Outcomes of Patients With Breast Cancer Who Present With Ipsilateral Supraclavicular or Internal Mammary Lymph Node Metastases

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Abstract

To evaluate outcome of breast cancer IM and SC node involvement, we evaluated 107 patients with IM or SC node involvement and a matched cohort of patients as controls. Patients with SC node involvement had a significantly poorer DFS and higher loco-regional recurrence rates compared with controls without SC node involvement.

Background: The prognostic implications of internal mammary (IM) and supraclavicular (SC) node involvement in locally advanced breast cancer is still unclear. **Patients and Methods:** We evaluated 107 patients with IM (n = 65) or SC (n = 42) node involvement who underwent operation at the European Institute of Oncology between 1997 and 2009 to assess their prognostic features. We subsequently analyzed matched cohorts, using the 107 patients as cases and another group of patients as a control cohort, to evaluate prognostic differences between patients with and those without IM or SC node involvement. **Results:** Five-year disease-free survival (DFS) was 84% in IM vs. 38.8% in SC node involvement ($P < .0001$), and 5-year overall survival (OS) was 96.9% in IM node vs. 57.1% in SC node involvement ($P < .0001$). No difference in outcome was found between patients with and controls without IM node involvement. Conversely, a statistically significant difference in DFS and locoregional recurrence was observed in patients with SC node involvement compared with controls without SC node involvement. **Conclusion:** SC node involvement correlated with a significantly poorer outcome in patients with locally advanced breast cancer. Adequate staging, including biopsy of suspicious locoregional ipsilateral lymph nodes, is mandatory in these patients. Patients with IM or SC node involvement should be treated with curative intent using combined-modality treatments.

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Introduction

The precise prognostic significance of internal mammary (IM) chain and supraclavicular (SC) lymph node involvement in patients with locally advanced breast cancer is still debated, and therapeutic choices in patients in whom IM or SC lymph nodes (or both) are involved are still not uniformly defined.

The IM lymph node chain is represented by a variable number of lymph nodes (average of 6) situated behind the intercostal muscles and costal cartilages. The nodes are generally located close to the IM vein and artery, and more often in the first, second, and third spaces. The first surgeon who explored the intercostal spaces was Handley in 1922[1] who found metastatic IM nodes in 4 of 6 patients. He suggested that radiotherapy should be applied to the parasternal region in patients with breast cancer. A series of 100 cases treated with IM node removal was published in 1959 by Bucalossi and Veronesi, showing the poor prognosis of patients with

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Table 1 Baseline Characteristics of Patients With SC or IM Node Metastases and Matched Groups

	Patients by Type of Node Metastasis Group						
	Internal Mammary (n = 65)	Control Group (n = 65)	*P* Value[a]	Ipsilateral Supraclavicular (n = 42)	Control Group (n = 42)	*P* Value[b]	*P* Value[c]
Variable	**n (%)**	**n (%)**		**n (%)**	**n (%)**		
Matching Variables							
Neoadjuvant therapy			–			–	<.0001
No	56 (86.2)	56 (86.2)		13 (31)	13 (31)		
Yes	9 (13.8)	9 (13.8)		29 (69)	29 (69)		
Year of surgery			–			–	<.0001
Before 2000	0 (0)	3 (4.6)		11 (26.2)	6 (14.3)		
2000-2003	27 (41.5)	28 (43.1)		24 (57.1)	25 (59.5)		
2003-2006	23 (35.4)	13 (20)		3 (7.1)	6 (14.3)		
2007-2009	15 (23.1)	21 (32.3)		4 (9.5)	5 (11.9)		
Age (years)			–			–	.007
<35	4 (6.2)	3 (4.6)		2 (4.8)	2 (4.8)		
35-50	35 (53.8)	35 (53.8)		9 (21.4)	11 (26.2)		
51-65	21 (32.3)	21 (32.3)		25 (59.5)	26 (61.9)		
>65	5 (7.7)	6 (9.2)		6 (14.3)	3 (7.1)		
Positive lymph nodes at surgery (n)			–			–	<.0001
None	1 (1.5)	1 (1.5)		7 (16.7)	7 (16.7)		
1-3	33 (50.8)	33 (50.8)		4 (9.5)	4 (9.5)		
4-9	14 (21.5)	14 (21.5)		6 (14.3)	6 (14.3)		
10+	17 (26.2)	17 (26.2)		25 (59.5)	25 (59.5)		
pT status			–			–	<.0001
pT0	1 (1.5)	1 (1.5)		6 (14.3)	6 (14.3)		
pT1	25 (38.5)	25 (38.5)		10 (23.8)	10 (23.8)		
pT2	30 (46.2)	30 (46.2)		9 (21.4)	9 (21.4)		
pT3-4	9 (13.8)	9 (13.8)		17 (40.5)	17 (40.5)		
Tumor subtype			–			–	.002
Luminal A	11 (16.9)	13 (20)		2 (4.8)	8 (19)		
Luminal B (Ki67 ≥14)	38 (58.5)	38 (58.5)		11 (26.2)	10 (23.8)		
Luminal B ($HER2^+$)	8 (12.3)	7 (10.8)		3 (7.1)	3 (7.1)		
$HER2^+$	3 (4.6)	2 (3.1)		7 (16.7)	4 (9.5)		
Triple negative	4 (6.2)	4 (6.2)		8 (19)	8 (19)		
NA	1 (1.5)	1 (1.5)		11 (26.2)	9 (21.4)		
Other Prognostic Factors							
Histologic type			.060			.128	.918
Negative	0 (0)	1 (1.5)		2 (4.8)	2 (4.8)		
Ductal	54 (83.1)	44 (67.7)		32 (76.2)	27 (64.3)		
Lobular	3 (4.6)	11 (16.9)		2 (4.8)	8 (19)		
Other	8 (12.3)	9 (13.8)		6 (14.3)	5 (11.9)		
Grade			.501			.004	.001
Unknown	11 (16.9)	12 (18.5)		26 (61.9)	33 (78.6)		
1-2	35 (53.8)	31 (47.7)		3 (7.1)	7 (16.7)		
3	19 (29.2)	22 (33.8)		13 (31)	2 (4.8)		
PVI			.129			.387	.850
Absent	28 (43.1)	35 (53.8)		18 (42.9)	21 (50)		
Present	10 (15.4)	13 (20)		5 (11.9)	3 (7.1)		
Focal	3 (4.6)	5 (7.7)		1 (2.4)	4 (9.5)		
Diffuse	24 (36.9)	12 (18.5)		18 (42.9)	14 (33.3)		

Table 1 Continued

Variable	Patients by Type of Node Metastasis Group						
	Internal Mammary (n = 65)	Control Group (n = 65)	*P* Value[a]	Ipsilateral Supraclavicular (n = 42)	Control Group (n = 42)	*P* Value[b]	*P* Value[c]
	n (%)	n (%)		n (%)	n (%)		
Treatment							
Surgery			.584			.369	.001
Conservative	43 (66.2)	40 (61.5)		14 (33.3)	18 (42.9)		
Mastectomy	22 (33.8)	25 (38.5)		28 (66.7)	24 (57.1)		
Radiotherapy			.0004			.332	.056
No	1 (1.5)	14 (21.5)		4 (9.5)	7 (16.7)		
Yes	64 (98.5)[d]	51 (78.5)		38 (90.5)[d]	35 (83.3)		
CT/HT			.144			.375	<.0001
No	1 (1.5)	1 (1.5)		5 (11.9)	4 (9.5)		
HT	9 (13.8)	20 (30.8)		15 (35.7)	12 (28.6)		
CT	7 (10.8)	6 (9.2)		15 (35.7)	12 (28.6)		
HT-CT	48 (73.8)	38 (58.5)		7 (16.7)	14 (33.3)		

Abbreviations: CT = computed tomography; HT = hormonal therapy; IM = internal mammary; NA = not available; PVI = peritumoral vascular invasion; RT = radiotherapy; SC = supraclavicular.
[a] χ^2 test comparing proportions between IM group and control group.
[b] χ^2 test comparing proportions between ipsilateral SC group and control group.
[c] χ^2 test comparing proportions between IM group and ipsilateral SC group.
[d] In the MI group, 1 patient received external RT, 2 patients received external RT plus IM chain RT, 34 patients locoregional RT, 9 patients locoregional RT plus IM chain RT, 3 patients IM chain RT, 3 patients received electron beam intraoperative radiotherapy (ELIOT), 12 patients received ELIOT plus external RT. In the SC group, 3 patients received external RT, 33 received locoregional RT, 1 received SC RT, 1 received ELIOT plus external RT.

IM node involvement.[2] In 1971, Urban and Marjani developed a radical surgical approach and claimed that prognosis of patients with breast cancer was improved by radical dissection of lymph nodes of the first to third spaces.[3] An international randomized trial was conducted by 5 cancer institutes in 1963 to 1966. A total of 1443 patients were randomized to either mastectomy or mastectomy plus IM node dissection. Five-year (70%),[4] 10-year (60.7% vs. 57%, respectively),[5] and 30-year survival (approximately 20%)[6] was identical both in patients who received mastectomy alone and in patients who underwent mastectomy and IM node dissection. However, the review of 1119 cases treated with IM node dissection showed that IM node involvement plays an important role as a prognostic factor: 10-year survival varied from 80.4% in patients with axillary and IM negative nodes to 30.0% in patients with both nodal sites involved. Intermediate survival rates (54.6% and 53.0%) were found when 1 or the other of the nodal stations (axillary and IM) was affected separately.[7] Moreover, many series of patients treated with radiotherapy of the IM chain after mastectomy showed a limited improvement in survival.[8]

Until recent years, the diagnosis of an SC ipsilateral adenopathy in the staging of locally advanced breast cancer was included in the stage IV category of tumor classification, even without evidence of further distant disease. Ipsilateral SC metastases from breast cancer are considered an ominous sign, representing a late stage of regional metastases, and despite aggressive local and regional treatment, cure is rare. Most patients have distant metastases within 1 year of detection of SC lymph node involvement. Radiotherapy alone or in combination with surgical resection was the standard of care previously. Although high local control rates were observed with this treatment strategy, survival for patients treated only with local therapy was dismal. In a trial conducted at the MD Anderson Cancer Center, 70 patients with ipsilateral SC adenopathy without evidence of distant disease received treatment in 3 prospective trials of neoadjuvant chemotherapy and then underwent mastectomy and axillary lymph node dissection and subsequent adjuvant chemotherapy followed by radiotherapy. Patients older than 50 years with estrogen receptor–positive tumors received tamoxifen for 5 years. At a median follow-up of 11.6 years (range, 4.8-22.6 years), disease-free survival (DFS) rates at 5 and 10 years were 34% and 32%, respectively. Overall survival (OS) rates at 5 and 10 years were 41% and 31%, respectively. The authors concluded that patients with ipsilateral SC metastases but no other evidence of distant metastases warrant combined-modality treatments (chemotherapy, surgery, and radiotherapy) administered with curative intent and proposed that patients with ipsilateral SC metastases should be included in the stage IIIB category of the tumor-node-metastasis classification because their clinical course and prognosis are similar to those of patients with stage IIIB locally advanced breast cancer.[9]

We conducted a retrospective analysis of 107 patients with either IM or SC lymph node involvement to evaluate prognostic features of these 2 disease presentations. We subsequently conducted an analysis based on matched cohorts, using the 107 patients described previously as cases and a control cohort of patients with the same clinicopathologic features, who had either undergone or had not undergone previous neoadjuvant chemotherapy, to evaluate prognostic differences between patients with and those without IM or SC node involvement.

Table 2 Observed First Events and Deaths in Patients with Breast Cancer Presenting With Ipsilateral SC or IM Lymph Node Metastases and of 2 Matched Comparison Groups

	Patients by Type of Node Metastases Group			
	Internal Mammary (n = 65)	Comparison Group (n = 65)	Ipsilateral Supraclavicular (n = 42)	Comparison Group (n = 42)
Event	n (%)	n (%)	n (%)	n (%)
Observed First Event	21 (32.3)	18 (27.7)	27 (64.3)	21 (50.0)
Locoregional Event	4	5	10	4
Distant Metastases	7	9	15	13
Others	10	4	2	4
Observed deaths	7 (10.7)	7 (10.7)	19 (45.2)	12 (28.6)

Patients and Methods

Patients

We extracted information from our institutional database, which includes data of all consecutive patients with breast cancer operated on at the European Institute of Oncology. We identified 107 patients (the study group) with either IM or SC lymph node involvement operated on between 1997 and 2009. Of these, 65 patients had IM lymph node involvement and 42 had SC lymph node involvement (2 patients presented with both IM and SC involvement and were included in the SC group).

In the IM group, diagnosis was determined from results obtained by lymph node biopsy in 56 patients, positron emission tomography in 8 patients, and lymph node ultrasonography in 1 patient. In the SC group, diagnosis was determined by clinical visit in 23 patients and results from lymph node biopsy in 15 patients, positron emission tomography in 2 patients, and lymph node ultrasonography in 2 patients.

Patients might have received (n = 38) or not received (n = 69) neoadjuvant treatment. Patients with metastatic disease at the time of surgery, those with bilateral breast cancer, and those with a history of previous cancer (other than skin cancer) were excluded.

Clinicopathologic data including age, tumor size, axillary lymph node status, tumor subtype (luminal A, luminal B, triple negative, and HER2-positive [HER^+]), tumor type (ductal, lobular, or other), tumor grade, peritumoral vascular invasion, estrogen receptor (ER) and progesterone receptor (PR) status, HER2 overexpression/amplification status, proliferative fraction (Ki-67), type of surgery, radiotherapy, and type of systemic treatment (either neoadjuvant or adjuvant) were recorded in a database and included in the analysis.

For each patient in the study group, we selected from the same database 1 matched patient (control group). The variables used to make the randomly assigned matches were as follows: age (within 5 years), tumor size at surgery (pT0, pT1, pT2, pT3-4), number of positive lymph nodes at surgery (none, 1-3, 4-9, > 9), tumor subtype (luminal A, luminal B, triple negative, $HER2^+$), and year of surgery (within 2 years). For 18 cases, no controls satisfying all the criteria could be found. For these cases, matching criteria were relaxed (ie, age within 10 years or year of surgery within 3 years) or not considered (ie, tumor subtype).

Pathologic and Immunohistochemical Analysis

All patients had pathologic evaluation performed at the European Institute of Oncology. Tumor grade was assessed according to the criteria of Elston and Ellis[10] based on the combined assessment of tubule formation, nuclear grade, and mitotic activity.

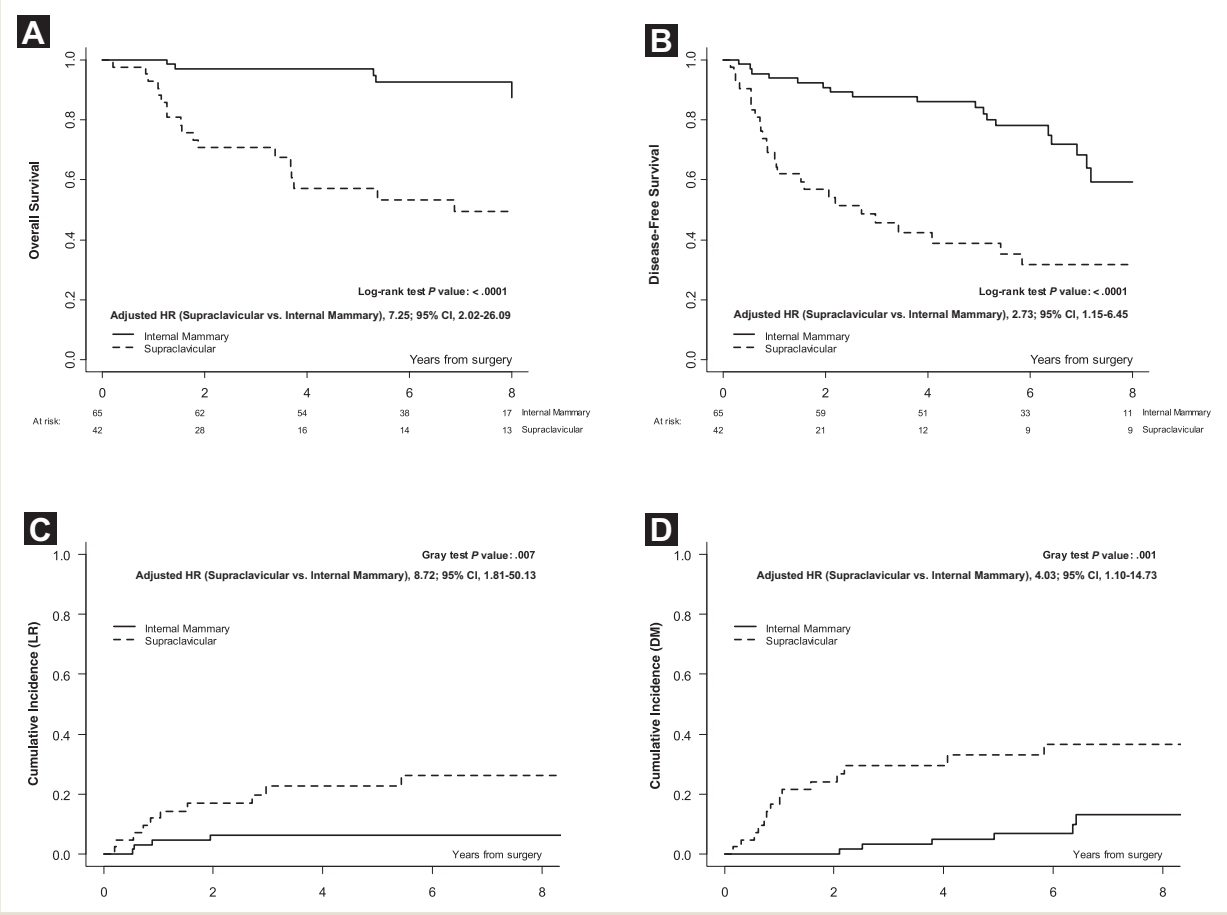
Immunostaining for the localization of ER and PR, HER2 protein, and Ki-67 antigen was performed on consecutive tissue sections. The following primary antibodies were used: the 1D5 monoclonal antibody (MAb) to ER (1:100 dilution; Dako, Glostrup, Denmark), the 1A6 MAb to PR (1:800 dilution; Dako, Glostrup, Denmark), the MIB-1 MAb to the Ki-67 antigen (1:100 dilution; Dako, Glostrup, Denmark), and the A0485 polyclonal antiserum (1:400 dilution; Dako, Glostrup, Denmark) to the HER2 protein.[11] Only nuclear reactivity was taken into account for ER, PR, and Ki-67 antigen, whereas only an intense and complete membrane staining in > 10% of the tumor cells qualified for HER2 overexpression (3+). Fluorescence in situ hybridization assay (using the PathVysion HER2 DNA kit, Vysis–Abbott, Des Plaines, IL) was performed in cases with equivocal (2+) immunohistochemical results to identify cases with gene amplification (HER2− chromosome 17 centromere ratio ≥ 2). The results for ER, PR, and Ki-67 were recorded as the percentage of immunoreactive cells observed among at least 2000 neoplastic cells. The value Ki-67 labeling index was divided into low (< 14%) and high (≥ 14%).[12] The tumor was regarded as positive for ER and PR if ≥ 1% of the cells showed nuclear staining.[13]

Immunohistochemical evaluation of ER, PR, Ki-67, and HER2 expression may be considered a surrogate means to identify molecular subtypes of breast cancer.[12] According to the immunohistochemical evaluation, we identified 4 tumor subtypes: luminal A (ER^+ or PR^+ [or both], HER2 negative [$HER2^-$, Ki-67 low), luminal B (ER^+ or PR^+ [or both], $HER2^-$, Ki-67 high, or ER^+ or PR^+ [or both], any Ki-67, HER2 overexpressed or amplified), $HER2^+$ [HER2 overexpressed or amplified, ER and PR absent] and triple negative (ER and PR absent, $HER2^-$).

Statistical Analysis

Differences in the distribution of subject characteristics between groups were evaluated by the χ^2 test. The end points evaluated were DFS, OS, cumulative incidence of local or regional recurrence (CI-LR) and cumulative incidence of distant metastases (CI-DM). DFS was defined as the time from surgery to events such as relapse (including ipsilateral breast recurrence), appearance of a second primary cancer (including contralateral breast cancer), or death, whichever occurred first. OS was defined as the time from surgery until the date of death (from any cause). The DFS and OS functions were estimated using the Kaplan-Meier method. The log-rank test

Figure 1 (A) Overall Survival (OS), (B) Disease-Free Survival (DFS), (C) Cumulative Incidence of Local or Regional (LR) Recurrence, and (D) Cumulative Incidence of Distant Metastases (DM) in Patients With Breast Cancer who Present With Ipsilateral Supraclavicular (SC) Lymph Node Metastases and Patients With Breast Cancer who Present With Internal Mammary (IM) Lymph Node Metastases. Univariate log-Rank Test *P* Values and Hazard Ratios (HRs) (SC vs. IM) Adjusted for Neoadjuvant Chemotherapy, age at Diagnosis, Number of Positive Lymph Nodes, Tumor Size, and Tumor Subtype are Reported



Abbreviation: CI = confidence interval.

was used to assess differences between groups. The CI-LR and CI-DM were defined as the time from the date of surgery to a local or regional recurrence and a distant metastasis, respectively.

The CI-LR and CI-DM functions were estimated according to methods described by Kalbfleisch and Prentice, taking into account the competing causes of recurrence.[14] The Gray test was used to assess cumulative incidence differences between groups.[15]

The hazard ratio (HR) comparing the SC group and the IM group was estimated with a Cox proportional hazards multivariable model controlled for neoadjuvant chemotherapy, age at diagnosis, number of positive lymph nodes, tumor size, and tumor subtype. The HRs comparing the IM group and its matched control group and the SC group and its matched control group were estimated with Cox proportional hazards univariate models.

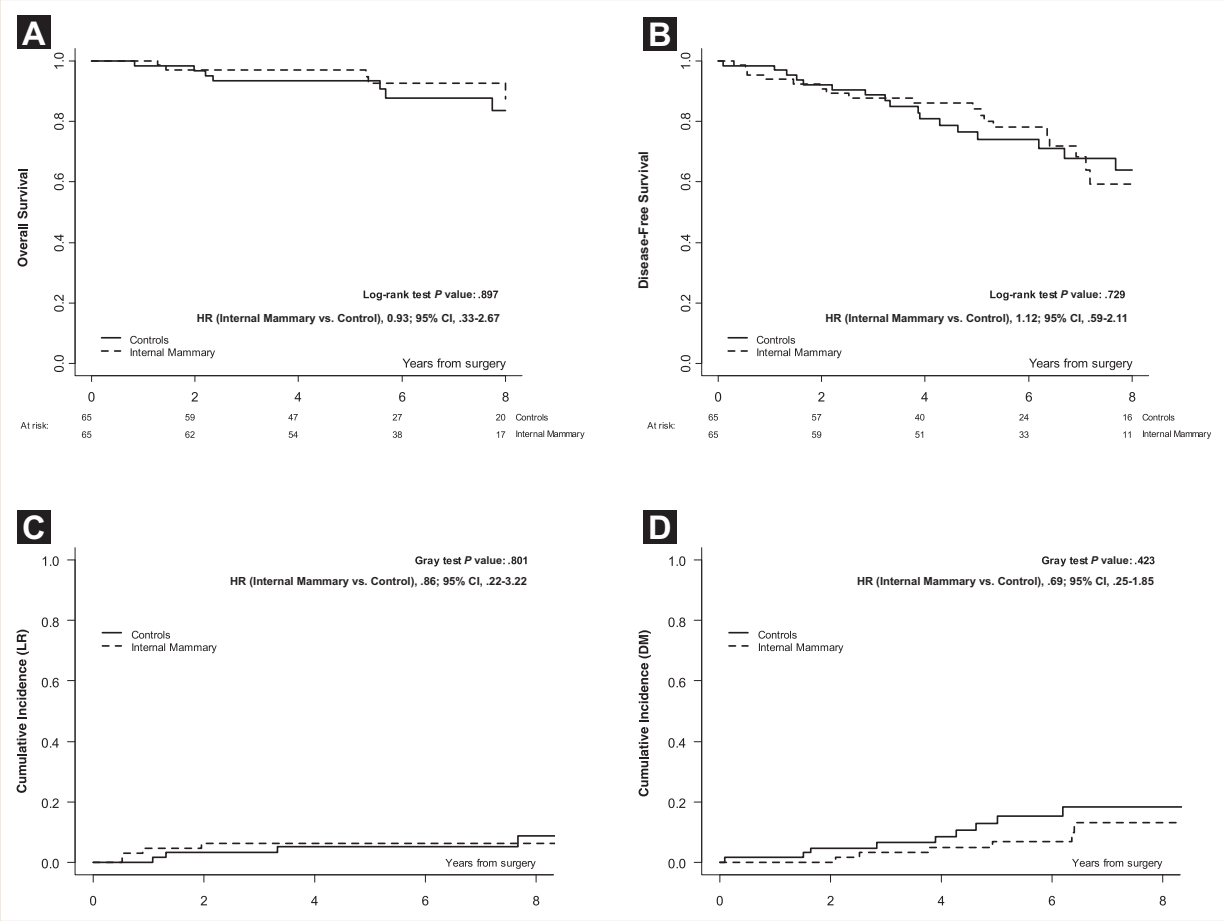
All analyses were carried out with SAS software (SAS Institute, Cary, NC) and the R software (http://cran.r-project.org/) with the cmprsk package developed by Gray (http://biowww.dfci.harvard.edu/~gray/). All reported *P* values are 2 sided.

Results

Baseline demographic, clinical, and pathologic characteristics and local and systemic treatments of patients with breast cancer who presented with ipsilateral IM or SC lymph node metastases and of 2 matched comparison groups are described in Table 1. Involvement of SC nodes was more frequent in patients with a high number of positive axillary nodes, larger tumor size, triple negative or HER2$^+$ disease, and in those who had received neoadjuvant treatment. As for local treatment, involvement of IM nodes was more frequent in patients who underwent a conservative operation, whereas involvement of SC nodes was more frequent in patients who underwent mastectomy. The majority of patients included in the analysis received locoregional radiotherapy.

Observed first events and deaths in patients with ipsilateral SC or IM lymph node metastases and of 2 matched comparison groups are reported in Table 2. At a median follow-up of 7 years, there was a statistically significant difference in outcomes according to the site of metastases (IM vs. SC) (Fig. 1): 5-year OS was 96.9% in IM

Figure 2 (A) Overall Survival (OS), (B) Disease-Free Survival (DFS), (C) Cumulative Incidence of Local or Regional (LR) Recurrence, and (D) Cumulative Incidence of Distant Metastases (DM) in Patients With Breast Cancer Presenting With Internal Mammary (IM) Lymph Node Metastases and a Matched Control Group. Univariate log-Rank Test *P* Values and Hazard Ratios (HRs) (IM vs. Control) are Reported



Abbreviation: CI = confidence interval.

node vs. 57.1% in SC node involvement, respectively (adjusted HR [SC vs. IM], 7.25; 95% CI, 2.02-26.09; $P < .0001$) and 5-year DFS was 84% in IM node vs. 38.8% in SC node involvement, respectively (adjusted HR [SC vs. IM] 2.73; 95% CI, 1.15-6.45; $P < .0001$). The difference was maintained both for locoregional recurrences (cumulative incidence at 5 years, 6.2% vs. 22.6% in IM node and SC node involvement, respectively; adjusted HR [SC vs. IM], 8.72; 95% CI, 1.81-50.13; $P = .007$) and for distant metastases (cumulative incidence at 5 years: 6.7% vs. 32.9% in IM and SC node involvement, respectively; adjusted HR [SC vs. IM], 4.03; 95% CI, 1.10-14.73; $P = .001$).

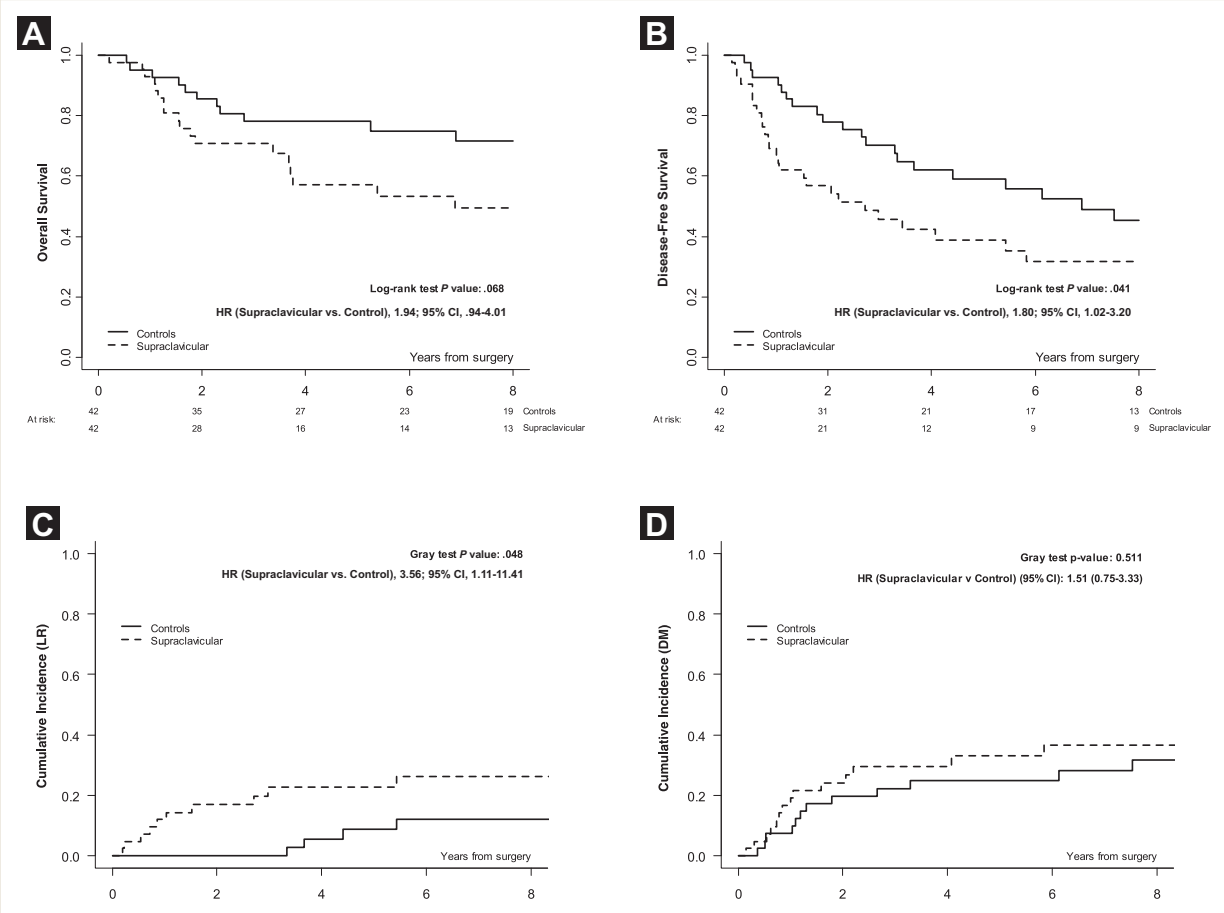
The comparison of the outcome between patients with IM lymph node involvement and the matched cohort of patients without IM lymph node involvement did not show any statistically significant difference in OS (5-year OS, 96.9% vs. 93.5%; $P = .897$), DFS (5-year DFS, 84% vs. 76.5%; $P = .729$), locoregional recurrences (cumulative incidence at 5 years, 6.2% vs. 5.1%; $P = .801$), or distant metastases (cumulative incidence at 5 years, 6.7% vs. 12.8%; $P = .423$) (Fig. 2).

Conversely, the comparison between patients with SC lymph node involvement and the matched cohort of patients without SC lymph node involvement showed a statistically significant difference in DFS (5-year DFS, 38.8% vs. 58.9%; $P = .041$) and locoregional recurrences (cumulative incidence at 5 years, 22.6% vs. 8.6%; $P = .048$), with a trend to different OS (5-year OS, 57.1% vs. 78%; $P = .068$) and cumulative incidence of distant metastases (cumulative incidence at 5 years, 32.9% vs. 24.9%; $P = .511$), which did not reach statistical significance (Fig. 3).

Discussion

The results of available trials raise a number of questions about the more appropriate treatment of patients with locally advanced breast cancer and either IM node or SC lymph node involvement. Radical mastectomy does not include removal of IM lymph nodes, which are the site of occult metastases in 20% of cases. Removal of IM lymph nodes has not been shown to improve prognosis. Postoperative radiotherapy to the IM chain is still controversial, as it is the prognostic significance of the involvement of IM lymph nodes.

Figure 3 (A) Overall Survival (OS), (B) Disease-Free Survival (DFS), (C) Cumulative Incidence of Local or Regional (LR) Recurrence, and (D) Cumulative Incidence of Distant Metastases (DM) in Patients With Breast Cancer Presenting With Ipsilateral Supraclavicular (SC) Lymph Node Metastases and a Matched Control Group. Univariate log-Rank Test *P* Values and Hazard Ratios (HRs) (SC vs. Control) are Reported



Abbreviation: CI = confidence interval.

We found a statistically significant difference in outcomes of patients with SC node and IM lymph node involvement, with the former having poorer DFS, OS, and cumulative incidence of both locoregional recurrences and distant metastases than the latter.

In a subsequent analysis based on matched cohorts, patients with IM lymph node involvement did not show any significant difference in DFS, OS, locoregional recurrences, or distant metastases compared with their matched cohort of patients without IM node involvement. Conversely, a significantly worse DFS and increased risk of locoregional recurrences were found in patients with SC lymph node involvement compared with their matched cohort of patients without SC lymph node involvement, with a trend to worse OS and a cumulative incidence of distant metastases in the former group.

In the randomized trial of mastectomy with or without IM node dissection conducted between 1963 and 1966, 5-year survival was the same in both groups—equal to 70%.[4] In the analysis carried out by Veronesi et al in 1985, 5-year survival was approximately 76.0% in patients with negative axillary lymph nodes and positive IM nodes and 50.0% in patients with both nodal sites involved.[7] In our analysis, 5-year survival was 96.9% in patients with IM lymph node involvement. As for SC lymph node involvement, 5-year survival was 41% in the series treated at the MD Anderson Cancer Center,[9] whereas we found a 5-year survival of 57.1% in patients with SC lymph node involvement. The improvement of OS over years of treating patients with locally advanced breast cancer and involvement of IM and SC lymph nodes might well be the result of the more tailored systemic treatments that have been available in recent years (including adjuvant endocrine treatments with tamoxifen; luteinizing hormone–releasing hormone analogues or aromatase inhibitors; adjuvant chemotherapy with anthracyclines and taxanes; anti-HER2 adjuvant treatment with trastuzumab), and possibly radiotherapy to the IM chain and to the SC fossa.

SC lymph nodes as well as IM nodes are part of a continuum in the regional lymphatic drainage of the breast. Axillary lymph nodes levels 1 to 3, SC lymph nodes, and IM nodes are not separated on the basis of functional differences but according to arbitrary anatomical boundaries.

In our study, SC lymph node involvement correlated with a significantly poorer outcome in patients with locally advanced breast cancer. Adequate staging, including biopsy of suspicious locoregional (IM or SC) ipsilateral lymph nodes, is mandatory in these patients because it may affect treatment.[7] Lymph node biopsy of both SC and IM nodes is a simple and safe procedure that provides useful information to apply to targeted radiotherapy in selected cases.

Moreover, based on our results, we endorse the recommendation to treat patients with either IM or SC lymph node involvement with curative intent using combined-modality therapy (surgery, radiotherapy, chemotherapy, hormonal therapy in women with ER^+ tumors, and anti-HER2 therapy in women with HER2 overexpressed/amplified tumors).[9] Such treatments provide these patients with the maximum chance of long-term DFS and OS.

Clinical Practice Points

- Prognostic implications of internal mammary (IM) and supraclavicular (SC) node involvement in locally advanced breast cancer is still unclear, and therapeutic choices in cases where IM and /or SC lymph nodes are involved are still not uniformly defined.
- We evaluated 107 patients with IM or SC node involvement, and a matched cohort of patients as controls. Five-year disease-free survival (DFS) was 84% in IM vs. 38.8% in SC node involvement ($P < .0001$), and 5-year overall survival (OS) was 96.9% in IM node vs. 57.1% in SC node involvement ($P < .0001$). No outcome differences were found between patients with and controls without IM node involvement, whereas a statistically significant difference in DFS and locoregional recurrence was observed in patients with compared with controls without SC node involvement.
- Adequate staging, including biopsy of suspicious loco-regional ipsilateral lymph nodes, is mandatory in these patients. Patients with IM or SC node involvement should be treated with curative intent using combined-modality treatments.

Disclosure

The authors have stated that they have no conflicts of interest.

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