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ORIGINAL ARTICLE

Loco regional failure pattern after lumpectomy and breast irradiation in 4185 patients with T1 and T2 breast cancer. Implications for nodal irradiation

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Abstract
The aim of this study is to determinate incidence and risk factors for loco regional failure (LRR) (breast, supraclavicular, axillary and internal mammary nodes) and indications for nodal irradiation. From January 1980 to December 2001, 4185 patients with T1−T2 breast cancer were treated with conservative surgery and whole breast radiotherapy without nodal irradiation at the University of Florence. The median age was 55 years (range 19−86). All patients were followed for a median of eight years (range 3 months to 20 years). Multivariate analysis showed as independent prognostic factors for isolated nodal relapse (NR) the presence of more than three positive lymph nodes (PAN) (p = 0.001), angiolymphatic invasion (p = 0.002) and pT2 (p = 0.02). However, only 4.8% of patients with more than three PAN developed NR as the only site of recurrence. Having one to three PAN was not associated with an increased risk of NR. We believe that it is not necessary to prescribe nodal irradiation to patients with negative or one to three PAN. Regarding patients with more than three PAN, the number of isolated NR is also small to routinely justify a node irradiation.

The overall survival of early breast cancer patients treated by conservative surgery and radiation has been well documented [1−3] while the patterns of failure and outcome of patients experiencing a local regional recurrence (LRR) (breast and supraclavicular, axillar and internal mammary nodes) are less well known. Previous studies have suggested that the incidence of LRR (breast, supraclavicular, axillar and internal mammary nodes) after lumpectomy and adjuvant radiotherapy in early breast cancer ranges between 4−20% and it is related to patient's age, status of surgical margin, presence of perivascular invasion and intraductal in situ carcinoma and lymph nodes status [4−8]. The optimal treatment of regional nodes in the setting of breast-conserving surgery and radiation after early-breast cancer is unclear.

The aim of the present analysis is to determinate the incidence and risk factors for loco regional failure

and to evaluate if a sub-group of patients should receive nodal irradiation.

Methods and materials

From January 1980 to December 2001, 4185 patients with pT1−T2 breast cancer underwent radiotherapy treatment at the University of Florence. In the current analysis we included patients without clinical and radiographic evidence of local or distant recurrence after surgery at the time of the first evaluation in the radiotherapy unit. None of the patients had prior malignant disease. The median age of the patient population was 55 years (range 19−86). No patients were lost at follow-up. All patients were followed for a median of eight years (range 3 months to 20 years).

The main characteristics of the patients are reported in Table I. Wide excision was performed

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Table I. Characteristics of the 4185 patients, University of Florence, 1980–2001.

Characteristic	N° of pz
Age	
<40 ys	359 (8,1%)
≥40–49 ys	1006 (24%)
≥50–59 ys	1310 (31,3%)
≥60–69 ys	1101 (26,3%)
≥70–79 ys	400 (9,6%)
≥80 ys	29 (0,7%)
pT	
T1	2779 (66,4%)
T2	1406 (33,6%)
Lymph node	
Unknown	100 (2,4%)
Negative	2870 (68,6%)
N+1–3	823 (19,7%)
N+ >3	392 (9,3%)
Histology	
Ductal NOS	1917 (45,8%)
NOS+Lobular	473 (11,4%)
Lobular carcinoma	613 (14,7%)
Others	1135 (26,9%)
Unknown	47 (1,2%)
Hormonal Receptor Status	
Negative	588 (14%)
Positive	2297 (55%)
Unknown	1300 (31%)

in 919 patients and 3266 patients underwent quadrantectomy. Whenever possible patients with positive surgical margins underwent reexcision, however, 621 patients underwent radiotherapy with positive surgical margins. Axillary dissection was performed in 3889 patients with a median number of 16 nodes removed. Positive axillary nodes were found in 1215 patients (29%). Sentinel lymph node biopsy was performed only on 170 (4%) patients and axillary dissection was performed in 100 (2.3%) patients.

According to the protocol followed in our Institute, radiotherapy was not given to supraclavicular fossa also for patients with positive axillary nodes. All patients received radiotherapy treatment (RT) only to whole breast.

All patients were treated with external beam radiotherapy to the whole breast using tangential fields with 6 MV photons. The mean dose delivered was 50 Gy, 2 Gy daily fraction (range 46–52). The tumour bed boost was administrated by electrons. At the discretion of the radiation oncologist the total boost dose (2 Gy daily fraction) ranged between 6 and 10 Gy for patients with negative surgical margins and between 14 and 16 Gy for patients with positive margins. In 23.3% of patients (972 of 4185) no boost was administered.

Chemotherapy was recommended in 924 patients (21.8%). Of those 20% received anthracycline based chemotherapy: 70% of these received four courses of epidoxorubicin (100 mg/m^2) followed by four

courses of IV CMF (cyclophosfamide 600 mg/m^2, metotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2) and 30% were treated with six courses of FEC chemotherapy (5-fluorouracil 500 mg/m^2, epidoxorubicin 75 mg/m^2, cyclophosfamide 500 mg/m^2). Sixty-five percent of the patients received six courses of IV CMF (cyclophosfamide 600 mg/m^2, metotrexate 40 mg/m^2 and 5-fluorouracil 600 mg/m^2) and 15% other types of chemotherapy. There were 133 patients (3.1%) treated with chemotherapy in different institutions. Tamoxifen was prescribed in 1504 patients (36%) whereas 2241 patients (63%) received no hormonal treatment. No such information is available for 40 patients (1%). Tamoxifen was not prescibed from 1980 to 1986. From 1987 to 1990 only 3.45% of patients (50 of 1504) were treated with tamoxifen.

Statistical analysis

For statistical analysis we considered as true LRR when failure developed as first site of recurrence and when loco-regional failure was followed by distant metastases not before six months. We chose this approach because this group of LRR could be a door from which cancer could spread elsewhere.

We considered as LRR any reappearence of tumoral disease in the breast, supraclavicular fossa, axilla and internal mammary chain. For LRR the follow-up routine procedure required clinical examination every six months, mammography and chest X-ray every year and in cases of clinical or radiological suspect breast or supraclavicular recurrence ultrasound and or chest CT.

Locoregional recurrence rate was analysed using the Kaplan Meier method (Statistica software) [9]. The actuarial probabilities of LRR for the different subgroups were then compared ("internal" comparison). The log-rank test [10] and the Cox model for logistic regression [11] were applied, when appropriate, to define the statistical significance of observed differences. The variables included in the Cox model for multivariate analysis were those judged to be of clinical significance, in addition to those linked with statistically significant difference, when submitted to univariate analysis (log-rank test).

Results

At the time of analysis 12.5% of patients (526/4185) had died of cancer, 4.2% (176/4185) had died of other causes and 83.9% (3512/4185) were still alive. Actuarial cause specific survival for the entire group was 96.9% (±0.2% SE), 93.1% (±0.4% SE), and 83.7 (±0.6% SE) at 3, 5 and 10 years, respectively (Figure 1).
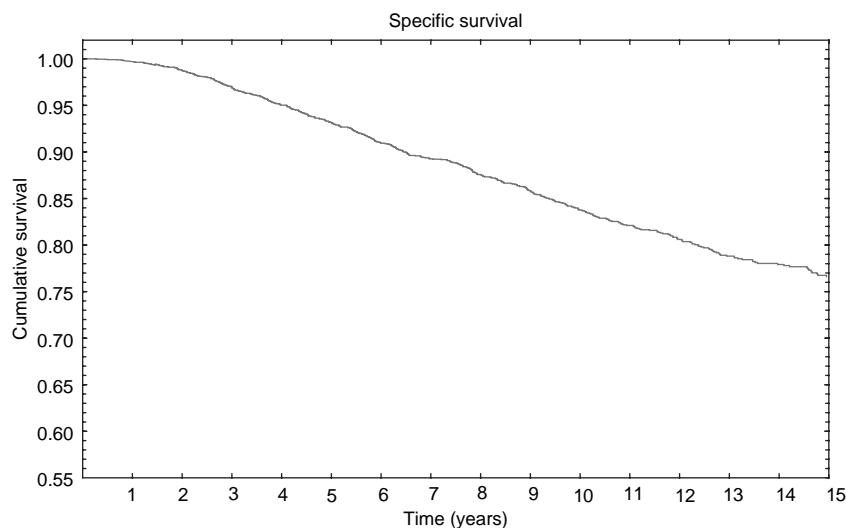
Figure 1. Cause specific survival for the entire group was 96.9% (±0.2%SE), 93.1% (±0.4%SE) and 83.7 (±0.6%SE) at 3, 5 and 10 respectively.

With a median time of all locoregional relapses (LRR) of 3.9 years (range 6 months–19 years), 224 patients of 4185 (5.3%) had loco-regional failure. With respect to nodal relapses (NR, any relapse in axilla, internal mammary chain or supraclavicular fossa) the median time was lower (2.7 years). Loco-regional relapse was the only failure present in 224 patients. Considering the different sites of LRR we found that the most common site was the breast (166/4185; 3.9%), that NR occurred in 1.3% (58/4185) of patients and supraclavicular relapse (SCR) in 0.7% (33/4185) (Table II).

The 3, 5 and 10-year actuarial rate for any LRR were 2.3% (±0.2%SE), 4.3% (±0.4%SE) and 7.4% (±0.5%SE), respectively (Figure 2). The 3, 5 and 10 years actuarial recurrence rates for SCR were 0.6% (±0.1%SE), 0.9% (±0.2%SE) and 1% (±0.1%SE), respectively, and for NR they were 1.0% (±0.1%SE), 2.0% (±0.2%SE) and 2.0% (±0.2%SE), respectively. Patients aged less than 40 years at diagnosis appear to have a higher LRR rate (14.4%; 49/339) compared to patients aged between 40–49 (8.2%, 83/1 006), 50–59 (4.2%; 56/1310) 60–69 (2.8%; 31/1 101) 70–79 (1.2%; 5/400) and patients aged more than 80 (0%; 0/29) (p = 0.00001).

Analysing the risk of relapse in non-irradiated sites for women under 50 years, who seem to be at higher risk of developing NR, we found that in this subgroup the NR rate was still very low (1.7%; 23/1345). (Table III). LRR rates for pathological tumour size were 4% (110/2 779) and 9.1% (114/1406) for pT1 and pT2 tumours respectively (p = 0.0002). NR rates for pT1 and pT2 were 0.8% (25/2779) and 2.3% (33/1406), respectively (p = 0.04). SCR rates for pT1 and pT2 were 0.5% (14/2779) and 1.3% (19/1406), respectively (p = 0.02).

Analysing LRR by axillary lymph-nodes involvement we observed no significant difference for patients with negative nodes and patients with less than three positive axillary nodes (p = 0.3). However a significant difference was found between patients with negative axillary nodes and patients with more than three positive axillary nodes (p = 0.02) or between patients with one to three positive nodes and more than three (p = 0.05) as shown in Figure 3.

We found a SCR in 12 women of 2870 (0.4%) patients with negative axillary nodes compared with eight women with 1–3 positive axillary lymph nodes (PAN) of 823 (0.9%, p = 0.9) and 13 of 392 (3.3%) women with more than three PAN (p = 0.01) (eight had more than three positive nodes but less than ten; five had more than ten positive axillary nodes). NR was found in 0.8% (24/2870) patients with negative axillary nodes, in 1.7% (14/823) of patients with one to three positive nodes and in 4.8% (19/392) of patients with more than three positive nodes (p = 0.007).

Table II. Site of recurrence in the 224 patients out of the 4185 developing loco-regional recurrence.

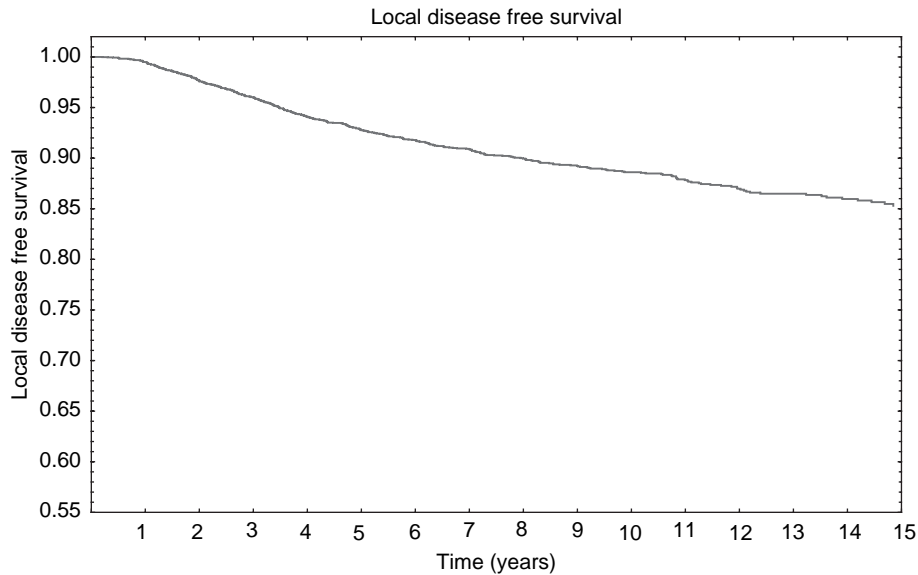| Site of recurrence	N° of patients	%
Breast		
Non operated quadrant	46	16.9%
Index quadrant	110	36.4%
Unknown quadrant	8	3%
Multicentric relapse	2	0.7%
Supraclavicular area	33	14.8%
Axilla	14	6.1%
Internal mammary nodal chain	11	5%

Local disease free survival

Figure 2. The 3, 5 and 10 years actuarial rate for any locoregional recurrence was 2.3% ($\pm$0.2%SE), 4.3% ($\pm$0.4%SE) and 7.4% ($\pm$0.5%SE) respectively.

We analyzed the rate of LRR according to the number of removed axillary nodes and we found that it was 3.5% (26/760) for patients with less than ten nodes removed, 5.5% (115/2074) for patients with 10 to 20 nodes removed and 5.5% (68/1251) for patients with more than 20 nodes removed (p = 0.53). We found that this result was neither statistically significant for NR (p = 0.3) nor for SCR (p = 0.9). We did not find any statistical significance for LRR, NR and SCR for the different systemic adjuvant therapies (chemotherapy and hormonal therapy).

Patients with positive angiolymphatic invasion had 6% (29 cases of 485) of LRR versus 3% (61 cases of 2068) for those with negative angiolymphatic invasion (p = 0.001). In 1632 patients the angiolymphatic status was unknown. Considering positive angiolymphatic invasion in relation to positive axillary lymph nodes we did not achieve statistical significance for NR in patients with positive lymph nodes (p = 0.6). However the result was statistically significant (p = 0.0001) in patients with negative lymph nodes.

Univariate analysis of histological grade demonstrated poorer prognosis (p = 0.002) of high grade in

comparison to intermediate and low-grade tumours with LRR rates of 3.1% (24/754), 1.8% (14/775) and 1.2% (7/575) respectively. No statistical difference between intermediate and low grade (p = 0.7) was noticed. Tumour grading of 2081 patients was unavailable. However for NR and SCR the histological grade was not found to be statistically significant (p = 0.19).

Other prognostic factors -such as the site of tumor, the extracapsular extention, the multifocality and the different histotypes- did not show any statistical significance at the univariate analysis neither for LRR nor for NR and SCR. Moreover, we reanalaysed the significance of each prognostic factor only in the sub group of patients with 1 to 3 positive axillary nodes. The results are shown in Table IV.

In the multivariate analysis for LRR G3 tumor (p = 0.01), age at presentation (p = 0.001), more than three positive lymph nodes (p = 0.004), pT2 (p = 0.001) and angiolymphatic invasion (p = 0.02) were statistically significant parameters. In the multivariate analysis for NR only pT2 (p = 0.02), angiolymphatic invasion (p = 0.002) and more than three positive lymph nodes (p = 0.001) were statistically significant (Tables V–VI).

Discussion

According to the protocol followed in our institution, we irradiate patients after conserving surgery with tangential beams to the whole breast only, independently of the numbers of PAN.

We have chosen this therapeutic approach due to two considerations:

Table III. Correlation between age and LRR.

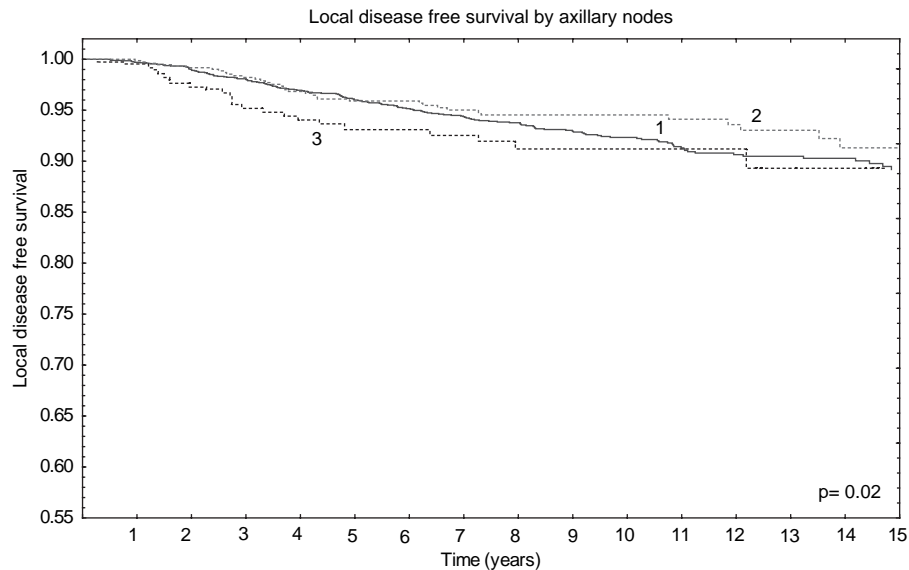| Age	N° of patients	BR	NR	SFR
<40 ys	339	44 (12%)	5 (1.4%)	2 (0.5%)
40−49	1006	65 (6.4%)	18 (1.7%)	11 (1%)
50−59	1310	36 (2.7%)	20 (1.5%)	10 (0.7%)
60−69	1101	19 (1.7%)	12 (1%)	8 (0.7%)
70−79	400	2 (0.5%)	3 (0.7%)	2 (0.05%)
>80	29	0	0	0

Figure 3. Local disease free survival by axillary status. 1 =negative axillary nodes; 2 =1–3 positive axillary nodes; 3 ≥3 axillary nodes.

– for patients with less than three PAN the low incidence of LRR does not justify regional nodal treatment;

– for patients with more than three PAN the main problem is the risk of distant metastases.

We have considered for this analysis only isolated LRR and NR or LRR and NR followed by distant metastasis after at least six months: this is so because we considered that NR concomitant with metastasis would not receive any benefit from a nodal irradiation because these patients already have a systemic disease.

The current study was conducted to determine the incidence and risk factors for LRR after adjuvant treatment in patients with early-breast cancer treated with conserving surgery to identify if a subgroup of

patients should be treated also with nodal irradiation.

Prognostic factors a like pT, angiolymphatic invasion and G3, more than three positive axillary nodes and age at presentation were independent prognostic factors for LRR [12–15].

Jobsen et al. [16] reported that age less than 40 is the only significant predictor of decreased LRR free-survival (p =0.001). Moreover the high LRR rate in young women was accompanied by even higher rate of distant metastases [14]. Arriagada et al. observed in patients aged less than 40 years a five-fold increased risk of developing a breast recurrence compared with patients older than 60 years [17,18]. However, in our series age was an independent prognostic factor for LRR but not for NR. In fact, the only independent prognostic factors for NR

Table IV. Crude and actuarial results for each prognostic factor only in the subgroup of patients with 1 to 3 positive axillary nodes.

Factors	% LRR crude	% LRR 8 years	% NR crude	% NR 8 years	p-value
pT1	3.5%	4.7%(±1.1%)	1.2%	1.8%(±0.7%)	0.22 LRR
pT2	5.6%	6.7%(±1.6%)	2.4%	2.9%(±1.%)	0.28 NR
G1	1.3%	4%%(±3.9%)	0%	–	0.007 LRR
G2	0.6%	0%	0%	–	–NR
G3	5.7%	8.2%(±2.6%)	3.2%	4.7%(±0.2%)	
*ALI					
Present	3.8%	4.5%(±1.9%)	1,7%	2.7%(±1.3%)	0.9 LRR
No	4%	6.3%(±1.8%)	1.9%	2.4%(±1.6%)	0.63 NR
AGE (years)					
< 40	9%	12%(±4.2%)	6%	3.6%(±2%)	
40–49	6.6%	7.4%(±2.2%)	1.7%	2.4%(±1.7%)	0.04 LRR
50–59	3%	2.8%(±1.8%)	1.5%	2.2%(±1.5%)	
60–69	2.2%	2.4%(±1.1%)	1.1%	0.9%(±0.8%)	0.5 NR
70–79	2.8%	3.6%(±2%)	2.8%	3.6%(±2%)	
> 80	0%	–	0%	–	

*ALI = angiolymphatic invasion.

Table V. Multivariate analysis for LRR.

Parameter	p value	Hazard ratio	95% C.I.
G1		1	
G2	0.54	1.3	0.5–3.2
G3	0.01	2.6	1.1–5.9
AGE			
50–59 ys		1	
<40 ys	<0.001	2.2	1.6–3.1
40–49 ys	0.003	1.3	1–1.7
60–69 ys	0.01	0.6	0.4–0.9
70–79 ys	0.01	0.4	0.2–0.8
>80 ys	0.45	0.4	0.4–7
Lymph node			
Negative		1	
N+1–3	0.7	0.9	0.7–1.2
N+ >3	0.004	1.6	1.1–2.3
ALI*			
No		1	
Present	0.002	1.5	1.1–2.2
pT1		1	
pT2	<0.001	1.4	1.1–1.8

*ALI = angiolymphatic invasion.

were more than three positive lymph nodes, angiolymphatic invasion and pT. However, we found that the percentage of NR in patients with pT2 tumours or presence of angiolymphatic invasion was very low (2.4% and 1.7%, respectively).

The role of regional node irradiation is controversial as different conclusions are noted in different series [19,20]. In our series for patients with one to three positive nodes, no prognostic factors was found to be significant for NR at the univariate analysis and having one to three positive nodes was not an independent prognostic factor at the multivariate analysis. This result confirmed that for patients with less than three lymph nodes node, irradiation is useless because the incidence of NR is low and it is not influenced by adjuvant treatment. In fact Galper et al. [21] reported that NR is uncommon among patients with negative or ont to three positive lymph nodes treated with conservative surgery, axillary dissection, and only tangential RT fields. Therefore,

Table VI. Multivariate analysis for NR.

Parameter	p-value	Hazard ratio	95% C.I.
Lymph node Negative		1	
N+1–3	0.11	1.7	0.8–3.2
N+ >3	<0.001	4.8	2.5–9.1
ALI*			
No		1	
Present	0.002	3.18	1.4–6.8
pT1		1	
pT2	0.002	1.8	1.07–3.1

*ALI = angiolymphatic invasion.

giving only tangential RT (without a separate nodal field) appears generally acceptable for patients with zero to three positive nodes. In our series the number of negative lymph nodes was not an independent prognostic factor for LRR and NR, in contrast with what had been reported by other authors [22].

Patients with more than three positive nodes are at higher risk of developing LRR and NR. Despite this we found that the percentage of isolated NR in patients with more than three positive nodes was 4.8%. This number is a low percentage of risk to justify a nodal irradiation, also considering the probability of late morbidity after surgery and radiotherapy [23,24]. Grills et al. [25] referred to 5 and 10-year rates of axillary failure and supraclavicular failure of 0.6% and 1.0% and 0.9% and 1.6%, respectively. Despite this they found a significant benefit for axillary relapses after RT in patients with more than three PAN, the result was not significant for SCR (p = 0.114). Confirming our results for patients with one to three positive axillary nodes: radiotherapy did not affect the rate of axillary failure or supraclavicular failure in patients with one to three positive nodes.

Conclusion

In our series only 1.7% and 4.8% of patients with one to three and more than three PAN, respectively, developed NR as the only site of recurrence. It seams unnecessary to prescribe nodal irradiation to patients with negative or one to three PAN. Regarding patients with more than three PAN, the number of isolated NR is also small to routinely justify node irradiation

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