Focus on the Actual Clinical Target Volume Irradiated with Intraoperative Radiotherapy for Breast Cancer

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Abstract. *Aim: Intraoperative radiotherapy (IORT) has been investigated as an exclusive adjuvant treatment option for early-stage breast cancer (BC). We analysed our experience on the technical aspects of this innovative approach in terms of identification of breast volume actually to be treated during IORT. Patients and Methods: A total of 315 patients at low risk of breast cancer recurrence underwent IORT as exclusive treatment after breast-conservative surgery. To evaluate the breast volume actually irradiated with IORT, we considered a sample of eight patients, chosen retrospectively as having enough clips to identify the tumour bed and IORT site in computed-tomography (CT). The clinical target volume (CTV) was assessed for each patient with two different methods: the first, cc-IORT, was considered during surgery according to the chosen collimator diameter and glandular thickness, while the second, cc-CT, was evaluated through computed-tomography performed after surgery. The cc-CT CTV was obtained by contouring the cc-IORT on the CT section on the basis of the clips placed by the surgeon on the resection margins. Results: In our experience, the 5-cm (50%) and the 6-cm (36%) diameter collimators have been the ones, used the most. The diameter of the collimator used did not appear to adversely affect the satisfactory aesthetic result. The comparison between CTVs showed that glandular breast volume contoured with CT (cc-CT) appeared to be three fold larger than the target identified at surgery and included in the area of chosen collimator (cc-IORT). Conclusion: The actual volume of breast gland irradiated with the IORT procedure appears to be larger than expected. This may be due to the area being prepared for IORT by placing tissue compactly.*

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The purpose of irradiation after breast-conservative surgery is to minimise the risk of local failure and thus to improve disease-specific survival without producing side-effects on the heart and lungs, nor worsening the aesthetic outcome. The standard procedure consists of breast external radiotherapy, including or not loco-regional lymph nodes, with doses around 50 Gy, in 25 fractions, delivered as daily treatment five days per week for five to six weeks. This treatment is able to reduce local recurrences to 0.5-1% per year, also delivering a good cosmetic result (1). Radiotherapy involves discomfort for patients who need to travel for several weeks to receive the treatment and it remains unclear whether it is necessary to irradiate the whole mammary gland or if it may be sufficient to cover only a limited volume of the breast, mainly the tumour bed, where the majority of relapses occur (2-5). On the basis of these considerations, accelerated-partial breast irradiation (APBI), where only a limited volume of the mammary gland is irradiated with a high dose in 1 to 10 fractions, delivered in up to five days, has become the object of scientific interest (6). In order to obtain adequate results in terms of local control of disease using APBI, proper patient selection is necessary, as indicated by the American Society for Radiation Oncology (ASTRO) and the European Society for Radiotherapy and Oncology (ESTRO) consensus (7, 8) and as confirmed by the results of the European Oncology Institute (9). Several methods for APBI can be used: interstitial and endocavitary (Mammosite) brachytherapy, 3D-conformal external radiotherapy (3D-CRT), and intraoperative radiotherapy (IORT) with electron beam. These modalities differ in both the technical and dosimetric aspects and they are difficult to compare (6). IORT offers several advantages: a very precise online delineation of the tumour bed, a high sparing of normal tissue and the

Table I. *Overall series of patients treated with intraoperative radiotherapy (IORT).*

Monoinstitutional experience of IORT 2009-2011	No. of patients	Dose (Gy)
Pilot trial with different radiation dose	205	18 or 21
'Off protocol' exclusive IORT	110	21
Exclusive IORT for breast relapse after previous external radiotherapy	17	21
IORT delivered as boost followed by external radiotherapy	50	10
Exclusive IORT to nipple areola during nipple sparing mastectomy	7	16
IORT for different indications (see reference 11 for details)	84	18 or 21

Table II. *Published guidelines for accelerated-partial breast irradiation.*

Prognostic factor	Guidelines followed for IORT indications		
	ABS (7)	ASBS (8)	Present report
Age (years)	≥45	≥45 yrs	≥45 yrs
Histology	Unifocal, invasive ductal cancer	Invasive ductal cancer or DCIS	Invasive ductal cancer, no EIC
Tumour size	≤3 cm	≤3 cm	≤2,5 cm
Surgical margins	Negative microscopic margins	Negative microscopic margins	Negative microscopic margins (≥5 mm)
No. of involved lymph nodes	None	None	None

ABS: American Brachitherapy Society; ASBS: American Society of Breast Surgeons; DCIS: ductal carcinoma *in situ*; EIC: extensive intraductal carcinoma.

possibility of immediate oncoplastic surgery; moreover, IORT allows for radiation treatment to be performed during the operation, with the maximum optimization time for the patient. This report investigates the actual entity of clinical target volume (CTV), of breasts irradiated by IORT, in order to reduce the risk of geographical missing residual microscopic disease.

Patientsxx and Methods

Since September 2009, a mobile dedicated-accelerator LIAC (Sordina, Padova, Italy) has been available at our Department of Radiation Oncology. We treated 389 patients, overall, since December 2011 (Table I). Three-hundred and fifteen patients underwent IORT as exclusive treatment, while eighty-four patients were excluded from intraoperative radiotherapy because they did not meet the selection criteria. All patients were fully informed about the treatment and signed an informed consent document. Some clinical and technical steps were routinely followed to optimize the treatment, such as patient selection, CTV identification and dosimetric evaluation of the prescribed dose.

Patient selection. We identified patients as candidates for IORT as exclusive treatment considering the American Brachytherapy Society (ABS) and American Society of Breast Surgeons (ASBS) indications as they were the only indication available in 2009 (Table II) (10).

CTV. The IORT treatment consists of different phases: the breast tumour is first removed, with at least 1 cm of macroscopical margin and submitted to immediate pathological analysis to ensure compliance with the pathological inclusion criteria (11). Sentinel node biopsy is then carried out to exclude positive findings. A wide mobilization of the mammary gland, below, from the *pectoralis* fascia and, above, from the skin, has to be carried out to obtain a good exposure of the tissues to the radiation beam. The diameter of the IORT-based collimator is then chosen according to the tumour size and the breast volume and a shielding disk of 1-2 cm larger than the collimator is positioned to protect the thoracic wall, heart and lung. After the treatment, the collimator and the disk are removed.

To evaluate the breast volume actually irradiated with IORT, we decided to consider a small sample of eight patients, chosen retrospectively; the patients had enough clips (three or more) identifying the tumour bed and a good CT definition of the IORT site, CT was performed only if the patients required external radiotherapy after an IORT boost. The CTV was assessed for each patient with two different methods: the first CTV (cc-IORT) was considered during surgery according to the chosen collimator diameter and glandular thickness, while the second CTV was evaluated through computed-tomography (CT), performed after surgery (cc-CT) (Figure 1); the cc-CT CTV was obtained by contouring the cc-IORT on the CT section on the basis of the clips placed by the surgeon on the resection margins. The volume evaluated according to the diameter of the collimator (cc-IORT) was obtained by multiplying the area actually irradiated by the thickness

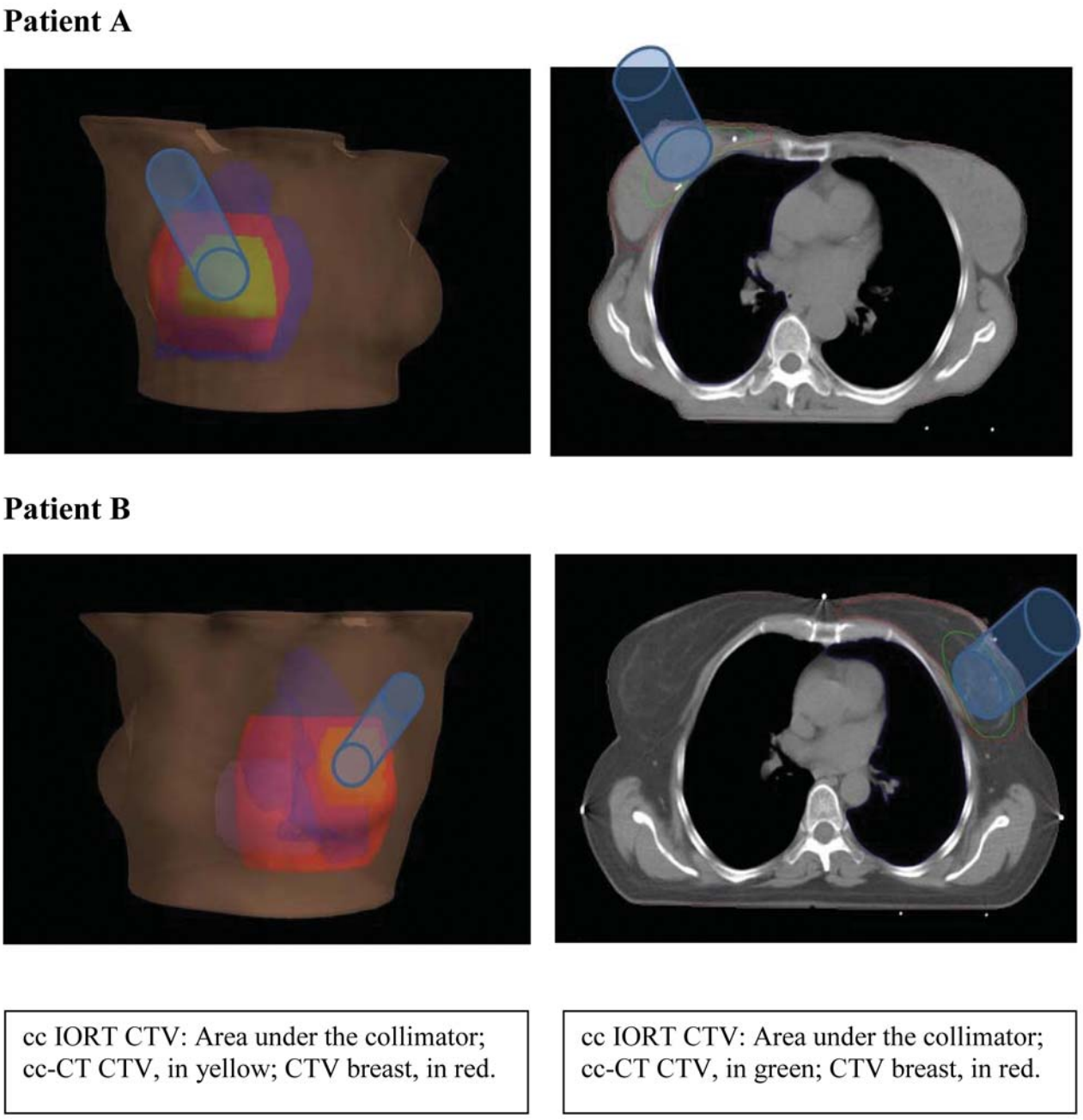

Figure 1. *Estimation of clinical target volume (CTV) by computed-tomography (cc-CT CTV) and during surgery (cc-IORT CTV) in two different patients.*

of the treated gland, considering the IORT CTV to be cylindrical in shape. The estimated volume, based on CT sections (cc-CT), was calculated by a treatment planning system (Eclipse; Varian, Palo Alto, CA USA). *In vivo* dosimetry was performed for each treatment with the mobile MOSFET system (Best Medical; Ottawa, Ontario, Canada) using a micro MOSFET 502-RDM inserted into a closed-end 6Fr brachytherapy catheter positioned below the disk, in the centre of the irradiation field.

Dosimetric evaluation of the prescribed nominal dose. During IORT, the thickness of the CTV was measured by the surgeon using a graded needle in at least three different points in the tumours bed. The beam energy and dose normalization were chosen by the medical physicist and the radiation oncologist, according to the target thickness. Usually the beam energy is selected to fully-cover the distal part of the target by R90. Dose normalization is made between 90% and 100% of peak dose. Based on beam energy, applicator size,

Table III. *Report of intraoperative radiotherapy (IORT)-based collimators chosen according to the pathological stage of the excised primary tumour.*

Pathological stage		Collimator diameter, n (%)		
		4 cm	5 cm	6 cm
pT	pT1a	5 (2%)	4 (1%)	1 (<1%)
	pT1b	26 (8%)	59 (19%)	13 (4%)
	pT1c	13 (4%)	95 (30%)	99 (31%)

prescription dose (PD) and dose normalization, the medical physicist computes the monitor units (MUs) also taking into account the daily output correction. The irradiation was split into two consecutive fractions; in the first, the expected dosimeter dose (EDD) was compared against the measured MOSFET dose (MD) and the result was assessed to correct the MUs, in the second fraction in order to achieve a better agreement with the prescription (12).

Results

Patient selection. Following the criteria listed in Table I, 315 patients with early-breast cancer underwent IORT as exclusive treatment. Eighty-eight patients received a standard dose of 21 Gy with electron beams of energy range between 4 and 10 MeV. Two-hundred and five patients were included in a pilot study conducted at our center to assess tolerance to and efficacy of different doses for exclusive IORT. According to the pilot study criteria, the delivered dose was chosen based on tumour size evaluated with frozen-section examination: 18 Gy in cases of less than 1-cm tumours (pT1a-pT1b; 73 patients) and 21 Gy for these with larger tumours (pT1c-pT2; 132 patients).

CTV. The choice of the collimator diameter was based on the primary tumour size and site, and on the breast volume. In our experience, the 5-cm (50% of cases) and the 6-cm (36% of cases) diameter collimators were the ones mostly used (Table III). The analysis performed on a small sample of eight patients treated with IORT to compare the difference between cc-CT and cc-IORT volume, is shown in Table IV. The comparison showed that as a consequence of the surgical manipulation, the breast volume contoured with CT (cc-CT), appeared to be three-fold (mean value=6±3 cm^3) larger than the target identified at surgery and included in the area of the chosen collimator (cc-IORT).

Dosimetric evaluation of the prescribed dose. The target thickness ranged between 9 and 17 mm. Radiotherapy was administered by electron beams with nominal energy of 6 MeV (16% of the patients), 8 MeV (40%) and 10 MeV (44%). After the comparison of EDD with the measured MD, the MUs were found to be correct in 20-25% of patients achieving a better agreement with the nominal dose prescription. The treatment was well-tolerated in the majority of patients. At a median follow-up of 19 months (range 7-37 months), the diameter of the used collimator did not appear to adversely interfere with a satisfactory aesthetic outcome, which was evaluated by the clinician and reported as excellent (no differences between the treated breast and the contralateral one), good (minimal differences between the two breasts), satisfactory (evident differences between the two breasts) and poor (dysmorphism in the treated breast) (Table V).

Table IV. *Comparison between clinical target volume (cm^3) assessed with computed tomography (cc-CT CTV) and during surgery (cc-IORT CTV): detailed analysis for selected eight patients.*

Patient	cc-CT	cc-IORT	Ratio cc-CT/cc-IORT
1	283	56	5
2	108	30	4
3	146	14	11
4	108	34	3
5	83	23	4
6	152	20	8
7	154	23	7
8	79	23	3
			median 3

Table V. *Relationship between the diameters of intraoperative radiotherapy (IORT)-based collimators and aesthetic outcome at a median follow-up of 18 months.*

Aesthetic result	Collimator diameter, n (%)		
	4 cm	5 cm	6 cm
Excellent	23 (7%)	51 (16%)	21 (7%)
Good	17 (5%)	89 (28%)	60 (19%)
Satisfactory	6 (2%)	24 (8%)	21 (7%)
Poor	1 (<1%)	2 (<1%)	0 (0%)

Discussion

APBI including IORT seems to be a valid option for adjuvant radiotherapy for patients with breast cancer, if at least three basic steps are followed: proper selection of candidate patients, precise detection of the breast volume to be treated (CTV) and accurate definition and delivery of the radiotherapy dose. As reported by others (6), the primary purpose of selection criteria for APBI is to identify a subset of patients with a very low risk of clinically-occult disease, remote from the lumpectomy cavity. ASTRO (7) and GEC-

ESTRO (8) developed a consensus statement for the use of APBI outside the context of a clinical trial, based on the results of a systematic literature review supplemented by the expert opinions of the Task Forces members. A retrospective analysis of 1,822 patients treated at the European Institute of Oncology (Milan, Italy) confirms the clinical validity of the proposed categories in IORT treatment (9).

As mentioned before, at our institution, IORT candidate patients are currently selected according to the factors listed in Table II. It should be noted that IORT is performed on the basis of pre-surgical data (age, clinical and radiological evaluation, breast size, location of the tumour) and from frozen-section data (11), as the results of the definitive histological findings are not available. This aspect appears to be the most limiting factor regarding the IORT technique, as the definitive pathological findings may reveal aggressive tumour features for which a limited radiation field is contraindicated, on the basis of current evidence (13). As yet, the few data available make the selection of patients more critical and it might be appropriate to consider, as carefully as possible, all the clinicopathological factors provided.

The principle of whole-breast radiotherapy is based on irradiating hypothetical microscopic foci of carcinoma left in the mammary gland, whereas the principle of APBI is to irradiate only a limited volume of the breast, mainly the tumour bed, where local recurrences occur most frequently. The actual extent of neoplastic foci-theoretically able to evolve into a clinically-detectable relapse in the breast is unknown. Consequently, the volume of breast tissue surrounding the lumpectomy cavity to be treated with APBI, particularly with IORT, after conservative surgery remains undefined. Considering historical analyses of mastectomies with conservative surgery, it seems that the majority of neoplastic residues are located strictly close to the tumour bed. In patients with a tumour of less than 2 cm in the major dimension, a 2-cm surgical margin may be sufficient to remove all tumour foci in 58% of cases, while with a 3-cm surgical margin, residual foci are demonstrable in 9-8% of cases (14). Moreover, around 5% of tumour residual foci are observed at 4-5 cm from the primary cancer site (14). In patients treated with APBI with 3D-CRT, the CTV had been defined by uniformly expanding the excision cavity volume by 10-15 mm and the planning target volume had been designed by adding a further 10-15 mm around the CTV, so that almost 5 cm^3 volume was to be irradiated (15). Initial data on efficacy and toxicity of IORT, evaluated in 58 patients treated following these instructions, show a 4-year estimated local relapse of 6%; these results appear comparable to other experiences with similar follow-up (16).

Furthermore, the technique of IORT has procedural differences that may influence the results, and the factors considered for the optimal external RT may not be the same. The definition of the diameter of the collimator, even considering the site of the tumour and the size of the breast, can be according to some known prognostic factors. In the IORT technique the CTV of the breast that needs to be irradiated is almost an area of 4 to 5 cm of minimum diameter around the cancer resection site (17). In our experience, the collimators of 5-6 cm diameter have been the ones mostly used; seemingly, this choice could be correct on the basis of Holland *et al*.'s pathological data (14) and the information provided by Vicini *et al*. (15, 16). It is well-known that the procedures of dissection, approaching, and provisional suture of the glandular tissue to form the CTV to be placed under the collimator can lead to the irradiation of a larger volume of mammary parenchyma. The CTV extension in IORT is still an unresolved problem: the quantification of volume irradiated by the different collimators and consequently the 3D evaluation of the mammary parenchyma included in the isodoses has not yet been defined. As pointed out, the comparison between cc-IORT and cc-CT CTVs showed that the glandular breast volume contoured with CT (cc-CT) appeared to be three-fold greater than the target identified at surgery time and included the area of the chosen collimator (cc-IORT). We also have to consider that the surgical technique is operator-dependent and that the individual surgical technique and expertise can affect the amount of tissue actually irradiated. The results of this volumetric analysis seem to support the actual possibility that the breast volume identified and treated with IORT may be greater than the tissue volume delimited by the chosen collimator.

Conclusion

The actual CTV of breast gland irradiated with IORT appears to be greater than expected, since in order to create a surgical bed for single-fraction radiotherapy, tissues are placed very close together and compacted. Thus, APBI larger than expected may be performed with IORT procedure. This preliminary evidence should be confirmed or disapproved by an analysis conducted on a larger cohort of patients.

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