Outpatient Biopsy of Breast Cancer

Influence on Survival

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From 1948 to 1975, at the Istituto Nazionale Tumori of Milan, 209 patients underwent extended radical mastectomy (ERM) for breast cancer classified as T1 N0-1 M0. In 57 patients (27.3%), the ERM was preceded by an excisional biopsy performed in the outpatient clinic (Group A), of which 75% were performed within 30 days of admission and 25% after 30 days (average, 25 days; range 5–99). The remaining 152 patients (Group B) underwent an extemporaneous frozen biopsy. There was no difference in the distribution of the histologic types in the two groups. The axillary lymph nodes (N) and the internal mammary chain (MI) were free of neoplastic invasion (N−, MI−) in 156 patients (74.6%), 44 in Group A (77.2%) and 112 in Group B (73.7%). Actuarial 10-year survival of the patients was 79.9% in Group A and 77.7% in Group B (p = NS). It was 90% in N− MI− patients of Group A and 81.9% in those of Group B (p = NS). Instead, for N+ patients, actuarial survival at 10 years was 50% in Group A and 67% in Group B (p = NS), and for MI+ patients it was 50% and 49.8%, respectively. These present data do not support the hypothesis that a delay between biopsy and radical surgery of breast cancer is an important prognostic factor.

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A FUNDAMENTAL PREMISE of the therapeutic strategy of malignant tumors is the necessity to confirm the histologic type before choosing a more adequate treatment. This necessity, indispensable when the therapeutic perspective is surgery in the first place, may have a certain degree of physical, functional, and esthetic impairment. However, the indication of an excisional or incisional biopsy to be performed prior to radical surgery has often been opposed because of the hypothetic risk of neoplastic dissemination.[1,2]

Breast cancer is one of the tumors for which there is strong opposition against the practice of performing the biopsy at a different time from radical surgery. The use of intraoperative excisional biopsy with extemporaneous histologic examinations by frozen section thus has become more widespread. However, in the last few years a series of factors has contributed to reevaluate this approach.

In the first place, better health education and more extensive screening of asymptomatic subjects for an earlier diagnosis has increased markedly the number for doubtful cases at clinicoinstrumental examinations, which has exposed the limits of various diagnostic examinations as regards very small alterations.[3,4] Moreover, an ever increasing number of women wish to know the exact nature of the breast alterations before consenting to mastectomy. The progressive increase in hospitalized cases and the lengthening of the waiting list has caused an increasing number of surgeons to perform, when justified, an ambulatory excisional biopsy.

Although not always necessary, this procedure has become requested more frequently—by the women themselves—than hospitalization.

In a few cases, the small dimensions of the alteration do not allow precise diagnostic definition from an extemporaneous histologic examination, or even exclude the possibility of its use. In hospital units where breast pathology accounts for a large part of the surgical activity, the predicted time for the intraoperative excisional biopsy and for histologic results considerably lengthens the operation time and consequently reduces the number of operations that can be performed, with a negative effect on the turnover of the unit.

In contrast, one can no longer rely only on the mammographic findings or the clinical characteristics of the alteration to decide in favor of a mastectomy. The recent widespread use of the practice of cytologic examination by needle aspiration has only partly resolved these problems.[3,5-7] In the last few years, more thorough study of the natural history of tumors, and of breast cancer in particular, has reshuffled the problem of risk of diffusion linked to biopsy. There is evidence that the long-term prognosis of cancer appears mainly a function of distant metastases connected to the T and N stage and histologic type of the tumors, rather than to the risk of diffusion

following biopsy or ablative surgery. Nonetheless, a study on the correlation between biopsy before mastectomy and long-term prognosis seemed equally interesting and justified.

Material and Methods

The investigation was conducted retrospectively on 209 patients who, between 1948 and 1972 at our institute, underwent extended radical mastectomy (ERM) for breast cancer. In all cases, the largest diameter of the tumor was ≤ 2 cm, and they were all classified as T1 N0-1 M0 according to the TNM classification.

Fifty-seven (27.2%) patients were submitted to a previous excisional biopsy. In all cases, the histologic diagnosis of cancer was made or confirmed by our Pathology Service. All the patients prior to the EMR had X-rays of the chest, cranium, rachis, and pelvis to exclude the presence of distant metastases.

Two groups of patients were identified: Group A, with a previous biopsy, and Group B, with extemporaneous intraoperative biopsy. They were then compared with evaluate 10-year survival, site of relapse, the interval between biopsy and ERM (≤ 30 and > 30 days), and the characteristics of the excisional or incisional biopsy.

The patients with lymph node metastases were classified as N+ (axillary lymph nodes) or MI+ (internal mammary chain), not taking into account the number of lymph nodes involved. A protocol of precautional radiotherapy, or chemotherapy was not foreseen for these patients. Radiotherapy was performed, according to the surgeon's judgment as to whether the surgery was radical or not, on a total of 26 patients, 25 of whom belonged to Group B. Follow-up of the patients operated on showed the same frequency in the periodic clinical examinations and the relative diagnostic controls in both groups, since it adhered to an ongoing protocol at our institute in the period concerned. All the patients were followed for at least 7 years after the radical surgery, except for three who were followed for only 5 years.

Statistical Analysis

The analysis of two-by-two contingency tables was done with chi square evaluation of the hypothesis of fixed marginals. When the frequencies of elementary cells of tables were very low, we used Yate's correction factor for the chi square test, or we evaluated the exact probability. Survival was evaluated by means of the life table method for computing survival rates. Statistical analyses of differences between survival rates were carried out by the log rank method.

Results

Of 57 patients who had a previous biopsy, 25% underwent radical surgery within 13 days, 50% within 18 days,

TABLE 1. *Group A and B Patients Subdivided According to Age*

Age (years)	Group A		Group B		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
41–50	21	36.8	19	12.5	40	19.1
51–60	11	19.3	55	36.2	66	31.6
61–70	14	24.6	42	27.6	56	26.8
>70	11	19.3	36	23.7	47	22.5
Total	57	100	152	100	209	100

and 75% within 30 days (average, 25 days; range 5–99 days). Examination of the surgical specimen revealed residual tumor in only ten (17.5%) patients.

The ages of the patients in Groups A and B ranged from 40 to 75 years. The distribution by age decade of the two groups showed a statistically significant imbalance in favor of Group A in the decade 41–50 years (36.8% for Group A compared with 12.5% for Group B), whereas the contrary, in favor of Group B, occurred in the successive decades (Table 1).

In both groups, the different histologic subgroups were represented equally: 90% were infiltrating ductal carcinoma, 9% infiltrating lobular carcinoma, and 1% medullary carcinoma. Histologic examination revealed that the axillary lymph nodes and internal mammary chains were free of metastatic diffusion (N−, MI−) in 156 patients (74.6%), whereas there were 53 (25.4%) cases of regional lymph node involvement, which were classified as N+ and/or MI+. The distribution, according to the involvement of different lymph nodal stations, shows the absence of statistically significant differences between the two groups (Table 2).

The 10-year survival of the 209 patients was 79% in Group A and 77% in Group B (Fig. 1). Table 3 reports the survival for Groups A and B in relation to the different lymph nodal stations involved. The survival of N− and MI− patients in the two groups was 90% and 81%, respectively, with no statistically significant difference. The 10-year survival as a function of lymph node involvement was 50% in Group A and 67% in Group B,

TABLE 2. *Group A and B Patients Subdivided According to the Presence of Lymph Node Metastases*

Lymph Node Station*	Group A		Group B		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
N− MI−	44	77.2	112	73.7	156	74.6
N+ MI−	9	15.8	25	16.4	34	16.3
N− MI+	3	5.3	5	3.3	8	3.8
N+ MI+	1	1.7	10	6.6	.11	5.3
Total	57	100	152	100	209	100

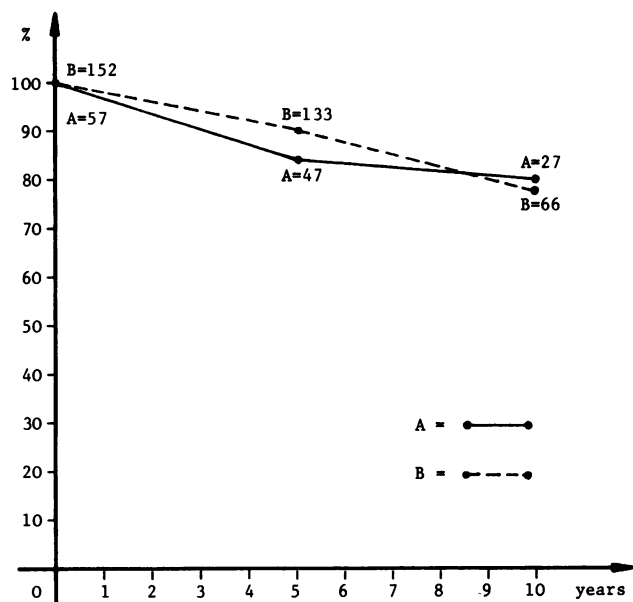* N, axillary; MI, internal mammary chain.

FIG. 1. Cumulative survival of 209 patients with breast cancer in relation to type of treatment. A: patients with preoperative biopsy. B: patients with intraoperative biopsy. Numbers indicate those patients at risk at 5 and 10 years.

with no statistically significant difference. As regards survival in relation to metastases of the internal mammary chain, which occurred in 19 cases (9%) and of which 11 also had axillary lymph node involvement, it was 50% in Group A and 49.8% in Group B.

Of the 45 patients who relapsed, 16 (35.5%) had a relapse in the skeleton, 11 (24.4%) in the lungs, and eight (17.7%) in locoregional sites. Table 4 reports the distribution of relapse in Groups A and B, in which there were no significant differences in the various types of metastatic localizations.

Conclusions

Our work unfortunately suffers from the typical defects attributed to many retrospective historic studies, indeed from the analysis of groups of nonrandomized

TABLE 3. *Ten-Year Survival in Relation to Lymph Node Metastases*

Lymph Node Station*	Group A No. of Patients	%	Group B No. of Patients	%	Total No. of Patients	%
N− MI−	44	90.0	112	81.9	156	84.1
N+ MI −	9	55.6	25	75.0	34	69.8
N− MI+	3	33.3	5	51.8	8	44.4
N+ MI+	1	—†	10	49.1	11	44.6
Total	57	79.9	152	77.7	209	78.3

* N, axillary, MI; internal mammary chain.
† Survival at 3 years.

TABLE 4. *Site and Frequency of the First Relapse of the Disease in Groups A and B*

Site	Group A No. of Patients	%	Group B No. of Patients	%	Total No. of Patients	%
Locoregional	2	15.4	6	18.7	8	17.8
Lungs	3	23.1	8	25.0	11	24.4
Liver	1	7.7	0	—	1	2.2
Bone	4	30.7	12	37.5	16	35.6
Multiple sites	—	—	2	6.3	2	4.4
Other sites	3	23.1	4	12.5	7	15.6
Total	13	100	32	100	45	100

patients. For example, it was difficult to identify, in several cases, the reasons for recourse to diagnostic biopsy in the patients of Group A. However, the most common cause was the clinical and radiologic characteristics of apparent benignancy.

To avoid any bias in selection, we included in the study all those patients who underwent extended mastectomy for breast cancer at the Instituto Nazionale Tumori and classified as T1, in order to have as homogeneous a group as possible. Moreover, the following characteristics suggest that this series is suitable for the investigation: 1) Of the whole series of patients who underwent ERM or RM during the period considered, almost all of the patients who underwent preoperative biopsy were T1. 2) The dimension of the tumors, ≤2 cm in diameter, was ideal for excisional biopsy, in that it is possible to remove completely all of the tumoral tissue even in outpatient surgery. 3) The T1 tumor has the best expected prognosis at 10 years, so that a possible negative effect on survival attributable to the biopsy cannot be masked by the rapid selection effected by some factors that aggravate the prognosis (*i.e.,* size of T, N+) in other stages of the disease.

There have been various studies on the prognostic significance of preoperative biopsy, excisional or incisional, in the treatment of breast cancer.[8-18] The absolute lack of risk of metastatic dissemination has not been demonstrated with sufficient certainty by such works. In fact, the characteristics of the various series were such that a solution to this query is impossible, *i.e.,* the small size of the series, the comparison between groups of patients nonhomogeneous for T and/or N, and an insufficient follow-up.

However, in these studies the survival of the patients with previous biopsy was similar to that of Group B (intraoperative biopsy) and in general, whether it was excisional or incisional had no influence on the prognosis. In our experience, there was also no difference in survival at 10 years between Groups A and B (Fig. 1), and the same analysis of the subgroups N− and N+

showed analogous results (Table 3). However, our studies confirm that the prognosis is mainly dependent on histologic characteristics and the stage of the primary neoplasm and regional lymph nodes.

Even if Groups A and B were not distributed homogeneously in the various decades of age (Group A patients were younger than those of Group B), there was no statistically significant differences in survival (Table 5).

Our conclusions are in agreement with those already expressed by most authors, with only two exceptions,[14,17] who reported a negative effect on survival of a delay of the mastectomy of more than 15 days after the biopsy. Moreover, our series does not allow an evaluation of the importance of the length of the therapeutic delay and the presence of residual neoplastic tissue, because it is too small to be broken into additional subgroups.

In the light of the present data, one can consider the use of excisional biopsy, for an initial ambulatory diagnosis, in T1 tumors (and mainly in cases without cytologic or radioclinical evidence of malignancy) to furnish diagnostic and prognostic information on the histologic type, hormonal receptors, and other biologic characteristics useful in the choice of successive treatment.

By comparison, as already stated, a similar diagnostic approach would have the advantages of shortening the actual hospitalization period, and the relative health service costs would exclude histologically benign cases from admission and would offer women the possibility of an informed consent and a conscious choice of the alternatives.

That the biopsy, or the therapeutic procedure performed successively (i.e., excisional biopsy, simple mastectomy or radiotherapy), does not modify the prognosis of breast cancer has been also demonstrated by the works of Peter and Fischer,[19-21] in which different therapeutic programs have not significantly influenced the incidence of cure in patients with breast cancer. This series of favorable data, which do not attribute much importance to the biopsy, must be considered carefully because they are based on retrospective studies. Therefore, before judging how the evaluations were reached, it would be advisable to wait for the results of a prospective randomized study.

The results of our study must be applied only to patients with neoplasms ≤ 2 cm in diameter (T1) submitted to radical mastectomy after biopsy and not to other categories, and they suggest the usefulness of a prospective study. In fact, outpatient biopsy of a breast cancer has some advantageous aspects: 1) select for admission and diagnostic work-up those patients with a confirmed diagnosis of carcinoma; 2) simplify preparation of therapeutic trials, facilitating inclusion and randomization of patients; and 3) inform the patients of the nature of the disease and permit their participation in the therapeutic decisions with greater awareness and responsibility.

TABLE 5. Survival at 5 and 10 Years According to Age

Age (years)	Group A			Group B		
	No. of Patients	5-year %	10-year %	No. of Patients	5-year %	10-year %
41–50	21	85.7	80.9	19	89.5	58.6
51–60	11	100	73.5	55	92.7	87.0
61–70	14	85.7	78.6	42	92.9	87.3
>70	11	90.9	81.3	36	85.6	61.9
Total	57	84.0	79.9	152	90.0	77.7

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