We prospectively studied 36 women (age range 25 to 58) with breast cancer receiving single agent doxorubicin (75 mg/m$^2$) as part of their adjuvant therapy. They had normal baseline ECG, liver biochemistry and 2-D echocardiography. Blood was taken 30 minutes after the first bolus injection for metabolite analysis. Echocardiograms were repeated at 3 and 9 weeks, prior to further doxorubicin doses and at 1 year.

57% of patients had Dol 7-d levels, ranging from 2 to 90 ng/ml. No patient developed cardiac failure (mean drop in LVEF of 3.5% after 1 year). Significant differences in diastolic function (Peak E) were found by 9 weeks (paired t-test, $p < 0.01$) which persisted at 1 year (paired t-test, $p < 0.05$) but not linked with LVEF changes. Dol 7-d levels at 30 minutes correlate with Peak E changes at 9 weeks (Kendal's rank correlation coefficient, $p < 0.01$) but not at 1 year ($p < 0.1$) and not with other variables such as age or smoking history. These results support the hypothesis that Dol 7-d levels are associated with early free radical damage to the heart but not with long term cardiotoxicity.

798 POSTER

## GEPARDO – A German trial of preop. chemotherapy with ADoc in breast cancer: First promising results

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**Purpose:** To assess the tolerability and efficacy of preoperative chemotherapy with adriamycin and docetaxel (ADoc) in patients with primary op. breast cancer.

**Patients and Methods:** In a prospective phase II-trial 195 patients with hi-stologically confirmed primary breast cancer (tumor > 3 cm, not T4) received dose-intensified adriamycin (50 mg/m$^2$) and docetaxel (75 mg/m$^2$) every 14 days and surgery after 4 cycles. Patients also were randomized to simultane-ous tamoxifen vs no tamoxifen. We report about an intermediate evaluation on 45 patients (T > 5 cm, N+ 58%)

**Results:** Response using best imaging was: CR 5%, PR 69%, NC 23%, PD 3%. Breast conserving surgery was performed in 74% of the patients. Hi-stol. CR was achieved in 6 patients (14.3%). Therapy was interrupted in 2 patients. Hemat. tox. III/IV 32/12%, gastroint.tox was mild as well as muco-sa and cutane tox..

Comclusion: 8 weeks of preop.Adocñtam efficiently reduce tumor size, achievehigh rate of PCR and breast concerving. Toxicity was well acceptable and tolerable in 95% of the patients.

799 POSTER

## Endometrial changes caused by tamoxifen

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**Purpose:** Prolonged therapy with tamoxifen gives rise to endometrial abnormalities and has been reported to increase the subsequent development of endometrial cancer six fold. This prospective study was designed to examine the time course over which endometrial abnormlities occur in an adjuvant setting.

**Methods:** Patients requiring adjuvant tamoxifen as part of their normal treatment for breast cancer underwent baseline pelvic examination, transvaginal ultrasound scanning (TVUS) to measure endometrial thickness (ET) and biopsy for histology and insulin growth factor-1 levels if ET was >7 mm. Subsequent TVUS (and biopsy if ET > 7 mm) was performed at 1, 2, 3, 6, 12, 24 and 36 months.

**Results:** Twenty seven patients have been studied for a mean of 15.8 months. The mean endometrial thickness has increased from 3.45 mm before tamoxifen (0 months) to 4.99, 5.7, 5.3, 4.98, 4.85, 5.55 and 6.6 mm at 1, 2, 3, 6, 12, 24 and 36 months. After 6 months therapy with tamoxifen, 41% of women had an increase in endometrial thickness of >100% and this had risen to 50% of women after 12 months therapy but had decreased to 40% after 24 months therapy.

**Conclusion:** Tamoxifen causes a rapid initial rise in endometrial thickness, perhaps due to oedema, but then continues to increase endometrial thickness progressively with increased duration of use.

800 POSTER

## Systemic therapy and acute reactions during adjuvant RT after conservative surgery in early breast cancer

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**Purpose:** To evaluate the influence of different adjuvant chemotherapy (CT) or hormone therapy (HT) regimens, on acute reactions during post-operative RT, in pts with stage I–II breast cancer treated in 12 Institutions of Northern Italy (Lombardy), in 1997.

**Methods:** The analysis concerns local toxicity (EORTC-RTOG scale) in 1610 pts (mean age 57 yrs, 69% post-menopausal, 31% N+). The whole breast was irradiated with 60Co or 4–6 MV photons at the mean ICRU dose of 50 Gy, plus a booster of 10 Gy in 1070 cases: 38% of pts had CT, 33.4% HT, 28.6% only RT.

**Results:** The incidence of acute skin reactions in pts treated with only RT was: grade (G)0 = 19.6%, G1 = 61.4%, G2 = 17%, G3 = 2%; in pts treated with HT: G0 = 14.3%, G1 = 66.2%, G2 = 17.3%, G3 = 2.2%; and in pts treated with CT: G0 = 12.4%, G1 = 62.2%, G2 = 21.1%, G3 = 4.3%. No acute toxicity involving lung or heart was detected. RT had to be interrupted in 35 cases owing to the toxicity of the combined treatment (RT + CT). There are no significant differences in acute cutaneous toxicity due to the types of chemotherapy (ADR based CT, CMF or others).

**Conclusion:** Post-operative RT was well tollerated, also with concomitant CT. The conclusive data including follow-up for cosmesis and survival will allow us to evaluate results and cost-effectivness according to different treatments and RT modalities.

801 POSTER

## Concurrent sequencing of full dose CMF chemotherapy and radiation therapy in early breast cancer

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**Purpose:** The aim of this study was to evaluate whether the concurrent sequencing of CMF chemotherapy and adjuvant tangent breast irradiation effects the ability to deliver optimum doses of both treatment modalities.

**Methods:** Between the years 1986–1998, 105 patients were treated with CMF chemotherapy and radiation therapy. 67 were treated with concurrently (group 1) and 38 sequentially (group 2). Patients were well balanced with respect to age (48 vs 49 p = 0.9), no. positive nodes (0.3 vs 1), comorbid conditions (12.5% vs 10%) and breast seperation (18 vs 19.2). Mean follow up was 2.8 yrs. in group 1 and 3 yrs. in group 2.

**Results:** There was no significant difference in the % of prescribed chemotherapy actually delivered in the two groups (95% vs 95%), chemotherapy delay (7.4 days vs 6.6 p = 0.22), or nadir platelet and granulocyte counts (179 vs 187 p = 0.09, 1272 vs 1473 p = 0.06). There was a small but significant delay in radiotherapy delivery (1.85 days vs 0.4 p = 0.006). Of the patients followed for >2 yrs. 66%, 27% and 5% had excellent, good or satisfactory cosmesis in group 1 compared with 75%, 25% and 0% in group 2. There has been no local failures in group 1 compared with one (2.4%) in group 2 and 1 (1.4%) distant failure in group 1 compared with 4 (11%) in group 2 to date.

**Conclusion:** It is possible to safely deliver optimum doses of CMF chemotherapy and radiation therapy concurrently.

802 POSTER

## Her 2 and topoisomerase (TOPO)IIα as predictive markers for node-positive (N+) breast cancer (BC) patients (PTS) randomised to adjuvant CMF or epirubicin (E) – cyclophosphamide (C)

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At ASCO '99 we reported the results of a clinical study where 777 pre- and post-menopausal N+ BC pts were randomised to: a) CMF (oral C) × 6; b) EC (E 60 mg/m$^2$, C 500 mg/m$^2$) d 1 i.v. q 3 wks × 8; c) high dose EC (HEC) (E 100 mg/m$^2$, C 830 mg/m$^2$) d1 i.v. q 3 wks × 8. The median follow-up is 50

mos. Out of 481 fixed and paraffin-embedded primary tumors, HER 2 and topo IIα were evaluable by IHC on 442 and 348 specimens, respectively (HER 2+ by m-abs CB11 or 4 D5: >1% + cells; topo IIα+ by clone KiS 1, Boehringer: >10% + cells). Results are reported below:

| | CMF | | EC | | HEC | |
|---|---|---|---|---|---|---|
| | n | 5 yrs EFS% | n | 5 yrs EFS% | n | 5 yrs EFS% |
| All pts | 255 | 66 | 267 | 60 | 255 | 70 |
| HER 2+* | 23 | 48 | 19 | 53 | 14 | 81 |
| HER 2– | 133 | 75 | 131 | 62 | 122 | 70 |
| Topo IIα+° | 52 | 61 | 57 | 61 | 52 | 74 |
| Topo IIα– | 64 | 74 | 67 | 56 | 65 | |

*HEC vs CMF: p = 0.10; °HEC vs CMF: p = 0.18

In the overall results on 777 pts, EC or HEC are not better than CMF. An interesting improvement in EFS was hypothesized and observed with HEC in HER 2+ or Topo IIα+ pts and is being further explored by: a) using a more sensitive assay for HER 2; b) elaborating a predictive model correlating HER 2 and Topo IIα.

803 POSTER

## Late treatment related morbidity in breast cancer patients randomized to postmastectomy radiotherapy and systemic treatment versus systemic treatment alone

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Purpose To assess the type, prevalence and degree of late treatment-related morbidity after mastectomy and adjuvant systemic treatment with and without postoperative irradiation (RT).

**Patients and Methods:** A historical prospective study including patients randomized in the Danish Breast Cancer Cooperative Group (DBCG) Trials 82 b and c and living in the county of Aarhus. We intended to study patients alive and without recurrence. Of the 331 patients originally treated in our department 104 met the inclusion criteria and 84 patients accepted to participate in the study. Forty-two patients were irradiated and 42 were non-irradiated patients. A structured interview and physical examination, using a standardized assessment sheet, was used. The assessment sheet was constructed on the basis of the late effects normal tissues (LENT) scoring system.

**Results:** The median length of follow-up from mastectomy was 9 years (range 6–13 years). Lymphedema (defined as a difference between ipsilateral and contralateral arm volume greater than or equal to 200 ml) was measured in 14% of the RT patients versus 3% of the no RT patients (NS). Slightly decreased shoulder morbidity was measured in 45% of the RT women versus 15% of the no RT patients, but moderate or more severe impairment of the shoulder morbidity was only seen in 5% of the irradiated and none of the non-irradiated patients (P = 0.004). Seventeen percent of the RT patients and 2% of the no RT patients found that impairment of shoulder movement caused symptoms (P = 0.001).

A multivariate analysis of factors possible contributing to lymphedema and impaired shoulder movement was performed. Factors included in the analyses were radiotherapy, chemotherapy, endocrine treatment, number of nodes removed, number of positive nodes removed, tumor size, age, obesity and smoking. The number of axillary lymph nodes removed and the age of the patient were found to increase the risk of lymphedema. Radiotherapy was the only factor shown to reduce shoulder movements.

**Conclusions:** Mild arm and shoulder morbidity was a common late complication to breast cancer treatment and was increased by the use of radiotherapy.

804 POSTER

## TC-99M tetrofosmin (T) pinhole-spect (P-SPECT) in breast cancer (BC) axillary lymph node staging

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**Purpose:** The number of metastatic axillary nodes represents in BC pts the most important prognostic factor, with more than 3 nodes indicating a worse prognosis. Since all conventional diagnostic methods are limitative, we propose Tetrofosmin P-SPECT as a new method in axillary lymph node metastasis detection.

**Methods:** After 740 MBq T injection, 180° P-SPECT imaging was performed around the involved axilla in 64 female pts, 55 with primary BC and 9 with benign lesions (B), using a circular HR single head gamma camera equipped with a pinhole collimator.

**Results:** Tetrofosmin P-SPECT was true positive in 28/28 BC pts with axillary lymph node metastases and true negative in 26/27 BC pts without metastases and in 9/9 B pts. P-SPECT identified 51% of the total removed metastatic nodes, determining the exact number in 6/6 pts with 1 node, in 2/2 pts with 2 nodes, in 3/6 pts with 3 and in 2/3 pts with 4 and showing more than 3 focal areas in 10 of the remaining 14 pts with over 4 nodes. P-SPECT thus correctly categorized 24/28 pts (≥3 or >3 metastatic nodes) for prognostic purposes.

**Conclusion:** Tetrofosmin P-SPECT appears a very accurate method in BC preoperative axillary lymph node staging and also gives useful prognostic information.

805 POSTER

## Phase II study of neaodajuvant chemotherapy combining epirubicin cyclophosphamide and vinorelbine (NEC) in locally advanced breast cancer (LABC): Preliminary results

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**Purpose:** Small size phase II have reported NEC in breast cancer. Our on going and larger phase II trial assess the clinical and pathological efficacy of NEC in patients (pts) with LABC.

**Patients:** Since 01/97, 20 pts have been enrolled. Planned treatment was: Vinorelbine 25 mg/m$^2$/d, d1&3, Cyclophosphamide 350 mg/m$^2$/d, d1–3 and Epirubicin 30 mg/m$^2$/d d1–3, every 15 days with GCSF support d5–10. Pts had 4 (13 pts) or 5 courses (3 pts) before surgery. Post operative treatment was no chemotherapy (3), NEC (4), anthracycline (3), paclitaxel (6) combined with radiothrepy and hormonotherapy when necessary.

Response: 17 pts are evaluable. 13 had an objective clinical response. There were 5 complete histological response, 5 partial response and 5 persistent tumor. 6 pts had positive nodes. Median follow up is 12 months. 1 pt had metastatic relapse. Further results will be presented in september 1999. Toxicity: All pts are evaluable for toxicity. WHO grade 3–4 neutropenia is the most frequent besides GCSF but require rarely hospitalisation. Grade >2 thrombopenia is uncommon. 4 patients suffer from abdominal pain but no ileus is observed.

**Conclusion:** These preliminary results with intensified neoadjuvant NEC are promizing. We try to increase response rate with two further courses before surgery without preventive GCSF. A longer follow up is required to assess survival data.

806 POSTER

## Infiltrating lobular carcinoma (ILC) treated with breast conservation: A retrospective study of the BCNIRTOG-Italy

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**Purpose:** There is no general agreement on the prognosis of ILC. In particular the possibility of a higher risk of local recurrence following conservative methods of treatment is reported due to the frequent multilocality of the lobular pattern. The aim of this retrospective study is to quantify the risk of local recurrence and distant metastatization in a population of patients with early-stage ILC suitable for breast conservation treated in some Centers collaborating at the Breast Cancer North Italy Radiation Therapy Oncology Group (BCNIRTOG).

**Methods:** 300 cases of ILC registered in 9 Radiation Oncology Depts. collaborating at the BCNIRTOG between 1980 and 1992 with a minimum 5-years of follow-up were collected. All the patients with stage I–II had been treated with conservative surgery, axillary dissection and postoperative irradiation. On the basis of the nodal status, 61 cases, received adjuvant chemotherapy and 67 hormonal therapy

**Results:** An overall local recurrence crude rate of 4.66% (14 cases; 13 invasive and 1 in situ) was observe. 32 patients developed distant metastases. The actuarial 10-year disease-free survival for T1 and T2 is 83.5% and 76.6%, respectively. The actuarial 10-year disease-free survival for N0 and N1 is 84.5% and 70.9%, respectively.

**Conclusion:** The results of this survey show that the outcome of ILC treated in our Centers is similar to that reported in the literature. In our experience the conservative approach to patients with early-stage ILC of the breast is safe and useful.