# *Risk of Internal Mammary Lymph Node Metastases and Its Relevance on Prognosis of Breast Cancer Patients*

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**The risk of internal mammary chain metastases according to some parameters and its prognostic relevance was evaluated on the basis of the experience collected at the National Cancer Institute of Milan where, from January 1965 to December 1980, 1085 patients were submitted to Halsted mastectomy plus internal mammary chain dissection. A multivariate analysis was carried out, resorting to a multiple linear regression with logistic transformation of the dependent variable. The selection of prognostic factors has been performed with a step-down approach. The frequency of metastases to internal mammary chain nodes was evaluated according to four criteria: age, site and size of primary tumor, and presence of axillary metastases. Data of this series indicate that the frequency of internal mammary node metastases is significantly associated with the age of the patients (younger patients have a higher risk) ($p = 0.006$) with the size of primary tumor ($p = 0.006$) with the presence of axillary node metastases ($p = 10^{-9}$). Patients with both axillary and internal mammary positive nodes have a very poor prognosis (10-year survival 37.3%) while patients with either axillary metastases only or internal mammary metastases only have an intermediate less grave prognosis (59.6% and 62.4%, respectively). As regards the risk of internal mammary nodes involvement, it appears that knowing the age, the size, and the axillary nodes status, it is possible to calculate with good approximation the probability of their invasion.**

AT THE END OF THE SEVENTIES, on the basis of prospective randomized clinical trials,[4] it was shown that the dissection of internal mammary chain associated to Halsted mastectomy was unable to achieve better results than Halsted mastectomy itself. Survival rates after the two surgical procedures were similar, the recurrence rate to internal mammary chain was very low in patients submitted to radical mastectomy, and the frequency of metastatic spread to endothoracic organs was not modified by internal mammary chain dissection.[8]

The role of enlarged mastectomy was also denied as a staging procedure because of the limited number of patients with negative axillary nodes and positive internal mammary nodes.[1,2,8] Thus, it was thought that the information obtained from the examination of the axillary nodes were complete enough to plan adjuvant treatments. However, a few question marks remained unanswered. In particular, as regards the prognostic value of internal mammary invasion, contrasting opinions were expressed by different investigators. Internal mammary metastases was considered by some to be constantly an ominous prognostic sign[5,6] and by others it was considered compatible with a prognosis not worse than that due to the invasion of axillary nodes.[7]

As regards treatment, radiotherapy on the internal mammary nodes in patients with cancer in the inner quadrants of the breast was introduced in many centers on the basis of the results of an international cooperative study showing some advantages at 5 years by the internal mammary dissection in medial cases $T_1$ $T_2$ with axillary metastases.[4] These results were, however, not confirmed in a more detailed analysis at 10 years on a considerable number of cases in a study carried out in our Institute.[8] Moreover, no efforts were done so far to identify possible groups of patients with a different risk of internal mammary nodes metastases and to verify if the level of information obtained by histologic examination of axillary nodes may be improved by the examination of the retrosternal nodes.

The aim of this paper is to evaluate the risk of internal mammary chain metastases according to a number of parameters and its prognostic relevance on the basis of the experience collected at the National Cancer Institute of Milan, Italy.

## Patients and Methods

From January 1965 to December 1980, 1085 patients were submitted to Halsted mastectomy plus internal mammary chain dissection at our Institute.

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TABLE 1. *Characteristics of the 1085 Patients*

| Criterion | No. of Patients | % |
|---|---|---|
| Age | | |
| ≤40 | 182 | 16.7 |
| 41–50 | 348 | 32.1 |
| 51–60 | 305 | 28.1 |
| ≥61 | 250 | 23.1 |
| Site of primary | | |
| Axillary tail | 6 | 0.5 |
| Superior lateral | 265 | 24.4 |
| Superior internal | 457 | 42.1 |
| Central and nipple | 116 | 10.7 |
| Inferior lateral | 90 | 8.2 |
| Inferior internal | 151 | 14.0 |
| Maximum diameter of primary* | | |
| ≤2.0 cm | 573 | 52.8 |
| ≥2.1 cm | 512 | 47.2 |
| Undetermined | | |
| Axillary node status** | | |
| Uninvolved | 546 | 50.4 |
| Involved | 537 | 49.5 |
| No. of involved nodes | | |
| 1 | 199 | 25.8 |
| 2 | 67 | 12.4 |
| 3 | 51 | 9.0 |
| ≥4 | 112 | 20.8 |
| Undetermined | 168 | 31.2 |

* Measured on surgical specimen.
** The status of axillary nodes was unknown in two patients.

TABLE 2. *Frequency of Internal Mammary Node Metastases According to Age, Site, and Size of Primary, and Axillary Involvement*

| Criterion | No. of Patients | I.M.N. Metastases | p |
|---|---|---|---|
| Total | 1085 | 18.5 | |
| Age | | | |
| ≤40 | 182 | 26.9 | |
| 41–50 | 348 | 18.6 | $6 \times 10^{-3}$ |
| 51–60 | 305 | 17.1 | |
| ≥61 | 250 | 14.0 | |
| Site of primary | | | |
| Lateral | 361 | 16.34 | .19 |
| Medial + central | 724 | 19.61 | |
| Maximum diameter of primary* | | | |
| ≤2.0 cm | 573 | 15.7 | |
| ≥2.1 cm | 404 | 22.5 | |
| Undetermined | 108 | 14.5 | $6 \times 10^{-3}$ |
| Axillary node status** | | | |
| Uninvolved | 546 | 8.9 | $1 \times 10^{-9}$ |
| Involved | 557 | 28.3 | |
| No. of involved axillary nodes | | | |
| 1 | 139 | 17.3 | |
| 2–3 | 118 | 24.6 | $6 \times 10^{-5}$ |
| ≥4 | 112 | 40.2 | |

* Measured on surgical specimen.
** The status of axillary nodes was unknown in two patients.

TABLE 3. *Multifactorial Analysis to Evaluate the Relevance of Characteristic of Primary on Presence of Nodal Involvement on Internal Mammary Chain*

| Criterion | $X^2$ | D.O.F. | P |
|---|---|---|---|
| Quadrants (diameter axillary N+ age)* | 6.91 | 5 | .22 |
| Diameter (quadrants axillary N+ age) | 3.56 | 1 | .059 |
| Age (quadrants axillary N+ diameter) | 8.3 | 2 | .015 |
| Axillary lymph nodes (quadrants age diameter) | 54.78 | 1 | $10^{-9}$ |

* D.O.F. = Degree of freedom.
** The adjustments are in parentheses.

Table 1 gives the characteristics of the patient population: the majority of patients were aged between 40 and 60, the internal and central quadrants were more frequently the site of the primary tumor (66.8%), approximately half of the patients had a breast cancer with a maximum diameter measured on surgical specimen of 2 cm or less, axillary node metastases were present in 49.5% of patients, and 18.5% of patients had IMN involvement.

### *Statistical Methods*

To evaluate simple contingency tables, Pearson $\chi^2$ was used. Survival curves were plotted following the product-limit method suggested by Kaplan and Meier. The multifactorial analysis was carried out resorting to a multiple linear regression with logistic transformation of the dependent variable. The selection of prognostic factors has been performed with a step-down approach. The risk of developing metastases at the internal mammary nodes has been calculated utilizing the estimated parameters (i.e., dependent variable in multiple regression analysis).

Probability (Positive internal mammary nodes)

$$= \frac{\exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4)}{1 + \exp(\beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4)}$$

$\beta_0\ \beta_1\ \beta_2\ \beta_3\ \beta_4$ estimated regression parameters.

$X_1$ = presence of axillary metastatic nodes.

$X_2$ = diameter of tumor greater than 2 cm.

$X_3$ = age of patients between 40 and 60 years.

$X_4$ = older than 60 years.

## Results

The frequency of metastases to internal mammary chain nodes was evaluated according to four criteria: age, site and size of primary tumor, and presence of axillary

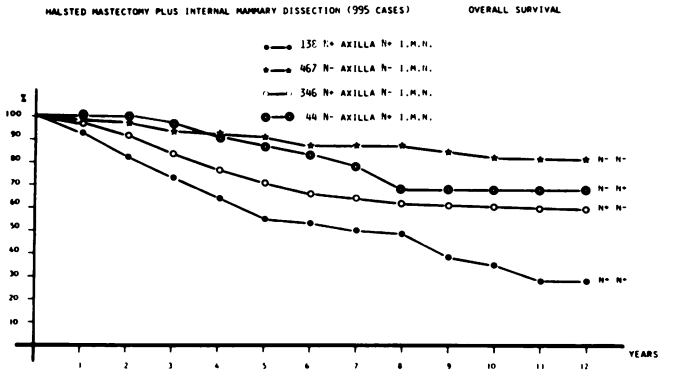


FIG. 1. Overall survival of 995 patients with breast cancer submitted to Halsted mastectomy plus internal mammary node dissection according to involvement of regional lymph nodes.

metastases. Table 2 shows that the age of patients, the maximum diameter of primary tumor, the axillary nodes status, and the number of axillary nodes involved are significantly related with the presence of internal mammary metastases, while the different frequencies observed according to the site of origin of primary tumor are not statistically significant. ($p = 0.75$).

Data of this series indicate that the frequency of internal mammary mode metastases is significantly associated with the age of the patient ($p = 0.006$), the size of primary tumor ($p = 0.006$) and with the presence of axillary node metastases ($p = 10^{-9}$). To evaluate the relative weight of these three significant criteria, a step-down analysis was carried out and results of the multifactorial analysis are given in Table 3. This analysis was carried out on 977 patients, since the 108 with an undeterminated maximum diameter were excluded. Age of the patients and axillary node involvement maintain a highly significant p value ($0.015$ and $1 \times 10^{-9}$, respectively) even if adjusted by the other criteria, while maximum diameter of primary tumor turns from a p value of 0.006 to 0.059. If survival of patients is evaluated according to the presence of axillary and internal mammary chain metastases (Fig. 1) it may be observed that three groups of patients may be identified: (a) patients with no regional metastases, with a good prognosis (10 years survival rate 82.1%), (b) patients with metastases at one of the regional node stations (either axillary or internal mammary) with an intermediate prognosis (10 years survival rate 59.6% and 62.4%, respectively), and (c) patients with both axillary and internal mammary positive nodes with a poor prognosis (10 years survival 37.3%).

To evaluate whether or not the additional information on the status of internal mammary nodes gives a better definition of prognosis than the evaluation of axillary nodes, only survival of patients was evaluated by number

TABLE 4. *Multivariate Analysis of Disease-free Interval According to Number of Metastatic Axillary Nodes and the Presence of Internal Mammary Nodes Metastases*

| Criterion | P |
|---|---|
| Number of metastatic axillary lymph nodes (internal mammary node metastases)* | $8 \times 10^{-4}$ |
| Internal mammary node metastases (number of involved axillary nodes) | 0.002 |

* The adjustments are in parentheses.

of axillary involved lymph nodes and the presence of internal mammary node metastases.

This analysis was carried out on 369 patients with positive nodes in which the number of metastatic axillary nodes was clearly specified.

The result of the step-down analysis is given in Table 4: it may be observed that the number of involved axillary nodes and the presence of retrosternal metastatic nodes maintain a highly significant p value.

The risk of internal mammary nodes involvement was then evaluated according to the status of axillary lymph nodes, the age of the patients, and maximum diameter of primary tumor. Results are given in Table 5: the table indicates that the risk of internal mammary nodes is relatively low in patients with negative axillary nodes, advanced age, and small primary tumor, while it goes up to 41% in N+ patients, and less than 40 with tumors larger than 2 cm. From the table it appears that knowing the age, the size, and the axillary status it is possible to calculate the probability of invasion of the internal mammary nodes.

TABLE 5. *Probability for Patient with Breast Cancer to have Metastases in the Internal Mammary Nodes According to Age, Status of Axillary Nodes, and Maximum Diameter of the Tumor*

| Age | Size | Risk of IMN Metastases (%) |
|---|---|---|
| | Positive Axillary Nodes | |
| Less than 40 | >2 cm | 41.2 |
| | <2 cm | 34.1 |
| 41–60 | >2 cm | 33.2 |
| | <2 cm | 26.8 |
| More than 60 | >2 cm | 24.9 |
| | <2 cm | 19.7 |
| | Negative Axillary Nodes | |
| Less than 40 | >2 cm | 16.3 |
| | <2 cm | 12.6 |
| 41–60 | >2 cm | 10.9 |
| | <2 cm | 8.3 |
| More than 60 | >2 cm | 8.5 |
| | <2 cm | 6.4 |

## Conclusions

Results of present analysis show that the information on the invasion of IMN may be useful in the staging process. The presence of metastases at the internal mammary chain is a worsening sign. However, when internal mammary nodes are involved and the axillary nodes are clear, the 10-year survival rate is of the order of 50–60% (Fig. 1). Therefore, it appears that examination of axillary nodes alone does not give complete prognostic information.

In this paper we have shown that the statistical analysis of these parameters (age, size of the tumor, and status of axillary nodes) provides an excellent tool to predict the risk of invasion of internal mammary nodes. According to the extent of the evaluated risk, it may be conceivable to consider possible treatment procedures in selected subgroups of patients. However, what appears important is to reconsider the value of the internal mammary nodes as a prognostic element and establish appropriate investigations to improve imaging techniques (lymphoscintigraphy, echotomography, CT, etc.) to be correlated with histopathological findings which may be obtained with a careful nondisfiguring biopsy of internal mammary nodes.

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