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The quality of breast conserving treatment in Denmark, 1989-1998 - a nationwide population-based study of the Danish Breast Cancer Co-operative Group.

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Background: Randomised studies have shown that breast conserving surgery followed by radiotherapy is associated with a prognosis similar to mastectomy alone. This formed the basis for recommending breast conserving surgery combined with radiotherapy as a standard treatment for suited breast cancer patients in Denmark. To test how well the results from the randomised studies apply to normal clinical practise and to evaluate the quality of the treatment, we performed an analysis of patients treated in Denmark over a ten-year period.

Material and methods: Between 1989 and 1998, 26.267 patients were registered with breast surgery in the database of the Danish Breast Cancer Co-operative Group (DBCG). 5201 or 20% had a lumpectomy. Of these, 4181 were included into the adjuvant treatment protocols of the DBCG and constitute the present material. 1020 patients were excluded from the protocols mainly because of old age (more than 75 years), patient denial and an insufficient number of lymph nodes removed. Univariate as well as multivariate analyses have been performed to determine survival and recurrence rates in relation to known prognostic factors and treatment variables.

Results: About 40% of the patients were aged less than 50 years, 27% had tumours less than 1 cm in diameter, 94% had free resection margins, 71% were node negative, and 69% were oestrogen receptor positive. 21% of the patients received chemotherapy and 17% tamoxifen. A total of 728 patients (17%) have died. The overall 10-year survival was close to 80%. There were 294 (7%) loco-regional recurrences, of these 155 (3.7%) located to the treated breast. The risk of developing loco-regional recurrences was increased in patients less than 50 years of age, if the resection margins were not free and with increasing number of positive lymph nodes. Adjuvant treatment decreased the risk of recurrence. Further details on treatment effects will be presented.

Conclusion: Survival and local control in this unselected population-based cohort treated with breast conservation was comparable to published series from controlled studies confirming the safety of this treatment method.

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Primary treatment with weekly docetaxel (Taxotere) and trastuzumab (Herceptin) for HER-2 overexpressing locally advanced breast cancer

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Background: Our recent trial showed encouraging results with weekly docetaxel (Taxotere®) in patients with locally advanced breast cancer (LABC) (Bines et al. San Antonio Breast Cancer Symposium 2002). Trastuzumab (Herceptin®) has been combined with weekly docetaxel in the metastatic setting (Esteva et al. J Clin Oncol 2002). We now report on this regimen in the neoadjuvant setting.

Objectives: (1) Clinical overall response (OR); (2) Pathological response; and (3) Safety profile.

Material and Methods: Between August 2001 and November 2002, 32 patients with LABC were enrolled. Median age: 45 years (21-63); clinical stage: 22% IIIA, 78% IIIB; median of major diameter: 85mm (45-140); 56% ER + and 59% PgR +; 100% HER-2 +++ (IHC DAKO). Treatment: Trastuzumab 4 mg/kg week 1, followed by 2 mg/kg weekly x 14 combined with 2 cycles of docetaxel as follows: 36mg/m^2 weekly x 6 followed by a 2-week break.

Results: At the time of this analysis, 32 patients were evaluable for safety and efficacy. The clinical OR was 72% (23/32) with PR of 47% and CR of 25%. The pathological complete response was 13% (4/32). The treatment was well tolerated with only 1 patient (3%) experiencing grade IV toxicity (anasarca). The most frequent grade III adverse events were alopecia (16%), neutropenia (9%), and headache (6%).

Conclusion: The combination of weekly docetaxel and trastuzumab showed substantial clinical activity with minimal toxicity in patients with an extremely unfavorable prognosis (large tumors, HER-2 +++). These results compare favorably with recent reports (Burstein et al. J Clin Oncol 2002). Supported by Aventis Pharma Brazil with the cooperation of Roche Brazil.

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In vivo-chemosensitivity adapted primary chemotherapy in patients with primary breast cancer. First results of the Gepartrio-Pilot trial.

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Background: Tumor response during the first 2-3 cycles provides valuable information about the chance to obtain a pathological complete remission (pCR = no invasive or in-situ tumor residuals) in patients (P) with primary breast cancer. P without early tumor remission show a very low pCR - rate. Prognosis remains poor in these P. We prospectively addressed this observation as an in-vivo-chemosensitivity test and explored a salvage regimen in this subgroup. Patients and methods: P with previously untreated operable (T>1.9cm) or locally advanced breast cancer were treated with 2 cycles TAC (Docetaxel 75mg/m*, Doxorubicin 50 mg/m*, Cyclophosphamide 500 mg/m* day 1, q day 22). In case of no palpable tumor (cCR) or a tumor reduction of > 49% (cPR), 4 more cycles TAC were administered (TAC6). Those P non responding were randomized to either additional 4 cycles TAC (TAC2+4) or 4 cycles NX (Vinorelbine 25 mg/m* day 1 + 8, Capecitabine 2000 mg/m* day 1–14, q day 22) (TAC-NX). Endpoints were pCR-rates (primary) and clinical response at surgery, toxicity, compliance, and the rate of cPR/cCR after 2 cycles TAC.

Results: From Oct 01 until Sep 02 304 (276 operable, 28 non-operable) P were recruited (median tumor size 4.0 cm). cCR/cPR after 2 cycles TAC was observed in 72%. So far data on 147 (107 TAC6; 24 TAC2+4; 20 TAC-NX) P at surgery are available. cCR rate was 45.8% in total (54% TAC6, 25% TAC2+4, 25% TAC-NX). pCR rate was 19.0% in total (26.2% TAC6, 0% TAC2+4, 0% TAC-NX). Grade III/IV Neutropenia was the most frequent toxicity (45.8% TAC, 26.3% TAC-NX). Serious adverse events were reported in 113 cases under TAC and 2 cases under NX. Treatment had to be discontinued due to toxicity only in 5 P during TAC.

Conclusions: TAC appears to be a highly effective preoperative treatment in breast cancer. Response after 2 cycles can identify P with a high or minimal chance of achieving a pCR and could be used as an in vivo chemosensitivity test. NX shows a better toxicity profile than TAC. Full analysis will be presented.

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Average tumor size and overall survival of patients with primary diagnosis of breast cancer influenced by a more frequent use of mammography

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From 1981 to 1990, 1656 consecutive patients with primary breast cancer were operated at the I. Frauenklinik der LMU Munich and Frauenklinik Berlin-Charlottenburg, Germany. In a contemporaneous analysis, we compared the average tumor size at the time of primary surgery and overall survival of patients treated during the years 1981-1985 (n=849) and during the years 1986-1990 (n=807), respectively. The mean follow-up was 63 months.Both patient groups were comparable in reference to age (p=0,77) and status of axillary lymph nodes (p=0,14). The average tumor size at time of the primary diagnosis continuously decreased during the study period (Pearson's correlation: 0,179, p<0,001). The average tumor size of patients operated until 1985 was 25 mm, compared to 21 mm in patients treated from 1986 on (p<0,001). While until 1985 in 19% (n=164) of the cases indication for operation was based on mammographical findings, this was the case in 27% after 1986 (n=215, p<=0,001). Unexpectedly, the reduction of the average tumor size at the time of the primary diagnosis did not lead to an increased overall survival: the median overall survival was 142 months in the first group (CI 95% 109-118) and 113 months in the later group (137-148, p=0,48). The observed decrease of the average tumour size at the

time of the primary diagnosis of breast cancer might be caused by a more frequent use of mammography. In line with recent data, this small reduction in tumor size does not necessarily translate into improved prognosis.

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Lack of pharmacokinetic interaction between erlotinib, docetaxel and capecitabine in breast cancer patients.

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Erlotinib (Tarceva™) is an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor being developed for the treatment of various solid tumors. This was a multiple ascending-dose safety and tolerability study in metastatic breast cancer patients with additional objective of characterizing the pharmacokinetics (PK) of erlotinib (E), both alone and in combination with docetaxel and capecitabine (D+C). We present here the PK of erlotinib, docetaxel and capecitabine, along with respective active metabolites. Patients were enrolled in three cohorts; Cohort A received 100 mg/day erlotinib for entire 21 day cycle, 825 mg/m^2 b.i.d. capecitabine for first 14 days of cycle and 60 mg/m^2 docetaxel i.v. on first day of cycle; Cohort B received same regimen as in Cohort A, but with an increase to 75 mg/m^2 docetaxel dose level; Cohort C received same regimen as in Cohort B, but with an increase to 1000 mg/m^2 b.i.d. capecitabine dose level. Erlotinib dosing was delayed until day 2 for the first dosing cycle in order allow for characterization of docetaxel and capecitabine PK in absence of erlotinib. PK sampling for erlotinib was performed on Cycle 1, Day 21 (E alone) and on Cycle 2, Day 1 (E + D + C). PK sampling for docetaxel and capecitabine was performed on Cycle 1, Day 1 (D+C) and on Cycle 2, Day 1 (E+D+C). To date, PK data was available from first two cohorts, both of which were comparable. Mean (± SD) Cmax for erlotinib in Cohort B was 1,593 (± 481) ng/mL (E alone) and 1,510 (± 480) ng/mL (E+D+C). Mean (± SD) AUC_{0-24hr} of erlotinib in Cohort B was 25,457 (± 11,251) ng.hr/mL (E alone) and 25,445 (± 10,708) ng.hr/mL (E+D+C). Therefore, mean exposure (Cmax, AUC_{0-24hr}) for erlotinib and its active metabolites (OSI-420 / OSI-413 co-measured) did not appear to change with concomitant adminstration of docetaxel and capecitabine. Mean (± SD) Cmax for docetaxel in Cohort B was 2,850 (± 826) ng/mL (D+C) and 2,197 (± 522) ng/mL (E+D+C). Mean (± SD) AUC_{0-24hr} for docetaxel in Cohort B was 3196 (± 830) ng.hr/mL (D+C) and 2,510 (± 1,020) ng.hr/mL (E+D+C). Mean docetaxel half life was unchanged (9.6 hr versus 10.8hr). Therefore, mean PK parameters for docetaxel indicated somewhat lower exposure in the presence of erlotinib. However, these results should be considered inconclusive considering the large interpatient variability and small number of evaluable patients. Mean (± SD) Cmax for capecitabine in Cohort B was 8,062 (± 6,932) ng/mL (D+C) and 4,975 (± 2,421) ng/mL (E+D+C). Mean (± SD) AUC_{0-24hr} for capecitabine in Cohort B was 5,857 (± 3,401) ng.hr/mL (D+C) and 5,948 (± 2,397) ng.hr/mL (E+D+C). Mean capecitabine half life was also unchanged (0.65hr versus 0.74hr). Mean pharmacokinetic parameters for capecitabine and its metabolites (5-FU and 5'-DFUR) did not appear to change in presence of erlotinib. In conclusion, there was no evidence for any PK interaction between erlotinib, docetaxel and capecitabine (or any metabolites thereof).

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Maximizing internal mammary sentinel lymph node identification

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Background: Lymph node mapping has caused renewed interest in the internal mammary nodes in breast cancer. Metastases in these nodes provide important prognostic information both in the presence and in the absence of metastases in axillary lymph nodes. Tracer injection in the dermal lymphatics over the tumor ensures a high rate of identification of the axillary sentinel lymph node (ASLN). Internal mammary sentinel lymph nodes (IMSLNs) are reportedly found in 0% to 35% of patients by conventional mapping methods.

Objective: We carried out a study to test the hypothesis that the addition of a tracer injection into the area of the deep fascia of the breast (near the muscle fascia) would increase the identification rate of IMSLNs.

Methods: Forty-seven consecutive patients with invasive breast cancer, regardless of site, underwent injection of both radioisotope and blue dye in the skin over the tumor and in the deep breast fascia. Pre-operative lymphoscintigraphy and/or intra-operative probe were used to identify the IMSLN. Patients with ductal carcinoma in situ or with known axillary lymph node metastases were excluded.

Results: An IMSLN was identified and biopsied in 24 patients (51%) in 1, 2 or 3 intercostal spaces. For lateral, central and medial lesions the identification rate was 47%, 40% and 75% respectively. A learning curve was evident with an identification rate of 30% for the first 20 patients, and 67% for the next 27 patients. There was 1 instance of metastasis to an IMSLN (2.1%) in a medial lesion. One patient had a small pleural perforation that required no treatment.

Conclusions: The identification rate for IMSLNs with deep fascial injection of tracer was higher than that reported for conventional mapping methods. There is a learning curve, and improvement in the technique of deep fascial injection may maximize identification of the internal mammary sentinel node in the same way that dermal injection ensures maximal ASLN identification. The clinical relevance of this technique in every-day practice has not been established.

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Breast cancer in the elderly - epidemiological characteristics and treatment approach

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Background. With the aging of the general population, cancer in the elderly has become increasingly common. It is commonly believed that the diagnosis of cancer in the elderly is delayed for a variety of reasons. Ageing also has an impact on cancer's biology and behavior, with some cancers evolving more slowly and the others becoming more rapidly invasive in older patients. There are also differences in the choice of treatment for elderly patients. The aim of the study was to investigate the epidemiological characteristics and the treatment approach in older breast cancer patients in comparison with younger ones.

Results. In our country, about 50% of cancer cases occur in people aged 65 or over. At the Institute for Oncology and Radiology of Serbia, there were about 1,200 newly registered breast cancer patients the year 2001. About 25% were over 65 years of age. The size of the tumor at diagnosis was on average smaller in younger groups than in older ones, both according to the clinical and pathological TNM. However, there was no significant difference either in the lymph node involvement or in the presence of distant metastases at diagnosis. The share of ductal carcinoma in all breast cancers was lower in elder patients than in younger ones (46 vs. 51%) while the situation was the opposite for lobular carcinoma (34 vs. 25%). However, there were no differences in the tumor grades. Hormonal receptors were more frequently positive in older women. About 80% of patients in both groups underwent surgery. However, there were differences in types of surgical procedures performed. Chemotherapy was 2,5-fold less frequently administered in older women; the difference was significant in each stage of the disease. There was also a significant difference in radiotherapy for each stage of breast cancer.

Conclusion. According to our data, there are some differences in the characteristics of breast cancer between patients over 64 and younger ones. There is a significant difference in the treatment approach for each stage of disease. Two questions remain to be further addressed: is breast cancer in elderly a different disease from breast cancer in younger patients, and, is there a rationale to treat elderly breast cancer patients differently from younger ones.

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Primary chemotherapy with gemcitabine (G), myocet (M) and docetaxel (T): results of a phase I/II trial

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Introduction: Combinations of anthracyclines, taxanes and gemcitabine are highly effective in breast cancer (BC). Current regimens might be improved by the use of liposomal doxorubicin formulations and by prolonging the