Efferent Vascular Invasion in the Axillary Nodes in Breast Carcinoma: A Potent Prognostic Factor

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Tumour cells in the efferent vessels of the axillary nodes in breast cancer (EV status) have been associated with poor prognosis since 1979. A prospective study (1980–1989) of all the nodes from 1 037 consecutive female patients with unilateral breast cancer whose treatment included axillary node dissection yielded 471 node-positive cases. Tumour cells were found in the efferent nodal vessels of 210 patients, while 252 were negative. In the remaining 9 patients efferent nodal vessels could not be identified. At follow-up, 62% of the node-positive patients had died of breast carcinoma, in contrast to 32% of node-negative patients. The prognosis in cases with 1–3 versus 4+ tumour-bearing nodes was highly significant, 36% and 64%, respectively having died of breast carcinoma,. Prognosis was not dependent on the number of EV+ nodes in those cases showing efferent vascular invasion, one positive node was enough. Differentiation between these nodal growth forms thus provides a strong prognostic indicator, available to all with access to routine surgical pathology. We confirmed the significance of both variables using Cox's regression analysis and showed that the number of positive nodes adds significant prognostic information to that of EV status, which is the stronger of the two prognostic indicators. EV+ patients with more than three positive nodes have more than a three times higher risk of dying than EV− patients with three or fewer positive nodes.

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The number of positive axillary nodes is, by tradition (1, 2), an important parameter in the assessment of breast cancer patients, and one that has stood the test of time (3). In 1979 it became apparent that further information could be gained from these nodes when it was found that the presence of tumour cells in the draining (efferent) nodal vessels had an association with poor prognosis (4). In 1983 a combination of this parameter with the mean nuclear area of the tumour cells was shown to give optimal prediction of disease outcome (5). A prospective series was set up to check on prognosis related to the efferent vascular (EV) status of the axillary nodes. This ran from 1980 to 1989 and comprised the axillary dissection specimens from 1 037 female patients from this district who had been surgically treated for breast carcinoma. The follow-up results, which are now available up to and including 1996, are presented in this paper.

MATERIAL AND METHODS

This series included 1 156 breast cancer patients and has been described in detail previously in connection with the identification of the various growth forms in nodal micrometastases (6); 119 patients were excluded from the series for reasons detailed in reference (6). These include bilateral cases and carcinoma in situ. Of the patient group, 471 cases had metastatic disease to one or more nodes in the axilla, the efferent vessels of which could be identified in 462 patients; 566 patients were node negative.

The axillary specimens had been fixed in formalin and the nodes dissected out by blunt dissection. The nodes were blocked individually after bisection through their greatest circumference and the hilar area (7). Sections from this paraffin-embedded material were stained with hæmatoxylin and eosin. In the routine pathology report the number and tumour status of nodes were recorded, including the number of nodes with tumour cells in their efferent vessels, which here we refer to as EV+ for positive efferent vascular status, and EV− for negative status (8). (Mean ages at operation in the EV+ and the EV− patients were 61 ± 13 and 60 ± 14 years, respectively.) In total, 4 627 positive nodes were investigated. The median in the EV+ patients was 9.5 (1–36), and 9.0 (1–22) in the EV− patients. In the node-negative patients the median was 8.0 (1–33). These records, and the detailed laboratory protocols have now been supplemented with follow-up data, including the 1996 data from the Central Bureau of Statistics, Oslo. Survival function- and proportional hazard regression analyses were used, as pro-

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grammed in SYSTAT 95/98 (9). Univariate survival curves were computed using the Kaplan–Meyer method. The proportional hazard regression method relies on the assumption that the ratio of the death rates in groups of patients does not change with time. This assumption was checked using plots of log-minus-log survival functions. Patients dying of causes other than breast cancer were censored at the time of death, i.e. treated as living up to their death and then excluded. The proportional regression analyses were adjusted using the diameter of primary tumour (up to 2.0, 2.1–5 and more than 5 cm) and mean nuclear area (up to 44, 45–64 and more than 64 μ^2). The measurement of mean nuclear area was done morphometrically, as detailed previously (5).

RESULTS

In Fig. 1, a survival curve using the number of tumour-bearing nodes in the axilla shows that patients with 1–3 tumour-bearing nodes had a significantly better prognosis than those with 4 or more positive nodes. Patients with EV− status (Fig. 2) had a significantly more favourable prognosis than those with EV+ status. In Fig. 3 the number of tumour-bearing nodes and EV− status are combined and compared with node-negative patients. Seventy-nine percent of EV+ patients with more than 3 tumour-bearing nodes died of breast cancer compared with 31% in the EV− group with fewer than 3 positive nodes. This group had a significantly poorer prognosis than node-negative patients.

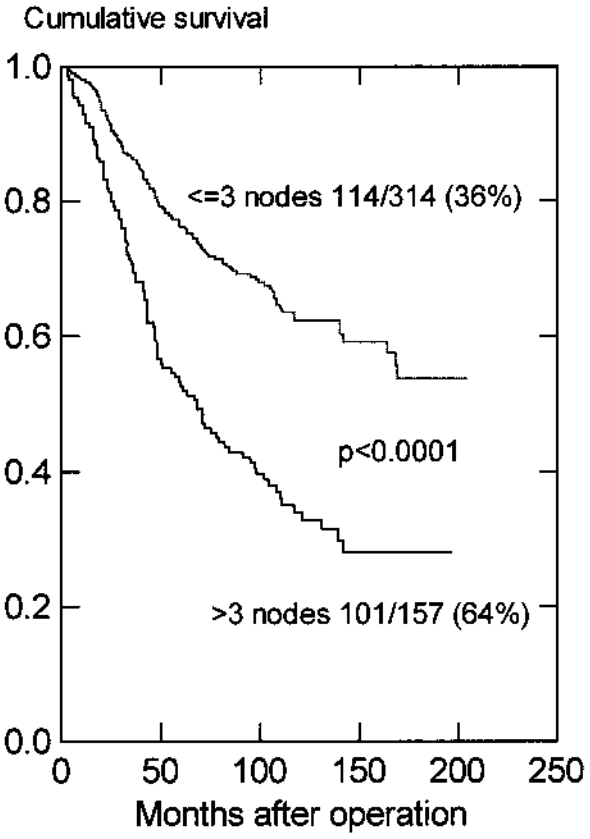

Fig. 1. Cumulative survival in patients with 1–3 positive and more than 3 positive nodes in the axilla.

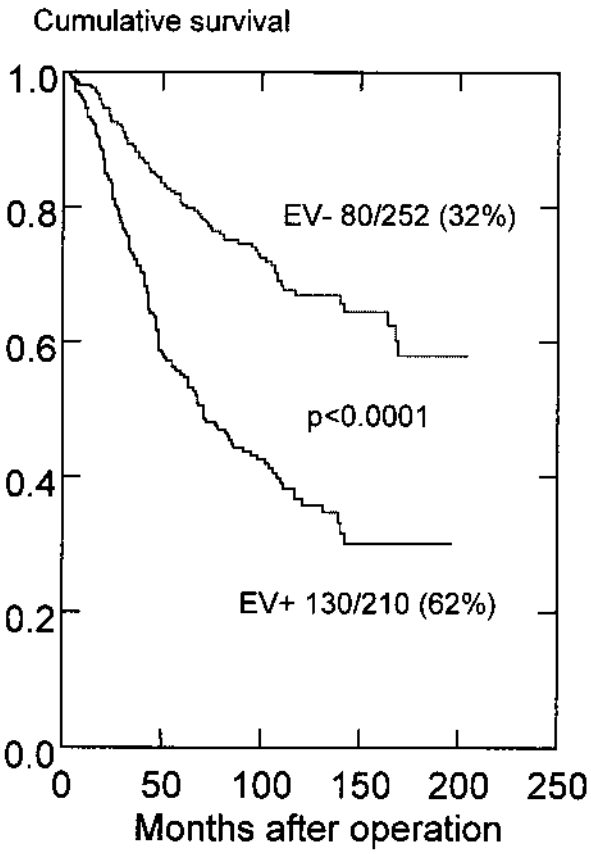

Fig. 2. Cumulative survival in patients without- and with tumour-cells in the efferent nodal vessels, i.e. EV− and EV+ patients.

The results of Cox's regression analyses are presented in detail in the Table 1, unadjusted and adjusted for diameter of the primary tumour and the mean nuclear area of the tumour cells. In a univariate regression analysis, both the number of positive nodes and the EV− status give highly significant risk estimates. Both variables have a relative risk higher than 2, EV status giving slightly stronger prognostic information than the number of positive nodes. The table also shows the results when both variables are considered simultaneously. EV− status was the stronger of the two, but the number of positive nodes added significant prognostisic information. EV+ patients with more than 3 positive nodes had a 3.2 times higher risk of dying of breast cancer than EV− patients with 1–3 positive nodes.

DISCUSSION

This series of 471 node-positive breast cancer patients followed the expected survival pattern, those with 1–3

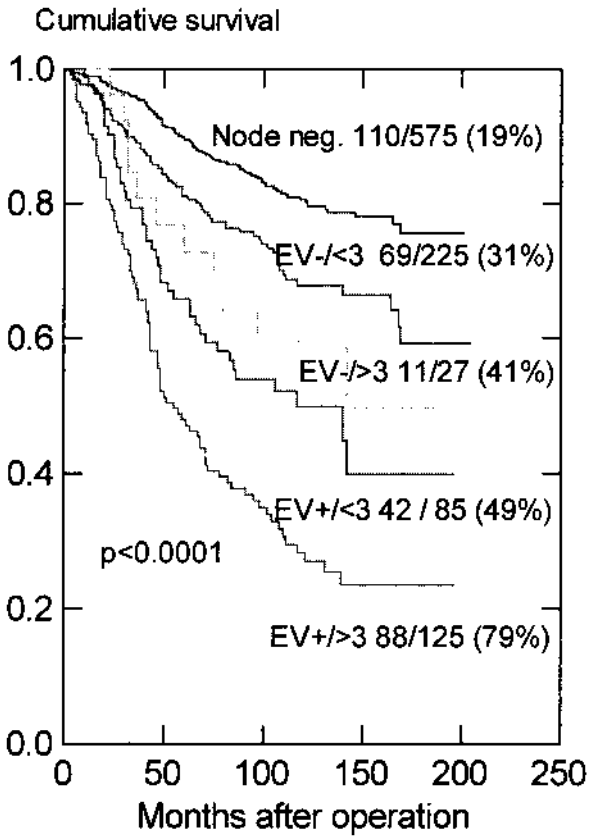

Fig. 3. Cumulative survival combining EV − status with the number of positive nodes in the axilla.

tumour-bearing nodes in the axilla showing better survival than those with 4 or more (10). When EV status was taken into consideration, the picture changed.

In contrast to the EV − patients, those with EV + nodes in the axilla were at high risk of dying of breast cancer. This risk also applied when only one EV + node was found in the axilla. Thus, the finding of one EV + node signals that tumour cells have had the opportunity to leak into the general circulation, and may have taken this opportunity in around 62% of the patients. Reference to the protocol showed that in 15 cases the one EV + node was the only tumour-bearing node in the axilla. Ten of these women had died of breast cancer, 5 had survived. This information warns us of a pressing need for radical postoperative treatment.

These two groups of patients, the EV − and the EV +, are not at different ends of the same scale, as is the case when the number of tumour-bearing nodes is used. They represent two distinct populations, each with its own characteristic behavioural patterns. The present work shows that the survival difference between them was greater than that between all the cases with 1 to 3 versus 4 or more tumour-bearing nodes and thus confirms that nodal efferent vascular status is indeed a strong prognostic indicator in breast carcinoma.

In the present series axillary dissection had been carried out and EV status recorded in the postoperative pathology report. To provide this information on high or low risk, the pathologist requires access to the axillary nodes. That gained, the technical procedure is straightforward and does not require special equipment or expensive methods. The present findings indicate that one half of the node-positive cases can be expected to have one or more EV + nodes. These patients are at high risk and in need of appropriate therapy. Distinction between them and the node-positive cases at low risk (the EV −) can only be made on the basis of nodal histology. Corresponding results have recently been reported by others (11).

With recognition of the sentinel node, the need to base axillary staging on axillary dissection (12) has been questioned (13, 14). Lack of tumour in the sentinel node is regarded as a marker of node-negative axillary status. In contrast, the presence of tumour in the sentinel node tends to be associated with other tumour-bearing nodes in the axilla. Chemotherapy may then be the treatment chosen (15).

The observation that the tumour status of the sentinel node correlates well with that of the rest of the axillary

Table 1

The relative risk of dying of breast cancer according to the number of positive nodes (No. nodes) in the axilla and EV status, unadjusted and adjusted for diameter of the primary tumour and mean nuclear area of the tumour cells, using the Cox proportional hazard model

Univariate	Multivariate		Estimate	S.E.	t-ratio	p-value	Rel. risk
No. nodes		Crude	0.840	0.138	6.081	0.000	2.32
		Adjusted	0.922	0.151	6.117	0.000	2.51
EV		Crude	0.946	0.144	6.585	0.000	2.58
		Adjusted	0.981	0.156	6.284	0.000	2.67
	EV	Crude	0.703	0.166	4.244	0.000	2.02
	No. nodes	Crude	0.504	0.161	3.128	0.002	1.66
	EV	Adjusted	0.720	0.177	4.062	0.000	2.05
	No. nodes	Adjusted	0.578	0.172	3.358	0.001	1.78

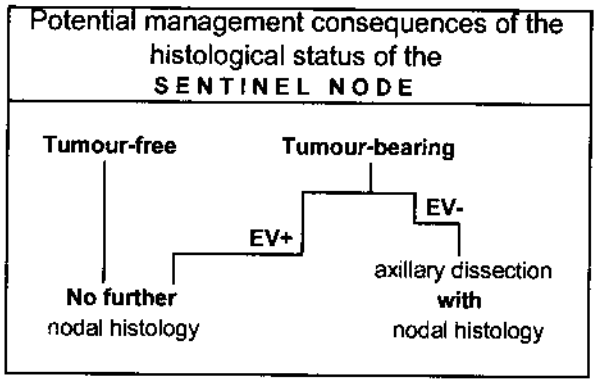

Fig. 4. The histological follow-through relevant to the status of the sentinel node in breast cancer patients.

nodes implies that no more information is to be gained from further nodal investigation in cases correctly diagnosed on this basis. If, however, the sentinal node is both tumour-bearing and EV +, the patient can, on the basis of that one node, be identified as at high risk, and in need of further treatment. Conversely, as a tumour-bearing EV − sentinal node gives no information on the EV status of any other tumour-bearing nodes in the axilla, histological investigation of the remaining nodes is indicated before a decision on further treatment can be reached. If the sentinal node and remaining axillary nodes are all EV −, the present work shows that the patient is at no greater risk of dying of breast carcinoma than her node-negative counterpart. The potential management consequences of the histological status of the sentinal node are summarized in Fig. 4.

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