SPEAKERS' ABSTRACTS

Session 1. Epidemiology and Genetics of Breast Cancer

Epidemiology and genetics of breast cancer

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Public awareness and media attention to the growing importance of breast cancer as a cause of morbidity and mortality in many developed countries has directed attention to the causes of breast cancer, and the prospects for prevention.

There has been considerable progress in identifying genes which confer increased risk in familial breast cancer during the past two years, and this new knowledge will be reviewed in this session. The implications for managing women with sporadic and familial breast cancer are now being considered. Research into means of preventing breast cancer will be stimulated by the molecular identification of women with greatly increased risk of breast cancer development. The environmental and cultural factors contributing to the increased incidence of breast cancer in many societies will be presented, and the prospects for effective interventions to control the epidemic will be reviewed. The relative importance of genetics and environment in the aetiology and behaviour of sporadic breast cancer will be discussed.

The influence of breast cancer surgery and its timing in the menstrual cycle on the probability of metastasis, and on the behaviour of systemic disease will be considered. Primary treatment strategies to overcome the possible effects of surgery on metastatic spread will be discussed.

S1
Inherited breast cancers

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Familial clustering of breast cancer was first described by physicians in ancient Rome;[1] the first documentation of familial clustering of breast cancer in modern times was published in 1866 by a French surgeon. This physician reported ten cases of breast cancer in four generations of his wife's family; four other women in this family died as a result of hepatic tumors.[2] It is now known that inherited breast cancer has several distinctive clinical features: age of onset is considerably younger than sporadic cases, the prevalence of bilateral breast cancer is higher, and the presence of associated tumors in affected individuals is noted in some families. Associated tumors may include ovarian, colon, prostate and endometrial cancers and sarcomas.[3] However, inherited breast cancer does not appear to be distinguished by histologic type, morphologic grade, metastatic pattern or survival characteristics.

Calculation of breast cancer risk for first degree relatives of women with breast cancer (mother–daughter or sister–sister) have yielded estimates of 50% of lifetime breast cancer risk in the presence of both premenopausal diagnosis and bilateral disease.[4] This contrasts sharply with the 7% calculated risk of breast cancer in first degree relatives of women with postmenopausal diagnosis and unilateral disease which does not differ significantly from the general population risk. The 50% breast cancer risk estimate in the presence of bilateral, premenopausal disease suggested the presence of an autosomal dominant susceptibility gene responsible for the development of breast cancer in this small subgroup of breast cancer families. This hypothesis was proven correct in 1991 with the description of one such gene, BRCA1.[5] BRCA1 has been isolated quite recently[6] and a third breast cancer susceptibility gene, BRCA2, has now been localized to chromosome 13.[7]

Women with germline BRCA1 mutations have an 85% lifetime risk of developing breast cancer; more than half of these women will develop breast cancer before the age of 50. Thus, while inherited BRCA1 mutations may be responsible for less than 2% of breast cancer diagnosed after age 70, as many as 30% of women diagnosed with breast cancer before the age of 45 may be carriers of BRCA1 mutations.[8] These studies further suggest that inherited mutations in BRCA1 are responsible for approximately half of all inherited breast cancer. Mutations in BRCA2 are thought to account for approximately 70% of inherited breast cancer which is not due to BRCA1 mutations, and is associated with an increased risk for male breast cancer.[7] There does not appear to be any increased risk for male breast cancer associated with germline mutations in BRCA1, but the risk of developing ovarian cancer in women with germline BRCA1 mutations is significant. Lifetime risk of developing ovarian cancer associated with BRCA1 mutations is more variable than breast cancer risk but ranges from 20% to 50%. In addition, BRCA1 mutation carriers may be at increased risk of developing colon and prostate cancer.[9]

BRCA1 is an extremely large gene, with exons spread over more than 100,000 bp of genomic DNA. The BRCA1 mRNA is 7.8 kb in length and the protein consists of more than 1800

amino acids. The initial reports describe seven different mutations;[6,10] six are point mutations near the 3' end of the gene and one appears to be a mutation outside the coding region that results in complete loss of BRCA1 messenger RNA. Many additional mutations are likely to be described in the coming months as additional investigators gain access to the reagents necessary to detect mutations in samples unrelated to the initial families. The BRCA1 protein sequence contains a zinc-finger motif often found in transcription factors (which regulate the transcription of DNA into messenger RNA) but otherwise appears unrelated to any previously described proteins.

Examination of a panel of 46 unselected breast and ovarian tumor samples provided surprising information: four previously unsuspected germline mutations were uncovered but not one somatic mutation was detected.[10] Absence of non-inherited BRCA1 mutations in these unselected tumors may be due to difficulty detecting mutations in tumors admixed with normal tissue or may suggest that BRCA1 mutations do not play an important role in the development of sporadic tumors. These data are particularly difficult to reconcile with observations of chromosomal alterations flanking BRCA1 in sporadic tumors and have raised the possibility of another, unidentified gene in the region that may be playing a role in the development of non-inherited breast cancer. Thus, although predictions that BRCA1 would fit the model of a classic tumor suppressor gene and would be an important gene in the development of as many as 50% of non-inherited breast cancer appeared to be well grounded, these predictions may not be borne out.

Elucidation of the basic mechanisms involved in the genesis of breast cancer and numerous potential applications await further study of BRCA1, BRCA2 and other breast cancer susceptibility genes. Patients carrying mutations in such genes might be targeted for interventions designed to reduce or eliminate risk. Questions of genetic heterogeneity can be addressed: do the various hereditary and non-hereditary forms of the disease involve the same or different loci? The mechanisms of the development of associated cancers in the various clinical syndromes associated with familial breast cancer may also be clarified. Finally, the influence of exogenous exposures may be addressed. The next several years should bring exciting developments in genetic epidemiology and molecular biology which may revolutionize present thinking about the role of hereditary factors in breast cancer and provide new tools for the diagnosis and treatment of breast cancer in women affected with both inherited and sporadic forms of breast cancer.

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S2
Breast cancer epidemics: genetic and environmental aspects

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Abstract not received.

S3
A review of nutritional aspects of mammary gland cancer

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Epidemiological studies reveal that breast cancer incidence rates vary fivefold around the world, and that offspring of migrants acquire the incidence rates of their host country. Thus it appears likely that lifestyle factors, especially diet, play an important role in the incidence of human mammary gland cancer. Breast cancer is a major public health problem among women in the Western world where diet is typically rich in fats and cooked meats, and high in calories. The specific components in the Western diet that could act as initiating agents in human breast cancer, however, are unknown. Several compounds that may play a role in the incidence of dietary related cancers are the heterocyclic amines (HAs) derived from cooked meats. Humans who eat cooked meats are exposed to HAs at the parts-per-billion levels in the diet. Many of these compounds are multipotent carcinogens in rodent models, and to date, three HAs have been shown to induce mammary gland cancer in rats. Besides carcinogens, diet may contain promotional factors that serve to enhance carcinogenesis. In

experimental studies with rodents, dietary fat has been shown to exert a profound influence on mammary gland carcinogenesis. Studies have shown that rats exposed to HAs and maintained on a high fat diet show a higher incidence and severity of mammary gland cancer than rats exposed to HAs and maintained on a low fat diet. Although the relationship between human breast cancer and dietary fat consumption is not definitive, the possibility that exposure to dietary carcinogens concomitant with a high fat diet influences the incidence of human mammary gland cancer deserves consideration. Finally, it is now generally recognized that humans are exposed to factors in their diets that may serve to be anticarcinogenic. For example, in the Orient where breast cancer rates are among the lowest in the world, soy (e.g. miso and tofu) is a dietary staple. Soy is rich in the phytoestrogen genistein, a compound shown to inhibit mammary carcinogenesis in animal studies. Thus, humans are exposed to a complex mixture of carcinogenic and anticarcinogenic agents through their diets. It appears necessary to examine the interaction between these factors in order to evaluate the influence of diet on human mammary carcinogenesis.

S4
Timing of breast cancer surgery and metastatic potential

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Abstract not received.

Session 2. Biology of Breast Cancer

S5
Growth factors and breast cancer: transformation, proliferation and metastases

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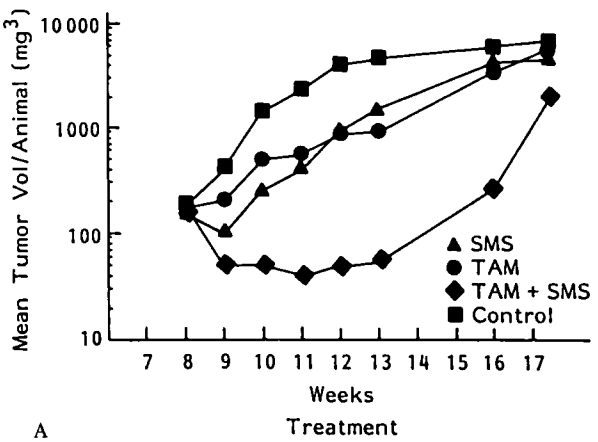
Research over the past decade has clearly demonstrated that proliferation of normal breast epithelial cells is regulated by a network of growth inhibitory and growth stimulatory peptides, and that neoplasia involves disruption of components of these proliferation control systems. We will review general principles of growth factor regulation of proliferation, and examine in more detail two examples of recent basic research which may have relevance to the goal of improving adjuvant therapies for breast cancer.

General concepts. Examples of molecular pathophysiology that contribute to neoplastic behaviour include unregulated autocrine or paracrine production of growth stimulatory peptides (documented examples: TGF alpha or IGF-II), hyperresponsivity to a mitogenic peptide due to an abnormally high level of mitogen receptors (documented examples: excess EGF receptors), or interruption of physiological growth inhibitory loops (such as those involving transforming growth factor beta). A theme which has emerged is that estrogenic stimulation or antiestrogen inhibition of breast cancer cell proliferation is associated with and mediated at least in part by changes in growth factors in the microenvironment of breast cancer cells. For example, antiestrogens upregulate the growth inhibitors IGFBP3 and TGF beta and suppress the growth stimulator TGF alpha, while estrogens have the opposite effect.

Examples of recent progress: (I) Growth factor control of neovascularization of metastatic lesions. Independent research in many labs (e.g. B Fisher, E Gorelik, J Himmele) has documented the surprising fact that primary tumors actually inhibit the proliferation of metastatic lesions in the same animal, and that surgical removal of the primary lesion accelerates the development of macrometastatic lesions from micrometastases. This phenomenon clearly is of potential clinical relevance, but until recently has remained poorly characterized. Recently, workers in Judah Folkman's lab have characterized a peptide growth factor that mediates this phenomenon. In the experimental system, pulmonary metastases develop spontaneously 4 weeks after a primary subcutaneous tumor is implanted. The metastatic burden was 10-fold higher in animals that underwent resection of the primary lesion at 14 days than in animals that underwent a sham operation. Serum from animals with intact primary tumors contained a peptide growth factor that potently inhibited neovascularization of metastatic lesions. This factor ('angiostatin') has been purified and identified as a 38 kDa fragment of plasmin. Implications of this work for clinical practice are considerable. It provides a novel rationale for neoadjuvant cytotoxic therapy to attempt to eradicate micrometastases prior to resection of the primary neoplasm. Furthermore, angiostatin-like peptides represent novel candidate agents for non-cytotoxic adjuvant therapies.

Examples of recent progress: (II) Enhancement of the IGF-I suppressive activity and efficacy of antiestrogens by co-administration of a somatostatin analogue. It is now generally recognized that in addition to its other actions, tamoxifen suppresses expression of the gene encoding IGF-I, a potent growth factor for breast cancer cells, in target organs for metastasis, and also lowers circulating levels of this mitogen. Prior research had demonstrated that somatostatin analogues such as octreotide also suppress growth hormone and IGF-I levels, and that co-administration of these agents resulted in maximal suppression, to approximately 20% of control values. We therefore compared the efficacy of tamoxifen to that of tamoxifen plus octreotide in the DMBA mammary tumor model. Drugs were administered after DMBA administration, but before the emergence of macroscopic tumors, a condition with some similarities to the clinical setting of adjuvant therapy. As expected, suppression of emergence of visible tumors was significantly greater ($p < 0.05$) in animals treated with tamoxifen than in those treated with placebo, but animals treated with the combination of tamoxifen + octreotide showed significantly fewer tumors than the tamoxifen alone group ($p < 0.05$). Despite this, there was no additive uterine toxicity. As octreotide is known to have no long term toxicity, trials to determine the clinical relevance of this observation are practical.



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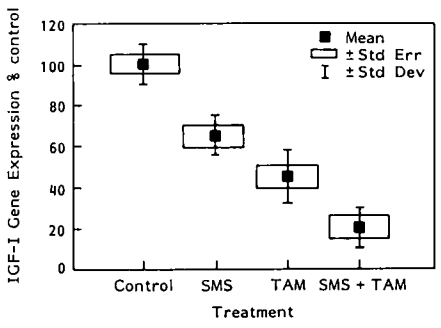

B

Effects of tamoxifen, octreotide or the combination on DMBA induced mammary tumors (A) and on IGF gene expression (B). Details in references 2 and 4.

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S6
Transferring growth factor research into clinics

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Many commonly used anti-cancer drugs are cytotoxic not only to cancer cells but to most actively proliferating cells as well, and as such have a small degree of selectivity. An alternative approach to generate more specific anti-cancer agents is through the use of targeted toxins. Cancer cells often over-express certain cell surface receptors and antigens as they proliferate. Protein toxins linked to cell binding moieties, including growth factors and antibodies to tumor associated antigens, termed immunotoxins, have been used as cell-specific cytotoxic agents. Specific cell populations can be targeted depending on the binding component selected. Classically, immunotoxins have been prepared as chemically linked conjugates of the receptor specific molecule and the toxin. More recently, they have been constructed as single-chain fusion proteins of the two molecules.

The Lewis-Y carbohydrate antigen is highly expressed on the surface of many carcinoma types including breast, lung, colorectal and prostatic. The monoclonal antibody BR96 binds to the Lewis-Y antigen, is rapidly internalized, and is reactive to a minimal amount of normal tissue, specifically gastro-intestinal epithelial cells and pancreas. A single-chain immunotoxin consisting of the variable heavy and light chains of BR96 fused to the binding defective protein toxin PE40 was constructed. PE40 is a truncated form of *Pseudomonas* exotoxin A (PE) in which the native binding domain (domain I) is deleted (leaving behind a 40 kDa protein that retains translocation and enzymatic activity). BR96 sFv-PE40 is thus cytotoxic by binding and internalizating through the BR96 antigen, translocating through domain II of PE, and ADP-ribosylating elongation factor 2 in the target cell through the enzymatic action of PE domain III. BR96 sFv-PE40 was found to be extremely cytotoxic towards a variety of BR96 antigen expressing breast carcinoma cell lines *in vitro*.

Athymic mice xenografted with H3396 or MCF-7 breast carcinoma cells responded to BR96 sFv-PE40 with complete regression and in some cases cures of their tumors. Unlike mice which do not express the Lewis-Y antigen, rats express the antigen and have a similar distribution pattern to that found in humans. Thus, rats represent a model in which normal tissue toxicities of BR96 sFv-PE40 would be readily apparent. Complete regression and cures of H3396 xenografts were found in athymic rats upon administration of well tolerated BR96 sFv-PE40 doses.

The dose-limiting toxicity of many immunotoxins that have been clinically evaluated is vascular leak syndrome (VLS). Different animal species were screened to determine if they would respond to BR96 sFv-PE40 with VLS. The dose-limiting toxicity in mice, dogs and monkeys was mainly liver toxicity. However, rats responded to BR96 sFv-PE40 with VLS at approximately 8 times the curative dose. Many compounds were evaluated as VLS inhibitors in rats administered with high-dose BR96 sFv-PE40. Prophylactic dexamethasone was found to prevent BR96 sFv-PE40 induced VLS in rats without blocking the antitumor activity of the immunotoxin.

Heregulin is a ligand with homology to EGF that binds to at least two HER family members, HER4 and HER3. We have constructed, expressed and purified a fusion protein, HAR-TX β2, consisting of a chimeric heregulin-β2 ligand fused to PE40. HAR-TX β2 specifically binds to breast carcinoma cells which express HER4 and/or HER3 on their surface and was cytotoxic towards a variety of human breast cancer cell lines including ZR-75-1, AU565, SKBR3, MDA-MB-453, T47D, BT474 and MCF-7. The ability of HAR-IX β2 to regress breast tumor xenografts in rodents is currently under investigation.

Immunotoxins such as BR96 sFv-PE40 and HAR-TX β2 offer exciting opportunities for the treatment of human cancer. However, insightful understanding and clinical management of dose-limiting toxicities including VLS are needed before immunotoxins become an accepted part of cancer chemotherapeutic regimens.

S7
Tamoxifen and endometrial cancer: from experiment to patient

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Tamoxifen stimulates the growth of human endometrial cancer but inhibits the growth of co-transplanted breast cancers in the same athymic mouse (Gottardis, *et al. Cancer Res* 1988; **88**: 812–815). This demonstration of the target site specificity of tamoxifen in a laboratory model was the first to suggest that tamoxifen could cause an increased incidence of endometrial cancer in patients receiving long-term adjuvant tamoxifen therapy. Since 1988, two concerns about tamoxifen therapy have been expressed: (1) longer tamoxifen therapy causes an increased incidence of endometrial cancer; (2) tamoxifen can cause high grade endometrial carcinoma with poor prognosis.

Through a survey of published literature, we have documented 209 cases of endometrial cancer that occur associated with tamoxifen treatment. Where documented, we found 79 patients received less than 2 years of tamoxifen and 97 patients received more than 2 years of tamoxifen. Contrary to general belief, the Stockholm study which first associated endometrial cancer with long-term tamoxifen therapy does *not* support the view that longer therapy elevates the incidence of endometrial cancer. Of the 16 patients who developed endometrial cancer, 7 cancers developed after patients stopped 2 years of tamoxifen, but only 4 patients developed endometrial cancer if they continued tamoxifen up to 5 years. The remaining 5 patients developed endometrial cancer during the first 2 years of treatment (Fornander, *et al. JNCI* 1993; **85**: 1850–1855).

To address the second issue, the literature survey demonstrates that where stated, the proportion of cases with early stage (75%) and good grade (82%) reported for tamoxifen-treated patients is similar to the SEER data for stage (74%) and grade (79%). Concerns about tamoxifen should be addressed by ensuring that patients do not have pre-existing endometrial cancer, followed by a gynecological examination only if spotting and bleeding occurs during tamoxifen treatment.

Session 3. Prognosis of Response and Tumor Markers

S8
Review of known prognostic variables

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In evaluation of prognostic variables in primary breast cancer, two different aims have to be considered. (a) Their use as a *prognostic* factor, describing groups of low and high risk for recurrence and death. Maximum information is obtained if the favourable group show e.g. an overall survival of approximately 100%, because these patients do not require further adjuvant treatment. (b) Their use as a *predictive* factor, describing the responsiveness of endocrine or cytotoxic therapy. Treatment could be intensified in cases at high risk and known responsiveness.

Established prognostic and predictive variables are: (1) tumor size; (2) axillary lymph node status; (3) grade, S-phase; (4) hormone receptor status; (5) age, menopausal status.

Tumor size. The TNM staging system is useful for estimating prognosis. There is a strong correlation between tumor size and risk of recurrence and death. The risk increases directly with increasing tumor diameters. Tumor size can be easily measured and documented by clinical and pathological procedures. In clinical practice tumor size is the most important factor in selecting women for breast conservation. In general, there is also a strong linear relation between tumor size and axillary lymph nodes involved. However, about 25% of patients with node negative tumors at the time of surgery develop distant metastases.

Axillary lymph node status. The number of axillary lymph nodes involved is still considered to be the main prognostic factor in the systemic adjuvant treatment of breast cancer. The risk of recurrence and death increases directly with increasing number of involved lymph nodes (risk categories: 0, 1–3, 4–9, 10+ positive nodes). There is general consensus that patients with node positive tumors will benefit from some form of systemic adjuvant treatment. Patients with node negative disease still have a risk of relapse within 10 years of about 20%–30%, which is why systemic adjuvant treatment is considered. However, the assessment of lymph nodes is limited because e.g. serial sectioning of nodes will reveal undetected axillary metastases in 10%–35% of all cases. Information on lymph node involvement will become even less important because a downstaging will occur in about 20% of cases with primary (neo-adjuvant) chemotherapy.

Grade, S-phase. Nuclear grade gives information on tumor differentiation. Patients with good nuclear grade (G1) demonstrate low recurrence and death rates. Besides this prognostic variable well differentiated tumors may show better response to endocrine treatment in contrast to poorly differentiated tumors. Grading evaluates the phenotypes of tumors, whereas all investigational effects to establish current prognosticators were directed to the underlying molecular changes. Because intra- and interobserver reliability is low, the value of this highly practicable factor is reduced. Therefore e.g. the detection of S-phase fraction measured by DNA flow cytometry is thought to represent a more objective method. S-phase fraction correlates with nuclear grade and hormone receptor status.

Hormone receptor status. Measurement of steroid hormone receptor concentration has been possible for more than 20 years now. Estrogen receptor (ER)-positive or -rich tumors demonstrate better prognosis compared to ER-poor tumors. There is also information that progesterone receptor (PgR) content has exceeded the power of ER as a determinant of prognosis. PgR may be important as a prognostic factor whereas ER is relevant as a predictor of endocrine response. Measurements of receptors can result in misleading data in young women (occupied receptors by estrogens) or in cases with nonfunctional ER (non DNA-binding ER).

Age, menopausal status. Patient's age and menopausal status are factors which are used clinically for prognostic assessment and treatment decisions. Young patients (<35 years) have a worse prognosis compared to older patients, which is only explained in part by a higher frequency of other poor prognostic factors in younger patients. Moreover, outcome in the elderly patient is confounded by concomitant disease. Nevertheless menopausal status is an excellent predictor for the efficacy of castration or tamoxifen. Besides this, age may be important for information on local recurrence after breast conservation (in-breast recurrence: high rates in patients younger than 35-40 years of age despite irradiation and low rates in patients older than 55, even without irradiation).

Two major questions are relevant for the use of systemic treatment in primary breast cancer: (1) Who does *not* benefit from adjuvant therapy? (2) Which *type* of treatment (cytotoxic and/or endocrine treatment) should be selected?

Patients with primary breast cancer and *very good* prognosis can be classified simply by such known prognostic factors as tumor size ($T < 0.5$–1.0 cm) and grade (G1) and *no* other factor of poor prognosis.

The decision to treat or not to treat outside clinical trials should be based on this information—the type of treatment on the menopausal and ER-status as classical predictive factors.

However, new more relevant prognostic and predictive factors are needed. Even today, all known new variables only will help us to understand the biology of breast cancer better and to achieve more precise interpretation of clinical trials.

S9
Prognostic variables and future predictors of response

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Both clinically and morphologically, breast cancer is an heterogeneous disease. The molecular changes that produce this diversity are now being rapidly elucidated. In many ways this new knowledge, combined with the general use of chemotherapy, is challenging our previous emphasis on the importance of prognostic factors related to survival, and replacing it with predictive factors based on *in situ* markers of biological behaviour and treatment response.

As recently reviewed by Clark (G Clark, 1994) there are three areas where prognostic markers are of value: (a) to identify those patients with such a good prognosis that no treatment subsequent to surgery is justified; (b) to identify those patients that have such a bad prognosis that aggressive therapy is warranted; and (c) to identify patients whose tumours would be responsive or resistant to particular therapies.

The most significant factors that predict survival are not unexpectedly related to proliferation, the degree of differentiation (nuclear pleomorphism) of the tumour and the extent of the disease. Any molecular change that contributes to one of these aspects of the tumour phenotype is thus predicted to have some prognostic significance. As tumours can have diverse ways of producing these phenotypes it is to be predicted that the reductionist approach will produce numerous sub-groups with marginally different prognostic differences, but that the most important measurements when applied to a large population will be the summation of these factors, as assessed by a routine examination of an H and E section by a good histopathologist. Thus, the molecular dissection of the mechanisms of breast carcinogenesis has more to offer in the identification or prediction of tumour behaviour and therapeutic response than in the identification of new prognostic factors.

When considering predictive factors in breast cancer, this can be addressed at the level of biological behaviour (i.e. metastatic and invasive potential) and as predictors of response or resistance to specific therapeutic modalities (for review, see Gusterson, 1995). Many of the molecular abnormalities found in tumours are potential targets for new therapeutic strategies, for example to inhibit angiogenesis, specific growth factor pathways and enzymes involved in the invasion. In the future it is to be predicted that pathologists will be required to carry out multiple analyses on small tumour samples or needle aspiration specimens. To produce results that can be used for patient management it is essential that these are reproducible.

As our level of knowledge about the molecular events involved in progression of tumours becomes increasingiy sophisticated it is of concern that as we approach the year 2000 there is still no internationally accepted classification or grading system for breast cancers. It is a priority that these should be established, along with quality control for all markers, so that results can be pooled into large multinational, multicentre studies. If this cannot be organised voluntarily it may be necessary for national authorities to enforce such changes.

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S10
Serum tumor markers for breast cancer

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Introduction. Detection and/or monitoring of circulating (serum or plasma) tumor markers might be useful in several clinical situations, including determination of risk to develop breast cancer, screening for early detection, determination of differential diagnosis, prediction of prognosis (either based on natural propensity of the cancer to metastasize and grow, or based on the response of the tumor to specific therapies), and/or monitoring patients with established breast cancer for detection of early relapse or estimation of current status during treatment of metastatic disease.

Several circulating tumor markers have been commonly associated with breast cancer. These include carcinoembryonic antigen (CEA), tissue polypeptide antigen (TPA), gross cystic disease protein (GCDP), and a family of mucin-like high molecular weight glycoproteins (CA15-3, CA549, breast cancer mucin, mammary serum antigen, and mucinous carcinoma antigen). In general, CA15-3 levels are more commonly elevated in patients with metastatic breast cancer than are CEA levels but both may be elevated by benign conditions.

Screening. Determination of susceptibility to breast cancer. Investigators have recently cloned the first gene known to be associated with familial breast cancer (BrCa1). Abnormalities in BrCa1 only account for a small percentage of those patients likely to get breast cancer, but the cloning of this gene is a significant step forward in the development of tests for genetic screening of women at risk for breast cancer. Initial assays will be based on detection of mutations/deletions in germ-line DNA. Serologic assays that detect either the abnormal BrCa1 protein product, or endogenous antibody response against abnormal BrCa1 protein, will be developed as well. Whether such assays will have any clinical utility remains to be investigated.

Screening for early breast cancer. Unfortunately, currently available circulating tumor markers, such as CA15-3 or CEA, are insufficiently sensitive and specific to be used to screen the general population. It is possible that new markers may become available for screening either blood or urine, but no satisfactory tissue or soluble marker is currently available to screen for breast cancer.

Diagnosis. Few if any markers separate breast carcinoma from other types of epithelial malignancies. CA15-3 and other mucin-based assays, as well as CEA, are frequently elevated in patients with non-breast epithelial, and even occasionally in non-epithelial, malignancies. The GCDP antigen is almost exclusively expressed by breast cancers. However, only approximately 40% of all breast cancers express GCDP. Markers associated with non-breast epithelial malignancies, such as CA125 (ovarian) and PSA (prostate) are also elevated in patients with breast cancer.

Prognosis. Predicting prognosis of patients with newly diagnosed primary breast cancer. Some, but not all, studies suggest that pre- and/or post-operative elevated CEA and/or CA15-3 levels are associated with a worse prognosis. None of these studies has determined whether elevated marker levels are independent of stage as prognostic factors. Since they are associated with more advanced stages of both primary and metastatic disease, elevated levels may simply reflect the presence of micrometastatic disease and may not be a predictor of biologic behavior.

Predicting prognosis of patients with newly diagnosed metastatic disease. Preliminary results from recent studies have suggested that certain tumor-associated markers that are reflective of biological behavior may be elevated in the circulation of patients with metastatic breast cancer. For example, the external domain of the HER-2/*neu* oncogene product designated *neu*-related protein (NRP) is elevated in approximately 40% of patients with metastatic breast cancer when compared to normal subjects. Elevated circulating NRP levels have been reported to be associated with worse outcome in patients treated with megestrol acetate. Likewise, certain angiogenic factors, such as basic fibroblast growth factor (bFGF), are also elevated in blood and urine of patients with breast cancer. These preliminary results suggest a promising method of predicting response to potential anti-angiogenic agents.

Monitoring. Monitoring patients to detect occult recurrent disease. Approximately 40% of those patients who will relapse exhibit a rising CEA and/or CA15-3 prior to the emergence of clinically or radiographically detectable disease. Although impending relapse can be predicted with some degree of certainty using rising tumor markers, the clinical utility of this observation is not clear. Treatment of asymptomatic metastases with systemic therapy has not been demonstrated to result in either increased cure or survival rates, and treatment of such patients is unlikely to provide improved palliation. Thus, routine screening of patients following primary therapy remains controversial.

Monitoring patients with metastatic disease. CEA and CA15-3 have been demonstrated to be reliable indicators of clinical course. Circulating levels of CA15-3 are elevated in approximately 75%–80% of patients with metastatic breast cancer. CA15-3 is more sensitive and specific than CEA, and can be used to supplement other clinical parameters during follow-up of patients with metastatic disease.

Summary. Many circulating markers have been proposed for breast cancer, with potential utility for identification, screening, prognosis, detection, or monitoring. Of the available markers, those with the greatest promise include BrCa1, p53, HER-2/*neu*, indicators of angiogenesis, and circulating tumor markers that provide an indication of clinical course, such as CA15-3 and CEA. However, the precise clinical utilities of all of these markers have yet to be determined.

It is especially important that the relative independence of the markers in relation to other available markers be determined so as to avoid the unnecessary cost and expense of redundancy. Moreover, it is important that the clinician be aware of the limitations in both sensitivity and specificity of each marker so as not to over- or underinterpret the predictive value of any test.

Session 4. Screening for Breast Cancer and Treatment of Early Lesions (DCIS)

S11
A critical review of screening for breast cancer

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Screening for breast cancer by mammography has been shown to be effective in reducing breast cancer mortality and is recommended as a current public health policy. In six random studies, breast cancer mortality was reduced by 24% (RR 0.76, CI 95%, 0.67–0.87; Wald & coll., *The Breast* 1993; **2**) in women between the ages of 50 and 70 who had been offered screening. On the basis of these results, some Northern European countries have instituted national screening programmes (the UK, Sweden, the Netherlands, Finland and Iceland) and others are about to do so (France and Italy).

Therefore it is now necessary to: identify the early indicators of efficacy that can better predict a reduction in mortality on the basis of the experience of the trials; verify that the early results of service programmes are the same as those of the controlled studies that have demonstrated an effective reduction in mortality; check that the possible adverse effects of screening (namely anxiety, radiation hazard, false positive cases, overdiagnosis) are limited as much as possible; keep the costs of the programme at a level acceptable to the public health system.

Recently it has been documented that the results of national programmes fully meet these requirements, but in some countries we have noticed an increase in spontaneous screening, taking place outside organized programmes, and we fear that this practice is unlikely to be the most cost-effective. Moreover, some questions are still moot points. What is the optimal interval between screenings? What is the effect of screening by mammography in women aged under 50 or over 70? What is the most appropriate response to women with a high-risk genetic history?

It seems to us that, when scientific opinion is not unanimous and the results of earlier studies are not thoroughly convincing, it is essential to invest new resources in research to respond to questions that are still open, rather that accept that different decisions will be made on the basis of individual opinions. It is for this reason that, for example, we have proposed that a new trial (Eurotrial-40) in the European ambit should be undertaken to find out if screening with state-of-the-art mammography—double views at annual intervals—helps to reduce mortality among women under 50 as well, and if so, to what extent.

S12
The treatment of DCIS from the point of view of the surgeon

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The management of duct carcinoma *in situ* (DCIS) is controversial. It is not clear whether all carcinomas are preceded by DCIS or if all DCIS leads inexorably to carcinoma. Until very recently most patients underwent mastectomy for DCIS. From recent studies, it appears that DCIS when managed by lumpectomy has outcomes very similar to stage I and II breast cancer in terms of local recurrence. A better understanding of the biology of DCIS would lead to better clinical management.

In a preliminary study the NSABP reviewed 78 patients from protocol B-06 who were found on review to have only DCIS, who were treated by mastectomy or lumpectomy with or without RT. The outcomes compare favorably to recurrence rates and treatment failure rates for patients with invasive cancers. Protocol B-17 was designed to address this question prospectively specifically for DCIS patients. Analysis reveals that DCIS is suitably treated by lumpectomy. Post-operative radiation therapy reduces the incidence of recurrence of DCIS or invasive breast cancer. Information from patterns of recurrence in invasive breast cancer treated on protocol B-06 will be explored to derive implications for selection of patients for breast conserving surgery whether invasive or intraductal.

As our knowledge of the biology of breast cancer improves we will undoubtedly be exploring the difference between precancerous states, DCIS and invasive cancer. It is reasonable to expect that this will lead to new treatments designed to control the growth of cancer cells, or the transition from lower states to more malignant states. The idea would be to prevent the development of invasive cancer. The ongoing NSABP protocol B-24 evaluates tamoxifen with respect to this point.

S13
Predicting patients who are likely to recur after conservative treatment for intraductal breast carcinoma (DCIS)

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With the acceptance and increased utilization of screening mammography, there has been a dramatic increase in the number of DCIS cases during the last 15 years. Historically, most patients with DCIS were treated with mastectomy which yielded a local recurrence rate of 1%; this is the standard to which other treatments are generally compared.

Recently, in spite of a lack of prospective randomized data, the majority of DCIS patients have been treated with breast conservation. The only prospective randomized trial published so far (NSABP B-17) yielded five-year actuarial local recurrence rates of 10% for DCIS patients treated with excision and radiation therapy and 21% for patients treated with excision alone.

Local recurrence is an important event when it occurs in a patient previously treated for DCIS and the early results of NSABP B-17 suggest that it is going to be a fairly frequent event in conservatively treated patients.

Not only is local recurrence demoralizing, more importantly, since approximately 50% of all local recurrences are invasive, it is also a threat to the patient's life. Therefore, predicting patients who are likely to recur locally after breast conservation therapy is extremely important.

We studied 402 patients with DCIS without microinvasion seen between 1979 and August 1994, in whom there have been a total of 27 local recurrences. In an attempt to predict the likelihood of local recurrence, we evaluated 16 prognostic factors by univariate analysis (log rank test). All statistically significant predictors of local recurrence by univariate analysis were then evaluated using a Cox multivariate regression analysis. The six factors listed below were significant predictors of local recurrence by univariate analysis; only two, treatment and nuclear grade, were significant predictors of local recurrence by multivariate analysis. Ten factors were not significant predictors of local recurrence by univariate analysis: ER, PR, S-phase, ploidy, P53, Her2-*neu*, microcalcifications, palpability, year of diagnosis, and age.

Univariate and multivariate *P* values of six prognostic factors found to be significant on univariate analysis

	Univariate *P* value	Multivariate *P* value
Treatment	0.000001	0.0001
Nuclear grade	0.0002	0.001
Tumor size	0.002	NS
Final margins	0.006	NS
Presence of necrosis	0.03	NS
Comedo architecture	0.05	NS

Treatment was the most important predictor of local recurrence. Patients treated by mastectomy seldom recurred (2/174), whereas 25 of 226 breast conservation patients experienced a local recurrence. When the multivariate analysis was limited to 226 breast conservation patients, the *P* value for nuclear grade increased to 0.0001 and tumor size became a significant factor ($P = 0.01$). The ten-year disease-free survival by nuclear grade for DCIS patients treated with breast conservation was 100% for nuclear grade 1, 82% for nuclear grade 2, and 54% for nuclear grade 3. High nuclear grade is the most important predictor of local recurrence in patients with DCIS treated with breast conservation.

A combination of significant prognostic factors can be used in selecting patients who are good candidates for breast conservation therapy. Mastectomy should be given strong consideration when the DCIS lesion is high nuclear grade, large, or has involved margins not amenable to re-excision.

When mastectomy is performed for DCIS at our Center, we use a procedure called glandular replacement therapy (GRT). GRT consists of a skin-sparing mastectomy (only the nipple–areolar complex is removed) and an immediate autologous tissue reconstruction (generally a free TRAM flap). Since DCIS does not involve the skin, there is no need to remove excess skin. The breast envelope, with its inframammary sulcus, is preserved just as it was created by nature, yielding the best cosmetic results that we have ever achieved.

Session 5. Surgery for Breast Cancer: Special Issues

S15
The American breast cancer tragedy: its impact on NSABP clinical trials

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Abstract not received.

S16
The surgical treatment approach of breast cancer relapse

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Following the introduction of breast conserving surgery (BCS) the issue of relapse in the conserved breast has become an important problem. Data from NSABP B-06 suggests that many relapses reflect disseminated disease; the breast relapse is simply one of the sites and in this sense serves as a marker or indicator.

On the other hand, there are undoubtedly recurrences which can be described as foci of residual disease and a third category which may be new primaries. When lumpectomy is not accompanied by radiation therapy recurrence rates are very high, approaching 50%. Post-operative radiation reduces this to 10% and later protocols where adjuvant tamoxifen and chemotherapy was given reduces this sgaom by half. It is important to differentiate between local residual disease which may be diminished by radiation therapy and metastases which may be decreased by systemic adjuvant therapy, and the interactions of both of these. Data from NSABP and other clinical trials indicate that both types of events and both types of effects are in operation. In case of locally recurrent breast cancer treatment choices will depend on analysis of specific factors. The use of a second course of radiation therapy and the selection of patients for a second lumpectomy, or for a total mastectomy, requires consideration of specific factors.

S17
Primary and secondary breast reconstruction with special emphasis on the use of prosthesis

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Breast reconstruction (BR) after mastectomy is considered today as part of the breast cancer treatment although the choice remains the one of the patient. The timing of the reconstruction is still a matter of controversy. It is usually admitted that immediate BR can be proposed safely in case of ductal *in situ* carcinoma when mastectomy is still indicated. However, an increasing number of patients require a BR at the time of the mastectomy whatever the histology. The risk of local morbidity related to the BR should be taken in consideration in order to avoid any delay for the adjuvant treatment. Studies on immediate BR indicate that such risk is low and does not seem to compromise the action of the adjuvant treatment. BR can be performed with a prosthesis in most cases. Prosthesis gave rise to a lot of investigations following the questions raised by the FDA since 1991. Recent studies have shown that silicone is not associated with a risk of cancer. At IGR (Villejuif) we have performed a retrospective comparison between 292 one by one matched patients, half of them implanted with a gel silicone prosthesis more than ten years ago. Local recurrence, metastasis and overall survival rate are significantly lower in the group with prosthesis. The risk of auto-immune disease, however, remains a matter of discussion requiring further epidemiological and immunological studies in collaboration with rheumatologists.

Session 6. Adjuvant Systemic Therapy I

S18
The primary use of chemotherapy for operable breast cancer. Does systemic therapy make surgery superfluous?

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Neoadjuvant chemotherapy has now been used for many years and was first introduced to treat locally advanced breast cancer. The treatment was in most cases followed by radiotherapy and surgery. The results were compared to historical controls.

In later years neoadjuvant chemotherapy has been used in less advanced cases with the purpose of reducing the tumor volume in the breast to facilitate breast conservation surgery. The influence of the chemotherapy on the primary tumor in the breast has also been used as a guide for further adjuvant chemotherapy either after primary radiotherapy or surgery. The most commonly used chemotherapy regimes have been a combination of anthracyclines, cyclophosphamide and 5-fluorouracil, in some studies combined with vincristine and/or methotrexate.

The technique for evaluation of the response has varied in different studies but has usually been a combination of clinical evaluation, mammography and/or echography. Overall response rates (CR + PR) have in most studies been very high, between 70% and 85%. Response rates have generally improved with increasing numbers of chemotherapy cycles and with dose intensity. This has led to a high frequency of breast conservation therapy, in some series up to 80%–90%. Local recurrence rate has usually been low after the combination of breast conservation surgery and local radiotherapy following neoadjuvant chemotherapy.

So far results from randomized studies comparing different strategies of therapy have not been published. Several such studies are however underway.

Whether the combination of neoadjuvant chemotherapy and radiotherapy will totally abolish the need for surgical treatment of the tumor area in the breast is difficult to answer. It is very difficult to be sure that the last tumor cells have been killed. It seems that a combination of neoadjuvant chemotherapy and radiotherapy only gives a higher local recurrence rate than if surgery is added to the treatment. The place of surgery after neoadjuvant chemotherapy can probably be better answered after the results of ongoing randomized trials are available.

S19
High dose chemotherapy as adjuvant therapy for breast cancer: where do we stand?

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Abstract not received.

S20
The role of anthracyclines in adjuvant chemotherapy of breast cancer: a critical appraisal

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Introduction. Many questions regarding the optimal cytotoxic therapy in primary breast cancer remain to be answered by analyses of results from present and future clinical trials. One of these relates to the role of anthracyclines which will be focused on in this review.

Anthracyclines in advanced disease. The treatment of advanced disease remains palliative, whereas the objective of adjuvant treatment is cure. As a consequence the most efficient among the available chemotherapy regimens should be offered to patients in the adjuvant setting.

In advanced breast cancer the anthracyclines are among the most efficient single agents and three of four major trials have demonstrated that regimens of CAF (cyclofosfamide, doxorubicin, 5-fluorouracil) were significantly superior to similar combinations of CMF (cyclofosfamide, metotrexate, 5-fluorouracil) with regard to response rate, time to progression and survival.[1]

Introducing anthracyclines in adjuvant treatment. A logical consequence of the findings in advanced disease is the introduction of anthracylines in the adjuvant setting. However, many investigators have been reluctant to take this step, mainly because of the potential risk of cardiotoxicity associated with long term administration of these agents. The demonstration of lack of benefit when adjuvant chemotherapy is prolonged beyond approximately 6 months, and the introduction of epirubicin which at hematological equitoxic doses is less cardiotoxic than doxorubicin,[2] however, has changed

this situation. Thus the recommended maximal cumulative doses of doxorubicin and epirubicin are 550 and 1000 mg/m^2 respectively. If the drugs are used as adjuvant therapy in combination with C and F, administered at standard dose intensity every 3 weeks for 9 cycles, the cumulative dose would be 360 mg/m^2 (9 × 40 mg/m^2) for doxorubicin and 540 mg/m^2 (9 × 60 mg/m^2) for epirubicin, which are equivalent to 65% and 54% of the maximum recommended doses, respectively.

Trials indicating benefit with adjuvant anthracyclines. Four published trials have reported a benefit concerning recurrence free survival or survival or both with the use of anthracylines. However, the design of some of these trials does not justify safe conclusions as to the role of anthracyclines. Thus in one of these trials [3] the benefit might be associated with the use of three (L-PAM + F + doxorubicin) rather than two drugs (L-PAM + F). In another trial from Milan [4] the benefit could rather be associated with the sequence of the drugs rather than with the role of doxorubicin itself. Thus 4 cycles of doxorubicin followed by 8 cycles of CMF was superior to 4 sequential treatment sequences each consisting of 2 cycles of CMF followed by 1 cycle of doxorubicin. A third trial reported 12 cycles of classical CMF to be inferior to 12 cycles of AVCF (V = vincristine), administered by a significantly different schedule (i.v. Days 1–6).[5]

The fourth trial compared a combination of MMFC (metotrexate, mitomycin C, 5-fluorouracil, cyclofosfamide) with MMAC (A = doxorubicin).[6] However, in this comparison F was administered i.v. 5 times and doxorubicin on Day 1 only during the 7 week cycles.

Trials indicating no benefit with adjuvant anthracyclines. So far six trials have been published, but these also made use of a range of regimens or schedules, which inhibits exact evaluation of the role of the anthracyclines. Thus one trial compared 4 cycles of AC with 6 cycles of CMF,[7] one trial compared 9 cycles of CMF with 3 cycles of MTV (mitomycin C, thiotepa, vindesine) followed by 3 cycles of EVM (epirubicin, vincristine, metotrexate),[8] one trial compared 12 cycles of CMF with 8 cycles of CMF followed by two cycles of AV,[9] and one compared PF + tamoxifen with PAF + tamoxifen.[10]

Another two trials compared CMF with a similar regime but with the substitution of metotrexate by doxorubicin or epirubicin. One of these compared 6 courses of i.v. CMF with 6 courses of i.v. CAF [11] and one compared 6 classical courses of CMF with 8 courses of i.v. CEF.[12]

Finally two major trials are on-going. One randomises patients to 6 classical courses of CMF or CEF,[13] and the other randomises the patients to 9 courses of i.v. CMF or CEF. Results from these two studies are not yet available.

Conclusion. No firm conclusions can be drawn so far, mainly because many of the published trials were not specifically designed to evaluate the role of anthracyclines. To answer the question about the role of adjuvant anthracyclines we must await the mature data from on-going comparisons of CMF vs. CAF/CEF, and the efficacy of the sequential use of doxorubicin followed by CMF should be confirmed. The long term evaluations should also include careful analyses of potential late adverse events, especially cardiotoxicity.

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Session 7. Adjuvant Systemic Therapy II

S21
Adjuvant systemic therapy: the issue of timing and sequence

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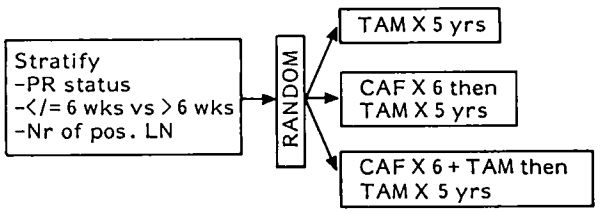
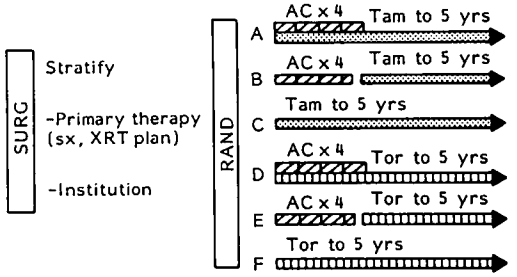
1. Preoperative adjuvant systemic therapy. Adjuvant therapy in breast cancer has been widely used during the last three decades. The rationale for its introduction was that adjuvant treatment may kill tumor cells released into the circulation at the time of primary surgery. Subsequent hypotheses ascribe to micrometastases, already present at the time of breast cancer diagnosis, the high risk for systemic relapse. Thus, a delay in starting adjuvant treatments may result in increased resistance to cytotoxics.[1] In animal models cyclophosphamide, tamoxifen and radiotherapy delivered before surgical removal of the primary tumor prevent the increased proliferation of residual tumor cells, suppress tumor growth and prolong survival.[2] Primary (preoperative) chemotherapy was tested in large, operable tumors.[3–9] Its beneficial effect resulted in an increased opportunity for breast-conservation, downstaging, and assessment of tumor response to the treatment. Data on the comparison between pre- and postoperative adjuvant treatment are limited although a large trial on this subject is being conducted. Preoperative adjuvant treatment should therefore be considered experimental. It is likely that the prophecy of G. Bonadonna that 'a modern sequential multidisciplinary approach could transform the role of surgery such that an operation would aid systemic treatment in achieving curability' will become reality.

2. Perioperative adjuvant systemic therapy. Adjuvant therapy in breast cancer is generally started a few weeks after removal of the primary tumor to allow healing of the surgical wound. It is likely that micrometastases continue to grow during this lag of time. Data suggest that the growth fraction in micrometastases is increased after removal of the primary tumor.[2] Two studies, published almost 20 years ago (Scandinavian and NSABP Trials [10,11]) tested a perioperative course of cyclophosphamide and thiotepa, respectively. The results showed a survival benefit for the treated patients (in the NSABP trial such benefit was seen only in the subgroup of premenopausal patients with more than 4 axillary lymph nodes involved). These trials were the basis for several other clinical trials studying immediate administration of adjuvant cytotoxic therapy after surgery. Four such randomized trials, which include more than 6000 patients, have been reported so far and were included in an overview performed by the EORTC Meta Analysis Unit. The results of the individual trials show controversial results. Of interest is the observation that emerges from the International Breast Cancer Study Group Trial V,[12,13] that patients with ER-negative primaries are more likely to benefit from perioperative adjuvant cytotoxics.

3. Sequencing adjuvant cytotoxics and endocrine therapies. Laboratory data and clinical evidence,[14–16] especially from the NSABP trials, indicate that the concomitant application of tamoxifen (delaying G1 transition in addition to estrogen withdrawal increasing the number of cells in G_0) together with chemotherapy (which is more cytocidal in dividing cells) might be detrimental. It is therefore hypothesized that the subsequent use of both modalities might overcome such negative interaction. Two large clinical trials were specifically designed to assess this issue: The Intergroup Trial INT 0100 Study (N+ postmenopausal, ER+ or PR+) started in May 1989 with the design:



and the International Breast Cancer Study Group Trial 12–93 (N+ postmenopausal, ER+ or ER–) started in May 1993 with the design:



Tam = tamoxifen, Tor = toremifene

Unpublished data from the IBCSG Trial VII also suggest that for patients with ER-negative tumors, the addition of chemotherapy after beginning with tamoxifen is detrimental.

In conclusion, questions are still open in the field of timing and sequencing of adjuvant therapies in breast cancer. Several ongoing trials are aimed at clarifying some of the relevant issues, which include: the role of preoperative administration of adjuvant treatments, and the potential antagonism of tamoxifen and cytotoxic drugs in the clinical setting.

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S22
Current role of adjuvant hormone therapy in the management of early carcinoma of the breast

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The world overview of adjuvant trials published in the *Lancet* in 1992 not only provided secure data on the advantages of adjuvant chemotherapy and adjuvant endocrine therapy, but also effectively set the agenda for the next quinquennium of randomised controlled trials. A whole raft of questions have been defined concerning the role of adjuvant hormone therapy in both pre- and post-menopausal women.

The dominant question for the post-menopausal group of women concerns the optimum duration of tamoxifen in order that we can make an accurate estimate of harm versus benefit. The importance of this question has been heightened by the recent description of a modest but significant excess risk of endometrial cancer for women on long-term or high-dose tamoxifen. A large number of trials are addressing the duration question, but the largest and most mature is the Cancer Research Campaign study in the UK. This trial has registered over 5000 patients with approximately 3000 randomised at the 2 year point. It is likely that an estimate of the difference between 2 and 5 years exposure to adjuvant tamoxifen will be available at the time of the meeting.

The questions concerning endocrine manipulation in premenopausal women are more complex. The overview suggested a similar order of benefits for both adjuvant chemotherapy or ovarian suppression. There was also indirect evidence to suggest that there might be a summation effect of the two modalities combined. For these reasons, current trials are investigating the benefit of gonadotrophin releasing hormone (GHRH) agonists either with a direct, head on comparison with CMF or in trials comparing CMF alone versus CMF plus a GHRH agonist. A large European consortium including the Cancer Research Campaign Group in the UK and a number of Scandinavian and Northern European centres have already recruited 2000 patients. Although not yet sufficiently mature, it is likely that an answer to this question will become available in a year or two. In addition, the power of this combined analysis will allow a search for qualitative or quantitative interactions between ovarian suppression and the presence or absence of oestrogen receptors in the primary tumour.

An early report by the Scottish Cancer Trials Group has already suggested that the expression of the oestrogen receptor in the primary tumour may predict preferential response to ovarian suppression.

The next generation of trials attempting complete oestrogen suppression in post-menopausal women using the new generation of oral aromatase inhibitors is likely to be launched in 1995.

S23
Future developments in adjuvant systemic therapy of breast cancer

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Controlled trials performed during the past two decades have established a few important points, namely the importance of dose size and dose intensity in improving treatment outcome, the superiority of anthracycline (doxorubicin)-based regimens, and the usefulness of primary chemotherapy in increasing the frequency of breast conserving surgery. Thus, future trials should be aimed at expanding the above mentioned key points. The importance of the sequential delivery of non-cross resistant regimens, such as doxorubicin → CMF, should be confirmed and may be further expanded, utilizing novel drugs such as vinorelbine and taxol. The problem of dose size could find a more positive answer from the trials involving high dose chemotherapy plus hematopoietic growth factors and reinfusion of peripheral progenitor cells. Prospective randomized trials testing high doses versus conventional drug regimens are required to confirm the early promising findings. Finally, a number of innovative studies should be designed to prove beyond doubt that in high risk tumors (e.g. $T \geq 3$ cm) neo-adjuvant plus adjuvant chemotherapy could represent a new effective treatment strategy.

Session 8. Radiation Therapy as Part of Primary Treatment

S24
Radiation therapies for breast cancer: current knowledge of advantages and disadvantages

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In the last few years important data have been published from randomized trials concerning the role of radiation therapy as part of the primary management of primary breast cancer. These trials have concerned (1) postoperative radiation therapy following breast conserving surgery for either invasive breast cancer or ductal carcinoma *in situ*, and (2) the effect on overall survival from postmastectomy radiation therapy. Three-dimensional conformal radiotherapy, biological models that can adequately predict the risk of side-effects in surrounding risk organs, and *in vitro* tests of individual radiosensitivity are currently emerging as potential strategies for more individualized treatment.

The efficacy of radiation therapy to decrease the risk of relapse in the conserved breast has been demonstrated over the years in several trials. However, patients selected for breast-conserving surgery often have low risk tumors and radiation therapy may constitute 'over-treatment' in many such patients. The Uppsala–Orebro study was designed to assess whether a standardized surgical procedure and a meticulous histopathological evaluation of the specimen to detect positive margins would obviate the need for routine postoperative radiation therapy in patients with stage I tumors. The initial report of the study in 1990 at a median follow-up of 29 months showed no significant difference between the treatment groups and the breast recurrence rate among the non-irradiated patients was fairly low (8%). This result was interpreted by the authors to suggest that radiation therapy may not be needed in this selected subgroup of patients. However, updated results at a median follow-up of 5 years showed a breast recurrence rate of 18% among the non-irradiated patients compared to 2% among those allocated to radiation therapy ($p = 0.0001$).

Similar observations were made in the Ontario trial which included node-negative patients with a tumor size of < 4 cm. At a median follow-up of 43 months the breast recurrence rate among the irradiated patients was 6% compared to 26% among the untreated controls. Although the breast recurrence rate was lower among untreated patients aged above 50 years than among younger patients, the authors concluded that they could not identify any subgroup of patients with such a low breast recurrence rate without radiation therapy that treatment would not be warranted.

These results extend and confirm the results of previously published trials. In summary, postoperative radiation therapy should probably continue to be routine for all patients treated with breast-conserving surgery. Definition of subgroups who may not need radiation therapy requires more information on risk factors for breast recurrences. The value of adjuvant systemic therapy, for instance, adjuvant tamoxifen, to prevent breast recurrences also requires further exploration.

The NSABP conducted a randomized trial of postoperative radiation therapy to the breast including 818 patients treated with breast-conserving surgery because of ductal carcinoma *in situ*. At a median follow-up of 43 months there was a significantly improved event-free survival among the women allocated to radiation therapy compared to the surgical controls ($p = 0.001$). Lumpectomy alone patients had a 16% breast recurrence rate compared to 7% among those treated with radiation therapy. This difference concerned both invasive and non-invasive recurrences. The authors concluded that breast irradiation after lumpectomy is more appropriate than lumpectomy alone for women with localized ductal carcinoma *in situ*.

A few years ago Cuzick *et al.* published an overview of long-term results from some of the more mature trials of postmastectomy radiation therapy. In that analysis, there was no overall survival benefit from radiation therapy. Instead, the irradiated patients showed a significantly poorer survival than the controls after 10–15 years. However, a recent updated report including information on cause-specific mortality no longer showed any significant detrimental effect among the patients allocated to radiation therapy. In fact, in the more recent trials there was a decreased mortality from breast cancer. On the other hand, this benefit was balanced by an increased non-breast cancer mortality, mainly from cardiovascular disease. These results suggest that adequate locoregional treatment of breast cancer with prevention of locoregional recurrences may improve overall survival. However, an increased cardiovascular mortality resulting from excessive doses to the myocardium may offset this benefit. The results highlight the importance of treatment technique and avoidance of excessive doses.

Three-dimensional conformal radiotherapy is currently being incorporated into routine practice in many treatment centers. Biological models that can adequately predict the risk of side-effects in surrounding risk organs and *in vitro* tests of individual radiosensitivity are currently emerging as potential strategies for individualized treatment. These possibilities may

in the future help to increase the therapeutic ratio of radiation therapy, that is, increase local control rate as well as diminish the risk of adverse side-effects.

S25
Quality assurance in early breast cancer post-operative external whole-breast irradiation: clinical aspects

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A Quality Assurance (QA) program in radiation oncology is defined by the objective and systematic evaluation of the quality and appropriateness of patient care, introducing corrective actions in the analysed procedure when relevant discrepancies with respect to predefined standards are measured.

Three principal areas must be the object of an inter-related educational, technical, physical and clinical evaluation: *structure*, *process* and *outcome*.[3,5]

From a physical point of view, comprehensive QA programs by the Medical Radiation Physics Community have been introduced to analyse, prevent or correct errors specifically in the radiotherapy *process*, i.e. in diagnostic patient data acquisition, treatment simulators and treatment units, treatment aid devices, dose computation and distribution, and treatment verification.[1,4]

From a clinical point of view, radiotherapy *process* involves several complex and critical steps: in early breast cancer post-operative external whole-breast irradiation, guide-lines have been suggested to set standards of 'adequacy' in both pre-treatment evaluation phase (clinical evaluation and therapeutic decision) and in treatment prescription phase (treatment modality and basic treatment technique).[2]

Nevertheless, guide-lines concerning treatment preparation and treatment execution phases are less defined, probably because these aspects are mostly technique- (and structure-) dependent and because clinical end-points, i.e. observed ranges of local control and morbidity rates, are considered adequate and acceptable by the Radiation Oncology Community.

As examples of an intra-institutional QA program, three aspects related to radiotherapy *process* (treatment preparation and execution) and to *outcome* will be analysed. (1) The accuracy of conventional methods to localise the Clinical Target Volume (CTV) by comparing palpation- and anatomically-defined CTV with ultrasonographic determination of breast tissue. (2) The accuracy and precision in treatment execution phase of daily set-up (geometrical accuracy) with respect to the five major variables related to the adopted treatment technique (craniocaudal and ventrodorsal shift; half-beam block, gantry and couch rotation error) and the identification of ideal margins to be included in the Planning Target Volume. (3) The systematic evaluation of acute and late toxicities following a qualitative and quantitative analysis [6] and the potential corrective actions to improve treatment outcome.

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S26
How to predict relapses after breast-conserving treatment

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The risk of local failure in the conserved breast is related to a multiplicity of factors. Although relative risks associated with individual parameters can often be quantitated, recurrence rate is a function of time, and risk factors are often interdependent, making quantitation of risk in the individual patient very problematical. Moreover, risks associated with patient- and tumor-related parameters can be estimated from retrospective or prospective studies, but the effect of treatment-related factors only from randomized trials.

A rational approach to risk assessment for individual parameters might involve calculation of relative risks with respect to the risk associated with an arbitrary reference situation. Unfortunately, the 'pure' effect of one factor is often confounded by effects of other factors, so that such idealized data do not exist. Nonetheless, existing studies allow notions of approximate relative risks to be established.

Factor	Relative risk
Patient age (< 35 vs. ≥ 35)	2–3
Extensive intraductal component (yes vs. no)	2–3
Tumor size (> 2 cm vs. ≤ 2 cm)	2
'Multifocality' (≥ 2 lesions vs. 1 lesion)	2
Vascular invasion (yes vs. no)	2
Resection margins (pos. vs. neg./close)	2
Adjuvant chemotherapy (yes vs. no)	0.5
Adjuvant tamoxifen (yes vs. no)	0.5
Breast irradiation (yes vs. no)	0.2

The data upon which these risk estimations are based will be presented.

At present only a crude estimation of individual risk is possible, more precise assessment requiring development of an adequate mathematical model, based on a data set containing well-defined pathologic and clinical parameters and an sufficient number of events for analysis. For the moment clinical decision making based on risk factors remains subjective, with more aggressive local measures (intensive boost therapy, re-excision, mastectomy) often proposed without a precise notion of risk, especially in young patients with one or more morphologic risk factors. A more objective approach to this problem is the object of current research.

Session 9. Women's Health Perception and Breast Cancer: Issues of Fertility, Hormone Substitution and Cancer Prevention

S27
Reproductive potential after adjuvant chemotherapy for breast cancer

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The beneficial effects adjuvant combination chemotherapy is able to achieve in premenopausal women (risk reductions in the annual rates of recurrence and death: 37% and 27%, respectively) are in part counterbalanced by the influence that some cytotoxic drugs exert on gonadal function. However, the majority of young premenopausal women are not permanently affected by early amenorrhea.

In the attempt to quantitate this aspect, we have retrospectively analyzed a series of 205 patients younger than 38 years of age at diagnosis of breast cancer, i.e. women potentially able to become pregnant and have offspring. All these patients were given CMF-based chemotherapy whose schedule varied according to different protocols activated in our Institute between June 1973 and July 1990. This case series, which includes 43% of patients with > 3 positive nodes, 54% with primaries > 2 cm and 36% with ER-negative tumors, was followed for a minimum of 67 mos from surgery.

Over the entire course of follow-up (median 13 years) a total of 62 women (30%) either developed permanent amenorrhea or entered early menopause (median 31 mos from surgery). During the same period of time, a total of 19 pregnancies occurred in 17 women. In 13 cases, patients had elective abortion, the median interval from end of chemotherapy to pregnancy being 16 mos (0–40). One patient had a spontaneous abortion at the age of 43 years. Five women gave birth to offspring, all of whom showed no fetal malformation; the median interval from end of chemotherapy to pregnancy was 56 mos (36–80). The median dose of cyclophosphamide delivered to patients who became pregnant was 10,800 mg (range 6,960–24,675), similar to the median dose delivered to the entire case series (10,800 mg; range 2,040–27,825).

Even in the absence of chemotherapy, young premenopausal patients with breast cancer are generally advised to wait 2 to 3 years before becoming pregnant to assure they will not have an early disease relapse. In our case series, 41% of the patients presented new disease manifestations within 3 years from surgery, 52% within 5 and 61% within 10 years. Among the 121 women in clinical complete remission 3 years after surgery, 20 were already amenorrheic; 10 women entered early menopause in the subsequent 2 years and 21 additional patients within 10 years after surgery.

Albeit limited in size, our case series allows some considerations: (a) the risk of disease relapse remains fairly high even after the first 3 years from surgery; (b) some patients, who can be considered potentially cured of their disease, may become menopausal and infertile during the waiting period; (c) no malformations were detected in the 5 babies born from mothers given adjuvant chemotherapy. However, present data and data available so far in the medical literature are not adequate to allow general guidelines. Pregnancy is still possible after adjuvant chemotherapy for breast cancer, but counselling should take into consideration the risk of disease relapse for the individual patient.

S28
Sex hormones and breast cancer: the issue of hormone replacement

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Menopausal therapy has, until recently, focused primarily on relief of short term symptoms. In double blind randomized trials both estrogen replacement therapy (ERT) (Coope, *et al.*) and medroxy progesterone acetate (Schiff, *et al.*; Loprinzi, *et al.*) have shown superiority over placebo in controlling hot flushes. Estrogen and progestagens have not been directly compared in randomized designs. Although drugs such as Clonidine are widely used for relief of hot flushes when ERT is believed contraindicated, a recent double-blind trial showed no superiority of Clonidine over placebo for relief of hot flushes (Wren BG, *et al.*). In recent years, veralipride, an antidopapinergic, has been shown superior to placebo for relief of hot flushes in randomized trials (Wesel S, *et al.*). In addition, topical estrogen can reduce epithelial urogenital atrophy, thereby relieving urinary symptoms such as frequency and dysuria. Such topical therapy generally however results in considerable systemic absorption (Sitrak-Ware, *et al.*). More recently, ERT has been shown to improve overall quality of life whether given transdermally (Daly E, *et al.*) or orally (Wiklund I, *et al.*).

It is also well known that ERT will decrease the rate of bone loss over time (Lindsay R, *et al.*) and can protect from cardiovascular events (Stampfer MJ, *et al.*). Progestagens used

alone may also have a protective effect on bone metabolism, but their long term use tends to lower HDL and elevate LDL (Eden JA) and thus may increase the risk of coronary artery disease (Lobo BA).

ERT has been clearly linked to the development of endometrial cancer, but the addition of progestins counteracts this increase in risk (Henderson BE). Whether estrogens modify the risk of developing breast cancer is more controversial. Five recent meta-analyses have shown no increase in the relative risk (RR) of breast cancer for ever users of ERT compared to never users. There is however a small increase in risk among current users (RR = 1.23, 95% CI 1.12–1 6; and 1.4, 95% CI 1.2–1.6). Similarly, long time users (> 15 years) show a RR of 1.3 (95% CI 1.12–1.6). There has been no clear association between risk and dose of estrogen. The addition of progestin to estrogen has been suggested to protect from breast cancer, but meta-analysis was not able to confirm this (Roy JA, *et al.*).

In summary, the benefits of ERT, in terms of short term reduction of side effects and long term reduction of osteoporosis and heart disease, probably outweigh the increased risk of endometrial cancer or any slight increased risk of breast cancer. As a result, several medical organizations now recommend ERT for otherwise healthy perimenopausal women (Society of Obstetricians and Gynecologists of Canada, SOGC).

The use of ERT in women who have already had breast cancer has, however, been poorly explored. Three case series suggest that women taking ERT for breast cancer show no dramatic increase in recurrence (Stoll BA; DiSaia PJ; Powles TE, *et al.*). Powles has shown that ERT given together with tamoxifen is effective for the relief of hot flushes, but the long term effect on breast cancer recurrence is unclear. A recent decision analysis suggested that ERT may be appropriate, in women with prior breast cancer, if the lyrnph nodes are negative and if menopausal symptomatology is severe (Goodwin PJ, *et al.*) A recent case report describes four women on long term ERT who developed metastatic breast cancer but then had disease regression with ERT withdrawal. This would suggest that ERT doses can at least affect the course of breast cancer (Dhodapkar MV, *et al.*)

Currently, there are at least three proposals for randomized studies of ERT in women who have had breast cancer (Vassilopoulou-Sellin R, *et al.*; International Breast Cancer Study Group; Cobleigh M, *et al.*). The results of these trials should shed further light on the appropriateness of ERT in women with previous breast cancer.

S29
The Women's Health Initiative: the road to scientific clarity?

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The US National Institute of Health has recently embarked on its most ambitious and expensive trial ever, called the Women's Health Initiative (WHI). The primary component of this project involves a randomized factorial trial to evaluate the effectiveness of three interventions for the prevention of cancer, cardiovascular disease, and osteoporotic fractures. The interventions to be tested are hormone replacement therapy, low-fat dietary pattern, and calcium plus vitamin D supplementation. A ten-year period of intervention is planned. A second goal is to evaluate strategies to achieve healthful behaviors that have established value, including smoking prevention and cessation, improved dietary pattern, achievement and maintenance of optimal weight, increased physical activity, and early cancer detection.

The central hypothesis leading to the development of the project has been that dietary fat is the main cause of breast cancer and that reducing fat intake will substantially reduce breast cancer incidence. However, as evidence has accumulated over the last several years, support for this hypothesis, primarily derived from international correlations, has diminished. In each of the six large prospective studies that have examined this association, little or no relation was seen between fat intake and breast cancer incidence. These observational studies have not been able to examine the influence of fat intake below 20% of calories, and have not examined the effect of fat before midlife. However, these limitations will also apply to the WHI, particularly since women even over the age of 70 years will be randomized. As in previous large randomized trials, long term dietary compliance is likely to be problematic; in the pilot study the difference in fat intake between the intervention and control groups after three years was small: 27% vs. 31% of energy. Most fundamentally, the trial cannot answer the question regarding the effect of dietary fat because the dietary intervention has been broadened to include an increase in consumption of fruits, vegetables, and whole grains. As increased intake of vegetables and vitamin A has been associated with reduced risk of breast cancer in multiple observational studies, a benefit of the dietary intervention—if of sufficient magnitude and duration—is expected irrespective of any effect of dietary fat.

Whether the trial of hormone replacement therapy (estrogen, estrogen plus progestogen, or placebo) will provide clear guidance for women is uncertain. Evidence that estrogen therapy will reduce risk of coronary disease and fractures is firm, so that the primary question is whether this will be balanced by increases in risks of breast and endometrial cancer. However, the benefit from heart disease and fracture reduction is likely to be rapid whereas the increases in breast cancer are likely to be delayed. Thus the time frame of this trial is not likely to be informative regarding the most important question of whether hormone replacement therapy should be continuous after menopause. The component of the trial relating to calcium and vitamin D is likely to provide clearer information on the benefits of this combination. However, available data more clearly support benefits from vitamin D, and this will not be distinguishable from any contribution of calcium in this study.

Although the WHI will provide additional data on health-related issues among women, by design it cannot answer questions about the relation of fat intake to risk of breast and other cancers. Although it will probably contribute to information on the effects of hormone replacement therapy, it will also probably not be able to address the most important practical questions about the optimal duration of treatment. The component of the WHI that seeks to enhance the adoption of lifestyle factors of proven benefit appears well justified.

S30
Breast cancer prevention: problems of current trials

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Abstract not received.

POSTER ABSTRACTS

BIOLOGY OF BREAST CANCER

P1
Growth inhibition of human breast cancer grafts in nude mice by boron neutron capture therapy

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Cell destruction in boron neutron capture therapy (BNCT) is due to the nuclear reaction between ^{10}B and thermal neutrons to release alpha-particles (^4He) and lithium-7 ions (^7Li). The ^4He kills cells in the range of 10 μm from the site of ^4He generation. Therefore it is theoretically possible to kill tumor cells without affecting adjacent healthy tissues, if ^{10}B-compounds could be selectively delivered ($^{10}B + {}^1n \rightarrow {}^4He + {}^7Li +$ 2.48 MeV). In the present study the cytotoxic effect of locally injected ^{10}B-compound solution or multilamellar liposome containing ^{10}B-compound on human breast cancer xenograft in nude mice was evaluated after thermal neutron irradiation. CRL 1500 cells (1×10^7) injected subcutaneously grew to a tumor weighing 100–300 mg after 2 weeks. At this time more than 50 μg ^{10}B-compound was locally injected into the tumor and irradiated with 2×10^{12} n/cm^2 thermal neutron. Tumor growth of ^{10}B-treated groups was suppressed compared with control groups. Histopathologically, hyalinization and necrosis was found in the tumor tissues. The tumor tissue injected with saline only and irradiated showed neither destruction nor necrosis. These data indicate that the accumulation of ^{10}B atoms to the tumor site is mandatory for the cytotoxic effect by thermal neutron irradiation.

P2
Is there a correlation between mutant p53 protein levels and *in vitro* chemosensitivity in specimens from breast cancer patients?

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We investigated the correlation between the level of mutant p53 tumor suppressor protein and the *in vitro* chemosensitivity of tumor specimens from 58 patients with primary untreated non-metastatic breast cancer. Mutant p53 protein was determined by ELISA, using antibodies that only recognize mutant p53 protein. Chemosensitivity was tested by performing the adenosine triphosphate cell viability assay. This *in vitro* assay has been shown to correlate with *in vivo* chemosensitivity of breast cancer. CMF chemosensitivity (CMF = cyclophosphamide, methotrexate and 5-fluorouracil) was determined at six concentrations ranging from 0.125 to 4 × peak plasma concentration (PPC). Instead of cyclophosphamide, its active metabolite 4-hydroperoxycyclophosphamide was used *in vitro*. The CMF chemosensitivity at 4 × PPC was compared to the amount of mutant p53 protein determined in the same tumor specimens by linear regression and Anova. Our results strongly suggest a correlation between the level of the mutant p53 protein and the *in vitro* CMF chemosensitivity ($r^2 = 0.15$): the higher the mutant p53 level in the breast cancer specimen, the higher the resistance to CMF. The variance analysis revealed a significant p value of 0.018. These data demonstrate that mutation of p53 can lead to enhanced chemoresistance, confirming the notion that p53 may be involved in chemotherapeutic agent-mediated apoptosis.

P3
Genetic alterations on chromosome 9, 11, 13 and 17 in human breast carcinomas analysed by qdPCR or microsatellite analysis using fluorescent DNA technology

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The development of spontaneous and familial breast cancer is based on multiple genetic alterations of tumor suppressor genes and oncogenes located on various chromosomes. Analyses of specific genetic alterations lead to more detailed information about the progression of disease or the chances to develop breast cancer. For detection of oncogene amplification quantitative differential polymerase chain reaction (dqPCR) can be used. dqPCR only requires small amounts of tumor material and therewith allows simultaneous analysis of various oncogenes. PCR-based microsatellite polymorphisms detecting differences in short tandem repeat sequences are much more informative for assessment of loss of heterozygosity (LOH) than standard two-allele RFLP markers. Simultaneous analyses of different genetic alterations reveal insight in tumor biology and perhaps information about the prognosis of the individual breast cancer patient. In order to determine oncogene amplification (erbB2, int-2, myc) and to investigate allele loss of tumor suppressor genes (p53, BRCA1, BRCA2, NME1, MTS1/cDK41), we have developed a rapid technique based on qdPCR and fluorescent DNA technology.

In a prospective study 60 breast cancer and 15 benign breast specimens (snap-frozen) with matched normal tissue (or genomic DNA isolated from blood leucocytes) were analysed. Oncogene amplification was measured by dqPCR with coamplification of a single-copy reference gene (γ-interferon gene) in the same reaction vial using one fluorescent labelled primer in each of the primer pairs. Frequency of allele loss was assessed using microsatellite length polymorphisms which were highly polymorphic and closely linked to the loci of interest. DNA sequences containing microsatellites were amplified by PCR reaction, in which one of the primers was fluorescent labelled. Fluorescent labelled PCR products were analysed and quantitated by polyacrylamid gel electrophoresis in an automated DNA sequencer (ALF™, Pharmacia, Freiburg, Germany). Results were analysed with Fragment Manager™ software (Pharmacia), which yields automatic quantitation of results in terms of peak size, height and area. Quantitation of peak area was used to calculate the change in allele ratio between normal and tumor DNA or between reference gene and oncogene for each patient. Oncogene amplification was found in 24% for erbB2, 25% for int2, and 23% for myc. LOH i.e. for chromosome 17 could be detected in 43% for TP53, 41% for BRCA1, and 45% or NME1 with simultaneous oncogene amplification (erbB2 25%, int2 25%, myc 10%). LOH and oncogene amplification correlated with high tumor grade and larger tumor size.

Quantitative differential PCR and microsatellite analyses combined with detection of fluorescent labelled PCR products by an automated laser DNA sequencer are powerful tools in determination of genetic alterations and have proved to be useful as routine analytical methods in oncology. Especially in the context of familial breast cancer, the detection of genetic alterations in lymphocytes derived from women prior to the outbreak of the disease requires the application of a routine analytical method.

P4
Phosphorylated human breast carcinoma cell membrane glycoprotein stimulates the host peripheral blood cytotoxic cells

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Patients with malignant tumors, i.e. with metastatic breast carcinoma (BCa), have defective lymphocyte responsiveness. Mucin-type antigens have been prepared and used as BCa markers. Several monoclonal antibodies have been developed against these membrane components. The BCa associates glycoproteins varied in their effects on PBL and NK cells. Five different groups were isolated from human BCa-cell membrane (GP I to GP V). Four (GP I to GP IV) inhibited, while GP V enhanced both inherent and IL-2 activated cytotoxic activities (Hakim, *Surgical Forum* 1975, **26**: 175–177; *FASEB Fed Proc* 1976, **35**: 514; *PSEBM* 1987; **185**: 158–176). EGF-R (C-erb B-2) is amplifed and over-expressed in several aggressive human breast cancer cell lines and metastatic breast tumors (Hakim, *J Surg Oncol* 1989; **40**: 21–31; *Diagnostics & Clinical Testing* 1989; **27**: 30–37). The object of the present study is to report the relationship between the C-erb B-2 product P 185 and GP V functions. The cell membrane glycoproteins were prepared from human breast cancer MCF-7, ZR-75-1, MC-ZWA and HS-0578T established cell lines and from tumor biopsies of patients with BCa at different stages. The monoclonal antibodies MAb-4D5, MAb-CAM-26, MAb-CAM-29 and MAb-BCM and MAb-MSA were examined for binding with the glycoproteins by well established immunoinhibition assays. GP V is an immunizing antigen which contains epitopes required to stimulate T-helper cells and antigen presentation by B-cells for antibody production. It is heavily glycosylated with several tyrosine residues. GP V lacks intrinsic kinase activity, binds to EGF-R and undergoes phosphorylation by interacting with transphosphorylating kinases. The binding of the tyrosines in GP V to EGF-R induces phosphorylation of tyrosine residues in GP V. Therefore, GP V acts as a cytoplasmic domain, undergoes transphorylation by other kinases, attracting to itself second messenger proteins that participate in the transduction pathway and thereby modulates signal transduction. In tumor biopsies, GP V levels varied directly with estrogen receptor (ER) and inversely with EGF-R levels. Although sera of normal (non-cancer) patients had non-significant, sera of patients with cancer of the breast at stages III and IV had significantly higher anti-GP V levels.

P5
Natural killer cells in patients with breast cancer (BC) and their relatives

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The numbers of large granular lymphocytes (LGL) and natural killer activity (NKA) (against K562, 18 h, effector:target ratio 50:1) were determined in 24 patients I–II stages with BC. The quantity of LGL and NKA in patients of the common group (group BC) did not differ significantly from the control group (some healthy relatives, group H). But mild reduction of LGL and NKA were determined in patients with BC, as well as in healthy people who had blood relatives with malignant neoplasms (groups BC* and H*). The group of patients with BC with specially low NKA (less than $M \pm \sigma$) was marked. The quantity of LGL and NKA of healthy blood relatives of these patients (H**) was less than non-relatives of the same patients and the group of patients with BC.

Group	*n*	LGL ($M \pm \sigma$)	NKA ($M \pm \sigma$)
BC	24	5.2 ± 1.8, $p > 0.05$	38.5 ± 14.3, $p > 0.05$
BC*	9	4.6 ± 1.7, $p > 0.05$	31.2 ± 13.4, $p < 0.05$
H	50	6.2 ± 1.4	41.4 ± 6.4
H*	18	5.1 ± 2.1, $p = 0.040$	32.2 ± 18.5, $p = 0.036$
H**	6	4.1 ± 1.8, $p = 0.005$	25.4 ± 17.4, $p = 0.028$

p = significance of differences in comparison with group H.

P6
Breast cancer adjuvant chemotherapy and menstrual function

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The aim of this study is to know the effects of chemotherapy for operable breast cancer in adjuvant setting on menses in the short and long term. These effects are classified into three groups—no amenorrhea, reversible amenorrhea and menopause—and reported according to the age range and the drug mean dose to onset of amenorrhea. Adjuvant chemotherapy alone was administered to 164 out of 659 premenopausal patients after surgery for operable breast cancer (1974–1990). Premenopausal status is defined by last menses during the previous 6 months. The age range is 22 to 56 years (median 44.5 years). Age of menopause was studied in free of disease patients. No patient under 31 years (9) developed amenorrhea following chemotherapy. 45% of the 13 patients aged 32 to 37 became amenorrheic and then recovered menses. Cyclophosfamide mean dose to onset of amenorrhea is 3.7 g/m^2, adriamycin (ADM) 114 mg/m^2, vindesine or vincristine (VDS-VCR) 6.5 mg/m^2, fluorouracil (FU) 5.2 mg/m^2. 70% of 31 patients aged 38 to 41 became amenorrheic (definitively, i.e. menopausal in 36%) after a mean dose of CPM of 3 g/m^2 (2.7 when irreversible), ADM 77 mg/m^2 (98), VDS 3.9 (3.2), FU 3 g/m^2 (2.7). 92% of 76 patients aged 42 to 48 became amenorrheic (menopausal in 89%) after a mean dose of CPM 2.6 g/m^2 (1.8), ADM 84 mg/m^2 (54), VDS 2.6 mg/m^2 (2.6), FU 3.4 g/m^2 (2.4). All the 35 patients aged 49 or older became menopausal after a mean dose of CPM 1.2 g/m^2, ADM 42 mg/m^2, VDS 1.6 mg/m^2, FU 1.6 g/m^2. Out of 31 patients with no disturbance of menses on chemotherapy, 5 are menopausal at a mean age of 42 years (range 35–48) after they received a cyclophosfamide mean total dose of 6.4 g/m^2, ADM 167 mg/m^2, VDS 7.8 mg/m^2, FU 8.8 g/m^2. 16 patients of mean age 43 are not yet menopausal after a cyclophosfamide mean total dose of 8.4 g/m^2, ADM 176 mg/m^2, VDS 6.7 mg/m^2, FU 8 g/m^2. Patients who experienced reversible amenorrhea (mean time period of 6.3 months (median 5 months, range 1–20 months) became menopausal at a mean age of 43 years (range 36–50) (16 pts). Mean age of menopause on chemotherapy is 47.5 years (range 39–56) (105 pts). Whatever were the disturbances of menses, menopause was premature when compared to mean age of menopause (51 years) of 120 premenopausal women operated on for breast cancer, not treated by adjuvant chemotherapy and free of disease. The onset of chemotherapy related ovarian failure is age and dose related: the older the patient, the lower the dose to induce non-reversible amenorrhea. Even if there is no amenorrhea on chemotherapy, patients evidence premature menopause.

P7
DNA image cytometry and oncogene detection in breast cancer

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Objective. Aneuploidy, high S-phase fraction (SPF%) and oncogene amplifications are indicators of poor prognosis in breast cancer. The goals of the present study with more than 110 primary breast cancer patients were: (1) to determine the frequency of diploid–neardiploid tumors by image cytometry (ICM); (2) to calculate SPF by ICM; (3) to demonstrate relations between ICM data (DNA Index, DI; Grade of Malignancy, GM) and oncogenes. *Study Design.* Imprint cytology immediately after tumor excision; staining (Feulgen technique); computerized ICM (interactive cell analysis, CYDOK); gene detection of EGFR, erb B-2, erb B-3 and c-myc by a standard differential PCR method (d-PCR). *Results.* The frequency of diploid–neardiploid breast tumors (DI 0.9–1.1) was low (22%). SPF (2.5c–3.8c) was only accessible in diploid–neardiploid tumors. Gene amplifications were predominantly seen in the DI range from 0.9 to 1.4. Tumors with low DNA GM had as much amplification of oncogenes as high DNA malignant tumors. Significant correlations between ICM data and oncogene values were not revealed. *Conclusion.* d-PCR enables the detection of gene deviations with minor alteration of the entire cellular DNA content. Simultaneous determination of both,

DNA and oncogenes, may be important to select patients at high risk for relapse as well as to induce the appropriate therapy.

PROGNOSTIC FACTORS / TUMOR MARKERS

P8
Prognostic relevance of aberrations of the *erbB* oncogenes in breast cancer: double-differential polymerase chain reaction (ddPCR) for clinical diagnosis

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The permissivity of normal cells to carry gene amplifications is rather unlikely. Host growth factors (autocrine and paracrine) that control the process of organ repair are known to be organ specific. Cells with high metastatic potential express a high number of functional receptors for growth factors. There is a physiological significance of inappropriate expression of *erbB* tyrosine kinases in abnormal cell growth. In this concern the amplification of growth factor receptor genes is a specific indicator for tumor cells, gaining possibility of invasive and metastatic growth. We studied genomic aberrations of the *erbB* family with a method to measure average gene copy number (AGCN) of *erbB-1*, *erbB-2* and *erbB-3* in tumor tissue. The method is based on differential polymerase chain reaction (dPCR). AGCN is thereby reflected by the ratio of concentration of the oncogene and a single copy housekeeping gene. We compared the ddPCR data with the results from dot-blots and DNA image analysis of tumor smears. Furthermore the measurements of the same parameters in tumor tissue, infiltrating border, normal tissue of the patients and a control group with benign breast diseases were compared. In the clinical evaluation the most significant cut-off values of AGCN were estimated for *erbB-1* at 0.40 ($p < 0.05$), for *erbB-2* at 2.00 ($p < 0.05$) and for *erbB-3* at 1.75 ($p < 0.05$) for the disease-free survival of 188 patients suffering from primary breast cancer. Remarkable results were rendered: patients with an AGCN value above 1.75 for *erbB-3* had an increased disease-free survival. However, the parameter with the highest clinical impact on disease-free survival was the ratio of the AGCNs of *erbB-1* and *erbB-2*. Early metastasis and decreased therapy response to a CMFp regimen was observed in patients with *erbB-1 erbB-2* ratios below 0.15 ($p < 0.001$, resp. < 0.01).

P9
Urokinase (UPA) and PAI-1 as selection criteria for adjuvant chemotherapy in node-negative breast cancer patients

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Morbidity and mortality in breast cancer are caused by the capability of the tumor cells for invasion and metastasis. Tumor-derived proteases are a prerequisite for the dissolution of the tumor surrounding structures enabling the tumor cell to invade and metastasize. Evidence has accumulated that the urokinase-type plasminogen activator (uPA) and its specific inhibitor PAI-1 play a central role in tumor-related proteolysis, invasion and metastasis. uPA and PAI-1 were quantified (ELISA) in tissue extracts of 339 breast cancer patients. Levels of uPA/PAI-1 are the strongest prognosticators (Cox) of disease-free survival (DFS) with a relative risk (RR) of 4.17, even surpassing the number of tumor-involved lymph nodes (RR: 3.87), hormone receptor status (RR: 2.32) and tumor size (RR: 1.52). In 132 node-negative patients uPA (RR: 3.4) and PAI-1 (RR: 4.9) are also found to be the strongest independent prognostic factors for DFS. S-phase, hormone receptors, cathepsin D and tumor size did not add prognostic information in the Cox model. Since uPA and PAI-1 are independent factors, node-negative patients can be grouped further by a combination of these two variables. Node-negative patients with tumors of low content of both uPA and PAI-1 have an especially good outlook (93% 5-year DFS) in contrast to patients with high uPA or PAI-1 (60% 5-year DFS) or even high content of both uPA *and* PAI-1 (45% 5-year DFS). Based on these results a prospective randomized study supported by the Deutsche Forschungsgemeinschaft (DFG) was initiated, in which patients with high values of uPA and/or PAI-1 are randomized to 6 cycles CMF versus observation. Patients with low content of both uPA and PAI-1 are distributed to observation only. 12 clinical centers in Germany are taking part in this trial; to date 250 patients have been recruited.

P10
The prognostic relevance of glutathione transferase and peroxydase activity in patients with early and locally advanced breast cancer (BC)

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Aim. To measure Glutathione-Transferase (GST), Glutathione-Peroxydase (GPx), 06-Alkylguanine-DNA-Alkyl transferase (Atase), Glutathione (GSH) and P-Glycoprotein (PGP) in BC and to correlate with prognosis (DFS and OS) in early (T1–2, N1, M0, T3aN0M0) and locally advanced (T3–4, N2 or N3, M0) BC. *Patients and methods.* From May 88 until November 91 histologically proven tumor tissue samples from 78 consecutive, untreated females with BC were obtained. 56 pts had early primary and 22 pts locally advanced disease. The activity of GST, GPx and Atase, as well as the level of GSH were measured biochemically and the expression of PGP with Western blotting. *Early breast cancer.* GST was significantly correlated with Atase, GPx and GSH. High GSH correlated with age ≥ 60 years (p = 0.01) and positive hormone-receptors (p = 0.06), whereas high GPx was related to node-positive status and high PGP to high grade and premenopausal status (p = 0.07). The 5-year estimated DFS was 74% for high and 57% for low GST. Higher GST was associated with longer DFS also in node-positive pts (p = 0.07) and hormone receptor negative pts (p = 0.04). In the multivariate analysis the likelihood of relapse in node-positive pts with high GST was one third with reference to pts with low GST (Hazard ratio = 0.36). *Locally advanced breast cancer.* GST activity was significantly lower than in early BC (p = 0.03). GST was significantly correlated with GPx and GSH, but not with Atase. High GSH correlated with low grade (p = 0.05). The estimated 4-year DFS was 75% for high and 46% for low GPx. In the multivariate analysis the likelihood of relapse in pts with high GPx was one fifth with reference to pts with low GST (Hazard ratio = 0.16). *Conclusions.* In early BC, GST seems to reflect the most important intrinsic parameter of the detoxifying system in tumor cells with prognostic relevance. In locally advanced BC the same holds true for GPx. Higher values of both parameters are significantly associated with longer DFS. The significant correlations between these parameters point out the presence of common regulatory elements. The current study needs further confirmation to clarify these interesting, but preliminary findings.

P11
Detection of biological markers from FNA cytology specimens from primary breast cancers

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Primary medical treatment of early breast cancer using systemic chemo-endocrine therapy is attracting increasing interest. As treatment is commenced prior to surgery, there is a need to determine prognostic factors from material obtained by fine needle aspiration (FNA). We have undertaken a randomised trial using neo-adjuvant (NEO) chemo-endocrine therapy vs. adjuvant postoperative chemo-endocrine therapy in stage 1 or 2 breast cancer. Patients receive 8 cycles of Mitozantrone and Methotrexate (4 cycles prior to surgery in the NEO group) with tamoxifen for 5 years and appropriate surgery and radiotherapy. Immunocytochemical analysis (ICA) and DNA analysis by flow cytometry is performed on cytological specimens obtained by FNA from all patients prior to treatment. By ICA, 76/103 (74%) were positive for oestrogen receptor (ER), 71/102 (70%) positive for progesterone receptor (PgR), and 34/98 (35%) positive for p53. Flow cytometry yielded the following results: aneuploid 54/69 (78%), mean S-phase fraction (SPF) 11.44 and diploid 15/69 (22%), mean SPF 2.07. In keeping with expected biological observations, we found significant positive correlations between ER and PgR ($p < 0.001$), PgR and ploidy ($p < 0.05$), ploidy and SPF ($p < 0.001$), while there was negative correlation between ER and p53 ($p < 0.001$), PgR and p53 ($p < 0.01$), PgR and SPF ($p < 0.01$). CerbB2 and Ki67 staining is currently being undertaken on these specimens. Immunocytochemical staining of EGFR, HSP27 and PS2 have so far proved unsatisfactory on our cytological specimens. Multiple biological prognostic markers can be adequately tested with cytological specimens from primary breast cancers. These markers may prove to be of value in determining prognosis and response to treatment in patients receiving primary medical therapy prior to surgical excision.

P12
Predictors of recurrence in small (± 1.0 cm) invasive axillary lymph node (LN) negative breast cancer (T1a,bN0M0)

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The incidence of T1a,bN0 breast cancer is increasing because of the broader use of screening mammography, but the precise prognosis of these small cancers and recommendations for adjuvant systemic therapy remain uncertain. This study was undertaken to determine whether standard histologic features including tumor size, tumor grade and the presence of lymphatic vessel invasion (LVI) have prognostic significance for patients (pts) with T1a,bN0 breast cancer and can identify poor and good risk subsets. *Methods.* From 1977–1990, 218 pts with T1a,bN0 breast cancers who had at least 5 LNs in their axillary dissection were diagnosed and had all surgery at SBMC, a large community hospital. Median LNs

resected = 14. All data including precise millimeter measurement of tumor size in 3 dimensions, histologic grade (HG), nuclear grade (NG) and presence or absence of LVI were recorded *prospectively* in routine surgical pathology reports (SPRs) by any of 13 staff pathologists. A breast pathology expert was not specifically designated to evaluate the surgical specimens. 150 pts had T1b cancers (> 5 but ≤ 10 mm) and 68 pts had T1a cancers ≤ 5 mm) of which 29 were microinvasive (invasive component ≤ 1 mm). Complete data regarding HG, NG and LVI were available for 196 of 218 pts. Since grade and LVI are not routinely recorded for all microinvasive cancers, these accounted for 16/22 pts without a complete data set. With median follow-up of 5.8 years (range = 2–16) there have been 13 recurrences; 8 systemic, 3 regional, 1 local (breast only).

	6-year recurrence free survival (RFS)	
1. Size		
T1a (n = 68) vs. T1b (n = 150)	98% vs. 90%	p = 0.06
2. HG		
Well/Mod. (n = 106) vs. Poor (n = 91)	98% vs. 88%	p = 0.007
3. NG		
Well/Mod. (n = 151) vs. Poor (n = 46)	98% vs. 80%	p = 0.0006
4. LVI		
Absent (n = 153) vs. Present (n = 52)	98% vs. 85%	p = 0.004

The combination of poor HG, poor NG and LVI occurred in 19 pts (9% of total) for whom RFS was only 65%. 82 pts with none of these factors had 100% RFS. 95 pts with 1 or 2 of these factors had 94% RFS ($p < 0.001$). *Conclusions.* This study, with histologic features recorded prospectively in routine fashion in SPRs in a community hospital setting, is a true test of the prognostic significance of these factors for T1a,bN0 breast cancer. Size, grade and LVI are predictors of recurrence and the results confirm the validity of LVI as a prognostic feature which should routinely be included in breast cancer SPRs. These standard histologic factors successfully identify a small subset of T1a,bN0 cancers with a substantial recurrence risk and show that, for the remaining majority of T1a,bN0 cancers, the recurrence risk is extremely small. These findings should aid clinicians in making adjuvant therapy decisions for pts with small invasive axillary LN negative breast cancer.

P13
Are immunohistochemically detected lymph node micrometastases in breast cancer independent prognostic factors?

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This study was an effort to evaluate the prognostic value of immunohistochemically detected micrometastases ($N_{1a\text{-}IHC}$) in axillary lymph nodes as well as its association with other prognostic factors. *Patients and methods.* Lymph nodes (n = 2012) of 163 patients with breast cancer (N_1: n = 59; N_0: n = 104) were examined for micrometastases using a monoclonal cytokeratine antibody. In addition to clinical features, histological findings, ER, PR, S-phase, ploidy, EGF-R, HER-2/neu oncoprotein, lectin-R, cathepsin-D and pS 2 were investigated. The mean follow up time was 48 ± 15 months. *Results.* Micrometastases were detected in 110 of 1814 negative nodes (6.1%), mostly in negative nodes of N_1-patients. In only 17 of 104 patients (16.3%) staged as N_0 by conventional histology, one or more micrometastases were detected immunohistochemically. A prognostic disadvantage of $N_{1a\text{-}IHC}$ patients compared with $N_{0\text{-}IHC}$ patients was significant for disease free survival (p = 0.003) as well as for overall survival (p = 0.006). Differences between $N_{0\text{-}IHC}$ and $N_{1a\text{-}IHC}$ tumors were found in tumor size, grading, ER, EGF-R and cathepsin D. By Cox regression, age, tumor size, number of extirpated lymph nodes, grading, S-phase, lymph and blood vessel invasion, but not the detection of micrometastases, were confirmed as independent prognostic factors in nodal negative patients. *Conclusion.* Immunohistochemically detected micrometastases are not independent prognostic factors. A correlation of micrometastases with other prognostic factors has been proven. Nevertheless, micrometastases in axillary lymph nodes are of prognostic value, indicating a need for systemic adjuvant therapy.

P14
Micrometastatic tumor cells in bone marrow versus nodal status in breast cancer: impact on prognosis in 727 patients with primary breast cancer

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Tumor cell detection (TCD) in bone marrow is a parameter that indicates tumor cell shedding and thus the beginning of systemic disease, and therefore it might compete with the axillary lymph node (ALN) status. Since 1985 a bone marrow biopsy was performed on both anterior iliac crests intraoperatively in 727 patients with primary breast cancer. After density centrifugation (Ficoll) the bone marrow interphase cells were smeared and stained with the 2E11 MoAb, that recognizes the core protein of TAG 12 tumor associated antigen. TAG 12 is a glycoprotein expressed by 97% of all mammary carcinomas. 315 patients were tumor cell positive (43.3%). Interestingly 30% of the patients with T1-tumors and/or negative ALN were also tumor cell positive. Complete follow-up data (44 months

median) were available in 625 patients (surgery before December 31, 1993). Metastases were found in 143 women, of whom 109 had tumor cells in bone marrow upon surgery (76%). Whether the first metastasis was visceral or osseous, TCD-rate was almost similar (73% vs. 76%). Of the 69 patients who died of disease, 57 (i.e. 84%) were tumor cell positive. Cox regression analysis revealed that TCD is a strong and independent prognostic factor for overall survival and for disease-free survival. Among the node-negative patients who developed metastases 53% had positive TCD. 14 of 19 patients with small tumors (T1) had positive TCD (74%), but only 8 of 19 were node-positive (42%). In conclusion the prognostic significance of TCD is similar, or even better than ALN-status, while TCD-associated morbidity is considerably lower than the morbidity of axillary lymphonodectomy. Therefore our data suggest that TCD might replace axillary lymphonodectomy in breast cancer patients with clinically free ALN or with ALN < 1.5 cm (sonographically). Prospective studies are planned to prove our findings.

P15
The site of the first relapse in operable, node-positive breast cancer patients in relation to prognostic factors and adjuvant treatment

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The first relapse site was analyzed in a group of 172 radically mastectomized, pre- (100) or postmenopausal (72), node-positive breast cancer pts, having been treated with chemo-, chemo-endocrine, or endocrine adjuvant therapy (133 pts), or without any adjuvant treatment (39 pts). The most common metastatic sites were soft tissue (35.4%), viscerals (27.3%) and bones (18.6%), while 15.1% pts developed multiple metastases, and only 3.5% first relapses were localized in the brain. The classical prognostic factors (tumor size, number of nodes involved and histologic grade of primaries) did not affect the first relapse site, while menopausal status affected the metastasizing only in the viscerals: a significantly higher percentage of postmenopausal pts developed visceral metastases. The endocrine adjuvant treatment slightly changed the site of the first relapse, but this did not reach statistical significance. The only prognostic factor that clearly influenced the first relapse site was steroid receptor status. The significantly higher percentage of pts with estrogen receptor positive (ER ≥ 10 fmol) tumors developed bone metastases compared to ER negative pts, while this ratio was inverse for viscerals. Both the ER and progesterone receptors' (PR) quantitative content significantly affected the first relapse site: tumors metastasizing in bones had significantly higher levels of both ER and PR, compared to those metastasizing in soft tissue, viscerals or multiple sites, while tumors in pts developing the metastases in the brain only, had extremely low levels of both receptors. It seems that our results, representing the biological nature of the tumors, could be useful in clinical practice for determining follow-up programs.

P16
Tumor biology factors rather than surgical and adjuvant treatment strategies determine long term survival and locoregional recurrences in breast cancer: 12 year results

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This study was designed to evaluate if data derived from tumor DNA provides independent long term prognostic information in terms of survival or recurrences including locoregional recurrences. 241 consecutive patients with stage I and II breast carcinoma (T1–3, N0–1, M0) entered a prospective clinical trial between 1977 and 1982. Surgical treatment consisted either of conservative breast surgery with axillary dissection or mastectomy. Patients were randomly allocated to an adjuvant therapy group (CMF) and an untreated control group. All patients were regularly followed up at least every three months for the first three years and at six month intervals thereafter. DNA flow cytometry was performed successfully from paraffin embedded tumor specimens from 191 patients. Ploidy index (PI) was defined as percentage of aneuploid cells calculated planimetrically from DNA histograms. After separate cut-off analysis, two groups were defined: Group A, PI less than or equal to 40; Group B, PI more than 40. Overall survival (OS), relapse-free-survival (RFS), and locoregional-relapse-free-survival (LRFS) were calculated according to the Kaplan–Meier method. Multivariate analysis using the Cox proportional hazards model was performed. The median follow-up of survivors was 152.3 months. Both in univariate and multivariate analysis, nodal status, grading and tumor size were significant prognostic factors. When DNA data were entered into the model, both DNA-index and SPF were revealed to be of only borderline importance for prognosis. PI provides highly significant prognostic information about OS ($p = 0.006$, relative risk 2.22), RFS ($p = 0.0001$, relative risk 2.99), and LRFS ($p = 0.0002$, relative risk 3.45). After 12 years, 58.1% of patients were alive in Group A vs. 36.6% in Group B (Mantel–Cox, 0.002). The figures for RFS are 60.3% vs. 37.5% ($p = 0.001$) and for LRFS 92% vs. 72% ($p = 0.0001$), respectively. Neither surgical treatment nor adjuvant chemotherapy had any significant impact on these results. Our findings confirm previously reported results showing that the proliferative activity of tumor cells in breast cancer is an independent prognostic

factor. This is true even with respect to locoregional recurrences, providing further evidence for breast cancer being a systemic rather than a localized disease. Thus, tumor DNA flow cytometry is an useful and necessary method to determine the individual risk of a patient for relapse in order to facilitate risk-adapted treatment strategies.

P17
Microvessel density (MVD) and blood and lymphatic vessel invasion (BLVI) in node-negative breast cancer: effect on recurrence-free survival

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MVD and BLVI were investigated with regard to their influence on recurrence-free survival (RFS) in 231 patients with node-negative breast cancer. We performed immunohistochemical staining for factor VIII-related antigen by counting 4 fields with an ocular raster at 200-magnification (total 1 mm^2). Each cell cluster ≥ 2 highlighted endothelial cells was considered one countable microvessel. We considered BLVI positive if at least one tumor cell could be detected without doubt in a positive stained lumen. 50 out of 231 patients experienced local or distant recurrence and had a mean MVD of 18.1/raster, whereas the mean MVD was 10.5/raster in the patients without recurrence in the follow-up (*t*-test, $p = 0.0001$). BLVI was positive in 40.6% of patients with recurrence and in only 6.2% of patients without recurrence, respectively (chi-square 39.966, $p = 0.0001$). In the Cox model MVD and BLVI remained the only statistical significant prognostic factors for RFS. When stratified for tumor diameter the total recurrence rate was 21.4% in the 10–30 mm diameter group ($n = 177$). In this group we found a recurrence rate of 4.2% in tumors of low MVD and negative BLVI and a recurrence rate of 50.0% in tumors of high MVD and positive BLVI (chi-square 48.555; $p < 0.0001$). In the ≤ 10 mm diameter group we observed only one recurrence out of 19 patients. In accordance with the suggestions of McGuire and Clark we conclude that MVD and BLVI could identify extremely low risk patients out of a low risk subgroup, the 10–30 mm tumor size and node-negative breast cancer patients.

P18
Female primary breast cancer with synchronistic isolateral supraclavicular metastases

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From 1954 to 1977, 2803 cases of primary female breast cancer were treated at Tianjin Cancer Institute and Hospital. Among them 99 cases (3.5%) had synchronistic ipsolateral supraclavicular lymph node metastases. In accordance with WHO staging criteria, in one case the primary tumor was classified as T_1; in 21 cases as T_2; in 27 cases as T_3; and in 50 cases as T_4. The patients were aged from 24 to 68 years old, mean age 46.7 years. The supraclavicular lymph node metastases were confirmed by biopsy pathological study. The treatment modalities of this study were sorted into four categories: (1) combined treatment with surgery plus postoperative radiation and chemotherapy; (2) radiation plus chemotherapy; (3) chemotherapy alone; and (4) no anticancer treatment at all. Except 6 cases in the fourth group which were lost to follow-up, regarded as dead, all others were followed closely. Among the first group surgery was performed with segmentectomy in 6 cases, mastectomy in 7 cases, modified radical mastectomy in 16 cases, classical radical mastectomy in 12 cases, and extended radical mastecomy in 3 cases. The 5-year survival rate as a whole was 9.1% (9/99). The best result fell upon the first treatment group, at 18.2% (8/44); for the second group it was 4.8% (1/21); for the other two groups there was no survival for 5 years. From this preliminary study it is suggested that breast cancer with synchronistic ipsolateral supraclavicular metastases should be treated aggressively. Primary cancer resection plus axillary supraclavicular and internal mammary line irradiation is advocated as the best choice, and the expected 5-year survival rate is up to 20%.

P19
Adjuvant therapy in patients affected by N– breast cancer randomized according to tumor proliferative activity

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Retrospective studies suggest that 3H-thymidine labeling index (3H-dT-LI) can identify subgroups of N– breast cancer patients with a poor prognosis who are potential candidates for adjuvant chemotherapy. On this premise, from January 1990 to December 1993 we enrolled N– breast cancer patients in a prospective clinical randomized trial in order to verify: (a) the feasibility and reliability of the 3H-dT autoradiographic assay in a prospective and consecutive series of N– patients; (b) the therapeutic efficacy of adjuvant chemotherapy for N– breast cancer patients with high tumor proliferative activity. After radical surgery, N– patients with a 3H-dT-LI of 2.3% (best prognostic discrimination value in a previous intramural retrospective N– breast cancer series) were randomized to receive: (a) FEC × 6 cycles; (b) no further therapy. 125 and 129 patients respectively were randomized to the FEC (arm A) and control (arm B) arms; both arms were well balanced according

to the common clinical pathological characteristics. 108/125 patients who were randomized to receive FEC chemotherapy completed their therapeutic plan. In the control group, 10/129 women received TAM adjuvant therapy and 5 were lost to follow-up. At 36 months of follow-up (median follow-up: 24 mos), disease-free survival was not significantly different in the FEC and control groups (91% vs. 89%, respectively; p = n.s., by log rank test). Lastly, 20 relapses were observed in the overall group of 519 N– breast cancer patients; the frequency of relapse was significantly different only between the fast and slow proliferating breast cancer groups but not between patients with different menopausal status, tumor size, tumor grade, surgery (RM or QDL), ER and PgR status and ploidy.

Partially supported by CNR n.93.02321.PF39.

P20
Steroid hormones, cations and tumor markers in breast cyst fluid and cancer risk

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Gross cystic breast disease (GCBD) is the most common benign disorder observed in 5%–10% of women around the age of 45–50 years. Although cysts are not considered to be premalignant lesions, they appear to be the sign of some pathological process occurring in breast tissue. Several reports have indicated that women with cysts are at two- to four-fold higher risk of later developing breast cancer due to the abnormal endocrine milieu detected in the breast cyst fluid (BCF). In this study we have investigated the concentrations of estradiol (E2), progesterone (PROG), testosterone (TE), dehydroepiandrosterone (DHA), DHA-3-sulfate (DHA-S), potassium (K+), sodium (Na+), β-HCG and CA 15-3 in BCF aspirated from 99 women. The mean age of the patients was 49.8 years (range 32–58). E2, PROG, TE, DHA, DHA-S, K+ and tumor markers showed significant accumulation in the BCF compared with their respective serum values. The K+/Na+ ratio proved to be useful in dividing cysts into type I (≥ 1), type II (< 1 but ≥ 0.1) and type III (< 0.1) subgroups. For type I BCF, higher DHA and DHA-S concentrations were detected. Linear regression analysis established a highly significant ($p < 0.001$) correlation between the concentration of E2 and DHA-S ($r = 0.686$), and also between the TE and DHA-S ($r = 0.711$). These findings indicate that the type I BCF might be a marker for 'active' GCBD of the breast, and suggest that it may be associated with an increased breast cancer risk, since this group of patients is supposed to have cysts with apocrine metaplasia. In addition, in case of type I BCF higher β-HCG and CA 15-3 concentrations were present. It is suggested therefore, that when BCF is aspirated, sex steroids, steroid precursors, cations and tumor markers should be routinely measured, and women with type I cyst should be regularly examined.

This work has been supported by a grant from the Ministry of Welfare (ETT T-01 461/1993).

P21
Metastatic pattern in operable breast cancer in relation to age and clinical and histological factors

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Distant metastases are the main cause of relapse and deaths in patients (pts) with operable breast cancer. The time of occurrence and site of metastatic disease influence overall survival time, quality of life and treatment decisions. A retrospective study was performed in an attempt to correlate the pattern of metastatic disease with age, clinical and histological factors. The study group included 1885 pts with operable breast cancer: 1068 of them were treated with radical mastectomy alone and 817 received postoperative radiotherapy. Adjuvant systemic therapy was not applied. During 10 years of follow-up distant metastases occurred in 759 pts. The most common sites of first metastatic manifestation were: bone (251 pts), lung (204 pts), lymph node/soft tissue (91 pts), liver (66 pts), brain (26 pts). In 121 patients metastases involved two or more sites. On multivariate analysis (Cox model) risk of development of metastases in particular site was analysed in relation to age, tumour size, extent of nodal involvement, histological type and grade (Bloom classification for ductal cancer). Regardless of the site nodal involvement, high grade, tumour size and age < 40 years correlated with higher risk of metastatic dissemination. Additionally lobular cancer was found to be a significant risk factor for metastases to bone and soft tissue. No special histological type was found to correlate with increased risk of metastases to lung, liver or brain.

P22
A mathematical model of tumour response to neo-adjuvant chemotherapy in operable breast cancer can predict for early relapse

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Current criteria of tumour reponses to neo-adjuvant chemotherapy for breast cancer do not accurately predict those tumours which will subsequently recur. We have developed a mathematical model of tumour reponse to chemotherapy, based on exponential cell growth, and Skipper's log-kill model of cytotoxicity. The model permits a tumour to have cells that are primarily resistant to the applied treatment. This model runs on an IBM compatible PC, and has been previously validated for inoperable breast cancer, in that it could accurately predict subsequent volumes during weekly chemotherapy (*ASCO* 1994; **13**: 68 (Abstract 73). We have applied this model to 47 women with operable breast cancer who were treated between 1985 and 1991 with four cycles of an adriamycin-based regimen prior to definitive locoregional surgery. Their median follow-up was 4 years, and their median survival has not yet been reached. We found that there was a significantly poorer relapse free survival (p = 0.025) for those tumours estimated by the model to have at least 15% of the primary tumour totally resistant to the chemotherapy. Furthermore there was a trend for the same group to have a worse overall survival. Those tumours that had a CR to the chemotherapy had a trend towards a better relapse-free survival. The application of such a model can identify the subgroup of tumours that are likely to relapse early, and are thus potentially able to benefit from additional systemic therapy.

P23
Estrogen receptor status correlates with CD16+ lymphocytes and depressive mood disorders in primary breast cancer patients

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As some authors have shown, estrogen receptor (ER) and depressive mood disorders (DMD) seem to be related to each other in breast cancer patients. 146 breast cancer patients admitted to hospital were blind studied. Depression was evaluated, during a semistructured interview, using the psychometric MMPI test and the DSM-III-R diagnostic criteria, excluding physical symptoms. ER was evaluated by the DCC method and peripheral blood natural killer cells (CD16+) by flow cytometry. ER+ patients scored higher, but not significantly, on the MMPI Depression scale (2D, p = 0.06), but were rarely diagnosed DMD (p = 0.007). By contrast, ER– patients scored lower on the MMPI Hypomania scale (9Ma, p = 0.006), were more frequently diagnosed dysthymic (p = 0.007) and had low CD16+ both in percentage (p = 0.01) and absolute number (p < 0.01). No correlation was observed between CD16+ and depression parameters. Using stepwise multiple regression the most predicting factors for ER status (23%) were the 2D, 9Ma scale values and DMD diagnosis (p = 0.0008). Dividing those patients treated (surgery and/or chemio-radiotherapy) from the untreated, we observed the disappearance of this correlation in the former group but confirmation of the results in the latter, whereas the statistic power decreased. No significant differences were observed with respect to other prognostic factors such as stage, tumor dimension, node involvement, histologic grade, age or menopausal status, nor reported stressful life events. Further studies are required to clarify the mechanisms that connect ER, CD16+ and DMD, but clearly the equilibrium of the immunoneuroendocrine system is modified during the natural history of breast cancer.

P24
A feasibility study of adjuvant chemotherapy (AdC) versus treatment in intermediate risk node negative (IRNN) breast cancer

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The use of AdC in IRNN patients remains controversial. It is unclear what proportion of these patients are offered or accept systemic therapy. There is no accepted criteria to define the IRNN category. There are numerous prognostic factors relative to tumour biology which could be used to define the IRNN category. We have elected to use a clinically applicable approach of size ≥ 1 cm but ≤ 3 cm without pathological evidence of vascular or lymphatic invasion. In this way, the majority of patients will be found to be eligible without requiring pathology review. Using the London Regional Cancer Centre database, N = 218 node negative patients were identified in 1993. Of these, 160 had tumours ≥ 1 cm but ≤ 3 cm and 111 had no lymphatic or vascular invasion, with 25 further patients for whom this data is not recorded. Therefore (111/218) 51% of all node negative patients per year would potentially be eligible. Our current guidelines for high risk patients (size ≥ 2 cm, high pathologic grade and ER negative if post-menopausal) include only 10 of these patients. We plan to randomize 200 IRNN patients to 6 cycles of oral CMF or 4 cycles of intravenous AC vs. no systemic therapy. We are in addition collecting tumour specimens to measure EGFR, C erb B-*2*, cathepsin D and p53. These factors will be evaluated to determine if they improve the determination of relapse

risk above that obtained using standard features. Preliminary data on financial impact and patient acceptability to randomization will be presented.

EXPERIMENTAL HORMONE THERAPY

P25
Endometrial squamous cell carcinomas and preneoplastic changes as a result of long-term tamoxifen treatment in the rat

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Tamoxifen (TAM) is a widely used and valuable antiestrogen in the treatment of breast cancer in women. The short-term adverse effects of this drug are minor but data has been accumulated recently that long-term medication with TAM increases considerably the risk of secondary cancers in the endometrium. In the rat TAM has proven to be a strong hepatocarcinogen which according to current knowledge is most probably based on TAM genotoxicity. Surprisingly toremifene (TOR), a new antiestrogen structurally closely related to TAM, has not shown any hepatic adverse effects in several comparative studies. The aim of the present study was to compare the long-term effects of this interesting pair of antiestrogens on rat endometrium. Data was collected from three separate studies. Female Sprague-Dawley rats were daily treated perorally with vehiche or with these two antiestrogens at equimolar doses (20 or 80 μmol/kg) for up to 52 weeks. Sacrifices were also made at 13, 20 and 26 weeks and recovery groups after 20–52 weeks of dosing were included. The uteri were studied macroscopically and histopathologically. Both drugs produced uterine atrophy. No preneoplastic or neoplastic changes were observed in control (0/109) or TOR-treated animals (0/62, low-dose; 0/64, high dose) or in the low-dose TAM group (0/25). However, squamous cell metaplasia with prominent keratinization was a common finding (10/104; 10%) in the high-dose TAM group. Further, in three of the metaplasias a focal dysplastic change could be observed; two of these animals (2/104; 2%) also showed a focal invasive squamous cell carcinoma. The carcinomas were also macroscopically detectable. The first case of metaplasia was observed at the 13 weeks time point. One of the carcinomas was found after 20 weeks and the other after 26 weeks of dosing, in both cases after a 12–13 week recovery period. The overall histopathological picture of these observed lesions argues against a mere hormonal etiology. TOR produced no lesions although the estrogen antagonist/agonist activities of these two drugs at the high dose level used are closely comparable. Thus a nonhormonal mechanism in TAM-induced endometrial carcinogenesis should be taken into consideration.

P26
Hepatic damage caused by long-term administration of tamoxifen to rats: relevance of DNA adduct formation to human exposure

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We have demonstrated that the short-term administration of tamoxifen to rats results in DNA damage which can be determined by ^{32}P-postlabelling. Such damage was either absent or present in trace amounts following the administration of toremifene, an analogue that does not cause liver tumours. In the present study, tamoxifen was administered in the diet (approximately 40 mg/kg/day) to three strains of female rats to determine the early morphological and biochemical changes associated with the development of liver cancer. Hepatic DNA damage determined by ^{32}P-postlabelling showed a time dependent increase from 500 adducts/10^8 nucleotides after 1 month to > 3000 adducts/10^8 nucleotides at 6 months. Determination of damage in the livers from six women exposed to tamoxifen showed a mean level of 36 adducts/10^8 nucleotides, not significantly different from control values. These results are encouraging with respect to potential human risk, but this does not exclude that in a genetically diverse population some individuals will be much more susceptible.

P27
Mode of action of toremifene

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Toremifene belongs pharmacologically to partial agonists and antagonists of estrogen action. It binds to ER and as a dimer complex to ERE of estrogen responsive genes, more specifically to the regulatory areas of them. Like tamoxifen, toremifene may induce or inhibit gene transcription. It is not known in detail which genes are affected. Other proteins, which are bound to the vicinity of ERE, can be tissue specific and participate in the regulation of gene expression. Therefore the final outcome of toremifene action is complex. In the classical target tissue, the uterus, toremifene causes cell proliferation and subsequent uterotropic effect which is more pronouced in mice than in rats. However, the maximal estrogenic effect is in all conditions lower than that of estradiol. In the liver toremifene does not induce cell proliferation. However, it regulates synthesis of specific proteins. Synthesis of SHGB is induced as with estradiol. By contrast, synthesis of serine

proteases, like antithrombin III, is inhibited, which is an antiestrogenic effect. In the bone toremifene and tamoxifen have a similar bone preserving effect after ovariectomy. This effect may be indirect, most probably regulation of osteoclast differentiation, because the compounds do not have significant effects on bone *in vitro*. Immunological effects of antiestrogens are not dramatic but tamoxifen and toremifene are known to delay significantly the development of autoimmune disease in NZB/NZW mice, being thus antiestrogenic in that model. Toremifene induces apoptosis *in vitro* in MCF-7 cells and *in vivo* in DMBA-induced rat tumors. Toremifene-induced apoptosis can be differentiated from spontaneous apoptotic events by electron microscopy. Based on preclinical safety studies toremifene is likely to be less carcinogenic than tamoxifen. Antitumor effects of tamoxifen and toremifene are comparable in several models. High-dose toremifene in mice significantly inhibits mouse uterine sarcoma growth although tamoxifen does not. In the meta analysis of clinical phase III studies tamoxifen 20, 30 or 40 mg shows equivalence to toremifene 60 mg daily. Higher dose of toremifene (200 or 240 mg daily) induces slightly higher response rate which, however, is not reflected as a longer disease free time. In phase II studies a small subgroup of patients (12% objective RR) benefits from high-dose toremifene as a second or third line treatment.

P28
Comparison of liver microsomal metabolism of tamoxifen and toremifene in different species

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We have compared the liver microsomal metabolism of tamoxifen and toremifene in rats, mice and humans. The major metabolic pathways of tamoxifen in all three species are N-demethylation and ring hydroxylation, with the latter being much more prominent in mice and the former more important in humans. Although the same pathways were observed for toremifene metabolism the N-demethylation pathway dominated in all species. Using liquid chromatography-electrospray ionisation mass spectrometry, the formation of putative genotoxic metabolites, 3,4- and 3', 4'-epoxytamoxifen were detected in the rat, while in extracts of mouse and human microsomal incubation mixtures only a smaller amount of 3,4-epoxytamoxifen was detectable. Using toremifene as substrate, 3,4-epoxytoremifene but not 3'4'-epoxytoremifene was formed by all species studied but in quantities much smaller than with the tamoxifen analogue. The relatively small amount of the reactive 3,4-epoxytoremifene generated by liver microsomes may explain why toremifene gives a much lower level of DNA damage, as assessed by ^{32}P-postlabelling, following its administration to rats, than does tamoxifen.

P29
The superior safety profile of toremifene compared to tamoxifen in nonclinical

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This study was a further effort to evaluate the effects of toremifene (TOR) and tamoxifen (TAM) in safety studies rats. Previously, we demonstrated that TAM was hepatocarcinogenic in female Sprague-Dawley rats whereas TOR was not (*Cancer Research* 1993; **5**: 4534) and that TAM produced DNA adducts in rat liver, but TOR did not (*Arch Toxicol* 1994; **68**: 272). In the present study, equimolar doses of TOR (42.4 mg/kg) and TAM (40 mg/kg) were given by gavage to female Sprague-Dawley (S-D) and Fischer (F344) strain rats for 2 or 12 weeks. At the end of 12 week administration, TAM produced liver DNA adducts in both strains as determined by the ^{32}P post-labeling method, whereas TOR yielded no adducts. Using placental type glutathione-S transferase as an immunohistochemical marker for preneoplastic liver lesions, after administration for 2 weeks of TAM, the incidence of liver altered foci/cm^2 was 1.56 in S-D rats and 0.67 in F344 compared to 0.37 and 0.27 respectively in controls. By 12 weeks, the incidence of foci was 7.03/cm^2 in S-D rats and 2.12/cm^2 in F344 rats after TAM, compared to 0.14/cm^2 and 0.17/cm^2 respectively in controls. At 12 weeks after TOR, S-D rats exhibited foci 0.13/cm^2 and F344 rats 0.26/cm^2, which were not elevated above controls. In conclusion, TAM was DNA damaging and initiated hepatocarcinogenesis in both strains of rats, although the S-D was more susceptible, and TOR was without genotoxic or carcinogenic activity.

P30
A proliferation study in uterine compartments of two different rat strains after 2 and 12 week administration of tamoxifen and toremifene

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Recently a high dose of tamoxifen (TAM) (45 mg/kg) was shown to induce endometrial neoplasia in Sprague-Dawley

rats, whereas an equimolar dose of the closely related toremifene (TOR) did not, providing a possible link to clinically observed TAM-related endometrial tumors. The etiology of the endometrial tumors is unclear. Both a hormonal effect, due to the partial estrogen agonism of TAM, and a possible genotoxic effect, due to the capability of TAM to induce DNA-adducts in rat liver, must be considered. The purpose with the current study was to evaluate the proliferation indices in the endometrial epithelium, stroma and myometrium of Sprague-Dawley and Fischer 344 rats, treated p.o. with TAM (5, 10, 20 and 40 mg/kg) and TOR (21.2 and 42.4 mg/kg). The treatment was for 2 and 12 weeks and PCNA (proliferating cell nuclear antigen) was used as marker. No preneoplastic or neoplastic changes were observed. At both time points all doses of TAM and TOR caused stromal and myometrial atrophy with decreased proliferation indices and slightly decreased labeling indices of the luminal epithelium compared to control animals. At both time points, but especially after 12 weeks, hyperplastic multilayer epithelia, occasionally with hypertrophic cells, focally replaced the normal columnar epithelium. The marker stained typically only the basal cell layer of these epithelial changes. The labeling indices of these cells were increased compared to the surrounding columnar epithelium but no differences between TAM and TOR were observed. Histologically the findings resembled estrogen stimulated epithelial changes, indicating that these changes were related to the estrogen agonism of TAM and TOR. Since no differences were observed between the two drugs a solely hormonal explanation for the TAM-induced neoplastic changes in the rat endometrium might not be sufficient.

P31
Post-menopausal endometrial changes during treatment with tamoxifene

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We have studied 57 post-menopausal women affected by mammary carcinoma and treated with long term tamoxifene (TAM) therapy. Each woman underwent outpatient hysteroscopy and subsequent endometrial biopsy in order to determine endometrial modifications and variations from usual endometrial post-menopausal atrophy. Hysteroscopy is always done without general anesthesia or dilatation of the cervical canal; endometrial biopsy was performed using PERMA or NOVAK curette. The patients were divided for analysis into three groups as follows: Group A, 9 patients presenting with abnormal uterine bleeding (AUB) and undergoing usual diagnostic routine for AUB; Groups B and C, 11 and 39, respectively, asymptomatic women receiving hysteroscopy and endometrial biopsy as planned by our protocol of surveillance during adjuvant TAM therapy. The asymptomatic patients were allocated to two groups by whether their cumulative dose of TAM was less than (Group B) or greater than (Group C) 15 g (equivalent to a 26 month course of TAM, 20 mg daily). The three groups did not differ by age, age at menopause or parity. We had a rate of inadequate biopsy specimen of 72.7% and 53.4% in Groups B and C respectively, which is usually consistent with atrofic endometrium. Nevertheless, at hysteroscopy we observed unequivocal signs of endometrial activity, such as vascular congestion and mucosal synechiae in 36.4% (B) and 43.6% (C), which is very unusual in the post-menopausal endometrial cavity. Moreover, we observed a higher degree (35.9%) of endocervical polypoid appearance (that made hysteroscopy very difficult) in Group C than in Group B (9.0%). The biopsy specimens were consistent with an endometrial hyperplasia or endocervical dysplasia in 25.7% of Group C patients, similar to those found in symptomatic Group A patients; none were found in Group B. We also found one case of metastatic mammary carcinoma in the endometrium of one asymptomatic Group C patient (otherwise deceptive in its macroscopic appearance) and one classic endometrial cancer in a symptomatic patient (A). Figures of polyps were similar in the three groups: 44.4% (A), 45.5% (B) and 43.6% (C). In conclusion, the cut-off value of 15 g of TAM cumulative dose is consistent with a characteristic appearance of endometrial activity and a higher prevalence of endometrial/endocervical hyperplasia in asymptomatic women. This makes them susceptible to intensive instrumental evaluation, the same as patients with AUB. The study is ongoing, particularly of patients treated with more than 36 g of TAM (i.e. 5 years of therapy).

P32
Adjuvant tamoxifen therapy reduces total cholesterol and LDL-cholesterol in postmenopausal women with breast cancer

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It is generally accepted that endogenous as well as exogenous sex steroids affect lipoprotein metabolism. Since estrogens are involved in breast cancer development the antiestrogen tamoxifen is widely used as adjuvant hormonal treatment in breast cancer patients. The estrogenic effect of tamoxifen on the liver has been shown to inhibit cholesterol synthesis and increase lipoprotein particle output resulting in a lowering of plasma total cholesterol and LDL in some studies, but not in others. In this study 62 newly diagnosed postmenopausal women with node positive breast cancer receiving adjuvant tamoxifen (20 mg per day) aged 48–79 years (x = 57.6) were studied. Total serum cholesterol, triglycerides, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol, apoAI, apoAII and apoB were determined before the surgery as well as 3, 6, 9 and 12 months after starting with tamoxifen treatment. Breast cancer

patients before the surgery had higher cholesterol, triglyceride and LDL-cholesterol levels than the average Croatian population. Tamoxifen significantly reduced total serum cholesterol (6–7 ± 0.8 mml/l vs. 5.1 ± 1.2 mml/l) ($p < 0.005$), LDL-cholesterol ($p < 0.01$), VLDL-cholesterol ($p < 0.01$) and Lp(a) ($p < 0.01$) from 0.93 ± 0.01 to 0.72 ± 0.02 g/l, but increased HDL-cholesterol ($p < 0.01$). These results suggest that these effects of tamoxifen on serum lipoproteins and presumed decrease in cardiovascular risk may prove to be an additional benefit to those patients who may well live long enough to be affected by risk factors other than a recurrence of their breast cancer.

P33
Adjuvant tamoxifen therapy in postmenopausal node-positive breast cancer patients

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Between September 1986 and December 1991, 236 postmenopausal women with operable (T1–2) primary breast cancer and axillary node involvement were included in the study. All the patients underwent surgery (total mastectomy or breast conserving surgery) and complete axillary dissection. All received postoperative irradiation and 20 mg tamoxifen for two years if remaining disease free. At the time of analysis average follow-up was 42 months (the range was 21–84 months). Our study in particular examines the duration of treatment effect and the relationship between prognostic variables (tumor size, number of positive nodes, degree of anaplasia, ER status) and treatment effect. Disease-free and survival curves were plotted according to the life table method of Kaplan–Meier. The log rank test was used to examine differences between curves. In our series the recurrence rate was 32.63% (77 patients). The local recurrence rate was 6.78% (16 patients). In conclusion, multivariate analysis compared overall and relapse free survival by tumor size, degree of anaplasia, number of involved nodes. All of these factors have strong and independent prognostic significance.

SURGERY, RADIOTHERAPY

P34
The influence of the width of free margins and other histological tumor findings on the recurrence after breast conserving therapy (BCT) of primary breast cancer

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Objectives. The relation between the width of free margins and recurrence after BCT is still unclear. Tumor size, growth pattern, histological grading, lymph node status and EIC might be of predictive value. A retrospective study was designed to answer these questions. *Patients and methods.* From October 1986 to June 1992 103 pre- and postmenopausal women with primary breast cancer, i.e. invasive ductal carcinoma, underwent lumpectomy and axillary dissection followed by radiotherapy with 50–60 gy using supervoltage equipment, mean observation time 49 months (31–92). *Results.* Recurrence was noticed in 8 patients (7%), 6 of which had an aggressive tumor growth pattern (75%) and 2 (25%) an expanding one. 4 of these patients each had free margins less than 5 mm or more. The med. tumor size was 2.2 cm; 5 patients were lymph node positive; grading 1 tumors or EIC did not occur. *Conclusion.* Local failure was correlated to an aggressive growth pattern and low grading. There was no correlation to the width of free margins, the tumor size, the nodal status or EIC.

P35
Sentinel lymphadenectomy for T1 breast cancer: a novel approach to assess axillary lymph node status

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Background. There is a direct correlation between tumor size and axillary lymph node involvement in invasive breast cancer. Positive lymph nodes are found in 24%–31% of T1 breast cancers (≤ 2 cm). The even lower rate (6%–19%) for tumors < 1 cm has led some surgeons to abandon axillary lymph node dissection (ALND) for this subgroup. However this approach leads to understaging of some patients and precludes them from adjuvant systemic therapy. We studied T1 breast cancer patients to identify predictors of nodal metastasis and to assess the feasibility and predictive value of a limited surgical staging procedure (sentinel lymphadenectomy) that has proven to be highly accurate in patients with lymphatic metastases of malignant melanoma. *Methods.* The study population comprised 259 patients with T1 breast cancer treated with modified radical or segmental mastectomy and ALND at the John Wayne Cancer Institute between 1/88 and 6/94. Of the 259 patients, 114 underwent sentinel lymphadenectomy before ALND. In this procedure, a vital dye injected into the tumor or biopsy site is carried via the lymphatics to the draining or 'sentinel' node. This sentinel

node is excised and its histology is compared with that of nodes in the ALND specimen. *Results.* Of the 259 patients, 62 (24%) had lymph node metastasis. Nodal involvement was identified in 11 (13%) of 88 patients with tumors ≤ 1 cm and in 51 (30%) of the remaining patients with tumors of 1.1–2 cm ($p = 0.001$). Age, hormone receptor status, presence of DCIS, histology, ploidy and S-phase were not significant predictors of lymph node metastasis. A sentinel lymph node was identified in 75 patients: this node accurately predicted axillary status in 71 patients, was the only positive axillary node in 9 of 16 patients with axillary involvement, and was 100% predictive of axillary status when the primary tumor was ≤ 1 cm. *Conclusions.* Tumor size was the only accurate predictor of axillary metastasis in T1 breast cancer. The significant incidence of axillary involvement from T1 tumors mandates accurate staging, even when the tumor is ≤ 1 cm. Sentinel lymphadenectomy may become a suitable replacement for ALND in these patients.

P36
Surgical issues in a protocol of primary chemotherapy of breast cancer

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In a multicentre clinical trial in 87 T2–T3, N0–N1, M0 breast cancer patients, primary chemotherapy consisting of 3 cycles of epirubicin at the dose of 120 mg/m2 every three weeks was administered in order to reduce the tumor burden and to allow a conservative surgery when the tumor diameter was reduced to < 3 cm. This was possible in 74% of the patients. Surgical issues taken into consideration were: the possibility of tumor progression; the delay of surgery due to the toxicity of the chemotherapeutic regimen; the difficulty, in some instances, of detecting the tumor after 3 cycles of chemotherapy. From the data obtained the following evidence can be drawn. (1) In no case during primary chemotherapy was an increase of tumor size observed. (2) In no case did surgery have to be delayed because of chemotherapy-related toxicity. (3) In 8 cases the tumor reduction was so marked as to make it difficult to detect: therefore, before starting chemotherapy, we deem it advisable to indicate the tumor localization and extension (for instance, with sterile carbon). (4) In no case was surgery accompanied by intra- or post-surgical complications. To conclude, it does not seem there are limitations to the combined chemotherapy–surgery treatment: in the vast majority of cases this approach allows a conservative surgery taking into account also the aspect of quality of life.

P37
Conservative breast surgery: experience in Western India

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In Western India the Gujarat Cancer and Research Institute is a regional cancer centre treating about 5000–6000 new cancer cases every year. Breast cancer forms about 10% of the total patients. Unfortunately the disease is seen among people of poor socio-economical class and at advanced stages of the disease. Early localised curable breast cancer forms only about 10% of the total breast cancer patients. Parity and breast feeding were not found to be aetiological factors. Management of early breast cancer is controversial and disputed. We performed modified radical mastectomy followed by CT in indicated patients up to 1990. This has produced satisfactory long term DFS. After 1990 we started doing CBS (quandrentactomy or wide excision) with axillary dissection followed by RT and CT. This paper describes the experience, comparision and acceptance of both types of modality in the state of Gujarat. CBS was only suggested to younger patients with higher socio-economical status. Both the procedures were comparable in acceptance and short term DFS. The exact figures are as follows: total number of surgically treated patients, 150; age group, 21–64 years; 54% premenopausal; 46% postmenopausal; early stages were 15%–20% and DFS (2 years) was 60%.

P38
Local recurrence after radical surgery for breast cancer

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From 1970 to 1979 primary radical mastectomy was performed in 656 patients. The study was designed to determine the risk factors for local recurrence by first and isolated place of relapse and influence of local recurrence on total survival. Minimal time of follow-up was 10 years. During this time local recurrence as single place of relapse appeared in 41 patients (6.2%). In this study it has been found that statistically significant risk factors for local recurrence are: metastases in more than 4 axillary lymph nodes; carcinomatic embolus in lymph or blood vessels; age 50. In this study there was no correlation between risk of local recurrence and size of primary. There was also no correlation between tumor differentiation according to Bloom and local recurrence. Probability of 10 years survival after local recurrence was 37%.

P39
Quality in the treatment of symptomatic breast cancer

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In May 1992 the National Co-ordination Group for Surgeons working in Breast Cancer Screening in the UK produced Quality Assurance Guidelines for surgeons working in breast cancer screening (NHSBSP Publication No. 2). This document laid out standards that should be achieved by breast surgeons dealing with the surgical consequences of a possible or definite diagnosis of breast cancer made in the Breast Screening Programme. We felt that these criteria could and should be applied to our symptomatic Breast Clinic in the Royal Victoria Hospital. We realised that the criteria would need to be altered, and that the first criteria which deals with the general performance of a screening unit would not be applicable. But with very little alteration it was possible to make the criteria fit a symptomatic Breast Clinic. The results of the application of these criteria to breast cancer patients seen in 1992 will be presented. The Clinic failed to meet 5 of the 15 criteria, and reasons for this failure will be presented.

P40
Salvage mastectomy for local recurrence following breast conservation surgery without radiation therapy

CC Cajucom and RC Tia

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This study was undertaken to analyze the results of modified radical mastectomy as a salvage procedure for local recurrence after breast conserving surgery without radiation therapy, and determine prognostic factors related to survival after the salvage procedure. Between 1975 and 1987, 128 pts with invasive ductal carcinoma, categorized as clinical stage I and II breast cancer, underwent breast conservation surgery without radiation therapy. After a median disease-free interval of 20 months (range 8–64 months), 25 pts developed local recurrence for which salvage mastectomy was performed. After a median disease-free interval of 52 months (range 8–75 months) after salvage procedure, 12 pts had chest wall and distant recurrences while 13 pts remained free of disease. The 5 year disease-free and overall survival rates after salvage mastectomy were 51% and 65% respectively. The size of the local recurrence (≤ 2 cm) ($p = 0.009$) and the number of pathologically positive axillary nodes at the time of salvage mastectomy (fewer than 4 nodes) ($p = 0.002$) were associated with a better prognosis.

P41
Laparoscopic oophorectomy: an adjuvant therapy in primary premenopausal breast cancer

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Ovarian ablation inhibits disease progression in pre-menopausal patients with breast cancer. Oophorectomy is established in the palliation of advanced disease; however its role as adjuvant therapy in early breast carcinoma remains unclear. Traditional surgical oophorectomy, chemical oophorectomy and ovarian radioablation are associated with significant morbidity. For this reason, a prospective trial was undertaken to assess Laparoscopic Oophorectomy (LO) as an alternative for the induction of menopause and to determine its role as adjuvant therapy in primary premenopausal breast cancer.

All premenopausal patients with breast cancer presenting over a 3 year period were offered LO. LO was performed at a median of 9 days following initial mastectomy or segmentectomy with axillary clearance. One × 10 and 2 × 12 mm ports provided access, and bilateral oophorectomy was performed using an endoGIA stapling device. Operative details and morbidity were recorded. Serum β-oestradiol, follicle stimulating hormone and luteinizing hormone were assayed pre-operatively and at post-operative intervals to determine efficacy at induction of menopause. Menopausal symptomatology was assessed using the Kupperman scoring index. All patients were commenced on tamoxifen post-operatively, and node-positive patients were referred for adjuvant chemotherapy. All patients remain under regular review.

In a consecutive series of 55 patients, mean operating time for LO was 20 minutes (15–45). Morbidity was minimal (1 conversion for bleeding; 1 wound infection). Serum β-oestradiol fell rapidly from a mean pre-operative level of 500 pg/ml to < 50 pg/ml at 1 week and < 25 pg/ml at 1 month. The majority of patients experienced only mild or slight menopausal symptomatology. All patients tolerated tamoxifen therapy. Twenty patients with node-positive disease were referred for adjuvant cytotoxic chemotherapy. At a median follow-up of 15 months (1–33), 1 patient developed local recurrence at 11 months and 1 patient died at 16 months with presumed metastatic disease.

Laparoscopic oophorectomy is a safe and straightforward procedure with minimal associated morbidity. This study demonstrates that rapid, total ovarian ablation is achieved by this technique, and supports its utilisation as adjuvant therapy in the management of breast carcinoma. Longer follow-up will determine the role to be played by laparoscopic oophorectomy in improving survival in pre-menopausal women with primary breast cancer.

P42
Breast conservation without radiotherapy in elderly breast cancer patients

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Although postoperative irradiation after breast conserving surgery is currently the treatment of choice, it is not clear whether all patients, even those with low risk for local recurrence, should receive this treatment. We have analysed our data retrospectively to investigate if irradiation has any benefit for older patients with respect to locoregional recurrence rates. Between 1983 and April 1994 345 women over 60 years of age with Stage I or II breast cancer and treated by quadrantectomy and axillary dissection were assigned to either receive adjuvant irradiation or no radiotherapy. Results of a pilot trial provided evidence that older patients with favorable tumor characteristics show a remarkably low recurrence rate without irradiation. Two thirds of the patients had tumors less than 2 cm, 75% had grade I or II tumors, 80% had immunohistochemical positive receptor status, 66% had negative axillary lymph nodes. Chi-square test and the Cox model were used for statistical analysis. After a median follow-up period of 44 months the multivariate model revealed lymphonode status ($p < 0.011$) as highly significant with regard to local recurrence free survival. Regarding the lymph node negative, receptor positive patients we were not able to identify a positive effect of adjuvant irradiation: both patients with or without irradiation had similar 3% locoregional recurrence rate. In a subgroup of patients who were lymph node negative, receptor positive and received adjuvant tamoxifen therapy, the local recurrence rates were as low as 2% in both groups. In the node positive subgroup irradiation decreased the locoregional recurrence rate (8% vs. 11%). We conclude that it is possible to avoid the morbidity and potential psychological side effects of radiotherapy in breast cancer patients over 60 years of age treated by breast conserving surgery (T1, N0, positive hormone receptor) without increased risk of locoregional recurrence.

P43
Adjuvant radiotherapy after breast conserving surgery with a modified technique

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We present a modified irradiation technique for high risk breast cancer patients (pts) having undergone breast conserving surgery. In 1982 we developed a two-field technique for a linear accelerator using photons and electrons with half beam blocking. An individual wax moulage compensates the different depth of the target volume in the electron portal. In this way we reduced the number of portals and the risk of hot spots. In a retrospective analysis we evaluated 154 pts regarding locoregional control. 68 pts were also investigated for cosmetic outcome and functional results. The median follow up is 38 months. 61 pts had chemotherapy simultaneous with irradiation. Total doses of 46–50 Gy in fractions of 2 Gy 4–5 times per week were administered. Only 5 (8%) pts showed distinct telangiectasia. 20 (29%) presented minimal and 43 (63%) no telangiectasia. We found skin fibrosis in 2 pts (3%). None of the interviewed pts had pulmonary complaints due to lung fibrosis. Tumor relapse in the breast was seen in 11 of 154 pts, one patient had an axillary recurrence (7.8% locoregional failure). Overall, 20 (13%) women developed distant metastases. The preliminary results show that the presented irradiation technique is safe. Cosmetic and functional outcome as well as locoregional control are comparable to international data. The complex target volume can be effectively and comfortably treated with this two-field technique. A prospective analysis has been started.

P44
Combining adjuvant therapy and radiation increase local control in N+ breast cancer treated by conservative surgery

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The first aim of this study was to evaluate the incidence of local and regional recurrences in a series of 302 consecutive patients with $T_1N_{0-1}M_0$ infiltrating ductal (71.55%) or infiltrating lobular (15.06%) breast carcinoma submitted to QuART between 1985 and 1993 at our institution. Median age of patients was 50.8 years (range 30–75) and PS = 0; 110 (36.4%) were positive nodes (11.92% > 3N; 20.42% ≤ 3N), 5.84% was G_1, 88.32% G_2 and 5.84% G_3; 100 ER+ and 60 ER unknown. All patients were submitted to radiotherapy (50 Gy with high energy + 10 Gy as a boost with orthovoltage in 5 weeks). Adjuvant i.v. q21 CMF or tamoxifen (30–20 mg/day, at least three consecutive years) were performed according to pre- or postmenopausal and hormonal receptor status in node-positive patients. All patients were followed up. 12 patients (3.97%) aged from 35 to 62 years (10 N–, 2 N+), 5 pre- and 7 postmenopausal, developed recurrence in the treated breast and in 5 of these it was associated with simultaneous distant metastases. Histopathology of primary breast cancer was infiltrating ductal carcinoma in 10 patients and infiltrating lobular in 2. Relapse-free interval

was 8–61 months (median 36.0 months). In one patient a wide reexcision was performed, in 6 a salvage mastectomy and in 5 only a diagnostic biopsy. Afterwards all patients were treated with chemo- or hormonal therapy; locoregional radiotherapy was associated in 2 patients. 4 patients (30%) (3 with distant metastases) died within 2–24 months. At median follow-up of 36 months (range 10–65 months) 8 patients are alive (7 disease-free and 1 with bone and liver metastases). 5-year overall actuarial survival was 68.8%. Site of locoregional recurrence (skin or axillary lymphonodes) and menopausal status were the most important prognostic factors. Moreover, patients who underwent adjuvant therapy because of node-positive status had a lower incidence of local and regional recurrence than negative nodes. This finding could be related with a synergism between radiotherapy and chemotherapy. In conclusion we believe that conservative surgery like QuART (plus adjuvant therapy in risk subset patients) is at present the routine procedure of choice in $T_1N_{0-1}M_0$ breast cancer in order to obtain a good cosmetic result with a very low rate of locoregional recurrence.

P45
Accelerated preoperative radiation treatment in operable (large T2 and T3) breast cancer

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In the last two decades many clinical studies on breast cancer were conducted on the possibility of tumor size reduction utilizing preoperative radiotherapy with standard fractionation up to a total dose of about 45–50 Gy; only a few reports experienced non-conventional schedules. In order to evaluate feasibility and efficacy, from January 1993 a pilot study on an accelerated preoperative radiation treatment (180 cGy twice daily for 10 days, total dose 36 Gy) was conducted on a group of patients with large T2 and T3 N0 breast cancer. The rationale for this new approach was according to the following considerations: (1) shortening the time of therapy and the total dose produces a better compliance for patient and surgeon; (2) the value of α/β for breast tissue is assumed to be 5 Gy (Beyer '92), suggesting the possibility of a higher local control with accelerated multifractionated treatments; (3) accelerated hyperfractionation is predicted to result in most sparing of late reacting normal tissues. Up to now ten patients have entered the study. All the patients, after a histologic proof of breast cancer, underwent standard procedure for staging and gave their informed consent. They were treated twice daily with 1.8 Gy/fraction, 5 days/week; the interval between the two daily fractions was 6–8 hours. The total dose was 36 Gy and the overall treatment time 12 days. Patients received treatment from opposed fields covering the whole breast. Assessment of tumor reduction was conducted 4 weeks after the end of treatment. 7/10 patients achieved a tumor reduction of > 50% and in 2/10 patients there was complete disappearance of the tumor. Only 1 patient failed to respond to treatment. Concerning the surgical procedures, 9/10 patients underwent quadrantectomy and the non responsive patient radical mastectomy. All the patients after 3–4 days from the end of radiotherapy experienced moderate redness lasting 24–48 hours. According to our preliminary results we can conclude that tumor response was as predicted and comparable with the results obtained with standard schedules. The reduced length of treatment time can shorten the intervals between time from diagnosis, induction therapy and surgery. The low incidence of acute effects and the absence of post-surgical morbidity make our schedule attractive for further studies.

P46
Identification of a subgroup of patients with breast cancer who may benefit from postmastectomy radiotherapy, combined with adjuvant chemotherapy

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The importance of postmastectomy radiotherapy combined with systemic therapy was further evaluated in 218 pts, treated from 1978 to 1989, in relation to the factors that significantly discriminate between locoregional recurrence (LR) and distant metastases: number of positive nodes in axilla (N), primary tumor size and histopathologic tumor grade. Adjuvant chemotherapy (CHT) consisted of CMF protocol for 6 months. Radiotherapy consisted of 45 to 50 Gy to the chest wall and regional nodes with/no electron boost of 10 Gy. The 5-year cumulative LR recurrence was lower in the pts treated by CHT + RT (16% vs. 7%), but only in the subgroup of pts with N3. With extranodal infiltration the difference is highly significant ($p = 0.003$) in favour of the irradiated pts. The relative odds for the other factors were smaller. *Conclusion.* The subset of pts with N3 or extranodal invasion mostly benefit from postoperative RT combined with CHT, not only by the significant reduction of LR recurrences, but probably by improved survival.

P47
Brachytherapy for breast cancer

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In 1987–1993 a total of 301 patients with breast cancer underwent interstitial treatment. Two methods of irradiation were applied. When patients refused surgery, external radiotherapy was given followed by implant radiotherapy for a dose of 20–30 Gy. Needle sources were applied for treatment; their active length was 30 mm with an increasing activity on the ends. The application of special template devices made it possible to implant radioactive sources in the strictly pre-set geometry. This allowed placement of the sources in the necessary geometry for the whole course of irradiation. Dosimetric planning was performed in Gray-equivalents to a selected isodose curve, mostly 85%. Treatment time was 20–50 hours. In cases when tumour was localised in the medial quadrant of breast, interstitial therapy was applied to the parasternal lymph nodes. During mastectomy catheters were placed in a. thoracica interna of the corresponding side. On the first or second postoperative day flexible radioactive sources were inserted into catheters. Their active length was 10–12 cm. Irradiation dose at a distance of 2 cm from the centre of source was 40–45 Gy. *Results.* There was minimum radiation effect on the adjusting organs and tissues. Local recurrence of tumour in the region of irradiation occurred in 5 patients. *Conclusion.* The application of interstitial radiotherapy in treatment of breast cancer is effective and the results of radiation treatment are encouraging.

PREOPERATIVE CHEMOTHERAPY / DOSE INTENSITY

P48
Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumors considered too large for conserving surgery: an update

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Mastectomy and axillary dissection have been the standard treatment in populations with an average breast tumor size of 45 mm. Adjuvant chemotherapy or endocrine manipulations have been classically reserved for axillary node positive and selected node negative patients with a high risk of micrometastatic disease. The treatment schedule in this trial was designed to try to improve survival as well as to assure good local control and to limit the need for radical surgery. Premenopausal patients with tumours considered too large for breast conserving surgery were randomized to receive either 4 cycles of neoadjuvant chemotherapy (Cylophosphamide, Adriamycin, 5 Fluoro-Uracil: CAF) (n = 200) or the same chemotherapy in a conventional adjuvant setting (n = 190). These patients have now been followed for a median of 66 months (range: 14–92). The 5-year probability of survival was 84% (78–90) for the neoadjuvant group (NEO) and 78% (72–84) for the adjuvant group (ADJ) (p = 0.18). Local recurrence-free rates were 74% (68–80) for NEO and 80% (74–86) for ADJ (p = 0.2). Metastatis-free rates were 72% (66–78) for patients treated with neoadjuvant chemotherapy and 65% (58–72) for patients treated in the adjuvant setting (p = 0.09). Breast conservation rates were identical, with 63% (56–70) and 62% (55–69) for the respective groups. In a multivariate regression analysis using a stepwise backwards procedure, the following parameters remained significantly associated with increased *metastatic relapse*: (1) young age (< 35) (relative risk, RR: 2.5), (2) clinically positive nodes (RR: 1.8), (3) large tumor size (T3 vs. T2) (RR: 1.65) and (4) timing of chemotherapy (ADJ vs. NEO) (RR: 1.5). When we tested for *survival*, the variables associated with a poor outcome were: (1) high percentage of tumor cells in S phase (> 5%) (RR: 2.6), (2) clinically positive nodes (RR: 2.3) and (3) large tumor size (RR: 1.6) (T3 vs. T2). Histological tumour grade (SER) and hormone receptor values were also tested in these models. Missing values were coded separately. In conclusion, despite the disappearance of the survival benefit seen at an earlier assessment, the present evaluation confirms a trend towards less or delayed metastatic recurrences in patients treated by chemotherapy upfront. A high S phase fraction continues to be associated with a pejorative prognosis, suggesting that these highly chemosensitive patients may benefit from intensified treatment regimes.

P49
Neoadjuvant chemotherapy in locally advanced breast carcinoma

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Sixty-two patients with locally advanced breast cancer were treated with neoadjuvant chemotherapy (NCT). 7 patients (10%) had T3 lesions, 39 (64%) had non-inflammatory T4 tumors and 16 (26%) had inflammatory carcinoma. 19 patients (1987–89) recieved CNF combination (CTX 600 mg, MT 12 mg and 5FU 600 mg/m^2), 21 patients (1989–91) had CAF1 (CTX 500 mg, ADM 50 mg and 5FU 500 mg/m^2) and 22 (1991–93) had CAF2 regimen (CTX 600 mg, ADM 60 mg and 5FU 600 mg/m^2). In 37/62 patients (60%), radical surgery was done after chemotherapy: 33 SEM and 4 lumpectomies. Radiotherapy was given to 18 patients as definitive treatment after chemotherapy and to 32 after surgery. The three treatment regimens were compared:

	CNF	CAF1	CAF2
Overall response to NCT	10/19 53%	8/21 38%	17/22 73%
Clinical CR after NCT	2/19 11%	3/21 14%	2/22 10%
Progression during NCT	2/19 11%	5/21 24%	2/22 10%
Radical surgery	8/19 42%	11/21 52%	18/22 81%
NED at end of treatment	11/19 58%	13/21 62%	18/22 81%
Loco-regional failure	1/11 10%	1/13 8%	— —
Distant failure	6/19 32%	7/21 33%	3/22 14%
Median follow up	41 months	22 months	15 months
Two year actuarial survival	76%	62%	64%

Conclusion. CAF2 regimen (600, 60, 600 mg/m^2) seems to achieve a higher response rate in locally advanced breast carcinoma. The small number of patients in each group and the variable follow up periods do not allow any statistical significant difference between the therapeutic value of the three drug regimens.

P50
A randomised trial of neo-adjuvant chemo-endocrine therapy for the treatment of primary breast cancer

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We report a randomised trial evaluating the role of neo-adjuvant (NEO) chemo-endocrine therapy prior to surgery in primary operable breast cancer. Since 1990 this trial has recruited 280 women with newly diagnosed stage 1 or 2 breast cancer confirmed on fine needle aspiration cytology and 200 of these patients are now assessable for response. The first 115 patients were treated using Mitomycin C, Mitozantrone and Methotrexate, but because of a drug interaction (haemolytic uraemic syndrome) we have now changed Mitozantrone 10 mg/m^2 with Methotrexate 30 mg/m^2 combined with tamoxifen 20 mg/day (2MT). Patients receive 8 cycles of 2MT (4 cycles prior to surgery in the NEO group), with tamoxifen continuing for 5 years and appropriate surgery and radiotherapy. The overall clinical response to NEO chemo-endocrine therapy was 85%, most of whom had a complete or nearly complete response. Only one patient showed evidence of progressive disease. Complete histological response was achieved in 10% of patients. There was a significant reduction in the requirement for mastectomy in patients receiving NEO therapy (13%) compared to those patients who received adjuvant therapy (28%) ($p < 0.0051$). At median follow up of 28 months, local relapse in breast (2 adjuvant, 1 neoadjuvant) and axilla (1 adjuvant, 0 neoadjuvant) was low despite the high incidence of positive pathological excision margins (18/99 adjuvant, 28/101 neoadjuvant). *Conclusion.* (1) Significant downstaging of primary breast carcinoma can be achieved with NEO chemo-endocrine therapy leading to a reduction in the requirements for mastectomy. (2) Positive excision margins may not be significant if patients are receiving combined chemo- and endocrine therapy.

P51
Low toxicity of primary chemotherapy with high dose epirubicin as single agent in operable breast cancer

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From January 1992 to October 1994, 83 patients have been accrued in a multicentre study on primary chemotherapy of T2-T3, N0-N1-N2, M0 breast cancer. Treatment consisted of an administration of high dose epirubicin (120 mg/m^2) as single agent every 21 days per 3 cycles, growth factors (G-CSF) being used only when needed. The end-points of the study were an amelioration of surgical approach, an increase of DFS along with a decrease of toxicity. Cardiac toxicity has been evaluated by ECG, echocardiography and/or radionuclide cineangiography carried out at the beginning and at the end of primary chemotherapy and every year during follow up. All patients have been treated with antiserotoninergic drugs in order to reduce nausea and vomiting. Eighty patients have completed the neo-adjuvant treatment: on the whole, 240 cycles have been administered, all of them at 100% of the projected dose. Seven out of 240 cycles (3%) have been delayed because of grade 1 leukopenia (5 cycles), grade 3 leukopenia (1 cycle) and technical reasons (1 cycle). No cases of cardiac toxicity have been recorded: in only 1 case sinus tachycardia without any modification of the instrumental findings has been reported. Alopecia has been observed in about 100% of subjects. Nausea has been reported in 31 out of 83 patients (33%) while episodes of vomiting have been sporadically observed. Three cases of grade 1 stomatitis (3%) and 2 cases of phlebitis (2%) also occurred. The preliminary data seem to confirm the low toxicity of this preliminary chemotherapy regimen, which allowed a less mutilating surgery (quadrantectomy) in 74% of patients.

	Toxicity
Cardiotox.	0/83
Grade 1 leukop.	3/83*
Grade 2 leukop.	1/83
Alopecia	82/83
Stomatitis	3/83
Phlebitis	2/83

* Repeated for 2 cycles in 2 patients.

P52
Outcome of extensive evaluation of women with ≥ 10 positive axillary lymph nodes prior to adjuvant therapy for breast cancer

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Women with ≥ 10 positive lymph nodes at diagnosis of primary breast cancer are at high risk of recurrence from occult metastatic disease despite conventional adjuvant therapy. Uncontrolled phase II reports indicate that the use of high dose chemotherapy and autologous bone marrow transplantation (ABMT) may substantially reduce recurrence rate and improve survival in this setting. From 2/93 to 10/94, 29 women were referred for participation in a randomized trial of the addition of ABMT to adjuvant FAC chemotherapy. All patients would have met eligibility requirements for a previous National Cancer Institute of Canada adjuvant trial, including clear surgical margins and normal CXR, abdominal ultrasound and bone scan (BS). Patients who gave informed consent had an additional CT scan of head, chest, abdomen and pelvis and bilateral bone marrow biopsies before registration. Of 28 pts, 2 declined, 3 had chest wall recurrence already at time of referral, 1 had positive bone scan on review and 1 had cardiac EF < 45%. Six of the remaining 21 pts were excluded from the trial. 28% (95% CI, 13%–49%) had metastases discovered on CT scan (lung 2 pts, liver 1 pt) or bone marrow biopsy (3 pts) not detected by routine screening. Although the number of pts is small, these data suggest that part of the improved outcome of patients with ≥ 10+ nodes receiving ABMT may be from exclusion of patients with a high probability of recurrence, who have evidence of metastatic disease, revealed by a more thorough evaluation than required for participation in previous adjuvant therapy trials. The importance of these exclusions and of ABMT in improving disease-free and overall survival for these women, can only be determined by currently ongoing randomized, controlled trials.

P53
Adjuvant high-dose epirubicin (HD-EPI) and cyclophosphamide (CTX) in patients with operable locally advanced breast cancer (LABC)

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The predominant failure pattern and cause of death in LABC remains distant dissemination, even if local control is of particular concern for patients' quality of life. In order to attempt to improve both distant disease-free survival and local control, in January 1990 we started a feasibility trial in premenopausal and younger postmenopausal patients affected by LABC surgically resected. The treatment consisted of HD-Epi (120 mg/m^2) plus CTX (600 mg/m^2), given every 3 weeks for 4–6 cycles, then followed by electron beam radiotherapy in stage IIIB patients only. As the study was limited to younger patients, 30 women are now fully evaluable (9 stage IIIA, 21 stage IIIB). Median age was 46 years (range 27–59), 26 premenopausal and 4 postmenopausal. The surgical approach consisted of quadrantectomy and axillary clearance in 5 pts (4 stage IIIA and 1 stage IIIB), and radical mastectomy in 25 pts. All stage IIIA pts had positive ER; 6/9 had G3 tumors. Twelve out of 21 stage IIIB pts had positive ER, 6 negative and 3 unknown;12 specimens were graded as G3, 7 as G2, and 2 as unknown.The total number of cycles was 6 in 6 pts, and 4 for the remaining 24 pts. The median follow-up was 46 months for stage IIIA pts and 41 months for stage IIIB pts (range 11–59 months). *Activity.* Out of 9 stage IIIA pts, only 1 local relapse was noted after 6 months, in a patient treated with quadrantectomy and radiotherapy who underwent salvage mastectomy. After 22 months, 1 case of local relapse, with synchronous brain metastases, and 1 case of visceral metastases and supraclavicular node involvement were noted. Out of 21 stage IIIB pts, 2 loco-regional relapses were noted (12 and 13 months, respectively = 9.5%), and six distant metastases (28.5%) were encountered as first site of failure. Bone was involved in 6/8 relapsed pts. The 2 loco-regional relapses preceded the development of distant metastases by 7 and 25 months, respectively. *Toxicity.* Alopecia was universal and vomiting was frequent: grade I–II in 19 pts, grade III in 6 pts (20%); leucopenia was reported in 10/30 pts (9 grade III = 30%, 1 grade IV), but recovery was always rapid. Stomatitis (grade I–II only) was noted in 9 pts (30%); 4 pts experienced grade I–II diarrhea. Amenorrhea occurred in 7/30 pts (23%). No case of cardiac toxicity was demonstrated by echocardiography. The only patient who subsequently developed cardiotoxicity had been treated for a bone relapse with FEC chemotherapy, receiving the maximum tolerated dose of Epirubicin (1000 mg/m^2), and had also been irradiated on the left chest wall (50 Gy/25). *Conclusions.* Despite a mainly hematological toxicity, all the patients completed the treatment

in a shorter period than with conventional therapy (FEC or CMF regimens). Preliminary results indicate that this treatment is feasible without severe toxicity, and the clinical outcome is encouraging for further studies.

P54
Multicycle high-dose chemotherapy (HDC) with peripheral blood progenitor cell (PBPC) support in high risk breast cancer (BC)

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Administration of high doses of chemotherapy with bone marrow support results in improved response rates in patients (pts) with metastatic BC. Solid tumor kinetics suggest that maximum cell kill is achieved using non cross resistant agents at maximum tolerated doses over multiple cycles. In an effort to improve long term survival, pts with high-risk BC (stage II, 10+ nodes or 4+ nodes/ER neg tumor; stage III) were given 3 cycles of epirubicin 200 mg/m^2 (D–4), cyclophosphamide 4 gm/m^2 (D–3), and MESNA 7.2 gm/m^2 (D-3, -2) with PBPC (D0) and filgrastim (D1) support. Prior to chemotherapy, PBPC were collected during filgrastim (12 μg/kg/d) administration. The planned intercycle interval was initially 28 days (n = 18), and subsequently reduced to 21 days (n = 6). Prophylactic antibiotics were commenced once WCC ≤ 1.0 × 10^9/l, until ANC 20.5 × 10^9/l for 2 days. 24 pts (12 with each of stage II and stage III BC) were treated, median age 41 years (range 29–52). Median GM CFC yield was high, 123.4 (range 26.3–273.4) × 10^4/kg wt. Recovery to ANC ≥ 5 × 10^9/l and platelets ≥ 20 × 10^9/l was delayed with successive cycles, although all patients had normal counts by d28 after chemotherapy. The frequency of severe mucositis also increased with each cycle. There was no correlation between numbers of GM-CFC infused and hematological recovery. Febrile neutropenia (T ≥ 38°C + ANC ≤ 0.5 × 10^9/l) occurred in 55% of cycles. All pts developed fatigue, which resolved within 2–4 months of the third cycle. No deaths have occurred on study. There was no increase in hematological or non-hematological toxicity with reduction of the intercycle interval from 28 days to 21 days. Left ventricular ejection fraction declined by a median 7% (range –20 to +3) from baseline to the end of treatment. Deterioration was uncommon with further follow-up, and a number of patients had improvement in LVEF. No patients developed symptomatic or radiological evidence of cardiac failure. Multiple cycles of high-dose epirubicin and cyclophosphamide with filgrastim-mobilised PBPC and filgrastim support can be delivered with acceptable toxicity at 21 day intervals. The efficacy of this regimen is to be assessed in a phase III randomized study.

P55
Is growth factor dependent high dose chemotherapy necessary for high risk localized breast cancer with four or more positive (+) axillary lymph nodes (LNs)?

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Since 1988, 14 breast cancer patients (pts) with 4 or more (+) axillary LNs have been treated with 1 of 2 sequential chemotherapy (chemoRx) regimens of 9 months duration: cyclophosphamide, methotrexate, fluorouracil, vincristine, prednisone (CMFVP) × 4 1/2 months followed by vinblastine, adriamycin, thiotepa, halotestin (VATH) × 4 1/2 months; or adriamycin 75 mg/m^2 q. 3 wks. × 4 followed by CMF or CMFVP × 6 months. ChemoRx differs from standard CMFVP-VATH (CALGB-8082) by shorter duration of 9 months (vs. 14) and greater dose intensity for adriamycin since maximal dose of 45 mg/m2 begins with cycle 1 (vs. 33% × 2, 67% × 2, 100% × 2). Adriamycin-CMF differs from Bonadonna (*JCO* 1991; **9**: 2134) by using oral cyclophosphamide day 1,8 type CMF and therefore having greater dose intensity for all 3 drugs compared to i.v. CMF. No growth factors were administered on any cycle to any pt. Both regimens differ from previous ones by adding chest wall RT and also adding tamoxifen after chemotherapy in all pts ≥ 50 and in pts < 50 if ER (+) or PR (+) and menopausal after chemoRx. RT for mastectomy pts (13/14) was 5000 cGy to chest wall, parasternal LNs and 4400 cGy to the axilla and supraclavicular region. Median age = 43 years (31–54). T classification: T1,2 = 9, T3 = 5. Median (+) axillary LNs = 9 (4–22). 6 pts had ≥ 10 (+) LNs. One pt refused further treatment after receiving half of the planned chemotherapy and also refused RT and tamoxifen. There were no treatment-related fatalities or hospitalizations. The median nadir WBC was 2,500 and the lowest WBC was 1,200. The lowest platelet count was 86,000 and no pts required platelet transfusions. 3/14 pts have developed trace arm edema. With median f/u of 43 months, recurrence free survival (RFS) is 85% and survival is 100%. Two pts have recurred at 11 and 22 months (both < 35 years old). One of the two recurrences was observed in the pt who had withdrawn from adjuvant treatment. All 12 pts who have reached 2 years without recurring remain free of disease from 2 to 6 years from diagnosis. *Conclusions.* (1)

Sequential non-growth factor dependent chemotherapy plus RT plus tamoxifen appears to be very effective adjuvant therapy for high risk LN (+) breast cancer and may be the most cost effective treatment for this group of pts. (2) Apparent improvement in chemotherapeutic efficacy compared to standard regimens may be due to both the sequential nature of the treatment and the greater dose intensity. (3) The addition of RT and tamoxifen to chemotherapy may also contribute to improved RFS. (4) This raises questions about the extent to which RT and tamoxifen may also be contributing to the apparent improvement in RFS being claimed for non-randomized adjuvant transplant programs that routinely include RT and tamoxifen as part of their treatment.

P56
Phase II adjuvant high dose FEC (HDFEC) plus G-CSF in breast cancer: preliminary results

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65 female patients (pts) with breast cancer were included to receive 6 courses of adjuvant treatment with HDFEC (5-FU 600 mg/m^2, day 1 and 8; EPI 80 mg/m^2, day 1; CTX 600 mg/m^2, day 1) plus G-CSF (5 μg/kg/day, from days 2 to 7 and 9 to 14). Patients with more than 4 positive lymph nodes, capsule disruption or diffuse fat or lymph node infiltration received concomitant radiotherapy (RT) (total dose 50 Gy). Median age was 52 years (range 33–72). 34 patients were premenopausal (53%). Distribution by stage was: stage I, 3 (4.6%); stage IIa, 26 (40%); stage IIb, 24 (36.8%); stage IIIa, 12 (18.5%). 26 (41%) patients received RT. 390 courses were administered.

TOXICITY	G0	G1	G2	G3	G4
Anemia	33.3%	36.8%	15%	12.3%	1.7%
Leukopenia	41.4%	13.8%	20.7%	12%	12%
Neutropenia	41.4%	5.2%	27.6%	8.6%	17.2%
Thrombocytopenia	71.9%	7%	5.3%	8.8%	7%
Mucositis	57.9%	28.1%	8.7%	5.3%	0%
Sepsis	87.8%	1.7%	10.5%	0%	0%
Emesis	21.1%	49.1%	24.6%	5.2%	0%
Alopecia	6.9%	1.7%	10.4%	81%	0%
Constipation	87%	1.8%	10.5%	0%	0%

There was no cardiac or neurological toxicity, nor toxic death. Our preliminary conclusion is that this HDFEC schedule shows a good tolerance; survival evaluation is not possible at this point (2 year follow-up).

P57
Repetitive cycles of high dose cyclophosphamide and doxorubicine with G-CSF mobilized PBSC in inflammatory breast cancer (IBC)

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Single high dose consolidation chemotherapy following conventional chemotherapy, radiation and surgery did not significantly improve the prognosis of IBC. In previous studies, we reported the prognostic significance of an early response to chemotherapy suggesting a possible gain by initial dose intensification. The present study was designed to determine the feasibility of administering 6 cycles of high dose cyclophosphamide (CPM) and doxorubicine (DOX) every 3 weeks with G-CSF mobilized PBSC support. PBSC were collected after an initial cycle of high dose CPM 6 g/m^2 + DOX 70 mg/m^2. In subsequent cycles (2 to 6) CPM was given at 3 g/m^2 + DOX 70 mg/m^2. GCSF only was administered after cycle 2. PBSC were reinfused on day 3 following cycles 3 to 6. Mastectomy was performed 3 weeks after the last course of chemotherapy. To date, 14 patients with IBC have entered this prospective pilot study and a total of 51 chemotherapy courses have been delivered at full protocol dosage and on time. Grade 3 toxicities included fever neutropenia (14), phlebitis (1) and severe vomiting (1). There was 1 death related to staph. aureus septicemia. So far, 9 patients are evaluable for clinical response (CR 7, PR 2) and 8 patients for histological response (CR 2, PR 6). Intensive neoadjuvant chemotherapy appears to be able to confer high clinical and histological response rates in this poor risk patient population.

P58
CMF vs. a more intensive sequential chemotherapy program as adjuvant treatments in stage II breast carcinoma with ≥ 10 involved axillary nodes: a prospective randomized trial of the GOIRC group

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Patients (pts) with primary breast cancer involving ≥ 10 axillary nodes have been recently considered as a group with particularly poor prognosis, deserving trials with high dose adjuvant chemotherapy and autologous bone marrow support. After surgery alone or after conventional adjuvant treatments, the prognosis has generally been reported using subgroup analysis and no specifically addressed trials are available. In this prospective randomized study, pts in pre- and postmenopause with stage II breast carcinoma and ≥ 10 axillary nodes were randomized to receive, after surgery, 6 cycles of adjuvant CMF (arm A) or a more intensive sequential chemotherapy including 3 cycles of PE (Cisplatin, Etoposide), 3 cycles of CMF, 3 cycles of AL (Adriamycin, Leucovorin/5-FU) (arm B). From October 1989 to September 1993, 108 eligible pts were randomized to A (55) and to B (53) from 15 participating centers of the GOIRC Group. Distribution of pts for age (median values 55 and 52 yrs), premenopause (33% vs. 40%), postmenopause with ≤ 60 years (51% vs. 34%) or > 60 years (16% vs. 26%), axillary involvement with ≤ 15 (60% vs. 66%) or > 15 positive lymphnodes (40% vs. 34%), was sufficiently balanced between A and B. After a median follow up period of 29 months, the 3-year actuarial relapse-free rates were 19% and 27% and the 3-year actuarial survival rates were 62% and 64% in A and B, respectively. These differences were not statistically significant. Considering pts in both arms together, those with > 15 positive nodes had a higher relapse rate (median values 23 vs. 24 months; $p = 0.12$) and a significantly shorter survival (median values 33 vs. 40 months; $p = 0.02$) than those with ≤ 15. At this point in time, a CT program more intensive than CMF did not significantly improve the prognosis in stage II breast carcinoma with ≥ 10 involved axillary nodes.

Supported in part by AIRC and by CNR Finalized Project ACRO.

P59
FEC_{21} vs FEC_{14} + G-CSF as adjuvant treatment for early breast cancer patients: a phase III multicentric, randomized study

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We have started a multicentric randomized trial in order to verify the effect of a 50% dose-intensity (DI) increase, obtained by accelerating FEC chemotherapy, on overall survival of early breast cancer patients (pts). Pts have been randomized to receive 6 cycles of: FEC_{21} (cyclophosphamide 600 mg/m², epirubicin 60 mg/m², 5-fluorouracil 600 mg/m²) every 3 weeks or FEC_{14} (same doses as FEC_{21}) + G-CSF, 5 mcg/kg day 4→11, every 2 weeks. ER positive pts also received Tamoxifen 20 mg/day. Main eligibility criteria: age ≤ 70 yrs; node positive pts with less than 10 involved nodes; high risk node negative pts defined by the presence of one or more of the following criteria: age ≤ 35 yrs, $T \geq 2$ cm, ER and PgR negative, high proliferative activity (TLI and/or S-phase cytofluorimetric measurement), poor histological or nuclear grading. From November 1992 to October 1994, 533 pts have been accrued. A preliminary analysis of toxicity and feasibility has been performed in the first 228 pts.

Patient characteristics

		FEC_{21}	FEC_{14} + G-CSF
No. of pts		120 (%)	108 (%)
Age	≤ 49	40 (33.3)	40 (37)
	≥ 50	80 (66.7)	68 (63)
N	0	39 (32.5)	32 (29.6)
	1–3	52 (43.3)	46 (42.6)
	4–10	29 (24.2)	30 (27.8)
pTl		54 (45)	57 (52.8)
pT2		56 (46.7)	40 (37)
pT3		5 (4.2)	4 (3.7)
pT4		3 (2.5)	6 (5.6)
pTx		2 (1.6)	1 (0.9)

% Main toxicity (WHO grade)

		FEC_{21}	FEC_{14} + G-CSF
N/V	I+II	65.1	63.9
	III	20.2	18.6
Mucositis	I+II	31.2	34
	III	0	4.2
Leukopenia	I+II	31.2	5.2
	III	2.8	2.1
Anemia	I+II	12.8	25.7
	III	0	3.2
Bone pain		0	33

94.5% and 95% of pts completed 6 cycles; mean duration of treatment was 110.1 (± 11.6) days and 72.6 (± 6.6) days, in the FEC_{21} and FEC_{14} arms respectively. Pts randomized in FEC_{21} actually received 92% of planned average DI and pts in FEC_{14} 94%; this means a 52% DI increase for the FEC_{14} arm. In conclusion, our results indicate that a 50% DI increase of a standard dose FEC regimen can be easily obtained with the support of G-CSF, without any increase in toxicity. The study is continuing to accrue pts, up to the intended 800 pts.

P60
Node positive premenopausal breast cancer patients: five year follow-up results of a randomised trial testing the role of the dose intensity and duration of chemotherapy

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In 1986, the FASG began a randomized trial aiming to investigate the concept of dose intensity as well as the optimal duration of treatment in patients with early breast cancer. Between 1986 and July 1990, 621 pts were included in the trial, and 595 of these pts are evaluable. The scheduled treatment has been as follows: arm A = FEC 50 for 6 cycles in 207 pts; arm B = FEC 50 for 3 cycles in 193 pts; arm C = FEC 75 for 3 cycles in 195 pts. 5-FU and Cyclophosphamide were given at a dose of 500 mg/m^2, Epirubicin at a dose of 50 mg/m^2 (arm A and B) or 75 mg/m^2 (arm C). Locoregional radiotherapy was administered after the third cycle of chemotherapy in all arms. Clinical prognostic factors such as tumor size, number of involved nodes, histological differentiation, hormonal receptors are equally distributed in the three arms. Toxicity was evaluated in 581 pts (207 arm A, 186 arm B, 188 arm C) for a total of 2301 cycles according to WHO criteria. For the three drugs, the mean dose intensity (administered dose/planned dose) is 96.3% in arm A, 99% in arm B and 99.2% in arm C. Grade 3–4 neutropenia per patient occurred in 12% of pts in arm A, 5% in arm B and 11% in arm C. In arm B there was significantly better tolerance than in the others (p = 0.005). Anemia and nausea/vomiting were less important in arm B (respectively p = 0.01 and p = 0.019). Patients receiving FEC 50 showed less alopecia ($p < 10^{-4}$). There was no difference as far as other non-hematological toxicities were concerned. None of the pts had to stop treatment because of cardiac toxicity. At a median follow-up of 5 years, 72 pts in arm A, 84 pts in arm B and 83 pts in arm C relapsed. There is no significant difference between the three arms (p = 0.11). Concerning distant metastasis, there is a trend in favour of FEC 50 × 6 cycles (p = 0.06) to reduce distant metastasis. Overall survival is not different in the three arms (p = 0.6). These five year results show no significant difference in terms of disease free survival and survival between the three arms. Nevertheless, there is a trend in favour of FEC 50 × 6 cycles (p = 0.06) to reduce distant metastasis.

P61
Randomized evaluation of low dose chemotherapy in stage I and II breast cancer patients

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Objective. In order to address the efficacy of low dose short time chemotherapy we performed a randomized clinical trial in patients with stage I and II breast cancer. *Materials and methods.* Between 1984 and 1990 823 evaluable patients entered the trial, and 794 eligible patients were randomized. Patients in stage I disease with negative estrogen and progesteron receptors were randomized between an untreated control and a low dose chemotherapy: doxorubicin 20 mg/m^2, vincristin 1 mg/m^2 day 1, cyclophosphamide 300 mg/m^2, methotrexate 25 mg/m^2 and 5-FU 600 mg/m^2 on day 29 and 33 were administered intravenously. 517 patients with ER+/PgR+ tumors and at least one axillary node metastasis were randomized to receive additionally 2 × 10 mg tamoxifen for at least 2 years to the identical chemotherapy regimen. Patients were stratified for number of involved nodes, tumor stage, type of operation, menopausal status and participating center. *Results.* After a median length of follow up of 5.3 years disease free and overall survival did not differ significantly between patients receiving or not receiving low dose adjuvant chemotherapy. The estimated disease free survival rates at 5 years were 67% in the treatment group and 70% in the control group. Several factors including grading, age and nodal status were tested for treatment interaction and found to be not significant. Subgroup analysis addressing the question whether receptor status plays a major role in determining a patient group favourably responding to short term chemotherapy did not show a significant treatment impact in patients with stage I disease with hormone receptor negative tumors or in patients with hormone responsive stage II breast cancer. *Conclusion.* Low dose short term chemotherapy is insufficient to improve prognosis of patients with breast cancer stage I and stage II tumors. These results provide evidence that reducing chemotherapy length and intensity is an inappropriate way to respond to certain side effects in patients receiving well dose adjuvant chemotherapy.

CONVENTIONAL ADJUVANT CHEMOTHERAPY

P62
CMF vs. alternating CMF/EV in adjuvant treatment of operable breast cancer: a single centre randomized clinical trial (Naples GUN-3 study

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The aim of this study was to test the hypothesis of Goldie and Coldman that the use of non cross-resistant regimens of chemotherapy could lead to maximal antitumor effect. We compared standard CMF (cyclophosphamide, methotrexate, fluorouracil) with alternating CMF/EV (epirubicin, vincristine) in the adjuvant therapy of early breast cancer. Stage II premenopausal node-positive or postmenopausal node-positive estrogen-receptor negative, and stage III breast cancer patients were eligible for the study. From January 1985 to December 1990, 220 patients were randomized (115 to CMF and 105 to CMF/EV). Toxicity was mild; neurotoxicity, vomiting and hair loss were more frequent in the CMF/EV group, while permanent amenorrhea and stomach ache occurred more often in the CMF arm. At a follow-up of 48 months, 133 patients (60.4%) had recurrence (62 on CMF and 51 on CMF/EV) and 54 (24.5%) died (30 on CMF and 24 on CMF/EV). There was no significant difference in disease-free and overall survival between the two arms. After adjusting for menopausal status and stage, the relative risk (RR) of recurrence for CMF/EV patients was 0.93 (95% CI, 0.64–1.35), while the RR of death was 0.85 (95% CI, 0.49–1.47). In conclusion, the Goldie–Coldman hypothesis is not confirmed in the adjuvant therapy of early breast cancer.

P63
Alternating and alternating-hybrid chemotherapy (CT) in breast cancer (BC)

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Since 1985 271 patients (pts) have been treated for BC by modified radical mastectomy, radiation therapy and adjuvant CT. This study aimed to compare the effect of i.v. alternating CMF-CVFP (62 pts) and alternating-hybrid CMF-CEF/HOP (37 pts) CT vs. 6 cycles of CMF alone (172 pts). (1) CMF on days 1 and 8 (mg/m^2)—Cph 500; Mtx 30; 5-FU 600. (2) Alternating CT—3 cycles of CMF (as for (1)) and 3 cycles of CVFP: on days 1 and 8—Cph 600; 5-FU 500; VCR 1.4; on day 9—Cis-pl 100. (3) Alternating-hybrid CT—on day 1—Cph 600; Epirubicin 80; 5-FU 500; on day 8—Adr 30; VCR 1.4; on day 10—Cis-pl. 100, that is, 3 cycles of CMF (as for (1)) and 3 cycles of CEF/HOP.

Results

Regimen	No. pts	DFS –4 years (%)
CMF	172	67.7
CMF-CVFP	63	68.4
CMF-CEF/HOP	32	76.3

Disease-free survival (DFS) in pts who received alternating-hybrid or alternating CT was better (76.7% and 68.4%) than that in pts who received CMF alone (64.7%; $p < 0.05$). A significant difference in DFS was seen in pts with more than 3 positive nodes: 68.2%, 60.9%, and 43.6%, respectively ($p < 0.05$). There was no difference in DFS for the pts without positive nodes. *Conclusion.* Alternating CMF-CVFP or alternating-hybrid CMF-CEF/HOP adjuvant CT is more effective in pts with ≥ 3 positive nodes. CMF adjuvant CT is an effective treatment in node negative BC.

P64
FPC vs. FAC (5-FU, CMP) and either doxorubicin or pirarubicin in advanced breast cancer

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Pirarubicin is an anthracycline without significant cardiotoxicity in preclinical and early clinical trials. The aim of this Phase III trial is to compare the antitumor activity and toxicity of Pirarubicin in combination with Cyclophosphamide and 5-Fluorouracil vs. standard FAC schedule. 94 patients with histologically proven advanced breast cancer have been enrolled in a randomized, open, comparable, multicentric trial in 6 centers in Croatia, with 87 of them being evaluable. The characteristics of patients in both groups were well balanced: age < 72, PS 0–3, evaluable lesion, no prior anthracycline therapy, absence of cardiopathy. Patients were given Cyclophosphamide and 5-Fluorouracil 500 mg/m^2 each, and either Doxorubicin or Pirarubicin 50 mg/m^2 every three weeks; 6 cycles. *Efficacy.* FAC group: CR 7/43, PR 12/43; FPC group: CR 6/44, PR 15/44; overall response: 23/43 (FAC) vs. 28/44 (FPC) (n.s.). *Toxicity* (myelosuppression, nausea/vomiting, stomatitis, diarrhea) was similar in both groups. Cardiotoxicity was not seen, probably due to low doses: 300 mg/m^2 anthracycline. *Alopecia.* FAC group: GR 2 8/43, GR 3 29/43; FPC group: GR 2 10/44, GR 3 11/44; $p < 0.0000001$ significantly favouring FPC. *Conclusion.* Pirarubicin gives better life quality to patients with advanced breast cancer and should be an anthracycline of choice in young, high risk patients with early breast cancer submitted to adjuvant chemotherapy, causing less alopecia.

P65
Adriablastin vs. CMF in adjuvant treatment of breat cancer (T3 N0–2 M0)

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This work evaluates the effectiveness of two schemes of adjuvant chemotherapy in patients with locally-advanced breast cancer T3 N0–2 M0. 302 breast cancer patients 55 years old and younger who had undergone preoperative radiation therapy (total dose 60 Gy to the breast and 40 Gy to the axillary and supra/infraclavicular regions each) followed by modified radical mastectomy were enrolled into a clinical trial carried out in 1985–1989. Beginning from the first day of the surgery, the patients were administered adjuvant chemotherapy with the drug Adriablastin (Doxorubicin), 50 mg/m^2 i.v. on the first and eighth day, every 4 weeks, 5 cycles (144 patients), vs. the classical CMF chemotherapy regimen up to 6 cycles (158 patients), according to the randomization. Duration of follow-up was 4.3–9.2 years (mean duration: 6.3 years). The overall 5-year survival rate was 62.1% in the Adriablastin group and 55.0% in the CMF group ($p > 0.05$). The disease-free 5-year survival rate was 53.9% in the Adriablastin group and 43.7% in the CMF group ($p < 0.05$). *Conclusion.* In breast cancer T3 N0–2 M0 patients, adjuvant chemotherapy with Adriablastin leads to a considerable reduction in the frequency of the development of recurrences and metastases of the disease and to an increase in disease-free survival in comparison with the 'classical' CMF chemotherapy regimen.

P66
Late survival after adjuvant chemotherapy with doxorubicin for 326 stage II breast cancers: 15-year results

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Between 1975 and 1986, 326 stage II breast cancers were treated with adjuvant AVCF following regional therapy (232 MRM, 94 tumorectomies, 304 irradiations). These 326 patients (pts) represented 44% of all stage II treated in our institution during this period. The AVCF regimen consisted of 4-week cycles of doxorubicin 30 mg/m^2 D1, vincristin 1 mg/m^2 D2, 5-fluorouracil 400 and cyclophosphamide 300 mg/m^2 D3 to D5. 224 (pts) had 6 cycles and 102 pts 12 cycles. 90 pts also received 30 mg daily tamoxifen for one year after chemotherapy. As at March 1994, the median follow-up was 130 months (range 86–221). 118 pts developed recurrences (7 local, 19 contro-lateral, 92 metastatic) and 104 died. Estimated DFS and OS:

	5-year	10-year	15-year
DFS (%)	76	64	54
OS (%)	85	70	58

Survival was affected by the number of involved nodes (258 pts were N+), menopausal status (OS at 15 years: 53% for MP+ and 65% for MP–) and SBR grading, but not by hormonal receptors, number of courses or adjuvant hormonotherapy. No significant cardiac toxicity was induced by doxorubicin either during or after treatment. These data established the long term efficacy and safety of AVCF regimen.

P67
The long-lasting effect of adjuvant CMF in node-positive (N+) breast cancer patients is mainly due to significant reduction of early relapses

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Randomized clinical trials have demonstrated that adjuvant CMF can improve the cumulative relapse-free survival in resected N+ breast cancer patients (pts). However, the chemotherapy-induced changes in the probability of relapse over time have not yet been studied in much detail. Within a competing risk framework, we have estimated the probability of first failure, distant metastasis and local-regional recurrence in 1452 N+ pts who entered randomized and non randomized clinical trials carried out at the Milan NCI. All patients underwent radical or modified radical mastectomy for breast cancer. In 575 cases no further treatment was performed, whereas 877 pts were given 6 or 12 courses of adjuvant CMF. In both series 60% of patients had 1–3 positive nodes, while there were more T1 tumors (43% vs. 25%) and more premenopausal pts (73% vs. 44%) in the CMF group. A post surgical time interval of 15 years was examined, and the minimum follow-up of pts was more than 11 years. The probability vs. time curve of first failure in non CMF given pts displayed an initial main peak (maximum at about 2 years after surgery) followed by a lower second peak covering roughly the fifth to sixth year, and a fluctuating plateau-like further portion. In comparison with non-treated women (bootstrap confidence bands), CMF-treated pts displayed a significantly lower first peak, while no difference between the two groups was detected in other portions of the probability curve. Similar findings were also observed when the first failure probability was split into the

probability of distant metastasis and local-regional recurrence. From this non randomized comparison we conclude that: (a) adjuvant chemotherapy, the effects of which are long-lasting, was only able to lower the probability of early relapse, with little or no changes for late events; (b) the reduction of the probability of early relapse due to adjuvant CMF was observed in local-regional recurrences as well as in distant metastases.

P68
Adjuvant polichemotherapy (FEC) in patients with axillary node-positive breast cancer

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In premenopausal patients with early breast cancer, adjuvant chemotherapy can improve survival. Its efficacy is uncertain in postmenopausal patients. Based on results obtained in advanced breast cancer with the use of adriamycin (ADR), we designed a non-randomized trial for patients with operable breast cancer with positive lymph nodes, including the 4-epi-adriamycin analog. The goal was to reproduce results achieved with adriamycin without high toxicity. The study was conducted between March 1987 and March 1991. *Features of patients.* 116 patients were included, with median age of 50 years (range 25–73). Menopausal status: 55 premenopausal and 54 postmenopausal. Stage: IIA, 9 (7.7%); IIB, 54 (46.5%); IIIA, 43 (37%); IIIB, 10 (8.6%). Clinical T: T1, 8 (6.8%); T2, 52 (49.5%); T3, 41 (35%); T4, 10 (8.5%). Nodal status: N < 4, 61 (65%); 4 < N < 10, 28 (27%); N > 10, 24 (34%). Ductal infiltrating carcinoma was found in 95 cases (82%). Progressive disease was seen in 51 patients (43%). Local relapse, 13 (25%); bone, 30 (58%); lung, 5 (9%); liver, 6 (11%); nodal, 6 (11%); pleura, 9 (17%). Complete follow-up, 7.5 years. The regimen administered was: 5-fluoruracil 450 mg/m^2 days 1 and 7; 4-epi-adriamicine 45 mg/m^2 day 1 and cyclophosphamide 450 mg/m^2 days 1 and 7. The cycle was given every 4 weeks per six. The treatment was well tolerated. Gastrointestinal toxicity grade 3 was observed in 21% and grade 2 haematological toxicity in 13%. One patient presented cardiac toxicity grade 2. Kaplan–Meyer and long-rank were used for statistical analysis. *Results.* 116 patients were evaluable for the analysis of prognostic factors and survival. The 5 year median overall survival was 65 months and the median disease free survival was 55 months. The 7 1/2 year median overall survival was 49 months and the median disease free survival was 46 months. Patients with one to three lymph node involvement had a statistical improvement in disease free survival ($p < 0.0001$). Age and menopausal status did not show any statistical significance. In conclusion we can say that this FEC regimen is as effective as FAC, showing a mild toxicity and non death related with the use of 4-Epi. Nodal status < 4 showed $p < 0.0001$.

P69
Long-term results of an ECOG study of adjuvant therapy in postmenopausal women with breast cancer

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A prospectively randomized trial to compare adjuvant efficacy of 12 cycles of cyclophosphamide, methotrexate, 5-fluorouracil, prednisone and tamoxifen (CMFPT) followed by observation or a total of 5 yrs of continuous tamoxifen (T) vs. 4 cycles of CMFPT followed by observation in postmenopausal women with operable node positive breast cancer was started by ECOG in 1982. In 1986 the study was modified to allow patients (pts) on CMFPT × 12 + continuous T to be randomized after completing 5 yrs of T to Step 2, namely to continue with T for life or to stop therapy. Pts were stratified for number of involved nodes and ER status. Median follow-up is 8.9 yrs. Of 962 pts entered, 803 pts were eligible; 403 have had a recurrence and 349 have died. Toxicity, during and after induction, was not statistically different in the 3 arms, and in pts randomized on step 2 toxicity is also not different for those on observation or T. Time to relapse is significantly longer for pts on CMFPT × 12 + continuous T than for CMFPT × 4 ($p < 0.009$); the difference between CMFPT × 12 + continuous T and CMFPT × 12 is not significant. Differences between 4 or 12 cycles of CMFPT are not significant. Relapse free rates at 10 yrs are 47% on CMFPT × 12 + continuous T; 46% on CMFPT × 12 and 40% on CMFPT × 4. Treatment differences in overall survival are not significant; the 10-yr survival rate is 56% for CMFPT × 12 + continuous T; 55% for CMFPT × 12 and 50% for CMFPT × 4. Second cancers occurred in 38 patients (10 on CMFPT × 12 + continuous T, 9 on CMFPT × 12, 19 on CMFPT × 4).

This study was conducted by the Eastern Cooperative Oncology Group: Doug C Tormey, Chairman, CA 21115.

P70
Evaluation of subjective chemotherapy impact (SCI) in a prospective clinical trial with primary chemotherapy in breast cancer patients

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A prospective clinical trial with primary chemotherapy in T2-T3, N0-N1-N2, M0 breast cancer patients was carried out.

Treatment consisted of 3 cycles of epirubicin 120 mg/m^2 administered every 3 weeks, followed by surgery and adjuvant chemotherapy with 8 cycles of CMF in N–, RE– and N+ patients. Subjective reactions of patients to chemotherapy were evaluated by administration of the Subjective Chemotherapy Impact (SCI) questionnaire which, for each treatment cycle, implies assessment of the number of days with 'disturbances' and of the number of days 'to be forgotten entirely'. During primary chemotherapy (from first to third cycle) the answers of 25 patients indicated that the mean number of days with 'disturbances' was 3.5 ± 0.5 of which 1 ± 0.1 were 'to be forgotten entirely'. As regards the adjuvant treatment carried out from the first to the eighth cycle in 14 patients, the mean number of days with 'disturbances' was 2.2 ± 0.5, of which 1 ± 0.5 were 'to be forgotten entirely'. These results do not show great variability, but rather uniformity, indicating that the patients display good tolerability to the chemotherapeutic regimens.

P71
Operable breast cancer with 1 to 3 positive axillary nodes: 10-year results of adjuvant CMF plus or minus adriamycin

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In an attempt to improve adjuvant treatment results in women with 1 to 3 positive axillary nodes, CMF was randomly tested against CMF followed by adriamycin. From November 1981 to July 1990, a total of 552 women were entered into the study. Local-regional treatment consisted of either radical mastectomy or conservative surgery plus breast irradiation. Main patient characteristics were fairly well balanced between the two treatment groups. CMF was delivered i.v./mg/m^2 (C 600, M 40, F 600) every 3 weeks for 12 courses when given alone and for 8 courses when followed by adriamycin. Adriamycin was administered at 75 mg/m^2 i.v. every 3 weeks for 4 courses. With a median follow-up of 9 years, the comparative 10-year results (in percent) are as follows:

	Total	Pre	Post	$T \leq 2$ cm	$T > 2$ cm
Relapse-free survival					
CMF	59	61	55	63	51
CMF+ADM	57	59	54	64	45
Overall survival					
CMF	75	77	71	81	63
CMF+ADM	75	71	67	81	65

Treatment was fairly well tolerated and devoid of life-threatening toxicity and important long-term sequelae. However, cardiac effects of different types and severity were documented in 12% of patients; these effects were generally reversible and were mainly related to irradiation to the left breast (60 Gy) rather than to the administration of adriamycin. Present findings indicate: (1) adriamycin, as given after CMF, failed to improve the 10-year results over CMF alone; (2) no difference in treatment outcome was evident between pre- and postmenopausal patients.

P72
Adjuvant chemotherapy after breast conservative treatment

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The aim of this study was retrospective evaluation of rates of local recurrences, metastases in premenopausal node-positive patients after breast conservative treatment and classic 6 × CMF postoperative chemotherapy. From 1 Jun 1986 to 31 Dec 1993, 194 patients (pts) aged from 33 to 75 years with clinically invasive breast carcinoma ($T \leq 30$ mm) were treated with conservative breast surgery (modified and plastic quadrantectomy) and breast irradiation. The whole breast received 50 Gy. Premenopausal node-positive pts received postoperative adjuvant (×6 CMF) chemotherapy, while postmenopausal node-positive patients received endocrine therapy. 5 year survival for the whole group of pts was 80%. Respectively, 71 premenopausal node-positive pts who received postoperative ×6 CMF chemotherapy were divided into 2 groups: N1 (1–3 lymph nodes), 50 pts; and N2 (4–12 lymph nodes), 21 pts. In group N1: 5 pts developed local recurrences, 4 distant metastases, 2 died. In group N2: 10 pts developed local recurrences, 6 distant metastases, 3 died. The amount of positive axillary nodes is the most important factor for disease free survival and overall survival rates after breast conservative treatment. A more agressive regime of postoperative chemotherapy than classic × 6 CMF is indicated in systemic treatment of premenopausal patients with N2 positive axillary nodes.

(CHEMO)ENDOCRINE ADJUVANT THERAPY

P73
Temporary ovarian ablation in premenopausal women with early breast cancer

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An overview of the treatment of early breast cancer highlights the potential importance of the role of ovarian ablation, by radiotherapy or surgical oophorectomy, as adjuvant therapy in the premenopausal patient. The role of temporary ovarian ablation using the LHRH analogue 'Zoladex' (goserelin acetate) as adjuvant therapy in the treatment of premenopausal early breast cancer is currently being evaluated in four large clinical studies. These studies have already recruited 4500 of the 6000 patients required. One of the studies directly compares 6 cycles of CMF (cyclophosphamide/methotrexate/5-fluorouracil), one of the most widely used adjuvant polychemotherapy regimens, with 2 years ovarian ablation with 'Zoladex', in patients 50 years or younger with stage II node-positive breast cancer. Approximately 1200 of the 1590 patients required have already been recruited into the study. As well as recurrence free survival and overall survival the trial also addresses the important issues of bone mineral density and quality of life. The other studies compare CMF or CAF (cyclophosphamide/adriamycin/5-fluorouracil) +/– 'Zoladex' alone or 'Zoladex' plus 'Nolvadex' (tamoxifen) in the treatment of pre-menopausal patients with stage I/II breast cancer.

P74
Adjuvant tamoxifen treatment in premenopausal patients

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On behalf of the South Sweden Breast Cancer Group.

From 1985 to 1990, 429 premenopausal patients with stage II primary breast cancer entered a trial on adjuvant tamoxifen. 214 patients were randomized to adjuvant tamoxifen (Nolvadex) 20 mg daily for two years and 215 patients were randomized to no adjuvant therapy. 72% of the tamoxifen treated patients and 69% of the controls were node positive. The median follow-up time in the present analysis is 5.7 years.

	Tamoxifen (214)		Control (215)	
Alive without recurrence	140	65.4%	133	61.9%
Alive with recurrence	14	6.5%	20	9.3%
Dead with recurrent breast cancer	56	26.2%	57	26.5%
Dead without recurrence	4	1.9%	5	2.3%
Contralateral breast cancer				
in years 0–5 from first diagnosis	8	3.7%	9	4.2%
> 5 years after first diagnosis	1	0.5%	6	3.0%
Other malignancy	3	1.4%	1	0.5%

There was no statistically significant reduction in recurrence-free survival or overall survival among patients treated with tamoxifen. Of the seven contralateral breast cancers that developed after five years, only one was observed among the tamoxifen treated patients. A protective effect of tamoxifen may thus be evident only after some years. The reduction in this material almost reaches statistical significance ($\chi^2 = 3.64$).

P75
Tamoxifen in patients with node-negative and receptor-positive breast cancer: the Heidelberg II and GABG II experience

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Introduction. The effectiveness and toxicity of an adjuvant tamoxifen (tam, Nolvadex®) therapy was studied in node-negative breast cancer (T1–3, R0, N0, M0). 713 patients were therefore randomized between 1979 and 1990 in a prospective trial comparing tam 30 mg/day for 2 years vs. observation only. 73 (10.2%) patients had to be excluded for various violations of eligibility criteria, so 315 patients could be evaluated for the control group and 325 patients for the tam group. Pre- and postmenopausal patients were recruited; median age at diagnosis was 62 years (range 32–90). 93.1% of the patients had either estrogen (ER) or progesterone (PR) receptor-positive tumors (≥ 10 fmol/ml), in 6.9% receptor status was unknown. Median time of follow up was 57 months (range 6–173); 88 (13.7%) patients have progressed and 72 (11.2%) have died. *Results.* Neither local disease-free (LDFS) ($p = 0.8$, log rank test), distant disease-free (DDFS) ($p = 0.09$) nor overall (OS) ($p = 0.2$) survival of all patients was significantly influenced by tam treatment. However, there was a significant benefit for patients with highly (≥ 100 fmol/ml) ER-positive tumors ($n = 262$) being treated with tam (LDFS: $p = 0.002$; DDFS: $p = 0.002$; OS: $p = 0.008$). Effectivity of tam was not dependent on PR-status. Older patients (> 70 yrs; $n = 153$) showed a prolonged DDFS ($p = 0.09$) and OS ($p = 0.05$) irrespective of ER-status. Significant side effects of tam were weight gain (7.9%), hot flushes (5.3%) and nausea (1.9%). Second primaries were found in 16 patients of the control group (5 × GIT, 3 × ovary, 3 × breast, 2 × endometrial, 1 × lung, 1 × leukemia, 1 × melanoma) and in 8 patients of the tam group (5 × GIT, 3 × endometrial). *Conclusion.* Adjuvant treatment with tam in node-negative breast cancer is safe and effective in patients with highly ER-positive tumors and in elderly patients.

P76
Tamoxifen in marker-positive disease-negative breast cancer patients: a prospective randomized study

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Breast cancer tends to recur in a relatively high percentage of patients even when diagnosed at early stages and adequately treated by surgery, radiotherapy and adjuvant chemo- or hormonal therapy. Patients presenting with a stage I disease have a 10%–30% chance of experiencing a relapse in 10 years, while those who present at stage II have a 40% to 50% chance of relapse by 5 years. Overt metastatic breast cancer is usually incurable and associated with limited survival. Distant metastases are the main cause of disease-related death in breast cancer patients. Increasing levels of tumor markers in breast cancer patients following treatment of the primary disease and adjuvant radiation and chemotherapy reflect subclinical development of metastatic disease. The treatment of either symptomatic or asymptomatic gross metastatic breast cancer is unrewarding. No curative modality has been developed yet, and current treatment does not lead to prolongation of the patients' survival. On the other hand, treatment of a subclinical tumor-load, being detected only by elevated levels of serum tumour markers, *may* prevent or delay the appearance of symptoms. A clear clinical benefit, however, has not been demonstrated so far. The efficacy of tamoxifen, a less toxic agent, in the treatment of early and minimal metastatic disease, detected only by increasing serum levels of tumor markers, is being studied prospectively in a randomized study. Our encouraging interim results show that the relapse rate within a median follow-up of 196 weeks was 28% (9/32) in the control arm and 0% in the tamoxifen arm (Fisher's exact test; $p = 0.003$). None of the patients with a relapse had positive progesterone receptors (PR). We may carefully conclude that early treatment may be warranted in young patients with negative PR and continuously increasing serum level of the marker.

P77
Adjuvant tamoxifen and chemotherapy in stage II breast cancer

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Data are presented for 104 patients with histopathological confirmed stage II breast cancer from 1988 to 1992. They were randomized to receive adjuvant therapy consisting of cyclophosphamide (C), methotrexate (M), 5-fluorouracil (F) and adriamycin (A) with or without tamoxifen over two years. This clinical trial was undertaken in order to decide whether adding tamoxifen to chemotherapy is effective for women with stage II breast cancer and positive axillary nodes. The results indicated that disease-free survival and survival were prolonged by the addition of the tamoxifen regimen; but that this effect depends on the patient's age, number of positive lymph nodes, level of ER receptor and type or grade of histopathology. The results also indicated that response to chemotherapy combination therapy is different. Only some of the patients demonstrated a marked effect. Whether this phenomenon is due to chemo-combination or intrinsic biologic properties of breast cancer remains to be ascertained.

P78
Late delayed adjuvant tamoxifen in breast cancer: results of a multicentric randomized trial

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Although adjuvant tamoxifen (TAM) has been proved to reduce recurrences and mortality in early breast cancer, many patients have not received any adjuvant TAM. As relapse can occur many years after primary treatment and TAM is often effective in these cases, a very pragmatic question can be asked: is there an opportunity to give to these patients a late delayed adjuvant TAM treatment to prevent recurrences and to reduce mortality? In this regard, a multicentric randomized trial (TAM 02) has been carried out in the FNCLCC Breast Group (French National Cancer Centers). *Aim.* The aim of the study is to evaluate recurrence and mortality reduction due to late adjuvant tamoxifen (LAT), to try to determine the longest reasonable delay for prescribing late adjuvant tamoxifen. *Materials and methods.* All patients had been previously treated for an early breast cancer, at least two years ago, without adjuvant TAM in the primary treatment; age under 75 years; no evidence of recurrence at the time of randomization. *Randomization.* After stratification between centers, treatment arm was allocated by randomization: A, late adjuvant treatment, TAM 30 mg for five years, TAM group; B, follow-up without any treatment, control group. *Inclusions.* From September 1986 to October 1989, 494 patients were included, 250 in the TAM group, 244 in the control group.

	Deaths		Recurrences		Loco regional	
	Evaluable	Events	Evaluable	Events	Evaluable	Events
Control	244	18	231	36	231	11
TAM	250	18	235	26	235	3
	N.S.		N.S.		$p = 0.02$	

We concluded that although no survival advantage was noted, patients given delayed TAM seem to have better disease-free survival as compared to patients who were left with no hormonal treatment.

P79
Adjuvant endocrine therapy in stage I–II breast cancer patients: progress report of two randomized controlled trials

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SITAM 1. The optimal duration for adjuvant tamoxifen therapy in women with stage I–II breast cancer is not well established. SITAM 1 is a large-scale randomized trial comparing 2 years with 5 years of tamoxifen in patients aged between 50 and 70 years. Patient entry started in March 1988 and is to close at the end of 1994. At the end of September 1994 this study had 2329 patients registered and 1471 randomized (actual randomization is carried out at 2 years post-operation) from 53 general hospitals across Italy. Median follow-up time for randomized patients was 52 months. Patients' characteristics were as follows: median age, 61 years; N0 = 52%, N1–3 = 30%, N > 3 = 18%; oestrogen receptor status, positive = 55%, negative = 16%, borderline = 5%, unknown = 24%. As at September 1994 the following events have been observed in randomized patients: local relapses 12, metastases 48, second primary 15, deaths 35. *SITAM 2.* The degree of hormone dependence of early breast cancer in patients under the age of 50 years is still uncertain and deserves further investigation. In September 1987, the UK Cancer Research Campaign launched a factorial (2 × 2) randomized trial comparing tamoxifen 20 mg die vs. ovarian ablation (or chemical castration by goserelin 3.6 mg every 28 days) vs. tamoxifen + ovarian ablation vs. control after 'primary therapy'. SITAM 2 is the Italian branch of this study and data will eventually be overviewed. SITAM 2 opened for recruitment on 1 January 1991, and as at September 1994 321 patients have been entered into this study from 31 participating hospitals. Median patient age is 44 years (range 21–50) and nodal (N) and oestrogen receptor (ER) status are distributed as follows: N0 = 49%, N1–3 = 33%, N > 3 = 18%; ER+ = 56%, ER– or borderline = 44%. The trial is ongoing and continues to accrue patients.

P80
Adjuvant therapy with high-dose medroxyprogesterone acetate (MPA) if added to chemotherapy (FAC) in patients with node-positive operable breast cancer

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Between 4/82 and 7/87, 394 evaluable patients (pts) with node-positive operable breast cancer (T_{1-3}, N_1) were entered in a multicenter randomized trial investigating the adjuvant effect of high-dose MPA (500 mg i.m. q d × 28, followed by 500 mg i.m. twice weekly (× 5 mos) added to chemotherapy with FAC (5-fluorouracil 500 mg/m^2, doxorubicin 40 mg/m^2, cyclophosphamide 500 mg/m^2 day 1 q 4 wks × 6). High dose MPA ameliorates FAC side effects, especially gastro-intestinal and bone marrow toxicity (*Ann Oncol* 1993; **4**: 295–301). We have now extended the median follow-up time of the patients to 84 months. Overall survival (OS) was 63% in the MPA+ and 59% in the MPA– group ($p > 0.05$); disease free survival (DFS) was 51% and 45% respectively ($p = 0.12$) and distant metastasis free survival was 61% and 51% respectively ($p = 0.12$). No differences between the two treatment groups were found in locoregional disease free survival. Within subgroups analyzed women between 40–60 years had significantly improved DFS when compared to women ≤ 40 or > 60 years ($p = 0.002$). The age group > 60 years showed significantly improved OS and DFS for the MPA+ group (p values respectively 0.008 and 0.05). *Conclusion.* High-dose MPA reduces the risk of metastatic disease and improves OS in elderly patients treated with CAF chemotherapy for node-positive breast cancer. No benefit of MPA was seen in premenopausal node-positive patients adjuvant treated with CAF chemotherapy.

P81
Node-positive postmenopausal breast cancer patients: five-year follow-up results of a randomized trial testing the role of hormonal therapy (HT), chemotherapy (CT) or combination

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On behalf of the FASG (French Adjuvant Study Group).

Between October 86 and July 90, 776 post menopausal patients (pts), 50–70 years old with node-positive breast cancer, initially treated by modified radical mastectomy or tumorectomy and axillary dissection, were randomized to

receive either tamoxifen (T) 30 mg/day for 3 years (Arm A, 193 pts) or chemotherapy with fluorouracil 500 mg/m^2, epirubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 (FEC 50) every 3 weeks for 6 cycles (Arm B, 183 pts), or both treatments (Arm C, 182 pts), or no medical adjuvant treatment (Arm D, 184 pts). All 742 evaluable pts received local radiotherapy after surgery (Arms A and D) or between the third and fourth cycles of FEC (Arms B and C). All the major prognostic factors such as patient age, tumor size, histological type and grade (HG), and hormonal receptor status (HRS) were well balanced between the four groups. Toxicity of FEC 50 was evaluated for 345 pts and 1984 cycles. They received 95% of the planned protocol dose. Grade 3.4 WHO neutropenia, nausea and vomiting were observed in 14%, 29% of pts and in 4%, 14% of cycles. 21% of pts suffered from grade 3 alopecia. The trials were analysed according to a 2 × 2 factorial plan permitting us to compare pts treated with or without HT (Arms A + C vs. B + D) or with or without CT (Arms B + C vs. A + D). At a median follow-up of 57 months, 225 relapses (A = 46, B = 73, C = 36, D = 70) and 145 deaths (A = 39, B = 38, C = 21, D = 47) were registered. There were no differences between the four arms for loco-regional recurrences but the distribution of distant metastasis was influenced by the treatment (p = 0.001), occurring more frequently in Arms B and D than in Arms A and C. Disease free survival was better for pts receiving HT (p = 0.0001) and was not influenced by CT (p = 0.37). We analyzed the influence of major prognostic factors (HG, HRS, and the importance of node involvement) on the results: efficacy of HT was not influenced while pts treated with CT showed better results in the negative progesterone receptors subgroup. Survival was different between the four arms (p = 0.007) and was improved by CT (Arm B + C; p = 0.01) and by HT (Arm A + C; p = 0.02). There is a trend in favour of combination HT + CT (Arm C).

P82
Breast cancer in the elderly: the case for clinical trials

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Thirty per cent of breast cancers occur in elderly women. In the 1980s two series of patients suggested elderly patients with breast cancer could be adequately maintained, long term, on tamoxifen alone, avoiding the need for surgery—the rationale being, that for this age group (accepted at that time as being over the age of 70 years) there were often other priorities than a diagnosis of breast cancer, such as inappropriateness of surgery and hospitalisation, other potential life threatening conditions. This led to several trials being launched to evaluate the roles of both surgery and tamoxifen in this age group. In the UK three trials were launched (CRC, Nottingham and St George's). All addressed slightly different questions evaluating management by primary surgery or tamoxifen. It has been difficult to draw conclusions from them, especially as they initially yielded contradictory results. The CRC Elderly Trial randomized 454 patients between tamoxifen alone (T) and tamoxifen plus immediate surgery (T + S). The trial's main endpoints were overall survival and time to change of management (COM), an endpoint more suited to the design of the trial than disease-free survival. With a median follow-up of 4.4 years, a statistically significant advantage in favour of the S + T group for COM has persisted: $\chi^2 = 32.14$, $p < 0.001$, Relative Risk (RR) = 0.4 (95% CI, 0.29–0.55). By 2 years post diagnosis about 43% on tamoxifen alone have undergone a COM compared with 20% in the S + T group. Overall, of the patients randomized to T alone who have had a COM, 71.6% (78/109) were due to progression of the disease and received surgery. Despite this large difference in COM in favour of immediate surgery, no statistically significant difference in overall survival is seen ($\chi^2 = 2.63$, $p = 0.1$), though the RR does suggest a trend in the same direction (RR = 0.74, 0.52–1.06). These results suggest that for many elderly patients, tamoxifen alone only delays surgery and should be reserved for those too frail to undergo immediate surgery. In the last two years all three UK trials have reached similar conclusions. It is only the availability of results from randomized clinical trials that permits the reliable assessment of potentially novel interventions. Without the results from these and other similar trials many patients could have received less than optimal treatment. It is imperative that these results are rapidly disseminated to those treating such patients.

PSYCHOLOGY, QUALITY OF LIFE, SPECIAL ISSUES

P83
Impact of biomedical, sociodemographic and language factors on baseline quality of life in two international adjuvant breast cancer trials

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The relative impact of biomedical, sociodemographic and language/cultural factors on baseline quality of life (QL) indicators is analyzed in two International Breast Cancer Study Group (IBCSG) randomized clinical trials in operable breast cancer conducted from 1986 to 1993. Baseline QL forms were submitted for 1262 of 1475 (86%) pre- and 1007 of 1212 (83%)

postmenopausal patients enrolled in these trials (Trials VI and VII). Patients were enrolled from 22 centers, representing 9 countries and 7 main languages. Preliminary analyses of variance show that language/cultural factors have the strongest impact. Biomedical factors have a less pronounced impact; premenopausal patients report generally worse QL than postmenopausal patients, and patients with poor prognostic factors have a tendency to report worse QL. Sociodemographic factors vary substantially among cultural and language groups. This investigation identifies covariates which need to be considered when evaluating the influence of treatment factors on QL in international breast cancer clinical trials.

P84
Influence of adjuvant chemotherapy on quality of life of patients with breast cancer

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An ICCG trial has shown that CMF and FEC have similar efficacy when given as adjuvant therapy for breast cancer. A total of 95 patients treated at Guy's Hospital with CMF ($n = 62$) or FEC ($n = 33$) for 6 months were evaluated at four time points (pretreatment, midpoint of treatment, and 1 and 6 months posttreatment) using the Rotterdam Symptom Checklist (RSCL) and the Hospital Anxiety and Depression (HAD) scale. A 21 item questionnaire modified from the Psychosocial Adjustment to Illness Scale was also administered 1 month posttreatment. Data for all four time points were available for 79 patients (83%). HAD scale anxiety and total scores improved significantly between the first two assessments ($p < 0.001$), as did psychological well-being measured using the RSCL ($p < 0.001$). Thereafter median scores for each of these factors remained stable. Median HAD scale depression scores were similar at all four time points. No differences were observed between patients receiving CMF or FEC. 28/79 (35%) patients reported moderate or severe tiredness before treatment. This increased to 46% at the midpoint of treatment and then reverted to pretreatment levels. Posttreatment questionnaires were completed by 91/95 (96%) patients. The frequency of moderate or severe problems in relation to individual items were: weight gain (47%), ability to work (45%), sexual function (32%), finances (16%) and relationships at home (10%). 52% of patients felt moderately or severely unwell during treatment, the same proportion finding treatment moderately or severely disruptive. A significant difference between CMF and FEC was only observed for 1 of the 21 items (ability to work: $p = 0.02$, with FEC treated patients faring worse). The overall impact of the two regimens on quality of life, as reported by patients, is similar.

P85
Quality of life assessment in an international randomized trial of temporary ovarian ablation vs. CMF in early breast cancer

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In an international trial comparing the LHRH analogue 'Zoladex' (goserelin acetate) and CMF (cyclophosphamide/methotrexate/5-fluorouracil) in pre/peri-menopausal women with node-positive stage II breast cancer, quality of life (QL) has been included as a primary endpoint. The Rotterdam Symptom Checklist is supplemented with questions regarding social support and coping with illness, translated into seven languages. The questionnaire is given to the patients before adjuvant therapy and at 3 and 6 months, and 1, 2 and 3 years after the start of treatment. In this paper we investigate whether the reliability, the structure and the level of impairment of QL at baseline is consistent over the different cultures involved. So far, baseline QL has been measured in 689 patients. Acceptance of the questionnaire is good, with an overall response of 78%. Only in 8 out of 45 items is non-response over 2.5%. Reliabilities are comparable between the different cultures (psychological distress: 83–89, physical distress: 68–85, activity: 57–80, social impairment: 67–84). Also, the factor analyses indicate a stable structure of the questionnaire with one psychological and several physical factors. However, the level of distress at baseline is different in the different cultures ($p < 01$ for all subscales). In conclusion, our QL questionnaire can feasibly be used in different cultures, but the cross-cultural generalization of results may have to be considered cautiously.

P86
German Breast Cancer Study Group (GBSG) trial "Therapy of Small Breast Cancer": six-year results of a prospective non-randomized study

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Study design. In stage pT1 N0 M0 breast cancer, mastectomy as the standard treatment was to be compared with radiotherapy of the remaining breast tissue. The study design, originally planned as a randomized trial, had to be changed into a prospective observation study due to the low randomization

rate. Univariate analysis of prognostic variables was the first step to a valid treatment comparison. Those factors determined as being significant were included together with the treatment effects in a multivariate analysis. A high therapeutic standard was guaranteed by quality control. *Results.* 1036 out of 1119 recruited patients are evaluable. After a medium follow-up of 48 months the following preliminary results can be reported. With the exception of death without recurrence from breast cancer the 143 events are evenly distributed among the two treatment groups. Locoregional recurrence of the whole patient population is 5%. Out of all prognostic factors examined only tumor size and grading are significant in regard to recurrent disease. Recurrence-free survival decreased in cases with 'uncertain' tumor margins, whereas the width of the margin had no influence on recurrent disease. There was no significant difference in quality of life between the two treatment groups. *Conclusions.* There is no significant difference between the two treatment groups in the occurrence of locoregional failure. Incomplete tumorectomy has a negative influence on recurrence. Quality of life seems more dependent on the acceptance of the therapy by the patient than on the therapeutic modality itself. The results of the six-year analysis currently being performed will be demonstrated.

Study 'Therapy of Small Breast Cancer'. Four Year Results of a Prospective Non-randomized Study, *Breast Cancer Res Treatm*; in press.

P87
Integrated therapy in locally advanced breast cancer: clinical and biological findings

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For the Gruppo Oncologico Nord-Ouest, Italy.

Sixty-six patients (pts) with locallly advanced breast cancer entered a randomized trial comparing a CEF/CMF regimen every 21 days with the same regimen plus GM-CSF every 14 days. The primary aims of the study are to correlate the dose-intensity (DI) of the two treatment arms with pathological complete response rate, disease free survival and overall survival. The secondary aims are to evaluate the modifications of several biological parameters (thymidine labelling index, expression of IGFl receptor and bcl2) induced by primary chemotherapy with different DI and to investigate their prognostic significance. Patient characteristics are as follows: median age 54 (range 26–69), median PS 0 (0–1); stage IIIA 27 pts, IIIB 19 pts, inflammatory breast cancer 18 pts, metastatic disease 2 pts (considered as protocol violation). 52 pts have received at least 3 courses of primary chemotherapy and are evaluable for response. The objective response rate is 82%: CR 4 (7.7%), PR 39 (75%), SD 9 (17%). Three complete responses are pathologically confirmed. At a median follow-up of 14 months (range 1–27) 60 pts are alive and disease free, 2 pts had metastatic disease at study entry, 3 pts relapsed and 1 pt died because of progressive disease. TLI, expression of IGF1-R and bcl2 have been evaluated before primary chemotherapy (T0), and at surgery (T1)

	T0 mean (range)	T1 mean (range)	
TLI	4.4 (0.5–10.5)	2.1 (0.01–3.9)	$p = 0.006$
IGF1-R	70 (20–100)	53 (20–100)	$p = 0.021$
bc12	17.4 (0–80)	23 (0–100)	$p = 0.1$

The study is still open for accrual.

Supported by grant from CNR 93.02290.PF39 and AIRC.

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The benefit of intra-arterial chemotherapy in locally advanced breast carcinoma

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Objectives. Superselective intraarterial chemotherapy can downstage extended tumor findings and make them operable secondarily. This was investigated by a prospective study. *Patients and methods.* From January 1993 to September 1994 16 pts were treated by superselective intraarterial chemotherapy (A. subscapularis and A. mammaria interna) via A. femoralis with 10 mg mitomycin C and 30 mg mitoxantron using digital subtraction angiography. Up to 4 courses every 3 weeks were administered. 2 pts had ulcerating primary breast cancer, the other 14 pts suffered from recurrence. *Results.* 1 of the 2 pts with primary breast cancer showed complete remission clinically and histologically, the other one needed systemic treatment due to progressive disease. 10 out of the 14 pts with recurrence could be downstaged and became operable secondarily. 2 pts had to be excluded bcause the procedure was not successful due to vessel problems. 1 pt showed good local response but had deterioration in other body areas and 1 pt showed progressive disease under treatment. The chemotherapy was tolerated well generally; in two cases leucopenia and vomiting were noticed. *Conclusion.* Superselective intraarterial chemotherapy is a valuable help in handling primarily inoperable breast cancer or recurrence. It was effective in 12 of 14 pts (82%).

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Assessing the cost of adjuvant therapies for locally advanced breast cancer in the Ukraine

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Two protocols are classically utilized in adjuvant chemotherapy of breast cancer: CMF (cyclophosphamide + methotrexate + fluorouracil) and FAC (fluorouracil + adriamycin + cyclophosphamide). Tamoxifen (T) is utilized in adjuvant hormonal therapy. In the Ukraine the minimal available cost of these regimens (per patient of height 165 cm and weight 65 kg, S = 1.7 m^2; US dollars) are: $269 (6 cycles of CMF on Bonadonna), $693 (6 cycles of FAC on Buzdar) and $146 (20 mg of T every day, total 2 years). We have assessed the need for adjuvant therapy in our region (on 100 pts) as: CMF 30%, FAC 10% and T 50%. Thus the total cost of adjuvant therapy of 100 pts in Ukraine is $22,301. In 1993, 455 new cases of local advanced breast cancer were diagnosed in the Lviv region (population approximately 2,750,000). We would need $101,470 for their adjuvant therapy, which is more than 30% of the annual budget of our region for all patients with malignant diseases in 1993. Due to the difficult economic situation in our young nation, only 5%–10% of cancer patients receive adequate drug therapy. We believe that the situation will improve in the Ukraine in the future.

Drugs	Total course dose per pts (1.7 m^2)	Min. available cost in $ (1 packing)	Cost per pt
CMF			269.28
C	14280 mg (6 cy)	20 (50 mg × 50)	114.24
M	816 mg (6 cy)	50 (50 mg × 10)	81.60
F	12240 mg (6 cy)	30 (1 g × 5)	73.44
FAC			693.60
F	5100 mg (6 cy)	30 (1 g × 5)	30.60
A	510 mg (6 cy)	10 (10 mg × 1)	510.00
C	10200 mg (6 cy)	30 (200 mg × 10)	153.00
T	14600 mg (2 yrs)	10 (10 mg × 100)	146.00

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Audit of the management of women < 50 with primary breast cancer

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Adjuvant chemotherapy is associated with significant overall survival benefits in premenopausal women with primary breast cancer and ipsilateral axillary lymph node metastasis. We have undertaken a population-based study to audit the management of women under 50 diagnosed with primary breast cancer during the first six months of 1993 and who were resident in the North West Region of England. The aim of this study is to ensure that women receive optimal management in the adjuvant setting. We sought information from histopathology reports from 20 pathology laboratories and from records held by the North West Regional Cancer Registry, which covers a population of 4.3 million. We excluded women who presented with either recurrent or distant disease, or who were clinically confirmed as peri- or post menopausal (n = 62). We had a study population of 212 and by a process of case note review we abstracted the following information: menopausal state, surgical procedure, axillary lymph node surgery, adjuvant therapy, tumor size, and tumor grade (where applicable). Results show that 78% (n = 167) of women received axillary lymph node surgery (sampling or clearance). Of the node-positive patients (n = 74) 38% had 24 nodes positive, and over three quarters of these patients received adjuvant chemotherapy (86%). Initial results suggest that on the whole most women received optimal systemic therapy.

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Multimodal management of 200 cases of breast carcinoma: a retrospective analysis

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The treatment of patients with breast cancer has evolved substantially over the last three decades. Combined modality therapy has become the treatment of choice for these patients. 200 cases of breast cancer managed by multimodality approach in the Department of Radiotherapy at AIIMS were evaluated retrospectively. The age group of these patients ranged from 26 to 80 years with a mean of 45.8 years (± 12.41 years). The median parity of the group was 3 (range 0–10). 114 (57%) of the patients were premenopausal, the rest being postmenopausal. All the patients were staged according to UICC TNM staging, 1989. 48 (24%) patients had early stage disease (stages 1 and 2), while 102 (51%) had locally advanced disease. Metastatic disease was seen in 50 (25%) patients at presentation. All these patients were treated by a combined modality approach comprising surgery, chemotherapy and/or radiotherapy. The overall median survival time was 66 months (50 to 80 months, 95% confidence limits). The median survival of patients with metastatic disease was 15 months as compared to 66 months for non-metastatic disease ($p < 0.01$). The mean

follow-up duration was 33 months (range 10 to 20 months). The overall 5-year survival was 52% (± 0.06). The 5-year survival for non metastatic cases was 58%.

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The natural history of stage II breast cancer treated with CMF-based adjuvant therapy

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From 1975 to 1980 the CALGB conducted a study of adjuvant therapy of node-positive primary breast carcinoma. Patients underwent a mastectomy and axillary lymph node dissection and were then randomized to one of three adjuvant chemotherapy regimens. These were: CMF alone, CMF + VP, and CMF + MER (methanol extraction residue of BCG). The chemotherapy was administered in a six-week loading schedule and then for two weeks on, two weeks off during the first year of therapy. A second year of therapy was then given in a two weeks on, six weeks off schedule. This was a multi-institution study with some of the institutions leaving CALGB during the 1980s. Follow-up for patients from these institutions was problematic, so during the past four years an intense effort has been made to locate and verify the disease status of all patients. Information about disease and death was obtained from a variety of sources outside CALGB. In addition, all CALGB paper records were re-reviewed by the Study Chair to verify relapse information and cause of death. The results of this follow-up effort are presented here regarding the long-term outcome of a large patient cohort with stage II breast cancer treated with adjuvant CMF-based chemotherapy. Emphasis is placed on the natural history of the disease rather than the therapeutic results of the three chemotherapy regimens. A total of 905 patients were registered to this study. Eighteen were cancelled and never received the study treatment. Another 46 patients were entered by a single foreign institution and did not receive therapy per protocol. In addition, no follow-up information was available for these patients after 1978. An additional 24 patients did not have stage II cancer (they had stages I, III or IV), and three patients had prior cancer before study entry that made them inevaluable for outcome of stage II disease. These exclusions leave 814 patients who form the basis of this report. The median follow-up is 15.5 years. *Results.* 248 patients (30%) are alive and relapse-free with a minimum follow-up into the 1990s. An additional 19 patients are alive in the 1990s with distant metastatic disease and are probably destined to die of these metastases. Ten other patients have had a chest wall or regional lymph node recurrence, but with 8–13 years of follow-up they have not displayed any other recurrence. One patient is known to be alive, but her disease status is unknown. Only 14 patients (2%) are irrevocably lost to follow-up. A total of 522 patients (64%) are known to have died, and only four do not have a known cause of death. 457 (88%) of the dead patients have died of relapsed and metastatic breast cancer. 15% of these relapses occurred > 10 years from study entry. Nine (1% of the total entries) died of direct, acute complications of the chemotherapy. Twenty patients (4%) have died of a second, and one of a third primary cancer. Thirty-five (7%) have died of a non cancer related problem. Seventy-four second or third primary cancers occurred; 50% of these were contralateral breast carcinomas. There were three cases of acute, and one case of chronic, myelogenous leukemia and one case of myeloma. *Conclusions.* We conclude that patients with stage II breast cancer who are treated with CMF-based adjuvant chemotherapy still have a high risk of relapse and death from metastatic disease, including > 15 years from the original diagnosis. In addition, there is a risk of developing, and dying from, a second or third primary cancer. The risk of developing acute leukemia is very low (< 1%). These natural history data indicate that stage II breast cancer is still difficult to cure despite use of CMF-based adjuvant chemotherapy.

Supported by grants from the National Cancer Institute, Bethesda, MD, USA.