Proffered Papers

Breast cancer, early disease

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Can sentinel lymph node biopsy avoid axillary dissection in N0 breast cancer patients?

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All patients at our Institute who undergo breast surgery and total axillary dissection for breast cancer of any size but with a clinically uninvolved axilla enter the study. The objectives are: (1) to identify the sentinel node which is first node to receive lymph from the tumor area by lymphoscintigraphy following injection of 99mTc-labeled human albumin subdermally overlying the tumor; (2) to mark the sentinel node thus identified by means of an indelible sign on the skin over the node; (3) to determine the feasibility of isolating this node surgically with the aid of a radioguided probe; and (4) to verify how often the node thus isolated is metastatic in comparison with involvement of the other removed nodes.

In a consecutive series of 163 women with operable breast carcinoma, 99mTc was injected on the day before surgery, and scintigraphic images of the axilla and breast were taken 10 min, 30 min and 3 hours later. During breast surgery a hand-held gamma ray detector was used to locate the sentinel node, and facilitate its removal separately via a small axillary incision. Complete axillary lymphadenectomy was then performed. The sentinel node was tagged separately from all other nodes. Permanent sections of all removed nodes were prepared for pathological examination.

The sentinel node accurately predicted axillary lymph node status in 156 (97.5%) of the 160 patients in whom a sentinel node was identified, and in all of the cases (45 patients) with tumor <1.5 cm in diameter. Of the 85 cases with metastatic axillary nodes, in 32 (37.6%) the only positive node was the sentinel node.

In the great majority of patients lymphoscintigraphy and gamma probe-guided surgery can locate the sentinel node in the axilla, obtaining important information on the status of axillary nodes. Breast cancer patients without clinical involvement of the axilla should undergo sentinel node biopsy routinely and may be spared complete axillary dissection when the sentinel node is free of disease.

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Prognostic impact of minimal residual disease in patients with early breast cancer (T1)

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Purpose: At the present time nodal status still is the best available prognostic factor in primary breast cancer. Immunocytochemical detection of tumor cells in bone marrow (TCD) is a marker of tumor dissemination, as axillary nodal status. Therefore TCD could replace nodal status in some subgroups of patients.

Methods: In a prospective study (1985–96) the intraoperatively aspirated bone marrow of 582 T1-patients were screened for micrometastatic cells. We used the monoclonal mucin-AB 2E11 (reactive with TAG 12) for cell detection.

Results: After a median period of 44 months follow-up results were statistically analyzed. 232 of 582 T1-patients were TCD-positive (39.8%). Distant metastases were found in 50 women. This subgroup displayed a 76% TC-detection rate, although only 56% of them have been nodal positive. 25 women have died during follow-up. Among these patients 70% were TCD-positive, but only 49% had axillary metastases. In a Cox regression model TCD was the best prognostic factor for disease-free and overall survival. Complications of bone marrow aspiration were negligible compared to axillary dissection (15%).

Conclusion: As previously shown, tumor cell detection in bone marrow is an outstanding prognostic factor in breast cancer (JNCI, 1996, 1652). In the present analysis we could confirm this data in patients with small tumors. Tumor cell detection could be an alternative to axillary dissection in a future concept of outpatient treatment of early breast cancer. To prove this statement, in prospective randomized studies nodal status should be replaced by TCD.

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Use of Tc-99 labelled colloidal albumin for preoperative and intraoperative localization of non-palpable breast lesions

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Clinically occult breast lesions are found frequently now that mammagraphic and ultrasonic screening are widespread. Several methods are used to localize suspicious occult lesions prior to excision, including skin-projection and introduction of a hooked-wire; all suffer from limitations. We have developed a new localization technique in which mammographic or ultrasonic images are used to guide the injection of 0.05 mg of ^{99m}Tc-labeled human serum albumin (6–8 MBq) directly into the lesion (cluster of microcalcifications and/or opacity) on the day before surgery. Subsequently a gamma ray detecting probe locates that lesion and guides its excision. Up to 31 July 1996 we had treated 115 patients with non-palpable breast lesions using this technique. In all cases the hot-spot was easily and quickly located both on skin projection and in the parenchyma. X-radiography and scintigraphy of removed specimens checked the presence and centricity of the lesion: in all cases the lesion was within the specimen, although in one case intraoperative re-excision was performed as activity was detected at a resection margin. Pathological examination revealed 69 cancer lesions and no case of carcinoma cell dissemination along the needle track; 68 of these patients were treated by breast conserving surgery, and one received a Patey mastectomy.

A limitation of the new technique is that tracer injection directly into the lesion cannot be verified before excision, and should therefore be performed by personnel experienced in the localization of breast lesions. In our hands the technique proved safe and accurate, allowing easy detection of the skin projection (permitting the surgeon to choose the best incision) and fast removal of the lesion, with the added advantage that resection margins could be checked during the operation. Our preliminary data indicate higher excision accuracy, better lesion centricity within the specimen and less need for margin radicalization compared to the hooked wire method.

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Tumor cell detection in breast cancer patients before and after neoadjuvant chemotherapy

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Purpose: The important goals of the neoadjuvant chemotherapy (NACT) concerns the operability of the primary tumor and the suppression of early 'tumor cell shedding'. The aim of our study was to investigate the influence of NACT on tumor cell detection (TCD) in bone marrow.

Methods: In 174 patients with primary breast cancer larger then 3 cm we performed a bilateral aspiration of bone marrow after NACT (3–4 cycles of Epirubicin/Cyclophosphamide). 174 patients without NACT with the same tumor size, hormone receptor status, grading and age (matched pairs) served as controls. In 42 women bone marrow puncture before and after

pCHT was performed. The interphase cells were marked with the antibody 2E11 (against the tumor-associated antigen TAG12).

Results: The rate of TCD were unchanged before and after pCHT (52.3%; n = 22). In only 4 patients the finding changed (2 from positive in negative and 2 viceversa). In the matched pair analysis there were tumor cells in the bone marrow in 51.7% of the cases (n = 90) after pCHT; and in 49.4% (n = 86) in the control group without pCHT. Distant metastases were diagnosed in 27 patients (24 TCD positive; 3 TCD negative, $p < 0.001$) in the study group.

Conclusion: Our results show that a reduction of tumor size by NACT is possible, but no suppression of tumor cell shedding. Moreover, it is unclear whether the NACT has an effect on the metastatic potential.

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Short term *vs* lifelong adjuvant tamoxifen in early breast cancer (EBC): A randomized trial (TAM-01)

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In 1986, a multicentric randomised trial was initiated to compare a lifelong adjuvant TAM to a short term adjuvant TAM. Were eligible patients with EBC receiving adjuvant TAM since 2–3 years, disease-free since primary treatment, aged 75 years or younger. From 9/1986 to 5/1995, 3793 patients were randomized; 1882 (49.6%) patients stopped TAM (control) while 1911 (50.4%) patients continued TAM (lifelong) at the same dose than previously prescribed, until recurrence or death. Data was updated 11/1996; an intent to treat analysis was performed. Main prognostic factors (age, tumor size, nodes involvement, hormonal receptors) and initial treatment were well balanced and mean TAM duration at randomisation was 28 months in each group. The mean follow up time is 54 months. Overall, 318 and 258 patients have relapsed in the control group and lifelong group, respectively, leading to a 5-year disease-free survival (DFS) rate of 76% and 82%, and a 7-year DFS rate of 71% and 77% ($p = 0.0025$). In contrast, overall survival (OS) does not differ between the two arms, with 86% and 85% 5-year OS rates, and 79% and 78% 7-year OS rates, respectively ($p = 0.49$). We conclude that although no survival advantage is noted, patients do benefit from longer TAM with significantly better DFS. Long term follow up is needed to (1) assess these results, (2) appreciate the decrease in incidence of controlateral BC, and (3) estimate the treatment-associated second cancer risk.

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The effect of oral clodronate on bone mineral density in women with primary breast cancer

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We have undertaken a double blind randomised two centre trial (RMH and TBCC) to evaluate bone mineral density (BMD) in over 300 patients with primary breast cancer given clodronate 1600 mg/day po (clod) or placebo (plac) for 2 years. Patients were accrued, randomised and received appropriate primary surgical, and medical treatment (chemotherapy and tamoxifen) and have completed follow up for at least 2 years without metastatic relapse. (RMH 103 clod, 93 plac, TBCC 53 clod, 62 plac). The median age, height, weight, menopausal status and type of primary surgical, adjuvant or neoadjuvant medical treatment were well matched for both treatment groups. BMD in the lumbar spine and hip were measured using dual energy xray absorptiometry (Hologic densitometer) at the start of clod/plac and after one and two years of treatment and calculated as % change of the initial treatment reading. The clod group had a small mean gain of 0.18% compared to the plac group which had a mean loss in spinal BMD of 2.2% (Treatment effect +2.38%, CI 1.36, 3.41 $p < 0.001$). Similarly the clod group had a mean gain of 0.40% in hip BMD compared to a mean loss of 0.34% in the clod group (Treatment effect +0.74%, CI −0.13, 1.6 p = NS). After 2 years the treatment effect for clod in spinal BMD was +1.73% (CI 0.12, 3.34 $p < 0.05$) and hip BMD +1.85% (CI 0.51, 3.20 $p < 0.01$). All subgroups of menopausal status and type of adjuvant/neoadjuvant medical treatment appeared to gain benefit. In patients who receive cancer treatment for primary breast cancer, these results indicate that use of oral clodronate will significantly reduce the loss of BMD.

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Randomized multicentric study of perioperative chemotherapy with mitoxantrone (MTZ) in early breast cancer

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Purpose: The aim of this multicentric randomized trial was to determine whether perioperative chemotherapy (POC) could change early breast cancer course.

Methods: A total of 578 women with early breast cancer (stage I to IIIA) were randomized to compare surgery followed by one course of POC (MTZ 14 mg/m^2) versus surgery alone. Premenopausal women with positive axillary nodes or negative hormonal receptors and grade 3 received adjuvant chemotherapy (fluorouracil, MTZ, cyclophosphamide) for 6 months. Menopausal women received tamoxifen.

Results: 554 patients were evaluable (192 premenopausal, 362 menopausal). Toxicity was acceptable: no infection, no cardiac event. Disease-free survival (DFS) and overall survival (OS) were not significantly prolonged in the chemotherapy arm. The interim analysis at 23 months median follow up in 1992 showed a significant benefit for the POC arm in term of metastase free survival (MFS) ($p = 0.02$, $\alpha = 0.05$). At final analysis at 7.4 years median follow up, in 1996, there was a trend towards improvement of MFS in the POC regimen ($p = 0.047$, $\alpha = 0.02$).

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Adjuvant radiotherapy in breast cancer and risk of ischaemic heart disease

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Purpose: To assess the occurrence of ischaemic heart disease (IHD) after breast cancer radiotherapy in long-term survivors.

Methods: In the years 1982 to 1989, 321 high-risk breast cancer patients from the county of Aarhus were included in the DBCG protocol 82 and randomised to post-mastectomy irradiation plus systemic treatment or systemic treatment alone. The chest wall was irradiated with 2 anterior shaped electron fields. Chest wall thickness was measured with ultrasound and electron energy chosen to include the clinical target volume in the 85% isodose. The target depth for the internal mammary nodes was chest wall thickness plus 0.5 cm and chest wall thickness minus 1 cm for the scar region. The median absorbed dose was 50 Gy in 25 fractions with 5 f/w. The median follow-up time was 8.3 years.

Ninety-five out of 122 survivors of this study group agreed to participate in a prospective study evaluating late morbidity including cardiac anamnesis, clinical examination, ECG and chest radiography. All left-sided breast cancer patients were offered a myocardial perfusion scintigraphy and 16 patients agreed. Only the result of this part of the study will be reported here. Sestamibi-SPECT scannings were performed as a rest/dipyridamole 2-day protocol. Scintigrams were blindly evaluated using a 5-point scale in a 20-segment model of the left ventricle.

Results: There was no difference between the scintigrafic findings in the two groups. Four of 9 study group patients, and 4 of 7 controls had significant defects on scintigraphy, indicating IHD. Only one patient showed an anterior defect, and this patient was a control patient. None of the patients had symptoms of IHD.

Distribution of scintigraphic defects:	Radiotherapy	Control
Reversible	2	1
Partly Reversible	1	1
Irreversible	1	2

Conclusion: Our scintigraphic data do not support any increased risk of IHD among survivors of breast cancer treated with optimal radiation technique.