and databases was quantified using RT-PCR. Given that pathologically confirmed complete eradication of the tumor in the breast (pCR) is a robust independent predictor of efficacy, the correlation of gene expression with pathologic complete response (pCR) was determined.
Overall, 89 of 95 patients were evaluable (mean age 49.9 years, mean clinical tumor size 6.4 cm). Eleven patients (12%) had a pCR. A total of 86 genes correlated with pCR ($p < 0.05$, unadjusted). Increased likelihood of pCR was associated with higher expression of proliferation-related genes (e.g., CDC20, E2F1, MYBL2, TOPO2A) and immune-related genes (e.g., MCP1, CD68, CTSB, CD18, ILT-2, CD3z, FasL, HLA.DPB1), and lower expression of estrogen receptor-related genes (e.g., ER, PR, SCUBE2, and GATA3). To further explore whether the findings bore a general vale, we tested the performance of the identified genes in predicting pCR in an independent group of neoadjuvant chemotherapy patients, for whom gene expression was measured using DNA microarrays. In 82 patients who had been treated with neoadjuvant paclitaxel and doxorubicin at the MD Anderson Cancer Center, DNA microarray data were available for 79 of the 86 genes identified as predictors in the RT-PCR study. These genes showed response discriminating value in the microarray data. More specifically, in univariate analysis 24 genes correlated with pCR with $p < 0.05$ (false discovery = 4 genes) and a total of 32 genes showed correlation with $p < 0.1$ (false discovery = 8 genes). Finally, the when the Recurrence Score assay was investigated in the 89 patients form the Milan study, a significant positive association with the likelihood of pCR ($p = 0.005$) was found. In other words, patients who are at greatest risk of recurrence according to the Recurrence Score are also those more likely to benefit from chemotherapy. In conclusion, quantitative expression of ER and other ER-related genes, proliferation genes, and immune-related genes are strong predictors of pCR in women with locally advanced breast cancer undergoing therapy with regimens containing anthracyclines and paclitaxel. Additional analyses are ongoing to refine the findings we have described by comparing the pattern of expression before therapy and after therapy for those who did not achieve a pCR. This will eventually lead to the definition of a predictor for testing in independent validation studies.

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Intensity modulated radiotherapy (IMRT) for prostate cancer: an update

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Technological advances made over the past two decades have enhanced the precision and improved the outcome of external beam radiotherapy of prostate cancer. 3D-CRT, and in particular IMRT, have greatly facilitated the ability to deliver higher tumor doses while concomitantly decreasing toxicity. The results of the MSKCC dose-escalation study in prostate cancer have confirmed this notion. Of the 1684 patients enrolled so far in this study, 304 patients underwent prostate biopsies 3.5 years after 3D-CRT/IMRT. Biopsy proven local control was dose dependent, increasing from a 44% local cure with 64 Gy to 77% with 75.6 Gy and 88% with 81 Gy. Long-term results of 81 Gy IMRT are now available for 171 patients, followed for a median of 6.3 years (range: 1–7.75 years) after treatment. The 5-year actuarial risk for grade 2 rectal bleeding was 4% and for grade 3 it was 0.5%. For urinary toxicity the risk was 9.5% for grade 2 and 0.5% for grade 3. No toxicities developed later than 62 months from completion of therapy. The incidence of erectile dysfunction post radiation was 44% among patients potent prior to treatment. The 6-year PSA relapse free survival was 91% ($n = 65$), 73% ($n = 71$) and 64% ($n = 35$) for patients with favorable, intermediate and unfavorable risk disease, respectively ($p = 0.008$). The post-treatment biopsy findings at 3 years correlated with long-term PSA relapse free survival, confirming that this biochemical marker indicates a local tumor cure. PSA relapse with a positive post-treatment biopsy in patients with favorable or intermediate risk disease was associated with an increased rate of distant metastases. In contrast, distant metastases in unfavorable risk patients did not correlate with biopsy findings, suggesting such patients may have micrometastatic disease at the time of initial treatment. These data indicate that high-dose (81 Gy) IMRT in localized prostate cancer is safe in that it involves an extremely low risk of complications, and is mandatory for achieving the maximal likelihood of local tumor cure.

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Image guided radiotherapy

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To account for geometrical uncertainties and variations during radiotherapy, safety margins are routinely applied. In many cases, these safety margins overlap organs at risk thereby limiting dose escalation. The aim of image-guided radiotherapy is to improve the geometrical accuracy by imaging the tumor and critical structures on the treatment machine just prior to irradiation. The NKI has collaborated in the development of a kilovoltage cone beam CT guided linear accelerator. A prototype system has been in use for about 2 years, and two commercially released systems have just been taken into clinical use. The system extends the regular accelerator with an extra kV tube and aSi imager. Scan times (with concurrent reconstruction in the background) on the commercial system range from 35 s (small field of view, head and neck) to 120 s (large field of view, prostate). Preliminary results show that the image quality of the commercial system is similar to that of the prototype system, i.e., prostate localization is well possible with about 4 cGy imaging dose. For other anatomical locations less dose is required (we use 1 cGy for head and neck and 2 cGy for lung, 4D scanning). The availability of high quality tomographic images and automatic image analysis (registration) on the treatment machine has quickly led to the introduction of many new clinical applications in our institute. The most exciting ones are high precision hypofractionated treatments of brain metastases and solitary long tumors with on-line tumor position corrections. Patient localization with 1 mm accuracy (for bony anatomy) is easily achieved with the current equipment. Pre- and post-treatment scans demonstrate negligible patient motion (bony anatomy), i.e., about 0.5 mm SD, both for brain and bladder cancer patients. Another advanced application that is now in routine clinical use is adaptive radiotherapy (ART) of prostate cancer, where we determine and adapt the plan to the average prostate position based on cone beam scans made during the first week of treatment. The availability of cone beam CT on the linear accelerator makes this technique very efficient, since the patient does not need extra appointments for CT scans. It is also more accurate, since problem duplicating the setup of the treatment machine on the CT scanner do not occur. An important tool that we have implemented for these protocols is automatic registration of a selected region of soft tissue anatomy. This tool is used for automatic localization of the prostate, as well as for lung tumor setup based on 4D (respiration correlated) cone beam CT. However, for all image-guided protocols, the residual uncertainties need to be taken into account, and the safe level of margin reduction evaluated. For instance our prostate ART protocol allows a reduction of the margin from 10 to 7 mm. In conclusion, cone beam CT guided radiotherapy is now very much a clinical reality. The involved physicians and therapists are very enthusiastic.

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Brachytherapy instead of surgery?

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Introduction: Defining an optimal tailored treatment in localized prostate cancer is not an easy task in lack of prospective randomized trials. The only way to find out which group of patients profit from a certain treatment method is analysing comparable long-term outcome data.
Material and Methods: *Initial PSA* (iPSA), *Gleason score* (GS) and *tumour stage* has all independent and significant influence on treatment results. Many authors have shown, that in patients treated with conventional external beam therapy with iPSA > 10ng/mL the PSA failure was over 50%. This cohort of patients has also a higher probability in both, in extra capsular invasion as well as in the treatment failure rate.
Brachytherapy as monotherapy in localized low- and intermediate risk prostate cancers results in experienced hands to similar long term survival rates as it can be achieved by radical prostatectomy performed in centres of excellence, however, quality of possible toxicities caused by both treatments is different. Operated high-risk group cancers need frequently postoperative radiotherapy complementary to radical prostatectomy to reach best possible cure. The possible addition of toxicities caused by radical prostatectomy and full dose radiotherapy result in higher risk of loosing quality of life for the patient, therefore, dose escalation radiotherapy (combined EBRT+Brachytherapy) seems to be more advantageous in this group. In case of dose escalation radiotherapy (>80–90 Gy_{BED}) complementary systemic treatment (androgen deprivation) could be advantageous in cases with high risk of systemic disease (iPSA > 30 ng/ml).