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.

Scientific Symposium
Local treatment of prostate cancer

122 Abstract not received

123 INVITED

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.

124 INVITED

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.

125 INVITED

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).

Results: Literature data clearly demonstrate, that combination of different prognostic factors in a given patient cohort can have a significant impact on biochemical and clinical outcome. Treatment decision should be influenced not only by outcome results, but also by individual preferences of the patients. This decision often includes preferences in possible side effects and psycho-oncological factors.
Conclusions: In lack of prospective randomized trials the outcome analysis of different experiences is the only method to learn more on optimal patient selection to different treatment methods. Good functioning interdisciplinary teams with high workload of patients could be the solution finding the optimal tailored treatment method for the individual patient.

Scientific Symposium
Chemo-radiotherapy or modified fractionation in head and neck cancer: two sides of the same coin

126 Abstract not received

127 INVITED

Chemo-radiotherapy in head and neck squamous cell carcinomas: an update

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In the recent years, the role of chemotherapy in HNSCC has been extensively studied in HNSCC, especially through the constitution of the MACH-NC data base which has been recently up-dated. It was based on the collection of up-dated individual patients data, the gold standard method for meta-analysis of randomized trials. For head and neck squamous cell carcinomas, the MACH-NC data base of randomized trials has been generated (17,858 patients), evaluating the effect of adding chemotherapy (CT) to local treatment. The main results were that the benefit associated with the use of CT depended on the timing of CT, concomitant RT-CT being more effective than adjuvant or neo-adjuvant CT. The overall improvement in survival at 5 years in favor of adding CT concomitantly to RT was 8%, and more pronounced when CDDP alone was used (11%) (100 mg/m^2 day 1, 22, 42 during the course of radiotherapy). The effect of poly or mono chemotherapy were not found to be statistically different, when given concomitantly to RT. The benefit associated with the use of concomitant CT was decreasing significantly with age, and more pronounced in younger patients. The effect of concomitant CT was found relatively unchanged, whether RT was conventional, altered fractionnated RT or adjuvant RT after surgery. In conclusion, the addition of CT to local treatment and especially to radiotherapy significantly improved survival.
More recently, and not included in the MACH-NC data base, a taxane-based induction chemotherapy (taxotere-5FU-CDDP) schedule was randomly compared to induction 5FU-CDDP a large series of patients with advanced HNSCC. A benefit in terms of loco-regional control, toxicity and survival was observed in favor of the taxotere-based chemotherapy, suggesting that this new combination may eventually lead to revisit the issue of induction chemotherapy in this type of cancer (Vermorken et al., ASCO 2004).
As mentioned above, the addition of CT, concomitantly to RT improves survival but has also been shown to increased both acute and late toxicity (Denis et al., IJROBP, 2003). Given this increase in toxicity, optimization is needed in order to improve efficacy and decrease toxicity, perhaps by using different schedules (ex: split dose CDDP) or new drugs and new radiation techniques such as Intensity Modulated RadioTherapy, IMRT). A new generation of cytotoxic agents is currently being tested in combination with ionizing radiation, including Taxotere, Taxol, Gemcitibine, or novel agents which are cytotoxic in hypoxic conditions (tirapazamine, Rishin et al., Proc. ASCO 2004). Whether these drugs may provide superior results, as compared to more conventional cytotoxic agents remains to be studied.
In addition, new generation of molecular targeting drugs have shown promizing results in pre-clinical studies and recently, a proof of principle have been obtained in a randomized trial, showing a benefit associated to the targeting of the Epidermal Growth Factor receptor concomitantly to irradiation (Bonner et al., ASCO 2004).
In conclusion, the updated MACH-NC data base has confirmed the benefit associated with the use of concomitant RT-CT. Optimization is needed to further increase the anti-tumor effect, while decreasing the toxicity.

128 INVITED

Modified fractionation in head and neck cancer – implication for current radiotherapy practice?

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One of the most investigated areas in the last ten years has been the importance of modifying the fractionation schedules in order to achieve an improved therapeutic ratio in radiotherapy. Especially in squamous cell carcinomas and most importantly in head and neck cancer we have gained a substantial amount of information due to the large number of randomized trials recently performed.
From a principal point of view one can manipulate the fractionation schedules by modifying the number of doses, reducing the overall treatment time, and modifying the dose per fraction. The limitation is both acute and late morbidity.
Three principles have been addressed in the randomized trials where the control arm normally has been conventional fractionation. One being the issue of hyperfractionation where more fractions with smaller dose per fraction are given to a higher total dose; accelerated fractionation where the same dose and number of fractions are given in a shorter overall treatment time, and a combination of the two. The results have shown that such a modification involving both acceleration and an increased total dose is likely to give a better tumour control, but at the same time the window for performing such a modification is limited when normal tissue morbidity is taken into account.
Not all patients are likely to benefit from the same modifications and recent research is about to identify patients which may have more benefit of one principle than another. Previous studies have indicated that poor histopathological differentiation and low expression of EGFr may compromise the ability of tumour to express accelerated regeneration. This problem was therefore addressed in a subset of the DAHANCA fractionation protocols. The study clearly indicated that the response to accelerated fractionation is heterogeneous and that tumour repopulation may be linked with factors influencing control of tumour differentiation and proliferation. Poor histopathological differentiation and lack of EGFr expression may indicate that such mechanisms are not functioning. This hypothesis, however, requests confirmation prior to application as a predictive factor.
With the background in the large randomized trials recently published and a subsequent meta-analysis will an overview and update of the fractionation principles for head and neck cancer be presented with special focus on the biological heterogeneity and its therapeutic implications.

129 INVITED

Chemo-radiotherapy or modified fractionation: exploitable mechanisms for new trends

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In radiotherapy, altered fractionation was investigated for two main "families" of schedules: hyperfractionation and accelerated fractionation. The former modality uses to deliver higher doses than conventional regimens through multiple daily sessions, delivering less than 1.5 Gy each. Declared target for hyperfractionation: to increase cell killing without enhancing toxicity in normal tissues. Accelerated fractionation also uses multiple daily sessions in order to shorten significantly the overall treatment time. The objective of this approach is to counterbalance tumour cell repopulation during treatment, especially in patients with fast growing tumors as Head and Neck carcinomas (HNSCC). Various mono-institutional and multicentric trials comparing conventional regimens to altered fractionation schedules show that patients with locally advanced disease draw a significant benefit – mainly in terms of loco-regional control – from hyperfractionation or acceleration, with some price to pay in terms of acute and late complications, the severity of which is shown to vary widely according to type of altered fractionation applied.
In the early 1980's a flurry of chemoradiation trials have been conducted in HNSCC. This approach was based on the implementation of four main mechanisms: (i) spatial cooperation; (ii) toxicity independence; (iii) protection of normal tissues; (iv) enhancement of tumor response. These concepts have been widely used in the literature and there is no doubt that they have influenced the development of combined modality strategies. While this has created a substantial body of empirical data, the drug-radiation schedules tried have often been selected without an underlying scientific hypothesis. In parallel with this, progress in molecular and cancer biology has generated a large number of non-cytotoxic drugs with new molecular targets and these are now in various stages of pre-clinical or clinical development. There is therefore a need for developing new mechanistic models to help investigators radiotherapy and cytotoxic or non-cytoxic compounds: spatial cooperation, cytotoxic