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The hTERT blood plasma level is affected by the surgical removal of the tumor in early breast cancer patients

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Introduction: Breast cancer is a heterogeneous disease with different clinical courses. In order to better determine the prognosis and response to the therapy of breast cancer patients several different prognostic and predictive factors are in use today, but they all have limitations. One of potential new prognostic and/or predictive factors is the enzyme telomerase. The activation of the enzyme telomerase seems to be a crucial step in breast cancer progression. The telomerase consists of two functional components: the catalytic subunit of human telomerase reverse transcriptase (hTERT) and telomerase RNA template. The hTERT is multiplied in tumor samples of most human cancers. Furthermore, we were able to detect the hTERT in blood plasma of breast cancer patients.
Aim: The aim of our study was to determine, whether the presence of the hTERT in blood plasma of early breast cancer patients is affected by the surgical removal of the tumour.
Patients and Methods: Two blood samples were collected from all 93 patients. The first blood sample was collected prior the surgery on the day of operation and the second blood sample was collected one day after the surgery. The presence of the hTERT in the blood plasma was measured before and after the surgery in every patient. From all blood samples the hTERT mRNA was isolated, then the reverse transcription to cDNA was performed which was amplified by semi-nested PCR. The PCR products were separated by polyacrylamid gel electrophoresis.
Results: Before surgery hTERT mRNA was detected in 44/93 (47%) patients. After the surgery hTERT mRNA was detected in 26/44 (59%) patients and not detected in 18/44 (41%) patients. Additionally, after the surgery the hTERT was detected in 16/49 (33%) patients that were negative for the presence of the hTERT before surgery.
Conclusion: The presence of the hTERT in the blood plasma of early breast cancer patients is affected by the surgical removal of the tumor. The clinical significance of our findings is not yet known.

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An open-label study of neoadjuvant capecitabine (C) and docetaxel (D) with/without trastuzumab (T) to determine the role of p53 mutations in clinical and pathological responses in patients with recently diagnosed breast cancer (BC)

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Background: Cellular proliferation, survival, and genomic integrity are controlled by various processes, one of which involves the tumor suppressor gene p53. Disruption of the function of p53 leads to uncontrolled proliferation of damaged cells as a consequence of checkpoint defects, genomic instability, and inappropriate survival. Because of its relationship to patient outcome and survival, p53 mutation status is a potential prognostic indicator. However, immunohistochemical analysis cannot accurately identify p53 mutation status and cannot differentiate between the several functional defects that arise from mutations at specific sites of this multifunctional gene.
Materials and Methods: The primary objective was to define the rate of pathological complete response (pCR) plus near pCR in the affected breast after 4 cycles of neoadjuvant treatment with C+D±T in patients with HER2-neu negative (HER2−) or HER2-neu positive (HER2+) BC, respectively. Eligible patients had infiltrating HER2− or HER2+ stage II/III BC with no evidence of metastases and no prior systemic or local primary treatment. HER2+ patients also received weekly T. The study enrolled 140 (109 HER2−, 31 HER2+) patients. Prior to systemic therapy, breast tumor biopsy yielding 50–100 ng of genomic DNA was done. To analyze the p53 mutation status, the AmpliChip p53 test (Roche Diagnostics, in development), a DNA microarray-based sequencing method, was used. The AmpliChip p53 test is designed to detect all substitution single base changes and single base deletions in all coding regions of the p53 gene.
Results: A biopsy sample was obtained from 88 patients. A total of 47 p53 mutations were found in 44 (50%) patients. The mutations included 32 missense, 6 frameshift, 8 non-sense, and 1 splice site mutation. The mutations were widely distributed in exon 2, 4, 5, 6, 7, 8, 9, and 10. The p53 mutation status including the type and location will be analyzed in relation to the clinical and pathological responses. Updated data including clinical and pathological outcomes will be presented.
Conclusions: The AmpliChip p53 test is a rapid and standardized method to detect p53 mutations. The findings suggest that p53 mutations occur in at least 50% of patients with recently diagnosed infiltrating HER2− and HER2+ BC and are distributed in different functional domains of p53.

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Wide local excision with resection of cavity margins – Is it overkill or astuteness?

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Introduction: Residual disease at excision margins after breast conservation surgery influences local recurrence and therefore necessitates further surgical intervention. Although primary resection of cavity margins ensures completeness of tumour excision, it is associated with greater disfigurement. This study aims to evaluate the re-operation rate for margin positivity after wide local excision (WLE) with and without cavity margin resection.
Methods: Data were collected retrospectively from 01/06/01 to 31/04/06 on all patients undergoing WLE with or without cavity margin resection under the care of 2 consultant surgeons; one routinely performed cavity margin resection while the other did not. WLE was by mammographic needle localisation with post-excision mammographic confirmation of complete excision of specimen. Histological results were obtained for all patients and details on re-operations obtained.
Results: 598 patients (mean age-56 years; range 22−91) underwent WLE+/− axillary node sampling. Of these 68 patients had benign disease. 281/530 underwent WLE + cavity margins resection and 39 required a re-operation. 37/39 had only 1 re-operation while the remaining 2 had 2 re-operations. 13/39 had re-excision of cavity margins of which 10 had no residual disease. One patient had a mastectomy for a recurrence, one had a prophylactic mastectomy and 6 had axillary node sampling. 249/530 patients underwent WLE without cavity margin excision. 64/249 underwent re-operation of which 58 had 1 re-operation and 6 had 2 re-operations. 38/64 had re-excision of cavity margins of which 27 had no residual disease. Three had a mastectomy for tumour recurrence and 4 had axillary node sampling. The difference in the re-operation rate is significant with a chi-square of 7.923 using the Pearson's test with a p value of <0.01.
Conclusions: WLE combined with cavity margins resection is associated with a significantly lower rate of re-operation. Younger patients, axillary node positivity, tumour grade and multi-focal tumours are more likely to have margin involvement and therefore subsequent re-operation. Pre-operative anticipation of these factors combined with mammographic confirmation of completeness of excision should help the surgeon make an intra-operative decision for or against cavity margins resection. This can avoid undue removal of excessive normal tissue and subsequent disfigurement.

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Comparison of the cost-effectiveness of upfront letrozole or anastrozole, or switched exemestane versus tamoxifen for early breast cancer in hormone receptor positive (HR+) postmenopausal women: the UK perspective

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Background: Three randomized controlled trials have demonstrated that, in postmenopausal women with hormone receptor-positive (HR+) early breast cancer, upfront adjuvant therapy for 5 years with aromatase inhibitors (AIs) (BIG 1−98: letrozole [LET]; ATAC: anastrozole [ANA]) or switching to an AI after 2−3 years tamoxifen (TAM) (IES: 2−3 years exemestane [EXE]) is superior to 5 years TAM. This analysis evaluates the cost-effectiveness from a UK NHS perspective of 5 years LET, 5 years ANA, or 3 years EXE (after 2 years TAM) versus 5 years TAM using the same health economic model so that the cost-effectiveness of the three AIs can be compared
Methods: A Markov model was used to estimate the incremental cost per quality-adjusted life year (QALY) gained with the 4 therapy options in postmenopausal women with HR+ early-stage breast cancer. Probabilities of breast cancer events (contralateral; locoregional; soft tissue, bone, and visceral metastases) and adverse events (endometrial cancer, hip and other fractures, cardiovascular disease, thromboembolic events, and arthralgia) were based on the latest early breast cancer (Lancet) overview; published results of the BIG 1−98, ATAC, and IES trials; and UK population-based studies as appropriate. Conservatively, no carryover effect has been

assumed for treatment with an AI after therapy discontinuation. Costs (2005 UK£) of breast cancer care were obtained from a primary costing study in Scotland; treatment costs for adverse events and health-state utilities (QALY weights) were obtained from published studies. Costs and QALYs were estimated over the remaining lifetime of a cohort of HR+ women aged 61 years, discounted at 3.5% annually.
Results: The incremental cost per QALY gained of LET vs TAM is £10,379 (95% CI £6,654−24,369), of ANA vs TAM is £11,428 (95% CI £6,131−53,125), and of sequential TAM and EXE vs TAM alone is £11,020 (95% CI £6,292−53,305).
Conclusion: Compared with 5 years of TAM, adjuvant treatment of postmenopausal HR+ women with LET or ANA for 5 years, or 2 years TAM followed by EXE for 3 years, is a cost-effective use of UK NHS resources. The mean results indicate that up-front use of LET is a more cost-effective use of NHS resources than ANA upfront or switching to EXE after 2−3 years of TAM, though the confidence intervals overlap.

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Breast conservation treatment with vs. without axillary lymph node dissection for clinical T1/2N0M0 breast cancer

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Background: The number of pathological axillary lymph node (ALN) metastases dissected during surgery is the most reliable prognostic factor and key indicator in determining post-surgical treatment. For these reasons, axillary lymph node dissection (ALND) has become popular in breast cancer treatment; however, ALND is associated with complications such as seroma, elevation disturbance, paresthesia, and edema of the upper arm. The aim of the present study is to examine the effectiveness of breast conservation treatment (BCT) without ALND for clinical T1/T2N0M0 breast cancer.
Materials and Methods: We enrolled 195 breast cancer patients clinically diagnosed as T1/T2N0M0 between July 1989 and March 2002 (age range, 21–84 years; median, 49 years). The follow-up phase ranged from 1 year 6 months to 17 years 5 months (median, 10 years 4 months). We provided BCT without ALND for 105 patients who agreed to receive this treatment and BCT with ALND for the others. The criteria for negative ALN metastasis was minor axis of the lymph node less than 5 mm on CT images and fat tissue in the hilum of the ALN that did not disappear on ultrasound images. In cases where hormone receptor expression was positive or unknown, nonsteroidal antiestrogen was administered for 5 years. In cases of T1c or T2 under 70 years old, neoadjuvant and/or adjuvant CAF therapy (C: cyclophosphamide, A: pirarubicin, F: 5-fluorouracil) was administered. After surgery, patients without ALND received tangential irradiation to both the breast and axillary regions, while patients with ALND received irradiation only to the breast region.
Results: Among 90 patients who underwent surgery with ALND, 78 patients had pathologically negative ALN metastasis (true-negative rate, 86.7%); none of these patients had more than four ALNS metastases. Five- and 10-year cause-specific survival was 100% and 98.8%, respectively, for BCT without ALND, and 100% and 98.7%, respectively, for BCT with ALND; there was no significant difference between the two groups. Five- and 10-year disease-free survival was 97.9% and 93.8%, respectively, for BCT without ALND, and 98.8% and 94.8%, respectively, for BCT with ALND; there was no significant difference between the two groups.
Conclusions: These results indicate that ALND is omissible in the case of BCT for clinical T1/T2N0M0 breast cancer treated by a combination of hormone therapy, neoadjuvant/adjuvant ACF therapy, and tangential irradiation to both the breast and axilla.

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Sequential taxane- and anthracycline-containing neoadjuvant regimens: the sequential order impact

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Background: Since NSABPB27 trial, one can consider as standard neoadjuvant treatment the sequence of 4 cycles of anthracycline based chemotherapy followed by 4 cycles of docetaxel. Based on the belief that the sequence order between anthracycline and taxane might be of interest. Oncologists started with taxane containing sequence when others began with anthracycline containing sequence. The present retrospective study assessed the impact of the sequence order.
Methods: One hundred and six patients with breast cancer were treated by neoadjuvant chemotherapy in 2 Spanish and 3 French oncologic centers between January 01, 2003 and August 31, 2006. The neoadjuvant chemotherapy regimens included EC (100 mg/m^2 of Epirubicin + 500 mg/m^2 of cyclophosphamide), AC (60 mg/m^2 of doxorubicin + 500 mg/m^2 of cyclophosphamide) or FEC (500 mg/m^2 of 5-fluorouracil + 100 mg/m^2 of Epirubicin + 500 mg/m^2 of cyclophosphamide) and docetaxel (100 mg/m^2). This study compared 52 patients treated by 4 cycles of docetaxel followed by 4 cycles of anthracycline-based chemotherapy (cohort A) versus 54 patients treated by 4 cycles of anthracycline-based chemotherapy followed by 4 cycles of docetaxel (cohort B).
Results: Dose intensities in the two cohorts were similar and higher than 95%. No statistically significant differences were observed between cohort A and cohort B in terms of clinical complete responses (CCR), conservative surgeries, histological responses (based on Sataloff TA criteria): 63%, 62% and 29% versus 47%, 53% and 29%, respectively. Nonetheless, the toxicity profile significantly differed according to the sequence order: Severe neurotoxicity ($\geqslant$grade 2) was higher in patients treated in cohort A (13% versus 2%; $p = 0.03$), but all patients recovered within 3 months. Anemias ($\geqslant$ grade 1) were higher in cohort B (49% versus 83%; $p = 0.0002$) and related erythropoietin administration was increased in cohort B (17% vs 10%; $p = 0.005$). Of note, the sequence of chemotherapy did not significantly influence other treatment-related toxicities.
Conclusion: The present study failed to identify an impact of the sequence of taxane administration on neoadjuvant chemotherapy efficacy. Nevertheless, starting neoadjuvant chemotherapy by taxane prevents the occurrence of severe anemia and erythropoietin prescription. These findings might allow a selection of the sequence order based on the toxicity profile.

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Impact of CT-based target delineation on the location of the internal mammary and median supraclavicular (IM-MS) field

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Background: Radiotherapy of the internal mammary and medial supraclavicular (IM-MS) lymph nodes is in most centres performed with a standard anterior mixed photon (6MV) and electron beam (12 MeV). The position of the field is based on surface anatomy and the dose is prescribed to a point. In this study we examined the impact of detailed CT-based target delineation on the conventional field borders and dose specification.
Materials and Methods: The CTV IM and MS was delineated on the CT-scans of forty conventionally simulated breast cancer patients (20 left and 20 right), following fixed guidelines. The depth and lateral position of the CTV IM and MS was measured on the central slice (IM-part), where the prescription point is located. Furthermore the deepest and most lateral position of the CTV (MS-part) was determined. Taken into account the requirements of the EORTC protocol 22922 (ipsilateral border of the IM part of the field at 5 cm from the midline), the CTV IM is outside the radiation field if its ipsilateral position is more than 3.8 cm from the midline (0.5 cm PTV margin and 0.7 cm penumbra).
Results: The mean AP diameter was 20.8 cm ($\pm$2.6). The mean depth and laterality of CTV IM on the central slice was respectively 2.7 cm ($\pm$0.8) and 3.9 cm ($\pm$0.4). In 52.5% of patients the lateral position of CTV IM is more than 3.8 cm from the midline. The mean depth and laterality of the CTV MS was 5.0 cm ($\pm$0.9) and 5.3 cm ($\pm$0.5). In 87.5% and 45% of patients, the depth of the CTV MS is more then respectively 4 cm and 5 cm.
Conclusions: The conventionally simulated direct anterior IM-MS field does not cover the target volume adequately in most patients. Firstly dose prescription to a point on the central slice of the IM-MS field is not adequate and results in underdosage of the MS-part since the deeper location of the lymph nodes cranially. Secondly the ipsilateral field border of the IM-part has to be shifted to the ipsilateral side in 52.5% of patients when full CT-data are taken into account. However, this is mostly not feasible when breast tangential fields have to match the IM-MS field, because it results in an ipsilateral shift of the matchline and as a consequence the cold triangle can be located in the CTV breast. Therefore not only field borders and dose prescription but also field set-up should be adapted to the CT-based target localisation and patient anatomy.