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Tumor Size-driven Dose of Intraoperative Radiotherapy for Breast Cancer: 18 Gy *Versus* 21 Gy

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Abstract. *Aim: To test whether a reduced total single dose of 18 Gy of intraoperative radiotherapy with electrons (IORT) may be tailored to safely treat patients in comparison with the standard dose of 21 Gy. (NCT01276938). Patients and Methods: From October 2009 to December 2011, 199 females affected by breast cancer were treated with conservative surgery and IORT with two different exclusive doses, 18 or 21 Gy. Results: The median follow-up was 91 months (16-104 months). Sixty-five patients (pT1a\b, pN0\mic, pMx, G1-G3) received 18 Gy and 134 patients (pT1c\2, pN0\mic, pMx, G1-G3) received 21 Gy. No significant difference in local recurrence-free survival or overall survival was detected in the 18 Gy-treated arm versus that treated with 21 Gy: 96.9% vs. 96.3%, p=0.72, and 96.9% vs. 95.5%, p=0.82, respectively at 5 years. Conclusion: The lower dose of 18 Gy achieved excellent results in terms of local toxicity and local control in early breast cancer.*

Breast-conserving surgery followed by whole-breast external radiation therapy (WBI) is usually the standard treatment for early breast cancer (1). Several clinical trials have demonstrated that about 90% of local recurrences after conservative breast surgery appear in the same area of the previous tumor (index quadrant) (2, 3).

According to this evidence, different trials on accelerated partial breast irradiation (APBI) were conducted with promising results (4-6). Several methods for APBI can be used: interstitial and endocavitary (Mammosite) brachytherapy, 3D-conformal external radiotherapy, and intraoperative radiotherapy (IORT) with photon or electron beam (7).

IORT can be used either as a single exclusive dose in patients with early breast cancer patients or added as a boost on the tumor bed in high-risk cases; two large prospective randomized trials using breast IORT, TARGIT-A (Targeted Intraoperative Radiotherapy) and ELIOT (electron IORT) (8, 9), compared with IORT (as a single dose or as a boost) *versus* external radiotherapy for early breast cancer and demonstrated a low local recurrence rate and a good survival rate, in both arms (10).

Performed in theatre during conservative surgery, exclusive IORT offers multiple advantages: Firstly, it allows reduction of hospital visits for the patient, but above all, it leads to a better delineation of the tumor bed and subclinical disease (8, 11). Furthermore, the greatest advantage of the IORT treatment protocol derives from reduction of normal tissue toxicity by reducing radiation to the skin and the adjacent normal breast gland and healthy tissue (12). Moreover, IORT has a potential advantage in efficacy related to overall survival due to reduced cardiopulmonary radiation doses (13).

Regarding radiobiological issues, delivering a high exclusive single dose, such as 21 Gy, avoids the problems of cancer cell repopulation and repair by increasing the tumor-kill effect of surgery and radiation therapy. This achieves early elimination of subclinical disease and avoids tumor growth between the time of surgery and the beginning of adjuvant fractionated radiotherapy (11). As a matter of fact, a single 21 Gy dose is considered to be biologically equivalent to 1.5-2.5 times higher the WBI (14).

The aim of this study was to evaluate toxicity in patients with breast cancer treated with two different doses of IORT to test whether a reduced single dose (18 Gy) of IORT may be tailored to safely treat patients with selected early breast cancer in comparison with the standard dose of 21 Gy.

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Patients and Methods

From October 2009 to December 2011, 199 patient candidates for IORT were included in a mono-institutional interventional study approved by the Ethics Committee (NCT01276938).

The median age at diagnosis was 67 (range=45-85) years. Females eligible for breast-conserving surgery, with biopsy-proven invasive carcinoma (ductal, cribriform, tubular, apocrine, mucinous) and with a primary mass of less than 2.5 cm, negative margin, intraductal component <25% and no previous history of cancer, were included in this study (Table I).

According to the major tumor diameter, evaluated with frozen section examination, patients underwent one of two different doses: <1 cm: a single dose of 18 Gy; 1-<2.5 cm: a single dose of 21 Gy. Thence the prescription single radiation dose was driven by tumor size.

According to the common linear quadratic formula (15, 16), considering for breast tumor a radiosensitivity α/β value of 4 Gy, 21 Gy in one fraction would be biologically equivalent to 70 Gy in 35 fractions, while 18 Gy in one fraction is equivalent to 60 Gy in 30 fractions.

After wide local excision, sentinel lymph node dissection, and surgical positioning of the appropriately-sized applicator on the tumor bed, a single dose of 18 Gy or 21 Gy was given using LIAC, a mobile linear accelerator (Sordina, Padova, Italy) delivering an electron beam with energies ranging from 4 to 10 MeV. The collimation of the beam was achieved by a hard-docking system, consisting of 4-, 5-, or 6-cm diameter perspex applicators, using electron energy of 6, 8 and 10 MeV, respectively. A shielding disk, made from lead and aluminum, was inserted between the residual breast gland and the pectoral muscle in order to limit thoracic wall irradiation.

In vivo dosimetry was performed for each treatment with a 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 middle of the irradiation field (17).

Protection of the chest wall was guaranteed by the absorptive properties of the lead and the aluminum and by the 9-mm distance created by the disk (18).

The total dose was delivered in two consecutive steps, in each of which half of the prescribed dose was given. This two-step procedure allowed the dose delivered at the first step to be controlled, and individually corrected at the second step.

The primary study endpoint was 5-year local relapse-free survival (LRFS) from IORT treatment, evaluated by annual mammograms and clinical examination, secondary endpoints were overall survival (OS) and evaluation of subcutaneous tissue toxicity. The differences between the 18 Gy and 21 Gy groups were analyzed using the chi-square test or Fisher's exact test for categorical variables and the Student *t*-test for continuous variables.

Table I. *Patient selection for enrollment in the intraoperative radiotherapy with electrons procedure.*

Parameter	Accrual favorable criteria
Age	>45 Years
Histology	Invasive not lobular carcinoma
	No extensive (<25%) intraductal component
Tumor size assessment	≤2.5 cm
Surgical margins	Negative (>5 mm)
Follow-up	Patient's availability
Radiological examinations	Patient's availability
Informed consent	Obtained

Results

The median follow-up was 91 months (range=16-104 months). Sixty-five patients (pT1a\b, pN0\mic, pMx, G1-G3) received 18 Gy and 134 (pT1c\2, pN0\mic, pMx, G1-G3) received 21 Gy.

Seven patients presented local relapse, two (3%) in the 18 Gy arm and five (3.7%) in the 21 Gy arm.

The cumulative 5-year LRFS and OS for the whole cohort were 96.5% and 96%, respectively. No significant difference in LRFS and OS was detected in the 18 Gy-treated arm *versus* the 21 Gy-treated arm: at 5 years: 96.9% *vs*. 96.3% p=0.72; and 96.9% *vs*. 95.5 p=0.82, respectively (Figures 1 and 2).

At final histological examination, 176 patients presented invasive ductal carcinoma and 23 patients other histology (none invasive lobular carcinoma or ductal carcinoma *in situ*) (Table II).

With regards to histology (invasive ductal carcinoma *vs*. other) and molecular subtype [luminal A, luminal B, human epidermal growth factor receptor 2 overexpression ($HER2^+$), basal-like], no significant differences were detected between the two groups.

With regards to toxicity, in nine patients, three (4.6%) in the 18 Gy-treated arm and six (4.4%) in the 21 Gy-treated arm, breast ultrasound during follow-up showed liponecrosis.

According to the Modified Late Effects Normal Tissue Task Force-Subjective, Objective, Management and Analytic (LENT-SOMA) scoring system (19), long-term follow-up of the subcutaneous tissue effects showed two patients (3.07%) had G2 fibrosis, 11 (16.92%) G1 and 52 (80%) had no fibrosis in the 18 Gy-treated group; in the other group treated with 21Gy, six patients (4.47%) had G2 fibrosis, 24 (17.91%) G1 and 104 (77.61%) had no fibrosis (Figure 3).

Discussion

Several randomized trials and large multi-institutional studies suggest that is fundamental to follow guidelines in order to better select a subset of women that are suitable candidates for IORT treatment (8, 9, 17, 20). According to the statement in the American Society for Radiation Oncology (ASTRO) consensus guideline, updated in 2017, it was established that IORT with electron use should be limited to women who otherwise meet 'suitable' criteria for partial breast irradiation (21).

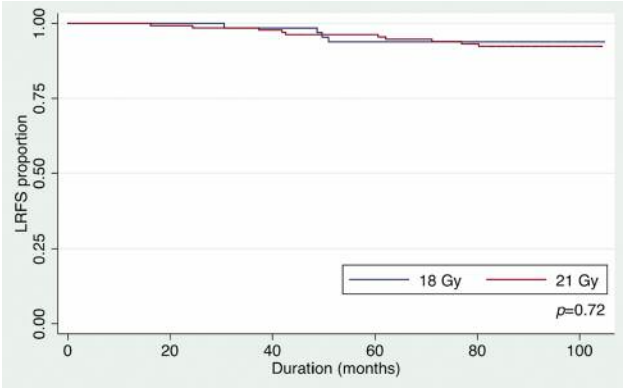

Figure 1. *Local recurrence-free survival according to intraoperative radiotherapy dose.*

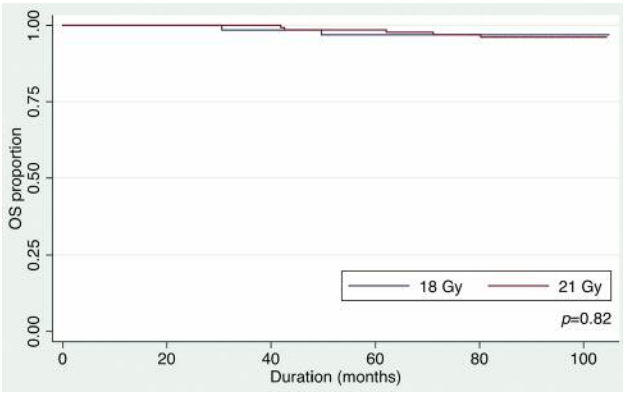

Figure 2. *Overall survival according to intraoperative radiotherapy dose.*

Table II. *Patient characteristics according to dose of intraoperative radiotherapy with electrons (IORT).*

Characteristic	IORT dose		*p*-Value
	18 Gy	21 Gy	
No. of patients	65	134	
Mean age (SD), years	66.1 (9.3)	67.0 (11.0)	0.551[a]
T-Stage, n			
T1a	8	0	<0.001[b]
T1b	57	0	
T1c	0	121	
T2	0	13	
Grading, n			
G1	13	21	0.070[b]
G2	48	89	
G3	4	24	
Histology, n			
DCI	56	120	0.494[c]
Other	9	14	

DCI: Ductal carcinoma *in situ*. [a]Student's *t*-test, [b]Fisher's exact test, [c]Chi-square test.

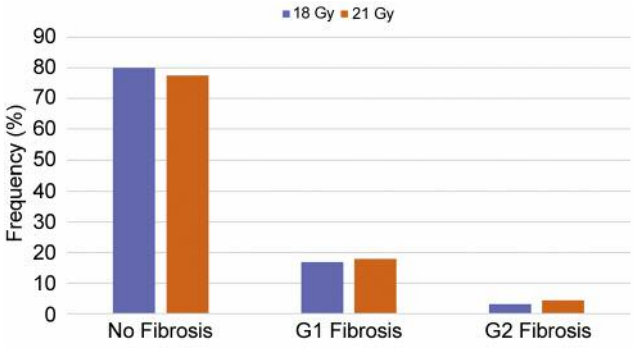

Figure 3. *Assessment of late toxicity (fibrosis) using the modified LENT-SOMA scale (19).*

Vaidya *et al*. in the TARGIT-A trial, a randomized, non-inferiority study, enrolled 3451 women older than 45 years from 33 international centers from 10 countries (UK, USA, Germany, Italy, France, Poland, Switzerland, Denmark, Canada and Australia). Patients were randomly assigned in a 1:1 ratio to receive targeted IORT with a dose of 20 Gy or WBI with a dose of 40-56 Gy with or without a boost (8). This trial demonstrated that the targeted IORT approach is non-inferior regarding its efficacy in controlling local recurrence in selected patients.

Veronesi *et al*. at the European Institute of Oncology (Milan, Italy) conducted a randomized trial comparing local recurrence and overall survival in patients treated by electron IORT (ELIOT) *versus* postoperative external radiotherapy. A total of 654 women were assigned to the external radiotherapy group (50 Gy with 10 Gy boost) and 651 to the ELIOT group (21 Gy with 6-9 MeV electrons). The outcomes were assessed at 5 years from the end of the accrual (median follow-up of 5.8 years). The conclusion of this randomized analysis was that IORT with electrons should be restricted to suitable patients due to an increased risk of ipsilateral breast tumor recurrences (4.4 *vs*. 0.4%, p=0.0001) (9).

Guenzi *et al*. in a recently published study retrospectively analyzed 470 patients with early breast cancer, comparing treatment with IORT and hypofractionated WBI. Local relapse was observed in 3.4% (8/235) among patients treated with IORT and 0.42% (1/235) among those treated with hypofractionated WBI (p=0.0192), these results also suggested that rigorous patient selection is needed (17).

Furthermore, Leonardi *et al*. conducted a study focused on the role of histology in patients with early breast cancer treated by exclusive IORT. The comparison of treatment outcome between 252 patients affected by invasive lobular carcinoma and 1,921 patients with ductal carcinoma highlighted a higher incidence of recurrence in patients with lobular carcinoma than in those with ductal carcinoma (22).

However, in conclusion, all the different trials focusing on partial breast irradiation over the past 10 years have shown that in properly selected patients with breast cancer, APBI and WBI had similar outcomes. In the last ASTRO consensus statement published in 2017, the suitability criteria for APBI were updated as follow: age ≥50 years, pTis or T1: low to intermediate nuclear grade, tumor size ≤2.5 cm, resected with negative margins at ≥3 mm (21).

As regards the single radiation dose, several studies were conducted to establish which is the most suitable, effective and safe. Veronesi *et al*. tested different radiation dose levels: 10, 15 Gy (as a boost) 17, 19 and 21 Gy (as an exclusive dose) and stated as a standard of care the 21 Gy dose level since it was found to be safe without major acute side-effects (23).

In our trial, we explored 18 Gy as a single dose as a de-escalated level for very early tumors with a size of less than 1 cm to assess the toxicity rate as well as long-term disease control. Biologically, in cases with early tumor, residual microscopic cancer cells after surgery may be well oxygenated, less proliferative and less aggressive (G3: 6% in the 18 Gy-treated group *vs*. 18% in the 21 Gy-treated group). Our results confirm that a lower dose of IORT for selected breast tumors may be as safe and effective as the 21 Gy dose: as observed in our research, potential late toxicity may be low. Although 21 Gy remains the more common dose for exclusive IORT with electrons in breast cancer, from our data no differences for the lower 18 Gy dose emerge. Delivering less radiation dose to women with breast cancer may be of radioprotective benefit with minor risk of long-term radiation-induced effects.

We report that IORT with a single dose of 18 Gy may be considered as an option for breast tumors smaller than 1 cm. This suggestion emerges from the evidence that the lower dose of 18 Gy, in one fraction, appeared to be able to achieve excellent results in terms of local toxicity, cosmetics and local control in selected cases with early breast cancer. A longer follow-up and further trials are necessary to confirm these results.

Conflicts of Interest

There is no conflict of interest to disclose.

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