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POSTER

Isolated tumor cells in the bone marrow (ITC-BM) of breast cancer patients before and after anthracyclin based therapy - Influenced by the HER2neu- and Topoisomerase IIa-expression/amplification of the primary tumor?

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Background: The immunocytochemical detection of ITC-BM of breast cancer patients is an independent prognostic factor in all stages of the disease. Both the expression / amplification of HER2neu and Topoisomerase IIa (TOP IIa), a key enzyme of DNA replication and main target of anthracyclines, in primary breast cancer tissue seem to have predictive value regarding the effectiveness of systemic therapies, what might possibly be expressed by a change of ITC-BM.

Methods: Tumor tissues of 52 pts that were screened for ITC-BM before and after anthracyclin based therapy (CTX) were examined for HER2neu and TOP IIa by IHC and FISH (TOP2A/HER2/CEP17 Multi-color Probe, Vysis). The correlation of these factors and their influence on clinical outcome was analysed retrospectively. Results: By IHC 30% of the tumors showed positive for HER2 (2+/3+), 23% were amplified in FISH analysis (HER2/CEP17 ≥ 2). TOP IIa overexpression ($>20\%$) was found in 23/48 pts (48%), FISH analysis was pos. in 6/42 pts (14.3%), with co-amplification of HER2 and TOP IIa in 75%. ITC-BM were present in 25% of pts before and 30% after CTX. The detection of ITC-BM before CTX correlated with HER2 (IHC and FISH), but not with TOP IIa. 43 pts had adjuvant, 6 neoadj., 3 palliat. CTX, regimens consisting of EC (6 pts), EC/CMF (18 pts), EC/Docetaxel (26 pts) and others (5 pts). 31 pts (53%) stayed neg for ITC-BM during CTX, 8 (16%) changed from neg to pos, 5 (10%) from pos to neg, and 8 (16%) stayed pos., which either was independent of the HER2- or TOP IIa status. After a median of 46 months (6-127) HER2-IHC ($p=0.005$), TOP IIa-IHC ($p=0.049$) and the detection of ITC-BM after completion of CTX ($p=0.047$) were sign. prognostic factors for overall survival (log-rank-test), whereas TOP IIa (FISH) neg. pts showed a slight but not significant trend ($p=0.09$) towards reduced distant disease free survival.

Conclusion: As shown previously, antiproliferative CTX has no or little effect on the elimination of ITC-BM. This seems to be independent of the HER2 or TOP IIa status of the primary tumor. Nevertheless, the detection of ITC-BM after CTX has, like the HER2 status, prognostic relevance for overall survival. For the development of new therapeutic strategies, it would be desirable to examine such factors on ITC directly.

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Long term results after conservative treatment for invasive breast carcinoma: A 20 year follow-up

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Background: Patients (pts) with invasive breast cancer treated by conservative treatment must be followed for a long time to ensure the efficacy of the procedure in terms of locoregional control. This study was performed to analyze the outcome of a large series of patients submitted to conservative surgery and definitive irradiation, and to evaluate the relationship between locoregional recurrence (LRR), distant metastases (DM) and survival.

Methods: From 1983 to 1998, 547 pts with early breast cancer stage I and II, underwent breast conservative treatment (BCT). Pts with axillary positive nodes received adjuvant chemotherapy, and pts with positive hormonal receptors received hormonotherapy. The following prognostic factors were analyzed for their ability to predict for a distant recurrence: pt age, menopausal status, tumor size, axillary lymph node status, histological grade, experience of LRR and interval from diagnosis to LRR. The outcome of pts after LRR (early ≤ 24 months or late >24 months) was documented and factors associated with a favorable survival following recurrence are identified.

Results: With a median f-up time of 78 (3-238) months, 25 pts experienced a LRR as their first site of recurrence and in 58 pts isolated DM were observed. The 20 years overall and cause-specific survival was $51.0\% \pm 17.7$ and $84.3\% \pm 4.6$ respectively. The 20 years cumulative incidence of LRR was $19\% \pm 12.5$ and the annual cumulative incidence of LRR within the first two years was 0.80% and between the 3th and 10th years was 0.48%. Between the 11th and 15th no LRR was observed and one pt experienced a LRR in a different quadrant from the primary tumor 16 years after the diagnosis. The cumulative incidence of DM at 20 years was 17.7 ± 2.6 and the annual cumulative incidence of DM within the first two years was 2.2% and between the 3th and 10th years was 1.3%. From the 12 th year until the end of the study none of the pts present in the study experienced a DM. The 15 years overall survival rate of pts who experienced LRR differed significantly from those pts who never experienced LRR, $72.5\% \pm 6.3$ vs $53.9\% \pm 11.7$ respectively ($p=0.005$; RR of death: 2.6; 95% CI: 1.3-5.0). The actuarial distant disease free survival (DDFS) of pts who never experienced LRR was significantly higher ($86.9\% \pm 1.9$) compared to the actuarial DDFS of pts who experienced LRR ($62.8\% \pm 9.8$) ($p<0.0006$; RR of DM: 3.2; 95% CI: 1.5-6.4). The 10 years DM probability in pts who developed an early LRR was $60\% \pm 17.3$ and $25\% \pm 10.8$ in pts who developed a late LRR (RR: 4; $p=0.041$; 95% CI: 1.05-15.2). The median f-up time for survivor pts after LRR was 44 months.

Conclusions: Long term survival rate was observed among pts who underwent BCT. LRR appears to be a significant predictor of DM and pts who sustain early LRR tend to display a more aggressive clinical course

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Interobserver variability of target volume delineation of breast tissue as well as of boost volume in 19 breast cancer patients after lumpectomy and axillary staging

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Purpose: To determine the interobserver variation in delineating the clinical target volume (CTV) of breast tissues as well as of corresponding boost volumes on computed tomography (CT) scans in breast cancer patients treated with breast conserving therapy (BCT).

Material and Methods: Nineteen consecutive breast cancer patients (mean age 53 yrs; 16 T1, 3T2) treated with breast conserving therapy agreed to participate in our study. Palpable glandular breast tissue was marked with a lead wire before CT scanning. Four radiation oncologists and 1 radiologist delineated CTV's. Indices of the corresponding CTV of all 19 patients were compared with one another specifically with respect to the delineation of breast tissue: BRI and to that of the boost volume: BOI. An index of 1.0 implicates that the location as well as the size of the CTV's is exactly the same. We then analyzed where in the breast tissue the magnitude of the observed differences was high or low (medial, lateral, cranial, caudal, outer, inner). With respect to the latter the following variables were also analyzed: i) the volume of the breast tissue; ii) the presence or absence of dense breast tissue; and specifically with respect to the boost: iii) the presence or absence of clips.

Results: The range of the BRI varied between 0.83 and 0.88. Observed differences were between the 5 physicians were largest in the upper-outer quadrant of the breast. The BOI varied between 0.45 and 0.60. Differences were less outspoken in the presence of clips.

Conclusions: Interobserver variation in the delineation of breast target volume on CT scans can be substantial (pending on the presence or absence of dense breast tissue). The differences are large in delineating the CTV of the boost volume. To reduce the interobserver variation, better imaging (including markers) and pathology studies relating glandular breast tissue to imaging may be needed in order to better visualize the true extent of the breast tissue (especially in postmenopausal patients) and the boost volume (especially in the absence of clips).

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Intramammary tumor location (ITL) does not influence prognosis, but the prevalence of axillary lymph node metastases

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The prognostic role of the ITL is discussed controversially (Lohrisch et al.,

JCO 2000;18:2828), and may significantly influence systemic treatment. The objective of this study was to analyze the impact of ITL on axillary lymph node involvement, relapse, and mortality risk, in patients both with and without systemic and loco-regional treatment.

Retrospective analysis was conducted of 2,414 patients, who underwent R0 resection of the primary tumor and systematic axillary lymph node dissection (at least 5 lymph nodes resected) for UICC I-III stage breast cancer. Patients with unknown ITL, multifocal tumor spread, central ITL, or tumor location within 15° of the border between outer and inner quadrants were excluded from the study. Median observation time was 6.7 years.

The ITL was within or between the medial quadrants of the breast in 33.6% of the patients (n=810) and in the lateral hemisphere of the breast in 66.4% (n=1,604). Tumor size, histopathological grading, and estrogen receptor status were balanced between patients with lateral and medial ITL. Metastatic axillary lymph node involvement was significantly associated with a lateral tumor location ($P < .0001$). The mean number of axillary lymph node metastases was increased by 29% in cases with lateral ITL (2.2 vs. 1.7, $P = .003$). In a multivariate logistic regression analysis, allowing for ITL, estrogen receptor status, grading and tumor size, ITL was confirmed as significant risk factor ($P = .02$) for axillary lymph node involvement. ITL, however, did not correlate with either disease free survival (DFS) or overall survival (OS), by univariate (DFS: $P = .41$; OS: $P = .57$) or by multivariate analysis (DFS: $P = .16$; OS: $P = .98$).

In contrast to previous reports, we conclude that there is no sufficient evidence to support any independent prognostic significance of ITL in early breast cancer. However, medial tumor location may lead to underestimation of the axillary lymph node involvement, and, thus, inadequate systemic treatment.

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Potential of radiation-induced subcutaneous fibrosis by concomitant use of tamoxifen in adjuvant breast cancer treatment

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In this study, we wanted to assess whether concomitant administration of tamoxifen (TMX) and adjuvant radiation therapy (RT) increases the risk of developing subcutaneous fibrosis after conservative or radical surgery in breast cancer patients. Therefore, we evaluated 149 women with breast cancer treated using adjuvant RT after conservative or radical surgery who took part among 399 patients with miscellaneous cancers included in the KFS 00539-9-1997/SKL 00778-2-1999 prospective study evaluating the predictive value of CD4 and CD8 T-lymphocyte apoptosis on the development of radiation-induced late effects. Median age was 57 years (range: 26-82). RT consisted of 50-Gy whole-breast or thoracic wall irradiation in 2-Gy fractions using either Co60 (n = 97) or 6-MV (n = 52) photons completed with a localized external electron boost up to 66 Gy. Adjuvant TMX concomitant with RT was prescribed at a dose of 20 mg/day for a period of five years in 91 patients (61%). All patients receiving TMX were hormonal receptor positive, and none of them received adjuvant chemotherapy. There were 20 premenopausal and 71 postmenopausal patients (median age: 60 years; range: 36-82). Acute and late toxicities were assessed according to CTC 2.0 and RTOG/EORTC grading systems, respectively. Breast volume and skin dose was estimated using physical RT parameters. In a median follow-up of 29 months (range: 23-73), 144 patients are alive with (n = 5) or without disease. Five patients died from breast cancer without any grade 3 side effects (1, 13, 33, 38, and 41 months). Acute toxicity was observed in all but 4 patients (3%). One hundred six (71%), 34 (23%), and 5 (3%) patients experienced grade 1, 2, and 3 acute side effects, respectively. No statistically significant difference was observed between the TMX and no TMX groups in terms of acute toxicity ($p = 0.58$). There was no significant correlation between the early and late toxicity ($R^2 = 0.05$). Thirty-five patients out of 91 (38%) in the TMX group and 15 out of 58 (26%) in the no TMX group experienced grade 2 or 3 late skin toxicity ($p = 0.11$). However, grade 2 or 3 subcutaneous fibrosis was significantly higher in patients treated with concomitant TMX (42 patients out of 91 (46%) in the TMX group vs. 10 out of 58 (17%) in the no TMX group; $p = 0.0002$). Breast volume and skin dose did not interfere with subcutaneous fibrosis. However, grade 3 telangiectasia incidence was more frequent but not statistically significant in patients with high breast volume irradiated with Co60 compared to 6-MV photons. We conclude that the concomitant use of TMX with RT increases significantly subcutaneous fibrosis. In patients treated with adjuvant hormonal treatment, TMX should be delayed until the completion of RT.

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The predictive value of specimen radiography to predict margins involvement in 188 breast intraclinical carcinomas.

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Background: This study was undertaken to evaluate the role of specimen radiography in predicting margins status for breast palpable lesions.

Material and methods: We retrospectively reviewed clinical, pathologic data and specimens radiography from 188 patients with DCIS referred in our centre between 1997 and 2000 for microcalcifications discovered at breast screening. The lesions were preoperatively localised by using a guide-wire. Specimen radiographic findings and clinico-pathological data were correlated with margin status.

Results: A total of 188 lesions revealed pure ductal carcinoma in situ (DCIS) in 125 (66%) and mixed carcinoma in 63 (34%). On specimen radiographs, the lesions were closed (<5mm) to one edge of lumpectomy in 74 (39%) cases. Histologic margins were positive in 86 cases (46%) and close (< 5 mm) in 51 (27%) cases. The factors associated with positive margins, in the univariate analysis, were a distance less than 5 mm from the tumour to the edge of the specimen radiograph ($p = 0.04$) and multifocality ($p = 0.05$). In the multivariate analysis (logistic regression), a radiologic margin <5mm was the only risk factor for close histologic margins. We therefore tested radiologic margin <5 mm as a potential tool to decrease the risk of close histological margins. Sensitivity, specificity, predictive positive and negative values are reported in Table 1.

Efficacy of specimen radiographs for detecting residual tumors

| | Pathologic findings | |
|---------------------|---------------------|-------------------|
| | Margins <5mm | Free margins >5mm |
| Incomplete excision | 82 (43.6%) | 6 (3.2%) |
| Complete excision | 60 (32%) | 40 (21.2%) |
| Se = 58% Sp = 87% | VPP = 93% | VPN = 40% |

Conclusions: Specimen radiograph findings were found to be a predictive factors of margins involvement when tumor distance to the margin was less than 5 mm and may therefore lead the surgeon to perform an additional excision.

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Breast cancer: immediate breast reconstruction after radical surgery

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Background: We reviewed the results of 11 years' experience with different techniques for immediate reconstruction in breast cancer patients.

Materials and methods: Between 1991 and 2002 a total of 611 breast cancer patients were operated. All patients were divided into 4 groups according to the type of breast reconstruction technique. Group I included 154 patients (stage IIa, IIb) who underwent quadrantectomy and regional lymph node dissection with immediate breast reconstruction using major pectoral (32) and latissimus dorsi (LD) (122) flaps. Group II - 386 women (stage IIa, IIb, IIIa) who underwent breast resection (70-90% of breast tissue and regional lymph nodes were removed). Breast was reconstructed using LD flaps. Group III - 46 patients (stage IIa, IIb, IIIa) who underwent modified radical mastectomy. Breast was reconstructed using LD (18) and pedicled TRAM (28) flaps. Group IV - 25 women (stage I, IIa, IIb, IIIa) who underwent skin/areola sparing mastectomy. In all cases breast was reconstructed using LD flap and silicone breast implant. Radiotherapy and drug therapy were administered depending on the stage of disease, receptor status, etc.

Results: In group I 5-year overall survival rate was 92.4% and 87.5% for stages IIa and IIb respectively. Local recurrence rate was 0% and 4.6%. Esthetic results: excellent - 21.6%, good - 49%, satisfactory - 26%, poor - 2%. In group II 5-year overall survival rates were as follows: IIa - 88.3%, IIb - 84.3%, IIIa - 72.4%. Esthetic results: excellent - 21.6%, good - 48%, satisfactory - 28.4%, poor - 2%. The rate of immediate postoperative complications was 7.3% (28 patients): total necrosis of the flap - 3, marginal necrosis - 2, wound suppuration - 2, bleeding - 3. In group III 5-year overall survival rates were as follows: IIa - 87.9%, IIb - 83.3%, IIIa - 73.6%. Local recurrence rate was 1.9%. Esthetic results: excellent - 21.7%, good - 49.6%, satisfactory - 28.4%, poor - 1%. The rate of immediate