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Orignal Article

Ductal carcinoma in situ and intraoperative partial breast irradiation: Who are the best candidates? Long-term outcome of a single institution series

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ABSTRACT

Aims: To report the long-term outcome of a single institution series of pure ductal carcinoma in situ (DCIS) treated with accelerated partial irradiation using intraoperative electrons (IOERT).

Methods: From 2000 to 2010, 180 DCIS patients, treated with quadrantectomy and 21 Gy IOERT, were analyzed in terms of ipsilateral breast recurrences (IBRs) and survival outcomes by stratification in two subgroups. The low-risk group included patients who fulfilled the suitable definition according to American Society of Radiation Oncology (ASTRO) Guidelines (size ≤2.5 cm, grade 1–2 and surgical margins ≥3 mm) (Suitable), while the remaining ones formed the high-risk group (Non-Suitable).

Results: Eighty-four and 96 patients formed the Suitable and Non-Suitable groups, respectively. In the whole population, the cumulative incidence of IBR at 5, 7 and 10 years was 19%, 21%, and 25%, respectively. In the Suitable group, the cumulative incidence of IBR remained constant at 11% throughout the years, while in the Non-Suitable group increased from 26% at 5 years to 36% at 10 years ($p < 0.0001$).

When hormonal positivity and HER2 absence of expression were added to the selection of the Suitable group, the cumulative incidence of IBR dropped and stabilized at 4% at 10 years. None died of breast cancer. In the whole population, 5-year and 10-year overall survival rate was 98% and 96.5%, respectively, without any difference between the two groups.

Conclusions: The overall and by group IBR rates were high and stricter criteria are required for acceptable local control for Suitable DCIS. Because of the concerns raised, IOERT should not be used in clinical practice.

Introduction

Accelerated partial breast irradiation (APBI) has recently been considered as a viable option to treat ductal carcinoma in situ (DCIS) with well-defined features, after breast-conserving surgery (BCS). In the updated guidelines on APBI released by the American Society of Radiation Oncology (ASTRO) [1,2] DCIS shifted from "cautionary" to "suitable" category, in line with the position previously taken by the American Brachytherapy Society [3]. The practice pattern has shown alternate trends in APBI utilization for DCIS and has been mainly addressed to elderly patients with small tumors [4]. The interest in APBI for DCIS is part of a more general policy aimed at reducing the treatment burden in all cases deemed at low risk [5]. Due to non-invasive nature, low mortality rate and no evidence of survival benefit from whole breast irradiation (WBI) [6], physicians have been striving to seek the optimal management of DCIS in the effort of minimizing both under- and overtreatment. Since previous attempts to omit radiotherapy (RT) in selected DCIS carried a high rate of ipsilateral breast recurrences (IBRs) [7–10], the use of APBI seems to be a reasonable compromise in order to improve local control.

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Pathological parameters based on size, grade and margin width identified by the Eastern Cooperative Oncology Group (ECOG) E5194 [7,8] and the Radiation Therapy Oncology Group (RTOG) 9804 trials [11] were adopted by ASTRO panelists to select DCIS suitable for APBI.

The aim of this study is to report the long-term clinical outcome of a mono-institutional series of patients affected by pure DCIS and treated with APBI using intraoperative radiotherapy with electrons (IOERT) after BCS. The impact of pathological and biological features has been analyzed in order to define the best DCIS candidates for IOERT and to identify the patients where such procedure is associated with unacceptable risk of recurrent tumor.

Methods and materials

Between 3/2000 and 5/2010, 207 patients with histologically proven DCIS were treated at the European Institute of Oncology (IEO) with IOERT.

The patients' data were entered into a database dedicated to IOERT. All patients were prospectively followed by one or more professional figures of the multidisciplinary team of the Institutional Breast Cancer Task Force. Of them, 180 patients gave written informed consent for the treatment and anonymous use of their data for educational and research purposes and were considered for the analysis. Approval of the Institutional Ethics Committee was also obtained for all investigations related to IOERT (N98/11).

In our practice, selection criteria for IOERT included patients aged ≥18 years, affected by pure DCIS, without any invasive component, of any radiological size, as long as BCS was feasible, clinically negative axillary nodes. All patients received BCS and most of them had sentinel node biopsy (SNB), according to our internal policy. The resection margin status was macroscopically evaluated in all directions and close margins (<1 cm) were sampled and subjected to microscopic examination. Definitive assessment of resection margins was performed after surgery. The perioperative procedures included the localization of DCIS using either Radioguided Occult Lesion Localization after injection of a radioactive tracer (technetium-99) into the lesion on the day before surgery or stereotactic mapping. In addition, post-surgery mammogram of the resected specimen was taken to check for any residual suspicious microcalcifications.

For the purpose of this study, the patients were classified, according to the recent ASTRO criteria, into the "Suitable" group [1], which included grade 1–2 DCIS, ≤2.5 cm in size and resection margins ≥3 mm; while those remaining formed the so-called "Non-Suitable" group, which embraced both the ASTRO cautionary and unsuitable groups and also included DCIS with unknown features.

DCIS was evaluated in routine hematoxylin and eosin slides. Pathological assessment included evaluation of histological type, the presence of necrosis and microcalcifications [12]. DCIS was subdivided according to morphology in three histologic differentiation grades (DCIS 1c, 2, and 3), following WHO guidelines [13]. Estrogen receptor (ER), progesterone receptor (PgR), Ki-67 labeling index and human epidermal growth factor receptor 2 (HER2) expressions were evaluated by immunohistochemistry, as previously described [14–16]. HER2 score 2+ was not considered for analysis because fluorescence in situ hybridization test was never performed.

Regarding the width of the resection margin, the closest distance of DCIS to the edge of the specimen was considered to define margin clearance, which was categorized as follows: less than 3 mm, from 3 mm to less than 10 mm and 10 mm or more.

IOERT consisted of a single dose of 21 Gy prescribed at the isodose of 90–100%, delivered with dedicated mobile linear accelerators. The technique did not differ from that applied for invasive breast cancer (BC) which has been described in previously published reports [17].

The use of hormonal therapy was at the discretion of medical oncologists and according to patients' preference. As per internal policy, tamoxifen dose was given either 10 mg every other day or 20 mg once a week for five years [18].

Statistical analysis

Patients' demographic, disease and treatment characteristics, overall and stratified by risk groups ("Suitable" and "Non-Suitable") were reported. Wilcoxon's signed-rank test for continuous variables, Chi-squared (or Fisher's Exact Test, when appropriate) test for binary variables and Cochran–Armitage's trend test for ordinal variables were used to compare the distribution of the evaluated characteristics between the risk groups.

The primary outcome was the incidence of any IBR, either isolated or concomitant to regional nodal recurrence.

IBR was also differentiated according to nature (invasive and non-invasive) and location with respect of the index breast quadrant (IBRs were considered true/marginal miss -TR/MM- if they occurred at the IOERT site, and elsewhere -EF- if the failure occurred outside the IOERT site within the breast). Contralateral BC, distant metastases and other primaries were also recorded.

The cumulative incidence of IBR curve functions was estimated according to methods described by Kalbfleisch and Prentice [19], taking into account the competing causes of recurrence. Gray's test was used to assess differences between groups.

Univariable Cox proportional hazard regression models were used to assess the association of risk group and clinical and histopathologic characteristics on IBR risk.

Disease-free survival (DFS) and overall survival (OS) were considered as secondary outcomes and defined by the standardized efficacy end-points (STEEP) criteria [20].

The DFS and OS functions were estimated using the Kaplan–Meier method. The log-rank test was used to assess differences between groups.

All analyses were performed using SAS software v.9.4 (SAS Institute, Cary, NC, USA) and R version 3.4.1.

Results

Characteristics of the patients, lesions and treatments are listed in Table 1. The median follow-up was 128.8 months (range, 8.7–216.2). All patients underwent quadrantectomy and in 88% of them, SNB was carried out, resulting tumor-free in all the cases.

Regarding surgical margins, 175 out of 180 specimens had no tumor cells on the resection surface. The remaining 5 presented focally positive margins and did not undergo re-excision. No microinvasive component was detected and all lesions were pure DCIS.

Breaking down the study population into the two categories for this analysis, 84 (47%) and 96 (53%) patients fell into the Suitable and Non-Suitable groups, respectively. APBI was delivered via IOERT at a median energy of 7 MeV and with a median collimator size of 4 cm in one single fraction of 21 Gy prescribed at 100% (73%) or 90% (27%, corresponding to 23 Gy at the 100% level) isodoses. Hormonal therapy was given to 46% of patients and consisted of Tamoxifen in 77% of cases.

Locoregional control

In the whole population, the cumulative incidence of IBR was 19.1%, 20.9% and 24.8% at 5, 7 and 10 years, respectively. In the Suitable group, the cumulative incidence of IBRs gradually increased to 11% within 5 years, then reached a plateau and

Table 1
Patient demographic, disease and treatment characteristics, overall and stratified by risk groups ("Suitable" and "Non-Suitable") according to American Society for Radiation Oncology Guidelines on Accelerated Partial Breast Irradiation [1].

Variable	Level	Suitable (*N* = 84)	Non-Suitable (*N* = 96)	Overall (*N* = 180)	*P*-value‡
Age in years, median (min–max)		58 (29–75)	55 (39–75)	56 (29–75)	0.19
IOERT beam energy in MeV, *N* (%)#	4–7	46 (55.4)	48 (50.0)	94 (52.5)	0.57
	8–10	37 (44.6)	48 (50.0)	85 (47.5)	
	Missing	1	0	1	
IOERT collimator size in cm, *N* (%)§	3–4	57 (68.7)	72 (75.0)	129 (72.1)	0.44
	5–6	26 (31.3)	24 (25.0)	50 (27.9)	
	Missing	1	0	1	
Isodose of prescription, *N* (%)	100%	57 (67.9)	74 (77.1)	131 (72.8)	0.22
	90%	27 (32.1)	22 (22.9)	49 (27.2)	
Gland thickness in cm, median (min–max)*		1.4 (0.7–2.5)	1.6 (0.9–3)	1.5 (0.7–3)	0.014
Familiarity, *N* (%)	No	56 (66.7)	66 (68.8)	122 (67.8)	0.89
	Yes	28 (33.3)	30 (31.2)	58 (32.2)	
Menopausal status, *N* (%)	Premenopausal	25 (29.8)	32 (33.3)	57 (31.7)	0.72
	Peri-Postmenopausal	59 (70.2)	64 (66.7)	123 (68.3)	
Lesion size in cm, median (min–max)**		1.2 (0.2–2.5)	1.7 (0.5–5.0)	1.3 (0.2–5.0)	N.e.§
Lesion size, *N* (%)	≤0.5 cm	6 (7.1)	4 (5.0)	10 (6.1)	
	0.6–1 cm	25 (29.8)	14 (17.5)	39 (23.8)	N.e.§
	1.1–2.5 cm	53 (63.1)	42 (52.5)	95 (57.9)	
	>2.5 cm	0 (0.0)	20 (25.0)	20 (12.2)	
	Missing	0	16	16	
Lobular in situ component, *N* (%)	No	72 (85.7)	86 (89.6)	158 (87.8)	0.57
	Yes	12 (14.3)	10 (10.4)	22 (12.2)	
Necrosis, *N* (%)	No	37 (44.0)	31 (32.3)	68 (37.8)	0.14
	Yes	47 (56.0)	65 (67.7)	112 (62.2)	
Microcalcifications, *N* (%)	No	21 (25.0)	22 (22.9)	43 (23.9)	0.88
	Yes	63 (75.0)	74 (77.1)	137 (76.1)	
Resection margins, *N* (%)	<3 mm	0 (0.0)	30 (31.3)	30 (16.7)	
	3–9 mm	14 (16.7)	12 (12.8)	26 (14.6)	N.e.§
	≥10 mm	70 (83.3)	52 (55.3)	122 (68.5)	
	Missing	0	2	2	
Histological subtype, *N* (%)	Solid	31 (36.9)	23 (24.0)	54 (30.0)	<0.001
	Cribriform	29 (34.5)	22 (22.9)	51 (28.3)	
	NOS	13 (15.5)	18 (18.8)	31 (17.2)	
	Papillary	7 (8.3)	2 (2.1)	9 (5.0)	
	Apocrine	3 (3.6)	2 (2.1)	5 (2.8)	
	Micropapillary	1 (1.2)	2 (2.1)	3 (1.7)	
	Comedonic	0 (0.0)	27 (28.1)	27 (15.0)	
DCIS grade, *N* (%)	1	10 (11.9)	1 (1.1)	11 (6.1)	
	2	74 (88.1)	37 (38.9)	111 (62.0)	N.e.§
	3	0 (0.0)	57 (60.0)	57 (31.8)	
	Missing	0	1	1	
ER, median (min–max)		90 (0–95)	80 (0–95)	90 (0–95)	<0.001
PgR, median (min–max)		40 (0–95)	10 (0–95)	25 (0–95)	0.008
ER and PgR, *N* (%)	Not expressed (Both 0)	13 (15.5)	28 (29.2)	41 (22.8)	0.007
	Incompletely expressed (ER < 50 or PgR < 50)	30 (35.7)	38 (39.6)	68 (37.8)	
	Highly expressed (ER ≥ 50 & PgR ≥ 50)	41 (48.8)	30 (31.2)	71 (39.4)	
ER, PgR and Hormonal therapy, *N* (%)	ER and PgR not expressed (Both 0)	13 (15.7)	28 (29.5)	41 (23.0)	0.086
	ER or PgR > 0 and No Hormonal Therapy	27 (32.5)	28 (29.5)	55 (30.9)	
	ER or PgR > 0 and Hormonal Therapy	43 (51.8)	39 (41.1)	82 (46.1)†	
	Missing	1	1	2	
Ki-67, median (min–max)		15 (1–65)	20 (3–70)	18 (1–70)	<0.001
Ki-67, *N* (%)	<14%	34 (40.5)	22 (22.9)	56 (31.1)	0.017
	≥14%	50 (59.5)	74 (77.1)	124 (68.9)	
HER2, *N* (%)	Not overexpressed	56 (80.0)	39 (49.4)	95 (63.8)	<0.001
	Overexpressed	14 (20.0)	40 (50.6)	54 (36.2)	
	Unknown	14	17	31	

‡Wilcoxon's signed-rank test for continuous variables, Chi-square (or Fisher's Exact Test, when appropriate) test for binary variables and Cochran–Armitage's trend test for ordinal variables; N.e.§: *p*-value not estimated, being criterion of categorization.
IOERT: intraoperative radiotherapy with electrons; MeV: megaelectronvolt; DCIS: ductal carcinoma in situ; NOS: not otherwise specified; ER: estrogen receptor; PgR: progesterone receptor; HER2: Human epidermal growth factor receptor 2.

maintained it up to 10 years. The mean time to IBR was 2.9 years. In the Non-Suitable group, the cumulative incidence of IBRs steadily continued to rise over time, reaching 36% at 10 years, with a greater than 3-fold increase compared to the Suitable group. The mean time to IBR was 4.3 years (Table 2). Regarding the location across the breast with respect of primary DCIS, 40% of IBRs were considered to be TR/MM in the Suitable group and 73% in the Non-Suitable group. While 70% of the IBRs were in situ in the Suitable group, 62% were in invasive cancers in the Non-Suitable group.

None of the patients in the Suitable group developed regional node recurrence, as opposed to 27% in the Non-Suitable group. Most IBRs received salvage mastectomy both in the Suitable and Non-Suitable groups (70% and 62%, respectively), while the remaining ones were treated with repeat quadrantectomy.

Univariate analysis of prognostic factors for locoregional control

Univariate Cox regression analysis of possible prognostic factors for IBR is illustrated in Tables 3 and 4.

Table 2
Cumulative incidence of in-breast breast recurrence (IBR), disease-free survival and overall survival in the whole population and by risk groups.

In-breast recurrence (IBR)					
		Cumulative incidence of IBR (95% CI)			
	IBR Events/At risk	5-yr	7-yr	10-yr	HR univariate (95% CI)
All patients	47/180 (26.1%)	19.1 (13.7–25.2)	20.9 (15.2–27.2)	24.8 (18.6–31.5)	–
Suitable	10/84 (11.9%)	11.0 (5.3–18.8)	11.0 (5.3–18.8)	11.0 (5.3–18.8)	Ref.
Non-Suitable	37/96 (38.5%)	26.1 (17.8–35.3)	29.5 (20.6–38.9)	36.4 (26.7–46.2)	3.65 (1.80–7.41)
Disease-free survival (DFS)					
		Disease-free survival proportion (95% CI)			
	Events/At risk	5-yr	7-yr	10-yr	HR univariate (95% CI)
All patients	63/180 (35.0%)	75.8 (68.8–81.4)	72.3 (65.0–78.3)	67.1 (59.6–73.6)	–
Suitable	18/84 (21.4%)	84.2 (74.3–90.5)	81.7 (71.4–88.5)	80.3 (69.9–87.5)	Ref.
Non-Suitable	45/96 (46.9%)	68.6 (58.2–76.9)	64.2 (53.6–72.9)	56.1 (45.4–65.5)	2.47 (1.43–4.27)
Overall survival (OS)					
		Overall survival proportion (95% CI)			
	Deaths/At risk	5-yr	7-yr	10-yr	HR univariate (95% CI)
All patients	7/180 (3.9%)	97.8 (94.2–99.2)	97.2 (93.4–98.8)	96.5 (92.2–98.4)	–
Suitable	4/84 (4.8%)	97.6 (90.8–99.4)	96.4 (89.2–98.8)	96.4 (89.2–98.8)	Ref.
Non-Suitable	3/96 (3.1%)	97.9 (91.8–99.5)	97.9 (91.8–99.5)	96.6 (89.7–98.9)	0.62 (0.14–2.79)

CI: confidence interval; HR: hazard ratio.

In the whole population (Table 3), HER2 overexpression, alongside other well-known risk factors, was associated with a lower local control. In the Suitable group, HER2 overexpression remained significant, in particular, the association with ER/PgR negative HER2-enriched subtype (Table 4). Expanding the ASTRO eligibility criteria for the Suitable group by adding positive hormonal receptors and HER2 absence of expression to pathological features, the 5-year cumulative incidence of IBRs dropped at 4.1% and maintained a plateau thereafter up to 10 years (Fig. 1, Panel C).

In the Non-Suitable group, the cumulative incidence of IBRs was significantly higher in patients under 50 (39% and 51.3% at 5 and 10 years, respectively) compared to those of age 50 and over (18.4% and 27.5% at 5 and 10 years, respectively, $p = 0.002$).

Survival outcomes and other events

No distant metastases have been documented for any patients and none died of BC, leading to the 10-year BC-specific survival of 100%. DFS included IBRs, contralateral BC, other primaries and death and was significantly lower in the Non-Suitable compared to the Suitable group. Five- and 10-year OS was higher than 96% both in the whole population and in the categorized groups (Table 2).

Contralateral BC was observed in 5 patients (2.8%), of whom 4 belonged to the Non-Suitable group, while other primary tumors in different sites were detected in 4.4% of cases (5 in the Suitable and 3 in the Non-Suitable groups).

Discussion

To our knowledge, this is the first investigation on the use of IOERT for DCIS and one of the largest series with long follow-up reported in the dedicated literature. The treatment of DCIS with IOERT was part of our clinical routine practice as personalized approach in the early 2000s and fell out of favor when the Groupe Européen de Curiethérapie of European Society for Radiotherapy and Oncology (ESTRO) [21] and the first version of ASTRO [2] guidelines did not allow APBI for DCIS. Our results showed that patients with pure DCIS had high risk of local failure when treated with IOERT. In fact, in the whole IOERT population, the 5- and 10-year rate of IBRs peaked at 19.1% and at 24.8%, respectively, which is comparable with the rate reported in the no RT arm of the randomized trials addressing the role of WBI after BCS [6]. Even when selection criteria based on pathological information of size, grade and margins according to the updated version of ASTRO guidelines [1] were applied, the IBR rate of 11% was disappointingly high. Once again, the local control achieved with IOERT was similar to the outcome of the two non-randomized prospective studies of surgery without RT in favorably selected DCIS from the ECOG and the Harvard-affiliated medical institutions [7–10].

The introduction of APBI in the DCIS management is aimed to improve local control compared to excision alone, while sparing the burden of WBI. APBI has been pursued in a number of studies throughout the literature, most of them showing favorable results.

In patients treated with different modalities of APBI, having the same characteristics as those enrolled in the ECOG trial, the 5-year IBR rate decreased from 6.1% to 0–2% in case of grade 1–2 DCIS, ≤2.5 cm and from 15.3% to 0–5.3% in case of grade 3, ≤1 cm [22,23]. Favorable outcome was also reported by several APBI studies, including two randomized phase III trials [24] using either external RT or brachytherapy (BRT), which involved higher grade and/or larger size DCIS. The range of IBRs in such unselected DCIS varied from 0% to 4% at 3–5 years follow-up [25–28] with BC-specific survival approaching 100% and OS >94% at 5 years. In the whole IOERT population, although local control was discouragingly low, long-term OS remained high, underlying the effectiveness of salvage therapies, which is consistent with other studies on IBR following BCS and WBI [29].

In the Suitable group, only the integration of biomolecular factors has allowed a reduction in IBR rate. As matter of fact, the criteria to define low-risk DCIS for de-escalating approaches are controversial and risk-stratification models for individualized treatments are not yet robust enough to be used on a large scale [30,31]. The potential role of biological markers in predicting disease outcome in DCIS has not been investigated as extensively as for invasive cancer and is challenged by conflicting results. A number of studies, including a meta-analysis [32–34], found that ER/PgR negativity and HER2 positivity were independent predictors of recurrence, often associated with each other [34], so that the corresponding phenotype was correlated with increased risk of recurrence, which is in line with our results [35]. In particular, HER2 overexpression appeared to be associated with increased cell prolif-

Table 3
Association between patients' demographic and disease characteristics and the development of in-breast recurrence (Univariate models) in the overall population.

Variable	Level	*N*	IBR/PY	Rate × 100 PY	5-Year Cumulative incidence of IBR	10-Year Cumulative incidence of IBR	HR univariate	95% CI	*P*-value
Age (years, continuous)	–						0.957	0.93–0.99	0.011
Age (years, categorical)	≤50	62	25/438	5.71	29.6 (18.6–41.4)	37.1 (24.8–49.4)	Ref.		
	>50	118	22/1010	2.18	13.7 (8.2–20.6)	18.4 (11.9–26.1)	0.389	0.22–0.69	0.001
IOERT beam energy (MeV)[#]	4–7	94	24/756	3.17	17.2 (10.3–25.6)	24.5 (16.1–33.9)	Ref.		
	8–10	85	23/680	3.38	21.5 (13.4–30.9)	25.4 (16.5–35.1)	1.117	0.63–1.97	0.70
IOERT Collimator size (cm)[#]	3–4	129	36/1021	3.53	20.3 (13.8–27.7)	27.2 (19.7–35.3)	Ref.		
	5–6	50	11/416	2.64	16.5 (7.6–28.2)	18.7 (9.1–30.9)	0.798	0.41–1.55	0.51
Isodose of prescription	100%	131	39/1049	3.72	21.4 (14.8–28.9)	27.3 (19.8–35.2)	Ref.		
	90%	49	8/399	2.01	12.7 (5.1–23.9)	17.5 (8.1–30.0)	0.547	0.25–1.19	0.13
Lobular in situ component	No	158	43/1283	3.35	19.1 (13.4–25.6)	25.5 (18.8–32.7)	Ref.		
	Yes	22	4/165	2.42	19.0 (5.7–38.3)	19.0 (5.7–38.3)	0.702	0.25–1.99	0.51
Necrosis	No	68	15/522	2.87	17.6 (9.7–27.6)	22.3 (13.2–33.0)	Ref.		
	Yes	112	32/926	3.46	20.1 (13.1–28.0)	26.2 (18.2–34.8)	1.319	0.71–2.45	0.38
Lesion size (cm)[*]	≤1	49	11/393	2.80	14.9 (6.5–26.6)	24.2 (12.8–37.5)	Ref.		
	1.1–2.5	95	25/783	3.19	21.1 (13.5–29.8)	25.8 (17.4–35.2)	1.247	0.62–2.51	0.54
	>2.5	20	8/144	5.56	25.4 (8.8–46.1)	30.7 (12.0–51.9)	1.864	0.79–4.41	0.16
Lesion grade[#]	1	11	1/100	1.00	9.1 (0.4–34.8)	9.1 (0.4–34.8)	Ref.		
	2	111	21/912	2.30	15.6 (9.5–23.0)	16.7 (10.4–24.5)	2.379	0.31–18.27	0.41
	3	57	25/425	5.88	28.3 (17.2–40.5)	43.8 (30.2–56.6)	6.158	0.81–47.05	0.080
Resection margins (mm)[**]	<3	30	12/200	6.00	37.2 (20.0–54.4)	40.9 (22.9–58.2)	Ref.		
	3–9	26	5/198	2.53	11.5 (2.8–27.1)	16.8 (4.9–34.9)	0.404	0.14–1.15	0.090
	≥10	122	28/1038	2.70	15.8 (9.9–22.9)	21.2 (14.3–29.0)	0.475	0.24–0.95	0.034
ER and PgR	ER and PgR not expressed (Both 0)	41	14/279	5.02	30.1 (16.6–44.7)	35.4 (20.8–50.3)	Ref.		
	ER > 0 or PgR > 0	139	33/1169	2.82	16.0 (10.4–22.6)	21.7 (15.1–29.1)	0.588	0.31–1.11	0.099
ER PgR and Therapy[§]	ER and PgR not expressed	41	14/279	5.02	30.1 (16.6–44.7)	35.4 (20.8–50.3)	Ref.		
	ER or PgR > 0 and No Hormonal Therapy	55	12/445	2.70	14.5 (6.7–25.2)	20.5 (10.8–32.2)	0.549	0.25–1.19	0.13
	ER or PgR > 0 and Hormonal Therapy	82	21/705	2.98	17.3 (10.0–26.4)	22.8 (14.2–32.7)	0.628	0.32–1.24	0.18
Ki-67 (continuous)	–						1.012	0.99–1.03	0.24
Ki-67 (categorical)	<14%	56	11/477	2.31	12.6 (5.5–22.8)	16.9 (8.2–28.3)	Ref.		
	≥14%	124	36/970	3.71	22.1 (15.2–29.9)	28.4 (20.5–36.7)	1.625	0.84–3.13	0.15
HER2[†]	Not overexpressed	95	19/793	2.40	17.0 (10.2–25.3)	17.0 (10.2–25.3)	Ref.		
	Overexpressed	54	23/387	5.94	31.5 (19.6–44.2)	41.2 (27.8–54.2)	2.430	1.33–4.44	0.004

IOERT: intraoperative radiotherapy with electrons; IBR: in-breast recurrence; PY: per year; MeV: megaelectronvolt; ER: estrogen receptor; PgR: progesterone receptor; HER2: Human epidermal growth factor receptor 2; CI: Confidence interval.

[*] 16 missing IBR/PY = 3/127.

[#] 1 missing IBR/PY = 0/11.

[**] 2 missing IBR/PY = 2/11.

[†] 31 missing IBR/PY = 5/268.

[§] 2 missing.

Table 4
Association between patients' demographic and disease characteristics and the development of in-breast recurrence (Univariate models) in "Suitable" group (*N* = 84).

Variable	Level	*N*	IBR/PY	Rate × 100 PY	5-Year Cumulative incidence of IBR[*]	HR univariate	95% CI	*P*-value
Age (years, continuous)	–					0.947	0.89–1.01	0.071
Age (years, categorical)	≤50	26	5/210	2.38	16.0 (4.9–33.0)	Ref.		
	>50	58	5/515	0.97	8.7 (3.2–17.9)	0.445	0.13–1.50	0.19
IOERT beam energy (MeV)[#]	4–7	46	4/390	1.03	8.9 (2.8–19.5)	Ref.		
	8–10	37	6/324	1.85	13.8 (5.0–27.2)	1.957	0.56–6.84	0.29
IOERT collimator size (cm)[#]	3–4	57	7/486	1.44	12.5 (5.4–22.6)	Ref.		
	5–6	26	3/228	1.32	8.0 (1.3–22.9)	0.986	0.25–3.86	0.98
Isodose of prescription	100%	57	8/498	1.61	12.3 (5.3–22.3)	Ref.		
	90%	27	2/227	0.88	7.7 (1.3–22.2)	0.566	0.12–2.66	0.47
Lobular in situ component	No	72	9/618	1.46	11.3 (5.2–19.9)	Ref.		
	Yes	12	1/107	0.93	9.1 (0.4–34.7)	0.688	0.09–5.31	0.72
Necrosis	No	37	3/312	0.96	8.1 (2.0–19.8)	Ref.		
	Yes	47	7/413	1.69	13.2 (5.3–24.9)	1.980	0.52–7.60	0.32
DCIS grade	1	10	0/97	0.00	0.0 (0.0–0.0)	Ref.		
	2	74	10/628	1.59	12.5 (6.1–21.2)	N.e.	N.e.	0.26[¶]
ER and PgR	ER and PgR not expressed (Both 0)	13	4/85	4.71	32.9 (9.2–59.5)	Ref.		
	ER > 0 or PgR > 0	71	6/641	0.94	7.1 (2.6–14.8)	0.205	0.06–0.74	0.016
ER PgR and Therapy[§]	ER and PgR not expressed	13	4/85	4.71	32.9 (9.2–59.5)	Ref.		
	ER or PgR > 0 and No Hormonal Therapy	27	0/246	0.00	0.0 (0.0–0.0)	N.e.	N.e.	0.002[¶]
	ER or PgR > 0 and Hormonal Therapy	43	6/385	1.56	11.9 (4.3–23.7)	0.339	0.09–1.21	0.097
Ki-67 (continuous)	–					1.017	0.97–1.06	0.44
Ki-67 (categorical)	<14%	34	4/305	1.31	8.8 (2.2–21.3)	Ref.		
	≥14%	50	6/420	1.43	12.4 (5–23.5)	1.103	0.32–3.80	0.88
HER2[†]	Not overexpressed	56	5/506	0.99	7.3 (2.3–16.2)	Ref.		
	Overexpressed	14	5/92	5.43	35.7 (12.2–60.4)	4.874	1.46–16.24	0.010

N.e.: Not estimated; IOERT: intraoperative radiotherapy with electrons; IBR: in-breast recurrence; PY: per year; MeV: megaelectronvolt; DCIS: ductal carcinoma in situ; ER: estrogen receptor; PgR: progesterone receptor; HER2: Human epidermal growth factor receptor 2; CI: Confidence interval.
[*] 10-year Cumulative incidence of IBR = 5-year Cumulative incidence of IBR in "Suitable" group (see Table 2).
[#] 1 missing IBR/PY = 0/11.
[¶] Based on a Poisson exact analysis.
[†] 14 missing IBR/PY = 0/12.
[§] 1 missing.

eration, higher cell motility and larger lesion extent with a greater probability of occult DCIS foci in the breast [36]. In our series, endocrine responsiveness was significantly associated with lower risk of IBRs only in the Suitable group, but the use of Tamoxifen did not have any statistical impact, neither in the whole population nor in the risk groups. Hormonal therapy is generally accepted as having a positive effect on local control in DCIS [37], but the use of adjuvant Tamoxifen is variable in clinical practice. In our series, the small number of patients (n = 83, 46%) receiving low-dose Tamoxifen did not allow any consideration on the effect of therapy.

No technical factors related to dose, applicator diameter and electron energy were found to be associated with the risk of IBR. However, the strong dependency of IOERT field on the surgical breech may have jeopardized the appropriate target coverage, especially considering the potential discontinuous growth of DCIS along the ducts [38]. Poor outcome was also described in two studies using intra-perioperative APBI modalities: with MammoSite BRT, Abbott and coll. [39] reported 9.8% of IBR at 5 years in unselected DCIS, while Zauls and coll. [40] showed an increased risk of failure for DCIS when compared with invasive carcinoma, describing an IBR rate of 11% at 4 years.

Another hypothesis to explain the poor local outcome with IOERT might be the different radiobiological response of DCIS to high single dose. In addition, larger lesion size was observed in the current series (median 1.3 cm) compared to those reported in the published studies with favorable outcome (median 0.5–0.8 cm) [23,27,41]. Lesion size proved to be an important predictor of IBRs [42] and might have partly contributed to the unfavorable study results. In the report by Benitez and coll. [43], DCIS with a mean size of 1.06 cm treated with MammoSite carried 4% incidence of IBR at 3 years.

In the current study, a different pattern of relapse was observed between the Suitable and Non-Suitable patients. In the latter group, the incidence of IBRs continued to rise over time. Most of IBRs were invasive and presented axillary involvement, in spite of the large proportion of index lesion negative SNB. This finding might be explained with the lack of contribution of WBI tangential fields on the first axillary level [44]. In the Suitable group, most of IBRs were in situ, reached a plateau, which is typical of in-situ IBRs [45,46] and occurred mainly outside the IOERT site, supporting the concept that low-grade forms of DCIS are more likely to be multicentric [47]. A series of 232 cases of grade 1 DCIS treated in our Institution with excision alone reported a 5-year IBR rate of 12% [48], which was similar to that observed in the Suitable group after IOERT, but with a more aggressive behavior. Partly due to the younger age of patients included in this series of surgery alone, the incidence of IBRs kept increasing over time, with no apparent plateau, and 58% of them were invasive. The absence of well-defined plateau was also observed in other randomized and non-randomized studies of surgery without RT [6–11].

The use of IOERT for DCIS raises some concerns related to the perioperative assessment of the ASTRO pathological criteria. The main weakness of any IORT-based APBI lies in the lack of the full histologic picture of the disease at the time of RT delivery and it is particularly crucial in case of DCIS, due to the characteristic disease heterogeneity. The risk of upgrading cases diagnosed as grade 1–2 on core biopsy to grade 3 DCIS or invasive cancers on the final histologic report can be as high as 19% [49] and one of the major criticisms for non-interventional trials of active monitoring [50]. In our series, on final pathology, the upgrade rate to grade 3 was 6.6% in 91/180 evaluable patients, while no invasive cancer was found.

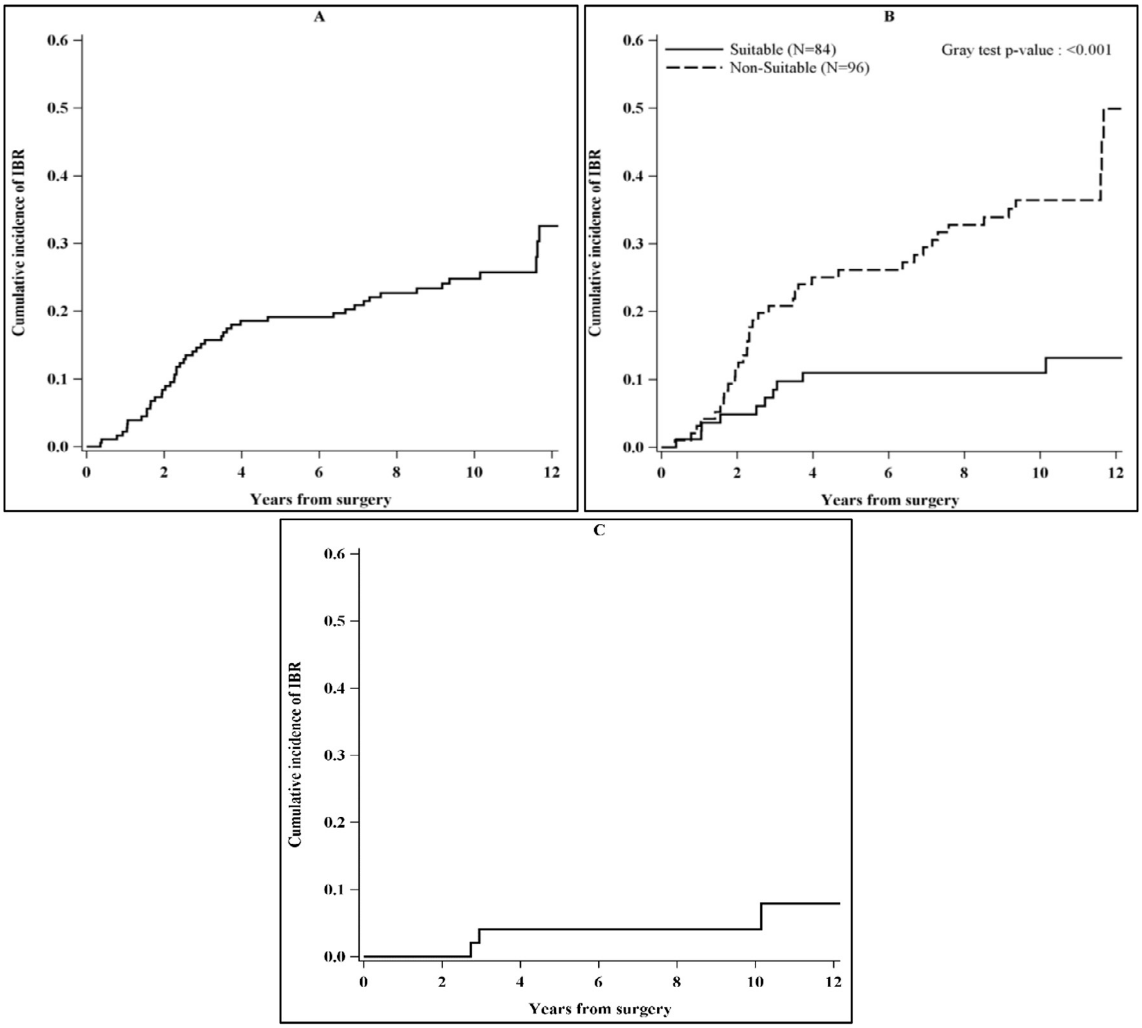

Fig. 1. Cumulative Incidence of in-breast recurrence (IBR), overall (Panel A), by risk groups (Suitable and Non-Suitable) using pathological information (Panel B) and in Suitable group using both pathological and biomolecular information (Panel C).

Furthermore, the intraoperative evaluation of margins for DCIS is more difficult than for invasive cancer, due to skipping lesions [38] and differential diagnosis with other intraductal epithelial proliferation and lobular in situ neoplasia [47]. Although in case of APBI the optimal margin width remains to be determined, the minimum of 3 mm recommended by ASTRO guidelines based on the ECOG data were confirmed to be adequate in our IOERT series. However, despite the care taken intraoperatively, margins resulted to be focally positive in 5 cases on the final histologic report.

There is a number of limitations to this analysis. Although data were prospectively entered into a dedicated database, this represents a retrospective study with an unplanned analysis by groupings and therefore is associated with intrinsic limitations. Grade 2 was the most represented grade in the Suitable group (Grade 1: 10/94 patients), therefore the results of the study mainly referred to intermediate grade.

While acknowledging the limitations, our study showed a substantial risk of IBRs in DCIS patients, including those identified by the ASTRO Suitable criteria, and highlighted the challenges of reliable pathologic characterization of DCIS in the intra-perioperative settings. In the light of these concerns, IOERT should not be used in the clinical practice. At the same time, the findings of the study suggest that further refinements of the selection criteria for DCIS may be necessary to improve risk assessment and treatment decision-making in the context of de-escalating programs.

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Conflict of interest

All the authors declare that there is no actual or potential conflict of interest.

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