Mammography before post-operative radiotherapy in conservatively managed breast cancer patients: is it useful?

¹M MASSACCESI, MD, ¹C DIGESÙ, MD, ¹G MACCHIA, MD, ¹F DEODATO, MD, ²M CIUFFREDA, MD, ²E CUCCI, MD, ¹L CARAVATTA, MD, ³G CORRADO, MD, ⁴G D A PADULA, MD, ⁵R DE VIZIA, MD, ⁶N CELLINI, MD, ⁶V VALENTINI, MD, ²G SALLUSTIO, MD, ³G FERRANDINA, MD, ⁷F PACELLI, MD and ^{1,6}A G MORGANTI, MD

¹Radiotherapy Unit, Università Cattolica del Sacro Cuore, Campobasso, Italy, ²Radiology Unit, Università Cattolica del Sacro Cuore, Campobasso, Italy, ³Gynaecologic Oncology Unit, Università Cattolica del Sacro Cuore, Campobasso, Italy, ⁴Department of Radiation Oncology, The Lacks Cancer Center, Saint Mary's Health Care, Grand Rapids, MI, USA, ⁵Radiology Unit, GEPOS Health Centre, Telesse Terme, Italy, ⁶Department of Radiotherapy, Policlinico Universitario "Agostino Gemelli", Università Cattolica del Sacro Cuore, Rome, Italy, and ⁷Surgery Unit, Fondazione di Ricerca e Cura "Giovanni Paolo II", Campobasso, Italy

Objective: The aim of this study was to evaluate the role of bilateral mammography undertaken before adjuvant radiotherapy in patients with conservatively managed invasive carcinoma of the breast.

Methods: Patients with invasive breast cancer referred to the Radiotherapy Unit of the Università Cattolica del Sacro Cuore, in Campobasso, Italy, between March 2002 and September 2006 were retrospectively reviewed. Patients were referred to our facility from other local and regional hospitals where they received breast-conserving surgery and adjuvant chemotherapy. They presented to our department for post-operative whole-breast radiotherapy. All patients underwent physical examination and bilateral mammography prior to adjuvant irradiation.

Results: 201 patients met the selection criteria as delineated. Of these 201 patients who underwent pre-radiotherapy mammography, 3 had suspicious findings on mammography. In two of those cases, the histopathological examination confirmed the presence of residual disease within the residual mammary gland. In one case, the pre-radiotherapy mammogram allowed for the detection of disease persistence which was not otherwise appreciated on physical exam. In the other case, the diagnostic imaging confirmed only the findings of the physical exam. In both cases of residual disease, the tumour was found elsewhere in the breast and not at the primary site. In one patient, the radiological re-assessment led to a false-positive result. No cases of contralateral synchronous breast cancer were observed. The overall adjunctive cost of this strategy including a routine mammography besides the clinical visit was €7012 for all patients.

Conclusions: No clear recommendation exists regarding post-operative mammography before adjuvant radiotherapy. In our experience, this strategy allowed for the detection of gross disease persistence after surgery which was not appreciated at clinical examination in 1 case out of 201. In this patient, adjuvant radiotherapy up to a total dose of 50 Gy would have been inadequate. Given the low cost of mammography, further investigation about its role in pre-radiotherapy evaluation is warranted.

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The role of post-operative radiotherapy in preventing local recurrence after breast-conserving surgery for early-stage invasive breast cancer is well established from multiple Phase III clinical trials [1–3]. Despite adjuvant radiotherapy, the cumulative incidence of ipsilateral breast tumour recurrence (IBTR) ranges from 2.2% to 5.2% [2–3]. Although the risk of developing IBTR persists

even after 15 years from the initial presentation [1], it is higher during the first 5 years [4], with an incidence of 5–10% [5]. Patients who develop local failure appear to have fewer disease-free intervals and substantially worse overall survival rates [6, 7].

With whole-breast irradiation, tumour doses of approximately 45–50 Gy are delivered to the entire breast over 3–6 weeks, often followed by a boost to the tumour bed. On a radiobiological basis, the risk of local recurrence after complete surgery is related to the density of clonogenic tumour cells when radiotherapy is initiated. If a residual macroscopic tumour is present, a

Address correspondence to: Dr Gabriella Macchia, Radiotherapy Unit, Department of Oncology, Fondazione di Ricerca e Cura "Giovanni Paolo II", Università Cattolica del Sacro Cuore, Largo A. Gemelli 1 86100 Campobasso, Italy. E-mail: gmacchia@rm.unicatt.it

prophylactic radiation dose is not enough to prevent a local failure; therefore, adjuvant whole-breast radiotherapy is inadequate.

The aim of this study was to evaluate whether a mammographic assessment before adjuvant radiotherapy can detect any residual macroscopic tumour within the remaining breast parenchyma in patients who have undergone breast conservation.

Methods and materials

Patients with invasive breast cancer who had received breast-conserving surgery and adjuvant chemotherapy in other local and regional hospitals and were referred to the Radiotherapy Unit of the Università Cattolica del Sacro Cuore, in Campobasso, Italy, between March 2002 and September 2006 were retrospectively reviewed. All patients had undergone lumpectomy with complete gross excision of primary tumour and axillary dissection or sentinel lymph node biopsy and adjuvant chemotherapy. Re-excision had been performed for positive resection margins. A given number of millimetres was the criteria to determine clear margin (positive margins, <1 mm; close margins, ≥1–3 mm).

Patients' clinicopathological information was retrospectively collected and included patient age, menopausal status, tumour size, histological subtype and tumour grade, which was scored according to the Scarff–Bloom–Richardson (SBR) grading system [8]. Status of steroid hormonal receptor expression was also recorded. All patients underwent a physical exam and bilateral mammography before irradiation.

Results

201 patients met the selection criteria. As shown in Table 1, most women had T1–T2, N0–N1 tumours and were post-menopausal. Ductal histology was the most frequently reported histology and most tumours had differentiation of grade II or III according to the SBR system, and expressed hormonal receptors. Patients received adjuvant chemotherapy with cyclophosphamide, methotrexate and fluorouracil [47 (23.4%)], anthracycline with or without other drugs [135 (67.2%)] or anthracycline and docetaxel with or without other drugs [19 (9.5%)]. Adjuvant therapy with oestrogen deprivation was prescribed in 124 (61.7%) patients. 4% of patients received conservative surgery despite having locally advanced disease (pT3 or pT4), owing to their refusal to undergo a mastectomy.

The median time interval between surgery and final chemotherapy was 163 days (range, 83–248 days). The median time interval between final chemotherapy and pre-radiotherapy mammogram was 46 days (range, 7–89 days). At the pre-radiotherapy mammographic assessment, 3 (1.5%) patients had suspicious features within the residual breast gland. Characteristics of these three patients are detailed in Table 2. No cases of synchronous contralateral breast cancer were observed.

The overall adjunctive cost of this strategy, which included a mammography in addition to the routine clinical visit (mammography in 201 patients and a biopsy

Table 1. Patient characteristics

Age, years (range)	55 (30–81)
Tumour grading	
I	15 (7.5)
II	78 (38.8)
III	82 (40.8)
Unknown	26 (12.9)
Histology	
Ductal	123 (61.2)
Lobular	11 (5.5)
Other	67 (33.3)
pT classification	
1	113 (56.2)
2	80 (39.8)
3	5 (2.5)
4	3 (1.5)
pN classification	
0	106 (52.7)
1	74 (36.8)
2	13 (6.5)
3	8 (4.0)
Oestrogen receptor expression	
Yes	157 (78.1)
No	44 (21.9)
Progesterone receptor expression	
Yes	133 (66.2)
No	68 (33.8)
Menopausal status	
Post-menopausal	148 (73.6)
Pre-menopausal	53 (26.4)

Data are number (percentage) unless otherwise indicated.

with histopathological exam in the patient with the false-positive result) was €7012.

Discussion

The American Cancer Society guidelines recommend that women treated with breast-conserving therapy should have their first post-treatment mammogram at least 6 months after completion of locoregional therapy [9], and every 6–12 months thereafter. To our knowledge, no clear recommendation exists regarding post-operative mammography before adjuvant radiotherapy except in cases of tumours containing calcifications, when a mammogram should be obtained after surgery to determine whether all calcifications have been removed [10, 11].

201 patients who were referred to our Radiotherapy Unit from local and regional hospitals after receiving breast-conserving surgery and adjuvant chemotherapy for invasive breast cancer had a mammographic assessment of residual breast cancer before starting adjuvant radiotherapy. In 1 (0.5%) case, the mammography led to a false-positive result. Conversely, in 2 (1.0%) patients, the mammography detected residual disease within the residual mammary gland. In one of these two patients, the post-operative mammogram allowed the detection of disease persistence which was not appreciated at clinical examination. In our opinion, this is not a negligible finding considering that the breast cancer detection rate of screening mammography varies between 4 and 7 per 1000 patients screened [12–15].

Table 2. Characteristics of patients with suspicious findings at the pre-radiotherapy mammography

Patient number	Age, years	Surgery	Histopathological features	OR	PR	Adjuvant chemotherapy	Pre-radiotherapy assessment		
							Clinical assessment	Post-operative mammogram	Histopathological features
1	61	Lower-outer right quadrantectomy and axillary dissection.	Grade I invasive cribriform carcinoma (4.5 cm maximum diameter), and grade I infiltrating lobular carcinoma (1.8 cm maximum diameter). Metastatic involvement of 1 out of 22 axillary lymph nodes. Clear surgical margins.	+	+	Six cycles of anthracyclines containing chemotherapy.	Negative: no abnormal finding.	Positive: size increase (16 mm vs 11 mm compared with the pre-operative mammogram) of one opacity within the upper-outer part of the right breast.	Positive: metastatic involvement of three intramammary lymph nodes.
2	42	Lower-outer right quadrantectomy and axillary dissection.	Grade III invasive ductal carcinoma (3.2 cm maximum diameter). Metastatic involvement of 1 out of 15 axillary lymph nodes. Close surgical margins (1.5 mm).	–	–	Six cycles of anthracyclines containing chemotherapy.	Positive: two palpable masses (~30 mm and 20 mm) within the upper-outer part of the right breast.	Positive: size increase (25 mm vs 10 mm compared with the pre-operative mammogram) of one opacity within the upper-outer part of the right breast and emergence of a new area of increased density of about 15 mm.	Positive: multiple ($n=6$) nodules of invasive ductal carcinoma. The largest nodule measured 30 mm and was infiltrating the pectoralis minor muscle.
3	50	Upper-outer left quadrantectomy and radical axillary dissection.	Grade III invasive ductal carcinoma (2.5 cm maximum diameter). Metastatic involvement of 2 out of 18 axillary lymph nodes. Clear surgical margins.	+	+	Six cycles of anthracyclines containing chemotherapy.	Negative: no abnormal finding.	Positive: spiculated opacity at the quadrantectomy site.	Negative: granulomatous foreign body reaction (suture wire).

OR, oestrogen receptor; PR, progesterone receptor; –, negative; +, positive.

In both cases of tumour persistence, the tumour was found elsewhere in the breast and not at the primary index site. If the pre-radiotherapy assessment had not been performed, a total radiation dose of 50Gy would have been delivered at this site with only a small chance of controlling the residual disease. However, these two lesions could perhaps have been noted on exam or mammography prior to surgery, thus mitigating the necessity and cost of post-operative mammography in all patients. Both of these pathological findings could have been owing to an underestimation of the true extent of the disease at diagnosis, which ultimately led to inadequate surgery. In fact, in both cases, the pre-radiotherapy mammogram as compared with the pre-operative mammogram revealed a size increase of a lesion which had been classified as probably benign at pre-operative imaging. Therefore, both these lesions can be considered as false-negative results of pre-operative breast imaging. In a report by Ganott et al [16], who analysed the causes of false-negative imaging as defined by cancer diagnosed within 1 year of a non-suspicious mammogram, it was reported that in most false-negative cases the lesions were seen prospectively but were interpreted as benign or probably benign [16].

Lack of standardisation of mammographic exams and surgical procedures was the major drawback of this study. However, it is conceivable that similar conditions may occur in clinical practice. In our experience, a pre-radiotherapy routine mammogram has been effective in avoiding an inappropriate treatment, at least in cases with a negative physical exam. In retrospect, given that both patients with lesions in this study had them before pre-operative mammogram and surgery were undertaken, we suggest to repeat the mammogram before radiotherapy, particularly in cases where a second lesion is detected in the breast pre-operatively. Further investigation of the role of post-operative mammography in pre-radiotherapy evaluation is warranted.

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