

Management of Early Stage Breast Cancer— Current Status of Treatment: Workshop Report

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INTRODUCTION

THE RECENT decade has seen the establishment of breast conserving procedures, adjuvant cytostatic and hormonal treatments and the systematic screening for breast cancer. Although the feasibility of breast conserving procedures is now formally established, many questions remain as to the role of different factors involved, which could determine to some extent the therapy or the selection procedures for the patients in which such a therapy is to be considered suitable. Also, for the systemic adjuvant treatments, many fundamental questions are still open as to the mechanisms of action and as to the patient groups that would profit from such therapy.

In a short period of time, the management of small breast lesions, which used to be a simple and straightforward procedure with mastectomy, has evolved into a complex decision making process, requiring the careful balancing of the effectiveness and side-effects of a number of treatment modalities [1].

In the workshop on early disease, the discussion concentrated on the different problems directly related to the breast conserving procedure, with specific interest in the treatment of ductular carcinoma *in situ* and the role of adjuvant therapy. This selection means that only a part of the valuable new information on the primary treatment brought to this conference in the numerous proffered posters could be discussed.

In this workshop report only abstracts of posters shown in this conference are given as references. The spontaneous and invited contributions to the

discussions in the workshop of many others were also of high importance.

BREAST CONSERVING THERAPY

At the occasion of this workshop the first data presentation of the EORTC trial on breast conservation was given [2]. A total of 903 patients was entered between 1980 and 1986. The survival curves and local recurrence rates are identical for the study and the control arms, in all studied subgroups. This trial is especially interesting because of the large number of stage II patients (85%). The results are still to be considered preliminary since the follow up time is relatively short.

FACTORS DETERMINING LOCAL RECURRENCE

a. *Tumor-related factors*

The two tumor-related factors which have been investigated as to their impact on local recurrence after breast conserving treatment are the volume of the primary tumor and the histology.

The data of the EORTC trial and from the Amsterdam group suggest that, within the limits of the indications used until now for breast conserving therapy, there is no influence of the volume of the primary tumor. The same incidence of local recurrences was found in stage I and stage II tumors [3]. The extent of resection seems to be a more important factor, and, indirectly, the volume of the tumor could influence the local control in so far as a less complete resection could occur more frequently with larger tumors, if the surgeon is not constantly aware of this problem. Also the data from Milan [1] confirm that volume by itself has only little impact on local control. In tumors with a diameter of less than 1 cm, the local recurrence rate was

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3.6% and in tumors with a diameter of more than 2 cm the local recurrence rate was 5%. In the data of the Rotterdam group however, tumor volume was suggested to be a prognostic factor for local recurrence [4].

A very important effect of the presence of ductal carcinoma *in situ* (DCIS) was described earlier by the Boston group. In the group from the Fondation Curie this influence could not be confirmed [5]. In a group of 131 patients without DCIS and 56 patients with DCIS no difference could be demonstrated in the local recurrence rate. Considering, however, a small group of 17 patients in which extensive DCIS was seen, a marginally significant effect was demonstrated. The negative role of the presence of DCIS was also suggested by the data of the Amsterdam group in which five local recurrences were seen in 71 patients with extensive DCIS and two local recurrences out of 208 patients with no or limited DCIS [3]. The data from Amsterdam would suggest that the higher dose of radiotherapy could correct for the presence of DCIS, which would imply the radiosensitivity of this type of tumor. Also the Marseille group did not detect an influence of the presence of DCIS [6]. It should be stressed again that, in this discussion on the role of the presence of extensive DCIS, clear resection margins could be the main determining factor. The differences observed in the different centers could be explained on the basis of different surgical approaches with more or less wide excisions as a routine procedure [5].

b. Treatment-related factors

The factor which is considered to be the most important in determining the local recurrence rate is the completeness of the surgical resection margins. However, the presence of residual tumor can be countered by the use of high-dose radiotherapy. In the Amsterdam group, no differences in local recurrence rate were demonstrated between wide, marginal and incomplete resections after the application of high radiation doses [3]. Management policies should include the assessment of the repercussions of the width of the resection and the sequelae related to higher radiation doses. It has to be kept in mind that the whole range over which local recurrences can fluctuate as a function of the different factors, is between 5 and 10% in the larger groups after tumorectomy and irradiation and about 30% after local resection without radiotherapy.

c. Patient-related factors

The only patient-related factor which has already been investigated is age. In the Fondation Curie, the recurrence rate was significantly higher for the patient group below 30 years [5]. Veronesi reported a local recurrence rate of 9.5% for the patients

below to 35 years and of only 3.5% for the patients above 35 years [1]. Finally, Spitalier from Marseille mentioned that the incidence of local recurrences is twice as high in patients below 40 years compared to those of older patients [6].

The diagnosis of local recurrence after breast conserving therapy is sometimes difficult, e.g. because of radiation induced fibrosis [7]. It appears that cytology can be misleading in these cases: fine needle aspirates from heavily irradiated breast tissue, without tumor recurrence, may give specific pictures of small clusters with microacinar cell arrangement, anisocytosis and anisonucleosis which may lead to false positive diagnosis of recurrence [8].

IMPACT OF LOCAL RECURRENCE

While in the past sometimes too much emphasis was placed on local treatment, it is now often suggested that breast cancer is always a systemic disease and that local control is a secondary, although desirable, aim. The finding that increasingly more aggressive loco-regional treatments did not improve the final outcome has led to the impression in some that a drastic reduction in local treatment will also not affect the survival. This reversal of reasoning is obviously a fallacy. A relatively important number of breast cancers is localized, as is demonstrated by the treatment results. Every remaining tumor activity or clinical relapse should be avoided as they carry a potential risk of being the source of secondary metastases. It would indeed be illogical to think that a primary tumor can generate metastases before first treatment but would not do so at relapse after initial therapy.

The first analyses of the breast conserving treatment studies have not yet yielded significant differences in survival between patients relapsing in the breast or not [9]. One has to be aware that, until now, the total number of patients surviving for sufficiently long time after rescue mastectomy may be too small to make a final statement. Indeed, the differences in local relapse, after different local management policies, are about 15–20%. Even with an incidence of 30–50% of new metastases occurring at relapse, it would still be difficult at this time to detect this influence.

It is true however that, although local recurrences should be avoided, the impact of a regrowth in a conserved breast is very different from the appearance of secondary tumor in a thoracic wall after mastectomy. This is probably due to the fact that thoracic wall recurrences are the expression of a much further spread of disease than local recurrences at the site of the excision. The difference in impact of the local recurrence in the conserved breast is clearly demonstrated in the material of the Marseille group where 72% of the patients survive

5 years after rescue treatment [6] and the data from Amsterdam showing 80% of distant metastases shortly after thoracic wall relapse [10].

TREATMENT OF LOCAL RECURRENCE AFTER BREAST CONSERVING THERAPY

Until now, the standard policy for the treatment of a local recurrence in most centers has been a mastectomy. However, there is now a clear development towards much more limited therapy of such recurrences. In Marseille, 50% of the rescue therapies are again breast conserving therapy combining a tumorectomy with a small volume of irradiation with an iridium implant [6]. This possibility of breast conserving rescue therapy is also included in the new trial set-up in Milan.

LATE SEQUELAE AND QUALITY OF LIFE

Studies of very long term follow-up patients having been irradiated in an adjuvant setting are now becoming available. The assessment of the CRC trial is a good example of this. They report an increased incidence of cardiovascular deaths and secondary malignancies outside the radiation therapy field as the causes of an increased death rate in the patients having received radiotherapy [11]. This initial report will obviously require further analysis as to the cause of non-breast cancer related deaths but it stresses again the importance of careful analysis of long-term effects of any therapy and the necessity to balance the potential benefits and possible drawbacks of any treatment. Apart from these sequelae, more detailed studies also become available on the impact of different treatment modalities on quality of life, for instance the psychological repercussions of mastectomy and the relationship between technical therapy factors and cosmetic results in breast conserving therapy [12, 13].

DUCTAL CARCINOMA *IN SITU*

The increasing use of breast screening programs leads to the detection of larger numbers of ductal carcinoma *in situ* (DCIS). Conventional simple mastectomy results in an almost 100% cure [14]. The main discussion point for the moment centers on the question of whether breast conserving therapy is a real option for the treatment of DCIS and on the potential role of radiation therapy in this. In the Linköping group [15], 24 patients received a mastectomy, one of these developed a contralateral invasive cancer. In the 41 patients in which a sector resection was carried out, there were three subsequent relapses of DCIS and four ipsilateral invasive cancers.

A retrospective study carried out by Lerut *et al.* [16], in the participating centers of the breast cancer cooperative group of the EORTC, analyzed 93 patients. In these, there was a 18% local recurrence

rate after simple resection and a 10% recurrence rate after local surgery, followed by radiation therapy. In the Royal Marsden group [17], there were 16 recurrences in 27 patients who underwent a limited excision and four recurrences in 27 patients in which a wide resection was performed. Of these local recurrences, 60% were *in situ* tumors and 40% invasive. The pathological finding of the Nijmegen study [18] did show that half of the DCIS tumors detected in a screening program were already more than 5 cm in diameter.

In conclusion, it can be said that local recurrence is still a major problem after conservatively treated DCIS. The new EORTC trial on this type of breast tumor is studying the impact of the radicality of the surgical margins and the role of the radiotherapy [19].

TREATMENT OF THE AXILLA

The surgical treatment of the axilla is done on the one hand for the regional control of the tumor [1] and on the other hand to provide the necessary prognostic information available on which to base possible adjuvant therapies. While the control rate of the regional nodes in the clinical N₀ stage is the same for irradiation and surgery, the prognostic information will only be available after dissection. The impact of this information was discussed to some extent, especially in view of the question of the quality of life. Indeed, axillary dissection does carry some morbidity for the patient and may, for the total group of patients, only yield limited information. In the patients who are clinically node negative, 25–30% are found to be histologically positive. In this group, the adjuvant chemotherapy would result in an improvement of about 10% of the survival, probably significantly less in the post menopausal patients. This would mean that of all the patients with a clinically negative axilla, only 2–3% would benefit from 100% axillary dissections and 30% adjuvant therapies.

It seems that for any assessment of experimental therapies, information on the nodal status in the axilla is still necessary as this would discern between biologically different diseases, making these data mandatory for careful staging. The usefulness of routine axillary clearance versus primary radiotherapy in N₀ patients is questionable.

ADJUVANT CHEMOTHERAPY

The different questions relating to the adjuvant therapies can be divided in three main problems: does it work? what is the mechanism? what is the price to pay?

The importance of large patient groups (e.g. pooling of data; meta analysis) and of long follow up periods was stressed.

In several groups, differences in absolute survival

remain after longer follow-up, with the effect of CMF most pronounced in patients below 50 years and the effects of tamoxifen in the patients above 50 years [20–23]. The longest follow-up available from Bonadonna in the Milan group still shows a significant positive effect for chemotherapy after a period of 11 years. Differences are found in all nodal stage groups for survival and relapse free survival. Statistical significance is however limited to the premenopausal patients.

The discussion on whether the adjuvant chemotherapy works through a castrating effect or due to cytotoxic mechanisms is still ongoing [20, 24, 25]. Based on a number of data, including the incidence of drug induced menopause, the difference in effect in pre- and postmenopausal women, the difference in impact in the oestrogen receptor positive and negative tumors, a number of hypotheses have been built to stress either the hormonal or the cytotoxic mechanism of the chemotherapy. A combination of cytostatic and hormonal therapies seems to give little additional effect over either of the two treatment modalities by itself.

In the discussion on possible difficulties caused by the combination of chemotherapy and radiotherapy, most data show no adverse effect of early or simultaneous chemotherapy [26]. The revival of interest in early adjuvant therapy is leading to new trials studying perioperative adjuvant therapy and neoadjuvant therapy. The effect of perioperative adjuvant chemotherapy is being studied in a recently initiated EORTC study [27].

The discussion as to the price to pay for the adjuvant treatment and its comparison to the poten-

tial benefits that can be derived from it is still heavily emotionally loaded. Some investigators consider the 10% increase in final survival 'a marginal effect', others enthusiastically confirm that 'this is a very big effect, rarely to be achieved in chronic diseases'. The whole discussion on the repercussions of the adjuvant chemotherapy on the quality of life is still centered around the acute toxicity and much longer follow-up periods will be necessary to be able to make an assessment on the late side-effects possibly related to the cytostatic therapy.

CONCLUSIONS

The management of early breast cancer is a very exciting field at the present time. After the very long process required to make breast conserving therapy acceptable, this treatment procedure is now widely accepted. The necessity carefully to balance the therapeutic advantages and the possible sequelae of the different steps in treatment such as surgery, radiotherapy and chemotherapy make a thorough investigation necessary of the impact of a number of tumor and treatment related factors, enabling more individual tailoring of the different treatment modalities in the future. No dramatic novelties have developed in recent years but the rapidly increasing practical knowledge of the different factors involved in the decision-making process are leading to a better adapted treatment schedule and a largely improved quality of life for the patients. In this process, it is very important to keep on a steady course and not to drop sound principles such as the necessity for local tumor control.

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