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The Correlation Between the Spread of Metastases by Level in the Axillary Nodes and Disease-free Survival in Breast Cancer. A Multifactorial Analysis

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Abstract—*Axillary lymph nodes were separated from 492 radical or modified radical mastectomies for primary breast cancer and examined according to their anatomical level corresponding to their position along the theoretical pathway of lymph drainage from the breast. The patterns of metastasis and the relationship between metastatized levels and disease-free survival were investigated to see whether complete axillary dissection is necessary for the staging and the planning of adjuvant therapy in breast cancer.*

Progressive involvement from level I (proximal) to level III (distal) was found in 206 specimens (80.8% of tumors with axillary metastases), while discontinuous or "skip" metastases were present in 49 (19.2%), including 38 (14.9%) with positive nodes at level II or III but not at level I. "Skip" metastasis was more frequent when fewer than four nodes were positive, and not related to either the size of the primary tumor or its location.

The effect of age, menopausal status, tumor size, node status, number of positive nodes, anatomic level of axillary node involvement, estrogen and progesterone receptors, and adjuvant therapies on disease-free survival was evaluated using a multivariate proportional hazard model and life table analysis. This showed that disease-free survival was strongly related to the number of positive nodes ($P < 0.001$), tumor size ($P = 0.001$) and level of node involvement ($P = 0.01$) as independent prognostic factors. Moreover, the subset of patients with four or more positive nodes and involvements of level III had a higher risk of recurrence (25% recurrence-free patients 5 years after mastectomy).

The high frequency of "skip" metastases and the prognostic value of both the level of involvement and the number of metastatic nodes suggest that a complete axillary dissection is needed in the surgical management of breast cancer to obtain all the data useful in the planning of adjuvant therapy.

INTRODUCTION

THE PATHOLOGICAL status of the axillary lymph nodes is regarded as the most important prognostic factor in breast cancer [1–3].

It is widely accepted that the number of positive nodes is a highly reliable pointer to the risk of recurrence after mastectomy [4–6], whereas the clinical usefulness of a detailed analysis of the anatomical levels of node involvement is questioned. This had been thought to take place stepwise from the periphery to the apex [7–9]. Partial dissection, limited to the proximal nodes, was thus seen as an adequate staging procedure [10–12]. Discontinuous or "skip" metastases have since been demonstrated and the usefulness of complete dissection is now apparent [13–15].

In this paper, a positive relationship is described between the level of metastatic involvement and disease-free survival (DFS). The prognostic value of the level of involvement strongly suggests that the establishment of the pattern of such involvement is an essential prelude to the choice of the operation on the axilla.

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MATERIALS AND METHODS

Four hundred and ninety-two women subjected to radical or modified radical mastectomy for breast cancer at the Institute of Oncology, University of Turin, between October 1977 and August 1984 were studied.

All tumors were staged according to the TNM system. Eligible patients had: (a) histologic diagnosis of infiltrating breast carcinoma; (b) no evidence of distant metastases; (c) complete axillary node dissection. Patients with fixed nodes and/or macroscopic extranodal involvement of the surrounding tissues were not included in the study.

The surgeon labelled the levels in the operating room. Levels were referred to the pectoralis minor muscle on the intact specimen: level I (proximal)—nodes lateral to its lower border; level II (middle)—nodes between the lower and upper border, plus the interpectoral; level III (distal)—nodes medial to the upper border [7].

Routine histologic processing of axillary lymph nodes was performed by locating the stained nodes after a 24 hr fixation in Bouin's solution. At least three sections of each node were examined. This technique permits one to find a higher number of lymph nodes than the manual dissection of the fresh specimen and gives results comparable with fat tissue clearing [9].

After mastectomy, 293 patients were irradiated, 101 received chemotherapy (CMF, six courses), and 253 hormonal therapy (tamoxifen, 20 mg daily); adjuvant therapies were variously combined. The level of involvement was not taken into account in the planning of adjuvant treatments. Follow-up ranged from 20 to 102 months (mean 57).

All data were processed with BMDP series of computer programs elaborated by the Health Science Computing Facility, UCLA [16]. The Pearson chi-square test was used to look for association between pathological features and levels and metastasis pattern in $r \times c$ contingency tables as implemented in BMDP-4F. The effect of multiple variables on DFS was evaluated by a stepwise proportional hazard analysis. The association of possible prognostic factors with DFS was estimated in a multifactorial analysis, using Cox's proportional hazard survival regression models [17] (BMDP-2L). Recurrence curves were calculated from the product-limit estimate of Kaplan and Meier [18] and statistical significance between curves was assessed using the Mantel–Cox test [19] (BMDP-1L).

RESULTS

The clinical and pathological features of the 492 patients examined are listed in Table 1.

The distribution of metastatic nodes by level is shown in Table 2. Two hundred and thirty-seven patients had no axillary metastases (pN0), 255 had node involvement (pN1). In 206 patients (80.8% of pN1), involvement was continuous. "Skip" metastases were found in 49 patients (19.2% of pN1): 38 (14.9%) in level II and/or III but not in level I; 6 (2.4%) in level III only.

The level of involvement was strictly related to the number of positive nodes: level III was more frequently involved when ≥ 4 positive nodes were present. This correlation was highly significant ($P < 0.001$). By contrast, there was no correlation with tumor size (pT) or location (Table 3).

The number of metastatic nodes was related to the metastasis pattern. When only 1–3 nodes were positive, "skip" metastases were more frequent ($P = 0.017$). No correlation was found between tumor size or location and the incidence of "skip" metastases (Table 4).

The influence on DFS of the level of axillary involvement was investigated using a multifactorial analysis. Age, menopausal status, tumor size (pT), node status (pN), the number of positive nodes, estrogen and progesterone receptors, and adjuvant therapies were the other possible prognostic factors tested in the whole series of patients. The covariate "level of involvement" entered in the Cox's models with the number of the highest level involved irrespective of the pattern, continuous or discontinuous, of metastasation. In pN0 patients the value was 0 (zero).

As shown in Table 5, in the univariate analysis (step 0 of the multivariate analysis) tumor size, node status, the number of positive nodes and the level were highly significant prognostic variables. The prognostic value of a single factor is affected by other related parameters. In the subsequent steps of the multivariate analysis, the variables were examined jointly in a Cox regression model to determine their independent effects. The number of positive nodes ($P < 0.001$), pT ($P = 0.001$), and the level of involvement ($P = 0.01$) emerged as independent prognostic factors.

Multifactorial analysis was then performed on patients divided by number of positive nodes (1–3, ≥ 4), and two independent factors, tumor size and anatomic level, were tested. In patients with a moderate risk of recurrence (1–3 positive nodes), neither tumor size nor the level of involvement influenced DFS. In high-risk patients (≥ 4 positive nodes), both the level ($P = 0.004$) and the tumor size ($P = 0.018$) were of prognostic value (Table 6).

Life table analysis confirmed the multifactorial data. The recurrence curves of patients divided by number of positive nodes and highest level of involvement were compared. In moderate-risk patients, recurrence was not related to level (Fig. 1). By contrast, the recurrence curves of high-risk

Table 1. *Clinical and pathological features (No. of patients)*

			All patients	pN0 patients	pN1 patients
Age	Range (years)		27–90	28–84	27–90
	Mean		57.3	57.9	56.7
Menopausal status	Premenopausal		171	72	99
	Postmenopausal		321	165	156
Tumor size (pT)	pT1		216	123	93
	pT2		213	100	113
	pT3		6	2	4
	pT4		57	12	45
Node status (pN)	pN0		237	237	—
	pN1		255	—	255
No. of examined nodes	Level I:	range	4–36	4–36	6–35
		mean	8.9	8.4	9.4
	Level II:	range	3–27	3–24	3–27
		mean	5.7	5.3	5.1
	Level III:	range	1–19	1–18	1–19
		mean	3.0	2.8	3.2
	Total:	range	6–50	6–45	7–50
		mean	17.7	16.4	18.9
No. of positive nodes	Level I:	range	0–22	—	0–22
		mean	1.8	—	3.5
	Level II:	range	0–27	—	0–27
		mean	1.1	—	2.1
	Level III:	range	0–15	—	0–15
		mean	0.6	—	1.2
	Total:	range	0–44	—	0–44
		mean	3.4	—	6.6
Estrogen receptor	Range(fmol/mg)		0–681	0–570	0–681
	Mean		44.2	43.1	45.2
Progesterone receptor	Range(fmol/mg)		0–520	0–520	0–33
	Mean		5.5	6.1	4.9
Histotype (infiltrating carcinoma)	NOS		282	116	166
	Ductal		137	79	58
	Lobular		52	25	27
	Other		21	17	4
Tumor site (quadrants)	Outer		272	129	143
	Inner		106	52	54
	Central		114	56	58
Surgical treatment	Radical		434	202	232
	Modified radical		58	35	23
Adjuvant radiotherapy	Administered		293	75	218
	Not administered		199	162	37
Adjuvant chemotherapy	Administered		101	19	82
	Not administered		391	218	173
Adjuvant hormonal therapy	Administered		253	122	131
	Not administered		239	115	124

patients showed differences between involvement as far as level III (25% disease-free 5 years after mastectomy) and that confined to level I or II (80% and 67.5% disease-free at 5 years, respectively), as shown in Fig. 2. These differences were significant ($P = 0.022$ and $P = 0.042$, respectively).

The risk of recurrence in patients with ≥ 4 positive nodes and involvement up level III was thus extremely high.

DISCUSSION

Knowledge of the pathway of axillary lymph node metastasation conditions the extent of node dissection in the surgical management of breast cancer.

In our series, "skip" metastases were found in 19.2% of patients with axillary involvement, and 26.3% of patients with less than four positive nodes. These data are intermediate between the figures

Table 2. Distribution of level of axillary lymph node metastases

Levels with metastases	No. patients	% total patients	% patients with metastases
None	237	48.2	
Continuous metastases			
Level I only	86	17.5	33.7
Level I and II	71	14.4	27.8
Level I, II and III	49	10.0	19.2
Discontinuous metastases			
Level II only	23	4.7	9.0
Level III only	6	1.2	2.4
Level I and III	11	2.2	4.3
Level II and III	9	1.8	3.5

Table 3. Relationship between pathological features and level of axillary involvement (pN1 patients)

	Highest level involved (percentage of patients)			*P* value (Pearson chi-square)
	I	II	III	
No. of positive nodes				
1–3	55.9%	34.7%	9.3%	< 0.001
⩾ 4	14.6%	38.7%	46.7%	
Tumor size				
pT1	41.2%	33.3%	26.4%	
pT2	30.3%	39.5%	30.3%	0.28
pT3	30.1%	36.2%	33.7%	
pT4	27.3%	34.1%	38.6%	
Tumor site (quadrants)				
Outer	33.1%	38.7%	28.2%	
Inner	35.7%	40.5%	23.8%	0.85
Central	35.5%	32.3%	28.2%	

Table 4. Relationship between pathological features and metastasis pattern (pN1 patients)

	Pattern of metastasis		*P* value (Pearson chi-square)
	Continuous	Discontinuous	
No. of positive nodes			
1–3	73.7%	26.3%	0.017
⩾ 4	86.9%	13.1%	
Tumor size			
pT1	78.8%	21.2%	
pT2	79.8%	20.2%	0.70
pT3	88.3%	11.7%	
pT4	86.4%	13.6%	
Tumor site (quadrants)			
Outer	82.4%	17.6%	
Inner	82.3%	17.7%	0.44
Central	73.8%	26.2%	

reported by Rosen *et al.* 3.8% [9] and Smith 33% [13].

In most of the papers quoted, the division of axillary tissue in three levels was made by the surgeon in the operating room. Therefore, differences between the reported figures coud be due to the different techniques of node examination. The highest percentage of "skip" metastases is reported in the papers in which specimens were processed by manual dissection and only one or two sections of

Table 5. *Multifactorial analysis* (492 *patients*)

Univariate comparison of prognostic factors (step 0)	
Factors examined	*P* value
Age	NS*
Menopausal status	NS
Tumor size (pT)	0.001
Node status (pN)	0.001
No. of positive nodes	< 0.001
Estrogen receptor	NS
Progesterone receptor	NS
Level of axillary involvement	< 0.001
Adjuvant radiotherapy	NS
Adjuvant chemotherapy	NS
Adjuvant hormonal therapy	NS

Multivariate comparison of prognostic factors (final step of stepwise proportional hazard regression)	
Independent factors	*P* value
No. of positive nodes	< 0.001
Tumor size (pT)	0.001
Level of axillary involvement	0.01

NS = not significant ($P > 0.05$).

Table 6. *Multifactorial analysis of patients divided according to the number of positive nodes: factors affecting DFS (final step)*

Factors	*P* value 1–3 positive nodes	*P* value ⩾ 4 positive nodes
Tumor size (pT)	0.28	0.018
Level of axillary involvement	0.28	0.004

each node were examined microscopically [13, 15]. The clearing of the axillary fat yields a higher number of lymph nodes, but most of the additional nodes recovered do not contain metastases and this technique is not recommended as a practical procedure [20]. Nevertheless, in a research setting more accurate processing than by manual dissection is required.

As far as the surgical management of breast cancer is concerned, the finding that 14.9% of patients with axillary metastases had no level I involvement is more important, since dissection confined to this level would miss one node-positive case out of seven. Moreover, dissection to level II would miss the 2.4% of pN1 cases with level III involvement only. This incidence of uncorrect stagings is consistent with that reported by Davies *et al.* [14] and Pigott *et al.* [15]. In our opinion, it is high enough to make incomplete dissection unacceptable.

Multifactorial and life table analysis demonstrated that the number of positive nodes and the

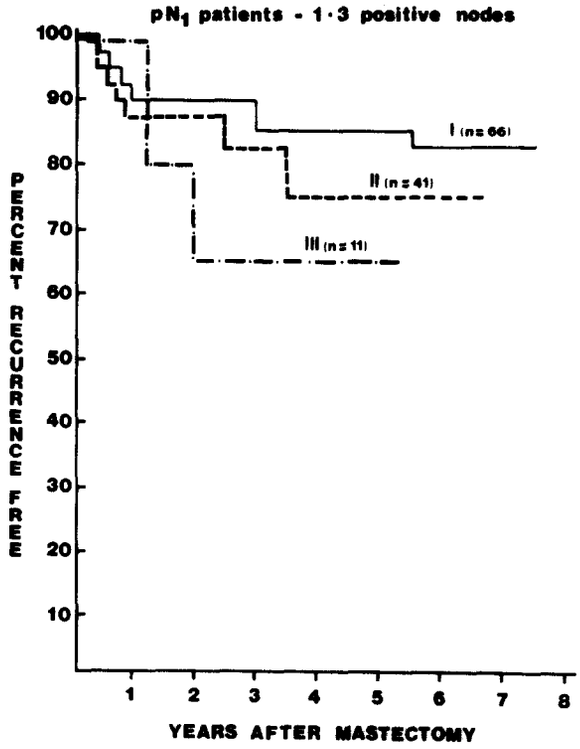

Fig. 1. *Recurrence curves of pN1 patients with* 1–3 *positive nodes, divided according to the highest level involved (I, II, III). the Mantel–Cox test indicates no significant difference between each pair of curves* ($P > 0.05$).

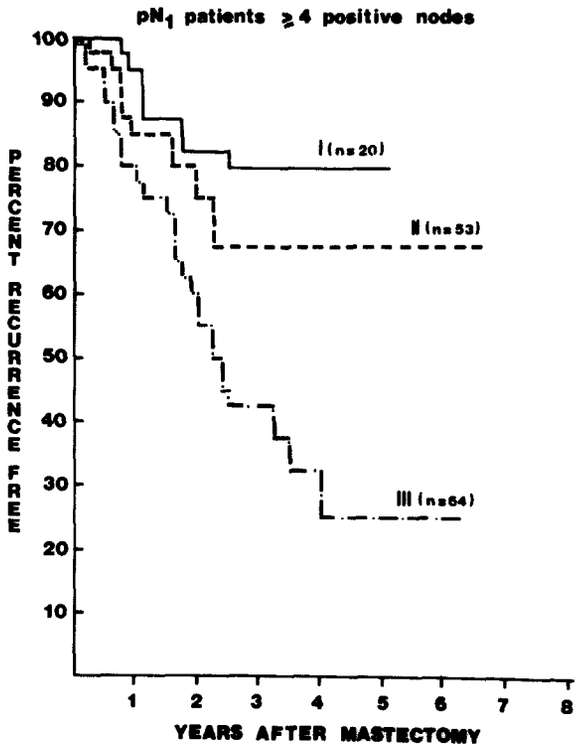

Fig. 2. *Recurrence curves of pN1 patients with* ⩾ 4 *positive nodes, divided according to the highest level involved (I, II, III). The Mantel–Cox test indicates a significant difference between I and III* ($P = 0.022$) *and II and III* ($P = 0.042$), *and no significant difference between I and II* ($P = 0.39$).

level of axillary involvement are independent prognostic factors. In detail, the subset of patients with ≥ 4 positive nodes and level III involvement had a significantly higher risk of recurrence than patients with the same number of positive nodes and level I or II involvement. These very high-risk patients are candidates for more aggressive adjuvant therapy.

The finding that partial dissection is not an adequate staging procedure suggests that the axilla must be thoroughly dissected in the correct staging of breast cancer. This suggestion is strengthened by the fact that both the number of positive nodes and the levels involved are prognostic factors and hence of assistance in the planning of adjuvant therapy.

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