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Breast cancer

Accelerated partial breast irradiation with intraoperative electrons: Using GEC–ESTRO recommendations as guidance for patient selection

Maria Cristina Leonardi [a,*], Patrick Maisonneuve [b], Mauro Giuseppe Mastropasqua [c], Anna Morra [a], Roberta Lazzari [a], Veronica Dell'Acqua [a], Annamaria Ferrari [a], Nicole Rotmensz [b], Claudia Sangalli [d], Alberto Luini [d], Umberto Veronesi [e], Roberto Orecchia [a,f]

[a] Division of Radiation Oncology, European Institute of Oncology, Milan, Italy; [b] Division of Epidemiology and Biostatistics, European Institute of Oncology, Milan, Italy; [c] Division of Pathology, European Institute of Oncology, Milan, Italy; [d] Division of Breast Surgery, European Institute of Oncology, Milan, Italy; [e] Scientific Directorate, European Institute of Oncology, Milan, Italy; [f] University of Milan, Italy

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ABSTRACT

Purpose: To evaluate outcomes among early-stage breast cancer patients after conservative surgery and full-dose intraoperative radiotherapy electrons (ELIOT) by applying the Groupe Européen de Curiethérapie–European Society for Therapeutic Radiology and Oncology (GEC–ESTRO) recommendations for partial breast irradiation (APBI).

Materials and Methods: One-thousand eight-hundred and twenty-two patients were stratified into the three GEC–ESTRO categories of "good candidates", "possible candidates" and "contraindication" in order to assess outcomes.

Results: All the 1822 cases except 7 could be classified according to GEC–ESTRO groups: 573 patients met the criteria to be included in the "good candidates" group, 468 patients in the "possible candidates" group and 767 patients in the "contraindication" group. Median and mean follow-up length was 3.5 years (range 0–10.5 years) and 3.8 years (SD 2.2), respectively.

The 5-year rate of in-breast tumor reappearances for "good candidates", "possible candidates" and "contraindication" groups were 1.9%, 7.4% and 7.7%, respectively (p 0.001). While the regional node relapse showed no difference, the rate of distant metastases was significantly different in the "contraindication" group compared to the other two categories, having a significant impact on survival.

Conclusions: Among the ELIOT population, the GEC–ESTRO recommendations enabled the selection of the good candidates with a low rate of local recurrence, but failed to differentiate the "possible candidates" and the "contraindication" groups.

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Initial results from phase I–II studies and a limited number of phase III studies [1] support the concept of accelerated treatment of breast cancer (BC) and restriction of irradiation to the tumour bed. However, the concept that accelerated partial breast irradiation (APBI) is not indicated for all patients in whom conservative treatment (CS) is performed still remains. There is general agreement that good candidates for APBI are patients at low-risk of harbouring occult microscopic disease distant from tumour bed, but there is no agreement on the role played by different clinical, pathological and biomolecular variables which define this low-risk group [2]. To overcome some uncertainties regarding the optimal use of APBI and the risk of an excess of personalised off-protocol radiation treatments, several consensus statements, based on published data and breast experts' opinions, have been published [3,4]. The Groupe Européen de Curiethérapie–European Society for Therapeutic Radiology and Oncology (GEC–ESTRO) [5] recommends 3 categories guiding patient selection for APBI: a "good candidates" group for whom off protocol APBI is an acceptable option; a "possible candidates" group for whom APBI is acceptable only in the context of clinical trials; and a "contraindication" group for whom APBI is not to be performed (Table 1e). We applied the GEC–ESTRO recommendations to patients who were given full-dose intraoperative radiotherapy (RT) with electrons (ELIOT) outside the remit of the phase III clinical trial at the European Institute of Oncology (IEO). Even though the validity of GEC–ESTRO statements is intended to be fully applied to multicatheter interstitial brachytherapy, experts tend to believe they are probably valid for other alternative techniques of APBI, including intraoperative RT. To assess the predictive ability, the outcome data from the ELIOT population categorised according to GEC–ESTRO recommendations were analysed in this study.

* Corresponding author. Address: Division of Radiotherapy, European Institute of Oncology, Via Ripamonti 435, 20141 Milan, Italy.
E-mail address: cristina.leonardi@ieo.it (M.C. Leonardi).

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Materials and methods

From January 2000 to December 2008, a total of 1822 breast cancer patients (mean age 58, range 33–83) with invasive early-stage breast cancer were treated at IEO using intraoperative RT with electrons directed only to the region of the tumour bed as part of CS [6]. All of them were treated outside of the ELIOT phase III randomised study and gave informed consent. This review was approved by IEO ethics committee.

Surgical treatment and ELIOT

The majority of patients received quadrantectomy with sentinel node biopsy alone (n = 1375). Axillary dissection was performed in 102 patients with clinical positive axilla and in 339 patients (19.8%), whose sentinel node was found to be metastatic during surgery. Fifty-four patients with positive intraoperative sentinel node did not receive axillary dissection as they had been enrolled in a specifically addressed clinical trial, whereas six patients received no dissection at all.

Details on the ELIOT technique have been previously described [7]. ELIOT was performed by means of two dedicated linear accelerators: NOVAC 7 (NRT, Italy) and Liac (Sordina, Italy). The single full-dose of 21 Gy prescribed at 90% of the isodose was given to 1800/1822 patients. The remaining 22 patients, treated at the beginning of the IEO intraoperative procedure as sole modality, received a lower full -dose (17–19 Gy). The follow-up length was 3.5 years (range 0–10.5 years) as median value and 3.8 years (SD 2.2) as mean value. The median collimator diameter was 4 cm (range 3–8 cm), while the median beam energy was 7 MeV (range 3–10 MeV).

Pathology

All the parameters requested by GEC–ESTRO recommendations were assessed and collected into the ELIOT database. Primary

Table 1
Distribution of patients' characteristics among patients classified according to the GEC–ESTRO recommendations.

Characteristics	GEC–ESTRO consensus statement groups Number of Patients (%)		
	Good candidates (n = 573)	Possible candidates (n = 468)	Contraindication (n = 767)
Age, year			
⩽40	–	–	14 (1.8)
41–50	–	211 (45.1)	207 (27.0)
>50	573 (100)	257 (54.9)	546 (71.2)
Tumour size, cm			
⩽3	573 (100)	468 (100)	731 (95.3)
>3	–	–	36 (4.7)
pT			
pT1	513 (89.5)	411 (87.8)	613 (79.9)
pT2	60 (10.5)	57 (11.2)	151 (19.7)
pT3	–	–	3 (0.4)
Margins			
Negative	573 (100)	448 (95.7)	733 (95.6)
Close	–	20 (4.3)	28 (3.7)
Positive	–	–	6 (0.8)
Tumour grade			
G1	173 (30.2)	129 (27.6)	160 (20.9)
G2	239 (41.7)	230 (49.1)	379 (49.4)
G3	143 (25.0)	99 (21.2)	213 (27.8)
Missing	18 (3.1)	10 (2.1)	15 (2.0)
LVI			
Absent	573 (100)	468 (100)	473 (61.7)
Focal	–	–	194 (25.3)
Diffuse	–	–	100 (13.0)
ER status			
Positive	507 (88.5)	428 (91.5)	681 (88.8)
Negative	66 (11.5)	40 (8.5)	86 (11.2)
Focality			
Monocentric/focal	573 (100)	440 (94.0)	722 (94.1)
Multicentric/focal	–	28 (6.0)	43 (5.9)
Histology			
Ductal	517 (90.2)	317 (67.7)	634 (82.7)
Lobular	–	121 (25.9)	80 (10.4)
Other histologies	56 (9.8)	30 (6.4)	53 (6.9)
EIC			
Absent	573 (100)	468 (100)	399 (52.0)
Present	–	–	368 (48.0)
Lymph node status			
Negative	573 (100)	269 (57.5)	365 (47.6)
pN1mi or pN1a (by ALND)	–	199 (42.5)	147 (19.2)
pNx; ⩾pN2a (⩾4 positive nodes)	–	–	255 (33.2)
Neoadjuvant therapy			
None	573 (100)	468 (100)	767 (100)

GEC–ESTRO group was not assessable for 7 patients.
Abbreviations: LVI = lympho-vascular invasion; EIC = extensive intraductal component; ALND = axillary lymph node dissection.

tumour 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 WHO classification [8]. Tumour grade was evaluated according to the Nottingham combined histological grade (Elston–Ellis modification of Scarff–Bloom Richardson grading system) [9]. Lymphovascular invasion (LVI) was assessed according to Rosen's criteria [10] and was considered present either when "focal" (detected only in one paraffin-embedded block) or "diffuse" (detected in two or more blocks). Hormone receptor status was assessed by immunohistochemistry [11].

The intraductal component (EIC) was divided into four classes, focal, reduced, extensive, and predominant, according to the quantity of intraductal carcinoma (DCIS) surrounding the invasive component (10%, 25%, ⩽50%, >50%, respectively) [12]. EIC was recorded as present when DCIS surrounding the invasive component was 25% or more. When DCIS was focal, representing not more than 10% of the invasive cancer, EIC was considered as absent.

All the specimens were routinely inked and the margins sampled perpendicularly: margins were considered free when the tumour was at least 1 mm distant from the inked surface. When the tumour was less than 1 mm but not inked, the margins were considered very close. Finally, margins were positive if the tumour was inked.

GEC–ESTRO categories

Only 7 patients out of 1822 could not be categorised into the GEC–ESTRO groups. All the requested parameters were collected into the ELIOT database, but some adaptations needed to be made regarding margin status. In fact, according to the IEO pathology guidelines, a surgical margin is considered negative when tumour is ⩾1 mm from the ink and not when it is ⩾2 mm, as suggested in GEC–ESTRO recommendations. In the ELIOT database there is no mention concerning the anatomic location of the cancer cells within 1 and 2 mm-distance from the inked surface since all these margins are classified as negative. As a result, in the "good candidates" category we classified patients with any margin of resection at a distance of 1 mm or greater from the tumour, while in the "possible candidates" group we only placed patients with malignant cells seen at <1 mm but not present at the inked margin.

Outcome measures

In-breast tumour reappearances (IBR) were defined as any local failure within the treated breast, before or at the time of regional or distant metastases. IBR included either true recurrence (near the site of primary tumour) or ipsilateral breast cancer (elsewhere recurrence, in quadrants other than that previously involved). A regional nodal failure (RNF) included any recurrence in the ipsilateral axillary, supraclavicular and /or internal mammary nodal regions. Distant metastases (DM) were defined as any recurrence to distant organs or structures other than in-breast or nodal reappearance. Disease-free survival (DFS) was defined as the time from diagnosis to the time of first event attributed to BC (local, regional, and distant failure). Cause-specific survival (CSS) was determined from the time of diagnosis until death due to BC. Overall survival (OS) was defined as the time from diagnosis to last follow-up or time of death.

Statistical analysis

Event rates were calculated dividing the number of events by the number of person-years of observation and presented as percent 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 GEC–ESTRO groups. Univariate Cox proportional hazard regression analysis was used to assess the prognostic significance of various clinical and histopathological characteristics of the tumour and of the GEC–ESTRO classification on IBR, RNF and DM. All analyses were performed with the SAS software version 8.2 (Cary, NC).

Results

Table 1 presents the breakdown of patient and tumour characteristics among patients classified by GEC–ESTRO categories. No patients received neoadjuvant therapy.

In the "suitable" group, 573 patients (31.5%) were included. It is worthwhile noting that we use 1 mm as a negative margin.

In the "possible candidates" group, 468 patients (25.7%) met at least one of the parameters which placed them as being at intermediate risk in APBI delivery. The main reasons for classifying patients in this category were age and limited nodal involvement, either microscopically involved or 1–3 positive lymph nodes. Lobular carcinoma was detected in one quarter of the patients, while the amount of close (but clear) surgical margins (<1 mm) was small (20 cases, 4.5%).

In the "contraindication group", 767 patients (42.2%) were allocated, as they fulfilled at least one of the "high-risk" characteristics identified by the GEC–ESTRO recommendations. The main reasons for including patients in this group were the presence of EIC, LVI and extensive lymph node involvement (⩾4 positive nodes).

Table 2
Five-year clinical outcomes for breast cancer patients treated with ELIOT categorised according to the GEC–ESTRO recommendations.

	GEC–ESTRO consensus statement						
	Good		Possible		Contraindication		
Patients	573		468		767		
Person-years	1845		1492		2970		
Outcome	Events	Rate* (%)	Events	Rate* (%)	Events	Rate* (%)	Log-rank *p*
In breast tumour recurrence	7	1.9	22	7.4	46	7.7	0.001
True local recurrence	6	1.6	12	4.0	28	4.7	0.052
Ipsilateral breast cancer	1	0.3	10	3.3	18	3.0	0.012
Regional lymph node failure	8	2.2	2	0.7	8	1.3	0.275
Distant metastases	5	1.4	5	1.7	23	3.9	0.016
Breast cancer related event	26	7.0	32	10.7	91	15.3	0.003
Disease free survival	34	90.8	42	85.9	110	81.5	0.004
Cause-specific survival	3	99.2	4	98.7	24	96.0	0.014
Overall survival	5	98.6	9	97.0	33	94.4	0.044

* 5-Year rate (%) assuming constant rate during the first 5 years.

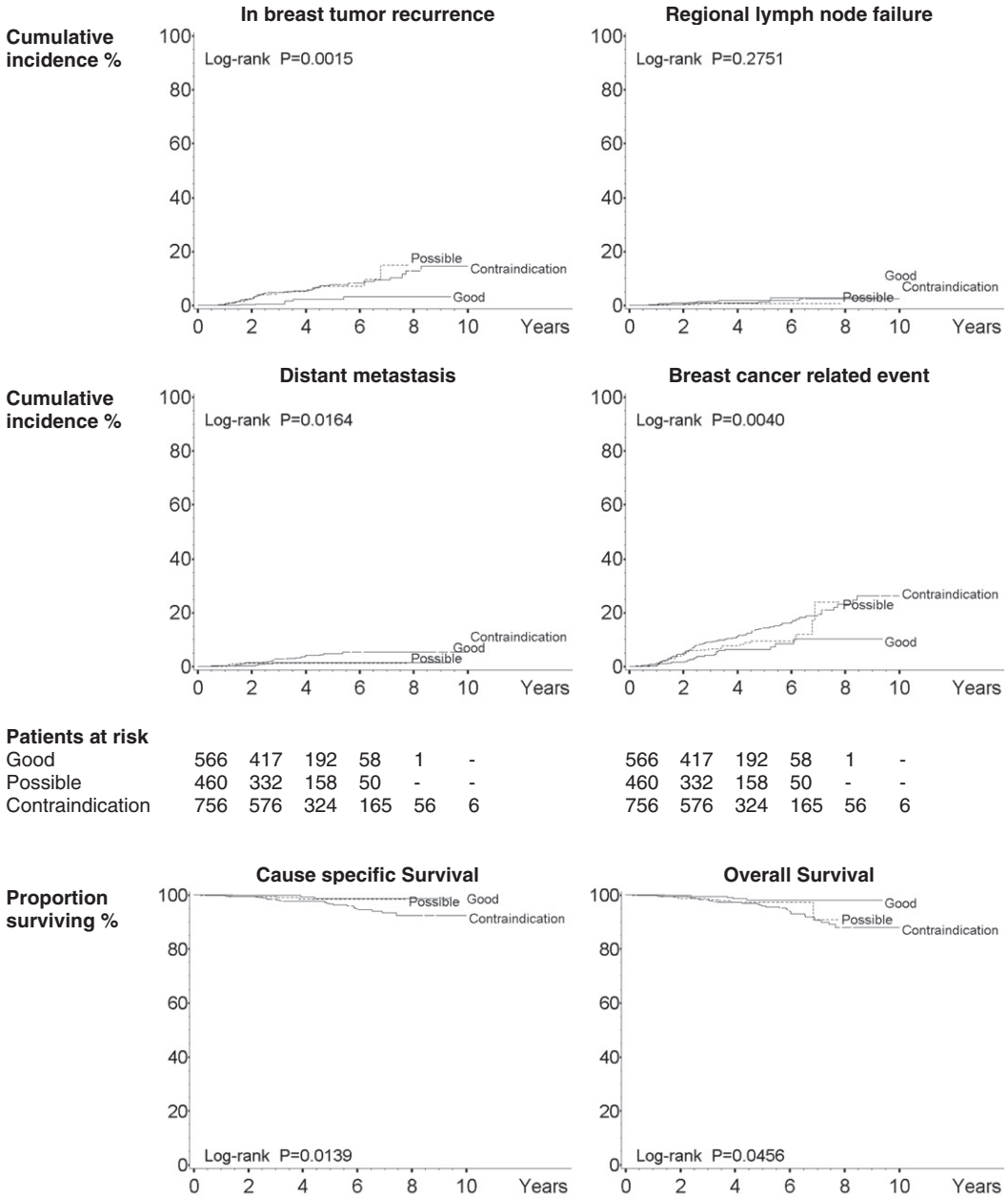

Fig. 1. Cumulative incidence of breast-related events and survival in patients treated with ELIOT categorised according to the GEC–ESTRO recommendations.

The application of GEC–ESTRO recommendations resulted in statistically significant differences in all of the clinical outcomes but RNF rate among the proposed groups. The incidence of IBR was similar in "possible candidates" and in "contraindication" groups (7.4% and 7.7%, respectively) and was significantly higher than in "good candidates" group (1.9%, p 0.001). Breaking the IBR down into true and elsewhere recurrence, the categories kept the same pattern of failure. Compared to "good candidates", the contraindication group showed statistically significant differences in the incidence of any BC-related events and in any survival endpoints (Table 2, Fig. 1). Regarding DM, there were statistically significant differences between the "contraindication" category and the other two categories (p 0.004). The "possible candidates" category showed no statistically significant differences compared to both "good candidates" and "contraindication" categories with regard to DFS (p 0.067 and p 0.20), CSS (p 0.51 and p 0.07) and OS (p 0.15 and p 0.36) (data not shown).

Regarding predictive factors of outcomes (Table 3), numerical limitations in the analysed population on tumour size >3 cm and on the age $\leqslant$40 years precluded any predictive analysis. An increase risk of IBR was significantly associated with age younger than 50 years, tumour size >2 cm, presence of LVI, multicentricity, and positive nodal involvement. Predictive factors for RNF were tumour size >2 cm. Risk factors for DM were tumour size >2 cm,

Table 3
Univariate analysis of clinical outcomes for patients with breast cancer treated with ELIOT categorised according to the GEC–ESTRO recommendations.

Variable	Ipsilateral breast tumour recurrence		Regional lymph node failure		Distant metastases	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age, year						
⩽40	3.64 (0.88–15.0)	0.07	–		–	
40–50	2.05 (1.28–3.28)	0.003	0.67 (0.20–2.32)	0.53	0.70 (0.29–1.69)	0.43
>50	1.00		1.00		1.00	
Tumour size, cm						
⩽3	1.00		1.00		1.00	
>3	2.42 (0.76–7.70)	0.13	–	–		
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
pT3/4	–	–	–	–	–	–
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	4.23 (0.63–32.6)	0.13	–	–		
Tumour grade*						
G1	1.00		1.00		1.00	
G2	3.31 (1.29–8.53)	0.01	0.84 (0.14–5.04)	0.85	2.49 (0.54–11.5)	0.24
G3	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	
Present	2.44 (1.51–3.96)	0.0003	1.50 (0.49–4.55)	0.48	2.52 (1.23–5.17)	0.01
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 + other histologies	1.00		1.00		1.00	
Lobular	1.44 (0.76–2.74)	0.26	–	–	0.79 (0.24–2.60)	0.70
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
GEC–ESTRO consensus groups						
Good candidates	1.00		1.00		1.00	
Possible candidates	3.89 (1.66–9.11)	0.002	0.31 (0.07–1.47)	0.14	1.23 (0.36–4.26)	0.74
Contra-indication	3.85 (1.73–8.59)	0.001	0.63 (0.24–1.70)	0.36	3.08 (1.17–8.10)	0.02

Abbreviations: LVI = lympho-vascular invasion; EIC = extensive intraductal component; ALND = axillary lymph node dissection.
* Not included in GEC–ESTRO recommendations.

presence of LVI, and lymph node metastases. The risk of IBR and DM increased by increasing the extension of nodal disease. Although hormone receptor status and tumour grade were not considered as categorisation criteria for GEC–ESTRO groupings, negativity was significantly associated with increased risk of IBR and DM, whereas high- grade tumour was significantly predictive for IBR, RNF and DM.

Overall, compared to the "good candidates" group, both the "possible candidates" and the "contraindication" groups showed a significantly increased risk of IBR (HR 3.89; 95% CI 1.66–9.11 and HR 3.85; CI 1.73–8.59, respectively). While no significant difference was seen with regard to RNF among the categories, DM rate was significantly higher in the "contraindication" category compared to the others (HR 3.80; 95% CI 1.17–8.10).

Discussion

We applied the GEC–ESTRO recommendations for using APBI to patients treated with intraoperative electrons to evaluate the ability to predict clinical outcome and appropriateness for treatment with APBI. Analysis of the ELIOT population stratified by the three GEC–ESTRO groups demonstrated statistically significant differences in the rate of IBR between the "good candidates" and the other two proposed categories, which shared a similar local failure rate. Therefore, GEC–ESTRO groupings, while successfully identifying low-risk patients ("good candidates"), did not detect any differences in terms of IBR between patients who might be treated with APBI ("possible candidates") and those who should not be treated with APBI ("contraindication"). This applied both to true recurrence and ipsilateral tumours, as all the three categories show a linear pattern of failure. The "good candidates" reported a low risk of clinically occult disease both near and distant from the original tumour site. The question whether this finding is correlated with a more indolent behaviour of residual disease rather than its absence will be answered by additional follow-up. Some randomised studies support the effect of whole breast RT (WBRT) on preventing IBR by the fact of lower incidence of ipsilateral tumour reappearance compared to the rate of contralateral BC [13,14]. The higher

aggressive tumour features in the other two subgroups carried the greater probability of occult residual microscopic disease in the breast, which accounts for the fact that most tumour reappearances occurred in a short time. Besides, ELIOT did not seem very effective in controlling true recurrence, raising the issue about the proper coverage of tumour bed in terms of volume and dosage. The single dose of 21 Gy was empirically chosen on the basis of the linear-quadratic model: its use has recently been allowed up to 18 Gy per fraction [15] and no serious adverse event has been reported so far. Since ELIOT is delivered under the direct visualisation of the tumour bed, it is not a matter of geographic missing or inter-observer differences in target volume delineation [16].

The median collimator was 4 cm: it means that from the sutured breech, as surgeons are used to doing full-thickness cavity closure, at least 2 cm of surrounding tissue has been irradiated. The ELIOT treated volume is not smaller than those reported using MammoSite or Intrabeam modalities [14]. If microscopic foci are within 10 mm from the edge of the original excision with negative margins in most cases, as found in a series from William Beaumont Hospital, the ELIOT field should be sufficient to provide control on true recurrence [17]. The pattern of relapse in the intermediate- and high-risk patient groups indicates that additional neoplastic foci tend to be located outside the boundaries of surgical and intraoperative treatment. A dose escalation study, along with the use of an increased median collimator diameter, is being investigated in our institution.

In our study, the "possible candidates" group remains a grey area for the application of APBI, because the rate of local failure was as high as that in the "contraindication" group, but the survival endpoints were not statistically different compared to the "good candidates" group. Although the findings are in line with a meta-analysis comparing APBI with WBRT [18], they collide with the increasing evidence that adjuvant RT after CS improves overall survival [19]. This could be due to the fact that they lacked sufficient statistical power.

In this study, age less than 50 years, tumour size >2 cm, and involved nodes, were found to be significant predictors for IBR on univariate analysis. Interestingly, patients with these unfavorable features remain eligible in the NSBP B-39/RTOG 0413 phase III trial comparing WBRT with APBI [20]. Oestrogen receptor status and high-grade tumours were identified as risk factors for the development of IBR, although not included in the GEC–ESTRO stratification criteria. In the MammoSite population grouped according to ASTRO guidelines, the univariate analysis indicated that negative ER status was the only significant predictor of IBR [21]. More uncertain remains the role of tumour grade, one of the strong predictors of IBR in EORTC "boost versus no boost" trial [22]. Poor histological grade, along with lymphovascular invasion, emerged as being significant for IBR in multivariate analysis, in both WBRT and APBI arms of the Christie Hospital Breast conservation trial [23]. Conversely, in the German–Austrian APBI phase II trial using interstitial multicatheter brachytherapy [24], tumour grade had no association with IBR or survival outcomes. In the ELIOT population, lobular carcinomas were not associated with worse local control when compared with other histological types, but this finding is contradictory in the literature [23,25].

EIC was not found to be associated with any study outcomes. In selected patients EIC is barely 1 cm beyond the primary tumour [17] and it might be likely to fall into the area excised by quadrantectomy. Similarly, positive or close margins did not influence the risk of IBR, but the small number of cases did not allow a meaningful evaluation.

Consistently with the literature [26], nodal involvement is strongly associated with IBR and DM characterised by the rate becoming progressively worse as the nodal burden becomes greater. Apart from LVI and EIC, many of the tumour features requested by GEC–ESTRO recommendations could be satisfied with an acceptable level of accuracy before delivering intraoperative RT through true-cut, core biopsy and frozen-section analysis. Besides, in this study the variable of age in itself is shown to be a very important criterion of selection and it might be the main key factor in the decision-making. Many studies point to young age as one of the most important factors related to local recurrence [27,28].The GEC–ESTRO panellists APBI review clearly showed how local failure decreased as age increased [5].

Conclusions

As among ELIOT population the "good candidates" group was clearly identified, these recommendations provide a useful guidance for selecting patients who may be treated with intraoperative RT in the routine clinical practice. The "possible candidates" group is confirmed to be a grey area which should be further investigated in a clinical trial in order to identify which tumour or patients' features are mostly involved in increasing the risk of failure.

Conflict of Interest Statement

All authors disclose that there are no actual or potential conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2012.10.018.

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