

## Symposia

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### The Importance of local control

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Studies on the risk of distant dissemination in relation to tumor size in breast cancer have shown a direct correlation over a broad range of sizes. Trials of mammography screening have indicated that size and nodal status are valid, intermediate end-points in terms of the mortality reduction from screening. This indicates that breast cancer, over a broad range tumor stages, is a local disease in a certain proportion of patients, and that progression over time will decrease that proportion. Failure of the primary treatment to control the disease locally may thus compromise survival. This supports strategies that aim to optimize local control. Overviews of randomized radiation therapy trials have indicated that the improved local control among the irradiated patients was associated with a moderately decreased mortality due to breast cancer, although problems related to radiation-induced cardiac disease prevented this benefit from being translated into an overall survival benefit. Six prospective controlled trials have specifically addressed the role of radiation therapy in locally advanced breast cancer (defined as T3 tumors or  $\geq 4$  involved nodes). All studies have shown an improved local control with radiation, four trials reported improved overall survival, which, however, was statistically significant only in one study. In these high-risk patients the substantial risk of systemic recurrence, suggests that the potential, overall survival benefit resulting from an improved local control can, at best, be moderate, although clinically worthwhile.

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### Value and indications of surgery in locally advanced breast cancers

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Locally advanced breast cancers (T3 > 7 cm, T4 or N2) carry a high risk of local recurrences and metastases. Hence, most authors advocate chemotherapy (CT) and/or radiotherapy (RT) as a first-line treatment, followed by mastectomy. Therefore, the indications for radical surgery and breast conservation in this population remain unclear.

**Material and Methods:** 942 patients with a locally advanced, non inflammatory, breast cancer were treated at the Institut Curie between 1981 and 1990. Median age was 58.5 years.

– 821 patients (group 1) had a tumor T3 > 7 cm (n = 439) or T4 (n = 382). 51% had initial RT, 35% initial CT and 14% a first-line mastectomy. After initial treatment, 51% of patients preserved their breast and 49% had a mastectomy.

– 121 patients were N2 (group 2). 62% had initial RT, 36% initial CT, and 2% initial surgery. 73.5% then had a conservative treatment, and 26.5% had a mastectomy.

**Results:** Median follow-up was 107 months.

– In group 1, the 5-year overall survival (OS) rate was 68% (66% after conservative treatment, 70% after mastectomy). (NS) 10-year rate was 41%. 5-year local recurrence rates were 9.3% after mastectomy and 18.5% after conservative treatment (p = 0.0001).

– In group 2, the 5-year OS rate was 49% (46.5% after conservative treatment, 56% after mastectomy (NS)). 10-year rate was 32%. 5-year local recurrence rates were 18% after mastectomy and 28.3% after conservative treatment (NS).

**Conclusion:** Locally advanced breast cancer is a heterogeneous group, and one should consider group 1 and group 2 patients as different entities. Both groups should be treated on a multimodality approach. If feasible, conservative treatment can be proposed after initial CT and/or RT, as OS rates do not seem to be affected by breast conservation.

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### Biological predictors of endocrine response in advanced breast cancer

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The development and progression of cancer is believed to involve multiple genetic events occurring in the pathways which regulate differentiation, proliferation and survival. These changes, which give cancer cells an altered phenotype, in essence allow them to thrive under conditions where normal cells are growth restrained. When this occurs in breast cancer, it can lead to an apparent loss of sensitivity to a major class of growth promoting molecules, the steroid hormones, and is clinically manifest either by an apparent failure to respond to antihormonal measures (which occurs in approximately 30–50% of women) or if an initial tumour remission occurs through the progressive development of an endocrine resistant state.

Since an ongoing focus of the Tenovus Cancer Research Centre is the identification of those aspects of the endocrine resistant phenotype which are responsible for primary and acquired resistance, biological factors which have been linked to these processes will be described. These include aspects of both steroid (ER, PR) and growth factor (EGFR, c-erbB-2, -3, -4, TGF $\alpha$ , heregulin) signalling pathways, together with their downstream components (c-fos, c-myc, p53), cell survival (bcl-2) and proliferation (e.g. Ki67). The possibility that such information will generate new therapeutic targets will also be addressed.

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### Endocrine treatment in advanced breast cancer

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Recent years have seen the development of a number of new agents for the endocrine therapy of breast cancer. The new aromatase inhibitors, which are highly potent and specific include both suicide and competitive inhibitors. Whereas the suicide inhibitor are exclusively steroids, competitive inhibitors consist of both steroidal and non-steroidal compounds. Substances in the former group include letrozole and exemestane and in the later group farozole, vorozole, letrozole and anastrozole. Compared with aminoglutethimide, these agents cause a more pronounced suppression of circulating estrogens. Both letrozole and anastrozole have now demonstrated a therapeutic benefit as second line therapy compared with megestrol and are now being introduced in first line studies and in the adjuvant setting. A series of new compounds have been developed in the search for drugs with enhanced antitumorigenic activity, less intrinsic agonist action and improved antitumoreffect compared with tamoxifen. Clinical efficacy has been demonstrated with toremifen and droloxifen. Preliminary data have also demonstrated the steroidal pure antiestrogen ICI 182780 to be active and this drug is now being introduced in first line studies in patients failing adjuvant tamoxifen. Preliminary data indicate that improved therapeutic outcome can be achieved when LHRH analogs are combined with antiestrogens. The anti-progestins, including megestrolone and onapristone have recently been introduced into clinic practice and preliminary data have demonstrated efficacy in patients with advanced breast cancer.

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### New drugs and new strategies for women with breast cancer

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It is likely that the medical treatment of breast cancer in the year 2000 will reflect a move in the following directions:

(1) Taxanes and/or High Dose chemotherapy will be incorporated in our