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REVIEW

Breast cancer electron intraoperative radiotherapy: assessment of preoperative selection factors from a retrospective analysis of 758 patients and review of literature

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Abstract

Purpose To report our experience with full-dose 21 Gy IORT in early breast cancer patients after breast-conserving surgery to define most important selection factors.

Methods Seven hundred and fifty eight patients, subjected to conserving surgery and IORT, were retrospectively analyzed evaluating most important clinical outcomes.

Results Median follow up was 5.2 years. Results from Cox analyses defined 2 groups of patients, "suitable" (age > 50 years, non lobular histology, tumour size ≤ 2 cm, pN0 or pNmic, ki67 ≤ 20%, non triple negative receptor status and G1-G2) and "unsuitable" for IORT, with a higher rate of breast related events moving from "suitable" to "unsuitable" group. The 5 year rate of IBR is 1.8% in suitable group with significant differences versus unsuitable (1.8 vs. 11.6%, $p < 0.005$). Same differences between two groups were evidenced in true local relapse (0.6 vs. 6.9%, $p < 0.005$) and in new ipsilateral BC (1.1 vs. 4.7%, $p < 0.015$).

Conclusions In our current practice we consider the following preoperative factors to select patients suitable for IORT: age > 50 years, absence of lobular histology, tumor size ≤ 2 cm, pN0 or pNmic, according to APBI consensus statement, including also ki67 ≤ 20%, non triple negative receptor status and G1–G2.

Keywords Partial breast radiotherapy · Intraoperative radiotherapy · Prognostic factors

Introduction

Whole breast radiotherapy (WBRT) after breast-conserving surgery (BCS) is currently the standard of care in patients with early breast cancer (BC) younger than age 70 [1], with a 5 year local recurrence of around 5–6% [2–4], while for those over age 70, the standard of care is represented by BCS with or without WBRT, evaluating carefully factors related to prognostic risk [5]. Postoperative adjuvant RT is generally delivered with a 5–6 weeks' conventional treatment. Despite the possibility to shorten the therapy duration with hypofractionated schedules [6], most of patients still undergo conventional external beam RT (EBRT) for about 30 consecutive days. Problems concerning the distance from RT centers and difficulties, such as comorbidities, to attend a daily treatment, are related to the omission of adjuvant RT in a few cases or to the choice of mastectomy to avoid postoperative RT.

During the last few years, the literature evidenced that most of local relapses are at the level of the same quadrant of the original tumor [7]. The use of accelerated partial breast irradiation (APBI) with a single session of intraoperative radiotherapy (IORT) can offer an alternative to EBRT in selected patients with the following advantages:

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avoidance of a long treatment duration, without waiting between surgery and radiotherapy; delineation of the tumor bed under direct visual and palpable evaluation; reduction of radiation-induced toxicity [7, 8]. Also in a subgroup of patients, such as the elderly, in which the use of postoperative RT is still controversial [9], full-dose IORT could represent an alternative to the omission of RT after BCS.

We present the results of a median 5.2 years follow-up in patients with early breast cancer after breast-conserving surgery and IORT after a stratification of all patients according to Groupe Européen de Curiethérapie-European Society for Therapeutic radiology and Oncology (GEC-ESTRO) and American Society for Radiation Oncology (ASTRO) recommendations, and results were compared and discussed. Moreove,r we considered other factors not included in previous recommendations, to access the possibility to get more reliable selection, based only on prognostic factors for patients eligible for IORT.

Materials and methods

From February 2006 to January 2016, 772 IORT procedures were performed on 758 patients at Papa Giovanni XXIII Hospital (ASST-PG23), Bergamo (Italy).

Median age was 64 (range 42–84 years).

Breast cancer was classified according to the AJCC TNM classification [10] of malignant tumors. Primary tumor size and focality were evaluated microscopically analyzing parenchima between foci. Histology and tumor grade were defined according to WHO classification [11] and the Nottingham Grading System (NGS) [12], respectively. Lympho-vascular invasion (LVI) according to Rosen's criteria [13] was described as focal or diffuse. Regarding the presence of intraductal component (EIC), patients were divided into three groups: absent, present in a percentage <25% (focal or reduced component), and present in a percentage >25%. For Estrogen (ER) and Progesteron (PR) receptors, status was considered as two groups according to immunohistochemistry [14]: positive or negative (<10%). HER2 immunohistochemistry (IHC) scores of 0 and 1+ were considered negative. HER2 IHC 3+, and fluorescent in situ hybridization (FISH)-amplified tumors were considered positive. All IHC 2+ tumors were tested for gene amplification by FISH [15]. Concerning mitotic index Ki-67, we used a validated cutoff value according to St Gallen International Expert Consensus on primary therapy in early BC 2015 [16], and we distinguished two groups: positive (>20%) and negative (≤20%).

Finally, surgical margins were divided into three categories: negative (a layer of 2 mm from inked surface free from malignant cells), close < 2 mm (the presence of malignant cells between 1 and 2 mm from the inked margin), and positive (malignant cells in the inked margin).

For most of patients ($n = 637$), quadrantectomy with sentinel node biopsy alone was performed, while in 135 patients, axillary dissection was executed.

All patients underwent electron IORT (ELIOT) at the level of tumor bed. It was performed by a dedicated linear accelerator NOVAC 7 HITESYS (NRT, Italy). The single full-dose of 21 Gy was prescribed at 90%. The energy was 9 MeV (D selector) for all patients. Beam collimation was performed using Perspex cylindrical applicators mounted in exit window head. Collimator diameters were 4 cm ($n = 294$), 5 cm ($n = 431$), and 6 cm ($n = 47$). A simple and useful solution was developed to guarantee an optimal treatment setup: a plex disk (diameter 2 cm larger than the correspondent applicator), positioned between the inferior part of the applicator and target volume, makes the tissue more uniform and compact, permitting an easy determination of treatment volume thickness. Moreover, a dosimetric build-up effect was obtained. To verify in real time the accuracy in dose delivering, in order to define an action level, micro-mosfet detectors were used for in vivo dosimetry. The mosfet was sandwiched between the disk and the target surface.

A the end of the procedure, four clips were inserted in breast tissue along the circumference of the applicator and one at the level of the deep margin, to distinguish the in-breast tumor recurrences (IBTR) between the true local relapse (in-RT field) and the new ipsilateral recurrence (out-RT field).

Ten patients with synchronous and three with metachronous breast cancer underwent bilateral surgery followed by IORT. For one patient, ipsilateral metachronous surgery and IORT were performed.

Patients with pathological positive lymph nodes, after surgery, underwent systemic therapy.

We retrospectively stratified all patients according to GEC-ESTRO [17] and ASTRO [18] classifications. Patients were divided into three groups: for GEC-ESTRO (Table 1), "low-risk," "intermediate risk," and "high risk"; and for ASTRO (Table 2), "suitable," "cautionary," and "unsuitable."

We evaluated the following outcomes [19]: IBTR—defined as any local relapse (LR) within the treated breast, including both true local (in the same quadrant of the primary tumor) and new ipsilateral recurrence (in quadrants other than that primarily involved); regional lymph node failure (RNF)—defined as any recurrence at the level of the ipsilateral axillary, supraclavicular, and internal mammary node areas; distant metastases (DM)—defined as any recurrence at the level of organs or structures different from ipsilateral or contralateral breast; cause-specific survival (CSS) and overall survival (OS), assessed from the date of surgery until death related to breast tumor and to the last follow-up or time of death, respectively.

Table 1 Patients' characteristics stratified according to GEC-ESTRO classification

Characteristics	Low risk candidates ($n = 350$)	Intermediate risk candidates ($n = 185$)	High risk candidates ($n = 237$)
Age			
40–50	–	9 (4.9%)	4 (1.7%)
>50	350 (100%)	176 (95.1%)	233 (98.3%)
Tumour size (cm)			
≤3	350 (100%)	185 (100%)	230 (97%)
>3	–	–	6 (2.5%)
pT			
pT1	308 (88%)	158 (85.4%)	182 (76.8%)
pT2	42 (12%)	27 (14.6%)	54 (22.8%)
Margins			
Negative	350 (100%)	161 (87%)	166 (70%)
Close ≤ 2		24 (12.9%)	48 (20.2%)
Positive	–	–	23 (9.7%)
Tumour grade			
G1	82 (23.4%)	18 (9.7%)	22 (9.3%)
G2	202 (57.7%)	134 (72.4%)	139 (58.6%)
G3	66 (18.9%)	32 (17.3%)	75 (31.6%)
LVI			
Absent	350 (100%)	185 (100%)	122 (51.5%)
Present	–	–	115 (48.5%)
ER status			
Positive	317 (90.6%)	179 (96.8%)	202 (85.2%)
Negative	33 (9.4%)	6 (3.2%)	34 (14.3%)
Focality			
Unifocal	350 (100%)	134 (72.4%)	183 (77.2%)
Multifocal	–	51 (27.6%)	54 (22.8%)
Histology			
Ductal	337 (96.3%)	92 (49.7%)	215 (90.7%)
Lobular	–	76 (41.1%)	14 (5.9%)
Mixed (ductal + lobular)	–	12 (6.5%)	2 (0.8%)
Other histologies	13 (3.7%)	5 (2.7%)	6 (2.5%)
EIC			
Absent	350 (100%)	185 (100%)	119 (50.2%)
Present	–	–	118 (49.8%)
Lymph node status			
Negative	350 (100%)	116 (62.7%)	159 (67.1%)
pN1mic or pN1a	–	69 (37.3%)	44 (18.6%)
pNx or >pN1a			34 (14.3%)

For the survival analysis, the start of observation was considered the date of breast surgery.

Statistical analyses were performed by Kaplan–Meier method, and with a 5 year ratio (CI at 95%), differences among groups were made using log-rank test (p value < 0.05). Prognostic relevance of characteristics considered for the outcomes was assessed by means of Cox proportional hazard regression analysis.

Results

Median follow up was 5, 2 years (range 0–9 years).

Among patients who underwent axillary dissection ($n = 135$), metastatic sentinel lymph nodes were evidenced in 95 and micro-metastatic type in 15 patients, respectively.

Considering international guidelines for APBI, we stratified patients in three groups according to GEC-ESTRO and

Table 2 Patients' characteristics stratified according to ASTRO classification

Characteristics	Suitable candidates ($n = 116$)	Cautionary candidates ($n = 381$)	Unsuitable candidates ($n = 275$)
Age			
≤50	–	–	13 (4.7%)
50-60	–	130 (34.1%)	86 (31.3%)
≥60	116 (100%)	251 (65.9%)	176 (64%)
Tumor size (cm)			
≤2	116 (100%)	324 (85%)	209 (75.6%)
2.1–3	–	57 (15%)	59 (24.5%)
≥3	–	–	6 (2.2%)
pT			
pT1	116 (100%)	324 (85%)	209 (75.6%)
pT2	–	57 (15%)	65 (24%)
Margins			
Negative	116 (100%)	359 (94.2%)	202 (73.5%)
Close ≤ 2	–	22 (5.7%)	50 (18.1%)
Positive	–	–	23 (8.4%)
Tumor grade			
G1	40 (34.5%)	62 (16.3%)	20 (7.3%)
G2	65 (56%)	242 (63.5%)	168 (61.1%)
G3	11 (9.5%)	76 (19.9%)	86 (31.3%)
LVI			
Absent	116 (100%)	381 (100%)	160 (58.2%)
Present	–	–	115 (41.8%)
ER status			
Positive	116 (100%)	335 (87.9%)	239 (86.9%)
Negative	–	46 (12.1%)	35 (12.7%)
Focality			
Unifocal	116 (100%)	336 (88.2%)	215 (78.2%)
Multifocal	–	45 (11.8%)	60 (21.8%)
Histology			
Ductal	109 (94%)	294 (77.2%)	241 (87.6%)
Lobular	–	68 (17.8%)	22 (8%)
Mixed (ductal ± lobular)	–	10 (2.6%)	4 (1.5%)
Other histologies	7 (6%)	9 (2.4%)	8 (2.9%)
EIC			
Absent	116 (100%)	343 (90%)	195 (70.9%)
Present	–	38 (10%)	80 (29.1%)
Lymph node status			
Negative	116 (100%)	365 (100%)	149 (54.2%)
pN1mic or pN1a	–	–	84 (30.5%)
pNx or ≥pN1a	–	–	34 (12.4%)

ASTRO recommendations (Tables 1, 2). Patients were inserted into each group according to the patient's (age) and tumor's characteristics (size, margins, grade, receptor status, histology factors, lymph nodes status).

Observing the two stratifications, most of our patients fall into the low-risk category ($n = 350$) for GEC-ESTRO, and into the cautionary category ($n = 381$) for ASTRO classification. These results can be explained considering that ASTRO is more restrictive than GEC-ESTRO particularly regarding age (≥60 vs. >50 year-old patients), tumor size (≤2 vs. ≤3 cm), and receptor status (estrogen receptor presence status vs any receptor status).

Applying GEC-ESTRO classification, we observed statistically significant differences among the three groups for

IBR ($p < 0.005$), true local ($p = 0.007$), and the new ipsilateral recurrences ($p < 0.005$) (Table 3): moving from low-risk (3.3% IBR, 2.4% true local, and 1% new ipsilateral recurrence) and intermediate-risk (9.5% IBR, 3.6% true local, and 5.9% new ipsilateral recurrence) groups to high-risk group (13.4% IBR, 8.6% true local, and 4.8% new ipsilateral recurrence), the incidence of breast-related events increased significantly.

Applying ASTRO classification, statistically significant differences for all the clinical outcomes, except for the OS ($p = 0.088$), were evidenced among the three groups (Table 4). In this case, moving from suitable group (1.2% IBR, 0% true local, and 1.2% new ispilateral recurrence) to cautionary (5.9% IBR, 3.2% true local, and 2.8% new ispilateral recurrence) and unsuitable (13.5% IBR, 8.4% true local, and 5.1% new ispilateral recurrence) groups the incidence of breast-related events increased significantly.

Evaluating most important prognostic factors for every outcome resulted from Cox analysis (Table 5)

(age > 50 years, non-lobular histology, tumor size ≤2 cm, pN0 or pNmic, ki67≤20%, non-triple negative receptor status and G1–G2), we defined two groups of patients, "suitable" and "unsuitable" for IORT. We evidenced statistically significant differences in all clinical outcomes, except for OS ($p = 0.231$), (Table 6) as in ASTRO stratification. Besides moving from "suitable" (1.8% IBR, 0.6% true local, and 1.1% new ispilateral recurrence) to "unsuitable" (11.6% IBR, 6.9% true local, and 4.7% new ispilateral recurrence) group a significantly higher rate of breast-related events was evidenced.

Discussion

Adjuvant WBRT after BCS, currently, represents the standard of care for most of early-staged patients, reducing by 15% the 10 year risk of any recurrence and by 50% with the addition of a boost to the surgical bed [3]. However,

Table 3 Differences for all clinical outcomes among "low-risk," "intermediate-risk," and "high-risk" groups in patients stratified according to GEC-ESTRO classification

	Number at risk	Numbers of events	Numbers censored	Ratio at 5 years (%)	CI at 95%	p-Value
In breast tumor recurrence						
Low	350	17	333	3.3	(1.0–5.7%)	<0.005
Intermediate	185	16	169	9.5	(4.3–14.7%)	
High	237	33	204	13.4	(8.1–18.8%)	
True local recurrence						
Low	350	15	335	2.4	(0.4–4.3%)	0.007
Intermediate	185	6	179	3.6	(0.4–6.7%)	
High	237	22	215	8.6	(4.4–12.9)	
New ipsilateral breast						
Low	350	2	348	1.0	(0.0–2.3%)	<0.005
Intermediate	185	10	175	5.9	(1.7–10.1%)	
High	237	11	226	4.8	(1.6–8.0%)	
Regional lymph node failure						
Low	350	9	341	1.8	(0.2–3.3%)	0.678
Intermediate	185	5	180	1.8	(0.0–3.8)	
High	237	9	228	4.8	(1.6–8.0%)	
Distant metastates						
Low	350	5	345	1.4	(0.0–2.7%)	0.007
Intermediate	185	4	181	1.3	(0.0–3.0%)	
High	237	14	223	5.9	(2.4–9.4%)	
Cause specific survival						
Low	350	5	345	98.3	(96.5–100.0%)	0.157
Intermediate	185	3	182	99.1	(97.4–100.0%)	
High	237	9	228	95.0	(91.7–98.2%)	
Overall survival						
Low	350	17	333	94.8	(92.0–97.6%)	0.056
Intermediate	185	6	179	97.5	(94.7–100.0%)	
High	237	20	217	90.8	(86.6–95.1%)	

Table 4 Differences for all clinical outcomes among "suitable," "cautionary," and "unsuitable" groups in patients stratified according to ASTRO classification

	Number at risk	Numbers of events	Numbers censored	Ratio at 5 years (%)	CI at 95%	p-Value
In breast tumor recurrence						
Suitable	116	4	112	1.2	(0.0–3.4%)	<0.005
Cautionary	381	24	357	5.9	(3.0–8.9%)	
Unsuitable	275	38	237	13.5	(8.5–18.5%)	
True local recurrence						
Suitable	116	3	113	0.0		0.018
Cautionary	381	16	365	3.2	(1.1–5.3%)	
Unsuitable	275	24	251	8.4	(4.5–12.3%)	
New ipsilateral breast cancer						
Suitable	116	1	115	0.0		0.029
Cautionary	381	8	373	2.8	(0.7–4.8%)	
Unsuitable	275	14	261	5.1	(2.0–8.2%)	
Regional lymph node failure						
Suitable	116	1	115	0.0		0.036
Cautionary	381	8	373	2.8	(0.7–4.8%)	
Unsuitable	275	14	261	5.1	(2.0–8.2%)	
Distant metastates						
Suitable	116	0	116	0.0		<0.005
Cautionary	381	5	376	1.2	(0.0–2.4%)	
Unsuitable	275	8	257	6.0	(2.7–9.3%)	
Cause specific survival						
Suitable	116	116	0	116	0.0	<0.005
Cautionary	381	5	376	98.4	(96.9–100%)	
Unsuitable	275	12	263	94.9	(92.0–98.1%)	
Overall survival						
Suitable	116	2	114	99.0	(97.1–100.0%)	0.088
Cautionary	381	20	361	94.1	(91.3–97.0%)	
Unsuitable	275	21	254	92.5	(88.9–96.1%)	

different options can be considered, such as APBI and hormone therapy alone, but still limited data are available about patients eligible for these alternative treatments.

IORT, a type of APBI, represents an attractive option as alternative to EBRT, reducing the classical fractionated schedule to a single fraction with the same equivalent dose, delivered during surgery. Particularly, among APBI techniques, IORT showed the advantages to delineate precisely the tumor bed under visual control, to perform an immediate oncoplastic breast surgery with good cosmetic results, to decrease normal tissues toxicity, easily shielding critical organs, and to reduce treatment duration [20].

Literature reports five randomized clinical trials comparing IORT and EBRT. The Christie Hospital trial [21] and the Yorkshire Breast Cancer Group trial [22] did not evidence any efficacy of IORT in terms of local control, with a higher recurrence rate with APBI than with WBRT. On the contrary, the Budapest randomized trial [23] showed that APBI produces similar long-term results compared with conventional EBRT in a strictly selected group of breast cancer patients (inclusion criteria: negative surgical margins, unifocal tumor, pT1, pN0, cN0, pN1 with nodal micro-metastasis, G1-2; exclusion criteria: prior breast or other neoplasms, age ≤ 40 years, the presence of intraductal component, invasive lobular histology, carcinoma in situ, and bilateral breast cancer).

Other two recent large, phase III-randomized trials analyzed the results obtained from the comparison between IORT and whole breast EBRT for the targeted intraoperative radiotherapy (TARGIT-A) trial [24] and the electron intraoperative treatment (ELIOT) trial [25].

Both TARGIT-A and ELIOT trials evidenced at a 5 year median follow-up that there are no differences between

Table 5 Significant prognostic factors for every outcome based on Cox analysis

Outcome		True local recurrence			Ipsilateral breast cancer			In breast tumor recurrence			Regional lymph node failure		
Predictive/risk factor	Number at risk	HR	CI 95%	p-Value	HR	CI 95%	p-Value	HR	CI 95%	p-Value	HR	CI 95%	p-Value
Age (year)													
>60	522	1.00	–	–	–	–	–	1.00	–	–	1.00	–	–
51–60	231	1.81	0.96–3.40	0.06	–	–	–	1.63	0.99–0.06	0.06	2.10	0.91–4.84	0.08
≤50	19	7.79	2.63–23.03	0.00	–	–	–	4.40	1.55–12.46	0.01	3.14	0.40–24.54	0.28
Histology													
Ductal + other	668	1.00	–	–	–	–	–	1.00	–	–	1.00	–	–
Lobular + mixed	104	0.31	0.07–1.27	0.10	3.20	1.36–7.56	0.01	1.11	0.57–2.17	0.77	2.21	0.87–5.63	0.10
Tumour size (cm)													
≤1.5	498	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
1.6–2	151	1.88	0.90–3.92	0.09	1.10	0.39–3.08	0.86	1.55	0.86–2.81	0.15	2.58	0.94–7.14	0.07
>2.0	122	2.21	1.08–4.51	0.03	1.24	0.44–3.48	0.69	1.81	1.01–3.23	0.05	3.15	1.18–8.44	0.02
Lymph node status													
pN0 + pN1mic	654	1.00	–	–	–	–	–	1.00	–	–	1.00	–	–
pN1a	84	0.95	0.37–2.43	0.92	1.61	0.54–4.79	0.39	1.17	0.57–2.37	0.67	0.74	0.17–3.16	0.68
≥pN2a	33	1.22	0.37–3.99	0.74	1.91	0.44–8.27	0.39	1.43	0.57–3.59	0.45	1.70	0.39–7.36	0.48
Tumour grade													
I, II	597	1.00	–	–	–	–	–	1.00	–	–	1.00	–	–
III	175	3.01	1.65–5.48	0.00	1.82	0.77–4.29	0.17	2.54	1.56–4.13	0.60	3.58	0.60–3.58	0.39
Ki67													
Negative	530	1.00	–	–	–	–	–	1.00	–	–	1.00	–	–
Positive (>20%)	237	2.98	1.62–5.50	0.00	1.82	0.77–4.29	0.17	2.54	1.56–4.13	0.00	1.47	0.60–3.58	0.39
Triple negative													
NT	716	1.00	–	–	–	–	–	–	–	–	1.00	–	–
Non TN	50	2.77	1.23–6.25	0.01	4.19	1.56–11.30	0.00	3.23	1.73–6.06	0.00	1.69	0.58–6.61	0.28
LVI													
Absent	657	1.00	–	–	–	–	–	1.00	–	–	1.00	–	–
Present	115	2.16	1.11–4.21	0.02	2.49	1.02–6.05	0.04	2.27	1.33–3.87	0.00	1.96	0.77–4.97	0.16

Outcome		Distant metastases			Cancer specific survival			Overall survival		
Predictive/risk factor	Number at risk	HR	CI 95%	p-Value	HR	CI 95%	p-Value	HR	CI 95%	p-Value
Age (year)										
>60	522	1.00	–	–	1.00	–	–	1.00	–	–
51–60	231	1.13	0.45–2.84	0.79	1.25	0.46–3.45	0.66	0.66	0.32–1.34	0.25
≤50	19	7.64	2.15–27.11	0.00	2.84	0.36–22.21	0.32	0.96	0.13–6.94	0.96

Table 5 continued

Outcome Predictive/risk factor	Number at risk	Distant metastases			Cancer specific survival			Overall survival		
		HR	CI 95%	p-Value	HR	CI 95%	p-Value	HR	CI 95%	p-Value
Histology										
Ductal + other	668	–	–	–	1.00	–	–	1.00	–	–
Lobular + mixed	104	–	–	–	0.82	0.19–3.57	0.79	0.65	0.23–1.81	0.41
Tumour size (cm)										
≤1.5	498	1.00	–	–	1.00	–	–	1.00	–	–
1.6–2	151	2.58	0.93–7.12	0.07	1.22	0.37–3.96	0.74	1.06	0.51–2.19	0.88
>2.0	122	3.22	1.21–8.62	0.02	1.27	0.39–4.15	0.69	0.81	0.35–1.87	0.62
Lymph node status										
pN0 + pN1mic	654	1.00	–	–	1.00	–	–	1.00	–	–
pN1a	84	3.97	1.56–10.08	0.00	5.83	2.16–15.77	0.00	2.14	1.16–3.95	0.01
≥pN2a	33	5.80	1.96–18.06	0.00	2.70	0.60–12.20	0.20	1.37	0.42–4.46	0.61
Tumor grade										
I, II	597	1.00	–	–	1.00	–	–	1.00	–	–
III	175	3.68	1.62–8.36	0.00	5.83	2.16–15.77	0.00	2.14	1.16–3.95	0.01
Ki67										
Negative	530	1.00	–	–	1.00	–	–	1.00	–	–
Positive (>20%)	237	3.38	1.46–7.82	0.00	4.96	1.75–14.07	0.00	2.47	1.35–4.51	0.00
Triple negative										
NT	716	1.00	–	–	1.00	–	–	1.00	–	–
Non TN	50	1.92	0.57–6.48	0.29	3.92	1.28–12.02	0.02	2.48	1.10–5.57	0.03
LVI										
Absent	657	1.00	–	–	1.00	–	–	1.00	–	–
Present	115	5.05	2.23–11.46	0.00	3.82	1.45–10.03	0.01	1.90	0.96–3.76	0.07

Table 6 Differences for all clinical outcomes between "suitable" and "unsuitable" for IORT from our classification

	Number at risk	Numbers of events	Numbers censored	Ratio at 5 years (%)	CI at 95%	*p*-Value
In breast tumor recurrence						
Suitable	298	6	292	1.8	(0.0–3.8%)	<0.005
Unsuitable	474	60	414	11.6	(8.1–15.1%)	
True local recurrence						
Suitable	298	3	295	0.6	(0.0–1.9%)	<0.005
Unsuitable	474	40	434	6.9	(4.2–9.6%)	
New ipsilateral breast cancer						
Suitable	298	3	295	1.1	(0.0–2.7%)	<0.015
Unsuitable	474	20	454	4.7	(2.4–7.0%)	
Regional lymph node failure						
Suitable	298	2	296	0.4	(0.0–1.3%)	<0.005
Unsuitable	474	21	453	4.0	(2–6.1%)	
Distant metastates						
Suitable	298	1	297	0.5	(0.0–1.3%)	<0.005
Unsuitable	474	22	452	4.1	(2.1–6.2%)	
Cause specific survival						
Suitable	298	1	297	99.4	(98.2–100%)	0.110
Unsuitable	474	16	458	96.3	(94.3–98.3%)	
Overall survival						
Suitable	298	12	286	96.3	(93.7–98.8%)	0.231
Unsuitable	474	31	443	93.0	(90.4–95.7%)	

IORT and EBRT in terms of overall survival, but LR rates remain significantly higher in the TARGIT (3.3 vs. 1.3%, $p = 0.042$) and in the ELIOT (4.4 vs. 0.4%, $p < 0.0001$) groups.

The 5 year LR increased from "suitable" to cautionary" to unsuitable" ASTRO groups, with a very low percentage of breast-related events in the suitable group. However, in the GEC-ESTRO, low- and intermediate-risk groups, higher percentages of IBR and LR than those in the ASTRO suitable and cautionary groups were evidenced. These results were evidenced also in the analysis of the European Institute of Oncology [19, 26] and are probably related to the differences between the two societies in the selection criteria.

In the literature, APBI generally was shown to be associated to higher frequency of local relapse compared with WBRT [27]. In our results (Table 3), the 5 year rate of IBR is 1.8% in suitable group with significant differences versus unsuitable (1.8 vs. 11.6%, $p < 0.005$). We evidenced results similar to those in the literature [23] regarding the incidence of LR (1.3%) rate after IORT. Same differences between the two groups were evidenced in true local relapse (0.6 vs. 6.9%, $p < 0.005$) and in new ipsilateral BC (1.1 vs. 4.7%, $p < 0.015$), with results being similar to those in the literature regarding the

incidence of new primary (0.8%, CI 0.4–1.4) after whole breast RT [28].

These results are interesting also from the point of view of the possibility to use IORT in a subgroup of patients as alternative to the omission of RT. Patients with low-risk BC, particularly the elderly, constitute a special population regarding prognosis and potential comorbidities. Therefore, limiting potential radio-induced side effects and maintaining a good quality of life is extremely important. In a group of elderly patients, Kunkler et al. showed [29] a statistically significant reduction in LR at 5 years in a low-risk population with the addition of RT to adjuvant endocrine therapy after BCS (4.1% without RT vs. 1.3% with RT, $p = 0.0002$), with no differences regarding OS and DM. Similar results were evidenced in the CALGB trial (1.5) in which a 3% reduction of local recurrence at 5 years was noted with the addition of radiotherapy (4% without RT vs. 1% with adjuvant RT, $p < 0.001$). The literature shows exploratory findings [30] also in a low-risk group of postmenopausal women with early-staged luminal A BC who may be spared breast irradiation, but conclusion is that further studies are needed. In an extended low-risk population (women under 60 years-old), literature [31–33] has evidenced that, at 5 year follow-up, RT after BCS is advisable even when selected adjuvant systemic therapy is

given. Fyles et al. [31] showed that the addition of RT to hormone therapy results in a significantly lower rate of breast relapse than administering hormone therapy alone (0.6% with RT vs. 7.7% without RT, $p < 0.001$), with no differences regarding DM and OS. Same results were evidenced in the Austrian trial [34], where the 5-year recurrence rate was 0.4% with RT and 5.1% without RT ($p = 0.0001$). Therefore, it is still difficult to identify the characteristics of patients with lowest risk of LR who could avoid RT after BCS [35]. In this contest, APBI, with its potential advantages compared with EBRT (shorter therapy time, improved cosmesis, and cost reduction), could be currently considered as alternative to the omission of RT in a favorable prognosis patients [29, 35].

Regarding axillary dissection ($n = 135$), during the initial years that we performed IORT, we included also patients with clinical positive nodes and we did not use to wait for the lymph node sentinel histology result. Literature widely demonstrated the influence of metastatic lymph nodes on prognosis in patients undergoing IORT [18], and we changed our practice, confirming the importance of performing IORT in patients with preoperative negative nodes (clinical and imaging assessment) and waiting intraoperative histology assessment of sentinel lymph node.

An unresolved problem regards the LVI that, from our statistical analyses, confirmed to be a fundamental predictive factor. Nevertheless, it can be evaluable only in the postoperative setting.

In conclusion, from our analysis, focused on evaluating an appropriate selection of early BC patients undergoing exclusively IORT, not generically APBI procedures as per GEC-ESTRO and ASTRO guidelines, we confirmed the importance of an adequate preoperative selection to define patients eligible for IORT.

In our current practice, we consider the following selection factors to make BC patients suitable for full-dose IORT: age > 50 years; the absence of lobular histology; tumor size ≤ 2 cm; pN0 or pNmic, according to APBI consensus statement [17, 18]; we include also non-triple negative status, G1-2, and a new factor—not inserted in GEC-ESTRO/ASTRO classifications—ki67 ≤ 20%.

In this contest, IORT is a feasible and safe technique, with results eing similar to EBRT regarding breast-related events in selected patients without significant late toxicities.

Compliance with ethical standards

Conflict of interest All authors declare no conflicts of interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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