# Symposia

## 972

### 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 indicate 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

R.I. Nicholson. *Tenovus Cancer Research Centre, University of Wales College of Medicine, Heath Park, Cardiff, UK*

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 lentarone 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 megace 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 antistrogenic 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 antiprogestins, including mefipristone 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

front-line strategies for high risk patients, if proven useful in the ongoing randomized clinical trials
(2) Some new "predictive" molecular markers will hopefully assist the medical oncologist in selecting patients who need aggressive therapies
(3) Some of the studies that currently evaluate the clinical potential of new agents, such as pure antioestrogens, liarozole, Capecitabine, Caelyx, Gemcitabine ... will clarify their role in the management of breast cancer
(4) Entirely new therapies, interfering with signal transduction or angiogenesis pathways will be assessed as an adjunct to chemotherapy and hormonal therapy

All these innovative drugs or strategies will be discussed.

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## A randomized single-institution study of high-dose chemotherapy with cyclophosphamide, thiotepa and carboplatin (CTC) in apical node-positive breast cancer

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Between May 1991 and December 1995, 97 patients were included in a study of high-dose chemotherapy (CTC) in stage II or III breast cancer. All patients were below 60 years and had a tumor-positive apical axillary lymph node at infraclavicular biopsy. The conservative treatment arm consisted of 3 courses of FEC: fluorouracil (500 mg/m$^2$), epirubicin (120 mg/m$^2$) and cyclophosphamide (500 mg/m$^2$). Responders were randomized and went on to definitive surgery, a fourth course of FEC, radiation therapy and two years of tamoxifen. Patients in the experimental arm additionally underwent high-dose chemotherapy with cyclophosphamide (6 g/m$^2$), thiotepa (480 mg/m$^2$) and carboplatin (1600 mg/m$^2$), followed by blood progenitor cell (PBPC) transplantation after FEC-4. Eighty-one patients were randomized: 40 to undergo conventional treatment only and 41 to receive CTC + PBPC transplantation. With a median follow-up of 42 months, the progression-free survival for all patients was superior to historical controls, but the curves of the two treatment arms are superimposable. Evidence from randomized studies is urgently required to establish the value of high-dose therapy in the treatment high-risk breast cancer.

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## Models of environmental effects on intestinal tumour development

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**Purpose:** Germ-free conditions can abrogate cellular proliferative effects of diets in mice, hence differing environments might affect spontaneous tumour development *in vivo* and can be studied in the "Multiple intestinal neoplasia" (MIN) mouse.

**Methods:** MIN carries a nonsense mutation in the mouse *Apc* gene, the earliest genetic defect in sporadic colon tumours. Heterozygous mice develop multiple polyps by 60 days of age. Mice were reared in conventional microbiological (two different diets), Specified Pathogen Free (SPF) and totally germ free environments. They were deemed ill for sacrifice independently of tumour assessments which were done blind. The small intestine was sub-divided into equal thirds and the polyps counted and measured under a X10 dissecting microscope.

**Results:** SPF Mice have higher small and large bowel intestinal tumour counts (mean ± SEM: conventional 21.4 ± 1.25 & 1.8 ± 0.21 *Vs* SPF: 33 ± 1.27** & 3.6 ± 0.32** respectively), which also reflected in their reduced survival (231.3 ± 9.5 *Vs 184.3 ± 5.0* days**). The terminal ileum accounted for the majority of the small bowel effect. Effects of dietary Fat showed similar increases in tumour number and also caused tumour enlargement. To date (n = 5) in totally germ-free MIN, there has been complete suppression of colonic tumour formation with no obvious small bowel effects. **$P < 0.01$.

**Conclusions:** The micro-environment can be manipulated both by microbiological and dietary means with powerful influences on early colonic tumour development. These effects will be discussed in the context of other micro-environmental modifiers which may lead to novel therapeutic approaches.

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## Hereditary nonpolyposis colorectal cancer is preventable

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The claim that these cancers are preventable, or at least detectable at an early stage, stems from a 10 year clinical screening program in which mortality from cancer was significantly reduced in members of hereditary nonpolyposis colorectal cancer (HNPCC) families who are at 50% genetic risk of being carriers of predisposing gene mutations (Järvinen et al. *Gastroenterology* 1995). Clinical screening and preventive measures should ideally be offered only to those family members who are mutation positive and avoided in those who are negative. This can now be accomplished through efficient mutation detection. Thus cancer prevention can be accomplished in *known* HNPCC families. However, a major challenge is that most HNPCC cases are presently undiagnosed. In this presentation a strategy is proposed by which patients newly diagnosed with colorectal or other HNPCC cancers can be relatively efficiently and reliably screened for HNPCC. In a pilot study of 500 such patients, 10 new cases of HNPCC (2%) were diagnosed in this way. These developments raise the possibility that, under certain general conditions, all newly diagnosed "sporadic" patients can be molecularly screened for HNPCC.

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## Epidemiology and screening of colorectal cancer

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Colorectal cancer is one of the most frequent cancers. It has been estimated in the European Union that the number of new cases was 135,000 each year. This cancer is unequally spread geographically, and is among the most frequent in Western Europe and North America. Considering the present state of knowledge, only the strategy of screening for intestinal tumours at their asymptomatic stage could reduce a problem such as colorectal cancer. Data from case-control studies provides evidence of the efficacy of screening by rigid proctosigmoidoscopy or colonoscopy. The effectiveness of screening with endoscopy has yet to be demonstrated. Compliance with such a strategy is not known. Case-control studies and randomised studies indicate that it is possible to reduce mortality from colorectal cancer in people who accept screening with faecal occult blood testing. Population-based studies rely on a biennial Hemoccult test. To be effective on colorectal cancer mortality compliance has to be between 55% and 65% in the first screening campaign, and to remain high in the succeeding ones. It has also been shown that the colorectal cancer screening strategy meets commonly accepted criteria for cost-effectiveness. The time has come to encourage colorectal cancer screening with faecal occult blood test despite the current limitations of available tests.

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## Staging and treatment of early rectal cancer

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Improved understanding of the biological features of rectal cancer and advances in diagnostic and surgical procedures result in an increased number of sphincter preserving operations in lower rectal tumors. The relevant diagnostic and treatment strategies along with their indications will be presented and analyzed.

New methods in preoperative staging with the use of three-dimensional endorectal ultrasonography which provides previously unattainable scan plans, the high-resolution magnetic resonance tomography by using an endorectal coil and the 3-D multi tissue CT-reconstruction enables the visualization of local tumor spread. These techniques improve therapy planning in rectal cancer by selecting patients for alternative therapeutical methods.

New local surgical techniques including transanal endoscopic microsurgery have been proven to fulfill radical oncologic guidelines for patients with early rectal cancer (uT1-2, G1-2).

Among the radical approaches an ultralow anterior rectal resection with colon-pouch creation and a coloendoanal anastomosis make it possible to extend the resection line to the ano-rectal junction without loss of continence.

Recently, a continent perineal colostomy has been developed. This technique can be used in cases where the removal of the rectal sphincter is