maximum tolerated dose and acute-intermediate toxicity [9]. The results of the phase I–II studies laid the foundation for the prospective, randomized phase III ELIOT trial [10] which investigated the efficacy of single fraction 21 Gy IOERT to the tumour bed compared with adjuvant whole breast irradiation (WBI) with conventional fractionation. The IOERT arm presented higher rates of 5-year in-breast recurrence (IBR) than the WBI arm (4.4% vs 0.4%), and higher regional node relapse rates, likely due to the smaller treated volume and the lack of non-intended axillary irradiation usually seen with the tangential fields. No significant difference in the 5-year rates of BC specific mortality and overall survival was observed between the two groups. The multivariate analysis showed that a tumour size larger than 2 cm axillary nodes involvements, grade 3 tumours and a triple negative molecular subtype were statistically significant predictors of IBR. In the following years, an international consensus panel of BC experts set and refined the eligibility criteria for APBI [11–13]. However, it remains challenging to fully apply these APBI guidelines in the case of IOERT as the complete pathologic report of the tumour is often not yet available when treatment is delivered. Therefore, great efforts must be made in gathering all relevant information concerning tumour biology by performing preoperative core needle biopsy and intraoperative frozen section assessment. Subgroup analyses conducted among patients treated in several institutions [14–17] confirmed the efficacy of IOERT in the suitable/good candidates category according to the American Society for Radiation Oncology (ASTRO) and the Groupe Européen de Curiethérapie – European Society for Radiotherapy & Oncology (GEC-ESTRO) criteria [11,13] (Table 1).

Patient selection for full-dose IOERT

Literature data points out that careful patient selection for IOERT as APBI is mandatory. The selection is a two-step process, consisting in a preoperative and intraoperative phase. The first-step includes physical examination, radiological work-up and biopsy of the tumour to assess breast size, tumour extent and location, histological and biological tumour features for clinical staging and excluding multicentricity. Thereafter, proper selection for APBI must be discussed in a multidisciplinary context, considering also patients' age and comorbidities. The subsequent selection is made during surgery and is based on the pathology results of the specimens frozen sections, including histologic type, resection margins and presence of metastases in the sentinel node. A negative sentinel node biopsy is now considered a pre-requisite for IOERT.

Pre-treatment investigations

- Physical examination (breast size, tumour extent and location)
- Mammography
- Breast ultrasound
- Biopsy for histological examination

Additional investigations (optional)

- Magnetic Resonance Imaging (MRI)

Intraoperative histologic assessment by frozen section

- Sentinel node biopsy
- Tumour size
- Surgical margin width

Intraoperative technical aspects

- Technical feasibility of IOERT (sufficient residual breast tissue)

Postoperative histological assessment

- Surgical margin width
- Histology
- Tumour size
- Lymph node assessment

Eligibility criteria

- Criteria according to APBI guidelines:
  - Age $\geq$50 years;
  - ductal and other favourable histologies;
  - unicentric and unifocal;
  - positive receptor status;
  - pN0 (i−/i+);

  to integrate with

- Criteria according to ASTRO/GEC-ESTRO criteria:
  - grade 1/2;
  - tumour size $\leq$ 2 cm;
  - Luminal A.

Evidence from literature and comments

Outside of clinical trials, patients should be selected according to the criteria set forward by the GEC-ESTRO and ASTRO/updated ASTRO guidelines for APBI [11–13].

Additional risk factors to be considered, emerged from mature results of the ELIOT randomised phase III trial [10]. Patients with

Table 1
Overview of clinical studies after full-dose IOERT.

Author	Study period	Follow-up (months)	Patients	Patient selection	WBI	Local recurrences (%)	DFS (%)	Overall survival (%)	Comments
Mussari et al. [47] 2006	10/2000–11/2002	Median 48	47	>45 years, size ≤2 cm, N0, G1–G2, positive estrogen receptors, no EIC on biopsy	No	0%	–	100%	Phase I–II trial, lobular histology included (13%)
VanderWalde et al. [42]/Olilla et al. [36]/Kimple et al. [41] 2013/2007/2011	3/2003–7/2007	Median 69	71	>48 years, IDC, size ≤3 cm, cN0	11 (46 Gy/2 Gy/fx)	15% (5 true, 3 elsewhere)	–	94.4%	Phase II study of pre-excision IOERT
Lemanski et al. [48,51] 2010–2013	11/2004–11/2007	Median 72	42	≥65 years, IDC, size ≤2 cm, N0, free margin >2 mm, positive estrogen receptors. No LVI or EIC in the primary biopsy	No	9.5% (3 true, 1 elsewhere)	92.7%	100%	Phase II trial
Veronesi et al. [49] 2010/Leonardi et al. [14,15] 2012–2013	1/2000–12/2008	Median 36.1	1822	Median age 58 years, median size 1.3 cm, 71.4% cN0	No	3.3% (2.3% true, 1% elsewhere); according to ASTRO-GEC-ESTRO subgroups: 1.5% (low risk) –8.8% (high risk)	–	94.4%; according to ASTRO-GEC-ESTRO subgroups: 98.6% (low risk) –94.4% (high risk)	Out-trial patients 22 pts included in the dose escalation studies The same population was categorized according to ASTRO and GEC-ESTRO guidelines
Maluta et al. [16,53] 2012–2014	6/2006–12/2009	Median 62	226	≥50 years, IDC, size ≤3 cm, no EIC,	No	1.8%	–	100%	–
Osti et al. [44] 2013	6/2007–10/2011	Median 27 months	110	>48 years, size <2.5 cm, cN0, no EIC	No	2.7% (2 true, 1 elsewhere)	92.9%	97.3	–
Veronesi et al. [10] 2013	11/2000–12/2007	Median 69.6	1305 (654 WBI and 651 IOERT)	>48–75 years, ≤2.5 cm, cN0	WBI in the control arm (50 Gy/2 Gy/fx)	4.4% vs. 0.4% in the WBI arm, ($p < 0.0001$)	.	96.8%	Randomized controlled equivalence trial
Hanna et al. [39]/Barros et al. [40] 2014	5/2004–7/2012	Median 50.7	187	>40 years (modified ≥50), IDC, size <3 cm (modified ≤2 cm), cN0	No	3.7% (4 true and 1 elsewhere)	92.5%	97.8%	Preoperative MRI; Intraoperative IORT feasibility: 81.2%; Portal film to check collimator-shield alignment; Eligibility modified after ASTRO/GEC-ESTRO guidelines
Cedolini et al. [50] 2014	1/2005–12/2009	Mean 69.46	77	≥48 years, IDC, size <3 cm, N0, N1mi, free margin >5 mm	4 pts <48 years	2% (0% in IOERT + EBRT group)	–	98.7%	Intraoperative IORT feasibility was 95.1%; 5 pts re-excised for positive margins
Philippson et al. [52] 2014	2/2010–2/2012	Median 23.3	200	≥40 years, IDC and other favourable, size ≤2 cm, pN0 (SN), free margin ≥1 mm, no EIC	No	0.5%	97.6%	98.9%	Risk adapted treatment volume: field diameter at least 40 mm larger than the tumour size
Kawamura et al. [38] 2015	12/2007–3/2010	Median 72	38	>50 years, size <2.5 cm, negative margins, cN0 since 2/2009	No	0%	100%	100% (BCSS)	Phase I/II dose escalation study Intraoperative IORT feasibility: 84,2%
Takanen et al. [17] 2017	2/2006–1/2016	Median 62.4	758	Median age 64; T1-T2, any N, any grade, any margin status, any histology, uni- and multi-focal tumours	No	1.2 % (low risk)-13.5% (high risk)	–	99% (low risk)–90.8% (high risk)	Patients' categorization according to ASTRO and GEC-ESTRO guidelines

LR: local recurrence; BCSS: breast cancer specific survival; OS: overall survival; LRFS: local recurrence free survival; DFS: disease free survival; ASTRO: American Society for Radiation Oncology; GEC-ESTRO: The Groupe Européen de Curiethérapie and the European SocieTy for Radiotherapy & Oncology; MRI: Magnetic Resonance; WBI: whole breast irradiation: IOERT: intraoperative radiotherapy with electrons; EIC: extensive intraductal component; LVI: lymphovascular invasion; IDC: invasive ductal carcinoma.

tumour size >2 cm, grade 3, triple negative status and ≥4 positive nodes should not be offered IOERT full dose.

It should be noted that the presence of lymphovascular invasion (LVI) and extensive intraductal component (EIC) could not be ruled out on microbiopsy, leaving a margin of uncertainty for the fulfilment of these criteria of the consensus guidelines [14,15]. The challenge of patient selection was described by Guenzi and colleagues, who showed that by the end of the selection process, only 43% of patients candidate for IOERT were eligible to receive this treatment. In addition, if definitive pathology proves to be worse than anticipated, additional WBI might be necessary even after full-dose IORT.

Peripheral breast tumour sites, namely the axillary tail and the inframammary fold, can be critical for IOERT delivery due to insufficient residual breast parenchyma affecting the correct exposure of the target volume to radiation. The same restrictions apply to IOERT in the boost setting.

To date, there is no consensus on the use of MRI to properly select patients for APBI. MRI is proven to detect disease characteristics (e.g. extension, multifocality, etc) that could change eligibility in a certain percentage of patients (11% in a pooled analysis from a systematic review) [18] who would otherwise be considered candidates based on standard workup.

IOERT as boost (IOERT-Boost)

Evidence: systematic review (Table 2)

Information on outcome after IORT-boost with electrons (IOERT-Boost) is available from various cohort analyses, with the largest deriving from a pooled analysis of the International Society of Intraoperative Radiation Therapy (ISIORT) Europe (Table 2). In these unselected retrospective studies, boost-IOERT plus WBI consistently resulted in high in-breast control rates, with observered 6- and 10-year local recurrence rates (LRR) of 0.8% and 2.7% respectively [19,20].In a matched-pair design study, 188 patients who received a boost with external beam electrons (6x2Gy) were compared to 190 patients after IOERT-boost. At 5-year follow up, IOERT-patients had no in-breast relapses, compared to 4.3 % for those who had electron-boost (p = 0.0018) [21].

In subgroups at "higher risk" for in breast recurrences (IBR), e.g. patients with locally advanced breast cancer (LABC) after primary systemic therapy (PST) or triple negative subtypes (TN), IOERT-Boost data compare favourably to those after other boost methods [22,23]. Following PST and a median follow-up (FUP) of 6 years, an observed 6-year local control rate (LCR) of 98.5 % was recorded [22], whereas specific TN-breast cancer subtypes turned out to be locally less controllable (8-year LCR of 89%) [23]. This observation that tumour biology represents an important negative predictor for IBR has been recently corroborated by the 10-years results of 770 patients of any risk profile [20]. In this analysis, TN and HER2+ subtypes (estrogen and progesteron receptor negative/Her2neu positive) turned out to be the only significant negative predictors for in breast relapses in uni- and multivariate analyses, with an HR of 15.02 and 12.87, respectively ($p < 0.05$)[20]. Surprisingly, no higher risk for IBR was seen for those with high-graded tumours (G3) and nodal involvement, although a trend toward higher risk was seen in the presence of in-situ components (HR of 2.11, p = 0.11), which confirms long-term data from the EORTC-Boost trial [24].

Although a boost has in principle been proven to be an effective means for local recurrence (LR) reduction in any age group [25,26], RT in general is currently questioned for elderly patients due to missing efficacy in survival endpoints [27]. However, in the light of ongoing de-escalation strategies, some of the IOERT-Boost patients classified as lower risk for recurrence are now rather considered to be eligible for PBI, either with full-dose IOERT or alternative techniques [28] depending on specific selection criteria [12,13]. A complete omission of RT in elderly women is still a matter of debate with somehow conflicting recommendations in various national guidelines or consensus statements [1,27].

Table 2
Evidence on IOERT-Boost.

Author	FUP	Patients	Patient selection	Technology	IORT dose (range)	EBRT	LC	OS/DFS	Comments
Merrick HW et al. (1997) [55]	°71 mo (up to 144)	21	Stage I–II	IOERT	D_{max}: 10–15 Gy	45–50 Gy Fx: 1.7–2 Gy	crude 100%	OS: crude 90.5%	nc
Dubois JB et al. [(1997) [54]	Min. 24 mo	101 51/50	Stage I–II (III)	IOERT/no	D_{90}%: 10 Gy	45 Gy Fx:2 Gy	crude 100% vs nc	nc	nc
Lemanski C et al. (2006) [57]	°109 mo (60–180)	50	Stage I–II	IOERT	D_{90}%: 9–20 Gy	50 Gy Fx:2 Gy	crude 96%	nc	nc
Ciabattoni A et al. (2004) [56]	nc	234 (122/112)	Stage I–II	IOERT/ext. e	D_{max}: 10 Gy	50 Gy Fx: nc	crude 100% vs 98.2% (nc)	nc	nc
Reitsamer R et al. (2006) [21]	°51/81 mo	378 (190/188)	Stage I–II	IOERT/ext. e	D_{max}: 10 Gy	51–56 Gy Fx: 1.7 Gy	***** 100% vs 95.7% (ss)	nc	nc
Ivaldi GB et al (2008) [31]	°8.9 mo (0.8–32.4)	204	Stage (0) I–III	IOERT	D_{max}: 13.3 Gy	37.05 Gy Fx: 2.85	****100%	nc	nc
Fastner G et al. (2013) [19]	°72.4 mo (0.8–239)	1109	Stage I–III	IOERT	D_{max}: 6–15 Gy	50–54 Gy Fx: 1.7–2 Gy	*** 99.2% vs 88.1% (ns)	OS: ***91.4%	nc
Fastner G et al. (2015) [22]	°59/67.5 mo (3–120)	107 (81/26)	Stage II–III	IOERT/ext. e	D_{max}: 10 Gy	51–57 Gy Fx: 1.7–1.8 Gy	*** 98.5%	OS: ***86.4%	nc
Fastner G et al. (2016) [23]	°97 mo (20–170)	71	Stage I–II	IOERT	D_{max}: 7–12 Gy	°54 Gy Fx:1.6–1.85 Gy	** 89 %	OS: **75%	nc
Kaiser J et al (2018) [20]	°121 mo (4–200)	770	Stage I–III	IOERT	D_{max}: 5–12 Gy	°54 Gy Fx:1.6–2 Gy	* 97.2%	OS: *85.7%	nc
Fastner G et al. (2020) [30]	°45 mo (0–74)	583	Stage I–II	IOERT	D_{max}: 11 Gy	40.5 Gy Fx: 2.7 Gy	crude 100%	DFS: ******97.8%	nc

° = median, mo = months, * = actuarial 10-year rate; ** = actuarial 8-year rate; *** = actuarial 6-year rate, **** = actuarial 9-months rate,***** = actuarial 5-year rate, ****** = actuarial 3-year rate ext. e = external electrons, LC = local control, OS = overall survival, nc = no comments, ss = statistical significant, ns = not significant, D_{90}% = 90%-reference-isodose, Fx: Dose per fraction, OS = overall survival, LC = local control, FUP: Follow-up.

Patient selection for IOERT-Boost

Eligible patients are those with histologically confirmed invasive breast cancer clinical stages I–III, who are candidates for BCS and WBI, with no limits to the kind of systemic treatment (substances and time sequence), age, molecular sub-type (Luminal A, Luminal B, HER2+ and TN [29]) tumour size and nodal status.

External beam radiation therapy

After surgery and IOERT-Boost, WBI can start as routinely when the wound is healed. There are no restriction in terms of WBI technique (e.g. tangential field techniques, IMRT or VMAT) after a 3D CT-based planning procedure in supine or prone position. WBI can be performed either with conventional fractionation (1.8–2.0 Gy up to 50 Gy), or with hypofractionation [1] (2.66–2.85 Gy per fraction up to 40.5 and 37.05 Gy, respectively) [30–32].

Using the linear-quadratic model, we calculated that a 10 Gy IOERT-Boost should be equivalent to 23 Gy in 2 Gy daily fractions (EQD2). Biological iso-effectiveness of higher single-doses, calculated with the LQ alpha/beta model, was shown for dose ranges between 10 and 18 Gy [33], with the upper threshold still being a matter of debate [34].The combination of boost IOERT and HF-WBI was first published by Ivaldi et al. in a phase II trial, showing acceptable treatment tolerance after short-term follow-up [31]. More evidence to support this regimen is expected from the multicentre "HIOB-trial" (ClinicalTrials.gov Identifier: NCT01343459), which started in January 2011 as an ISIORT investigator initiated study. In this trial, Boost IOERT of 10 Gy is combined with hypofractionated WBI (15 × 2.7 Gy) for stage I/II breast cancer. Annual in-breast recurrence rates are defined as benchmarks for successful treatment, in three different age groups (>50, 41–50, ≥35–49). Superiority of the intervention is defined by rates of in-breast control below the best-published results of "state-of-the-art" radiation therapy. Beside tumour related endpoints, major emphasis has been placed on cosmetic outcome. While this study is still recruiting patients, an interim analysis on 3yrs-results has recently been published, showing very low early and late toxicity, satisfactory cosmetic results, and no locoregional recurrence [30].

Technical aspects of IOERT (full-dose and boost-concept)

IOERT procedures

IOERT is delivered either with conventional or mobile linear accelerators (Linacs) and does not interfere with surgical procedures according to standard oncologic criteria of BCS. After the excision of the tumour, the surgeon mobilizes the part of the remaining breast around the tumour bed by separating the deep side from the fascia of the major pectoral muscle and the superficial side from the subcutaneous tissue at the level of the anterior adipose lamina, to expose the target volume to the radiation beam. The surgical margins are then temporarily approximated to restore the anatomy of the gland and to allow IOERT to be delivered [9,35]. When IOERT is given before tumour excision, the surgeon makes an incision on the skin over the tumour and inserts the applicator over the intact tumour [36]. However, IOERT after tumour removal represents the preferable sequence with highest clinical evidence.

To spare underlying tissues from radiation, a shielding disc available in various diameters, can be inserted between the surface of the pectoralis muscle and the posterior side of the reconstructed mammary gland. The shielding disc is generally made of two layers of different materials: one of high and the other of low atomic number. For example, lead and aluminium can be used in combination, with lead facing the breast parenchyma to stop electrons, while the aluminium blocks the electrons back-scattered by the lead [37]. Alternative materials can be used [38–40], allowing for transmission of up to 15% of the maximum prescribed dose. Although the use of a shielding disc is recommended in case of full-dose IOERT, it is not mandatory, as the treated tissues can stop most of the electrons depending on their energy and the thickness of the tissue itself. A shielding disc is not used when IOERT is administered before tumour excision [36,41,42] and is optional when IOERT is performed as boost. In order to avoid an unwanted dose delivery by electrons escaping through the applicator wall, a skin retractor (with hooks to a plastic ring in order to stretch skin margins away from the radiation field) is advantageous.

IOERT is delivered through applicators (tubes) with different diameters, ranging from 3 to 12 cm, either flat ended or bevelled. For BC, applicator sizes usually range from 4 to 6 cm. The sterile applicator (poly methyl methacrylate (Perspex) or metal) is placed directly in contact with the target volume. Depending on the system, docking is either performed by rigid tube attachment to the linear accelerator (hard docking) or the applicator firmly clamped to the operation table while moving the gantry until it reaches the proper position through laser alignments (soft docking). The applicator size is chosen in order to ensure the proper coverage of a given target volume around the surgical sutured breech, depending on the tumour size and location. Electron energies range between 4 and 12 MeV and are chosen according to the needs of the clinical target volume (CTV) definition (Supplementary table A.1). For exact treatment positioning, a mobile operating table with six degrees of freedom could help to reach particularly difficult target position. Furthermore, for soft-docking systems, a camera and light-source should be installed at the head of the Linac, in order to visually check the correct alignment between the head itself and the electron applicator, (via monitor) as well as to document the treated area (Fig. 1a).

Irradiated volume, post treatment patient care and technical requirements for IOERT delivery are reported as supplementary material (Supplementary item A.1–A.4, Supplementary table A.2).

Dose prescription

The dose can be prescribed at D_{max} (100%) or at D_{90}. D_{max}, D_{90}, D_{45} and their corresponding tissue depths (d) should be specified along the central beam and clinical axis (in mm) respectively (Figs. 1b and c). As illustrated in Fig. 1b, this axes discrimination is only relevant if the electron tube ending has a beveled angle (15°, 30° or 45°), at 0°the two axes coincide. V90 is defined as the volume of tissue included in the 90% isodose and should be reported in ml (cc). As for geometric reasons, depending on available planning systems, V90 can be calculated by the formula of a rotating ellipsoid ($4 \times 3.14/3 \times a^2 \times b$) (Fig. 1d).

Full dose IOERT

The most commonly used dose is 21 Gy prescribed at the depth of the 90% isodose (which corresponds to 23.3 Gy at 100%). To make a comparison for standard fractionated treatment, the biological equivalent dose (BED) using α/β ratio of 4 Gy/50 Gy is 75 Gy while for single fraction 21 Gy is 131 Gy [43].

Other investigators reported a dose of 21 Gy prescribed at the 100% isodose [16,44]: in this case the whole target was included in the 80% isodose and covered by the dose of 16.8 Gy. The aim for this dose reduction was to be as close as possible to the BED of 50 Gy with conventional fractionation; in fact, the BED for single dose of 16.8 Gy is 87 Gy, which is comparable to 75 Gy BED of standard fractionation scheme of 2 Gy in 25 sessions. When IORT is delivered to the intact tumour (prior to excision), the dose is decreased to 15 Gy at 90% isodose, since no chest wall shielding is applicable in this setting. In this case, the energy of electrons is chosen to cover the intact tumour plus a 1.0 cm margin beyond the 90% isodose line [36,42,45]. The authors state that chest wall

Fig. 1a. Treatment position: Tube adjustment by laser-light and monitor support (dedicated linac).

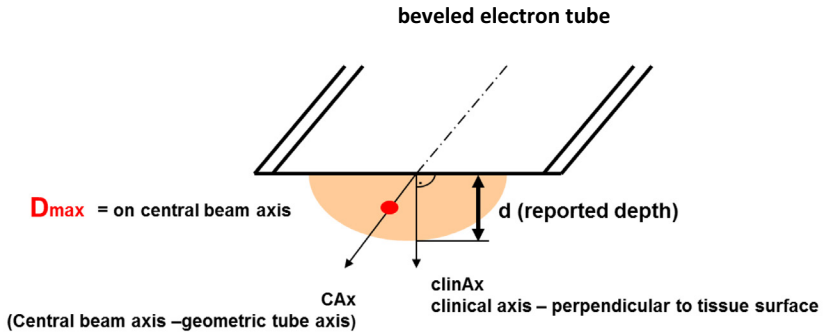

Fig. 1b. D_{max} (100%), D_{90}, D_{45} and their corresponding tissue depths (d) of the tumour bed (brown) should be specified along the central beam and clinical axis (in mm) respectively.

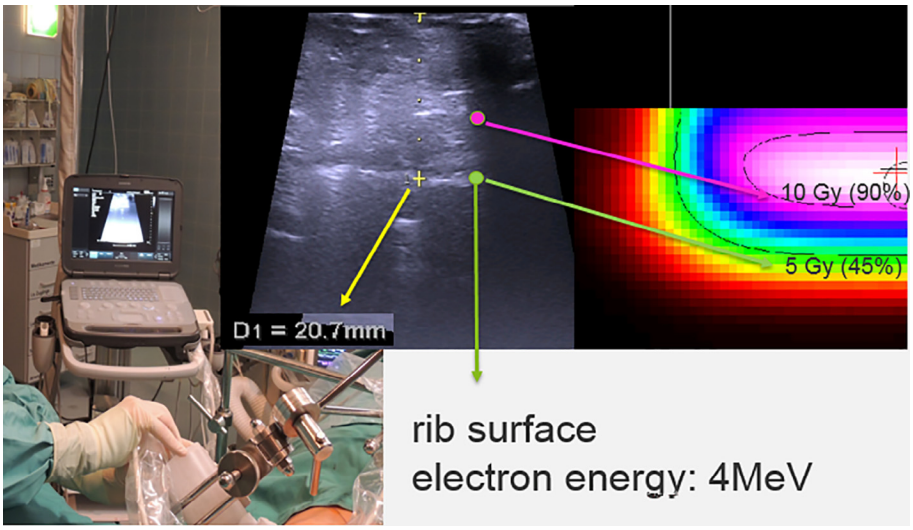

Fig. 1c. Tissue depth measurement by ultrasound (along the clinical axis), corresponding electron energy and dose prescription of D_{max} 11 Gy.

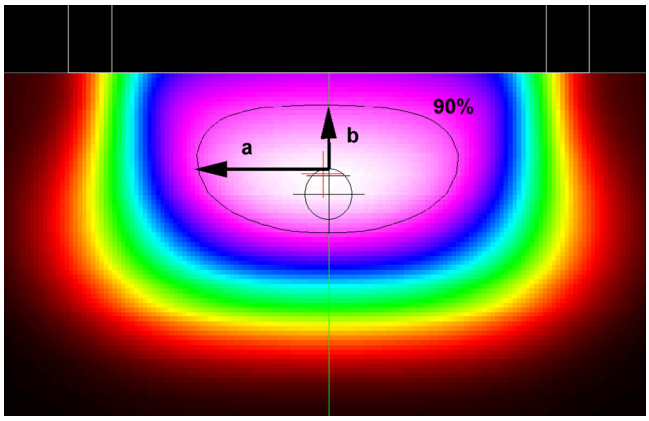

Fig. 1d. V90 is defined as that tissue volume which is encompassed by the 90% isodose and should be indicated in ml. As for geometric reasons, depending on available planning systems, V90 can be calculated by the formula of a rotating ellipsoid ($4 \times 3.14/3 \times a^2 \times b$). b = half of distance between the two 90% depths, a = radius of the 90% isodose.

dose was initially limited to 10 Gy and subsequently raised up to 15 Gy [41].

Evidence from literature and comments

The dose of 21 Gy at the 90% isodose was established as the maximum tolerated dose after a phase I and subsequently tested in a phase II study to assess acute and intermediate toxicity. Both were conducted at the European Institute of Oncology in Milan [46].

IOERT Boost

The dose prescribed as boost usually ranges from 9 Gy to 12 Gy at the 90% isodose (10 Gy and 13 Gy at D_{max}) [19,30,31]. Exit doses at the anterior rib surface should not exceed a limit of 7 Gy (Fig. 1c).

More technical aspects concerning treatment delivery, care during the course of IOERT, recording and reporting as well as applicator removal are described in detail in the supplementary material (supplementary item A.5–A.8).

Acknowledgements

Intraoperative radiotherapy (IORT) is a multidisciplinary oncological activity requiring a close collaboration of team members, using optimal tools and techniques. The authors of this guideline acknowledge the remarkable contribution of all the health professionals involved in the care of patients who are candidates for IORT procedures.

Authors are grateful to the ESTRO/ACROP reviewers Giovanni Battista Ivaldi, Roland Reitsamer, Mario Ciocca and Birgitte Vrou Offersen for their useful and constructive comments and for the logistic support from Eralda Azizaj.

Conflicts of interest statement

Felipe Calvo, Maria Cristina Leonardi and Philip Poortmans are member of the IOeRT Consortium, established on 21 December 2019, supported by Sordina IORT Technologies spa; Philip Poortmans is medical advisor of Sordina IORT Technologies spa, starting from 1 April 2020 on; Felix Sedlmayer received HIOB study grants from IntraOP Medical; Elena Sperk received travel grants and speaker honorarium from Zeiss Meditec AG, Oberkochen, Germany.

The other authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.04.059.

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