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Possibilities of gene therapy and radiotherapy

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Several experimental studies have shown that the efficacy of radiation therapy on tumor cells could be improved by gene transfert. One of the first approach consisted to increase radiation-induced apoptosis by targeting some genes involved in the regulation of apoptosis. Indeed, the transduction of wild type p53 gene via an adenovirus has been shown, *in vitro* and *in vivo*, to marquedly increase radiation sensitivity in various p53 mutated human carcinoma cell lines. A second approach consisted of targeting genes involved both in radiation-induced double strand break DNA repair and radiation sensitivity (DNA-PKcs/Ku70–86 genes). Some other aspects have been recently developped such as the use of radiation-inducible promotors (tPA or EGR1). The combination of such promotor with a gene able to modulate radiation sensitivity may allow to have a temporal and spatial control of the transgene expression by radiation, as shown recently with the EGR1-TNFα construct. Another approach has been proposed for the transgene expression, using a anaerobic clostridium vector, thus targeting selectively hypoxic radioresistant areas in the tumor. In conclusion, preliminary results of combining radiation therapy with the transfert of genes able to modulate radiation sensitivity are promizing and this approach certainly needs further investigations.

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Clinical use of multi-segment intensity modulation

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Purpose: The use of intensity modulated radiation therapy (IMRT) has become an important research topic in recent years, however, clinical application of IMRT has been limited. This work reports on nearly four years of clinical experience with multi-segment IMRT.

Methods: More than 100 patients have been treated with multi-segment IMRT using automated and non-automated treatments with MLC-equipped treatment machines.

Results: Multi-segment IMRT has been useful for high dose conformal treatments at sites including brain, head and neck, lung, prostate, and liver. With computer-controlled treatment delivery, such treatments can be performed accurately, quickly, and effectively. The presentation will describe required treatment planning tools and methods, and will analyze the possibilities for improved dose distributions, improved target volume coverage, improved NTCPs, as well as quality assurance and commissioning requirements.

Conclusion: Multi-segment IMRT is within technical reach of many in the radiotherapy community, and can provide significant improvements over normal conformal therapy approaches. *Supported in part by National Institutes of Health Grant P01-CA59827.*

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Towards prediction of radiosensitivity

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The three radiobiological factors of tumors which have shown to be associated with the chance of local control after radiotherapy are proliferation rate, degree of hypoxia, and intrinsic radiosensitivity. To maximize the chance of accurate outcome prediction, all three should be measured, along with known clinical predictors. This has not been achieved to date for technical reasons but remains an important goal. This paper will concentrate on ways to measure one of these; radiosensitivity.

The most direct assay is that of clonogenic survival, but is technically difficult and is takes several weeks to complete, making it an unlikely candidate for routine clinical use. Several indirect assays for cell kill exist, including those for DNA and chromosome damage, each of which can be measured by a variety of techniques. No assay has a one to one relationship with cell kill for tumor cells, although several have shown reasonable correlations, suggesting their use as clinical predictors. Their advantage is an assay time of at most a few days, allowing tests to be completed before the start of radiotherapy.

There has been recent rapid progress in the cloning and understanding of genes affecting sensitivity to ionizing radiation, leading to the hope that screening a panel of such genes for expression, function or mutation would lead to prediction of intrinsic radiosensitivity. Genes of interest are those involved in DNA repair by end-joining, including the DNA-PK complex and XRCC4, those involved in repair by recombination, including the rad52 group homologs, and the ATM gene. Present knowledge of these will be discussed. Prediction by "gene screening" is still not possible because of the complexity of the response to radiation, but there is hope that this will become feasible in the near future.

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Is cisplatin–taxol (PT) the standard treatment in advanced ovarian cancer. The NOCOVA

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An European Canadian study has included 680 patients with advanced ovarian cancer in a trial comparing Cisplatin/Cyclophosphamide (PC) with Cisplatin/Taxol (PT). The doses were Cisplatin 75 mg/m^2, Cyclophosphamide 750 mg/m^2 and Taxol 175 mg/m^2. Taxol was given as a 3 hours infusion. Chemotherapy was given every 3 weeks. The two groups were well balanced according to FIGO stage histologic type, grade and residual tumor.

Distribution of FIGO stage was PC stage II 7%, stage III 73%, stage IV 19%. PT stage II 6%, stage III 74%, stage IV 19%.

In the PC arm 35% had no or minimal residual tumor versus 39% in the PT arm.

The mean number of courses was 6 in both groups. Overall 62% of the patients experienced disease progression.

Final analysis for progression free survival, crude survival and toxicity are not available at the moment, but will be ready at the presentation.

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Comparative study of intravesical instillation of epirubicin, BCG, or BCG + INH in intermediate and high risk pTa–pT1 papillary carcinoma of the urinary bladder. First results of EORTC 30911

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Purpose: To compare intravesical Epirubicin, BCG, and BCG + INH with respect to time to first recurrence, time to progression, duration of survival and incidence of side effects.

Methods: 958 patients were randomized in this phase III trial by 42 institutions, 318 to Epirubicin, 321 to BCG, and 319 to BCG + INH.

Results: Except for more frequent liver function disturbances in the BCG + INH group, no differences in adverse effects were observed. Interim data show a shorter time to first recurrence on Epirubicin ($p = 0.01$). It is too early to assess the long term results.

Conclusion: Based on this interim analysis the addition of INH does not appear to reduce the incidence of BCG side effects while it does increase liver function disturbances. Epirubicin is associated with a shorter time to first recurrence.

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Neo-adjuvant chemotherapy in adult soft tissue sarcoma. EORTC Protocol 62847

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Purpose: Patients with a "high risk" soft tissue sarcoma, as defined in trial 62771, have 50% chance of developing distant metastases, with subsequent poor survival. The value of neo-adjuvant chemotherapy was tested in a randomized phase II to test the feasibility and accrual-rate to start a phase III study with endpoints overall- and disease-free survival.

Study-Design: Patients with a high risk soft tissue sarcoma were randomized in two arms: three cycles of doxorubicin 50 mg/m^2 and ifosfamide 5 g/m^2 followed by surgery +/– radiotherapy versus surgery +/– radiotherapy alone.

Results: Between April 1986 and May 1995 150 patients were entered; 134 patients were eligible. Male/female ratio: 3/2; median age 53 years. Both arms balanced for eligibility, stratification and localisation of the tumour. In