

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. In this trial, 13 German clinical centers take part; to date 628 patients are recruited. It is now going to be extended to an European trial, supported by the BIOMED-2 program.

P46 15 year update of the naples GUN trial of adjuvant breast cancer therapy: Evidence of interaction between c-erb-B2 expression and Tamoxifen efficacy

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From February 1978 to December 1983, 433 patients (pts) were enrolled in the GUN trial. Ten year results have already been reported (Bianco et al., Lancet, 1988). Postmenopausal pts (n = 308) with (N+) or without (N-) lymph node metastases were randomized to receive either Tamoxifen (TAM), 30 mg qd for 2 years or no therapy. Premenopausal N+ pts (n = 125) were randomized to receive either CMF x 9 cycles or CMF x 9 cycles plus Tamoxifen (TAM), 30 mg qd for 2 years. Overall 206 pts were randomized to receive TAM versus 227 pts not receiving the antioestrogen (no TAM). c-ErbB2 expression was evaluated on 245 paraffin-embedded specimen by immunohistochemistry. At 15 years, when the median follow-up was about 11 years, TAM was effective in improving both Disease Free Survival (DFS) (p = 0.0008) and Overall Survival (OS) (p = 0.05). When pts were stratified according to menopausal and lymph-node status DFS and OS benefits were observed in all subgroup of pts receiving TAM. More interestingly, when we evaluated the c-erbB2*TAM interaction the following results were found:

	Relapses Obs/Exp		Deaths Obs/Exp	
	c-erbB2- (n = 182)	c-erbB2+ (n = 63)	c-erbB2- (n = 182)	c-erbB2+ (n = 63)
TAM	0.83	1.17	0.85	1.56
no TAM	1.18	0.89	1.15	0.64

According to these data TAM seemed to improve DFS and OS only in c-erbB2- pts, while showing a paradoxical detrimental effect in c-erbB2+ pts. A multivariate test for interaction adjusting by lymph node status, menopausal status, nuclear grade, estrogen receptor (ER) status and ER*TAM interaction confirmed the predictive value of c-erbB2 expression (OS p = 0.007; DFS p = 0.04). In conclusion, a) at 15 years adjuvant TAM reduces relapse and death rates independently by nodal and menopausal status; b) in our randomized trial c-erbB2 expression is a strong predictor of adjuvant tamoxifen failure independently by ER, ER*TAM interaction and other major prognostic variables.

P47 Locally advanced breast cancer (LABC): Prognostic variables affecting results

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Purpose: To evaluate the prognostic significance of clinical and histopathological indicators on disease free survival (DSF), overall survival (OS) and objective response (OR) rates in Locally Advanced Breast Cancer (LABC) patients (pts) treated with a multimodality therapy.

Patients and Methods: Three-hundred sixty-seven assessable LABC pts entered onto two consecutive randomized trials performed in our Medical Oncology Dept. and North-West Oncology Group (GONO) cooperative centers. In the first study 117 pts were randomly allocated to receive either 3 courses of primary FAC (5-FU 600 mg/sqm, ADM 50 mg/sqm, 5-FU 600 mg/sqm day 1 every 21) followed by local-regional treatment (surgery and/or radiotherapy) and 6 courses of adjuvant chemotherapy consisting of 3 FAC alternated with 3 CMF (CTX 600 mg/sqm, MTX 40 mg/sqm, 5-FU 600 mg/sqm day 1 every 21) or the same program in which chemotherapy was preceded by oral Dethylstilbestrol (DES 1 mg/day for 3 consecutive days). In the second study 150 pts were randomized to receive either a standard primary FEC (5-FU 600 mg/sqm, EpiDX 60 mg/sqm, CTX 600 mg/sqm day 1 every 21 days) or an accelerated FEC every 2 weeks with GM-CSF (5 μ g/kg/day for 10 days s.c.).

Results: ORs to primary chemotherapy was 64% (95% C.I. 58-70%). On univariate analysis, performed on pts characteristics at diagnosis, pts with inflammatory breast cancer (IBC) had a significantly lower probability of response than pts who did not (p = 0.04); no other differences in response rates were observed between pre-menopausal and post menopausal pts, estrogen (ER) and/or progesterone (PgR) receptor positivity, stages of disease (IIIA vs IIIB). The median PFS and OS of the whole group were 3.5 and 5.1 years respectively. On univariate analysis, performed at surgery, no correlations were observed between age, menopausal status, stage of disease (IIIA vs IIIB), response to primary chemotherapy (pathological complete response, residual disease \geq 1

cm) and DFS or OS. Pts with ER and/or PgR receptor positivity had a better OS rates compared to pts with ER and/or PgR negative tumors (p = 0.02 and p = 0.03 respectively); hormonal receptor positivity did not affect DFS. Pathological evidence of IBC significantly correlates with OS (p = 0.0005) but not with DFS (0.07). The number of positive nodes at surgery significantly predicts both DFS and OS (p = 0.0003 and p = 0.003 respectively).

Conclusion: in LABC pts treated with a multimodality therapy hormonal receptor positivity at surgery significantly correlates with a better OS; IBC significantly correlates with a poor outcome however is nodal status at surgery the strongest prognostic factor associated with PFS and OS. A multivariate analysis will be presented.

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P48 Prognostic value of estrogen receptor (ER) status in breast cancer patients with five or more axillary lymph nodes (LN) involved

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Objective: To find parameters influencing the risk of relapse in breast cancer patients with five or more positive axillary LN treated with adjuvant intensive chemotherapy.

Methods: 31 patients up to 65 years of age received six cycles of an anthracycline containing chemotherapy regimen followed by intensive chemotherapy with peripheral blood progenitor cell rescue and local irradiation. Patients with ER+ tumors continued on adjuvant therapy with tamoxifen later. Survival analysis identified ER status as prognostic factor for relapse in our series. ER+ and ER- patients were homogeneous for age, menopausal status, number of involved axillary LN, and expression of Ki-67, c-erb-b2, and p53.

Results: Median number of positive axillary LN was 10. Median relapse free survival was 23 months for ER- patients and no ER+ patient has relapsed with a median follow up of 23.5 months (p = 0.0008). ER+ patients tended to have lower stages of the disease but the adjusted analysis yielded ER status as an independent factor for risk of relapse.

Conclusion: Our preliminary data show that in our series ER status appears to be the main predictor of relapse. We can not rule out that adjuvant treatment with tamoxifen is responsible for the better outcome of ER+ patients.

P49 Predictive parameters of response in primary CMF chemotherapy of breast cancer

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Introduction: In breast cancer, primary chemotherapy has proved to be useful in the evaluation of drugs effectiveness. It also permits a greater rate of conservative surgical procedures.

Objective: To assess factors that may predict the response to primary chemotherapy.

Design: Longitudinal study.

Patients and Methods: From January 1990, 150 patients with breast cancer were treated with primary chemotherapy. Conditions to join the study were tumor size greater than 3 cm. and age less than 66. Tumor diameter was measured by mammography. All patients had a positive cytology or a minute open biopsy that was also used for the evaluation of nuclear grade and the immunocytochemical determination of hormone receptors and c-erb-B2 expression. Patients were treated with CTX, 600 mg/m²; MTX, 40 mg/m²; and 5-FU, 600 mg/m²; on days 1 and 8, for three cycles.

The tumor response was evaluated by mammography.

Results: A good response was assessed in 52% of cases (6% CR, 46% PR \geq 50%). The proportion of responses was 30% in grade 1 tumors; 49% in grade 2 tumors and 73% in grade 3 tumors (p < 0.01). Negative/positive estrogen receptors were associated with responses of 66% vs. 41% (p < 0.002).

Tumor diameter, progesterone receptors and c-erb-B2 expression were not related to response.

Conclusion: High nuclear grade and lack of estrogen receptors expression are predictive parameters of good response to primary CMF chemotherapy in operable breast cancer.

P50 Effectiveness of postoperative radiotherapy in controlling subclinical locoregional disease in breast cancer patients with positive axillary nodes

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Background: Results of randomized trials indicate that postmastectomy radio-

therapy (RT) improves survival in breast cancer patients (pts) with positive nodes treated with adjuvant systemic therapies. This impact on survival will depend on effectiveness (EF) of RT in eradication of subclinical locoregional disease. The aim of the study is to examine the EF of RT in preventing locoregional recurrences in relation to dose and degree of nodal involvement.

Materials and Methods: Analysis was performed in the group of 1082 breast cancer pts with positive nodes treated with mastectomy alone (438 pts), with postoperative RT with low dose of 36–40 Gy (512 pts) or with high dose of 50 Gy (132 pts). The EF of RT was estimated by comparing the rates of local (chest wall) and regional (nodal) recurrences in pts treated with surgery alone and with RT with two dose levels in relation to the degree of nodal involvement.

Results: In pts with 1–3 positive nodes the rates of local recurrences was 15.5% with surgery alone, 5.7% with low dose RT (EF = 63%) and 3.6% with high dose (EF = 77%); regional recurrences occurred in 18.8% with surgery alone, 7.2% with low dose RT (EF = 62%) and 3.6% with RT of 50 Gy (EF = 81%). In pts with >3 positive nodes the respective rates for local recurrence were 23% with surgery alone, 16.4% with low dose RT (EF = 30%), and 10.4% with high dose RT (EF = 55%); The rates for regional failures were 36% with surgery alone, 18.1% with low dose RT (EF = 50%) and 5.2% with high dose RT (EF = 86%).

Conclusions: Effectiveness of RT in controlling subclinical disease shows dose-response relationship and is lower in preventing chest wall than nodal recurrences in patients with many (>3) positive nodes. In this subgroup of pts doses > 50 Gy should be delivered to the chest wall, with careful planning of RT to avoid excessive dose to lung and heart and prevent increased late morbidity and cardiac mortality.

Thursday, February 26, 1998

9.00–18.00

Surgery/DCIS

P51 Lack of correlation between menstrual phase during operation and prognosis of premenopausal patients with early breast cancer in a randomized study of adjuvant chemo-endocrine therapy

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There is much controversy concerning the prognostic significance of the menopausal phase during operation in early breast cancer patients. We evaluated the correlation in 837 premenopausal patients in a randomized study of the adjuvant chemo-endocrine therapy. We divided the patients into the follicular phase group (F: mastectomy was done within 14 days after the onset of the last menstruation) and the luteal phase group (L: mastectomy after 15 days or more). 351 patients in F group and 365 in L group were evaluated, excluding 43 patients with irregular menstruation cycles just before the menopause, and 78 with unknown cycles. There were no significant differences between the two groups in the background factors such as age, UICC stage, tumor size, histological type, node status, operation method, ER status, and type of adjuvant therapy. Recurrence of malignancy and death occurred in 14% (48/351) and in 11% (40) in F group, and in 16% (57/365) and in 13% (47) in L group, respectively, at the median follow-up period of 8.2 years (range 4 to 17 years). There was no significant difference between the group in relapse-free survival ($p = 0.4651$), or in overall survival ($p = 0.5255$). We could not find any significant differences in subgroup analyses by age, stage, tumor size, node status, and ER status.

In conclusion, in this randomized study of Japanese breast cancer patients whose prognosis has been known to be much better than in western countries, we could not find any relation between menstrual phase during operation and prognosis of early breast cancer patients.

P52 Aesthetic results of the breast cancer conservative treatment in the lower quadrants

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The quality of the cosmetic outcome of the breast cancer conservative treatment is strictly related to the primary location of the tumor.

It's widely accepted that the lower quadrants can leave more residual deformities than the others. In order to prevent these poor results a new surgical approach has been adopted: a wide lumpectomy associated with a superior pedicle mammoplasty (with post operative irradiation) was the treatment of choice in the last 25 cases of lower quadrants tumors.

In the last five years ('92–'97) at the Clinica Chirurgica I of the University of

Florence 1299 cases of breast cancer have been treated: 966 with conservative procedures and 220 located in the lower quadrants (127 central, 51 outer, 42 inner).

A case-control study (with a ratio 2:1) has been settled between the cases treated with the wide excision and the postoperative irradiation and the cases with the wide excision included in a superior pedicle mammoplasty (plus post-operative irradiation). The patients were matched by age, size of the tumors, location (central, inner, outer) and radiation dose received.

The results demonstrate that there is a significant improvement of the cosmetic outcomes with this kind of approach. The Authors also discuss the indication to a mono or bilateral mammoplasty, concerning the discrepancy between the level of the inframammary crease and the breast size.

The poor cosmetic results of the treatment of the lower quadrants tumors can be avoided utilizing a remodeling mammoplasty which, through a redistribution of the residual breast volume, can preserve a normal appealing breast.

P53 Is axillary lymph node dissection indicated for early stage breast cancer? A decision analysis

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Background: Axillary lymph node dissection (ALND) has been a standard procedure in the management of breast cancer. Presently ALND is performed primarily for staging purposes in an effort to guide adjuvant systemic treatment. Recently its routine use has been questioned, however, because the knowledge gained may not change adjuvant treatment and/or the benefit of any change would be small. The purpose of our study is to provide quantitative estimates for the survival benefits to be expected from performing ALND in clinically node negative patients.

Methods: A decision model was constructed to quantify the survival benefits of ALND. Patients were grouped by age, tumor size and hormone receptor status. The model predictions for outcome of adjuvant systemic therapy strategies were based on overviews from the Early Breast Cancer Trialist Cooperative Group (EBCTCG) as well as data from three large Cancer in Leukemia Group B studies (CALGB). Quality of life adjustments were also incorporated in the model. We assumed that patients not undergoing ALND received axillary radiation therapy (ART), that the two procedures were equally effective in preventing axillary recurrence and that any survival benefits accruing from local control in the axilla were equal for surgery or radiation.

Results: Outcome data for all patient groups are provided as well as a detailed discussion of two patient examples. For most patients, there are no survival benefits from the performance of ALND. Small benefits averaging from 2–6 weeks improvement in overall survival are seen, mostly in the group of patients who are ER positive and have small primary tumors. With increasing adverse effects of adjuvant systemic therapy on quality of life, the benefits of ALND increase, since node negative women may avoid adjuvant systemic treatment.

Conclusion: ALND provides a survival advantage for only a small percentage of patients with carcinoma of the breast. We recommend that it no longer be used routinely but on a more selective basis with a full understanding on the part of both physician and patient of the benefits and risks to be expected.

P54 Sentinel lymph node biopsy in breast cancer – Which tumors are suitable?

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Sentinel node biopsy becomes more and more established in breast cancer therapy. Results from approximately 1000 patients show that this method has a sensitivity of 80–100% in detecting the most likely positive axillary lymph node. The overall predictive value of the SN representing the status of axillary metastases is 95–100%. However, there is only little experience about the limits of the method.

Patients and Methods: We studied SN detection with preoperative lymphoscintigraphy and intraoperative detection with a γ -probe in 95 patients with primary breast cancer, including 8 cases, where excision of the primary tumor was performed several days before. Tumor sizes ranged from pT1a up to pT4.

Among our patients there were also 9 cases of local recurrence and SN detection was done in order to find remaining lymph nodes after previous clearance of the axilla.

Results: We found a strong relation between the detection rate and the tumor size together with a dependence of the predictive value in respect to the tumor size. While pT1 tumors ($n = 37$) showed a detection rate of 90% and a predictive value of 97%, detection rate decreased to 62.5% with a predictive value of 60% in pT3/4 tumors ($n = 16$). According to our experience tumors with a diameter