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Original Paper

Prognosis of Patients with Breast Cancers Up to 1 cm in Diameter

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The prognosis of patients with tumours measuring up to 1 cm diameter was examined. 336 patients treated at Guy's Hospital between 1975 and 1994 were reviewed. Of these, 103 (31%) were lymph node-positive, with approximately one third of these having one node involved, one third two to three nodes and one third four nodes or more. A similar proportion of those with palpable and impalpable tumours had axillary node involvement. Patients with axillary node involvement had a significantly worse prognosis and those node-positive patients with impalpable cancers had a significantly worse outcome compared with node-positive palpable cases. When patients were subdivided on a basis of nodal status and age (≤ 50 or > 50), node-positive women aged > 50 fared significantly better than younger women. These data suggest the need to know accurately the axillary nodal status of patients with small breast cancers, whether symptomatic or detected by screening. This knowledge will allow women with curable cancers to be identified together with those who have a worse prognosis and who will be likely to benefit from systemic adjuvant therapy.

Key words: breast cancer, small tumours, axilla, screening
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INTRODUCTION

In order to improve the prognosis of women with breast cancer, it has been assumed that earlier diagnosis will be effective since there is a correlation of tumour size with outcome. As further evidence of the value of early diagnosis, mammographic screening has been shown to save lives in women aged 50 or over [1–3]. Prognostic indices have been derived, based on tumour size, type and axillary nodal status, and all have indicated that tumours less than 1 cm in diameter carry a better prognosis [4, 5].

A series of 169 node-negative patients treated at the Breast Unit, Guy's Hospital, was studied and it was found that women with tumours up to 1 cm diameter had a prognosis similar to that of age matched controls without breast cancer, that is, they were cured of their disease by effective local treatment [6].

Because the incidence of axillary nodal involvement has been reported as infrequent in patients with tumours up to 1 cm, it has been argued that axillary dissection might be avoided in many of these cases [7]. However, others have suggested that the incidence of lymph node metastasis is not negligible in this particular group [8].

To address the important issue of axillary lymph node metastasis and its prognostic significance in patients with cancers up to 1 cm, a review has been conducted of 336 patients treated at the Breast Unit, Guy's Hospital, between 1975 and 1994.

PATIENTS AND METHODS

Between 1 January 1975 and 31 December 1994, there were 355 patients with invasive breast cancers 1 cm or less, measured clinically for palpable cancers and pathologically in those with impalpable lesions. These cases comprised 12% of the total group of those patients with breast cancer who were treated by either mastectomy or breast conservation therapy during this time.

There were 19 patients who were excluded because axillary nodal status was unknown, one treated by total mastectomy, the remainder having a wide local excision and tamoxifen because of their advanced age. Information was retrieved from the Clinical Oncology Database concerning both clinical and pathological features, together with follow-up status. All patients were seen every 3 months for the first 3 years after diagnosis, then 6 monthly for 2 years and thereafter annually.

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Table 1. Comparison of the histopathology of patients with palpable and impalpable cancers up to 1 cm diameter, according to axillary node status

	Palpable		Impalpable	
	Node-negative	Node-positive	Node-negative	Node-positive
Ductal grade I	18 (75%)	6 (25%)	14 (64%)	8 (36%)
Ductal grade II	55 (75%)	18 (25%)	31 (72%)	12 (28%)
Ductal grade III	28 (56%)	22 (44%)	7 (37%)	12 (63%)
Lobular	13 (59%)	9 (41%)	14 (82%)	3 (18%)
Tubular	6 (75%)	2 (25%)	4 (80%)	1 (20%)
Other	27	4	16	6
Total	147 (71%)	61 (29%)	86 (67%)	42 (33%)

Survival curves were calculated by the method of Kaplan and Meier [9], with significance being determined using the log-rank test [10]. Multivariate survival analysis was performed using Cox's proportional hazards model [11].

RESULTS

Of the 336 patients with tumours up to 1 cm, 128 (38%) had impalpable lesions. Of these, 81 (63%) were diagnosed since 1988, when cases from the National Health Service Breast Screening Programme (NHS BSP) started to be seen at Guy's Hospital. A comparison of the histopathology of the palpable and impalpable cases is given in Table 1. This shows a similar distribution of histological types in the palpable and impalpable groups. For patients with ductal grade I, II, lobular and tubular carcinomas, there were similar rates of axillary nodal involvement but for those with ductal grade III cancers, those with impalpable cancers were more likely to have nodal involvement, 63% versus 44%, although this did not achieve statistical significance ($P = 0.19$, Fisher exact test).

Table 2 shows the number of lymph nodes containing metastases in the histological subgroups. Overall, 44% of node-positive cases had one node involved, 32% had two or three nodes, and 24% had four or more axillary nodal metastases.

Both 10 year relapse-free survival (RFS) and overall survival (OS) for the subgroups of patients based on nodal status and palpability of tumour were calculated. As would be expected, there was a significantly better RFS and OS for node-negative compared with node-positive cases (80% versus 65% and 90% versus 60% respectively, $P < 0.001$, Table 3). There was no overall difference in RFS or OS for those with palpable and impalpable tumours. Similarly, when the subgroups with node-negative disease were compared, there was no difference between the cases with palpable cancers and those with impalpable tumours.

However, the 10 year overall survival of the group with palpable tumours and axillary node involvement was 73% compared with 41% for those with impalpable tumours and positive axillary nodes (chi square = 2.9, $P = 0.09$). When adjusted for histology, this difference became significant (chi square = 6.5, $P = 0.01$).

When the patients were subdivided by age (< 50 and ≥ 50), and nodal status (positive or negative), this revealed differences based upon age. Ten year relapse-free survival for node-negative cases aged ≥ 50 was 85% compared with 75% for node-negative women < 50 (chi square = 6.25, $P = 0.01$). For node-positive cases, the 10 year RFS was 60% for both ≥ 50 and < 50 groups (chi square = 0.03, $P = 0.86$). Figure 1 gives OS of the subgroups based on age.

Five variables were entered into the Cox multivariate analysis; pathological nodal status, histological tumour type, age, menstrual status and tumour size. Of these, histology and number of involved axillary nodes emerged as significant (chi-square = 32.7 and 11.6 respectively, $P < 0.0001$ and $P = 0.0007$). Significant prognostic variables for survival in node-negative cases were histological type and age (chi-square 15.6 and 3.9, $P < 0.0001$ and 0.05, respectively). For node-positive cases, the significant variables predicting survival were tumour

Table 2. Extent of nodal involvement in node-positive cases subdivided by tumour type and grade

Histology	One node	Two nodes	Three nodes	Four or more nodes
Ductal I	9	0	2	3
Ductal II	11	6	6	7
Ductal III	15	10	1	8
Lobular	4	2	2	4
Tubular	2	0	1	0
Other	4	0	3	3
Total	45 (44%)	18 (17%)	15 (15%)	25 (24%)

Table 3. Ten year relapse-free survival (RFS) and overall survival (OS) of subgroups of patients with tumours ≤ 1 cm

Group (*n*)	RFS (%)	*P*	OS (%)	*P*
Node-negative (233)	80		90	
		< 0.001		< 0.001
Node-positive (103)	65		68	
Palpable (147)	75		95	
		0.73		0.12
Impalpable (86)	75		90	
Palpable node-negative (147)	78		78	
		0.12		0.12
Impalpable node-negative (86)	95		95	
Palpable node-positive (61)	70		73	
		0.43		0.09
Impalpable node-positive (42)	40		43	

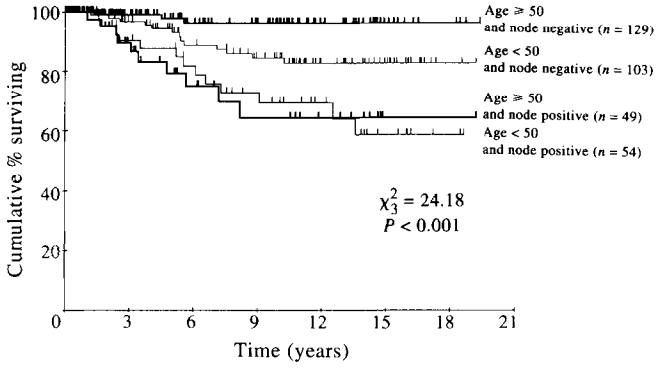

Figure 1. Overall survival of patients with tumours up to 1 cm in diameter by age and axillary nodal status.

type and impalpable tumour (chi-square 16.4 and 6.48, $P < 0.0001$ and $P = 0.01$).

DISCUSSION

This study has shown that among patients with the smallest detectable invasive breast cancer, identified by palpation or mammography, there is a relatively high incidence of axillary nodal metastases (31%) when a careful pathological examination is carried out. The percentage nodal positivity was similar in cases with either palpable and impalpable tumours (29% versus 33%). As well as the relatively high rate of nodal positivity, two or more nodes being involved in 56% of cases.

Axillary node involvement was associated with a significantly worse prognosis among patients with both palpable and impalpable lesions. Impalpable cases had a worse prognosis despite having better histological grades. Potentially, these would be the screen-detected cases with lymph node involvement. In the multivariate analysis of node-positive cases, the major determinants of survival were tumour type and impalpable tumour.

How robust is the finding that impalpable node-positive tumours have a worse prognosis? Very few (5) factors were included in the Cox proportional hazards model and all of these are recognised as being relevant to prognosis of breast cancer and would need inclusion and adjustment for anyway. The only multiple analyses performed were the two separate ones for node-positive and node-negative patients. Adjustment of the significance level for two subgroup analyses had the effect of changing the observed *P*-value from 0.01 to 0.02 [12]. Thus, this finding is still significant. The observed relative risk was 3.5, which is considerable, although the 95% confidence interval was 1.4 to 8.9, so it is likely that the effect is small but real.

Age had an important impact on prognosis of patients without axillary node involvement. There was a significantly better 10 year relapse-free and overall survival for those aged ≥ 50 compared with women < 50. This finding is consistent with our previous observation that timing of surgery in premenopausal patients had a significant impact on prognosis [13]. A recent meta-analysis confirmed that overall there was a significant effect with an advantage for women undergoing tumour excision in the luteal phase [14].

These data suggest that axillary surgery will continue to be necessary for screen-detected cancers until an accurate method of pre-operative imaging becomes available. Attempts to predict axillary nodal status by use of prognostic markers such as progesterone receptor status, DNA flow cytometry and S-phase fraction have proved unsuccessful [15, 16]. If axillary sampling is performed it is necessary that 10 nodes should be examined before it can be assumed that the axilla is truly negative [17, 18]. With a positive axilla, systemic adjuvant therapy is likely to be indicated. Thus, if axillary surgery is to be omitted when treating patients with small and screen-detected cancers, this should be carried out only within prospective clinical trials.

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