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Breast radiotherapy

# Ipsilateral axillary recurrence after breast conservative surgery: The protective effect of whole breast radiotherapy

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ABSTRACT

*Background and purpose:* Whole breast radiotherapy (WBRT) is one of the possible reasons for the low rate of axillary recurrence after breast-conserving surgery (BCS).

*Patients and methods:* We retrospectively collected data from 4,129 consecutive patients with breast cancer ⩽2 cm and negative sentinel lymph node who underwent BCS between 1997 and 2007. We compared the risk of axillary lymph node recurrence between patients treated by WBRT ($n = 2939$) and patients who received partial breast irradiation (PBI; $n = 1,190$) performed by a single dose of electron intraoperative radiotherapy.

*Results:* Median tumour diameter was 1.1 cm in both WBRT and PBI. Women who received WBRT were significantly younger and expressed significantly more multifocality, extensive in situ component, negative oestrogen receptor status and HER2 over-expression than women who received PBI. After a median follow-up of 8.3 years, 37 and 28 axillary recurrences were observed in the WBRT and PBI arm, respectively, corresponding to a 10-year cumulative incidence of 1.3% and 4.0% ($P < 0.001$). Multivariate analysis resulted in a hazard ratio of 0.30 (95% CI 0.17–0.51) in favour of WBRT.

*Conclusions:* In this large series of women with T1 breast cancer and negative sentinel lymph node treated by BCS, WBRT lowered the risk of axillary recurrence by two thirds as compared to PBI.



The incidence of nodal recurrence in the axilla in patients undergoing sentinel node biopsy (SNB) is much lower than expected, considering that 5–10% patients with negative SNB actually have one or more positive axillary nodes [1]. In a large series of patients with negative SLNB the axillary recurrence rate at 5 years was lower than 1% [2]. But the most surprising data came from the American College of Surgeons Oncology Group (ACOSOG) Z-0011 trial where, after a median follow up of 6.3 years, the incidence of axillary nodal recurrence was 0.9% in patients with a positive SLNB who did not receive axillary dissection (AD) [3]. These figures were again much lower than expected, considering that 27% of patients had additional positive axillary nodes in the arm receiving AD. In fact, these phenomena had been reported even in the pre-SLNB era. In the 09-98 trial carried out at the Milan National Cancer Institute, patients who received breast conserving surgery without any axillary surgery experienced 9% of axillary nodal recurrence despite 28.9% of patients being found to have positive axillary nodes in the arm receiving AD [4].

Several hypotheses might explain these results. First, the effect of adjuvant medical treatments, which are now recommended to virtually all patients after surgery. Second, a self-immune response which might be able to control the overt appearance of the disease. Third, the effect of whole-breast radiotherapy (WBRT) which gives some coverage of the first level of the axilla [5,6].

Partial breast irradiation (PBI) has been increasingly used over the years to reduce irradiation side effects and to improve quality of life of patients by selectively treating the tumour bed and reducing time and fields of irradiation. The PBI technique performed in our institution is a single intraoperative dose of electrons (ELIOT) which is administered via dedicated mobile accelerators. The intraoperative radiation field encompasses only the tumour bed of the breast gland; the axillary nodes do not receive any dose of radiation. The aim of this study was to determine whether there is a protective effect of WBRT on axillary nodal reappearance. In order to answer this relevant question, we retrieved the medical records

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of a large consecutive series of patients who had been operated on at the European Institute of Oncology (IEO) in Milan, Italy, for small breast cancer (BC) (⩽2 cm) with negative sentinel node biopsy. We evaluated axillary lymph node recurrence comparing patients who received postoperative WBRT to those who received intraoperative partial breast irradiation (PBI).

## Patients and methods

Between 1997 and 2007, 18,937 patients were operated on for an invasive BC at the IEO, and their data were prospectively entered into the Institutional Breast Cancer Database. All cases were discussed at the weekly multidisciplinary meeting. For the present study, we retrieved information on 4129 patients who underwent conservative surgery for a small BC (⩽2 cm), who had a negative sentinel node biopsy and received postoperative WBRT or PBI. Patients who underwent axillary dissection, males, patients with synchronous distant metastases, bilateral or recurrent tumour, previous invasive cancer, and those receiving primary medical treatment were not included.

### *Radiation treatment description*

During the time frame of the study, external breast radiotherapy transitioned from 2-dimensional (2D) to 3-dimensional (3D) conformal treatments (3DCRT) at the end of the 1990s. Simulation and treatment were performed with the patient in the supine position, using immobilization devices, such as expanded polyurethane moulds, with both arms extended above the patient's head. A chest computer tomography (CT) scan in quiet respiration was acquired to encompass the entire lung volume. Breast clinical target volume (CTV) included the palpable breast tissue demarcated with external radio-opaque markers and the glandular tissue visualized on the CT images. In the 2D radiotherapy period, the breast CTV was outlined and dose distribution was checked only on the three most representative CT images, while subsequently target and non-target structures (organs at risk, OARs) were contoured on all the CT images and treatment planning using 3D tools. Axillary nodes were at no point contoured for breast-only radiotherapy.

The breast CTV was limited ventrally within 3 mm from the skin and dorsally to the anterior surface of the pectoralis fascia, excluding the bony thorax and lung. The planning target volume (PTV) was manually shaped applying a margin to the CTV of from 1 cm to 1.5 cm, sparing the heart and without crossing the midline. Generally, the cranial margin of the radiation fields fell below the head of the clavicle, at the level of the second intercostal space. No axillary nodal levels were intentionally included in the radiation fields. A treatment planning CT scan was generated using two opposed tangential fields using 6MV photon beams. Wedge filters were employed. Either no or very small collimator rotation was applied. The 100% tumour dose was specified at the isocentre (International Commission on Radiation Units and Measurements ICRU point) [7].

The whole breast irradiation schedule consisted of either 50 Gy in 25 fractions (fx) + sequential boost (10 Gy/5 fx) to the tumoural bed with a direct electron field or 45 Gy in 20 fractions + concomitant boost (5 Gy/20 fx) to the tumour bed with direct photon beam. According to the ICRU recommendations, the dose variation throughout the treated volume ranged between 5% and +7% [7,8].

Intraoperative irradiation with electrons was administered with dedicated mobile accelerators equipped with cylindrical Perspex applicators of various diameters (4–10 cm), flat-ended or bevelled (NOVAC 7 Hitesys, Latina, Italy and Liac, Info and Tech, Rome, Italy). After tumour excision, the breast gland was widely mobilized by separating it in each direction both posteriorly from the fascia of the pectoralis major muscle and superficially from the subcutaneous tissue. A dedicated aluminium-lead shielding disc, greater in size compared to the radiation field, was placed between the gland and the pectoral muscle, to protect the thoracic wall and the muscle plane. The surgical breach was then temporally restored in order to expose the most homogeneous target tissue to intraoperative radiotherapy.

Technical parameters (collimator size, electron energy) were chosen according to the thickness of target volume, tumour location and type of surgical incision. The applicator was then connected to the head of the treatment unit with a hard docking system and centred on the breast target. Irradiation was applied for several minutes, and at the end, the collimator and the thoracic disc were removed and surgery proceeded to completion. The intraoperative radiation field encompassed only the tumour bed of the breast gland and no axillary nodes were irradiated at any dose. Furthermore, the breast parenchyma on the axillary tail was considered a contraindication for intraoperative radiotherapy.

The dose prescription of 21 Gy in single fraction was calculated to be theoretically equivalent to a full course of conventional external beam radiotherapy based on the linear–quadratic model. The maximum dose (Dmax) was not prescribed, but rather the 90% isodose, bringing up the Dmax to 23.2 Gy. Less than 100 patients took part in the phase I study and received a lower dose (17 and 19 Gy). Three hundred and seventy-one patients included in the present analysis were enroled in the phase III randomized study ELIOT, whereas the remaining others were treated outside the clinical trial [9].

### *Statistical methods*

Association between categorical variables and type of radiotherapy (WBRT or PBI) was evaluated by the Chi square test and the Chi square test for trend, as appropriate. For the calculation of cumulative incidences, only first events were considered. For instance, for the calculation of the cumulative incidence of axillary recurrences (with or without ipsilateral breast recurrence), we counted the first axillary recurrences alone or in combination with a local recurrence in the ipsilateral breast as events, while we treated all other events as competing events (i.e. local recurrence in the ipsilateral breast recurrence, distant metastases, other primary tumour, contralateral breast cancer and death as first event). Cumulative incidences were compared across different subgroups by means of the Gray test. Multivariable Cox proportional hazards models were applied to evaluate radiotherapy as an independent prognostic factor. In the models we included all the variables that were associated with the event of interest ($P < 0.10$) in univariate analysis. Adjusted hazards ratios (HR) with 95% confidence intervals (CIs) were reported. As a sensitivity analysis, a matched-cohort study was carried out. We matched each patient in the PBI group to a patient in the WBRT group, according to year of surgery (within 2 years), age (within 5 years), year pT (⩽0.5 cm *vs.* >0.5–1 cm *vs.* >1–2 cm) and multifocality (yes *vs.* no). Those variables were chosen *a priori* as potential confounders in the analysis of the axillary recurrence risk. Competing risk survival analysis and Cox proportional hazards regression models were then repeated.

All analyses were carried out with SAS software (SAS Institute, Cary, NC) and R software, version 2.12.2 (http://www.rproject.org).

## Results

In Table 1 we reported the characteristics of all the patients included in the study ($n = 4129$), the patients in the PBI group ($n = 1190$) and the patients in the WBRT group ($n = 2939$). The tumour size was similar in the two groups (median diameter 1.1 cm in both groups). On the other hand, women who received