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Patterns and risk factors for locoregional failures after mastectomy for breast cancer: an International Breast Cancer Study Group report

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Background: Rates and risk factors of local, axillary and supraclavicular recurrences can guide patient selection and target for postmastectomy radiotherapy (PMRT).

Patients and methods: Local, axillary and supraclavicular recurrences were evaluated in 8106 patients enrolled in 13 randomized trials. Patients received chemotherapy and/or endocrine therapy and mastectomy without radiotherapy. Median follow-up was 15.2 years.

Results: Ten-year cumulative incidence for chest wall recurrence of >15% was seen in patients aged <40 years (16.1%), with ≥4 positive nodes (16.5%) or 0–7 uninvolved nodes (15.1%); for supraclavicular failures >10%: ≥4 positive nodes (10.2%); for axillary failures of >5%: aged <40 years (5.1%), unknown primary tumor size (5.2%), 0–7 uninvolved nodes (5.2%). In patients with 1–3 positive nodes, 10-year cumulative incidence for chest wall recurrence of >15% were age <40, peritumoral vessel invasion or 0–7 uninvolved nodes. Age, number of positive nodes and number of uninvolved nodes were significant parameters for each locoregional relapse site.

Conclusion: PMRT to the chest wall and supraclavicular fossa is supported in patients with ≥4 positive nodes. With 1–3 positive nodes, chest wall PMRT may be considered in patients aged <40 years, with 0–7 uninvolved nodes or with vascular invasion. The findings do not support PMRT to the dissected axilla.

Key words: adjuvant treatment, breast cancer, locoregional recurrence, postmastectomy radiotherapy

introduction

Postmastectomy radiotherapy (PMRT) in patients with breast cancer reduces the risk of locoregional recurrence (LRR) by a proportionate 60%–70% [1], and improvement in locoregional control can impact overall survival (OS). The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview showed that one breast cancer death would be avoided for every four LRR prevented [1]. The reported absolute risk of LRR after mastectomy without radiotherapy (RT) varies widely [2] and thus conclusions regarding indications for PMRT are not uniform. Furthermore, the 4 : 1 ratio of LRR to OS reported by the EBCTCG may differ among patient subgroups. Kyndi et al. [3, 4] reported a larger translation of LRR reduction into survival benefit in patients with more favorable prognostic factors, e.g. in hormone receptor-positive patients compared with hormone receptor-negative or HER-2-positive patients.

In addition to the indications for PMRT, there is also controversy about the optimal radiation target volume. A recent survey on the radiotherapeutic management of invasive breast cancer in North America and Europe found marked differences in physician opinions. For example, internal mammary chain irradiation was offered more often by

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European than North American radiation oncologists, whereas those from North America were more likely to irradiate the supraclavicular fossa and axilla [5].

In a previous report from the International Breast Cancer Study Group (IBCSG) 1138 LRR were recorded among 5352 breast cancer patients treated with mastectomy without PMRT and followed for a median of 14.5 years: an overall LRR rate of 21.3%. Among these, the most common site of LRR in breast cancer patients without PMRT was the chest wall (53%), followed by the supra/infraclavicular region (26%) and the axilla (13%). Tumor relapse at the internal mammary region was rarely reported (1%) [6]. The number of positive axillary nodes and tumor grade were significant risk factors for LRR. In addition, peritumoral vessel invasion (PVI) for premenopausal patients and tumor size for postmenopausal patients were also significant prognostic factors [6]. In a subsequent IBCSG study, the number of examined uninvolved nodes was found to be a significant risk factor for LRR [7]. In this study, patients with 1–3 positive nodes in the presence of PVI, young age or few uninvolved nodes had an increased risk of LRR.

The aim of the present analysis is to study the rates and risk factors of local, axillary and supraclavicular recurrences separately, not only to guide patient selection for PMRT but also to guide radiation target volume when radiotherapy is indicated.

patients and methods

design of the studies

IBCSG Trials I–IX and 11–14 (13 trials in total) accrued 12 409 patients from 1978 to 1999. Results of the treatment comparisons, detailed definitions for menopausal status, patient characteristics and eligibility have been described elsewhere [8–17] and are summarized in Supplementary Table S1 (available at *Annals of Oncology* online). With the exception of trial V, where patients were entered before the pathological work-up was completed, patients were included only if the tumors were pT1, pT2 or pT3 and the resection margins were free of tumor cells. Study guidelines required axillary dissection and that at least five (trials I–IV) or eight (trials V–IX and 11–14) lymph nodes should be removed in the axillary specimen. All patients on trials I–V were to receive mastectomy without RT. Patients on trials VI–IX and 11–14 received either mastectomy without RT or breast-conserving surgery, mostly with RT. Patients treated with breast-conserving surgery were excluded from the present analysis. The 13 randomized trials evaluated the timing and/or duration of chemotherapy, endocrine therapy, chemoendocrine therapy or no adjuvant therapy. Institutional review boards reviewed and approved the protocols and informed consent was required according to the criteria established within the individual countries.

For trials I–V, VIII–IX and 11–14, a central pathology review process included the histological evaluation of primary tumor specimens for invasion of lymphatic or blood vessels around the primary tumor was undertaken [18]. No central pathology review was conducted for trials VI–VII, and the information about vessel invasion was provided by the local pathology work-up from the participating centers. PVI was defined as the presence of tumor cell emboli within a vessel space, which were identified by associated fibrin clot and/or an endothelial cell lining. The study protocol required that at least two sections of primary tumor be taken at right angles to one another to include the interface of the growing tumor border and the adjacent breast tissue. Generally, ~6 cm^2 of breast tissue immediately adjacent to the primary tumor, but within 1 cm of the tumor border, was available for the assessment of PVI.

patient selection

As in our previous reports [6, 7], the population studied comprised patients assigned to receive total mastectomy without RT but with adequate systemic treatment, defined as three or more courses of classical cyclophosphamide, methotrexate, and 5-fluouricil (CMF) for premenopausal node-positive patients, three or more courses of CMF or tamoxifen for 1–5 years for postmenopausal node-positive patients, chemotherapy and/or endocrine therapy for pre- and postmenopausal node-negative patients or endocrine therapy alone for patients with hormone receptor-positive tumors. These criteria resulted in the exclusion of 768 patients who were assigned lesser adjuvant therapy and 3441 patients who received breast-conserving surgery. An additional 82 patients who had PMRT were also excluded. Twelve patients were excluded due to missing information regarding number of uninvolved nodes. The total number of patients excluded was 4303, and the remaining 8106 patients were included in this analysis.

statistical analysis

The following variables were defined for the analysis: nodal involvement status (0, 1–3, ≥4 lymph nodes involved), tumor size (≤2 or >2 cm), estrogen receptor (ER) status (<10 or ≥10 fmol/mg of cytosol protein, or, in later years, based on immunohistochemical results), age (<40, 40–49, 50–59, ≥60 years), histological grade (1, 2, 3) and PVI (yes or no). To account for missing values, we included an additional category (unknown). The number of uninvolved lymph nodes was defined as the number of nodes examined less the number of positive nodes.

This analysis considered the following four types of recurrences: local, axillary, supraclavicular and distant. Internal mammary recurrences were rarely reported (<1%) and were not included in this analysis [6]. Only the first documented recurrence, possibly in combination with other sites, was considered.

The time to recurrence was determined as the number of years from randomization until the first proven recurrence or the date of last follow-up (or death). If no recurrence or death was documented, then time to recurrence was censored at the date of last follow-up. Statistical methods for competing risks were used in this analysis, including cumulative incidence estimation [19, 20] and competing risks regression analysis [21]. Results from competing risk regression analyses were converted to hazard ratios. Analysis for each recurrence type was carried out separately. For each type of recurrence, all other failures, including death, were treated as competing risks. When evaluating a particular recurrence type, only those other types of recurrence not in combination with the type of interest were considered competing risks. Cumulative incidence curves were compared using the method of Gray [20]. Wald tests [22] were used to determine statistical significance of each risk factor in the regression models, first for each risk factor overall and then for each individual hazard ratio. A two-sided P value <0.05 was considered statistically significant. To account for multiple comparisons in the regression models, we considered a hazard ratio to be statistically significant if its two-sided P value was <0.05 and the corresponding overall Wald test had a P value <0.05.

The influence of number of uninvolved nodes on recurrence risk was descriptively evaluated using a subpopulation treatment effect pattern plot (STEPP) analysis [23] in which patients were divided into overlapping subgroups based on the number of uninvolved nodes. Each subgroup was designed to contain at least 200 patients and to overlap with the previous subgroup by at most 100 patients. The 10-year cumulative incidence of recurrence was determined within each subgroup, and the results were plotted on a graph (versus the midpoint of the interval) to illustrate how risk changes as the number of uninvolved nodes increases.

For the group of patients with 1–3 positive nodes, risk profiles considering age, PVI and number of uninvolved nodes were modeled, giving estimates of 10-year cumulative incidence for local, axillary and supraclavicular relapse separately.

results

Table 1 summarizes the patients and tumor characteristics of the 8106 eligible patients. The median follow-up for all patients was 15.2 years and the trial-specific median follow-up ranges from 9.7 to 25.3 years. The 10-year cumulative incidence of local, axillary and supraclavicular recurrence in different patients groups is also shown in Table 1. In general, the absolute level of LRR was highest for the chest wall: a 10-year cumulative incidence for local failure of >15% was documented in patients below age 40 (16.1%), in ≥4 positive lymph nodes (16.5%) and in patients with 0–7 uninvolved lymph nodes (15.1%). In regard to supraclavicular failure, only patients with ≥4 positive lymph nodes exceeded a 10% cumulative risk level (10.2%). Axillary failure rates were relatively rare with a risk far below 10%. A 10-year cumulative risk of ∼5% could be demonstrated for patients below age 40 (5.1%), ≥4 positive lymph nodes (4.9%), patients with unknown tumor size (5.2%) and patients with 0–7 uninvolved nodes (5.2%). Details are given in Table 1.

Table 1. Ten-year cumulative incidence of local recurrence, axillary recurrence and supraclavicular recurrence

Risk factor	No. (%) of patients	Local percent (SE)	Axillary percent (SE)	Supraclavicular percent (SE)
Age, years				
<40	949 (12)	16.1 (1.2)	5.1 (0.7)	6.3 (0.8)
40–49	2607 (32)	10.5 (0.6)	2.7 (0.3)	6.1 (0.5)
50–59	2452 (30)	9.6 (0.6)	2.4 (0.3)	6.3 (0.5)
≥60	2098 (26)	10.8 (0.7)	2.5 (0.3)	3.5 (0.4)
Nodes involved				
None	2555 (32)	6.8 (0.5)	1.3 (0.2)	2.2 (0.3)
1–3	3260 (40)	10.3 (0.5)	2.6 (0.3)	4.8 (0.4)
4–10	1744 (22)	15.4 (0.9)	4.9 (0.5)	8.8 (0.7)
≥11	547 (7)	19.9 (1.7)	4.9 (0.9)	14.8 (1.5)
Tumor size, cm				
≤2	3200 (39)	8.7 (0.5)	2.4 (0.3)	3.5 (0.3)
>2	4623 (57)	12.4 (0.5)	3.0 (0.3)	7.0 (0.4)
Unknown	283 (3)	12.9 (2.1)	5.2 (1.4)	3.8 (1.2)
Tumor grade				
1	1126 (14)	8.2 (0.8)	1.3 (0.4)	2.0 (0.4)
2	3520 (43)	10.7 (0.5)	2.6 (0.3)	4.3 (0.3)
3	3036 (37)	12.3 (0.6)	3.5 (0.3)	8.4 (0.5)
Unknown	424 (5)	11.1 (1.6)	3.8 (0.9)	4.5 (1.0)
Estrogen receptor status				
Negative	2383 (29)	10.6 (0.6)	3.1 (0.4)	7.7 (0.5)
Positive	4760 (59)	11.3 (0.5)	2.5 (0.2)	4.4 (0.3)
Unknown	963 (12)	10.0 (1.0)	3.6 (0.6)	5.5 (0.7)
Peritumoral vessel invasion				
No	3823 (47)	8.6 (0.5)	2.0 (0.2)	3.8 (0.3)
Yes	2754 (34)	14.1 (0.7)	3.8 (0.4)	7.5 (0.5)
Unknown	1529 (19)	11.3 (0.8)	3.3 (0.5)	6.2 (0.6)
Nodes uninvolved				
0–7	1925 (24)	15.1 (0.8)	5.2 (0.5)	9.3 (0.7)
8–11	1953 (24)	11.4 (0.7)	2.9 (0.4)	5.6 (0.5)
12–16	2126 (26)	9.8 (0.7)	2.2 (0.3)	4.3 (0.4)
≥17	2102 (26)	7.9 (0.6)	1.3 (0.2)	3.2 (0.4)
Nodes examined				
≤10	1940 (24)	12.5 (0.8)	3.8 (0.4)	5.7 (0.5)
11–14	2076 (26)	9.4 (0.6)	3.5 (0.4)	6.0 (0.5)
15–19	2053 (25)	11.7 (0.7)	2.2 (0.3)	5.3 (0.5)
≥20	2037 (25)	10.3 (0.7)	2.0 (0.3)	5.1 (0.5)

The cumulative incidence of distant failure exceeded the incidence of all sites of LRR in both node-positive and node-negative patients (Figure 1).

Multivariable competing risk regression analyses for local, axillary and supraclavicular recurrences are shown in Table 2. Age, number of positive lymph nodes and number of uninvolved lymph nodes were highly significant parameters for all individual locoregional relapse sites. The risk for supraclavicular recurrence was lower in patients with positive ER status [hazard ratio = 0.71, 95% confidence interval (CI) 0.58–0.87, Table 2] compared with negative ER status. Larger tumor size and PVI were significant predictors for local und supraclavicular failure but only of borderline significance for axillary relapse. Tumor differentiation, especially grade 3, was a highly significant predictor for supraclavicular failure (Table 2). A descriptive STEPP analysis shows a decreased risk of local, axillary, supraclavicular as well as distant recurrences with increasing number of uninvolved nodes examined (Supplementary Figure S1, available at *Annals of Oncology* online).

Looking specifically at patients with 1–3 positive nodes, risk profiles considering age, PVI and number of uninvolved nodes were modeled giving estimates of 10-year cumulative incidence separately for chest wall, axillary and supraclavicular recurrences (Supplementary Table S2, available at *Annals of Oncology* online). All patients <40 years at diagnosis and almost all groups of patients with PVI or 0–7 uninvolved nodes had >10% 10-year cumulative incidence for chest wall relapse (Supplementary Table S2, available at *Annals of Oncology* online). For axillary recurrences, only patients <40 years combined with PVI and low numbers of uninvolved nodes had 10-year axillary relapse rates above 5%. For supraclavicular relapse, the combination of PVI and low numbers of uninvolved nodes had relapse rates above 5%.

discussion

In our study of 8106 patients treated with mastectomy without RT, the absolute LRR rates at the chest wall, axilla and supraclavicular fossa varied. Generally, the risk factors for locoregional failure at any site were also risk factors for the individual anatomical subsites with the exception of ER status. Positive ER status was found to be associated with an increased risk of recurrence at the chest wall but not the supraclavicular fossa. This may be a chance finding, as a study by Kyndi et al. reported a greater survival benefit of PMRT in patients with ER-positive disease, in which a prevented isolated chest wall recurrence might be more meaningful in diminishing the risk for subsequent distant spread of the disease.

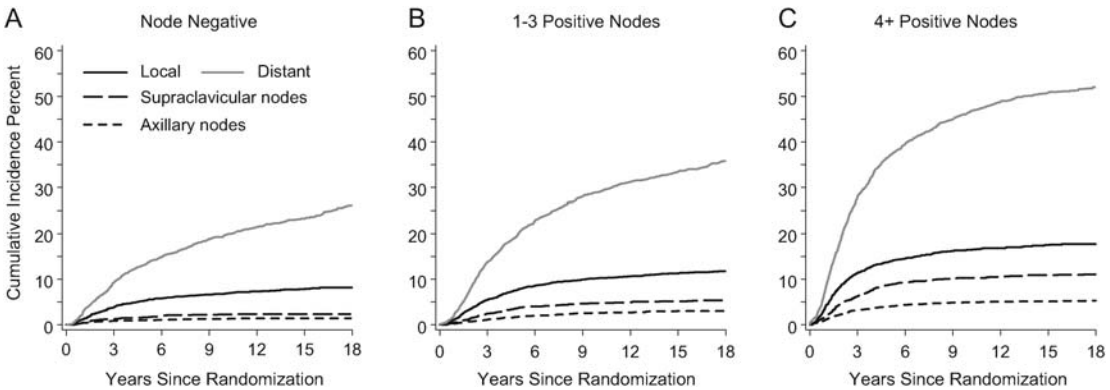

Figure 1. Cumulative incidence of local, axillary, supraclavicular and distant recurrence according to nodal status at diagnosis for node-negative (A), 1–3 positive nodes (B) and ≥4 positive node (C) subpopulations.

In the Danish and Canadian randomized trials, which demonstrated a breast cancer-specific survival advantage of PMRT, the radiation target volume included both the chest wall and regional lymph nodes in the axilla, supraclavicular fossa and internal mammary chain [24–26]. However, it is unclear if comprehensive locoregional RT as prescribed in the Danish and Canadian trials is essential for the survival improvement or RT to a more limited target volume may achieve comparable outcome. Controversial reports about the LRR rates and the potential harmful effects of large-field comprehensive locoregional irradiation such as cardiovascular morbidity, lymphedema, pneumonitis and brachial plexopathy [1, 27, 28] leave this issue unresolved.

It is well accepted that patients with ≥4 positive nodes should receive PMRT to the chest wall [29]. Several guidelines also advise additional irradiation of the supraclavicular lymph nodes in these patients [30] (http://www.nccn.org/professionals/physician_gls/PDF/breast.pdf; http://www.senologie.org/download/pdf/s3_leitlinie_en.pdf). In our study, patients with ≥4 positive nodes had the highest 10-year cumulative incidence of local (16.1%) and supraclavicular failure rates (10.2%). This finding is consistent with the study by Strom et al. [31], who found a 15% risk for supraclavicular failure at 10 years in patients with ≥4 positive nodes after mastectomy. Furthermore, we observed the highest hazard ratio (3.28, 95% CI 2.37–4.53) for supraclavicular failure in patients with ≥4 positive nodes compared with node-negative patients, which was highly statistically significant. These findings support the inclusion of supraclavicular nodes in PMRT for patients with ≥4 positive lymph nodes.

In contrast, failures in the dissected axilla were uncommon with the reported failure rates of ~3% [6, 31]. In our study, the 10-year cumulative incidence of axillary recurrence ranged from 1.3% (grade 1 tumor, pN0 or ≥17 uninvolved nodes) to ~5% (≥4 positive nodes; unknown tumor size age below 40 or 0–7 uninvolved nodes). Therefore, our data supports the recommendations in many radiotherapy guidelines not to irradiate the dissected axilla. This recommendation is also appropriate for patients with positive nodes and extracapsular tumor spread (10-year axillary failure rates 3.2% and 4.9% in patients with 1–3 and ≥4 positive nodes, respectively) [32].

The most controversial aspect of PMRT is its impact on patients with 1–3 positive lymph nodes. The EBCTCG overview showed that PMRT reduced LRR rates (5-year absolute gain of 16.1%) and resulted in a statistically significant improvement of breast cancer mortality (15-year absolute gain of 8.1%, $P = 0.001$) in these patients [33]. Despite this level I evidence, the necessity for PMRT in patients with 1–3 positive nodes remains contentious because the overview data are mainly driven by the Danish trials, which had a number of extensively discussed therapeutic weaknesses. Seventy percent of the St Gallen expert panel did not routinely recommend PMRT in these patients but 72% would support its application in the presence of additional risk factors including young age or PVI [29]. The retrospectively constructed risk profiles for patient with 1–3 positive nodes in our study found a 10-year risk level for chest wall recurrence of >10% in patients aged <40 years; PVI was present; or there were fewer than eight uninvolved nodes. This finding may indicate that at least chest wall radiotherapy should be considered in these groups, which is also supported by data from MacDonald et al. [34]. Furthermore, only patients with both PVI and fewer than eight uninvolved nodes had a relapse risk level in the supraclavicular fossa of >5% and only patients with a combination of all three risk factors of age <40 years, PVI and fewer than eight uninvolved nodes had a relapse rate in the axilla of >5%. These observations may inform appropriate radiation target volume but should be interpreted with caution due to the retrospective character of our study. We used age, PVI and number of uninvolved nodes in the risk profiles since they were the main parameters for LRR in patients with 1–3 positive nodes and dividing the profiles further would result in small numbers of patients in each subgroup. Other studies yielded similar supraclavicular recurrence rates ranging from 1% to 5% in patients with 1–3 positive nodes [32, 35–39]. Yu et al. [40] found lymphovascular invasion, extracapsular extension and numbers and levels of involved axillary nodes as prognostic factors for supraclavicular relapse and concluded that patients with two or more of these risk factors might benefit from supraclavicular RT. The actively recruiting SUPREMO trial (http://www.supremo-trial.com) evaluates the role of PMRT in patients with 1–3 positive nodes. A recently reported phase III

Table 2. Full model multivariable Analysis of local recurrence (A), axillary recurrence (B), and supraclavicular recurrence (C)

Risk factor	Hazard ratio (95% CI)	*P* value[a]
A. Local recurrence		
Age, years		
<40	1.00	*<0.0001*
40–49	0.68 (0.56–0.83)	0.0001
50–59	0.63 (0.51–0.77)	<0.0001
≥60	0.70 (0.57–0.86)	0.0009
Nodes involved		
None	1.00	*<0.0001*
1–3	1.34 (1.11–1.60)	0.0017
4–10	1.85 (1.51–2.27)	<0.0001
≥11	2.10 (1.60–2.74)	<0.0001
Tumor size, cm		
≤2	1.00	*0.012*
>2	1.22 (1.06–1.40)	0.0066
Unknown	1.43 (0.99–2.07)	0.059
Tumor grade		
1	1.00	*0.31*
2	1.14 (0.92–1.42)	0.22
3	1.23 (0.99–1.54)	0.063
Unknown	1.13 (0.78–1.64)	0.53
Estrogen receptor status		
Negative	1.00	*0.084*
Positive	1.18 (1.01–1.37)	0.039
Unknown	1.02 (0.81–1.29)	0.84
Peritumoral vessel invasion		
No	1.00	*<0.0001*
Yes	1.40 (1.21–1.62)	<0.0001
Unknown	1.08 (0.90–1.31)	0.42
Nodes uninvolved		
0–7	1.00	*0.014*
8–11	0.96 (0.80–1.15)	0.63
12–16	0.90 (0.75–1.09)	0.30
≥17	0.73 (0.60–0.89)	0.0023
B. Axillary recurrence		
Age, years		
<40	1.00	*0.0054*
40–49	0.59 (0.41–0.85)	0.0043
50–59	0.53 (0.36–0.77)	0.0010
≥60	0.57 (0.38–0.85)	0.0061
Nodes involved		
None	1.00	*0.0024*
1–3	1.66 (1.09–2.52)	0.019
4–10	2.44 (1.52–3.92)	0.0002
≥11	1.90 (1.06–3.41)	0.031
Tumor size, cm		
≤2	1.00	*0.087*
>2	0.98 (0.74–1.30)	0.88
Unknown	1.82 (1.03–3.22)	0.039
Tumor grade		
1	1.00	*0.053*
2	1.58 (0.96–2.58)	0.070
3	1.94 (1.18–3.19)	0.0090
Unknown	1.92 (0.97–3.78)	0.060
Estrogen receptor status		
Negative	1.00	*0.83*
Positive	0.98 (0.73–1.31)	0.87
Unknown	1.10 (0.73–1.64)	0.65
Peritumoral vessel invasion		
No	1.00	*0.055*
Yes	1.41 (1.04–1.91)	0.027
Unknown	1.06 (0.73–1.55)	0.75
Nodes uninvolved		
0–7	1.00	*<0.0001*
8–11	0.69 (0.49–0.97)	0.031
12–16	0.55 (0.38–0.80)	0.0018
≥17	0.34 (0.21–0.53)	<0.0001
C. Supraclavicular recurrence		
Age, years		
<40	1.00	*0.0007*
40–49	1.12 (0.83–1.51)	0.47
50–59	1.24 (0.92–1.68)	0.16
≥60	0.71 (0.50–1.00)	0.049
Nodes involved		
None	1.00	*<0.0001*
1–3	1.94 (1.42–2.64)	<0.0001
4–10	3.02 (2.17–4.20)	<0.0001
≥11	4.39 (2.95–6.55)	<0.0001
Tumor size, cm		
≤2	1.00	*0.015*
>2	1.35 (1.09–1.67)	0.0063
Unknown	0.87 (0.44–1.72)	0.68
Tumor grade		
1	1.00	*<0.0001*
2	1.57 (1.05–2.35)	0.030
3	2.57 (1.72–3.84)	<0.0001
Unknown	1.63 (0.84–3.16)	0.15
Estrogen receptor status		
Negative	1.00	*0.0035*
Positive	0.71 (0.58–0.87)	0.0008
Unknown	0.83 (0.60–1.13)	0.24
Peritumoral vessel invasion		
No	1.00	*0.034*
Yes	1.34 (1.07–1.67)	0.0095
Unknown	1.17 (0.88–1.54)	0.27
Nodes uninvolved		
0–7	1.00	*0.0014*
8–11	0.86 (0.67–1.11)	0.25
12–16	0.77 (0.59–1.02)	0.064
≥17	0.54 (0.39–0.74)	0.0001

[a]Overall Wald test *P* values are shown in italics for each risk factor.

randomized trial by Whelan et al. [41] shows a significant disease-free survival advantage of breast plus regional nodal RT compared with breast RT alone in patients treated with breast-conserving therapy of whom 85% had 1–3 positive nodes. However, whether this finding is equally applicable for selected patient subgroups that had a mastectomy remains to be confirmed.

Our study found a reduced risk of any type of LRR with increasing number of examined uninvolved nodes (Supplementary Figure S1). This finding is in line with other studies [42, 43]. Although the number of uninvolved nodes

may reflect individual anatomic variability, fewer uninvolved nodes examined might be associated with inadequate surgery or pathological understaging, which could lead to local or systemic undertreatment. Other studies have shown that the risk for LRR decreases with the total number of lymph nodes examined [2] and the nodal ratio (proportion of lymph nodes examined that contain tumor) is correlated to the risk for LRR [44]. We have made a separate multivariable analysis in which the number of uninvolved nodes is replaced by the total number of examined nodes with very similar results (data not shown). In the analyses for a former publication from our group [7], we investigated a number of approaches to the statistical modeling including the use of nodal ratios and found that grouping patients into quartiles of positive nodes and uninvolved nodes resulted in improved model fit.

To conclude, in this analysis of 13 IBCSG randomized trials involving over 8000 patients, the chest wall is the most common site of locoregional failure sites after mastectomy. Patients who were aged <40 years, had ≥4 positive nodes or had 0–7 uninvolved nodes experienced a 10-year cumulative incidence for local failure of ≥15%. PMRT to the chest wall should be considered in these patients. Our study also supports the application of supraclavicular RT in patients with ≥4 positive nodes. Irradiation of the dissected axilla is not indicated. No clear recommendation on PMRT could be given for patients with 1–3 positive nodes but PMRT to the chest wall may be considered in the presence of the risk factors of young age (<40 years), PVI or few uninvolved nodes (0–7).

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disclosure

The authors have declared no conflicts of interest.

references

1. Clarke M, Collins R, Darby S et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 366: 2087–2106.
2. Taghian A, Jeong JH, Mamounas E et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. J Clin Oncol 2004; 22: 4247–4254.
3. Kyndi M, Sorensen FB, Knudsen H et al. Estrogen receptor, progesterone receptor, HER-2, and response to postmastectomy radiotherapy in high-risk breast cancer: the Danish Breast Cancer Cooperative Group. J Clin Oncol 2008; 26: 1419–1426.
4. Kyndi M, Overgaard M, Nielsen HM et al. High local recurrence risk is not associated with large survival reduction after postmastectomy radiotherapy in high-risk breast cancer: a subgroup analysis of DBCG 82 b&c. Radiother Oncol 2009; 90: 74–79.
5. Ceilley E, Jagsi R, Goldberg S et al. Radiotherapy for invasive breast cancer in North America and Europe: results of a survey. Int J Radiat Oncol Biol Phys 2005; 61: 365–373.
6. Wallgren A, Bonetti M, Gelber RD et al. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 2003; 21: 1205–1213.
7. Karlsson P, Cole BF, Price KN et al. The role of the number of uninvolved lymph nodes in predicting locoregional recurrence in breast cancer. J Clin Oncol 2007; 25: 2019–2026.
8. Castiglione-Gertsch M, Johnsen C, Goldhirsch A et al. The International (Ludwig) Breast Cancer Study Group Trials I-IV: 15 years follow-up. Ann Oncol 1994; 5: 717–724.
9. Ludwig Breast Cancer Study Group. Combination adjuvant chemotherapy for node-positive breast cancer. Inadequacy of a single perioperative cycle. N Engl J Med 1988; 319: 677–683.
10. Ludwig Breast Cancer Study Group. Prolonged disease-free survival after one course of perioperative adjuvant chemotherapy for node-negative breast cancer. N Engl J Med 1989; 320: 491–496.
11. International Breast Cancer Study Group. Duration and reintroduction of adjuvant chemotherapy for node-positive premenopausal breast cancer patients. J Clin Oncol 1996; 14: 1885–1894.
12. International Breast Cancer Study Group. Effectiveness of adjuvant chemotherapy in combination with tamoxifen for node-positive postmenopausal breast cancer patients. J Clin Oncol 1997; 15: 1385–1394.
13. International Breast Cancer Study Group. Endocrine responsiveness and tailoring adjuvant therapy for postmenopausal lymph node-negative breast cancer: a randomized trial. J Natl Cancer Inst 2002; 94: 1054–1065.
14. International Breast Cancer Study Group. Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. J Natl Cancer Inst 2003; 95: 1833–1846.
15. Thurlimann B, Price KN, Gelber RD et al. Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93. Breast Cancer Res Treat 2009; 113: 137–144.
16. International Breast Cancer Study Group. Toremifene and tamoxifen are equally effective for early-stage breast cancer: first results of International Breast Cancer Study Group Trials 12-93 and 14-93. Ann Oncol 2004; 15: 1749–1759.
17. International Breast Cancer Study Group. Effects of a treatment gap during adjuvant chemotherapy in node-positive breast cancer: results of International Breast Cancer Study Group (IBCSG) Trials 13-93 and 14-93. Ann Oncol 2007; 18: 1177–1184.
18. Davis BW, Gelber RD, Goldhirsch A et al. Prognostic significance of peritumoral vessel invasion in clinical trials of adjuvant therapy for breast cancer with axillary lymph node metastasis. Hum Pathol 1985; 16: 1212–1218.
19. Kalbfleish JD, Prentice RL. The Statistical Analysis of Failure Time Data. New York, NY: Wiley 1980.
20. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. Ann Stat 1988; 16: 1141–1154.
21. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc 1999; 94: 496–509.
22. Fleming TR, Harrington DP. Counting Processes and Survival Analysis. New York: Wiley 1991.
23. Lazar AA, Cole BF, Bonetti M, Gelber RD. Evaluation of treatment-effect heterogeneity using biomarkers measured on a continuous scale: Subpopulation Treatment Effect Pattern Plot. J Clin Oncol 2010; 28: 4539–4544.

24. Overgaard M, Hansen PS, Overgaard J et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997; 337: 949–955.
25. Overgaard M, Jensen MB, Overgaard J et al. Postoperative radiotherapy in high-risk postmenopausal breast-cancer patients given adjuvant tamoxifen: Danish Breast Cancer Cooperative Group DBCG 82c randomised trial. Lancet 1999; 353: 1641–1648.
26. Ragaz J, Jackson SM, Le N et al. Adjuvant radiotherapy and chemotherapy in node-positive premenopausal women with breast cancer. N Engl J Med 1997; 337: 956–962.
27. Pierce S, Recht A, Lingos T et al. Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer. Int J Radiat Oncol Biol Phys 1992; 23: 915–923.
28. Lingos T, Recht A, Vicini F et al. Radiation pneumonitis in breast cancer patients treated with conservative surgery and radiation therapy. Int J Radiat Oncol Biol Phys 1991; 21: 355–360.
29. Goldhirsch A, Ingle JN, Gelber RD et al. Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. Ann Oncol 2009; 20: 1319–1329.
30. Aebi S, Davidson T, Gruber G et al. Primary breast cancer: ESMO Clinical Recommendations for Diagnosis, Treatment and Follow-up. Ann Oncol 2010; 21Suppl 5v9–v14.
31. Strom E, Woodward WA, Katz A et al. Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. Int J Radiat Oncol Biol Phys 2005; 63: 1508–1513.
32. Gruber G, Cole BF, Castiglione-Gertsch M et al. Extracapsular tumor spread and the risk of local, axillary and supraclavicular recurrence in node-positive, premenopausal patients with breast cancer. Ann Oncol 2008; 19: 1393–1401.
33. Darby S. Overview of randomised trials of radiotherapy in early breast cancer. Cancer Res 2009; 69 (Suppl 24) (Abstr MS3–1).
34. Macdonald SM, Abi-Raad RF, Alm El-Din MA et al. Chest wall radiotherapy: middle ground for treatment of patients with one to three positive lymph nodes after mastectomy. Int J Radiat Oncol Biol Phys 2009; 75: 1297–1303.
35. Vicini FA, Horwitz EM, Lacerna MD et al. The role of regional nodal irradiation in the management of patients with early-stage breast cancer treated with breast-conserving therapy. Int J Radiat Oncol Biol Phys 1997; 39: 1069–1076.
36. Recht A, Pierce SM, Abner A et al. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol 1991; 9: 988–996.
37. Recht A, Gray R, Davidson NE et al. Locoregional failure 10 years after mastectomy and adjuvant chemotherapy with or without tamoxifen without irradiation: Experience of the Eastern Cooperative Oncology Group. J Clin Oncol 1999; 17: 1689–1700.
38. Livi L, Scotti V, Saieva C et al. Outcome after conservative surgery and breast irradiation in 5,717 patients with breast cancer: implications for supraclavicular nodal irradiation. Int J Radiat Oncol Biol Phys 2010; 76: 978–983.
39. Truong PT, Jones SO, Kader HA et al. Patients with T1 to T2 breast cancer with one to three positive nodes have higher local and regional recurrence risks compared with node-negative patients after breast-conserving surgery and whole-breast radiotherapy. Int J Radiat Oncol Biol Phys 2009; 73: 357–364.
40. Yu JI, Park W, Huh SJ et al. Determining which patients require irradiation of the supraclavicular nodal area after surgery for N1 breast cancer. Int J Radiat Oncol Biol Phys 2010; 78: 1135–1141.
41. Whelan TJ, Olivotto I, Ackerman I et al. NCIC-CTG MA.20: an intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol 2011; 29 (18 suppl) LBA1003.
42. Vinh-Hung V, Cserni G, Burzykowski T et al. Effect of the number of uninvolved nodes on survival in early breast cancer. Oncol Rep 2003; 10: 363–368.
43. Salama JK, Heimann R, Lin F et al. Does the number of lymph nodes examined in patients with lymph node-negative breast carcinoma have prognostic significance?. Cancer 2005; 103: 664–671.
44. Truong PT, Woodward WA, Thames HD et al. The ratio of positive to excised nodes identifies high-risk subsets and reduces inter-institutional differences in locoregional recurrence risk estimates in breast cancer patients with 1-3 positive nodes: an analysis of prospective data from British Columbia and the M. D. Anderson Cancer Center. Int J Radiat Oncol Biol Phys 2007; 68: 59–65.