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Feature Articles

NIH Consensus Meeting on Early Breast Cancer

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A CONSENSUS DEVELOPMENT conference on the treatment of early-stage breast cancer was organized on 18–21 June 1990, by the National Cancer Institute and the Office of Medical Applications of Research of the National Institutes of Health. The objective was to evaluate the results of breast conservation and adjuvant therapy in node-negative breast cancer. Data were presented by 30 experts, 19 from the U.S.A. and Canada and 11 from Europe. A panel of observers, chaired by William C. Wood, agreed to prepare a consensus document. The panel was composed of specialists and generalists from the medical profession and related scientific disciplines, clinical investigators, methodologists, and public representatives.

Results of breast conservation trials were presented by investigators from the U.S.A. (NSABP and NCI trials) and from Europe (Milan, EORTC, and Danish trials), with collation of a large quantity of data on both survival and local control. The trials, which included nearly 5000 patients, evaluated different surgical techniques (quadrantectomy, lumpectomy, wide resection) and different radiotherapy procedures (high-energy irradiation without boost, with boost by external irradiation, and with boost by implantation of radioactive material).

Most of the trials were first-generation, comparing the conservation treatment with mastectomy, although some early data were presented from second-generation trials, comparing different conservative procedures. The length of follow-up in most trials was considered adequate, since at least half of the evaluated patients had been followed up for more than 10 years, some having been treated up to 17 years ago.

The conclusion of the panel was unequivocal: breast conservation should be the treatment of choice for stages I and II breast cancer. The statement reads: "Breast conservation is an appropriate method of primary therapy for the majority of women with stage I and II breast cancer and is preferable because it provides survival equivalent to total mastectomy and also preserves the breast". But what is meant by the majority of women? In the consensus report, it means all women with breast cancer up to 4 cm in maximum diameter but not women with multicentric breast malignancies, including those with gross multifocal disease or diffuse microcalcifications detected by mammography, or patients for whom breast conservation would produce unacceptable cosmetic results such as women whose tumours are large in relation to breast size and those with certain collagen vascular diseases.

It is, however, admitted that certain pathological and clinical factors may influence treatment selection because of a potentially adverse impact on local recurrence after breast conservation. These factors are controversial; examples include the presence of extensive intraductal carcinoma within and adjacent to the primary tumour, extensive lymphatic involvement and age under 35–39 years. Local control is one of the fundamental objectives, together with cosmetic results and, obviously, the maximum possible survival. Treatment options for good local control include a variety of local surgical procedures and postoperative radiation therapy. Although local control can be obtained in some patients with local excision only, no subgroups were identified in which radiation therapy can be avoided.

As regards diagnosis, fine needle aspiration cytology is recommended as well as limited incisional biopsy for large lesions. In excisional biopsy, the excision should be wide and definitive. The surgical removal of the primary tumour should be generous but a margin of normal tissue of more than 2 cm is not recommended (for cosmetic reasons), and the removal of the overlying skin should be limited to superficial surgical tumours.

Axillary dissection (at least the first and second level) is recommended as routine for staging and for prevention of axillary recurrence. Separate incisions should usually be done for the primary tumour excision and for axillary dissection, to give better functional and cosmetic results.

For postoperative radiotherapy, which is considered an essential component of conservative treatment, megavoltage radiation therapy to the whole breast to a dose of 45–50 Gy is recommended, whilst the precise indications for boost irradiation are not well defined. However, the panel recognized that boost irradiation has been used in most trials. Boost irradiation should be delivered by electron beam, or implantation, to 10–15 Gy since higher doses may produce cosmetic impairment.

According to the panel, "At present no data indicate any increased risk of secondary malignancies or contralateral breast cancers resulting from breast irradiation. Longer follow-up of this population is necessary to solve this issue fully". For the combination of postoperative radiotherapy and adjuvant chemotherapy, should the latter be indicated, no precise recommendations about the sequence and timing of radiation therapy and chemotherapy could be made.

In future research, efforts should be made to identify subgroups that may be treated with surgical excision without irradiation and subgroups that do not require axillary node dissection. Other research objectives should be to establish: (1) the optimal margin for local primary excision in the presence and absence of extensive intraductal cancer; (2) whether boost irradiation is required in patients with pathologically negative margins and whether boost irradiation produces a high probability of local control in patients with microscopic involvement

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of margins; and (3) the optimal sequence and timing for radiation therapy and systemic adjuvant therapy.

The conclusions adopted by the consensus panel are likely to have an important influence on the treatment policy of early breast cancer throughout the world. The acceptance without reservation of the principle of breast conservation by appropriate combined surgical-radiological procedures will influence medical opinion, convincing the profession of the need to proceed in the direction of less mutilating procedures whenever such techniques will obviously not interfere with survival rates, so that breast cancer patients, once cured of their disease, will enjoy a life as close to normal as possible. This will, in turn, increase the confidence of women that they will receive more humane treatment and will stimulate their participation in prevention and detection programmes.

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Adjuvant Chemotherapy in Node-Negative Breast Cancer NCI Consensus Conference

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THE DATA from six randomised clinical trials on adjuvant chemotherapy in node-negative breast cancer were presented at the National Cancer Institute consensus conference. Overall, despite differences in patients' selection criteria, drug combination, dose intensity and duration of adjuvant treatment, it was felt that adjuvant chemotherapy can reduce the rate of disease recurrence by about a third. To date mortality has been reduced in nearly all trials but the decrease has not been statistically significant in most. However, the rate of death in node-negative patients is low, so a clinically important reduction in mortality may require a long follow-up to achieve statistical significance. Among the various chemotherapy regimens, more benefit was seen in trials in which antimetabolites were administered intravenously than in trials in which such drugs were given orally. The results of the six trials can be summarised as follows.

The Swiss investigators [1] reported an increased, albeit not statistically significant, 14 year relapse-free and overall survival favouring patients treated with oral chlorambucil, methotrexate, and fluorouracil (LMF) given for 6 months, followed by BCG immunotherapy up to relapse or 2 years. 122 node-negative patients entered the study, but no attempts were made to select patients with unfavourable prognosis.

The 7-year results of the study performed at the Milan Cancer Institute [2] showed that women with node-negative and oestrogen receptor (ER) negative breast cancers benefitted from intravenous cyclophosphamide, methotrexate and fluorouracil (CMF) administered every 3 weeks for twelve courses. Both relapse-free (control 42% vs. CMF 85%, $P = 0.0001$) and overall survival (58% vs. 86%, $P = 0.006$) were statistically significant and results were not influenced by menopausal status or tumour size. Only 90 patients could be entered into the study. In both treatment groups, half the tumours were histologically classified as highly undifferentiated (grade 3) and two-thirds had high proliferative activity.

In the West Midlands Oncology Association trial [3], 574 unselected patients were randomised to receive either simple mastectomy with axillary sampling or the same plus oral LMF for eight cycles. At the 5-year analysis, no difference in outcome was evident either in terms of relapse-free or overall survival. When the effect of prognostic factors was analysed, regardless of the treatment assigned, patients presenting with poorly differentiated tumours were at a high risk of disease relapse ($P = 0.0006$) and death ($P = 0.0001$) compared with women with moderately or well differentiated tumours.

Investigators of the International Breast Cancer Study Group [4] reported their experience in 1275 unselected patients with node-negative tumours, two-thirds of whom received one cycle of perioperative intravenous CMF. After a median follow-up of 5 years, women who received perioperative CMF had a significantly greater relapse-free survival (74%) than patients in the control arm (68%, $P = 0.03$), but the overall survival was not different between the two groups. The treatment effect was large for patients with ER-negative tumours and the greatest benefit was observed in ER-negative postmenopausal women, both in terms of relapse-free (79% vs. 56%, $P = 0.0003$) and overall survival (91% vs. 70%, $P = 0.0008$).

425 patients with node-negative and either ER-positive tumours measuring 3.0 cm or more or ER-negative tumours of any size were entered into the Intergroup Study [5]. Women were randomised to either observation or to six cycles of CMF plus prednisone (CMFP). The 5 year relapse-free survival was 61% vs. 83%, respectively ($P < 0.0001$). A treatment benefit was observed in premenopausal and postmenopausal women as well as in patients with ER-positive or ER-negative tumours, but patients in the untreated group with ER-positive tumours measuring 3 cm or more had the most unfavourable prognosis—only 42% were free of disease relapse. Overall, 86% of women treated with CMFP were alive at 5 years compared with 80% in the observation group.

The National Surgical Adjuvant Breast and Bowel Group studied patients with node-negative and ER-negative tumours. 737 eligible women were randomised to methotrexate followed by fluorouracil for twelve cycles or to no postoperative therapy. 5 year analysis indicated a significantly prolonged relapse-free survival ($P = 0.0007$) in the treated group. The benefit was unrelated to menopausal status, tumour size, and type of surgery (total mastectomy or lumpectomy) and both local–regional and distant metastases were decreased. A trend towards an improved 5 year overall survival favouring untreated patients ($P = 0.09$) was also observed.

As far as prognostic factors that may influence treatment decision-making are concerned, the consensus panel made the following points: (1) in general, the risk of recurrence increases with increasing tumour size; (2) patients with hormone receptor positive tumours have a better prognosis than those with receptor negative tumours; (3) high nuclear grade is associated with a higher rate of relapse; (4) measurements of cellular proliferation in breast cancer specimens have a strong correlation with outcome; (5) high levels of the protease cathepsin D are associated with unfavourable prognosis; and (6) HER-2/*neu*, epidermal growth factor receptor and stress-response (heat shock) proteins require further investigation.

The many unanswered questions about the adjuvant systemic treatment of node-negative breast cancer make it imperative

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