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CLINICAL TRIALS IN LOCALLY ADVANCED BREAST CANCER

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Abstract

Survival after treatment of locally advanced breast cancer is poor and resembles that for untreated breast cancer. Although retrospective comparisons have suggested that the addition of systemic treatment might be beneficial, a literature survey of the controlled clinical trials failed to show consistent survival benefits of any treatment modality. The local control, or time to local progression, on the other hand seems to be improved by increasing the dose of radiotherapy, or by the addition of endocrine or cytostatic treatment. Further studies should be undertaken to find better means to subdivide patients in different treatment groups. Since the present treatment modalities are unlikely to improve survival more than marginally, clinical studies are necessary to search for the best palliative treatment, until experimental work provides us with better treatment tools.

Key words: Breast cancer, locally advanced, clinical trials.

Locally advanced breast cancer affects a significant proportion of breast cancer patients. Unfortunately, the condition is not well-delineated from less advanced cases on the one hand or from metastatic cases on the other and its definition depends on both clinical judgement and on the methods available for diagnostic evaluation. Often, the term locally advanced breast cancer is used synonymously with inoperable breast cancer without detected distant metastasis.

Breast cancer may be considered as locally advanced, or inoperable, if the primary tumour is fixed to the chest wall (T4a) (1) or there is oedema or ulceration of the skin or skin nodules over the breast (T4b), or because the tumour clinically has the character of inflammatory breast cancer (T4d). Often, oedema of the skin must extend over more than 1/3 of the breast in order to make the case inoperable (2). To what extent a breast cancer is considered as inoperable solely due to its large size (T3) is probably subject to wide variation between surgeons. Other criteria of the primary tumour, such as hyperthermia pattern or malignancy grading, may also influence the decision.

Ipsilateral axillary lymph node metastases fixed to one another or to other structures (N2) usually render the case inoperable. Sometimes, microscopically involved apical lymph nodes after a biopsy is the only criterion of inoperability (2).

Clinically involved superclavicular lymph nodes are, according to the present TNM classification of UICC (1), considered as distant metastasis (M1), but must from a biological point of view be regarded as a criterion of locoregional advancement.

Thus, different reports on the survival of locally advanced breast cancer may refer to different selections of patients, which may explain differences in frequency as well as differences in outcome or treatment.

Locally advanced, or inoperable breast cancer, accounts for 5–20% of all breast cancer cases in western countries, but for a larger proportion of cases in developing countries. The frequency seems to have diminished over the time. In a Swedish material from the 1930s 19.1% of the breast cancer patients were considered as locally advanced (3) whereas a population-based survey in Stockholm county in 1976 revealed 7% such cases (4). In patients who were under 71, only 4% were inoperable. A lower frequency may obviously be the result of 'earlier' detection of the disease, but it may possibly also be caused by a dilution of lethal breast cancer cases with less malignant cases.

There is a wide range of clinical presentations of this condition. On the one extreme, there is the patient who presents with a slowly growing large tumour, perhaps seeking medical advice due to a complication, such as a bleeding ulcer or infection and with a history of several

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years. On the other extreme hand there is the rapidly progressing cancer of the so-called inflammatory type.

The survival of patients with locally advanced breast cancer varies from material to material. In the cohort of all breast cancer cases reported to the Norwegian cancer registry in 1953 through 1967, 7% were considered as stage III cases. After some mathematical modeling, the cure rate was considered as less than 20% (5). The median survival time of those who died from breast cancer was 2.1 years but many patients survived for long periods of time. The median survival is similar to the median survival of 2.7 years in untreated patients (6).

In these patients, distant metastasis is the main problem, but uncontrolled local growth may contribute to poor quality of life.

The role of local therapy

There is no formal trial that has compared local treatment alone to no treatment. Several retrospective studies on patients treated initially with local therapy, mainly radiotherapy or radiotherapy plus surgery, are published (7–9) showing poor survival of the patients. The radiotherapy dose seems to influence the duration of local control, but not that of survival (7, 8). Survival, however, was positively correlated to the magnitude of the response to irradiation. This might be the reason why Zucali et al. (9) in their retrospective study found a significant survival benefit in those who were surgically treated after radiotherapy compared to those treated with radiotherapy only.

Systemic therapy in locally advanced breast cancer

The poor survival due to distant metastasis and the obvious results of systemic treatment in advanced breast cancer have led to the adoption of such treatment also in locally advanced breast cancer. Several reports have indicated that multidrug chemotherapy may induce regression of the primary tumour in this state and, compared to non-randomized controls, might prolong survival (7, 10, 11). In a randomized study of patients with operable stage III breast cancer Gröhn et al. (12) found that the combination of postoperative radiotherapy and six courses of doxorubicin, vincristine and cyclophosphamide significantly improved disease-free survival and overall survival compared to those either treated with radiotherapy or with chemotherapy. However, that study comprised only approximately 40 patients in each group.

In a controlled study, Schaake-Koning et al. (13) studied radiotherapy alone or radiotherapy plus a combination of chemotherapy and tamoxifen. Chemotherapy was in a randomized way given entirely after the end of radiotherapy or before and after the local treatment. After a median follow-up period of 5.5 years, there was no difference in survival between the groups. Although there was a slight delay in recurrence in the combined treatment groups, this was not statistically significant. Nor was there any difference between the two groups according to the timing of chemotherapy and radiotherapy.

Recently, the results of an EORTC study on the additional value of immediate endocrine therapy (castration in premenopausal and tamoxifen in postmenopausal women) and chemotherapy (cyclophosphamide, methotrexate, 5-fluorouracil for 12 courses) to radiotherapy were published (2). Both chemotherapy and endocrine therapy significantly improved the disease-free survival. This was achieved mainly through a prolongation of the time to local and regional progression. No significant difference in survival was observed in this study, which comprised 383 evaluable patients. A graph shows survival for the four treatment groups. From this the median survival can be estimated to vary between less than three years (radiotherapy plus chemotherapy) and 4.5 years (radiotherapy plus chemotherapy plus endocrine therapy). The effect of endocrine therapy was found only in patients with oestrogen receptor positive tumours. The authors were astonished that the systemic treatment had little effect on the occurence of distant metastases in spite of its effect on the local disease. Even in the combined treatment groups, local regional progression continued to be a problem.

A direct comparison between systemic treatment and radiotherapy has been performed in 87 postmenopausal patients with tumours exceeding 5 cm on clinical measurement or with 'gross nodal involvement' (14). If radiotherapy was given, a dose of 40 Gy in 15 fractions was applied. The systemic treatment consisted in tamoxifen 20 mg b.d. No statistically significant differences were observed in overall survival, time to distant metastases or duration of response, although it should be borne in mind that the statistical power of this study is low. The objective response rate following radiotherapy was, however, significantly higher than after tamoxifen.

The addition of systemic therapy to local treatment

After a retrospective survey which showed poor results of local treatment alone in advanced breast cancer, the Milan group (15) conducted a controlled clinical trial on 132 evaluable patients. All patients were to be treated with doxorubicin and vincristine for three cycles, followed by either radiotherapy or surgery, and a further seven courses of the same chemotherapy. Only minor, if any, differences in survival, distant metastasis or local control were found between the treatment groups. The authors concluded that the combined treatment had improved the results in comparison to their previously reported series of patients treated with radiotherapy alone (9). Since neither radiotherapy nor surgery prevented local relapses, they suggested a study on combined surgery and radiotherapy.

Papaioannou et al. (16) conducted a trial on preoperative chemotherapy plus surgery in locally advanced breast cancer, i.e. tumours 5 cm or greater, but patients with skin nodules or skin changes exceeding 1/3 of the breast were excluded. After surgery, the patients were randomized to postoperative radiotherapy or not and all patients were given 10 further courses of chemotherapy. Premenopausal patients were also oophorectomized and all patients received tamoxifen. Unfortunately, 42% of the patients were 'disqualified' after randomization due to major protocol violations and only 57 patients in one group and 48 patients in the other were evaluable. There were significant differences in age and nodal involvement between the two groups. The authors were aware that these facts severely reduced the value of the study, which mainly indicated poor survival and recurrence-free survival in spite of the combined treatments.

Discussion

It is obvious that locally advanced breast cancer constitutes a major therapeutic problem. In terms of survival, or time to distant metastasis, none of the treatment modalities under examination in the reported clinical trials has been convincingly more successful than any other. According to abstracts submitted to various meetings, a number of similar trials are underway but the preliminary results do not seem to change the situation. In spite of effect on local morbidity neither radiotherapy, surgery nor systemic treatments has changed the appearance of distant metastasis or survival.

Unfortunately, the statistical power of most of the trials is such that even substantial survival differences should be difficult to reveal.

Local control is also a problem. There seems to be a correlation between the dose of radiotherapy and local control (7) but this has not yet been confirmed by randomized studies. The addition of endocrine and/or cytostatic therapy, on the other hand, has enhanced the local effect of radiotherapy and/or surgery (2). Patients who respond to initial chemotherapy or to radiotherapy seem to have better survival compared to those who do not respond. If effective combination chemotherapy is given prior to local treatment, surgery and radiotherapy seem to give similar local and distant control (15). The combination of surgery and radiotherapy plus combination systemic treatment has not been studied in properly conducted clinical trials (16).

It is obvious that locally advanced breast cancer is a heterogeneous group of diseases and that further efforts should be undertaken in order to find better means of dividing the patients into different treatment categories. If we accept that the available treatment modalities give similar overall survival results, further trials should include the measurement of 'quality of survival' in order to define, if possible, the best palliative approach. Poor treatment results also lead to continuous efforts to find better methods of treating the disease. Effective cytostatic therapy after oestrogenic stimulation is being studied, since preliminary results are promising (17). Intraarterial chemotherapy has given good local results in small series of patients (18, 19) and might be included in further trials, since the local treatment results could also be improved. It is not likely, however, that present treatment modalities, used in other combinations, will have more than marginal effects on survival. The hope for the future is that experimental research will give better therapeutic tools.

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