

384

POSTER

99mTc-sestamibi scintigraphy in axillary lymph node metastases detection in patients with primary breast cancer undergoing curative surgery

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Background: Lymph node status is the primary prognostic discriminant in patients with breast cancer (BC). Although axillary dissection represents the methods of choice for obtaining such information, less invasive staging procedures has been suggested. Preoperative non-surgical techniques include ultrasonography, CT-scan, MRI, 18F-FDG PET, and positive radio-pharmaceutical scintigraphy. The aim of this study was to evaluate the usefulness of 99mTc-sestamibi scintigraphy (SS) in patients with confirmed primary BC undergoing surgery.

Patients and Methods: A series on 159 women (median age 54 years, range 36-78 years) with confirmed primary BC were enrolled in the study. Breast-conserving surgery or mastectomy with axillary dissection was performed in all patients, as indicated by the tumor staging. Once they had given the informed consent, each patients underwent SS. Images were acquired using a single detector gamma-camera equipped with a parallel-hole low-energy high-resolution collimator (256 x 256 matrix, 140 keV energy setting) 10 minutes after 750 MBq radiopharmaceutical I.V. administration, using single-photon emission computed tomography (SPECT) technique. A focal 99mTc-sestamibi uptake and a mass-to-background ratio of more than 1.4 was considered as a positive result in detection of axillary node metastases.

Results: Final pathology showed 33 (20.8%) pT1b, 90 (56.6%) pT1c, and 36 (22.6%) pT2 breast carcinomas. The greatest diameter of the tumor (size) ranged from 8 and 30 mm (median 16 mm). Sixty (37.7%) patients had axillary metastases at surgery (N1), while 99 (60.3%) patients had negative nodes (N0). The average of nodes removed was 19.9±2.1, and the average of positive nodes was 2.7±1.2. The age of the patients significantly correlated with both size (R=0.24, F=9.55, p=0.002) and the number of positive nodes (R=0.33, F=7.11, p=0.0009), and subsequently there was a direct relationship between number of positive nodes and size (R=0.31, F=6.08, p=0.016). Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of SS were 81.4%, 91.0%, 84.2%, 91.0%, and 87.4%, respectively. The sensitivity was higher in patients with 3 or more positive nodes (N=27/28, 96.4%), while patients with 2 (N=25) and 1 (N=7) positive nodes the sensitivity was 80.0% and 28.6%, respectively.

Conclusions: 99mTc-sestamibi scintigraphy may be useful in patients undergoing surgery for breast cancer, although its sensitivity is low when the number of involved nodes is two or less. This suggests that others imaging techniques should be used in conjunction with SS when a preoperative assessment of axillary lymph node status is required.

385

POSTER

Role of HER2 in wound-induced breast carcinoma proliferation

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Background: Clinical and experimental data raised the possibility that surgical removal of the primary tumor promotes the growth of metastatic lesions. The aim of the present study was to analyze the impact of surgery on proliferation of breast carcinomas, in particular those overexpressing HER2.

Methods: Proliferation of breast carcinoma cells was evaluated on histological sections of primary breast carcinomas and in *residu* al tumor found in re-excision specimens, by MIB-1 immunohistochemistry and on *in vitro* cell lines by a colorimetric assay. EGF-like growth factors were measured by displacement of ¹²⁵I-EGF from its receptor. Cellular damage was measured by creatine phosphokinase level. Down-modulation of HER2 was performed by cytoplasmic expression of anti-HER2 antibody and by inhibition with anti-HER2 antibody trastuzumab.

Results: *Residu* al breast carcinomas surgically-removed within 48 days from a first surgery were found to display a significant increase in proliferation if they were HER2-positive. Accordingly, wound drainages and

post-surgical sera from breast carcinoma patients were found to stimulate the *in vitro* growth of HER2-overexpressing breast carcinoma cells. Removal of the HER2 oncoprotein from the cell membrane led to a dramatic decrease in the *in du* ced proliferation. The level of EGF-like growth factors in post-surgical sera, as well as the level of drainage-*in du* ced proliferation, was directly correlated to the amount of surgical damage evaluated by cpk levels (r=0.77, p=0.002 and r=0.69, p=0.009, respectively). Treatment of HER2-positive tumor cells with trastuzumab, if given before the growth stimulus, abolished drainage-*in du* ced proliferation.

Conclusions: HER2 overexpression by breast carcinoma cells plays a major role in the post-surgery stimulation of growth of breast carcinoma cells. Partially supported by AIRC.

386

POSTER

High-dose chemotherapy with stem cell support in high-risk primary breast cancer. An analysis of the effect on overall survival the Danish experience from a comparison study

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Background: To analyse retrospectively the effect of high-dose chemotherapy with stem cell support in patients with high-risk primary breast cancer. The effect on overall survival was compared to a control group of patients from the same study period having received conventional therapies.

Material and methods: One hundred and thirty-two patients younger than 55 years and with more than 6 positive axillary lymph nodes and without any signs of metastatic disease received after curative surgery three cycles of inductive chemotherapy by cyclophosphamide, epirubicin and 5-fluorouracil (FEC) in standard-dose. After harvest of peripheral blood stem cells one cycle of high-dose chemotherapy (HDC) including cyclophosphamide, tiotepa and carboplatin (CTCb) was administered. All patients received loco-regional radiotherapy and tamoxifen was administered to patients with estrogen receptor positive tumors. A comparative group of 775 patients with the same prognostic characteristics was identified in the national database and included in the analysis as the control group.

Results: The statistical analysis of the patient materials identified a series of well-known prognostic factors nearly equally distributed in the two treatment groups, only age and number of positive nodes showed some bias. Estrogen receptor (ER) appeared also to be a strong prognostic and predictive variable and should therefore be included in the analysis. The effect of HDC on overall survival is of the same size in patients with ER+ and ER- tumors. The improvement of overall survival by HDC compared to the control group is significant (p=0.045) with a relative risk of death of 0.72 (CI: 0.52-0.9).

A total of 122 patients received FEC as adjuvant therapy. The overall survival of this sub-group compared to the group of 132 having received HDC is slightly inferior but not to a statistical significant level. Two cases of toxic deaths (1.5%) was registered.

Conclusion: We conclude that our analysis of the effect of HDC in relation to the selected comparison group is valid. The effect of HDC on overall survival is significant in comparison to all patients in the control group also when compared to the subgroups with known ER status. However the overall survival of the HDC-group is not significantly superior compared to patients having received FEC as adjuvant therapy. This high-dose regimen is feasible and well tolerated.

387

POSTER

Added value of blue dye in sentinel node biopsy for breast cancer

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Sentinel node biopsy in breast cancer is a new rapidly advancing minimally invasive procedure which enables nodal staging of clinically node negative breast cancer patients without performing complete axillary dissection. There are still controversies over the added value of Blue Dye when lym-

phoscintigraphy and gamma probe is used. In our series 91 consecutive patients with invasive breast carcinoma were operated by a single surgeon, using lymphoscintigraphy, gamma probe and Blue Dye. The sentinel nodes (SLN) were histologically examined by HE and immunohistochemistry.

Lymphoscintigraphy was successful in 81 patients (89%). After the injection of Blue Dye, SLN could be identified in all 91 patients. Metastases in the SLN were present in 35 patients. We retrieved 128 SLN, of these were 93 hot and blue, 19 only hot and 16 only blue. The distribution of metastatic and nonmetastatic SLN between these three labelling groups was not different ($P=0.9361$). We could not show any difference in the metastatic involvement of SLN in the patients in whom preoperative lymphoscintigraphy could visualise the SLN preoperatively compared to those in whom it could not ($P=0.7315$). False negativity calculated in our initial series of 36 patients was 0%.

Our study showed added value of Blue Dye in detection of metastatic and nonmetastatic SLN.

388

POSTER

The evaluation of early regional recurrence using clinical examination and ultrasonography of the axilla after omitting axillary clearance in patients with tumour negative sentinel nodes

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Background: According to the previous reports, axillary recurrence rate has been practically zero after omitting axillary clearance in breast cancer patients with tumour negative sentinel nodes. However, the findings have been based mainly on the clinical examination of the axilla and the low axillary recurrence rate may thus be an underestimation. We aimed to evaluate the regional recurrence rate one year after the operation by clinical examination and ultrasonography of the axilla. The other purpose was to evaluate the rate of false positive findings in the ultrasonography of the axilla.

Methods: Altogether 189 breast cancer patients, who underwent sentinel node biopsy without axillary clearance between 06.06.2000- 28.12.2001, were enrolled in a prospective study. Clinical examination, mammography as well as ultrasonography of the breast and the axilla were performed one year after the operation. One patient had deceased due to non-breast cancer related cause. Three patients (2%) did not show up for the follow up appointment.

Results: One patient underwent mammography and ultrasonography but did not attend the clinical examination and 15 patients (8%) underwent clinical examination and mammography but not ultrasonography. No findings suspicious for local or regional recurrences were detected in these 16 patients.

The remaining 165 (87%) patients underwent mammography, clinical and ultrasound examination without findings of regional recurrence. However, two patients (1%) had enlarged but not clearly suspicious lymph nodes in the ultrasonography of the axilla and a fine needle aspiration cytology was performed. The cytological finding was benign in both cases. A control ultrasound without abnormal findings was performed after three or six months in these patients.

Conclusions: The risk for early regional recurrence when omitting axillary clearance in patients with tumour negative sentinel nodes seems low when evaluated by clinical examination and ultrasonography. Additionally, the ultrasonography of the axilla may be useful in the follow-up of these patients with a negligible false positive rate.

389

POSTER

Shift in pattern of care for breast cancer by sentinel node biopsy

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Background: Many studies describe the advances of the sentinel node (SN) biopsy. This less mutilating technique causes less morbidity resulting in faster recovery. Still, there are some adverse effects of the SN procedure, including the chance of more operations possibly resulting in longer overall hospital stay and higher costs. In our clinic we started using the SN technique as operation of choice since January 2001. We investigated the impact on number and kind of operations, days in hospital and overall costs.

Patients and methods: All patients treated operatively for primary breast cancer in our clinic in 2000 ($n=106$) and 2001 ($n=134$) were included. All

patients in 2000 underwent axillary lymph node dissection (ALND), and all patients in 2001 suited for this technique underwent SN biopsy. We perform SN biopsy using a preoperative lymphoscintigram in combination with peroperative use of Patent Blue V and the gamma probe.

Results: There were no significant differences between the patients in both groups. In 2000 all patients underwent ALND, whereas in 2001 patients underwent SN biopsy when suitable (83%). Reasons not to perform a SN procedure were tumour size or palpable lymph nodes. SN biopsy was successful in 94% and revealed metastasis in 34 cases (33%). In 15 patients (44% of positive SNs) this was the only site of metastasis. 70 patients (67%) had a negative SN and needed no further operative treatment. But, because of the SN procedure, patients were operated more often in 2001 than in 2000: In 2001 47% had two operations and 9% had three operations, compared to 2000 when 32% had two operations and 2% had three operations. Note that 25 patients (24%) in 2000 and 45 patients (33%) in 2001 had a first operation for diagnosing malignancy, without SN or ALND procedure. In 2001 more operations were performed in an out-patient setting (24% vs 15%, $p=0.011$), and overall hospital stay was significantly shorter than in 2000 (5.7 days vs 6.7 days, $p=0.045$). As well, overall costs per patient were lower in 2001 (* 3.325 vs * 3.896, $p=0.046$).

Conclusions: Since the introduction of the SN biopsy: 1) ALND can be avoided in 67% of patients suited for this technique. 2) Patients undergo significantly more operations, but overall hospital stay is significantly shorter, with significantly reduced costs.

390

POSTER

Breast cancer in the elderly: a 20 years audit

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Breast cancer is a disease that affects women > 70 years of age much more frequently than other age groups. Epidemiological data show that more than 40% of breast cancers occur in the elderly.

We analyzed a database of 1950 breast cancer cases treated in UCHG, between 1982 and 2002. This yielded 384 cases (20%) of >70 with breast cancer. We achieved complete data only on 279 patients. The median age was 77 years (range 70-93). The most common type of tumour was ductal carcinoma (74.5%) and 51.5% were high grade tumours. The average pathological diameter was 30mm (range 5-90). Surgical management consisted of mastectomy in 87% and wide excision in 12% depending on histological features, size and co-morbidity. Axillary surgery done on 63.5% of cases where clinically indicated and 58% of them showed pathologically positive nodes. 45% of cases were stage II at diagnosis. 71.8% of tumours were oestrogen receptors positive.

From our data 9% of these women received adjuvant radiotherapy and non received adjuvant chemotherapy. Overall, locoregional recurrences developed in 7% and there was no association between type of surgery and the risk of recurrence. Distance metastasis observed in 0.4% of cases and all when more than 3 nodes involved. We reported 6% incidence of bilateral breast cancer.

The disease-free and overall survival mean was 32, 37 months respectively for all women over 70 years.

The optimal treatment for older women is definitive surgery to guarantee local control and thus improve the quality of life.

391

POSTER

Basal and retinoic acid-stimulated sodium-iodide symporter expression in breast cancer

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Tissue-specific sodium-iodide symporter (NIS) gene expression may allow for a new approach in anti-cancer therapy. In thyroid cancer NIS expression is retained, like in normal thyroid – this makes the tissue concentrating iodides and enables efficient therapy of thyroid malignancy with radioactive ¹³¹-iodine. In some cases of thyroid cancer radioiodine uptake may be enhanced by re-differentiation therapy with retinoic acid. As suggested previously, NIS protein is present in some cases of breast cancer, but it is still not clear, what is the basal level of gene expression and if it could be stimulated to amount sufficient for therapy.

The aim of the study was to analyze the basal NIS expression in primary cultures of breast cancer cells and to stimulate it by *all-trans* retinoic acid