Intraoperative radiotherapy with electrons (ELIOT) for early breast cancer: the European Institute of Oncology experience

Roberto Orecchia[1,2], Maria Cristina Leonardi[1], Patrick Maisonneuve[3], Anna Morra[1], Roberta Lazzari[1], Federica Cattani[1], Veronica Dell'Acqua[1], Nicole Rotmensz[3], Giuseppe Viale[2,4], Alberto Luini[5], Paolo Veronesi[2,5], Viviana Galimberti[5], Stefano Zurrida[2,5], Oreste Gentilini[5], Mattia Intra[5], Umberto Veronesi[6]

[1]Division of Radiation Oncology, European Institute of Oncology, Milan, Italy; [2]University of Milan, Italy; [3]Division of Epidemiology and Biostatistics, [4]Division of Pathology, [5]Division of Breast Surgery, [6]Scientific Directorate, European Institute of Oncology, Milan, Italy

Corresponding to: Orecchia Roberto. Division of Radiotherapy-Advanced Radiation Centre, European Institute of Oncology, Via G. Ripamonti 435, 20141 Milan, Italy. Email: roberto.orecchia@ieo.it.

Abstract: Partial breast irradiation (PBI) as an alternative to whole breast irradiation (WBI) is an attractive approach tested in several phase II and a few phase III studies, using different modalities of irradiation. Intraoperative radiotherapy (RT) with electrons allows the reduction of a whole course of WBI to a single session during surgery. The European Institute of Oncology (Milan, Italy) conducted a series of investigations aimed proving the safety and the effectiveness of intraoperative RT as a full dose PBI. The single dose of 21 Gy was calculated to be theoretically equivalent to a full course of conventional WBI. This ultimate form of hypofractionation carried some concern regarding the long-term impact on breast parenchyma. Phase I and II studies and a number of off- protocol patients have shown feasibility and good short-term results in both disease control and cosmesis. The results of the ELIOT randomized phase III trial comparing intraoperative RT to conventional WBI are discussed in the context of a worldwide scenario including other four randomized studies and one metanalysis, so far. From the analysis of the available data, the adequate patient selection emerges as mandatory to make intraoperative RT and other PBI modalities a reasonable alternative to conventional WBI. Further investigations are required to fully understand the weight of clinical and histologic variables classically associated with increased risk of local recurrence. In addition, the role of molecular classification in the pattern of recurrence after PBI will be more and more predominant.

Keywords: Partial breast irradiation (PBI); intraoperative electrons; breast cancer (BC)

Submitted Dec 23, 2013. Accepted for publication Feb 17, 2014.
doi: 10.3978/j.issn.2218-676X.2014.02.04
Scan to your mobile device or view this article at: http://www.thetcr.org/article/view/2094/2759

Partial breast radiation therapy (PBI) as a component of breast conservation therapy is an emerging paradigm in the treatment of women with early breast cancer (BC) (1). Over the past two decades there has been a radical change in BC radiation. In the nineties almost all the women received whole breast irradiation (WBI), which was almost always performed with conventional fractionation. Nowadays, a number of radiation oncologists are delivering alternate breast radiotherapy (RT) strategies from WBI with hypofractionated schemes to PBI. In a survey (2) where physicians were asked how often they used the breast irradiation regimens, Balloon-PBI was the second most common irradiation technique after conventionally fractionated WBI, although this technique is not currently supported by clinical phase III trials. PBI is an attractive treatment approach that offers patients shortened overall treatment times and a potential decrease in the radiation dose delivered to non-target portions of the breast and adjacent tissues. Over the past decade, PBI has spread quickly, showing a 10-fold increase between 2002 and 2007 (3) and thousands of women are being currently treated with different modalities in clinic practice. At the 13th St Gallen expert consensus meeting, the majority of the Panel recognized the safety and efficacy of some forms of PBI in

selected patients, although the issue about the definition of a suitable group still exists (4). The NSABP B-39/RTOG 0413 trial, closed in April 2013, enrolled a large number of patients with estrogen negative status, 1 to 3 positive axillary lymph nodes and younger than 50 years old, which might clarify the appropriateness of PBI in this setting (5).

The rationale for PBI is based on the observation that the majority of local recurrences (LR) were close to the region of the primary tumor (6). Therefore, limiting the radiation target volume to the originally involved portion of the breast would achieve local control equivalent to WBI in selected cases. The ideal patients are the ones with low risk of harboring distant tumor cells or with distant tumor cells which remain dormant, because of the intrinsic indolent nature and/or the effect of systemic therapies. The previous studies on PBI failed to achieve acceptable local control because of the poor patient selection, the inadequate target definition and dose prescription. Over time, the eligibility criteria and the radiation technique have been refined, achieving annual LR rate lower than 1%, with best figures about 0.5% (7). So far, five phase III randomized trials and one metanalysis evaluating PBI have been published. In the first two randomized studies, the Christie Hospital (8) and the Yorkshire Breast Cancer Group trials (9), PBI showed poor local control, because both of them were inadequate to modern standard. Conversely, the Hungarian trial based its success on strict selection criteria, including only low-risk BC patients. At ten years follow-up no difference was found regarding LR and any survival endpoint (10). In the more recent Targit-A trial, where more than 80% of patients fell into the ASTRO suitable group, the preliminary results, after two years and a half, showed similar LR rate among PBI and WBI patients. After five years, LR in the intraoperative arm was greater than that in WBI arm (3.3% *vs*. 1.3%, P=0.042) (11). In the ELIOT trial (12), both true LR and new ipsilateral BC were significantly more common in the intraoperative RT arm than in WBI arm, while no differences in any survival endpoint was noticed. The correlation between PBI and an increased risk for both local and regional recurrence, without any impact on survival, was also outlined by the metanalysis (13). Different modalities of PBI have been used, each of them with their own advantages and drawbacks. Intraoperative RT with electrons with one single fraction of 21 Gy has the advantage of one short procedure that includes both surgery and RT at the same time. Extending the operation by few minutes (the whole procedure, in fact, from preparing the tumor bed to delivering the prescribed dose, takes not more than 15 minutes), avoids long treatment course and solves the practical question of travelling back and forth from the RT centre, which in some countries or circumstances might be an obstacle. In addition, intraoperative RT with electrons allows a great decrease in the radiation dose delivered to non-target tissues, since skin is moved away from the radiation field and ribs, lungs and heart are properly shielded. Furthermore, the intraoperative modality allows a precise delineation of the tumour bed, which is identified under visual control, avoiding any geographic miss. The development of this technique was made possible by the availability of new mobile linear accelerators, which are able to enter the operating theatre to administer the treatment. The Milan experience started in 1999 at the European Institute of Oncology (14).

After short phase I and II studies, a single dose of 21 Gy was selected. The technical details have been previously described (15).

The dose of 21 Gy, prescribed at the 90% isodose in a single fraction, was delivered immediately after the tumor removal, through a round Perspex applicator tube. The diameter of the collimator was chosen according to the site and the size of the tumor. The energy of the electron beams was selected according to the measured thickness of the reconstructed gland. To protect the underlying critical structures (ribs, lung, heart), an aluminum and lead disc was placed between the mammary gland and the superficial fascia of the major pectoral muscle.

From a radiobiological point of view, the treatment of 21 Gy in a single fraction was supposed to be equivalent to the conventional treatment of 60 Gy in 30 fractions, by using the linear quadratic equation. Assuming that the alpha-beta ratio of breast tumor cells and early side effects is equal to 10, giving a single-dose treatment of 21 Gy should result in the same local control and acute toxicity as conventionally fractionated doses of 65 Gy. Conversely, assuming that the alpha-beta ratio of breast tumor cells is equal to 4, 21 Gy in a single dose should be equivalent to 131 Gy in 2 Gy fractions. However, more severe side effects (such as fibrosis) in late responding tissues (which have alpha-beta ratios of 3 or lower) might be expected from the single-fraction treatment, since biologically equivalent dose higher than 168 Gy is achieved (16). Although the LQ-model seems not to fit well in a high dose per fraction region, at present, it remains the most reliable reference model (17). From a clinical point of view, IEO Phase I and II studies (14) have shown feasibility and good short-term results in both disease control and cosmesis. Out of

101 patients who took part in the dose escalation study, 16 patients (16%) developed breast fibrosis that was mild in 15 and severe in one, while two patients reported mild pain on the tumor bed, with a mean follow-up of 42 months. Patients who did not enter the phase III ELIOT trial, although being treated according to the same schedule of 21 Gy, were analyzed apart in a report (18) with a median follow-up of 36.1 months. Among them, 34 (1.9%) reported breast fibrosis, which was severe in two cases, and 14 (0.8%) experienced moderate skin retraction. The ELIOT phase III study, comparing the intraoperative PBI with conventional WBI, started in November 2000 and the accrual continued till December 2007 (12). At that time, the eligibility criteria considered as adequate for selecting patients for intraoperative treatment were based on simply clinical and tumor features: small tumors, up to 2.5 cm , clinically negative axillary nodes and age over 48. This age cut-off was set to include only women in peri- or postmenopausal status, for whom the risk of LR throughout the breast is considered lower than in young patients. A total of 1,305 BC patients were randomized before surgery in the study (654 in the conventional WBI arm and 651 in the intraoperative RT arm). Due to ineligibility after surgery or protocol violation, 119 patients were excluded and a total of 1,186 patients were available for analysis (601 in the conventional WBI arm and 585 in the intraoperative RT arm). The primary endpoint was the incidence of in-breast reappearances, including true local relapse (defined as any recurrence near the site of the primary tumor) and ipsilateral BC. The study was designed as an equivalent trial. The equivalence was based on the expected 5-year rate local relapses in the conventional arm of about 3% and in the intraoperative RT arm of no more than 7.5%.

Among the ELIOT phase III patients, acute side effects were limited with a statistically significant difference in favor of the intraoperative RT arm (P=0.0002), except for a higher incidence of fat necrosis. In particular, fewer skin side effects were observed in the intraoperative RT arm, compared to WBI arm, because of the skin sparing. No differences between the two arms were observed for mammary fibrosis, mammary retraction, pain or burning.

Based on these data, the expected toxicity seems not to be confirmed by clinical observations. However, as late morbidity can increase over time (19), the final assessment should be made after follow-up period longer than five years.

Regarding local control, among off-protocol patients at 36 months (18), a LR rate of 3.6% was observed, of which more than 60% were true recurrences, whereas the remaining was considered second ipsilateral cancers, occurring outside the index quadrant. This group of patients, excluded from the ELIOT trial because they did not fully satisfied the strict eligibility criteria, was at higher risk of failure compared to in protocol patients. In fact, the number of patients aged 50 or under, with tumor size larger than 2 cm, more than three positive lymph nodes, grade 3 and high Ki-67 was greater than in ELIOT trial patients. With an annual rate of in-breast reappearances of 1.21%, the cumulative incidence would achieve 6.05% at five years. Most of the factors deemed prognostic for LR are well-known. In univariate analysis, the risk of LR increased with the increase of tumour size, number of positive lymph nodes and proliferative index (Ki-67). In addition, the presence of LVI and HER2 over expression, the absence of ER/PR receptor status, and the young age confirmed to be risk factors. In multivariate analysis, age <50 and tumour size >2 cm remained independent predictors of local relapse.

Combined with increasing evidence that WBI improves long-term overall survival, BC experts have been striving to identify the proper eligibility criteria to safely select patients for PBI. Several consensus statements from different breast experts panels have been published. The most expansive recommendations were released in 2009 by the American Society for Radiation Oncology (ASTRO) (20), and in 2010 by the European Society for Radiation Oncology (GEC-ESTRO) (21). These recommendations outlined three patient groups, based on clinical and pathologic risk factors. Whether these guidelines optimally define the risk categories remain in question. Numerous studies have failed to find a correlation between risk stratification and rates of LR. A pooled analysis including more than two thousand patients, showed a similar 5-year rate of local, regional and distant failure between PBI and WBI patients categorized according the ASTRO groupings (22).

We are aware that these guidelines for PBI cannot be fully applied to intraoperative RT, since they are based mainly on histopathologic features, which are not entirely available at the time of delivering intraoperative irradiation. This is without doubt one of the greatest issues connected with intraoperative techniques, because the definitive pathologic report can show histologic or biomolecular features for which WBI would be the best choice. TARGIT-A trial included the possibility to complete the treatment by adding WBI, in case of critical pathological findings. However, some efforts to improve the pre-irradiation pathologic tumour evaluation can be made. Being able to rely on a good quality standard of

preoperative and intraoperative pathologic assessment, many of the tumour features requested by ASTRO and GEC-ESTRO recommendations might be satisfied. In fact, true-cut or core biopsy specimens and intraoperative frozen sections can show the type of histology, grading, hormonal receptor status, margin resection involvement and sentinel lymph node status. We applied the ASTRO and GEC-ESTRO recommendations for the use of PBI to off-protocol patients treated with intraoperative electrons, to evaluate the ability to predict clinical outcome (23,24).

ASTRO groupings observed stricter criteria compared to ESTRO and this difference affected the correct identification of the risk categorizes. The "suitable" or "good" candidates showed a very low rate of in-breast recurrences, which was 1.5% and 1.7% according to ASTRO and ESTRO, respectively. While both the consensus guidelines successfully pinpointed this subgroup of patients with low-risk of LR, there was no agreement in the identification of the higher risk subgroups. ASTRO, due to strict selection criteria, kept on detecting differences between the intermediate and high risk groups, (4.4% and 8.8%, respectively), while ESTRO, with looser selection criteria, failed to notice any differences between the groups (7.4% and 7.8%, respectively). In the ASTRO and ESTRO favourable groups, patients reported a low risk of LR both near and distant from the original tumor site. Conversely, in the more unfavorable groups, patients developed high LR rate both in the index quadrant and in the remaining breast. This finding may be the expression of a form of radioresistance and the presence of a great amount of distant tumor cells associated with more aggressive tumors.

In the ELIOT phase III trial (12), the majority of patients shared the same tumor features as the suitable ASTRO group. The two arms were perfectly balanced at baseline, except for a higher frequency of G1 tumors in the intraoperative RT arm. After median follow-up of 5.8 years for all patients, 35 in-breast reappearances, with a 5-year LR rate of 4.4%, were observed in the intraoperative RT arm compared to four cases, with a 5-year LR rate of 0.4%, in the conventional WBI arm (P=0.0001). Breaking down the in-breast reappearance incidence according to the site of recurrence, an excess of "true local relapses" was found in the intraoperative RT arm (21 cases, 2.5%) compared to the conventional WBI arm (4 cases, 0.4%) (P=0.0003). The occurrence of a new tumor in the ipsilateral breast, at a distance from the index quadrant, was observed only in the intraoperative RT arm, with 14 events (1.9%, P=0.0001). This finding supports the effect of WBI on preventing LR, already highlighted by some randomized studies (25). Therefore, in the intraoperative RT arm an excess of recurrences in the ipsilateral breast was detected, both in the index quadrant and in the other quadrants of the same breast compared to the conventional WBI arm. Interestingly, in the Hungarian study, the relapse rate in the arm with PBI was 5.5% at five years, which was similar to that recorded in the intraoperative RT arm of ELIOT study (26). In the latter one, the observed LR rate was within the prespecified equivalence margin of 7.5%, but it was significantly greater compared to that observed in the conventional WBI arm. Because of this great difference between the two arms, ELIOT phase III trial failed to demonstrate the equivalence.

An important point to emphasize is that, in spite of the increased LR incidence in the intraoperative RT arm, the 5-year overall survival was similar in the two arms (96.8% in the intraoperative RT arm and 96.9% in the WBI arm), with an equal number of distant metastases and deaths after a median follow-up of 5.7 years.

The analysis aimed at identifying characteristics associated with the rate of local relapse was restricted to patients treated with intraoperative RT, since the low number of recurrences in WBI arm prevented any further investigation. In multivariate analysis (12), tumor size greater than 2 cm (HR 2.24), ≥4 positive lymph nodes (HR 2.61), high grade tumor (HR 2.18) and triple negative subtype (HR 2.40) presented a significantly increased risk of in- breast reappearances. Patients receiving intraoperative RT with at least one of these high-risk factors had a significant increase in the 5-year LR risk, from 1.5% to 11.3%. Several studies have investigated the association of the molecular subtypes with rates of local recurrence, but the impact is still unclear. Some studies have shown that the basal or triple-negative and HER2+ subtypes are associated with an increased risk of LR (27). Among the ELIOT trial patients, molecular subtypes remain independent predictors of local relapse. In fact, compared to Luminal A patients, the other subtypes showed a significant increase in local recurrence rate.

A stratification of LR according to site of in-breast failure was carried out among the ELIOT out-trial patients (18). Patients in the Luminal A category had a very low risk of both true local relapse and new ipsilateral BC, luminal B and triple negative subtypes had higher incidence of LR in both the index quadrant and in the remaining breast, while for HER2+ patients the true recurrences were prevalent.

When we applied the ASTRO guidelines to patients

enrolled in the ELIOT phase III trial, the suitable patients according to ASTRO treated with intraoperative electrons presented a local relapse rate as low as those treated with WBI, whereas the cautionary and the unsuitable groups showed better local control when treated with WBI. It means that aggressive tumors have a larger amount of distant microscopic disease, which might be controlled by extended radiation fields. Since 2011, the NCCN guidelines (28) recognized the use PBI for the ASTRO suitable group. The results from the ELIOT phase III trial strengthen the indication of the use of PBI for this subgroup of patients. It should be pointed out that patients belonging to the ASTRO "cautionary" or "unsuitable" category are not necessarily at higher risk of LR, but should be encouraged to take part in specifically addressed clinical trials (29). However, for the time being, the safe applicability of intraoperative breast irradiation should be limited to patients classified "suitable "according to ASTRO, as emerged by the results of ELIOT phase III.

Acknowledgments

Funding: We thank the Italian Association for Cancer Research, the Jacqueline Seroussi Memorial Foundation for Cancer Research, the Umberto Veronesi Foundation, the American Italian Cancer Foundation, the Lombardy Region for their contribution and support to the ELIOT study.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Frederik Wenz and Elena Sperk) for the series "Intraoperative Radiotherapy" published in *Translational Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2014.02.04). The series "Intraoperative Radiotherapy" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Offersen BV, Overgaard M, Kroman N, et al. Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: a systematic review. Radiother Oncol 2009;90:1-13.
2. Hoopes DJ, Kaziska D, Chapin P, et al. Patient preferences and physician practice patterns regarding breast radiotherapy. Int J Radiat Oncol Biol Phys 2012;82:674-81.
3. Husain ZA, Mahmood U, Hanlon A, et al. Accelerated partial breast irradiation via brachytherapy: a patterns-of-care analysis with ASTRO consensus statement groupings. Brachytherapy 2011;10:479-85.
4. Goldhirsch A, Winer EP, Coates AS, et al. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 2013;24:2206-23.
5. Radiation Therapy Oncology Group 0413/National Surgical Adjuvant Breast and Bowel Project B-39. Available online: http://www.rtog.org/clinicaltrials/protocoltable.aspx, accessed December 12, 2013.
6. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 2002;347:1227-32.
7. Polgár C, Van Limbergen E, Pötter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother Oncol 2010;94:264-73.
8. Ribeiro GG, Magee B, Swindell R, et al. The Christie Hospital breast conservation trial: an update at 8 years from inception. Clin Oncol (R Coll Radiol) 1993;5:278-83.
9. Dodwell DJ, Dyker K, Brown J, et al. A randomised study of whole-breast vs tumour-bed irradiation after local

excision and axillary dissection for early breast cancer. Clin Oncol (R Coll Radiol) 2005;17:618-22.
10. Polgár C, Fodor J, Major T, et al. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. Radiother Oncol 2013;108:197-202.
11. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. Lancet 2014;383:603-13.
12. Veronesi U, Orecchia R, Maisonneuve P, et al. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. Lancet Oncol 2013;14:1269-77.
13. Valachis A, Mauri D, Polyzos NP, et al. Partial breast irradiation or whole breast radiotherapy for early breast cancer: a meta-analysis of randomized controlled trials. Breast J 2010;16:245-51.
14. Luini A, Orecchia R, Gatti G, et al. The pilot trial on intraoperative radiotherapy with electrons (ELIOT): update on the results. Breast Cancer Res Treat 2005;93:55-9.
15. Veronesi U, Gatti G, Luini A, et al. Intraoperative radiation therapy for breast cancer: technical notes. Breast J 2003;9:106-12.
16. Rosenstein BS, Lymberis SC, Formenti SC. Biologic comparison of partial breast irradiation protocols. Int J Radiat Oncol Biol Phys 2004;60:1393-404.
17. Kirkpatrick JP, Meyer JJ, Marks LB. The linear-quadratic model is inappropriate to model high dose per fraction effects in radiosurgery. Semin Radiat Oncol 2008;18:240-3.
18. Veronesi U, Orecchia R, Luini A, et al. Intraoperative radiotherapy during breast conserving surgery: a study on 1,822 cases treated with electrons. Breast Cancer Res Treat 2010;124:141-51.
19. Gorodetsky R, Lotan C, Piggot K, et al. Late effects of dose fractionation on the mechanical properties of breast skin following post-lumpectomy radiotherapy. Int J Radiat Oncol Biol Phys 1999;45:893-900.
20. Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 2009;74:987-1001.
21. Polgár C, Van Limbergen E, Pötter R, et al. Patient selection for accelerated partial-breast irradiation (APBI) after breast-conserving surgery: recommendations of the Groupe Européen de Curiethérapie-European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) breast cancer working group based on clinical evidence (2009). Radiother Oncol 2010;94:264-73.
22. Wilkinson JB, Beitsch PD, Shah C, et al. Evaluation of current consensus statement recommendations for accelerated partial breast irradiation: a pooled analysis of William Beaumont Hospital and American Society of Breast Surgeon MammoSite Registry Trial Data. Int J Radiat Oncol Biol Phys 2013;85:1179-85.
23. Leonardi MC, Maisonneuve P, Mastropasqua MG, et al. 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. Int J Radiat Oncol Biol Phys 2012;83:806-13.
24. Leonardi MC, Maisonneuve P, Mastropasqua MG, et al. Accelerated partial breast irradiation with intraoperative electrons: using GEC-ESTRO recommendations as guidance for patient selection. Radiother Oncol 2013;106:21-7.
25. Gujral DM, Sumo G, Owen JR, et al. Ipsilateral breast tumor relapse: local recurrence versus new primary tumor and the effect of whole-breast radiotherapy on the rate of new primaries. Int J Radiat Oncol Biol Phys 2011;79:19-25.
26. Polgár C, Fodor J, Major T, et al. Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma--5-year results of a randomized trial. Int J Radiat Oncol Biol Phys 2007;69:694-702.
27. Nguyen PL, Taghian AG, Katz MS, et al. Breast cancer subtype approximated by estrogen receptor, progesterone receptor, and HER-2 is associated with local and distant recurrence after breast-conserving therapy. J Clin Oncol 2008;26:2373-8.
28. NCCN Clinical Practice Guidelines in Oncology for Breast cancer. Available online: ww.nccn.org/professionals/physician_gls/f_guidelines.asp
29. Vicini F, Arthur D, Wazer D, et al. Limitations of the American Society of Therapeutic Radiology and Oncology Consensus Panel guidelines on the use of accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 2011;79:977-84.

Cite this article as: Orecchia R, Leonardi MC, Maisonneuve P, Morra A, Lazzari R, Cattani F, Dell'Acqua V, Rotmensz N, Viale G, Luini A, Veronesi P, Galimberti V, Zurrida S, Gentilini O, Intra M, Veronesi U. Intraoperative radiotherapy with electrons (ELIOT) for early breast cancer: the European Institute of Oncology experience. Transl Cancer Res 2014;3(1):59-64. doi: 10.3978/j.issn.2218-676X.2014.02.04