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How Do the ASTRO Consensus Statement Guidelines for the Application of Accelerated Partial Breast Irradiation Fit Intraoperative Radiotherapy? A Retrospective Analysis of Patients Treated at the European Institute of Oncology

Maria Cristina Leonardi, M.D.,[*] Patrick Maisonneuve, Ing.,[†] Mauro Giuseppe Mastropasqua, M.D.,[‡] Anna Morra, M.D.,[*] Roberta Lazzari, M.D.,[*] Nicole Rotmensz, M.Sc.,[†] Claudia Sangalli, D.M.,[§] Alberto Luini, M.D.,[§] Umberto Veronesi, M.D.,[¶] and Roberto Orecchia, M.D.[*,‖]

[*]Division of Radiation Oncology, European Institute of Oncology, Milan, Italy; [†]Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy; [‡]Division of Pathology, European Institute of Oncology, Milan, Italy; [§]Division of Breast Surgery, European Institute of Oncology, Milan, Italy; [¶]Scientific Directorate, European Institute of Oncology, Milan, Italy; and [‖]University of Milan, Italy

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Summary

Patients on the ELIOT trial were treated with full-dose intra-operative electrons as part of their breast-conserving treatment and categorized into three subgroups according to ASTRO APBI guidelines. The 5-year rate of ipsilateral in-breast recurrence (IBR) increased as patients moved from "suitable" to "cautionary" to "unsuitable" groups (1.5%, 4.4% and 8.8% respectively). This

Purpose: To verify how the classification according to the American Society for Therapeutic Radiation Oncology (ASTRO) consensus statement (CS) for the application of accelerated partial breast irradiation (APBI) fits patients treated with intraoperative radiotherapy with electrons (ELIOT) at a single institution.

Methods and Materials: The study included 1,822 patients treated with ELIOT as the sole radiation modality outside of a clinical trial at the European Institute of Oncology after breast-conserving surgery for invasive breast cancer, who were classified into CS groups of suitable, cautionary, and unsuitable. The outcome in terms of ipsilateral breast recurrence, regional node relapse, distant metastases, progression free-survival, cause-specific survival, and overall survival were assessed.

Results: All the 1,822 cases except for 25 could be classified according to ASTRO CS: 294 patients met the criteria for inclusion into the suitable group, 691 patients into the cautionary group, and 812 patients into the unsuitable group. The 5-year rate of ipsilateral breast recurrence for suitable, cautionary, and unsuitable groups were 1.5%, 4.4%, and 8.8%, respectively ($p = 0.0003$). Whereas the regional node relapse showed no difference, the rate of distant metastases was significantly different in the unsuitable group compared with the suitable and cautionary groups, having a significant impact on survival.

Reprint requests to: Maria Cristina Leonardi, M.D., Division of Radiation Oncology, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy. Tel (+39) 02-57489037; Fax (+39) 02-94379227; E-mail: cristina.leonardi@ieo.it

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confirms the clinical appropriateness of ASTRO selection criteria for APBI with intraoperative electrons.

Conclusion: In the context of patients treated with ELIOT, the ASTRO guidelines identify well the groups for whom APBI might be considered as an effective alternative to whole breast radiotherapy and also identify groups for whom APBI is not indicated. © 2012 Elsevier Inc.

Keywords: Intraoperative electrons, Breast cancer, Partial breast irradiation, Consensus statement, ASTRO

Introduction

The presence of certain drawbacks, such as the length of overall treatment time, social and economic distress, and integration with systemic therapy, has led to an increased use of accelerated partial breast irradiation (APBI) in clinical practice. Favorable initial clinical results from randomized and nonrandomized studies are bound to increase this tendency further (1, 2). The main concern remains the lack of a long-term follow-up.

The primary aim of postoperative breast radiotherapy (RT) is tumor control in the affected breast. Extensive data confirm that conservative management is as effective as mastectomy in terms of local control, disease free-survival, and overall survival for early-stage breast cancer (3). Furthermore, the Early Breast Cancer Trialists' Collaborative Group meta-analysis (4) demonstrated that whole-breast RT (WBRT), by preventing local recurrence, improves survival. The trials specifically addressed to APBI are designed to investigate whether a radiation field limited to the tumor bed achieves the same local control and benefits as does WBRT over a prolonged period. Given these considerations, caution should be mandatory, and patient selection might represent the key to successful APBI.

The American Society for Radiation Oncology (ASTRO) created a task force to provide guidelines for the application of APBI outside of a clinical trial, based on a systematic literature review and the opinions of breast cancer experts (5). The ASTRO Consensus Panel proposed three patient groups for off-protocol APBI: a suitable group, for whom APBI is acceptable; a cautionary group, for whom caution and concern should be applied; and an unsuitable group, for whom APBI is not considered appropriate (Table 1). We applied the ASTRO guidelines to patients who were given full-dose intraoperative radiotherapy with electrons (ELIOT) outside of a clinical trial. Although the consensus statement (CS) was not created for intraoperative radiotherapy (IORT), this retrospective analysis of the outcome according to the proposed groups might be interesting and hypothesis-confirming. The outcome resulting from categorizing the ELIOT population into the three ASTRO groups is presented and discussed in this article.

Methods and Materials

Between January 2000 and December 2008, 1,822 patients (mean age, 58; range, 33−83) underwent quadrantectomy followed by ELIOT to the tumor bed as sole radiation modality, outside of a clinical trial (6), at the European Institute of Oncology (IEO). These patients did not take part in the randomized Phase III trial, which was ongoing in the same period, because they did not fulfill all the requested eligibility criteria or they refused to be randomized to WBRT.

ELIOT with a single dose of 21 Gy prescribed at 90% of the isodose was delivered to all but 22 patients. The latter patients entered Phase I−II trials and were treated with a lower full-dose (17−19 Gy).

Surgery

More than 80% of the patients (n = 1,375) received quadrantectomy with sentinel node biopsy alone. In the remaining cases, six patients did not receive surgical axillary assessment at all, 54 patients with positive sentinel nodes did not undergo subsequent axillary dissection because they were part of a specifically addressed clinical trial, and 441 patients had complete axillary dissection.

IORT

Technical details and rationale have been previously reported (7). ELIOT is performed by means of two dedicated linear accelerators, NOVAC 7 (NRT, Italy) and Liac (Sordina, Italy). The collimator diameter is selected according to tumor dimension and location, surgical resection, and breast size, and the appropriate beam energy is chosen on the basis of gland thickness. The median collimator diameter was 4 cm (range, 3−8 cm), and the median beam energy was 7 MeV (range, 3−10).

Pathology

All the parameters requested by the Consensus Panel were assessed and collected into the ELIOT database. Primary tumor size, as well as focality, were macroscopically recorded and then microscopically confirmed, evaluating the parenchyma between the foci; histological type was evaluated according to the World Health Organization classification (8). Tumor grade was evaluated according to the Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom Richardson grading system) (9). Lymphovascular invasion (LVI), assessed according to Rosen's criteria (10), was classified as "focal" when present in one only paraffin-embedded block and as "diffuse" when detectable in two or more blocks. Hormone receptor status was assessed by immunohistochemistry, as previously described (11), evaluating the presence or absence of estrogen receptor and progesterone receptor: the presence $\geq$1% of immunoreactive cells was defined as hormone receptor positivity.

To record and quantify the presence of intraepithelial ductal neoplasia (also known as intraductal carcinoma or ductal carcinoma *in situ*, DCIS) (12), the cases were divided into four classes, according to the quantity of DCIS surrounding the invasive component: focal, when the DCIS was up to 10%; reduced, when it was $\leq$25%; extensive, when it was $\leq$50%; and predominant when it was >50%.

The specimens were all oriented by surgeons, which was helpful in evaluating the margin status, both macroscopically and microscopically. As is routine procedure, the specimens were inked and the margins sampled perpendicularly to perform the assessment of margin status more precisely. Margins were considered free when the tumor was at least 0.1 cm distant from the inked surface. When the tumor was less than 0.1 cm but not

Table 1 Criteria defining suitability for accelerated partial breast irradiation according to the American Society for Radiation Oncology (ASTRO) consensus statements

	ASTRO guidelines		
	Suitable	Cautionary	Unsuitable
Patient factors			
Age, years	≥60	50–59	<50
BRCA1/2 mutation	Absent	Absent	Present
Pathologic factors			
Tumor size, cm	≤2	2.1–3.0	>3
pT	pT1	pT0 or pT2	pT3–pT4
Margins	Negative	Close	Positive
Grade	Any	Any	Any
LVI	No	Limited/focal	Extensive
ER status	Positive	Negative	Any
Multicentricity	Uncentric	Unicentric	Present
Multifocality	Unifocal	Unifocal	Multifocal
Histology	Invasive ductal*	Invasive lobular	Any
Pure DCIS	Not allowed	≤3 cm	>3 cm
EIC	Not allowed	≤3 cm	>3 cm
Nodal factors			
Nodal stage	pN0 (i^-,i^+)	pN0 (i^-,i^+)	pN1, pN2, pN3
Nodal surgery	SNB or ALND	SNB or ALND	Not performed
Treatment factors			
Neoadjuvant therapy	Not allowed	Not allowed	Yes

Abbreviations: ALND = axillary lymph node dissection; DCIS = ductal carcinoma in situ; EIC = extensive intraductal component; ER = estrogen receptor; LVI = lymph-vascular invasion; SNB = sentinel lymph node biopsy.

* Or other favorable subtypes (mucinous, tubular, colloid, etc).

inked, the margins were considered very close. Finally, margins were positive if the tumor was inked.

ASTRO consensus statement groups

All the requested parameters but one were collected into the ELIOT database. The only missing parameter was the *BRCA1/2* mutation status, because according to IEO policy, the *BRCA* test was optional, being at the patient's discretion. Regarding margin status, in the ELIOT database, there is no mention regarding the anatomic location of the cancer cells within 0.1 cm and 0.2 cm from the inked surface because we classified a distance >0.1 cm as being negative. As a result, in the category suitable, we classified patients with any margin of resection at a distance of ≥0.1 cm from the tumor, and in the cautionary group, we only located patients with malignant cells seen at <0.1 cm.

Regarding the extensive intraductal component (EIC), according to the IEO pathology guidelines, we included patients having focal and reduced EIC not exceeding 3 cm in the cautionary group and placed patients having extended or prevalent EIC exceeding 3 cm in the unsuitable group.

Outcome measures

Ipsilateral in-breast reappearance (IBR) was defined as any local failure within the treated breast. A regional nodal failure (RNF) was scored for a relapse that occurred within the ipsilateral axillary, supraclavicular, infraclavicular, and/or internal mammary nodal regions. Distant metastases (DM) were defined as any recurrence in distant organs or structures other than in-breast or nodal reappearance. Progression-free survival was defined as the time from BCS to the time of first evidence of local or distant disease. Cause-specific survival was determined from time of BCS until death from BC. Overall survival was defined as from the time of BCS to last follow-up or time of death from any cause.

Statistical analysis

Event rates were calculated by dividing the number of events by the number of person-years of observation and presented as percentage at 5 years. Plots of the cumulative incidence of various events and survival plots were drawn using the Kaplan-Meier method. The log-rank test was used to assess the survival difference between ASTRO CS groups. Univariate and multivariate Cox proportional hazard regression analysis was used to assess the prognostic significance of various clinical and histopathological characteristics of the tumor and of the ASTRO CS classification on IBR, RNF, and DM. All analyses were performed with the SAS software version 8.2 (Cary, NC).

Results

Table 2 presents the distribution of patients and tumor characteristics. All but 25 patients could be categorized into the three proposed groups. No patients received neoadjuvant therapy. It should be pointed out that we use 0.1 cm as a negative margin. In the suitable group, 294 patients (16.4%) were included.

In the cautionary group, 691 patients (38.5%) met at least one of the parameters for which caution was recommended in APBI delivery. The main reason for classifying patients in this category was age, with more than 60% of patients aged 50 to 59 years.

In the unsuitable group, 812 patients (45.2%) were allocated as fulfilling at least one of the unsuitable characteristics identified by the panel. The main reasons for inclusion in this group were lymph node involvement, age <50 years, LVI, and extended or prevalent EIC. Analysis for IBR showed the rate became higher as the categorized patients moved from suitable to cautionary to unsuitable groups (Table 3, Fig. 1). Conversely, the risk of RNF did not significantly differ among groups, partly because of the small number of events (only 18 nodal recurrences). The risk of DM is similar for the suitable and cautionary groups but increased significantly for the unsuitable group.

During follow-up, 31 patients died from BC. Survival estimates for cause-specific survival were 99.1%, 98.7%, and 96.5% at 5 years (Table 3, Fig. 1). The risk of death from BC was highest among the unsuitable group, and the suitable and cautionary groups carried the same probability. The probabilities of progression-free survival within the 3 groups were distributed similarly to those for cause-specific survival.

To determine whether there was an association between pathological and clinical variables and the development of IBR, univariate analysis was performed. The cumulative local relapse

Table 2 Distribution of patients' characteristics according to the American Society for Radiation Oncology (ASTRO) consensus statement groups

Characteristics	ASTRO consensus statement group No. of patients (%) Suitable (n = 294)	Cautionary (n = 691)	Unsuitable (n = 812)
Age, year			
<50	–	–	364 (44.8)
50–59	–	434 (62.8)	221 (27.2)
60+	294 (100)	257 (37.2)	227 (28.0)
Tumor size, cm			
≤2	294 (100)	601 (87.0)	639 (78.7)
>2 to ≤3	–	90 (13.0)	137 (16.9)
>3	–	–	36 (4.4)
pT			
pT1	294 (100)	599 (86.7)	634 (78.1)
pT2	–	92 (13.3)	175 (21.6)
pT3	–	–	3 (0.4)
Margins			
Negative	294 (100)	673 (97.4)	777 (95.7)
Close	–	18 (2.6)	29 (3.6)
Positive	–	–	6 (0.7)
Tumor grade			
G1	91 (31.0)	197 (28.5)	170 (20.9)
G2	148 (50.3)	298 (43.1)	397 (48.9)
G3	46 (15.6)	179 (25.9)	228 (28.1)
Missing	9 (3.1)	17 (2.5)	17 (2.1)
LVI			
Absent	294 (100)	633 (91.6)	577 (71.1)
Focal	–	58 (8.4)	135 (16.6)
Diffuse	–	–	100 (12.3)
ER status			
Positive	294 (100)	588 (85.1)	726 (89.4)
Negative	–	103 (14.9)	86 (10.6)
Focality			
Monocentric/focal	294 (100)	294 (100)	739 (91.0)
Multicentric/focal	–	–	73 (9.0)
Histology			
Ductal	268 (91.2)	515 (74.5)	677 (83.4)
Lobular	–	118 (17.1)	82 (10.1)
Other histologies	26 (8.8)	58 (8.4)	53 (6.5)
EIC			
Absent	294 (100)	498 (72.1)	641 (78.9)
Present	–	193 (27.9)	171 (21.1)
Lymph node status			
Negative	294 (100)	294 (100)	315 (38.8)
Positive	–	–	497 (61.2)
Neoadjuvant therapy			
None	294 (100)	691 (100)	812 (100)

Abbreviations: EIC = extensive intraductal component; ER = estrogen receptor; LVI = lymph-vascular invasion.
ASTRO group could not be assessed for 25 patients.

rate was not significantly influenced by margin status, histological types, or EIC. An increased risk of local relapse was significantly associated with age <50 years, tumor size >2 cm, high grade, diffuse LVI, estrogen receptor negative status, multicentricity, and positive lymph nodes. Factors predictive for RNF were tumor size >2 cm and high grade. Risk factors for DM were tumor size >2 cm, high grade, diffuse LVI, negative estrogen receptor status, and lymph node metastases. The risk of local relapse and DM increased by increasing the extension of nodal disease (Table 4). On multivariate analysis, young age, diffuse LVI, extensive axillary involvement, and high tumor grade were confirmed to be the most important predictive factors for IBR (Table 5). Overall, compared with the suitable group, the unsuitable group showed a significantly increased risk of IBR (hazard ratio, 5.84; range, 1.82–18.7), and the cautionary group recorded an increased risk of IBR (hazard ratio, 2.89; range, 0.86–9.68) that did not achieve statistical difference. No significant difference was seen with regard to regional nodal and distant relapse rates between the categories, although the unsuitable group had a substantially increased risk of DM compared with the one reported in suitable group (hazard ratio, 2.60; range, 0.78–8.69).

Discussion

The ASTRO guidelines for APBI are clearly not intended to guide selection of patients for IORT. In fact, at the time of delivering intraoperative irradiation, the whole pathological and biomolecular tumor view has yet to become available. Because the ASTRO Task Force based the selection criteria for APBI mostly on pathological features, the issue concerning the selection criteria for this kind of APBI is left open. However, it is worth pointing out that preoperative pathologic assessment of Tru-Cut or core biopsy specimens can define the type of histology, the tumor grade, and the hormonal receptor status before intraoperative irradiation. In addition, intraoperative assessment on frozen sections, which are routinely performed at IEO, is able to provide reliable information on tumor size, margin resection involvement, and sentinel lymph node status in real time. Histology, grade, and macroscopic multifocality can be still defined intraoperatively. Apart from pure DCIS, the only risk factors that are not able to be assessed with an acceptable level of accuracy before ELIOT are represented by LVI and EIC. Therefore, although we found a good correspondence between the three groups and the outcome of ELIOT off-protocol patients, we are aware that IORT users cannot be guided by these recommendations to a full extent. However, if we are able to rely on a good quality standard of preoperative and intraoperative pathologic assessment, many of the tumor features requested by ASTRO CS can be satisfied before IORT. Although its potential utility is not yet assessed and its use among ELIOT patients was occasional, breast magnetic resonance imaging might help further prevent patients with multicentric or extended multifocal disease from having APBI (13).

Additionally, in the context of APBI, the weight of each factor that predicts for IBR is not known. Lobular histology, which is consistently represented in the cautionary group and to a lesser extent in the unsuitable group (118/691 and 82/812, respectively) did not seem to have an impact on IBR, despite its being a well-known factor associated with additional ipsilateral disease (14). EIC failed to predict for an increased risk of IBR in this retrospective analysis, despite a consistent number of EIC positive specimens (193 cases of 691 in the cautionary group and 171 of 812 cases in the unsuitable group). According to the literature, EIC and young age represent two of most important predictors of IBR, although conflicting data do exist (15). Recent publications show that the average maximum distance of intraductal extension

Table 3 Five-year clinical outcomes for breast cancer patients treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statement

	ASTRO consensus statement						
	Suitable		Cautionary		Unsuitable		
Patients	294		691		812		
Person-years	1,009		2,416		2,837		
Outcome	Events	Rate* (%)	Events	Rate* (%)	Events	Rate* (%)	Log-rank *p*
Ipsilateral breast tumor recurrence	3	1.5	21	4.4	50	8.8	0.0003
Regional lymph node failure	3	1.5	9	1.9	6	1.1	0.55
Distant metastases	3	1.5	8	1.7	22	3.9	0.047
Breast cancer related event	14	6.9	46	9.5	87	15.3	0.0025
Progression free survival	17	91.6	58	88.0	109	80.8	0.0005
Cause-specific survival	2	99.1	7	98.7	22	96.5	0.026
Overall survival	3	98.6	13	97.5	30	95.2	0.039

ASTRO group was not assessable for 25 patients.
* Five-year rate (%) assuming constant rate during the first 5 years.

was 1.19 cm in the early tumor stage (16); because in the ELIOT study quadrantectomy was mandatory, a consistent amount of EIC might have been removed by the more extensive conservative surgery. In the European Organization for Research and Treatment of Cancer (EORTC) boost vs. no boost trial (17), a clinical factor represented by the age <50 years, along with high histological grade, were the most important risk factors for local recurrence, whereas margin status had no significant influence. In the ELIOT population, age is confirmed to be one of the most important predictive parameters for IBR. Interestingly, although ASTRO guidelines did not consider tumor grade as a significant predictor of risk, high- grade lesions were significantly associated with local recurrence, DM, and regional failure within the ELIOT population, in contrast to EORTC findings.

The two randomized Phase III studies on IORT, Targeted Intraoperative Radiotherapy (TARGIT) and ELIOT, enrolled patients on the basis of a few factors such as age, clinical tumor size, unifocality, and clinical axillary status. Although results from ELIOT are pending, the TARGIT trial showed a rate of local recurrence as low as 1.20% at 4 years, which compares well with the rate of 0.95% of WBR RT (1). We commenced the ELIOT studies in 1999, and off-protocol patients were treated without taking into consideration most of the parameters recently identified by ASTRO CS. Currently, we expect to improve the selection of patients judged suitable for ELIOT by following these recommendations as closely as possible.

The application of ASTRO CS guidelines for APBI to a large cohort of patients treated with MammoSite brachytherapy catheter on the American Society of Breast Surgeons MammoSite Registry Trial failed to differentiate patients for whom APBI is associated with worse rate of IBR (18). In fact, the only statistically significant difference between the three groups was seen in the rate of DM, and no difference was detected in local or regional failures. The only factor correlated with local and distant recurrence was

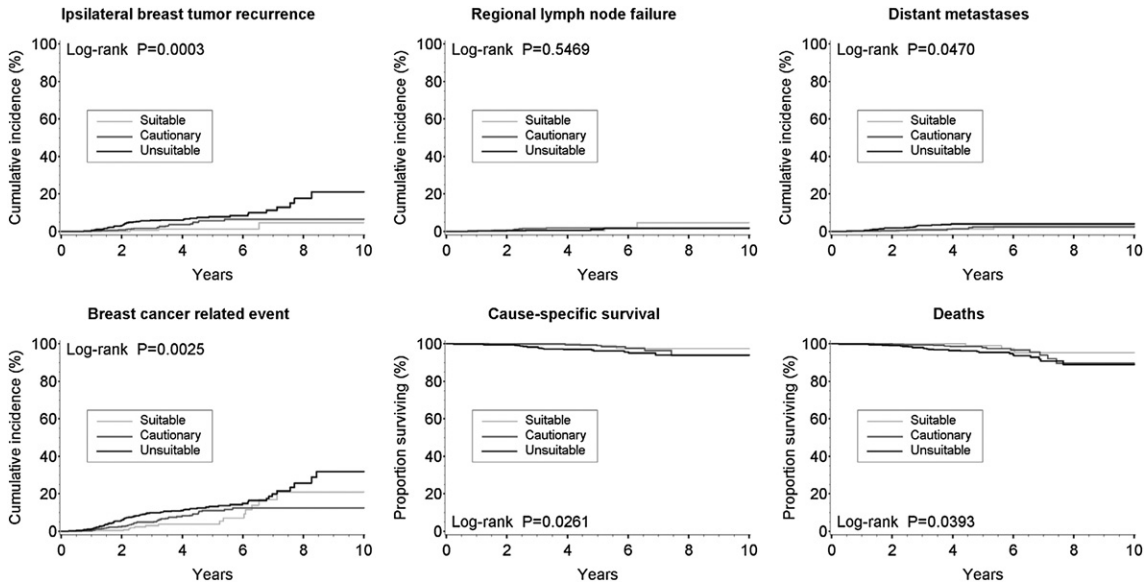

Fig. Cumulative incidence of breast-related events in patients treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology consensus statement.

Table 4 Univariate analysis of clinical outcomes for patients with breast cancer treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statements

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, year						
<50	1.00		1.00		1.00	
50–59	0.47 (0.27–0.80)	0.006	4.26 (0.53–34.1)	0.17	0.87 (0.29–2.67)	0.81
60+	0.41 (0.24–0.71)	0.002	4.43 (0.56–35.0)	0.16	2.12 (0.80–5.62)	0.13
Tumor size, cm						
≤2	1.00		1.00		1.00	
>2 to ≤3	2.48 (1.45–4.24)	0.0009	4.64 (1.79–12.0)	0.002	2.68 (1.24–5.76)	0.01
>3	2.87 (0.89–9.18)	0.08	–	–		
pT						
pT1	1.00		1.00		1.00	
pT2	2.42 (1.46–4.01)	0.0006	3.83 (1.48–9.87)	0.006	2.22 (1.03–4.77)	0.04
pT3	–	–	–	–	–	–
Margins						
Negative	1.00		1.00		1.00	
Close	1.70 (0.54–5.41)	0.37	–	–	1.19 (0.16–8.72)	0.86
Positive	4.53 (0.63–32.6)	0.13	–	–		
Tumor grade						
1	1.00		1.00		1.00	
2	3.31 (1.29–8.53)	0.01	0.84 (0.14–5.04)	0.85	2.49 (0.54–11.5)	0.24
3	8.32 (3.28–21.1)	<0.0001	7.14 (1.61–31.6)	0.01	11.9 (2.80–50.7)	0.0008
LVI						
Absent	1.00		1.00		1.00	
Focal	1.67 (0.88–3.21)	0.12	1.67 (0.48–5.82)	0.42	1.69 (0.64–4.45)	0.29
Diffuse	3.99 (2.17–7.32)	<0.0001	1.14 (0.15–8.69)	0.90	4.25 (1.73–10.4)	0.002
ER status						
Positive	1.00		1.00		1.00	
Negative	2.68 (1.58–4.55)	0.0003	1.74 (0.50–6.02)	0.38	3.59 (1.72–7.50)	0.0007
Focality						
Monocentric/focal	1.00		1.00		1.00	
Multicentric/focal	2.24 (1.03–4.88)	0.04	2.78 (0.64–12.1)	0.17	0.68 (0.09–5.00)	0.71
Histology						
Ductal	1.00		1.00		1.00	
Lobular	1.42 (0.74–2.70)	0.29	–	–	0.77 (0.23–2.52)	0.66
Other histologies	0.81 (0.33–2.02)	0.65	–	–	0.66 (0.16–2.77)	0.57
EIC						
Absent/focal	1.00		1.00		1.00	
Extensive	0.64 (0.34–1.22)	0.98	0.49 (0.11–2.13)	0.34	0.67 (0.26–1.73)	0.41
Lymph node status						
Negative	1.00		1.00		1.00	
pN1mi or pN1a (by ALND)	1.98 (1.11–3.52)	0.02	0.53 (0.12–2.35)	0.40	2.56 (1.03–6.35)	0.04
pNx; ≥pN2a (≥4 positive nodes)	2.12 (1.21–3.69)	0.008	0.65 (0.18–2.38)	0.51	4.73 (2.15–10.4)	0.0001
ASTRO consensus group						
Suitable	1.00		1.00		1.00	
Cautionary	2.89 (0.86–9.68)	0.09	1.27 (0.34–4.69)	0.72	1.11 (0.30–4.19)	0.88
Unsuitable	5.84 (1.82–18.7)	0.003	0.72 (0.18–2.86)	0.64	2.60 (0.78–8.69)	0.12

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; EIC= extensive intraductal component; ER = estrogen receptor; HR = hazard ratio; LVI = lymph-vascular invasion.

negative estrogen receptor status, which is consistent with our results. A possible explanation could be the lack of complete pathologic information on the MammoSite population, because the registry trial did not collect all the parameters requested for categorizing patients according to the three groups proposed by ASTRO Task Force.

The ELIOT patients classified as unsuitable according to ASTRO guidelines show the worst results in terms of outcome. The unsuitable group included patients with limited clinical evidence supporting the use of APBI and therefore represents a critical population in which well-designed prospective trials are expected to provide an answer to the questions. For this purpose,

Table 5 Multivariate analysis of clinical outcomes for patients with breast cancer treated with full-dose intraoperative radiotherapy with electrons categorized according to the American Society for Radiation Oncology (ASTRO) consensus statements

Variable	Ipsilateral breast tumor recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age, year						
<50	1.00		1.00		1.00	
50−59	0.48 (0.28−0.84)	0.01	4.40 (0.54−35.6)	0.16	0.87 (0.28−2.71)	0.80
60+	0.41 (0.23−0.72)	0.002	4.13 (0.51−32.3)	0.18	2.27 (0.83−6.20)	0.11
Tumor size, cm						
≤2	1.00		1.00		1.00	
>2 to ≤3	1.45 (0.81−2.60)	0.21	2.87 (1.06−7.82)	0.04	1.30 (0.57−2.97)	0.53
>3	1.31 (0.39−4.41)	0.66	−	−	−	−
Margins						
Negative	1.00		1.00		1.00	
Close	1.82 (0.55−6.08)	0.33	−	−	1.61 (0.20−12.9)	0.65
Positive	3.52 (0.46−27.2)	0.23	−	−		
Tumor grade						
1	1.00		1.00		1.00	
2	2.72 (1.04−7.13)	0.04	0.67 (0.11−4.16)	0.67	1.80 (0.38−8.58)	0.46
3	5.38 (1.97−14.7)	0.001	5.39 (1.10−26.4)	0.04	7.64 (1.63−35.9)	0.01
LVI						
Absent	1.00		1.00		1.00	
Focal	1.49 (0.75−2.96)	0.25	1.61 (0.44−5.86)	0.47	1.71 (0.62−4.75)	0.30
Diffuse	2.03 (1.03−3.99)	0.04	0.83 (0.10−7.32)	0.87	2.31 (0.86−6.25)	0.10
ER status						
Positive	1.00		1.00		1.00	
Negative	1.56 (0.84−2.94)	0.16	0.54 (0.15−2.01)	0.36	1.44 (0.62−3.35)	0.39
Focality						
Monocentric/focal	1.00		1.00		1.00	
Multicentric/focal	1.50 (0.67−3.38)	0.33	3.85 (0.84−17.6)	0.08	0.51 (0.07−3.81)	0.51
Histology						
Ductal	1.00		1.00		1.00	
Lobular	1.97 (1.00−3.90)	0.05	−	−	1.58 (0.45−5.55)	0.48
Other histologies	0.79 (0.25−2.50)	0.69	−	−	0.92 (0.16−5.21)	0.92
EIC						
Absent/focal	1.00		1.00		1.00	
Extensive	0.59 (0.31−1.14)	0.11	0.68 (0.15−2.99)	0.61	0.78 (0.30−2.07)	0.62
Lymph node status						
Negative	1.00		1.00		1.00	
pN1mi or pN1a (by ALND)	1.29 (0.69−2.40)	0.43	0.32 (0.07−1.50)	0.15	2.05 (0.79−5.36)	0.14
pNx; ≥pN2a (≥4 positive nodes)	1.80 (1.01−3.22)	0.047	0.57 (0.15−2.17)	0.41	3.92 (1.71−8.97)	0.001

Abbreviations: ALND = axillary lymph node dissection; CI = confidence interval; EIC= extensive intraductal component; ER = estrogen receptor; HR = hazard ratio; LVI = lymph-vascular invasion.

there is great encouragement from the ASTRO task force to enroll these patients into the ongoing Radiation Therapy Oncology Group 0413/National Surgical Adjuvant Breast and Bowel Project B-39 randomized clinical trial, which can settle the many of concerns more satisfactorily than can any retrospective analysis (19). This Phase III study started in 2005 to compare WBRT with APBI and is now enrolling patients with high-risk features (young age, T2 tumors, 1−3 positive nodes).

The key to success of APBI lies in the identification of patients at low risk of recurrence elsewhere. In categorizing patients as suitable or unsuitable for APBI, the panel considered all the clinical and pathological parameters that are well recognized as being linked to risk of failure both on the basis of APBI and WBRT studies. The low rate of breast events in the suitable group confirms the appropriateness of pathologic selection criteria. It should be pointed out that we also take as a negative margin the distance of 0.1−0.2 cm from the tumor, which is considered close according to ASTRO CS and falls into the cautionary group. The low rate of LR in the ELIOT population strengthens the opinion that a margin of ≥0.1 cm is considered sufficient to keep the rate of IBR as low as possible (20). On the other hand, because a high dose of radiation to the tumor bed has been found to decrease the risk of local relapse associated with close margins, a single fraction of 21 Gy corresponding to an equivalent biological dose of 65 Gy in conventional fractionation should be effective for local control (7). However, the impact of ELIOT full-dose on breast parenchyma and the potential difference with conventional WBRT toxicity are still unknown. The small number of cases with

positive margins (9%) in our study could not demonstrate a significant association with IBR.

In conclusion, this retrospective analysis confirms the clinical validity of the proposed categories: in the clear identification of suitable and unsuitable patients, the ASTRO recommendations offer useful guidance to judge the appropriateness of APBI using ELIOT.

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