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Internal Mammary Node Status: A Major Prognosticator in Axillary Node-Negative Breast Cancer

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Background: The internal mammary lymph nodes (IMN) have received little attention in recent years, yet are a well-documented site of metastasis and a major prognostic factor in early-stage breast cancer.
Methods/Results: Ten-year follow-up of the final 195 patients treated by extended radical mastectomy (ERM) in this practice (selected largely on the basis of medial tumor location, and comprising 15% of all patients treated from 1965 to 1978) found IMN+ in 24% of all cases: 36% of AX+ versus 18% of AX− patients ($p = 0.0023$). In a multivariate analysis, the disease-free survival impact of IMN+ ($p = 0.004$) was second only to axillary node involvement ($p < 0.0005$), and surpassed tumor size ($p = 0.077$). IMN+ was equally frequent for tumors less than, or greater than, 2 cm (24%), and was not significantly related to patient age. Among AX− patients, there was a twofold greater risk of recurrence or death at 10 years for IMN+ than for IMN−. Among T1N0 patients, 19.6% were IMN+.
Conclusions: Failure to consider IMN status in the steadily enlarging cohort of T1N0 breast cancers may result in the undertreatment of a significant proportion of stage I patients. Systemic adjuvant therapy should be considered for T1N0 patients with central or medial tumors.
Key Words: Breast cancer—Metastasis, internal mammary and axillary—Prognosis.

The internal mammary lymph nodes (IMN) are a well-documented site of metastasis in primary carcinoma of the breast, yet in an era that conceptualizes breast cancer as a systemic disease from the outset, concern about the significance of IMN involvement has faded. The proportion of axillary node-negative breast cancers has increased, as has the intensity of the search for prognostic factors to define high-risk subsets of node-negative patients who might benefit from systemic adjuvant treatment. During the last decade, whether in clinical trials or routine practice, the IMN have been virtually ignored in this pursuit. This article presents 10-year results of the final group of patients to be treated in our practice by extended radical mastectomy (ERM), with particular attention to patterns of IMN involvement and prognostic impact in patients with negative axillary nodes.

PATIENTS AND METHODS

Between 1965 and 1978, 1,288 patients with invasive primary operable breast cancer were treated by the senior author (JAU) on the Breast Service at Memorial Sloan-Kettering Cancer Center, and were the basis of an earlier report (1). All had either radical (RM), modified radical (MRM) or extended radical (ERM) mastectomies: This study reports in de-

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tail on the 195 patients (15% of the total) who had ERM.

All patients were judged operable on clinical grounds, the only exclusions being supraclavicular or distant metastases, arm edema, inflammatory carcinoma, or medical contraindications to general anesthesia. Operative technique was as previously described, using an incontinuity intrapleural technique for IMN resection (2). All patients had full axillary dissections and pathologic specimens were examined without special nodal "clearing" techniques. Patients were staged both clinically and pathologically, by the 1983 American Joint Committee on Cancer (AJC) classification (3). Median length of follow-up was 10.3 years, and was complete at 5 years in 97% and at 10 years in 93% of all patients.

STATISTICAL METHODS

All statistical analyses were done using BMDP programs (BMDP Statistical Software, Los Angeles, CA, USA,1988 release). Overall and disease-free survival used the life table method (BMDP 1L), censoring patients dying cancer-free but considering deaths of unknown cause to be cancer related. Survival differences were tested by the log rank method (BMDP 1L), group means compared by t tests (BMDP 3D), and correlations among categorical variables by the Pearson χ^2 test (BMDP 4F). Multivariate analysis for covariates of survival used the Cox proportional hazards model, with stepwise regression by the maximized partial likelihood ratio method (BMDP 2L). Stepwise logistic regression (BMDP LR) was used to test the dependence of IMN involvement on age, tumor size, and axillary nodal status (4).

RESULTS

ERM was used with decreasing frequency during the period studied, from 21% (1965–1970) to 10% (1975–1978) of all operations, and was done selectively in patients with larger, more centrally/medially located tumors (Table 1) in an effort to maximize the frequency of IMN involvement. Nevertheless, 42% had T1 (2 cm or less) tumors and 61% had pathologically negative axillary nodes. Postoperative radiotherapy was given to most node-positive patients, and only six patients received systemic adjuvant chemotherapy (three with 1-3 N+, and six with >3 N+), starting in 1975.

TABLE 1. *Patient characteristics (n = 195)*

Mean age (yrs)		50.5 (range 26–76)	
Tumor location (%)			
UOQ		8.2	
LOQ		2.6	
UIQ		59.0	
LIQ		20.2	
Central		10.2	
Tumor size (pathologic) (cm)			
Mean		2.7	
Median		2.5	
Range		0.5–8.0	
Tumor size distribution (cm)			
0–1		8%	
1–2		34%	
2–3		34%	
3–4		13%	
4–5		5%	
>5		6%	
Tumor type			
Invasive duct[a]		93%	
Invasive lobular		7%	
Clinical node status			
Negative		75.4%	
Positive		24.6%	
Axillary node status (by highest level+)			
Neg		61%	
I+		21%	
II+		9%	
III+		9%	
AJC stage	I	II	III
Clinical	40%	53%	7%
Pathologic	28%	65%	7%
Postoperative rt.	No 66%		
	Yes 34%		
Postoperative chemo.	No 95%		
	Yes 5% (1975–1978 only)		

UOQ, upper outer quadrant; LOQ, lower outer quadrant; UIQ, upper inner quadrant; LIQ, lower inner quadrant; central, central quadrant.

[a] Includes 3% medullary, colloid, tubular.

Table 2 presents survival by axillary node status. Ten- year disease-free survivals exceed 50% in all groups of node-positive patients except the 17 with level III involvement: 11.8%. Table 3 lists survival by axillary and IMN status, and demonstrates

TABLE 2. *Extended radical mastectomy survival by axillary node status*

	5-yr		10-yr	
	Overall %	NED %	Overall %	NED %
Node − (n = 120)	85.6	78.5	77.4	70.6
Node + (n = 75)	75.9	59.6	65.5	52.9
I+ (n = 41)	84.6	69.2	71.1	62.7
II+ (n = 17)	93.8	81.3	93.8	73.5
III+ (n = 17)	38.6	17.7	25.8	11.8
Total (n = 195)	81.9	71.3	72.8	63.9

NED, no evidence of disease.

TABLE 3. *Extended radical mastectomy survival by axillary and internal mammary node status*

	5-yr		10-yr	
	Overall	NED	Overall	NED
AX−/IM− (n = 98)	88.8	81.6	81.3	74.4
AX−/IM+ (n = 22)	70.2	65.9	58.5	53.9
AX+/IM− (n = 48)	86.1	67.8	73.4	59.3
AX+/IM+ (n = 27)	61.1	46.2	53.0	41.8

NED, no evidence of disease.

equivalent survivals among patients with AX+/IM− and AX−/IM+, and an excellent 10-year NED survival of 41.8% for the 27 patients with AX+/IM+. Local recurrence as the first sign of treatment failure was 1%. An additional 2.6% of patients had local recurrence coincident with or subsequent to the development of distant metastases.

Table 4 demonstrates that in multivariate analysis, axillary node involvement is the strongest predictor of disease-free survival, followed closely by IMN status, and then by tumor size.

In Table 5, age, tumor size, and axillary node status are examined individually for the risk of IMN metastasis. The apparent trend to less frequent IMN metastases in older patients is not significant. IMN metastases were equally frequent in patients with tumors 2 cm or less (26%) and >2 cm (26%). IMN metastases were significantly more frequent in patients with AX+ than AX−: 36% versus 18%, p = 0.0023.

TABLE 5. *Internal mammary lymph node (IMN) status by age, tumor size, and axillary node status (considered separately)*

	No. IMN+/total	% IMN+
Age (yrs)		
<40	9/26	35
41–60	35/144	24
>60	5/25	20
t size (cm)[a]		
0–1	5/14	36
1–2	15/63	24
2–3	12/64	19 (2–3 vs. 3–4, p = 0.037)
3–4	10/25	40
4–5	3/10	30
>5	4/12	33
Ax. node negative	22/120	18 (vs. ax. pos., p = 0.0023)
Ax. node positive	27/75	36
Level I+	14/41	34 (vs. ax. neg., p = 0.027)
Level II+	6/17	35
Level III+	8/17	47 (vs. ax. neg., p = 0.0067)
Total patients	47/195	24

[a] t size indeterminate in seven patients.

TABLE 4. *Determinants of extended radical mastectomy no-evidence-of-disease survival*

	χ^2	p
Univariate		
Ax. node status (path.)	13.5	0.0002
i.m. node status	10.7	0.0011
Tumor size	6.72	0.0095
Ax. node status (clinical)	5.13	0.023
Tumor location	2.01	0.016
Age	0.36	0.55
Multivariate		
Ax. node status (path.)	13.5	<0.0005
i.m. node involvement	8.1	0.004
Tumor size	3.1	0.077

Table 6 considers the above variables simultaneously, demonstrating IMN+ in 14–25% of AX− and 20–71% of AX+ patients. In the AX+ group, IMN appear more frequently involved in younger patients, but not significantly so.

Table 7 separates patients by axillary node status and within each group shows comparable rates of IMN+ for all size groupings, and no significant trends.

After adjusting for axillary node involvement, patient age and tumor size added no statistically significant value in predicting IMN status for any of the above groupings of patients.

DISCUSSION

Handley and Thackray began in 1947 the first systematic biopsy study of the IMN in breast cancer patients, finding IMN+ in 4 of 5 unselected cases in their first report (5), and in 22.3% of 1,000 patients

TABLE 6. *Internal mammary lymph node (IMN) involvement by age, tumor size, and axillary node status*

Age (yrs)	t size (cm)	IMN+/total	IMN+ %	Milan IMN+ % (23)
Axillary node negative				
<40	>2	2/8	25	16.3
<40	<2	1/7	14	12.6
41–60	>2	6/42	14	10.9
41–60	<2	9/43	21	8.3
>60	>2	2/9	22	8.5
>60	<2	1/6	17	6.4
Axillary node positive				
<40	>2	5/7	71	41.2
<40	<2	1/2	50	34.1
41–60	>2	13/40	33	33.2
41–60	<2	7/15	47	26.8
>60	>2	1/5	20	24.9
>60	<2	1/4	25	19.7

TABLE 7. *Internal mammary lymph node (IMN) involvement by tumor size and axillary node status*

Tumor size (cm)	No. IMN+/total	IMN+ %
Axilla negative		
0–1	4/12	33
1–2	7/44	16
2–3	4/39	10
3–4	3/12	25
4–5	1/4	25
>5	2/4	50
Total axilla negative	21/115 (t size indeterminate in 5 patients)	18
Axilla positive		
0–1	1/2	50
1–2	8/19	42
2–3	8/25	32
3–4	7/13	54
4–5	2/6	33
>5	2/8	38
Total axilla positive	28/73 (t size indeterminate in 2 patients)	38

reported in 1975 (6). The IMN were consistently more often positive with medial/central than with lateral tumors, and with positive than with negative axillary nodes. The results of an international prospective randomized trial comparing RM and ERM in 1,453 (7) patients, as well as the separately reported Milan subset of that trial (8), were quite similar (Table 8). Of note, ~10% of AX− patients had IMN+, versus 18% in the present study.

The role of local treatment

Over the last 2 decades, interest in local treatment to the IMN (always a controversial topic) has faded. Although patients with untreated IMN metastases have a dismal prognosis (9), the benefit of IMN treatment by either radiotherapy or surgery has been difficult to prove.

Although both the Oslo (10) and Stockholm (11) randomized trials of perioperative IMN radiotherapy demonstrated a survival advantage in treated patients, a recent meta-analysis of all such prospective randomized trials (n = 7,941) (12) found no 10-year survival advantage, and an excess mortality beyond 10 years in the irradiated patients.

Similarly, the major surgical trial of IMN treatment comparing ERM with RM (1,453 patients treated at four institutions reported at 5 (7) and at 10 (13) years) found no overall or disease-free survival advantage for ERM. A subset of 192 patients with AX+ and inner quadrant tumors had better survival with ERM, an advantage also seen in a 15-year follow-up report of the comparable Institut Gustave Roussy patients (n = 243) (14). Although the statistical validity of small subset analyses is of course open to question, this group was likeliest to be IMN+, and thus to benefit from treatment. In a detailed analysis of the Milan patients from the above trial (n = 737) (8), there was no 10-year survival advantage in any grouping of patients by tumor size, location, or axillary node status.

Despite the evidence from Ferguson's small randomized trial (n = 112) (15) and other large retrospective studies (n = 3,119) (16–18) suggesting a role in patients with medial tumors, ERM is no longer performed in this practice. Local treatment for the overwhelming majority of patients consists of either MRM or wide local excision, axillary dissection, and radiotherapy. Although the tangential-field irradiation given to the latter group rarely encompasses the IMN, parasternal recurrence after breast conservation has fortunately been rare (19).

TABLE 8. *Percent positive internal mammary lymph nodes by axillary node status and tumor location in other series*

	Medial/ central	Lateral	Total
Axilla negative			
Handley (6) (n = 465)	10.6	4.3	7.7
Lacour et al. (7) (n = 605)	10.4	7.9	9.1
Veronesi and Valagussa (8) (n = 161)	10.2	8.6	9.3
Axilla positive			
Handley (n = 535)	48.1	21.5	35.0
Lacour et al. (n = 786)	36.2	21.9	27.9
Veronesi and Valagussa (n = 181)	36.4	26.0	30.4
Total			
Handley (n = 1000)	29.9	13.9	22.3
Lacour (n = 1391)	24.1	16.2	19.7
Veronesi (n = 342)	24.1	17.7	20.5

Prognostic considerations

IMN metastases have historically been considered a grave prognostic sign, indicative of advanced disease. For Handley, patients found to be IMN+ received simple mastectomy and radiotherapy (6), whereas for Haagensen (20), IMN involvement was a sign of inoperability and primary radiotherapy was given. In fact, 10-year NED survivals for AX−/IMN+ patients are quite comparable to those of AX+/IM− patients, in the range of 50%, both in this study (Table 3) and others (17,18,21). Nevertheless, 10-year mortality is *doubled* in AX−/ IMN+ patients compared with those with all nodes negative. The importance of identifying for systemic adjuvant therapy this higher-risk group of patients was emphasized first by Morrow and Foster in 1981 (22) and later by Veronesi et al. (21,23), yet to date the IMN have received little attention, either as a prognosticator in AX− breast cancer or as a stratification variable in clinical trials.

To what degree does IMN involvement add to the prognostic information already gained from other variables, especially the axillary nodes? Both this study and that of Veronesi et al. (23) demonstrate a *highly significant ($p = 0.004$, $p = 0.002$) correlation of IMN status with NED survival after correcting for axillary node involvement.* In our data, IMN status outranked tumor size in survival impact (Table 4).

Granted its importance, can IMN status reliably be predicted short of surgical biopsy? The following are possibilities.

1. *Radiologic imaging:* Turner-Warwick's studies (24) with autoradiography demonstrated the presence and location of IMN, as did the subsequent experience of Osborne et al. (25) and others with lymphoscintigraphy, which has proven useful in planning radiotherapy. Although computed tomography and magnetic resonance imaging scans can image the IMN, to date there has been no study providing simultaneous histologic correlation with the results of noninvasive imaging in a large series of patients. The value of these techniques for predicting IMN metastases, particularly in AX− patients, remains unproven.

2. *Tumor location:* the studies of Haagensen (20), as well as those of Handley (6), Lacour et al. (7) and Veronesi et al. (8,21) (Table 8), all demonstrate more frequent IMN+ in patients with medial/central tumors (as, historically, did patterns of parasternal recurrence (26)). Medial tumor location was the most important variable governing selection of patients for ERM in this series.

3. *Tumor size:* IMN+ occurs often in patients with larger tumors, as high as 58% (for $T > 8$ cm (20) and $T > 7.5$ cm (27)). Over the smaller size ranges seen more typically today, IMN+ is less frequent: 16.3% ($T < 3$ cm) (20), 15.7% ($T < 2$ cm) (23), 14% ($T < 2.5$ cm) (26), and 26% (this study).

4. *Age:* The study by Veronesi et al. (23) is the only one to demonstrate a significant ($p = 0.006$) correlation of age with IMN+: 26.9% if <40 years versus 14% if >60 years. A similar trend in the present study is not statistically significant.

5. *Multivariate analyses:* The analysis of 1,085 ERM patients treated in Milan (23) proposed simultaneously considering (in order of importance) axillary node status, age, and tumor size in predicting IMN involvement: These findings are given alongside those of the present study in Table 6. Both confirm the importance of axillary node status in predicting IMN+, but our data demonstrate no additional value for age or tumor size. This discrepancy may be on the basis of the smaller sample size in our data and/or biases introduced by different patterns of patient selection.

Implications

The IMN in operable breast cancer are a prognosticator second only to axillary node status, yet are almost universally ignored in clinical trials and everyday practice. In fact, IMN status actually is of little concern in any patient for whom systemic adjuvant therapy is already planned. It is among T1N0 patients that knowledge of IMN status may be of increasing relevance, for the following reasons:

1. *T1N0 patients represent an ever-increasing proportion of all breast cancers.* Of (Surveillance, Epidemiology, End Results program) SEER patients, 23.1% (28) (1977–1982), and 44% of our own patients (1) (1975–1978) were pathologic stage I. This proportion has since become higher as a result of earlier diagnoses in the 1980s.

2. *Approximately 80% of T1N0 patients (and 90% for tumors <1 cm) are cured by local therapy alone* (29). Ten to 20% of these patients are actually IMN+ and would benefit from systemic adjuvant treatment, whereas the remainder are "truly node-negative" and, particularly for $T < 1$ cm, receive even less marginal benefit from chemotherapy or hormonal therapies.

3. *Small tumor size is no assurance of IMN negativity.* Like axillary nodes, which are positive for the smallest tumor sizes in ~20% of patients (1,28), IMN+ for the smallest tumors is ~10–20% (or in this series, selected for medial tumors, 4 of 12 patients with $T < 1$ cm, and 11 of 56 [19.6%] with $T < 2$ cm).

The therapeutic dilemma posed by the IMN is that the survival benefit of ERM in an era of ever-earlier diagnosis remains unproven (and probably unprovable), routine IMN biopsies may be both technically cumbersome and subject to sampling error, and the promise of noninvasive lymph node imaging has not yet been realized. Because the risk posed by unrecognized IMN involvement is overwhelmingly a systemic one, these data suggest that for T1N0 breast cancer patients, central or inner quadrant tumor location may be a valid indication for systemic adjuvant therapy.

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