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Eur J Cancer, Vol. 28A, No. 8/9, pp. 1415–1418, 1992.
Printed in Great Britain
0964–1947/92 $5.00 + 0.00

Axillary Dissection of Level I and II Lymph Nodes is Important in Breast Cancer Classification

Christen K. Axelsson, Henning T. Mouridsen and Karin Zedeler, on behalf of The Danish Breast Cancer Cooperative Group (DBCG)

In order to define the term "a node-negative patient", the axillary nodal status at the primary operation for breast cancer was evaluated in 13851 patients registered by the Danish Breast Cancer Cooperative Group (DBCG). The determinants for node negativity in primary breast cancer were the number of lymph nodes removed and the tumour size. The number of lymph nodes removed should be at least 10 to exclude misclassification of node-positive patients as node negative. There was a strong relationship between tumour size and the percentage of node-negative patients. Another observation was that high rate of node negativity was associated with low histological grade. The age of the patients had no influence on node negativity. Where 10 or more negative lymph nodes were removed, significantly better axillary recurrence-free survival ($P < 0.0001$), over-all recurrence-free survival ($P < 0.0001$) and survival ($P < 0.005$) were found.
Eur J Cancer, Vol. 28A, No. 8/9, pp. 1415–1418, 1992.

INTRODUCTION

AXILLARY NODE negativity in primary breast cancer has paramount significance for staging of the disease, and thereby for the prognostic evaluation and the planning of the adjuvant treatment. But what is a "node-negative patient"? Usual definitions focus on the number of lymph nodes excised at operation exclusively, but there is no common agreement with respect to the desirable number of lymph nodes to remove [1]. Furthermore, the therapeutic aspect and the complications to axillary lymphadenectomy are still a topic for debate.

The present paper describes the experiences gathered in the register of The Danish Breast Cancer Cooperative Group (DBCG)—a nationwide programme for treatment of primary breast cancer.

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This paper was presented at the EORTC Breast Cancer Working Conference, 3–6 Sep. 1991, Leuven, Belgium.

MATERIALS AND METHODS

DBCG was established in 1976. The structure of the organisation and a detailed description of the inclusion into protocols has been given elsewhere [2].

Surgical treatment

The primary surgical treatment was total mastectomy or, in a minor proportion, breast conserving treatment. Both operations were performed in connection with a partial axillary dissection.

Postoperative treatment and follow-up

Patients with no evidence of distant metastases as evaluated by physical examination, X-ray of chest, and bone scintigraphy or X-ray of the central skeleton, entered prospective trials of adjuvant therapy and follow-up (the DBCG 77 and 82 programs) [2]. High risk patients (tumour > 5 cm, and/or positive nodes, and/or skin/fascia invasion) received adjuvant systemic therapy and/or radiotherapy. Low risk patients (tumour 5 cm, and negative nodes, and no skin/fascia invasion) were observed and received no adjuvant therapy.

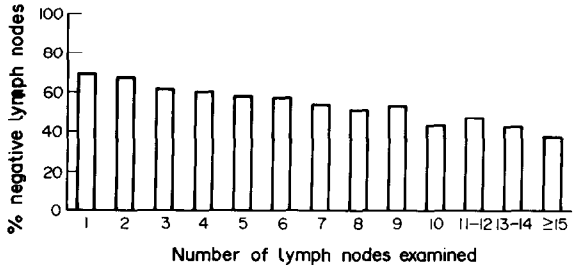

Fig. 1. The frequency of negative lymph nodes (%) in each group of patients classified according to the number of lymph nodes examined in the resected specimens (n = 13851)

Follow-up studies as described earlier [2] were continued for 10 years or until recurrence or death.

Patho-anatomical examination

Patho-anatomical examination was performed according to directions in the protocols. Briefly, the tumour diameter was recorded, lymph nodes were counted, and every lymph node was examined histologically for tumour spread. Serial sections to detect micrometastases were not performed as a routine. The tumour was classified according to the WHO classification.

Exclusions from the protocols

In the DBCG 77 and 82 protocols, patients were excluded if no nodes were demonstrated in the axillary specimen. In the DBCG 82 protocols, age ≥ 70 years excluded the patients from protocols. In order to have comparable results from the two programs, DBCG 77 and 82, patients from DBCG 77 ≥ 70 years of age were excluded in the following.

Statistics

Differences between groups were evaluated by means of the χ^2 test. The recurrence-free survival and crude survival were calculated by the life table method. The log-rank test was used for comparisons. All P values given are those for a 2-tailed test.

RESULTS

13851 patients < 70 years of age were included into the DBCG 77 and 82 programs. The inclusion into the low risk protocols DBCG 77 A and 82 A comprised 7145 patients. The median time of follow-up at the time of this analysis is 76 months.

A nearly linear relationship between the number of examined lymph nodes and the percentage of node negativity was observed steadily decreasing from about 70 (one node examined) to 45% (10 nodes examined). With more than 10 nodes examined approximately 45% node-negative patients remained (Fig. 1).

In the low risk patients (n = 7145), a highly significant correlation between number of nodes examined and axillary recurrence-free survival ($P < 0.0001$) (Fig. 2) was found. Likewise, the number of nodes examined was highly significantly correlated to over-all recurrence-free survival ($P < 0.0001$) (Fig. 3) and survival ($P < 0.009$) (Fig. 4). A comparison between groups revealed that where 10 or more lymph nodes were examined and negative, a significantly better axillary recurrence-free survival ($P < 0.0001$), over-all recurrence-free survival ($P < 0.0001$) and survival was found ($P < 0.005$) compared with groups with less than 10 nodes examined.

There was a strong relationship between tumour size and the percentage of node-negative patients (Fig. 5). If the tumour size

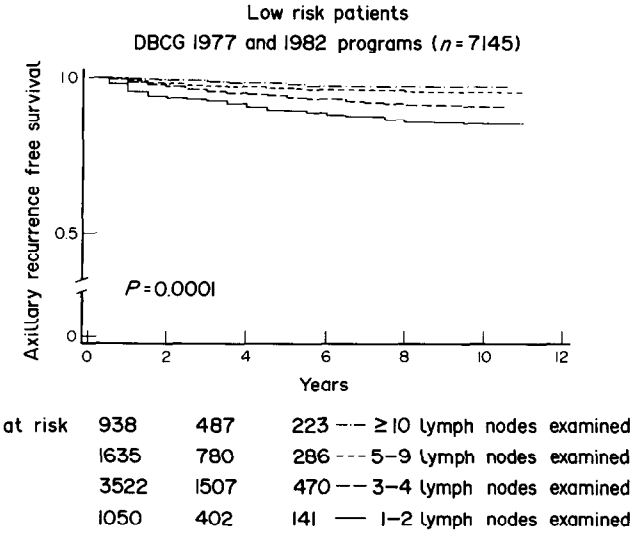

Fig. 2. Axillary recurrence-free survival in the DBCG low risk group of patients. Median observation time = 76 months. Difference between groups ≥ 10 nodes vs. < 10 lymph nodes examined: $P <$ 0.0001.

was less than 15 mm, there were 75% node-negative patients. A larger diameter was associated with decreasing node negativity. With a tumour diameter of 50 mm only 35% of the patients were node negative. From 1978–1982 the median tumour size was 30 mm, and from 1983–1990, 20 mm.

There was no relationship between age and tumour size, number of lymph nodes examined, and node negativity (Table 1).

Tumour grade influenced node negativity. The lowest grade of anaplasia was accompanied by the highest rate of node negativity (Table 2; $P < 0.0001$). Tumour grade was also correlated to tumour size (Table 3). A higher tumour grade was found when tumour size increased ($P < 0.0001$).

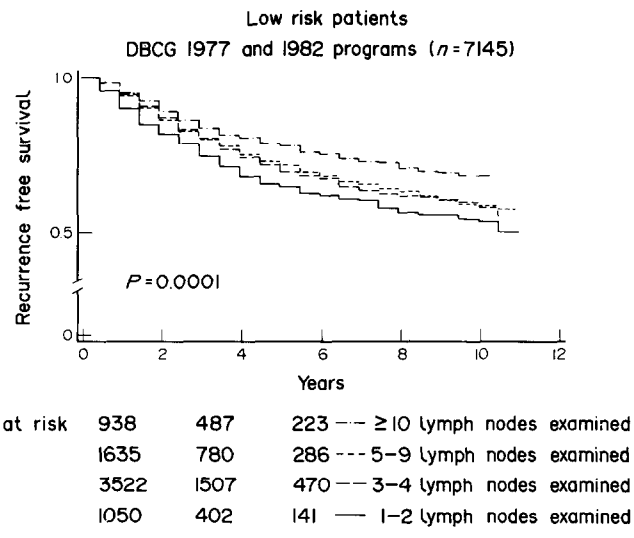

Fig. 3. Over-all recurrence-free survival in the DBCG low risk group of patients. Median observation time = 76 months. Difference between groups ≥ 10 nodes vs. < 10 lymph nodes examined: $P <$ 0.0001.

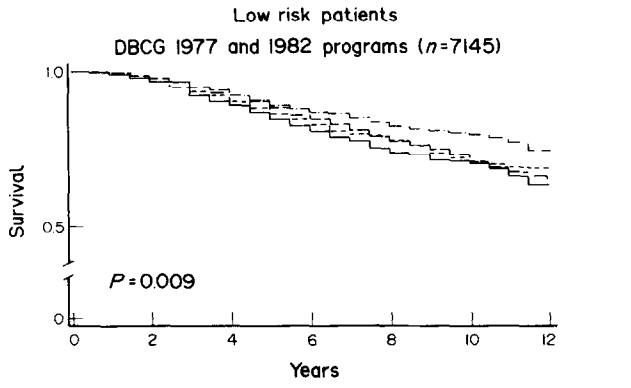

Fig. 4. Survival in the DBCG low risk group of patients. Median observation time = 76 months. Difference between groups ≥ 10 nodes vs. < 10 lymph nodes examined: $P < 0.005$.

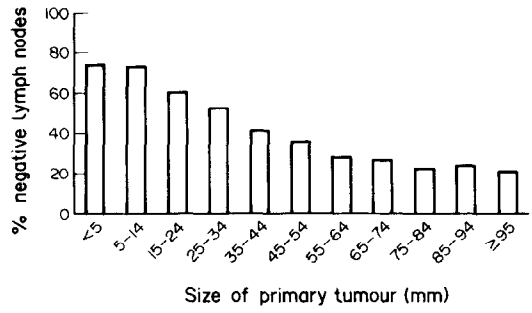

Fig. 5. The frequency of negative lymph nodes (%) in each group of patients classified according to the size of the primary tumour (n = 12699).

DISCUSSION

The results emphasise that the main determinants for node negativity in primary breast cancer are the number of lymph nodes examined in the axillary specimen, and tumour size. Another observation was that high rate of node negativity was associated with low histological grade. Tumour size and grade were to some extent correlated. The age of the patients had no influence on node negativity.

The risk of underestimating the stage by removing too few lymph nodes has been analysed earlier from DBCG [3, 4]. The last report [4] comprised 3128 low risk patients (DBCG 77 A protocol) with a median follow up of 6.5 years. The estimated 5-year probability for developing axillary recurrence was 19% in patients with no lymph nodes examined, 10% when 1–2 removed and negative nodes, 5% when 3–4, and 3% when more than five negative lymph nodes were demonstrated. The study also revealed a significantly decreased survival in groups of patients with less than five negative nodes compared with groups of patients with five or more negative nodes. It was concluded, that misjudgement of the qualitative axillary nodal status was modest, provided that at least five lymph nodes were removed.

In a recent report from two Danish hospitals [5] the axillary nodal status was analysed in 960 consecutive cases of primary breast cancer. It was concluded that the probability of finding at least one metastatic node increased continuously up to about 10 removed nodes. The percentage of node positivity in each subgroup seemed to level off above 10 nodes at about 64% suggesting that this represents the true rate of node positivity at the time of primary surgery. Furthermore, it was demonstrated that in lymph node-negative patients, who did not receive any adjuvant treatment, the 4-year recurrence-free survival was significantly associated with the number of nodes removed, provided that less than 8–10 nodes were removed.

Others [6, 7] compared the sampling technique (with median 3–5 nodes examined) with axillary clearance (with 20.6 nodes [7] or ≥ 26 nodes [6] examined). Irrespective of technique they found that 35 [6] and 39% [7] of the patients were node positive. It was concluded that the sampling technique was as effective at demonstrating positive nodes as the axillary clearance method. But it was also stated that, to quantify accurately the degree

Table 1. The relationship between age and median tumour size, number of lymph nodes and node negativity (DBCG 77 and 82 programs)

Age (years)	No. of patients	Tumour size* (mm)	No. of lymph nodes*	Node-negative (%)
< 40	1295	20	6	56
40–49	3763	20	6	57
50–59	4266	20	6	57
60–69	4527	20	6	56
n	13851			

*Median.

Table 2. Relationship between tumour grade and nodal state (DBCG 77 and 82 programs)

Tumour grade	No. of patients	Node negative (%)
1	3565	63
2	5616	51
3	1992	44
n	11173	$P < 0.0001$

Table 3. Relation between tumour size and tumour grade (DBCG 77 and 82 programs)

Tumour size (mm)	No. of patients	Tumour grade (%)		
		1	2	3
≤ 10	1474	45	45	10
11–30	6397	33	50	17
31–50	1673	22	53	24
> 50	633	17	51	32
n	10180	$P < 0.0001$		

of positive node involvement, which is important for precise staging, a more complete axillary dissection was required than was necessary to ascertain negativity and positivity [6]. The sampling technique was rejected by others [8].

The discrepancies between these trials and the present study may be ascribed to the total number of patients in the study groups, i.e. several hundreds [6, 7] compared with several thousands. Another striking difference is that the patients in the present nationwide study were operated on in 84 surgical departments and the histological examination took place in 31 institutes of pathology. When the study was undertaken in a single unit [7], the percentage of node-positive patients after axillary sampling surpassed, though insignificantly, that of node-positive patients after axillary clearance, indicating that the trained surgeons most likely "cleared" the axilla for the positive nodes during the sampling procedure. This is in accordance with the finding that the clearance procedure following immediately after the sampling procedure did not contribute further to the number of positive nodes.

The other important parameter for node negativity was tumour size. This parameter was a significant prognostic factor of recurrence-free survival and survival in univariate and multivariate analyses in the low risk group of patients of DBCG [9]. It is also generally accepted as an important prognostic factor in studies of high risk patients [10, 11].

Another observation in the present series was that a high rate of node negativity was associated with low histological grade. The surgeon has no influence on tumour size or tumour grade, which are mutually related. Only indirectly by aiming at an earlier diagnosis and the subsequent treatment of smaller tumours of lower grade can a rise in node negativity be secured.

Other factors concerning node negativity are newer modalities as detection of micrometastases by histology or immunochemistry, the status of the internal mammary nodes, and detection of altered glycosylation in the primary tumour. The standard defining the axillary tumour state is conventional histology. Reports employing serial sectioning and differentiation between micrometastases, i.e. less than 2 mm, and macrometastases seem to have important implications for the prognostic outcome of patients entered into randomised trials [12, 13]. After the demonstration of the very low frequency of internal mammary metastases without simultaneous axillary metastases and the lack of benefits on recurrence-free survival and survival after removal of internal mammary nodes [14], most centres excluded dissection of these nodes. Also, ultrasonography [15] and lymphoscintigraphy [16] have been unsuccessful in revealing nodal involvement. In this respect, as with the newest modality—prediction of lymph node involvement by detection of altered glycosylation in the primary tumour [17]—more information from larger trials is needed.

In conclusion, on the basis of the present paper, a node-negative patient with primary breast cancer is a patient with ≥ 10 lymph nodes removed and negative from the axilla at the operation. Thereby, the risk of misclassification is strongly reduced, and this is correlated with a highly significant improvement of prognosis.

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