

Sounding Board

Comments on Primary and Adjuvant Treatments of Breast Cancer

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HISTORICAL APPROACH TO BREAST CANCER TREATMENT

VICTORY in the fight against breast cancer has been attempted for many decades by extensive use of one treatment modality, i.e. radical surgery. In recent years the use of adjuvant therapies (cytotoxic chemotherapy, endocrine therapy) have been championed. The rationale of this approach is based on the presence, following apparently definitive surgery, of a subclinical disease either local-regional or systemic that ultimately causes the death of the patient. The evolution of the concepts for the management of breast cancer is summarized in two recent papers by Fisher [1] and Tagnon [2].

In the past, local treatment was considered 'radical' when total mastectomy and *en bloc* dissection of regional nodes, even if clinically uninvolved, was performed. The aim was to prevent metastatic spread. Regional lymph node dissection, considered initially mandatory in the presence of involved nodes, has become in many cases an elective dissection with a 'prophylactic significance'.

In the wake of this conviction, during the forties and fifties, radiotherapy was combined with surgery. At the end of the sixties radiotherapy was more and more frequently employed to sterilize possible occult neoplastic foci in nodes of the supraclavicular fossa and internal mammary chain. In this case, too, the procedure had developed from a local support therapy into a 'prophylactic' approach, which was then abandoned at our Institute during the middle seventies. This period wit-

nessed a significant change in the pathobiologic and therapeutic approach to breast cancer, considering that lymphatic and hematogenous dissemination is present in most patients, but with an unpredictable tumour biological behaviour.

Thus, a 'radical' loco-regional approach was felt of lesser importance for a cure. The imperative for a new 'prophylactic' approach became the sterilization of occult tumour cells disseminated throughout the body. Because of their small size and good vascularization these microscopic foci are thought to be more easily destroyed by cytotoxic drugs. Also, strengthening the natural defences of the organism seemed a feasible approach. However, the idea of 'prophylactic' immunostimulation was soon abandoned because of lack of positive results. In contrast, cytotoxic polychemotherapy was increasingly employed. More recently it has been shown that the more advanced a tumour, the more probable it is that it contains malignant cells which are or will acquire a resistance to drugs [3]. This finding would constitute the most significant theoretical argument in favour of early prophylactic chemotherapy. On the other hand in a major proportion (50-70%) of breast cancer patients with positive axillary nodes adjuvant polychemotherapy is provided when systemic cancer cell proliferation is minimal or absent; cytotoxic drugs have little effect, if any, on dormant tumour cells [4].

PRESENT TREATMENT OF BREAST CANCER

The management of operable breast cancer today focuses on local therapy, and on the means (irradiation, polychemotherapy, endocrine therapy) to destroy clinically undetected local-regional

Table 1. Disease-free survival and survival at 9 years following radical mastectomy and lesser local-regional therapy*

Study group	Number of patients	Life table†			
		Disease free survival (%)	<i>P</i> Value ‡	Survival (%)	<i>P</i> Value ‡
<i>Clinically negative nodes</i>					
Radical mastectomy	362	62	—	60	—
Simple mastectomy plus radiation	332	64	0.5	61	0.8
Simple mastectomy	365	62	0.9	58	0.8
<i>Clinically positive nodes</i>					
Radical mastectomy	292	42	—	41	—
Simple mastectomy plus radiation	294	41	0.6	40	0.7

*NSABP Protocol B-04. Analysis employed a two-sided chi-square.

†Adjusted to radical mastectomy patients relative to age and tumour size.

‡Related to radical mastectomy patients.

From Fisher [18].

or systemic spread.

The following questions need to be answered:

1. Is radiotherapy needed after conservative surgery?

Except for some dissenting opinions [5–7], there is agreement that radiotherapy is not necessary after radical surgery, because survival rates are the same with surgery alone [8–13]. Radiotherapy for patients with conservative surgery (lumpectomy), on the contrary, is always provided. However, if irradiation is certainly necessary after lumpectomy, its use after quadrantectomy may be questioned: in fact this surgical procedure meets all the requirements of 'radical' surgery for solid tumours. The multicentricity of breast cancer should not be a sufficient reason to support this assumption. The same problem exists in thyroid cancer. Occult tumour foci are present in more than 50% of patients in the contralateral thyroid gland upon histological examination [14–16]. However, in our experience recurrence of thyroid papillary cancer does not exceed 5% even when only lobectomy is performed [16]. The same may be true for cancer of the breast. Recurrence in the ipsilateral breast after quadrantectomy is not a major problem and it can be controlled by mastectomy without impact on the prognosis [17].

2. Is axillary dissection needed when lymph nodes are clinically not involved?

Complete axillary dissection is undoubtedly needed in the presence of clinically suspicious or positive axillary nodes, but 'radical' surgery extended to clinically uninvolved regional lymph nodes should be reconsidered: a clinical trial carried out in the United States [18] shows that immediate 'radical' axillary dissection achieves the same results as delayed removal at the clinical appearance of node metastases both in terms of disease-free interval and overall survival (Table 1).

Similar results were obtained comparing mastectomy with or without radiotherapy of axillary nodes [19, 20].

However the 'wait and see' policy, universally accepted for tumours of the skin and the thyroid for which regular observation of the patient is recommended, is not accepted for breast cancer. Nevertheless, an international trial has shown that the removal of the internal mammary lymph nodes does not improve the prognosis of breast cancer patients [21–23]. In our experience total removal of the regional lymph node chains [24] of the breast (axillary, supraclavicular and mediastinal) has not modified the outcome of locally advanced breast cancer. There is no reason to believe that sole removal of the axillary lymph nodes could be more effective. Some authors justify axillary dissection for prognosis and as a basis for the decision to administer or withhold adjuvant therapy. This approach is in contrast to the findings that involvement of the internal mammary lymph nodes has an equally poor prognosis [23, 25, 26] (Fig. 1). But despite this, only the axillary node status is taken into consideration as to the decision of adjuvant chemotherapy; definitely, this approach appears illogical.

3. Is adjuvant chemotherapy needed in patients with positive nodes?

Information available on the pathobiology of breast cancer in patients with regional (axillary, parasternal) lymph node metastases invite a critical review of the philosophy of systemic adjuvant therapy. A therapeutic programme without adjuvant treatment of patients with positive axillary nodes is considered 'unethical' today. This is in spite of the fact that patients with positive axillary nodes do not always have a poor prognosis depending on the number of nodes involved. Accordingly, the percentage of 10-year survival is approx. 70%

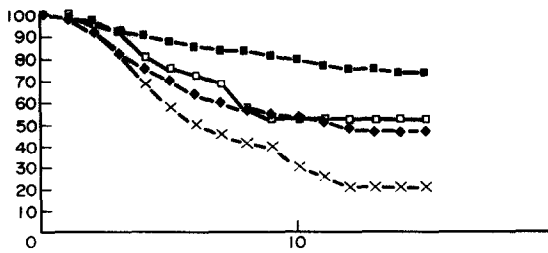


Fig. 1. Survival of 1117 patients following radical mastectomy and axillary and internal mammary node dissection in relation to lymph node status. Updated from Veronesi et al. [26]. ■ Axillary and internal mammary lymph nodes negative (511 patients). ♦ Axillary lymph nodes positive and internal mammary nodes negative (393 patients). □ Axillary lymph nodes negative and internal mammary nodes positive (51 patients). × Axillary and internal mammary lymph nodes positive (162 patients).

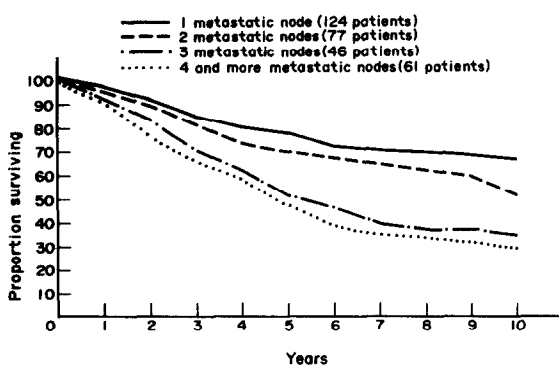


Fig. 2. Actuarial survival rates of 308 patients with breast cancer and positive axillary nodes in relation to the number of positive nodes [27].

for patients with one positive node, while it drops to 25% when four or more lymph nodes are involved (Fig. 2) [27]. Moreover, prognosis of survival depends on other factors than the state of the regional lymph nodes [28–31].

Data available in the literature, on adjuvant chemotherapy, are contradictory [32–37]. The American Consensus Conference [38] has not provided new concepts and the conclusions were based on studies with questionable comparability. The question should be answered: how many studies were carried out with inconclusive results and not published? In the studies published, often not enough consideration has been given to the adequacy of surgical treatment. Equally important is (1) how comparable were different patient groups at least in terms of extent of the disease? and (2) how much attention has been given to the length of the follow up? In the following an attempt is made to answer these questions: The first report on breast cancer patients with positive axillary nodes treated either with surgery alone or with surgery and CMF (cyclophosphamide, methotrexate and fluorouracil) at the National Cancer Institute of Milan [39], favoured the adjuvant groups; it favoured even postmenopausal patients in whom the use of adjuvant chemotherapy is considered

Table 2. First CMF study: 10-year results related to stratification variables

	Controls (%)	CMF (%)	P
Disease-free survival total	31.4	43.4	<0.001
Nodes 1–3	37.7	50.8	0.002
>3	20.3	27.9	0.05
Premenopause	31.4	48.3	0.0005
Postmenopause	32.2	38.2	0.32
Overall survival total	47.3	55.2	0.10
Nodes 1–3	53.4	60.5	0.22
>3	33.5	43.8	0.22
Premenopause	44.8	59.0	<0.02
Postmenopause	50.1	52.1	0.89

From Bonadonna et al. [40].

questionable at present. The recurrence rate 3 years after mastectomy [39] in postmenopausal patients was 23/97 (23.7%) for surgery alone, as compared to 6/112 (5.4%) for surgery and CMF therapy; the recurrence rate in patients with more than four positive lymph nodes was 40.7% in the control group and 8.8% in the adjuvant CMF group. After 10 years, however, the data [40] showed recurrence in 20.3% of the controls and in 27.9% of the CMF-treated postmenopausal women, while in cases with more than four positive lymph nodes recurrence was 32.2% in the controls and 38.2% in the CMF group. Moreover, the latest results on the whole series published in 1985 [37, 40] show that adjuvant chemotherapy yields only modest results: at 10 years, the percentage of disease-free patients is higher in those who have been treated, i.e. 43.4% vs. 31.4% of the controls ($P < 0.001$). However, the difference in overall survival at 10 years was only 7.9% in favour of those patients treated with CMF and the P value was not statistically significant ($P = 0.10$). An analysis of the sub-groups does not differ greatly from these results except for premenopausal patients (Table 2).

CONCLUDING COMMENTS

It seems reasonable to conclude that so-called 'adjuvant' treatments following radical surgery did not change systemic behaviour of breast cancer, i.e. overall survival essentially remained unchanged. Despite all adjuvant therapies, breast cancer mortality remains unchanged or even increases [41], indicating that adjuvant treatments are not effective.

Accordingly, a critical approach is needed before adopting too rapidly 'consensus' solutions without adequate and convincing factual support. On the other hand, as long as no new adjuvant therapies are available which are significantly more effective

than traditional ones, there is no reason to continue to plan new long term studies. Moreover, the question arises whether results obtained in a clinical trial can be confirmed in routine practice.

At present, multicentre international efforts are warranted which consider more the realities encountered in daily practice. Above all, the management of breast cancer should be re-evaluated because of the hasty reports during the seventies, when it was thought that a solution was close at hand, have immobilized the exploration of other avenues.

The comparison of published studies is done in order to reach these 'consensus conclusions' which are biased by the fact that not all results are published and that contrary conclusions based upon unpublished data are often neglected. Also, in these

'consensus' meetings, experts usually participate who are proponents of adjuvant chemotherapy.

In the future, multicentre and international approaches are warranted, to avoid the problems of evaluation encountered with adjuvant chemotherapy in the past. Accordingly, standardization of the methods of selection of patients, collection of data and their proper analysis considering an identity of time and the diversity of place are obligatory premises for the identification of similarities and the interpretation of the differences. The annual collection of data of patients treated and their follow-up regardless whether they were entered in a controlled clinical trial or not is advisable to avoid loss of information on many thousands of patients.

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