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Scientific Article

Long-Term Results of Intraoperative Radiation Therapy for Early Breast Cancer Using a Nondedicated Linear Accelerator

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Purpose: To present the long-term results of intraoperative radiation therapy (IORT) for early breast cancer using a nondedicated linear accelerator.

Methods and Materials: The eligibility criteria were biopsy-proven invasive carcinoma, age ≥40 years, tumor size ≤3 cm, and N0M0. We excluded multifocal lesions and sentinel lymph node involvement. All patients had previously undergone breast magnetic resonance imaging. Breast-conserving surgery with margins and sentinel lymph node evaluation using frozen sections were performed in all cases. If there were no margins or involved sentinel lymph nodes, the patient was transferred from the operative suite to the linear accelerator room, where IORT was delivered (21 Gy).

Results: A total of 209 patients who were followed up for ≥1.5 years from 2004 to 2019 were included. The median age was 60.3 years (range, 40-88.6), and the mean pT was 1.3 cm (range, 0.2-4). There were 90.5% pN0 cases (7.2% of micrometastases and 1.9% of macrometastases). Ninety-seven percent of the cases were margin free. The rate of lymphovascular invasion was 10.6%. Twelve patients were negative for hormonal receptors, and 28 patients were HER2 positive. The median Ki-67 index was 29% (range, 0.1-85). Intrinsic subtype stratification was as follows: luminal A, 62.7% (n = 131); luminal B, 19.1% (n = 40); HER2 enriched 13.4% (n = 28); and triple negative, 4.8% (n = 10). Within the median follow-up of 145 months (range, 12.8-187.1), the 5-year, 10-year, and 15-year overall survival rates were 98%, 94.7%, and 88%, respectively. The 5-year, 10-year, and 15-year disease-free rates were 96.3%, 90%, and 75.6%, respectively. The 15-year local recurrence-free rate was 76%. Fifteen local recurrences (7.2%) occurred throughout the follow-up

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period. The mean time to local recurrence was 145 months (range, 12.8-187.1). As a first event, 3 cases of lymph node recurrence, 3 cases of distant metastasis, and 2 cancer-related deaths were recorded. Tumor size >1 cm, grade III, and lymphovascular invasion were identified as risk factors.

Conclusions: Despite approximately 7% of recurrences, we may infer that IORT may still be a reasonable option for selected cases. However, these patients require a longer follow-up as recurrences may occur after 10 years.

Introduction

Despite the efforts dedicated to awareness campaigns and screening policies, breast cancer remains among the most prevalent cancers worldwide.[1] Fortunately, early diagnosis and proper treatment yield reasonable disease control rates. Generally, conservative surgery not only allows breast conservation but also conservation of lymph node chains, as the analysis of the sentinel lymph nodes avoids elective dissection of the axilla in most cases. In addition, owing to immediate oncoplastic procedures, the eventual deformity in conservative surgery is markedly less striking.

Radiation therapy (RT) is paramount in breast-conserving therapy for early breast cancer, as revealed by several studies and meta-analyses.[2] In recent years, robust level 1 medical evidence has demonstrated that RT strategies can adapt to new times: conventional fractionation of 5 to 6 weeks can be replaced by moderate hypofractionation (3 weeks)[3-7] or ultrahypofractionation (in 1 week[8] or 5 weekly doses[9]). This strategy of shortening the treatment time through hypofractionation and the question of whether this approach should only be applied to some subgroups[10] (elderly patients with early luminal tumors might not benefit from RT in addition to surgery and hormonal therapy) appropriately align with the challenging times associated with the COVID-19 pandemic.

From this point of view, accelerated partial breast irradiation (APBI) is an old strategy but remains interesting owing to the possibility of not only reducing the treatment time but also the volume of irradiation. By using different strategies, several researchers have demonstrated that in well-selected patients, equivalent oncological effectiveness is possible, with a lower level of toxicity than conventional treatments. Among APBI strategies, studies have been conducted using low- and high-dose-rate interstitial brachytherapy, balloon brachytherapy, partial 3-dimensional conformal or intensity modulated RT, intraoperative RT (IORT) using brachytherapy, electron- or kilovoltage photon-beams, and stereotactic body RT with tracking capabilities.

In 2004, our institution launched the IORT program using a nondedicated linear accelerator (ndLINAC) instead of purchasing a dedicated machine because of its costs and the possibility of expanding this approach to other centers in other developing countries. Our initial results are reported elsewhere.[11-15] Of note, good local control, low complication rates, and good cosmetic results were achieved in well-selected patients. Additionally, some advantages of the use of ndLINAC were recognized, such as the image guidance approach (2-dimensional image taken intraoperatively for alignment between the collimator and the lead shield) and the potential use of higher electron beam energies than those available in dedicated machines.

This study aimed to reveal the long-term results of our study, with a focus on local control and survival.

Methods and Materials

We established a single-institution, prospective, phase 2 cohort in May 2004, which comprised patients with early invasive no special type breast carcinoma who fulfilled the study's eligibility criteria. The local ethics committee approved the research protocol, and each patient signed an informed consent form before inclusion in the study. The inclusion criteria, surgery issues, and radiation aspects are described elsewhere.[11] Of note, eligible patients were older than 40 years, had lesions <3 cm, had clinically negative lymph nodes, had histologically confirmed invasive no special breast carcinoma, and had undergone breast magnetic resonance imaging (MRI) to rule out multifocality and multicentricity. Suspected cases were referred for histologic confirmation of new tumor foci.

During surgery, after sentinel lymph node and margin evaluation,[16] the shielding disc was placed beneath the target parenchyma and above the muscle. The shielding discs consisted of 3 joined 3-mm layers made of lead (face down), aluminum (middle), and silicon (face up) to avoid backscattered electron absorption effects in the breast parenchyma after disc interaction. Breast parenchyma was approximated over the disc. Subsequently, the patient was transferred to the ndLINAC room under general anesthesia. Patient transport followed the recommendations of the hospital infection control committee. IORT was delivered from the collimator surface to the bottom of the shield according to the thickness of the breast parenchyma to be treated. A single dose of 21 Gy was then administered. A portal film or an electronic portal imaging device scan (both 2-dimensional images) was used to ensure alignment between the collimator and shield. If the alignment was unsatisfactory, appropriate corrections were made by the radiation oncologist. Briefly,

these corrections involved changing the position of the shield to the collimator, which was performed carefully to maintain the target breast parenchyma in the desired position. Another image was then captured, and this procedure was repeated until the alignment was considered appropriate. After treatment completion, surgery was performed in the operating room. According to the definitive pathologic results, a multidisciplinary team evaluated the need for adjuvant systemic therapies.

Statistical method

The following variables were analyzed: age on the procedure date; clinical and pathologic staging; definitive histology; systemic treatments (frequency and types); follow-up time; cumulative incidence of local, locoregional, and distant recurrences at the last follow-up; and death rates. In addition, data on the outcomes of patients who experienced cancer-related events were collected. Descriptive and frequency analyses were conducted by calculating the means, standard deviations, medians, and interquartile ranges. The Kolmogorov-Smirnov test was used to verify the normal distribution of the numerical variables.

Survival estimates were calculated using the Kaplan-Meier method with the log-rank test for comparison. All outcomes were considered from the date of surgery. Overall survival was defined as the time to death by any cause, disease-free survival until the detection of the first recurrence, local disease-free survival until recurrence in the treated breast, and locoregional-free survival regarding lymph node recurrences. Univariate and multivariate analyses were performed, and odds ratios were calculated using logistic regression. Statistical analyses were performed using Statistical Package for the Social Sciences software version 20. For statistical formalism purposes, a significance *P*-value of 5% and 95% confidence interval were selected.

Results

Patient characteristics

A total of 209 patients were included, and the follow-up period was ≥1.5 years. The median age was 60.3 years (range, 40-89). Table 1 shows the patient characteristics.

Overall, 14 deaths occurred during the study period, 6 of which were related to breast cancer. Notably, 57% of all deaths occurred before the 10-year follow-up. Twenty-three other cancer-related events occurred. Among them, 15 local recurrences and 3 cases of lymph node metastasis were the first breast cancer-related events. Most local or locoregional recurrences (75%) occurred after the 10-year follow-up.

Figure 1 illustrates the overall survival and disease-free survival outcomes. The 5-year, 10-year, and 15-year overall survival rates were 98.0%, 94.7%, and 88.0%, respectively. Based on univariate analysis, a tumor size of ≤1 cm (pT1a or b) was associated with better survival (P = .026). The 5-year, 10-year, and 15-year disease-free rates were 96.3%, 90.0%, and 75.6%, respectively. Larger tumors >1 cm or >2 cm (pT1 vs pT2) were associated with worse outcomes (P = .009 and P = .027, respectively), such as histologic grade 3 (P = .020).

Figure 2 shows the actuarial local recurrence-free survival. Fifteen local recurrences (7.2%) (as the first event) occurred throughout the follow-up period. The median time to local recurrence was 140.7 months (range, 12.8-187.1). None of the variables were related to local or locoregional recurrence. However, lymph vascular invasion was marginally significant in both groups (P = .075). Only 3 cases of lymph node metastasis as the first breast cancer-related event were recorded.

Figure 3 illustrates the follow-up of all patients who had breast cancer-related events. Of note, some cases had >1 event after the first event but were still followed up. The treatments administered to these patients varied, but in general, patients with local and regional recurrence underwent mastectomy with or without axillary lymphadenectomy, whereas those with metastatic disease were administered systemic therapies according to the tumor subtype and the patient's current condition. Of the mastectomy cases, 1 had lymph nodes in the pathologic specimen, which led to further postmastectomy external beam RT, including the chest wall and lymph node sites.

Table 2 shows the exploratory analysis results of cases of local recurrence as a function of grouping by subtype. Notably, a predominance of Luminal A and B cases was found among patients with local recurrence, mainly because of the initial selection of treatment cases. Of the Luminal A and B cases, 2.88% and 2.4%, respectively, had local recurrence within the entire sample. Univariate analysis was performed to correlate the studied variables with local recurrence, overall survival, and disease-free survival (Table E1). A pathologic tumor size >1 cm and histologic grade 3 were associated with worse overall and disease-free survival (Table E1). The presence of lymphovascular invasion was related to local recurrence; however, the difference was not statistically significant (P = .074; Table E1). The calculated odds ratios, according to clinically significant variables, revealed that tumor size, histologic grade, and lymphovascular invasion are risk factors for these patients (Table 3).

Discussion

This study sought to reveal the long-term results of our single institutional series involving well-selected patients, 100% of whom underwent local staging with breast MRI to rule out multicentricity and multifocality. This fact can be considered unprecedented when our data are

Table 1 Patient characteristics

Characteristic		N	%
Age, y	40-49	46	22.0
	50-59	56	26.8
	60-69	76	36.4
	70-79	26	12.4
	≥80	5	2.4
cT	Nonpalpable tumor	141	67.5
	≤2 cm	58	27.7
	2.1-3 cm	10	4.8
pT	≤1 cm	57	27.3
	1.1-2 cm	117	56.0
	2.1-3 cm	33	15.8
	>3 cm	2	0.9
pN	Negative	190	90.9
	Micrometastasis	15	7.2
	Macrometastasis	4	1.9
Margin status after frozen sections	Initially free	128	61.2
	Free after 1 ampliation	62	29.7
	Free after 2 ampliations	15	7.2
	Free after 3 ampliations	3	1.4
	Free after 5 ampliations	1	0.5
Margin status at definitive pathology	Free	206	98.6
	Positive	3	1.4
Definitive histology	DCIS	2	1
	NOS carcinoma	196	93.8
	Invasive lobular carcinoma	1	0.5
	Mucinous carcinoma	7	3.3
	Tubular carcinoma	1	0.5
	Papillary-type carcinoma	1	0.5
	Neuroendocrine carcinoma	1	0.5
Histologic grade	I	32	15.3
	II	113	54.1
	III	64	30.6
Nuclear grade	I	16	7.7
	II	109	52.2
	III	84	40.1
Lymphovascular invasion	Negative	187	89.5
	Positive	22	10.5
Ki-67 status	≤14%	86	41.1
	>14%	62	29.7
	Unavailable data	61	29.2

(*continued on next page*)

Table 1 (*Continued*)

Characteristic		N	%
Estrogen receptor status	Positive	196	93.8
	Negative	13	6.2
Progesterone receptor status	Positive	193	92.3
	Negative	16	7.7
HER2 status	Positive (FISH included)	28	13.4
	Negative	181	86.6
Intrinsic subtypes	Luminal A	131	62.7
	Luminal B	40	19.1
	Luminal HER2	25	12.0
	Pure HER2	3	1.4
	TNBC	10	4.8

Abbreviations: cT = clinical tumor size; DCIS = ductal carcinoma in situ; FISH = fluorescence in situ hybridization; HER = human epidermal growth factor receptor; NOS = nonspecial type; pN = pathologic lymph node status; pT = pathologic tumor size; TNBC = triple-negative breast cancer.

compared with those of other studies. In a previous publication,[11] the unprecedented use of portal films or electronic portal imaging devices in all patients was assessed to optimize the alignment between the collimator and protective lead shields placed beneath the breast parenchyma. By combining these facts with the treatment experience obtained using ndLINACs, higher electron beam energies than those available in dedicated/exclusive machines could be employed.

In our previous publication, we reported toxicity and esthetic results. The median time of appearance of late toxicity was of 8 months. Fibrosis was observed in 21 patients, whereas fat necrosis was seen in 15 cases. At the 1-year evaluation, 92.7% had a score of good or excellent.[13] We believe that this study provided a background to support IORT as an option in selected patients, even if some findings from recent years are considered, and may have shed light on the role of APBI modalities in breast cancer treatment:

1. With the onset of the COVID-19 pandemic, there has been increased interest in therapeutic strategies focusing on treatment de-escalation, shortening treatment time, and reducing the burden on health services. In the last 2 years, we saw the publication the findings of the FAST trial[9] and the FAST-FORWARD trial,[8] which have undisputedly validated ultrahypofractionated whole-breast RT for most patients.
2. During the pandemic, the results of long-term studies, namely the TARGIT[17] and ELIOT[18] trials, which revealed the advantages and disadvantages of using IORT, were published. In the ELIOT study, local recurrence rates were significantly higher in patients treated with IORT, whereas in the TARGIT study, the

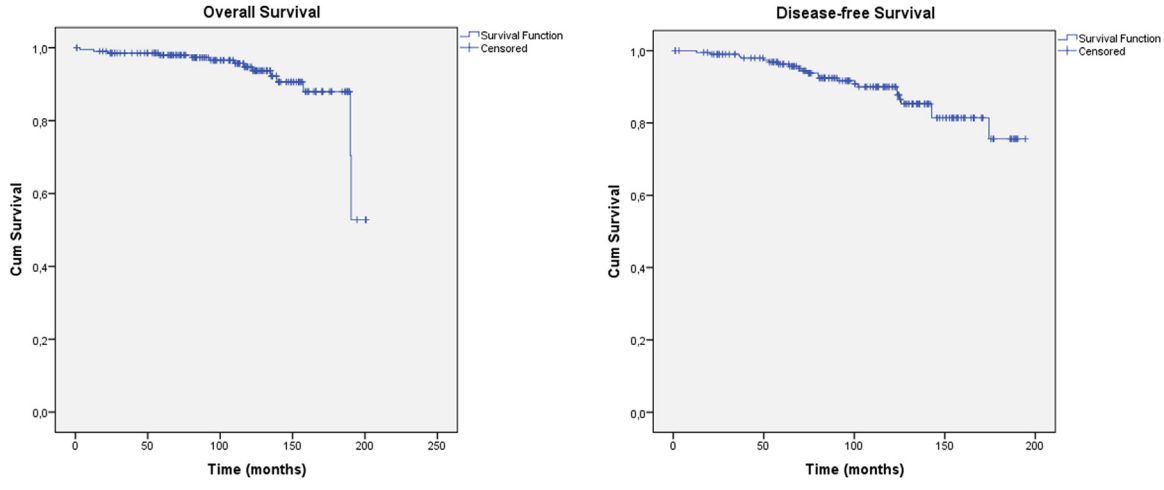

Figure 1 Overall survival and disease-free survival.

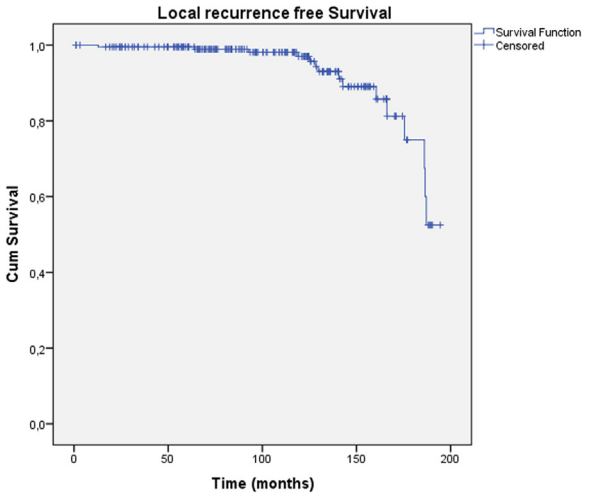

Figure 2 Local recurrence-free survival.

differences in breast recurrence-free survival were similar among study arms.

3. Other studies exploring different forms of APBI have been conducted over the last 5 years, such as the NSABP B-39/RTOG 0413,[19] RAPID,[20] Florence,[20] Hungarian Brachytherapy,[21] and IMPORT LOW[22] trials. Overall, these studies revealed the equivalence in local control outcomes and some advantages in terms of toxicity and treatment time.
4. Studies validating the omission of RT after breast-conserving surgery in selected patients (generally postmenopausal patients with tumors in the early stages and positive hormone receptors) have been published in recent years, such as the PRIME-2 trial.[23]

Based on the information collected, and the conclusions of the main meta-analyses that compared APBI with whole-breast RT,[24-28] which suggested higher recurrence rates in APBI cases, with no difference in overall survival, and the caution regarding the inclusion of IORT as a safer modality of APBI in the main treatment guidelines,[29-34] the following statements highlight relevant information regarding IORT that should be known by a daily practice clinician:

1) IORT competes with other forms of APBI. According to the data, recurrences with IORT are higher than those with other forms of APBI, and the logistics and cost of treatment are more complex with IORT than with other forms of APBI (especially external beam APBI).
2) APBI competes with radiation therapy omission. Although nonirradiated patients will have more recurrences, they will achieve the same survival as irradiated patients.
3) APBI competes with whole-breast RT ultrahypofractionation. The logistics of ultrahypofractionation are the same, if not better, than those of APBI, and the toxicity rates are equivalent. Furthermore, 1 to 5 APBI fractions do not differ from 5 whole-breast RT fractions in terms of treatment time.

Of note, the randomized studies involving APBI, especially IORT, did not uniformly follow the patient selection criteria. Many of the studies selected their inclusion criteria before the publication of the main guidelines. Furthermore, currently known criteria were not considered for patient selection (eg, grouping by intrinsic subtypes), in which interpretation of the main data are dependent on retrospective assessments involving independent predictors. Of note, subset analysis of patients enrolled in the ELIOT trial serves as an example.[35] Luminal A cases (grouped in the retrospective analysis) had a local recurrence rate of 1.5% versus 4.4% for the entire IORT arm (in the 2014 publication).[36] In our study, 62% of cases were Luminal A cases, of which 2.8% had local recurrence at any time during follow-up (also one-third of the entire sample). The remaining subtypes were poorly represented

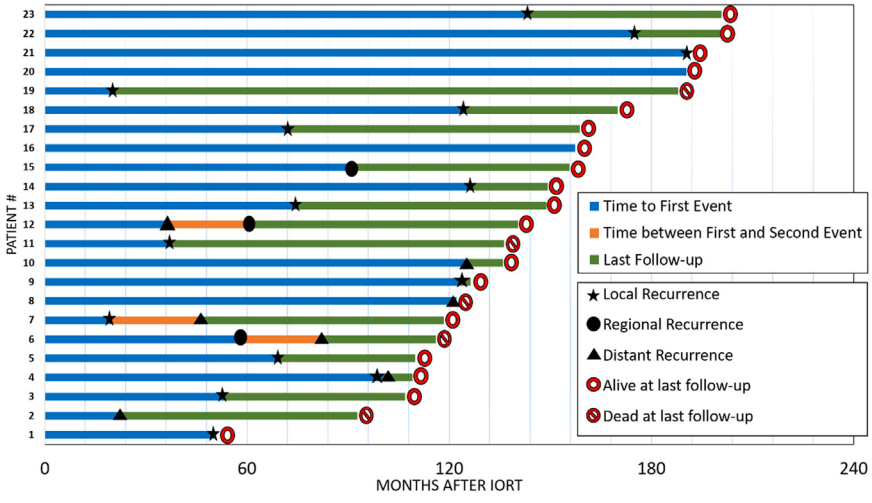

Figure 3 Outcomes of patients with breast cancer events.

Table 2 Exploratory analysis of local recurrence outcome

Parameter	Local recurrence cases	Total cases	% from total cases	% from total sample
Luminal A	6	130	4.62	2.88
Luminal B	5	40	12.50	2.40
Triple positive	3	25	12.00	1.44
HER2 enriched	0	3	0	0
Triple negative	1	10	10.00	0.48

Abbreviations: HER2 = human epidermal growth factor receptor type 2.

Table 3 Significant risk factors associated respectively with the survivals' outcomes (variables that entered the equation were age, tumor size, histologic grade, margins status, lymphovascular invasion, and molecular subtypes)

		95% confidence interval		
Survival type	Odds ratio	Lower	Upper	*P*
Overall survival				
pT > 1 cm	7.7	0.9	62.3	0.056
Disease-free survival				
pT > 1 cm	4.1	1.3	12.6	0.015
Histologic grade 3	2.5	1.1	5.8	0.032
Local disease-free survival				
LVI positive	4.8	1.3	17.4	0.016
Histologic grade 3	3.3	1.0	10.5	0.045

Abbreviations: LVI = lymphovascular invasion; pT = pathologic tumor size.

in our sample to draw further conclusions; however, in larger studies (such as ELIOT and TARGIT trials), even if poorly represented, triple-negative and HER2-positive patients might have contaminated the recurrence endpoints if a separate analysis was not conducted in the original publications.

Regarding patient selection, although contemporary guidelines suggest caution when considering IORT in the same manner as other forms of APBI, when the IORT cases were retrospectively analyzed and grouping is performed based on the American Society for Radiation Oncology and European Society of Radiotherapy and Oncology suitability criteria, the local recurrence rates can be very interesting, as revealed by Horst et al.[15] Among >3200 patients in 11 trials (including our study), the American Society for Radiation Oncology "suitable" and European Society of Radiotherapy and Oncology "good" patients treated with IORT had local recurrence rates of 0.66% and 0.61%, respectively. These recurrence rates, despite no significant gains in survival, are interesting compared with those observed in the PRIME-2 trial at the 10-year follow-up to assess local recurrence: 9.8% versus 0.9% for nonirradiated and irradiated patients, respectively.[24] Further, recurrence did not occur in patients >70 years, in addition to the 2.8% failures in luminal A patients. Any RT modality should be considered for patients included in the main studies that explore the role of RT omission, as there is no guarantee that a hypothetical patient undergoing conservative surgery will tolerate hormone therapy. Further, after 5 years, the patient may still experience a relapse, undergo another operation, and receive new hormonal treatment. Preliminary data suggest that RT is more cost-effective than hormone therapy.[37]

Differences in outcomes between the forms of APBI may be due to uncertainties across seminal studies. Table E2 shows some parameters that may represent uncertainties in the interpretation of results, specifically when the different forms of treatment are compared. If the statistical methodology is radically considered to validate a study, only the external beam APBI studies and the Hungarian study can be confirmed to have a satisfactory statistical design Table E2. Nonetheless, contemporary studies involving APBI have revealed interesting rates of local control without impairing patient survival, regardless of their drawbacks. As a result, IORT is continuously performed in selected patients at our institution, despite the lack of a randomized study to validate our approach in the performance of IORT (with ndLINAC). Our selection criteria involved the performance of breast MRI in addition to the criteria recommended by the guidelines. Additionally, owing to the use of ndLINAC, IORT was

initiated for breast cancer cases in 2004 without major investments in equipment. Of note, this strategy can be easily replicated in other centers.

Although our results suggest low local recurrence rates at follow-up (LR = 7.2% over 15 years), we did not compare our rates with those of the main studies as we performed a single-arm trial (without a control arm), grouping patients at a "low speed" (just >200 patients in 15 years). However, comparable results were observed in terms of local control and toxicities in addition to the experience gained with ndLINAC treatment. When the recurrence rates from historical studies of external beam RT are considered, the rates were found to be comparable to those of our study. For example, a meta-analysis by the Oxford group revealed that at 15 years of follow-up, RT reduced the rates of local recurrence in well-selected patients to approximately 15% compared with approximately 7% observed in our study, which also had a 15-year follow-up period.[38]

Cost was not considered in this study. Specifically on cost, it is important to note that breast cancer is among the most prevalent malignancies, which means it is 1 of the most. costly oncologic treatments. Thus, it is worth thinking of cost effectiveness along different RT types and fractionations. Deshmukh et al have shown through a prospective trial that hypofractionated RT was better than conventionally fractionated RT or IORT.[39] However, they considered dedicated equipment for such comparisons, which makes IORT through ndLINAC advantageous. On the other hand, Eisavi et al reported their results of systematic review based on current evidence, showing that IORT was associated with lower costs compared with external beam RT.[40]

Our study had several highlights, including the long-term follow-up, capability and the low rate of events to detect higher risk factors, such as tumor size >1 cm, histologic grade 3, and lymphovascular invasion. The presence of these features may aid decision making regarding APBI. Furthermore, patients with later recurrences could be identified during follow-up (>10 years). Even when located in the same initially affected quadrant, these recurrences have a differential diagnosis of a second primary tumor. Although this hypothesis should be refuted for these patients, they should not be exempt from continued long-term posttherapy follow-up.

Table E3 shows a simple comparison between APBI and other forms of RT for breast cancer. Despite more complex logistics, IORT can be advantageous even when strong competitors, such as whole-breast RT in ultrahypofractionation, are available, as an even faster and less toxic treatment than whole-breast RT and other forms of APBI, would be administered. In a review, Offersen et al suggested that the breast-parenchyma target volume of IORT is the smallest among the APBI modalities, and IORT spares the skin and chest wall, unlike other forms of APBI.[41]

In the near future, adequate selection criteria, such as oncogenomic panels, will be available for more intensive treatment of patients or treatments that could be excessive may be discarded. New forms of treatment may be employed in daily practice, such as stereotactic body RT in the breast cancer treatment scenario, whether as part of neoadjuvant, adjuvant, or definitive strategies. Because of the advent of the Internet, telemedicine practices, and the use of artificial intelligence, information is being disseminated and interpreted by clinical practitioners at an ever-increasing speed. Accordingly, the main selection criteria chosen by scientists may be modified earlier than 10 or 15 years for application in the relevant studies.

Currently, we are pleased with the results observed in our patients treated with IORT, as nearly half a century of medical evidence is available on this topic. The choice of IORT for use in our institution was strategic, and the results led to the generation of new knowledge. We believe that APBI can still be used in clinical practice, especially if decisions are supported by multidisciplinary teams.

Conclusions

Our long-term results support the use of IORT with ndLINACs in terms of local control and survival outcomes. Some of the analyzed predictive factors were found to influence our results, such as tumor size, histologic grade, and lymphovascular invasion, despite the low event rate. Despite the trend of treatment de-escalation, IORT for breast cancer is still applicable for selected patients.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101233.

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