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Original Paper

Selecting High-risk Early Breast Cancer Patients: What to Add to the Number of Metastatic Nodes?

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High-risk early breast cancer patients are usually identified by the number of metastatic axillary nodes. To study whether other easily and inexpensively detectable morphological factors are able to detect high-risk patients, we performed a retrospective analysis of tumour size, and skin/fascia and nipple invasion. The data consisted of 941 node-positive cases registered between 1978 and 1991. Tumour size, and skin/fascia and nipple invasion were closely associated with the number of metastatic nodes (χ^2 test). The number of metastatic nodes, tumour size, skin/fascia and nipple invasion significantly affected disease free survival (DFS) and overall survival (OS) at univariate analysis. These results were confirmed by multivariate analysis with a model containing the number of metastatic nodes, tumour diameter categories, skin/fascia invasion, nipple invasion and adjuvant therapy as covariates: all variables significantly and independently affected risk of relapse and of death. All the variables studied were prognostic, within individual nodal categories, for both DFS and OS. In conclusion, the number of metastatic nodes is not the only prognostic tool with which to select high-risk patients for new intensive adjuvant programmes. Tumour size, and skin/fascia invasion or nipple invasion, taken singly or combined, are valuable prognostic factors that can identify patients with few metastatic nodes and poor outcome. On the basis of our data, we believe that a reconsideration of the pT4 category within the pTNM classification is in order, that is, chest wall invasion should be substituted by fascia invasion, and combined skin/fascia invasion could be a subcategory of each class defined by tumour size.

Key words: early breast cancer, prognostic factors, lymph node metastasis, tumour size, skin invasion, fascia invasion, nipple invasion, pTNM
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INTRODUCTION

OVER THE last 10 years, retrospective analysis of prognostic factors in consecutive or selected breast cancer series has been primarily conducted with the aim of selecting node-negative cases with an unfavourable prognosis as candidates for adjuvant medical treatment. More recently, the goal for prognostic factor assessment has shifted to the identification of node-positive patients with a very high risk of relapse after primary surgical treatment. In fact, aggressive adjuvant strategies such as high-dose chemotherapy with haematological growth factor or stem cell transplantation support are now available for these patients [1]. Thus far, the only eligibility criterion of most trials on high-dose adjuvant chemotherapy is the number of metastatic nodes [2] but there is evidence that morphological evaluation of the primary tumour could provide additional prognostic information [3, 4]. A simple method that identifies node-positive, high-risk patients could be useful in selecting candidates for aggressive adjuvant strategies.

To establish whether pathological variables that reflect the degree of local invasion could help identify, among node-positive operable breast cancer patients, those with a high risk of recurrence or death, we conducted a retrospective analysis on the large database of the Division of Medical Oncology of the University of Naples "Federico II", focusing on tumour size, skin/fascia and nipple invasion. The aims of the study were: (a) to investigate the relationship between the variables studied and the number of metastatic nodes; (b) to determine their prognostic relevance in both disease free (DFS) and overall

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survival (OS) by univariate and multivariate analysis; and (c) to assess whether, by the use of these variables, it is possible to identify patients with a worse prognosis who could possibly be candidates for an aggressive adjuvant medical approach.

PATIENTS AND METHODS

From 1 January 1978 to 31 December 1991, 941 consecutive patients with node-positive breast cancer were referred to the Division of Medical Oncology at the School of Medicine of the University of Naples "Federico II" for medical treatment and follow-up. Adjuvant chemotherapy or tamoxifen were assigned according to the protocols of the University Group of Naples (GUN) randomised trials [5, 6]; patients not eligible for randomised trials were treated with adjuvant chemotherapy if premenopausal and tamoxifen if postmenopausal. Median age was 55 years (range 25–91). Patients had received radical or modified mastectomy or quadrantectomy with axillary nodal dissection at the Surgical Oncology Division; after quadrantectomy, they received irradiation of the residual gland. Slides from the surgical specimens were read at the Human Pathology Laboratory, Institute of Pathology.

The present retrospective analysis was performed by the operative unit of the Clinical Data Analysis Centre for Southern Italy, within the special project Clinical Applications of Oncological Research of the National Research Council (CNR-ACRO).

Seven variables for each case were used for this analysis: number of metastatic nodes (1–3, 4–9, 10 or more), histology (ductal, lobular, other), tumour size (≤2 cm, 2.1–5 cm, >5 cm), skin invasion (negative, positive), fascia invasion (negative, positive), nipple invasion (negative, positive), adjuvant medical treatment (no, yes). All pathological variables were defined during routine readings of standard stained sections. Nipple invasion was considered negative when nipple or areola slides were not available because of conservative surgery to spare the nipple/areola complex with tumour free resection margins. The frequency distribution of the studied variables is shown in Table 1. Skin and fascia invasion were combined in a single variable (both negative, one or two positive) because of their low prevalence; the combined skin/fascia variable was used for analysis. Relationships between variables were studied with contingency tables evaluated by χ^2 test.

Survival analyses were conducted as of 30 June 1994; the median follow-up was 60 months. The Kaplan–Meier product limit method [7] was used to estimate DFS and OS curves. The date of entry was defined as the date of surgery; DFS was defined as the time elapsed from the date of entry and the first event among local recurrence, contralateral breast tumour, distant metastasis and death without evidence of disease; OS was defined as the time elapsed from the date of entry and the date of death or the last follow-up date. Statistical significance of DFS and OS between groups of patients was assessed by the Mantel–Haenszel test [8]. Multivariate analysis to test the independent prognostic role of the covariates studied was performed with the Cox proportional hazard regression model [9]; covariates with k modalities ($k > 2$) were transformed into $k - 1$ dummy variables. The results are expressed as relative risk for each modality as compared with the basal modality of the same covariate; 95% confidence intervals (CI) have been calculated. All statistical analyses were performed using the BMDP statistical package (BMDP Statistical Software, Los Angeles, California, U.S.A.).

RESULTS

Tumour size, skin/fascia and nipple invasion were closely associated with the number of metastatic nodes, which is independent of the histological type (Table 2). In addition, skin/fascia invasion was closely correlated with nipple invasion ($P < 0.0001$) and both were correlated with tumour size ($P < 0.0001$ for both). They were unrelated to the histological type ($P = 0.81$ and $P = 0.68$, respectively), and histological type was also unrelated to tumour size ($P = 0.59$). The number

Table 1. Characteristics of patients

Variable	Number	%
Histological type		
ductal	750	79.7
lobular	94	10.0
other	97	10.3
Number of metastatic nodes		
1–3	453	48.2
4–9	261	27.7
10 or more	227	24.1
Tumour size*		
≤2 cm	248	27.2
2.1–5 cm	557	61.2
>5 cm	106	11.6
Skin invasion*		
negative	816	90.3
positive	88	9.7
Fascia invasion*		
negative	843	94.1
positive	53	5.9
Nipple invasion*		
negative	658	71.5
positive	262	28.5
Adjuvant systemic therapy		
no	79	8.4
yes	862	91.6

* Data not available for all patients.

Table 2. Correlation between studied variables and number of metastatic nodes

	Number of metastatic nodes			
	1–3	4–9	10 or more	
Variable	No. (%)			*P*
Histology				0.14
ductal	361 (48.7)	209 (28.2)	172 (23.2)	
lobular	36 (38.7)	28 (30.1)	29 (31.2)	
other	51 (54.3)	19 (20.2)	24 (25.5)	
Tumour size				<0.0001
≤2 cm	151 (62.7)	61 (25.3)	29 (12.0)	
2.1–5 cm	261 (47.2)	162 (29.3)	130 (23.5)	
>5 cm	25 (23.8)	24 (22.9)	56 (53.3)	
Skin/fascia invasion				0.0001
negative	385 (50.2)	214 (27.9)	168 (21.9)	
positive	39 (32.2)	36 (29.8)	46 (38.0)	
Nipple invasion				<0.0001
negative	346 (53.6)	172 (26.6)	128 (19.8)	
positive	88 (33.6)	77 (29.4)	97 (37.0)	

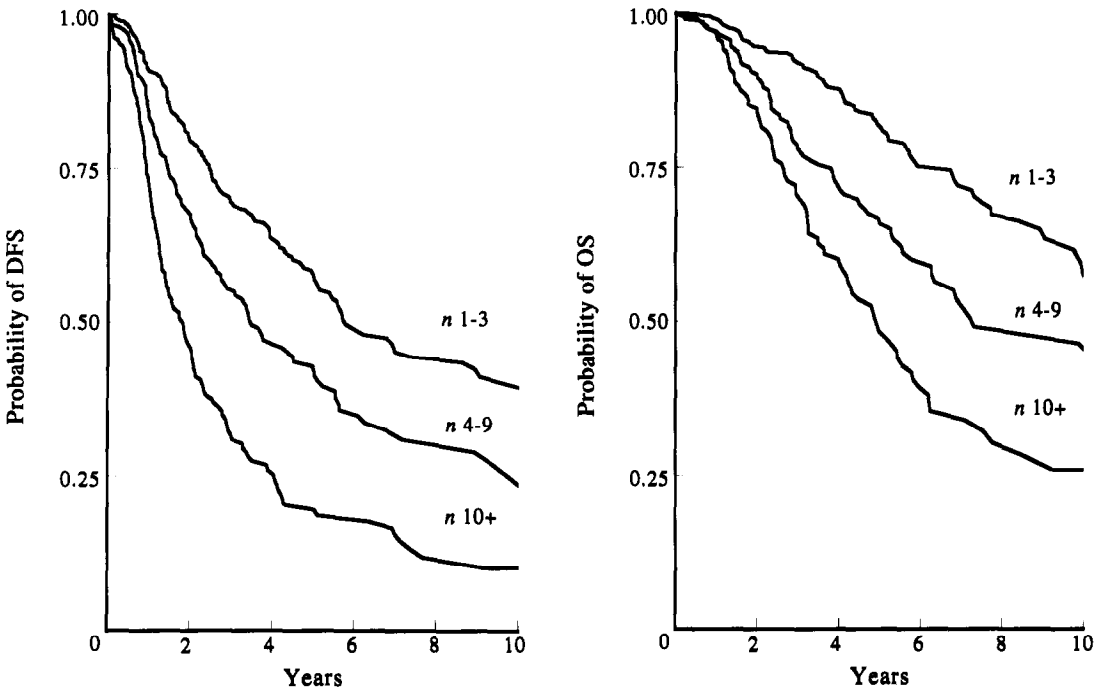

Figure 1. DFS and OS curves according to the number (*n*) of metastatic nodes.

of metastatic nodes, tumour size, skin/fascia and nipple invasion significantly affected DFS and OS in a univariate analysis (Figures 1–4). Histological type did not affect OS, but those with tumours other than ductal and lobular had a slightly better DFS (data not shown). These results were confirmed by multivariate analysis with a model whose covariates were the number of metastatic nodes, tumour diameter categories, skin/fascia invasion, nipple invasion and adjuvant therapy. All variables significantly and independently affected both risk of relapse and of death (Table 3).

The 5 year DFS and OS in subgroups formed by combining nodal categories with either tumour size categories or skin/fascia or nipple invasion are reported in Tables 4–6. All the *P* values for these stratified analyses were less than 0.0001. All the variables studied had a clear prognostic effect, within each nodal category, on both DFS and OS.

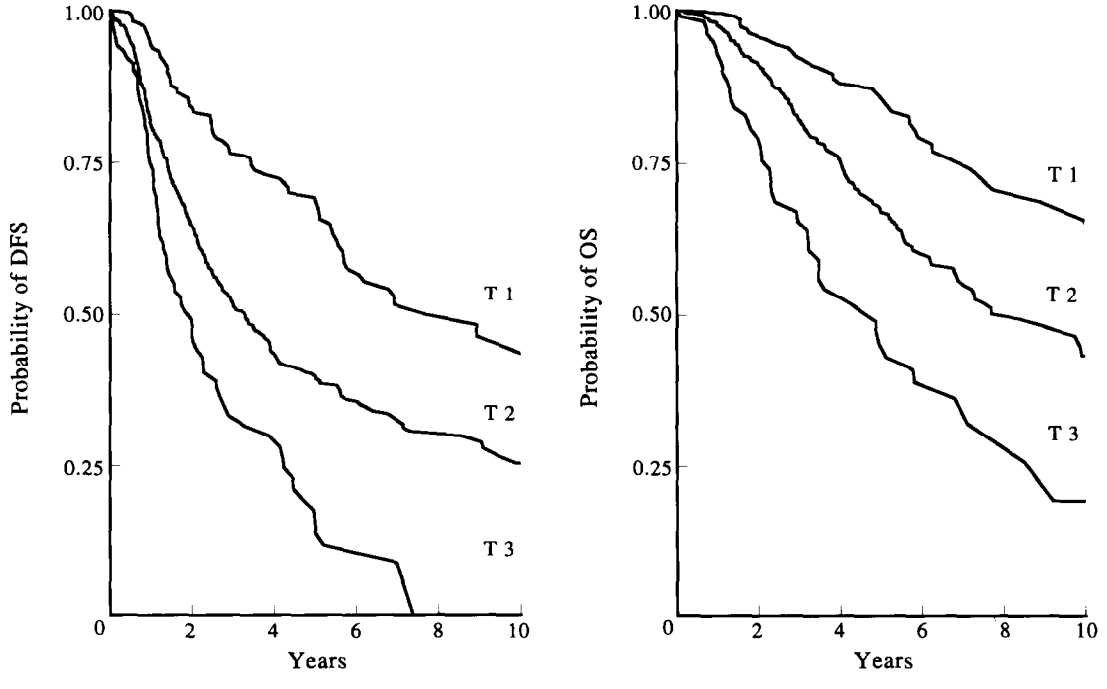

Figure 2. DFS and OS curves according to tumour size (T).

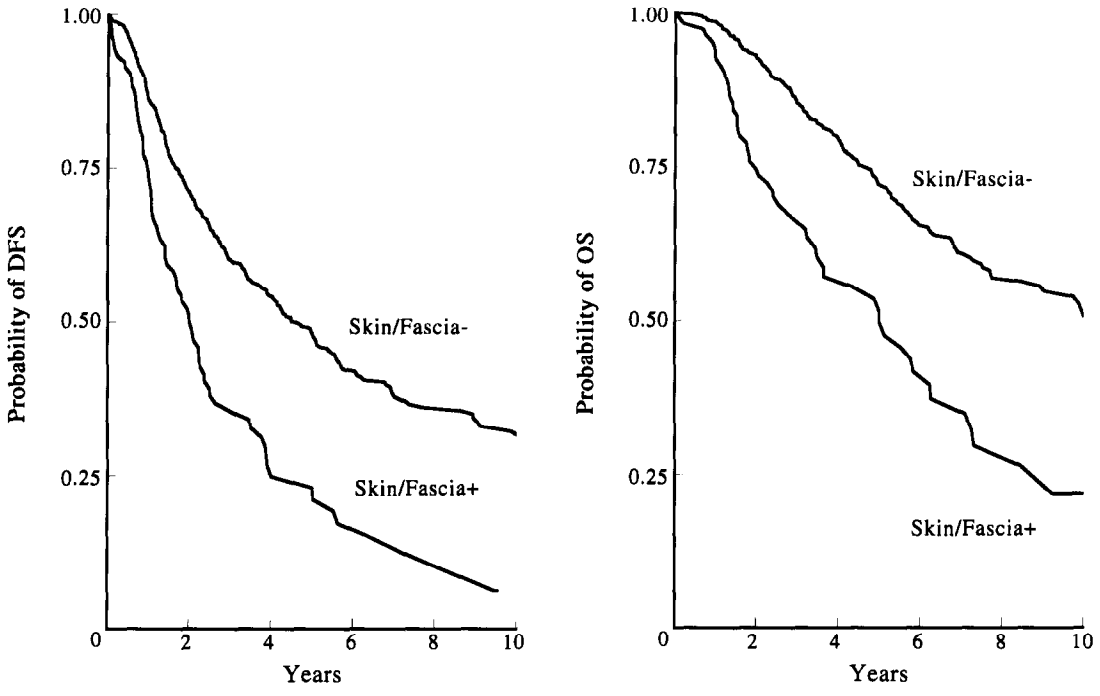

Figure 3. DFS and OS curves according to skin/fascia invasion.

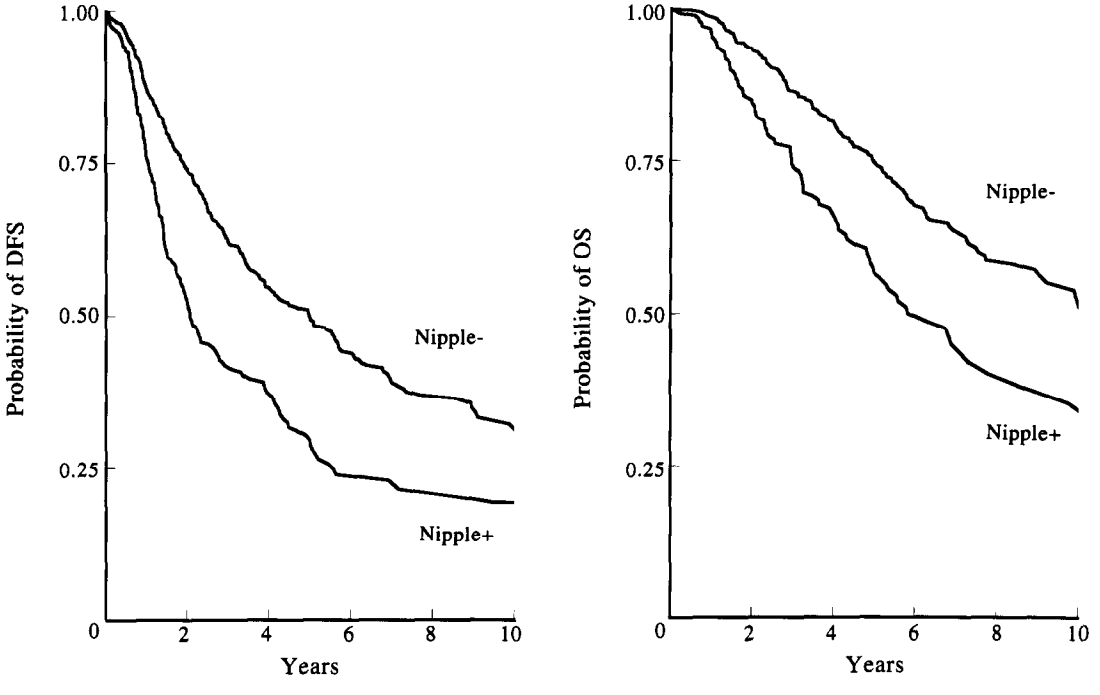

Figure 4. DFS and OS curves according to nipple invasion.

DISCUSSION

Morphological prognostic factors of breast cancer are easy to record and have a high degree of reproducibility; their evaluation adds neither manpower nor costs to routine practice. In addition, they are strong predictors of patient outcome. Paradoxically, they are not applied in clinical practice, the selection of patients for trials on new aggressive therapeutic strategies being based exclusively on the number of metastatic nodes. Tumour size and other local invasion variables play a role in planning the extent of surgery, but not in the decision-making process for postsurgical treatment. This strategy has some limitations. Indeed, integration of the number of metastatic nodes with several morphological parameters, routinely recorded by pathologists, may help to define subgroups of node-positive patients that have different risks of relapse or death.

We investigated the use of morphological variables that reflect local invasion to detect high-risk patients regardless of the number of metastatic nodes. Although these variables are strictly

Table 3. Multivariate analysis by Cox model

Variable	Relative risk (95% CI) Relapse	Death
Number of metastatic nodes		
4–9 vs 1–3	1.58 (1.24–2.01)	1.69 (1.21–2.35)
≥10 vs 1–3	2.42 (1.88–3.12)	2.38 (1.69–3.35)
Pathological tumour diameter		
2.1–5 cm vs ≤2 cm	1.74 (1.34–2.26)	1.68 (1.17–2.41)
>5 cm vs ≤2 cm	2.31 (1.61–3.33)	2.25 (1.38–3.65)
Skin/fascia invasion		
Yes vs No	1.39 (1.06–1.82)	1.44 (1.02–2.04)
Nipple invasion		
Yes vs No	1.36 (1.09–1.69)	1.44 (1.08–1.93)
Adjuvant systemic therapy		
Yes vs No	0.49 (0.37–0.66)	0.44 (0.31–0.63)

CI, confidence interval.

Table 4. Five-year DFS and OS according to number of metastatic nodes and tumour diameter

Nodal categories Tumour diameter	Patients at risk	Patients relapsed	DFS %	Patients dead	OS %
1–3 metastatic nodes					
≤2 cm	151	48	74	23	90
2.1–5 cm	261	108	54	49	82
>5 cm	25	14	38	6	68
4–9 metastatic nodes					
≤2 cm	61	20	71	9	91
2.1–5 cm	162	89	40	51	65
>5 cm	24	19	21	12	49
≥10 metastatic nodes					
≤2 cm	29	12	55	7	71
2.1–5 cm	130	92	25	48	60
>5 cm	56	41	20	30	46

Table 5. Five-year DFS and OS according to number of metastatic nodes and skin/fascia invasion

Nodal categories Skin/fascia invasion	Patients at risk	Patients relapsed	DFS %	Patients dead	OS %
1–3 metastatic nodes					
negative	385	114	63	67	86
positive	39	19	41	11	67
4–9 metastatic nodes					
negative	214	108	46	57	73
positive	36	22	41	15	56
≥10 metastatic nodes					
negative	168	104	32	62	59
positive	46	38	14	27	47

Table 6. Five-year DFS and OS according to number of metastatic nodes and nipple invasion

Nodal categories Nipple invasion	Patients at risk	Patients relapsed	DFS %	Patients dead	OS %
1–3 metastatic nodes					
negative	346	130	62	63	85
positive	88	39	53	16	82
4–9 metastatic nodes					
negative	172	84	50	43	76
positive	77	49	32	31	57
≥10 metastatic nodes					
negative	128	74	37	40	66
positive	97	78	15	50	46

associated with the presence and the number of metastatic nodes, and with each other, tumour size, skin/fascia and nipple invasion are independent variables predictive of patient outcome.

The strong prognostic role of tumour size observed in the present study, independent of the number of metastatic nodes, is consistent with results observed in several very large series: 24 740 breast cancer cases reported by Carter and associates [10] and 4034 cases reported by Ciatto and associates [3]. The pattern of prognosis according to tumour size within nodal categories found in our series is more regular and informative than in the series of node-positive patients of the B04 NSABP study [4], probably because of the higher number of cases in our series. We found that prognosis was related to tumour size when we applied our data to the unusual categorisation of tumour size (2 and 4 cm cutpoints) used by Fisher (data not shown). Interestingly, in addition to the possibility of selecting high-risk patients, within subgroups with fewer than 10 metastatic nodes, the outcome of patients with small (pT1) tumours, but with 10 or more metastatic nodes, is not worse than that of patients with fewer metastatic nodes but pT2 or pT3 primary tumours (Table 4).

The pTNM classification [11] combines, within the same variable, both the pathological diameter of the primary tumour (pT1, pT2 and pT3 categories) and the presence of chest wall (ribs or intercostal muscles or serratus anterior muscle) or skin invasion (pT4 category), independently of the size of the primary tumour. This kind of categorisation is clearly based on the belief that in a hypothetical prognostic graded scale, pT4 is worse than pT3. This was undoubtedly true some decades ago, when the "regional" (clinical evidence of chest wall or skin invasion) presentation pattern of breast cancer at diagnosis was as frequent as the localised one [12, 13]. Now, chest wall invasion, which is one of the two aspects of the pT4 category, is very rarely, if ever, seen in practice: none of the pT4 cases in the database at our Institution, from 1978, was due to chest wall invasion. Pectoralis fascia, which we combined with skin in a single variable, may be reasonably considered the deepest anatomical structure that can be found to be invaded by operable breast cancer. Thus, category pT4 is codified on the basis of microscopic skin invasion, usually not visible at clinical or mammographic examination. Consequently, "pT4" is not the worse variable in measuring tumour size. In addition, retrospective studies conducted on relatively recent series, show that the outcome of pT4 cases is identical to—rather than worse than—that of pT3 cases [3, 14]. Therefore, we propose that category pT4 (eventually combining

skin with fascia invasion) should integrate tumour size. However, skin/fascia invasion predicts an unfavourable outcome in all nodal subgroups (Table 5), the probability of DFS for positive cases being very poor. These patients should be candidate for the most aggressive available adjuvant strategies.

Different patterns of nipple invasion have been described [15, 16]. In our series, nipple involvement was defined *positive* independently of the type (stromal, ductal or both) of the nipple/areola complex invasion. A similar approach was probably adopted by pathologists of the NSABP, because in the 15 year survival analysis [4], they found nipple invasion in approximately 15% of more than 600 patients. However, considering that more than one-third of the B04 trial cases were node-negative, the prevalence of nipple invasion can be considered consistent with our sample. Interestingly, in the report of Fisher and associates [4], combined nipple invasion and tumour size, in addition to number of metastatic nodes, was the only variable that maintained a significant and independent prognostic power at multivariate analysis with seven other morphological variables derived from the primary tumour or the axillary nodes. Following this finding, the authors attempted to define prognostic subgroups by combining number of metastatic nodes and nipple invasion. However, due to the relatively small number of cases in some subsets, their conclusions as to the possible role of nipple invasion were not definitive. Our series compares very well with the B04 node-positive series: in each subgroup the number of cases in our series is 2–5 times greater than in the NSABP study. Although the 5 year overall survival in various subgroups was higher in our series, the "message" is essentially the same: patients with four to nine metastatic nodes and nipple invasion have a very poor outcome and should be considered for intensive adjuvant strategies.

In conclusion, two major considerations arise from the present study. Firstly, there is sufficient evidence to challenge the notion that the number of metastatic nodes is the only prognostic tool with which to select high-risk patients for new intensive adjuvant programmes. Other variables (tumour size, skin/fascia invasion or nipple invasion, taken singularly or combined) are equally powerful in identifying patients with few metastatic nodes and poor outcome. Secondly, the pTNM classification should be "revisited": the pT4 category seems no longer valid, either clinically or pathologically. Our data suggest that: (i) chest wall invasion should be substituted by fascia invasion; and, (ii) combined skin/fascia invasion should be a subcategory of each pTNM class defined by tumour size.

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