

# Prognosis of Breast Cancer with Axillary Node Metastases after Surgical Treatment Only

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**Abstract**—Out of 753 patients with breast cancer treated with radical mastectomy from 1968 to 1970 at the National Cancer Institute of Milan, Italy, 308 had histologically proven positive nodes. The number of positive nodes was not dependent on the location of the primary tumour, its diameter and the patient's age.

Extracapsular invasion was related to the number of positive nodes at a statistically significant level:  $P$  value  $2 \times 10^{-9}$ . Survival was influenced by the number of positive nodes and extension of metastases beyond their capsule and age. Each of these criteria had an independent impact on survival.

Three subgroups with different prognosis were identified in patients older than 40: (a) with a single involved node and 69.9% 10 year survival rate, (b) patients with two or more nodes with metastatic deposit still confined within node capsule and 47.4% 10 year survival rate, (c) patients with two or more involved nodes and extracapsular invasion and 25.3% 10 year survival rate.

In patients younger than 40 no subgroup was identified: this group had an intermediate 10 year survival rate (50.9%).

The authors conclude that there is a need (a) of re-consideration of the prognosis of patients with positive nodes and (b) to agree on the definition of "high-risk patients".

## INTRODUCTION

THE PROGNOSIS of patients with breast cancer and positive nodes is certainly an important issue to be investigated, because axillary node involvement is considered the major criterion for the selection of patients eligible for adjuvant treatments and because most of the published papers are based upon patients already submitted to adjuvant chemotherapy [1, 2]. Patients with positive nodes may not be considered as a homogeneous group and the number of nodes involved may not be the only way to identify subgroups with different prognoses.

We studied a homogeneous group of patients consisting of 753 patients submitted to radical mastectomy without further treatment and with a

minimum follow-up period of 10 years. The results are reported here.

## MATERIAL AND METHODS

From 1968 to 1970, 753 consecutive patients with breast cancer were submitted to radical mastectomy at National Cancer Institute, Milan. Out of these 308 had histologically positive nodes. Table 1 summarizes the characteristics of these patients: 60 (19.5%) were younger than 40 and 156 (50.6%) were post-menopausal women. Primary breast cancer was located at the external quadrants in most patients. All the excised axillary nodes were manually screened by the pathologist and when suspicious nodes were found, they were included in paraffin for microscopical evaluation. If no suspicious node were found three to eight were selected for histological examination at random. A mean number of 5.0 axillary nodes was histologically examined. No patient had adjuvant chemo- or radiation therapy. Contingency tables were evaluated by mean of chi-square analysis and survival by means of the Kaplan

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Table 1. Main characteristics of 308 patients with breast cancer and axillary positive nodes

Criteria	No. of patients	%
<i>Number of nodes involved</i>		
One	124	40.2
Two or three	123	39.9
Four or more	61	19.9
<i>Extracapsular invasion</i>		
No	211	68.5
Yes	97	31.5
<i>Site of primary</i>		
External quadrants	267	86.7
Inner quadrants	41	13.3
<i>Diameter of primary*</i>		
< 2 cm	143	46.4
> 2 cm	102	53.6
<i>Age of the patients</i>		
Less than 41	60	19.5
41–50	80	26.0
More than 50	168	54.5
<i>Menopausal status†</i>		
Pre-menopause	140	45.4
Post-menopause	156	54.5

\*63 patients had a non-measured or greater than 5 cm diameter.

†Information not available for 12 patients.

Table 2. Relation between site of primary and number of nodes involved

No. of nodes	Inner (%)	Outer (%)	Total
1	21 (51.2)	103 (38.5)	124
2–3	14 (34.1)	109 (40.8)	123
> 4	6 (14.7)	55 (20.7)	61
Total	41 (100)	267 (100)	308

$P = 0.29$ .

and Meier method. A step down multivariate analysis was also carried out by using the Cox's regression model.

## RESULTS

Out of the 308 patients with positive axillary lymph nodes 124 had one node involved, 77 two nodes, 46 three nodes and 61 four or more nodes. Table 2 gives the relationship between the location in the breast of primary tumour and the number of nodes involved: it may be observed that location did not influence the number of nodes involved. The size of the primary tumour seems to be associated with the number of metastatic nodes; primary cancers with a maximum diameter more than 2 cm constitute 39.0% of patients with a single positive node and 53.4% of patient with four or more positive

nodes as shown in Table 3. However, statistical analysis failed to show a significant  $P$  value. Table 4 gives the distribution of patients by age and number of positive nodes: it may be noted that the three groups of patients identified by number of positive nodes are well balanced among the three age categories.

The invasion of neoplastic growth beyond the capsule of lymph nodes is clearly related to the number of positive nodes: Table 5 shows that 12.1% of patients with one node involved had an extracapsular invasion, while this occurred in 50.8% of patients with four or more nodes involved.

Figure 1 shows a progressively worse prognosis with increasing number of positive nodes, the 69.9% 10 year survival observed in patients with one node involved falls to 32.0% in patients with four or more nodes through intermediate values. The extracapsular invasion is also related with a bad prognosis as shown in Fig. 2: the 71.2% 10 year survival rate for patients whose metastatic disease is still contained within the nodes capsule becomes 36.6% when this limit is overcome.

The age of the patients is also significantly related with survival, as shown in Fig. 3: the 10 year survival of 51.6% observed in patients younger than 40 increases to 73.5% in patients older than 50.

A multivariate analysis was carried out taking into consideration the three variables significantly related with survival to evaluate the relative weight of each of these criteria. It may be observed from Table 6 that age, number of positive nodes and extracapsular invasion of metastatic growth have an independent and significant impact on survival.

## DISCUSSION

In a previous paper on 743 patients with breast cancer submitted to surgical treatment at our institute [3], we showed that the frequency of nodal involvement decreases with age and that node metastases are more frequent in tumours of the upper-outer quadrant and of the axillary tail of the breast. We drew the conclusion that nodal status and the number of nodes involved are the most important prognostic factors in breast cancer survival confirming other reports [4]. In this paper we analysed the prognosis of patients with positive nodes only. Three criteria were found to influence survival: the number of positive nodes, extracapsular invasion and age of the patients. The prerequisite for patients entered in this study was the homogeneity of surgical treatment; for this reason patients submitted to radical mastectomy who did not receive any kind of post-operative treatment were selected. The choice of these criteria led to the consequence that the patients were treated in an 18 month period by the same surgeons with an identical surgical technique and that the follow up period

Table 3. Relation between diameter of primary and number of positive nodes

Diameter	Number of nodes						Total
	1	%	2-3	%	> 4	%	
< 2 cm	64	(60.9)	53	(56.9)	41	(46.6)	158 (55.2)
> 2 cm	41	(39.1)	40	(43.1)	47	(53.4)	128 (44.8)
Total	105	(100)	93	(100)	88	(100)	286 (100)

$P = 0.12$ .

Table 4. Relation between age of the patients and number of nodes involved

Age	1	%	2-3	%	> 4	%	Total	%
< 4	23	(18.6)	22	(17.9)	15	(24.5)	60	(19.5)
41-50	32	(25.8)	30	(24.4)	18	(29.6)	80	(25.9)
< 50	69	(55.6)	71	(57.7)	28	(45.9)	168	(54.6)
Total	124	(100)	123	(100)	61	(100)	308	(100)

$P = 0.63$ .

Table 5. Relation between number of involved nodes and extracapsular invasion

No. of nodes	No. of patients	Extra-capsular	%
1	124	15	12.1
2-3	123	51	41.5
> 4	61	31	50.8
Total	308	97	31.5

$P = 2 \times 10^{-9}$ .

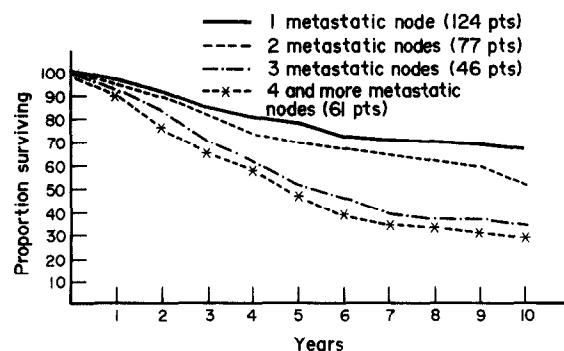


Fig. 1. Actuarial survival rates of 308 patients with breast cancer and axillary positive nodes according to the number of positive nodes.

was of 10 years at least. The point of weakness is the relatively poor pathologic sampling of lymph nodes since 5.0 nodes were histologically examined on the average in that period. However the length of follow up and the fact that these patients received a very homogeneous surgical treatment reduces the importance of this negative point in our opinion. As a matter of fact the limit refers to inadequate

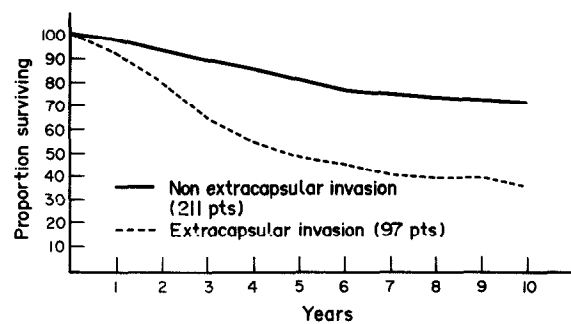


Fig. 2. Actuarial survival rates of 308 patients with breast cancer and axillary positive nodes according to the extension of secondary deposits beyond the capsule.

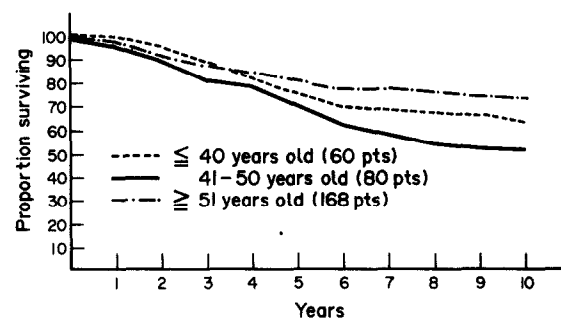


Fig. 3. Actuarial survival rates of 308 patients with breast cancer and axillary positive nodes according to age of the patients.

evaluation of the prognosis of patients with a single node involved only and with no extracapsular extension. In fact all palpable lymph nodes only were sampled from the operative specimen. The number (and the survival rate) of these patients is certainly underestimated in particular for those with embolic metastases, most of whom were probably missed

Table 6. Multivariate analysis of survival

Criteria	P
Age (No. of positive nodes, extracapsular invasion)	0.003
No. of positive nodes (age, extracapsular invasion)	0.0006
Extracapsular invasion (age, no. of positive nodes)	0.0006

and classified in the group of patients with negative nodes. This poor sampling is most probably the reason of the relatively low percentage of patients with positive nodes (41.4%) in this series as compared to the 53.2% observed at our own institute in 1012 patients treated from January 1983 to March 1984 (Veronesi, unpublished data).

Three main groups of patients with different prognoses may be certainly identified according to our data in patients older than 40:

- (i) patients with a single node involved and a good relatively prognosis: the 10 year survival rate is 69.9%. The extracapsular invasion does not significantly modify this rate. If the considerations made on the pathologic sampling are taken into consideration it may be hypothesized that the survival rate may also be higher;
- (ii) patients with two or more positive nodes and secondary deposits still confined within lymph nodes capsule: 47.4% 10 year survival rate;
- (iii) patients with two or more positive nodes and invasion of the perinodal fat: 25.3% 10 year survival rate.

A fourth group of patients with an intermediate survival rate (51.6%) is constituted by patients younger than 40. It is worth noting that in this particular subgroup neither the number of nodes nor the extent of secondary deposits seem to affect survival at a statistically significant level. This may be due to the relatively small number of patients (60) in this group. The most important finding is that in this group of patients the 10 year survival rate is not particularly low, confirming that age, even if important in the assessment of prognosis of

breast cancer patients, is not one of the major prognostic indicator [3].

These results are of a certain importance since they indicate that the assessment of prognosis of breast cancer patients with regional node metastases should be based not only upon the number of positive nodes but also upon the extension beyond the capsule as a minimum requirement. A more detailed evaluation may be done taking into consideration other "new" biological variables such as oestrogen and progesterone receptors, the labelling index, tumour necrosis, grading and so on as done by others [5-13]. It must not be forgotten however that these "new" criteria should be considered within homogeneous groups defined by the number of positive nodes and extension beyond the capsule and age, when patients with axillary positive nodes are taken into consideration.

The data of this study, even with the limitations resulting from pathologic sampling, are also important, because the results are not biased by any kind of adjuvant treatment; an adequate evaluation of the risk of death from breast cancer with positive nodes after surgery could be made. Adjuvant treatments are usually planned for patients with positive nodes because they are considered at "high risk" of death: as a matter of fact this study indicates that patients with a single node involved may not be considered in this group because of their high 10 year survival rate (69.9%). Patients with two positive nodes at least and extracapsular invasion certainly fall into the "high risk" category. The third group (which includes patients with two or more positive nodes and no extracapsular invasion as well as patients younger than 40) with an approx. 50% chance of survival may or may not be classified as high risk.

There is a great need (a) of a re-evaluation of survival of patients with positive nodes submitted to surgical treatment only, since our data need confirmation, (b) to evaluate other possible prognostic indicators under the same conditions in order to have a better evaluation of the risk of death.

Finally there is a need to agree upon the definition of "high-risk" patients. In our opinion patients with less than 50% of chance of long term (10 years) survival should fall into the high risk category no matter by which other criteria this group is defined. "Adjuvant" treatments should be given to these patients only.

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