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*Clinical trial*

# Predictors of local recurrence after conservative surgery and whole-breast irradiation

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*Key words:* breast cancer, conservative surgery, local recurrence, radiotherapy

**Abstract**

*Purpose*. To identify independent factors associated with increased risk of local recurrence (LR) in patients with breast cancer treated with conservative surgery and radiotherapy with or without systemic therapy.

*Methods and materials*. Between January 1997 and December 2001, 969 women were treated at the Radiation Oncology Department in Chieti. We retrospectively analyzed 802 of them who were treated with conservative surgery and whole breast irradiation with or without systemic therapy. Tangential fields delivering 50 Gy to the whole breast were used and a boost was added for a total dose of 60 Gy. $\chi^2$-test or Fisher's exact test were used to identify independent significant factors that are predictive for LR. Kaplan–Meier method was used to calculate the 8-year rates of recurrence according to age, histologic findings, tumor size, number of positive nodes, margin status, receptor status and systemic therapy use: log-rank test was used to compare these curves. Cox proportional hazard model was used to obtain hazard ratios and 95% CI of LR for each covariate.

*Results*. Median follow-up time was 63.1 months. LR occurred in 33 (4.1%) of 802 patients. Percentage of LR was greater in $<50$ year-olds compared with 50–64 year-olds and $\geq 65$ year-olds (9.8% versus 4.1 and 2.0%, respectively). LR was 18.8% in women with a tumor size $>3$ cm versus 3.5, 4.0, 5.5% in women with a tumor size of 0.1–1, 1.1–2, 2.1–3 cm, respectively. The 8-year LR rate calculated with Kaplan–Meier method was $6.54 \pm 1.51$. Multivariate Cox regression analysis showed that independent significant factors that are predictive for LR were: age $<50$, tumor size $>3$ cm, positive margin or unknown status, and hormonal therapy alone versus chemotherapy or combined therapy.

*Conclusions*. Age and tumor size were the most important and statistically significant factors that correlated independently with higher rates of LR. Women $<50$ years old and with a tumor size $>3$ cm had a higher risk of LR. Also margin status and systemic therapy could influence LR risk.

## Introduction

Several randomized studies have demonstrated that overall survival in patients with early breast cancer was similar for those who were treated with conservative surgery followed by radiotherapy and those who underwent mastectomy [1,2]. So, breast-conserving surgery followed by external beam radiation therapy is accepted as a standard option for local treatment of early stage invasive breast cancer. Unfortunately, in women with previous breast cancer, local recurrence (LR) is a common finding. Most of the women who experienced LR were treated with total mastectomy, so LR was also considered as a cosmetic and psychological problem. Local recurrent rates vary between 4 and 20% [3,4,8]. Controversy exists in literature regarding patterns of LR. Many factors have been found to be predictive for breast LR: age [8–11], menopausal status [8], histological grade and type [8,13–14], tumor size [11], number of positive nodes [12], status of surgical margins [8,15–16], receptor status [11] and systemic therapy use [15]. The identification of local relapse predictors are of great clinical valued in selecting women who are at high risk of LR, and for these patients more aggressive treatment should be considered.

The aim of this retrospective study was to identify independent factors associated with increased LR risk in patients with breast cancer treated with conservative surgery and radiotherapy with or without systemic therapy.

## Material and methods

We retrospectively reviewed 969 women treated at the Radiation Oncology Department in Chieti. All women

were treated between January 1997 and December 2001. Of these 802 were treated with conservative surgery and whole breast irradiation and formed the cohort for this study. The remaining 167 women who had received mastectomy and chest wall irradiation were excluded from our analysis, since our objective was to identify prognostic factors for increased risk of LR after conservative surgery and whole-breast irradiation. All 802 women underwent surgical excision of primary tumors (lumpectomy) and axillary dissection. Forty-nine (49) of them did not undergo axillary dissection because they had negative sentinel lymph node biopsy for early breast cancer. Nine (9) of them had positive sentinel lymph node, so they underwent axillary dissection after sentinel node detection. Radiotherapy was administered with a standard technique using medial and lateral tangential fields to deliver a dose of 50 Gy, with a dose of 2 Gy per fraction, to the whole breast. A variable electron energy boost was added for a total dose of 60 Gy. The electron energy boosts used were 6, 7 and 8 MeV. Treatment was given daily, 5 days per week for 6 weeks. The following patient characteristics and pathological features were assessed: age, histological findings, tumor size, node and margin status, estrogen receptor (ER) status, progesterone receptor (PR) status and systemic therapy use. Histopathological features of the tumor were recorded as reported by the pathologists at the time of surgery. Variable doxorubicin-based schedules were used for patients with histologically proven lymph node involvement. Tamoxifen was used for postmenopausal patients after the end of chemotherapy or after surgery in those patients who did not receive chemotherapy. Local recurrence was defined as recurrent tumor in the ipsilateral breast located at or near the primary tumor site. Recurrence free survival (RFS) was defined as the interval between initial tumor diagnosis and LR. Patients were followed at 3-month intervals for the first year and then at 6-month intervals for the four following years. Later, asymptomatic patients were followed up ones a year. Follow-up was defined as the time, expressed as median, between diagnosis of primary cancer and time of death or last control. Last controls were performed in 2005.

### *Statistical analysis*

At the time of surgery, patient characteristics were expressed in terms of frequency and percentage. LR was considered the end point of this study. $\chi^2$-test or Fisher's exact test, when appropriate, were used to compare patient characteristics in the two groups (patients with or without LR) and to identify independent factors which predicted LR.

The Kaplan–Meier method was used to estimate LR rate and the associated standard error (SE) at 8 years of follow-up, after stratifying patients for age, histological findings, tumor size, node status, margin status, ER status, PR status and systemic therapy use. Statistical differences between LR curves were evaluated using the Log-rank test. Multivariate analysis was performed using Cox proportional hazard model, with a stepwise approach to estimate the hazard ratio and relative 95% confidence intervals (95% CI) for each covariate. A $p$ value of 0.05 or less was considered statistically significant. All statistical analysis was performed using SPSS® Advanced Statistical™ 13 (2004, Chicago, IL, USA) software package.

## Results

The median follow-up was 63.1 months. At the time of diagnosis, mean age of the 802 women was 60.8 years (range: 32–88 years); 15.2% were $<50$ years old, 46.3% were 50–64 years old and 38.5% were $\geq 65$ years old. Tumor histology results were as follows: 530 (66.1%) invasive ductal or lobular cancer, 44 (5.5%) ductal or lobular *in situ* cancer (DCIS or LCIS), 206 (25.7%) both invasive and *in situ* and 22 (2.7%) with other histologies. Tumors were grouped according to size: 173 (21.6%) were 0.1–1 cm, 472 (58.8%) 1.1–2 cm, 90 (11.2%) 2.1–3 cm and 16 (2.0%) $>3$ cm. Other tumor factors examinated were lymph node invasion status (negative, 1–3 positive nodes and $>3$ positive nodes) and estrogen and progesterone receptor status (positive or negative). Adjuvant systemic therapy was administred in 684 (85.3%) patients. Two hundred and ninety-one (291) patients were treated with hormonal therapy alone (tamoxifen) and 206 patients were treated with chemotherapy alone. One hundred and eighty-seven (187) women were treated with chemotherapy followed by hormonal therapy for at least 5 years. One hundred and eighteen (118) women received only radiotherapy without systemic therapy (Table 1).

LR was observed in 33 (4.1%) of the 802 patients treated. Using $\chi^2$-test we found that age and tumor size were independent, statistically significant factors for LR ($p<0.001$ and $p<0.05$, respectively) (Table 2).

Percentage of LR was greater in $<50$ year-olds compared with 50–64 year-olds and $\geq 65$ year-olds (9.8% versus 4.1 and 2.0%, respectively). LR was 18.8% in women with a tumor size $>3$ cm versus 3.5, 4.0 and 5.5% in women with a tumor size of 0.1–1, 1.1–2 and 2.1–3 cm, respectively (Table 2).

The 8-year LR rate calculated with Kaplan–Meier method was $6.54 \pm 1.51$. A significant Kaplan–Meier 8-year, LR risk was observed in women $<50$ years with a rate of $14.37 \pm 4.31$ and in women with a tumor size $>3$ cm with a rate of $30.56 \pm 15.74$ (log-rank test: $p<0.001$ and $p<0.05$, respectively) (Table 3).

The 8-year recurrence free survival was 85.6% in $<50$ year-olds versus 94.8% and 94.8% in 50–64 and $\geq 65$ year-olds, respectively, and was 96.3% in women with tumor size of 0.1–1 versus 92.9, 90.9 and 69.4% with tumor size 1.1–2, 2.1–3 and $>3$, respectively.

Multivariate Cox regression analysis adjusted for histology, node status, ER status and PR status, revealed that independent significant factors predictive

*Table 1.* Patient characteristics and pathological features

| Variable | Number of patients (%) | Variable | Number of patients (%) |
|---|---|---|---|
| *All patients* | 802 | *ER status* | – |
| *Age (years)* | – | Positive | 538 (67.1) |
| < 50 | 122 (15.2) | Negative | 202 (25.2) |
| 50–64 | 371 (46.3) | Unknown | 62 (7.7) |
| ≥65 | 309 (38.5) | *PR status* | – |
| *Histology* | | Positive | 481 (60.0) |
| Invasive (ductal + lobular) | 530 (66.1) | Negative | 252 (31.4) |
| *In situ* (DCIS + LCIS) | 44 (5.5) | Unknown | 69 (8.6) |
| Invasive + *in situ* | 206 (25.7) | *Tumor size (cm)* | – |
| Other histotypes | 22 (2.7) | 0.1–1 | 173 (21.6) |
| *Margin status* | – | 1.1–2 | 472 (58.8) |
| Negative | 761 (94.9) | 2.1–3 | 90 (11.2) |
| Positive | 20 (2.5) | > 3 | 16 (2.0) |
| Unknown | 21 (2.6) | Unknown | 51 (6.4) |
| *Node status* | – | *Systemic therapy* | – |
| Negative | 517 (64.5) | None | 118 (14.7) |
| Positive: 1–3 | 165 (20.6) | Chemotherapy | 206 (25.7) |
| Positive: > 3 | 114 (14.2) | Hormonal therapy | 291 (36.3) |
| Unknown | 6 (0.7) | Chemotherapy + hormonal therapy | 187 (23.3) |

*Abbreviations:* DCIS = ductal carcinoma *in situ*; LCIS = lobular carcinoma *in situ*; ER = estrogen receptor; PR = progesterone receptor.

for LR were: tumor size > 3 cm ($p < 0.01$), positive ($p < 0.05$) or unknown margin status ($p < 0.01$), hormonal therapy alone versus chemotherapy or combined therapy ($p < 0.05$). In women with 50–64 and ≥65 years LR risk decreased with respect to women with < 50 years ($p < 0.001$) (Table 4).

## Discussion

With a follow-up of 63.1 months, LR observed in our study was 4.1% ($6.54 \pm 1.51$ rate calculated with Kaplan–Maier analysis). The findings of the present paper are in agreement with other published studies considering follow-up duration. Some authors [8] found an LR rate of 6.3% at 5 year follow-up. Other studies [11] analyzed LR rates in women treated with a radiation dose of 50 Gy versus women treated with an additional boost of 16 Gy for a total dose of 66 Gy, corresponding to 5-year actuarial rates of LR of 7.3 and 4.3%, respectively. Another study [13] subclassified a "true local recurrence" confined to the original quadrant of the primary tumor, and an "elsewhere recurrence" located outside the original quadrant of the primary tumor. The rates of such recurrences were 3, 7 and 13% at 5, 10, 15 years, respectively. Touboul et al. [14] observing 528 patients between 1976 and 1993 found five- and ten-year recurrence rates of 6.8 and 14, respectively. (Table 5).

Variable LR rates could be explained by the different method used, not only follow-up is different, but also tumor therapy and namely surgical techniques used for excision of the primary tumor could be different. It is clear that variations in LR rates after breast conserving surgery are positively affected by radiotherapy.

Regarding LR, definition of "young age" varies according to the studies from < 35; < 40; < 50 years old [17–22]. Although definition varies, it has been demonstrated that young women have higher local relapse rates after conservative surgery followed by radiotherapy. McBain et al. [8] analyzed different age groups (< 30 years old, 30–39, 40–49, 50–59, 60–69 and > 70 years old) and they identified age as the strongest predictive factor for LR. In particular, the adverse effects of young age were seen in women < 40 years old. Although some authors [11–12] evaluated risk of both LR and locoregional recurrence (LRR), they found that young age at the time of diagnosis was an important significant factor, which increased recurrence in the ipsilateral breast and in the regional nodes. In this context, other authors have demonstrated that young age increased LR risk [10,23]. Some studies have found no significant differences in LR rates when women < 50 years were compared with women > 50 years old [24]. In our study, we considered three age groups: women < 50 years old, 50–64 years old and ≥ 64 years old. Age < 50 years was the factor that influenced LR most ($p < 0.001$), this is in agreement with previous literature.

Other factors such as histological grade [8] and type [18,25] have been seen as LR predicting factors. Vicini et al. [26] analyzing 500 women with stage I or II breast cancer evidenced that an extensive intraductal component (EIC) within an invasive cancer was associated with higher LR rates. Indeed, our study did not identify histology as a statistically significant predictor factor of

*Table 2.* Patient characteristics and pathological features expressed in frequency (percentage) for patients without or with local recurrence

| Variable | No local recurrence ($n=769$) | Local recurrence ($n=33$) | $\chi^2$-test |
|---|---|---|---|
| *Age (years)* | – | – | $<0.001$ |
| $<50$ | 110 (90.2) | 12 (9.8)*** | – |
| 50–64 | 356 (95.9) | 15 (4.1) | – |
| ≥65 | 303 (98.0) | 6 (2.0)* | – |
| *Histology* | – | – | n.s. |
| Invasive (ductal + lobular) | 511 (96.4) | 19 (3.6) | – |
| *In situ* (DCIS + LCIS) | 40 (90.9) | 4 (9.1) | – |
| Invasive + in situ | 196 (95.1) | 10 (4.9) | – |
| Other histotypes | 22 (100.0) | – | – |
| *Tumor size (cm)* | – | – | $<0.05$ |
| 0.1–1 | 167 (96.5) | 6 (3.5) | – |
| 1.1–2 | 453 (96.0) | 19 (4.0) | – |
| 2.1–3 | 86 (94.5) | 5 (5.5) | – |
| $>3$ | 13 (81.2) | 3 (18.8)* | – |
| Unknown | 50 (100.0) | – | – |
| *Node status* | – | – | n.s. |
| Negative | 496 (95.9) | 21 (4.1) | – |
| Positive: 1–3 | 158 (95.7) | 7 (4.3) | – |
| Positive: $>3$ | 109 (95.6) | 5 (4.4) | – |
| Unknown | 6 (100.0) | – | – |
| *Margin status* | – | – | n.s. |
| Negative | 732 (96.2) | 29 (3.8) | – |
| Positive | 18 (90.0) | 2 (10.0) | – |
| Unknown | 19 (90.5) | 2 (9.5) | – |
| *ER status* | – | – | n.s. |
| Positive | 517 (96.1) | 21(3.9) | – |
| Negative | 190 (94.0) | 12 (6.0) | – |
| Unknown | 62 (100.0) | – | – |
| *PR status* | – | – | n.s. |
| Positive | 461 (95.8) | 20 (4.2) | – |
| Negative | 239 (94.8) | 13 (5.2) | – |
| Unknown | 69 (100.0) | – | – |
| *Systemic therapy* | – | – | n.s. |
| None | 112 (94.9) | 6 (5.1) | – |
| Chemotherapy | 198 (96.1) | 8 (3.9) | – |
| Hormonal therapy | 279 (95.9) | 12 (4.1) | – |
| Chemotherapy + hormonal therapy | 180 (96.2) | 7 (3.8) | – |

*Abbreviations:* DCIS, ductal cancinoma *in situ*; LCIS, lobular carcinoma *in situ*; ER, estrogen receptor; PR, progesterone receptor; n.s., not significant.
***$p<0.001$ $\chi^2$-test versus ≥50 years.
*$p<0.05$ $\chi^2$-test versus $\leq 3$ cm.

local recurrence. In this study we found ductal cancer *in situ* (DCIS) and lobular cancer *in situ* (LCIS) to be associated with a high but not statistically significant LR. This could be due to the small number of women with LCIS or DCIS (only 5.3% of the study population) included in our study. It is known that the presence of extensive intraductal component (EIC) increases the risk of local recurrence. So, women with EIC were no longer treated with conservative surgery, and in agreement with the surgeons we decided to use only total mastectomy.

Large tumor size has been defined as another important pattern of failure in breast cancer. Some studies [12] considered a median of pathologic tumor size of 1.5 cm with a range between 0 and 7.0 cm. They observed that patients with a larger tumor diameter had higher risk of LR, loco-regional recurrence (LRR) and metastases than patients with a smaller tumor size. Our study confirmed that a large tumor diameter is associated with a higher risk of LR, but our statistically significant value was observed for tumor size $>3$ cm. Furthermore, we did not find a relation between tumor size and distant recurrence because in our study metastases occurred also in patients with a smaller tumor size.

Positive nodes have also been shown to influence the development of LR especially LRR after conservative surgery plus radiation therapy. Indeed, 31% of 1153

*Table 3.* Subgroup analysis of 8-year Kaplan–Meier local recurrence outcome

| Variable | Number of patients | LR rates (SE) | Log-rank test |
|---|---|---|---|
| *All patients* | 802 | 6.54 (1.51) | – |
| *Age (years)* | – | – | $p < 0.001$ |
| < 50 | 122 | 14.37 (4.31) | – |
| 50–64 | 371 | 5.17 (1.36) | – |
| ≥65 | 309 | 5.24 (2.93) | – |
| *Histology* | | | n.s. |
| Invasive(ductal + lobular) | 530 | 6.85 (2.18) | – |
| *In situ* (DCIS + LCIS) | 44 | 10.48 (5.00) | – |
| Invasive + *in situ* | 206 | 6.01 (1.90) | – |
| Other histotypes | 22 | – | – |
| *Tumor size (cm)* | – | – | $p < 0.05$ |
| 0.1–1 | 173 | 3.69 (1.48) | – |
| 1.1–2 | 471 | 7.11 (2.62) | – |
| 2.1–3 | 90 | 9.14 (4.78) | – |
| > 3 | 16 | 30.56 (15.74) | – |
| Unknown | 51 | – | – |
| *Node status* | – | – | n.s. |
| Negative | 517 | 5.59 (1.28) | – |
| Positive: 1–3 | 165 | 8.83 (4.59) | – |
| Positive: > 3 | 114 | 5.77 (2.70) | – |
| Unknown | 6 | – | – |
| *Margin status* | – | – | n.s. |
| Negative | 761 | 6.57 (1.72) | – |
| Positive | 20 | 10.28 (6.89) | – |
| Unknown | 21 | 10.00 (6.71) | – |
| *ER status* | – | – | n.s. |
| Positive | 538 | 5.49 (1.36) | – |
| Negative | 202 | 9.37 (3.86) | – |
| Unknown | 62 | – | – |
| *PR status* | – | – | n.s. |
| Positive | 481 | 5.84 (1.49) | – |
| Negative | 252 | 8.34 (3.45) | – |
| Unknown | 69 | – | – |
| *Systemic therapy* | – | – | n.s. |
| None | 118 | 5.25 (2.09) | – |
| Chemotherapy | 206 | 7.60 (3.89) | – |
| Hormonal therapy | 291 | 6.97 (2.22) | – |
| Chemoterapy + hormonal therapy | 187 | 5.77 (2.37) | – |

*Abbreviations:* SE, standard error; DCIS, ductal carcinoma *in situ*; LCIS, lobular carcinoma *in situ*; ER, estrogen receptor; PR, progesterone receptor; n.s., not significant.

women were found to be axillary node positive and they were three times more likely to develop LRR [12]. While some studies [27–29] confirmed that positive nodes increased either LR or LRR rate, in our series as in other studies [14,30] axillary node status did not influence the rate of LR.

Several studies [8,16] have reported an increased risk of LR in patients with positive surgical margins. Park et al. [15] reviewed 2140 patients who were placed into four groups: negative, close, focally positive and extensively positive margins. Women with extensively positive margins had a higher risk of LR than women in the other three groups. Another study found that positive margins were not associated with a significant risk of LR [18,31]. Also in the present study, a higher risk of LR was seen in patients with positive margins, not statistically significant at the univariate analysis. Further, the Cox proportional hazard model evidenced a higher LR risk in women with positive or unknown margin status; this datum had a low statistically significant value ($p < 0.05$ and $p < 0.01$).

Receptor status has also been reported as a risk factor increasing LR. Bartelink et al. [11] examined hormone receptor status. Estrogen and progesterone status were subdivided into three categories: negative, positive and unknown. They showed that the absence of progesterone receptor was a predictable factor for LR. We were not able to show any statistically significant

*Table 4.* Hazard ratios (95% CI) of local recurrence estimated using multivariate Cox regression method

| Variable | Hazard ratio[a] (95% CI) | *p*-Value |
|---|---|---|
| *Age* | – | – |
| < 50 | 1.00[b] | – |
| 50–64 | 0.24 (0.09–0.62) | $p < 0.001$ |
| ≥65 | 0.09 (0.03–0.32) | $p < 0.001$ |
| *Tumor size (cm)* | – | – |
| 0.1–1 | 1.00[b] | – |
| 1.1–2 | 1.27 (0.44–3.67) | – |
| 2.1–3 | 1.56 (0.38–6.48) | – |
| > 3 | 7.04 (1.41–35.06) | $p < 0.01$ |
| *Margin status* | – | – |
| Negative | 1.00[b] | – |
| Positive | 4.05 (1.01–18.67) | $p < 0.05$ |
| Unknown | 7.41 (1.50–36.61) | $p < 0.01$ |
| *Systemic therapy* | – | – |
| Chemotherapy + hormonal therapy | 1.00[b] | – |
| Chemotherapy | 1.08 (0.24–4.97) | – |
| Hormonal therapy | 3.18 (1.02–10.22) | $p < 0.05$ |
| None | 0.66 (0.21–2.07) | – |

[a]Adjusted for histology, pathologic nodal status, ER status and PR status.
[b]Reference category.

*Table 5.* LR rates in literature

| Authors | Follow-up (months) | LR rates (%) |
|---|---|---|
| McBain et al. [8] | 76.8 | 6.3 at 5 years |
| Bartelink et al. [11] | 61.2 | 4.3–7.3 at 5 years |
| Freedman et al. [13] | 80.0 | 3–7–13 at 5, 10, 15 years |
| Touboul et al. [14] | 87.5 | 6.8 –14 at 5, 10 years |
| Our study | *63.1* | *6.5 at 8 years* |

relation between receptor status and LR, but we observed that LR occurred in women with negative as compared to positive estrogen and progesterone receptors.

Some studies have described a low risk of LR in women treated with conservative surgery plus radiotherapy followed by chemotherapy [32]. Other studies confirmed that women who did not use chemotherapy or hormonal therapy had a higher risk of either LR or LRR [12]. Also Park et al. [15] observed a relation between margin status and systemic therapy. There were no differences between patients receiving or not receiving systemic therapy, when their surgical margins were close, negative and extensively positive. On the other hand, a different LR rate was shown between women with focally positive margins receiving or not receiving systemic therapy (7 versus 18%).

In our study, patients subjected to either adjuvant chemotherapy or chemotherapy followed by hormonal therapy were less likely to develop LR than those who were given hormonal therapy alone. Although these latter data show a low statistical significance ($p < 0.05$), nonetheless they could provide useful elements on how to use systemic therapy in breast cancer. Clearly, there are limitations in a retrospective study like ours and these results should be interpreted with caution.

## Conclusion

Age and tumor size are the most important factors that independently correlated with an increased risk of LR after conservative surgery and whole-breast irradiation. Also margin status and systemic therapy could influence development of LR. The present study showed some limits like all retrospective studies, and clearly further investigations are necessary to gain more insight into the factors involved with LR, to identify prognostic elements that could help in choosing the best treatment of breast cancer.

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