according to prognostic factors. Randomized trials devoted to localized prostate cancers treated with optimized techniques of radiotherapy, plus short term HT, will be rewied.

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Brachytherapy of the localized prostate cancer: indications, results and side effects

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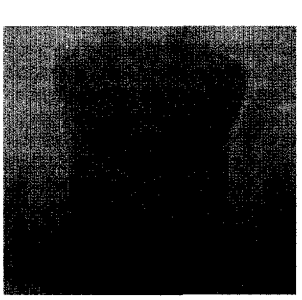
Introduction: Brachytherapy for prostate cancer could be applied as monotherapy or as a boost in combination with external beam irradiation.

Methods: Permanent (seeds) and temporary (remote afterloading) implantations are possible.

Results: The most important prognostic factors for disease free survival are initial PSA, Gleason (or WHO) grade and stage. For functional outcome the initial prostate volume and lower urinary tract symptoms best characterised by the IPSS score provide the best guide to outcome. There are no prospective randomised studies proving different types of radiation treatment, but in high/intermediate risk cases the long-term treatment results of combined EBRT and low-dose-rate (LDR) or HDR brachytherapy are favourable. HDR BT alone is not a standard treatment, it represents still subject of clinical experiments. The treatment decision always represents also the effectiveness of the work of a given interdisciplinary group. If a group can offer a bright spectrum of treatment variations, the most effective schedule seems to be as follows: (a) at low-risk patients permanent implants (Fig.1) or radical prostatectomy, (b) at intermediate- or high-risk patients combined external beam treatment and local dose escalation boost using a temporary implant (Fig. 2). Interstitial brachytherapy of the prostate (both seeds and HDR) is not indicated if (a) the patient has a shorter life expectancy than 5 years, (b) the patient has not only local disease, (c) TUR was performed previously, (d) there is a large prostatic defect according to previous TURP, (e) the tumour has a smaller distance to the rectal mucosa than 5 mm, (f) the patient has general contraindications for adequate anaesthesia and/or operative treatment, (g) the treatment is not to complete because of technical problems based on anatomical abnormalities. Long term results in the literature show, that treatment results with permanent implants alone are equal to that of the radical prostatectomy in the case of low-risk patients. The role of additional hormonal deprivation is not yet clear.



Conclusion: Patients with higher risk have a clear advantage of combined external beam and interstitial implantation. Thus of medium or high-risk prognostic groups have a clear benefit due to the treatment in terms of results and economics. Patients have the best chance for best possible cure, if the treatment will be coordinated and performed by experienced interdisciplinary teams.

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The development and expectations of IMRT in the treatment of prostate cancer

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With the recognition that higher doses of irradiation are critical for achieving maximal tumor control among patients with clinically localized prostate cancer, enhanced modes of conformal radiotherapy delivery systems would represent attractive directions to pursue. IMRT is an advanced form of 3-Dimensional Conformal Radiotherapy (3D-CRT) that has been shown to significantly improve the conformality of the dose distribution. Treatment planning is based on the inverse technique and uses an iterative computer-driven optimization method to generate treatment fields with varying intensities over the cross-section of the beam. The combination of multiple intensity-modulated fields produces custom-tailored conformal dose distributions with steep dose gradients at the boundaries between the target and the normal structures.

We have demonstratedthat IMRT improves the conformality of high-dose radiotherapy delivery compared to conventional 3D-CRT. In one study, 20 randomly selected patients were planned concomitantly by both techniques and the resulting plans were compared with DVH analyses for a number of dosimetric parameters. This study indicated that while on average 98 $\pm$ 2% of the clinical target volume would receive 81 Gy with IMRT, only 95 $\pm$ 2% would receive the same dose with 3D-CRT ($p < 0.01$). At the same time, the percentages of the rectal wall (9 $\pm$ 3% vs. 13 $\pm$ 4%) and bladder wall (28.8 $\pm$ 8% vs. 32 $\pm$ 9%) volumes carried to 75 Gy were significantly decreased with IMRT ($p < 0.01$). These data provided evidence supporting the notion that IMRT significantly improves the conformality of radiation treatment in prostate cancer.

The improved conformality and reduction of irradiated rectal tissue with IMRT translated into a decrease in rectal toxicity and provided an opportunity for the safe delivery of radiation doses to as high as 86.4 Gy. To further validate the IMRT approach, the toxicity outcomes of 171 patients treated with IMRT to 81 Gy were compared with 61 patients treated with the 3D-CRT approach to the same dose level. Acute and late urinary toxicities were not significantly different for the two methods. However, the combined rates of acute grade 1 and 2 rectal toxicities and the risk of late grade 2 rectal bleeding was significantly lower in the IMRT patients ($p = 0.05$ and 0.0001, respectively). The 5-year actuarial rates of grade 2 rectal bleeding were 2% for IMRT and 10% for 3D-CRT ($p < 0.001$). We have recently analyzed the outcome of 772 patients treated with IMRT (698 to 81 Gy and 74 to 86.4 Gy. With a median follow-up of 24 months (range, 6 to 60 months), only 11 patients (1.5%) have thus far developed grade 2 rectal bleeding, and four (0.5%) have experienced grade 3 rectal toxicity. The 3-year actuarial rate of $\geq$ grade 2 rectal bleeding was 4%. exhibit rates ofseries) Thus, the improved conformality and reduction of irradiated rectal tissue with IMRT translated into a decrease in rectal toxicity and provided an opportunity for a safe escalation of dose to 86.4 Gy. As both local control and long-term PSA relapse–free survival are dose-dependent, these data confirm that IMRT represents a noteworthy advancement in the ability to deliver high-dose radiation in prostate cancer.

(Describe preliminary outcome data and show that it is not worse than 3D)

The implementation of IMRT requires strong medical physics support and collaboration. The technical aspects of treatment delivery, careful evaluation of treatments plans balancing the normal tissue constraints with the need for optimal target coverage and quality assurance protocols are demanding. Although the margins we routinely use the planning target volume remain the same for 3D-CRT and IMRT, given the enhanced degree of conformality of the dose distribution for the latter, organ motion issues remain important for the clinician to be aware of and address. Yet, despite these technical challenges of IMRT, the reduced toxicity profiles we have observed with this approach which in turn has improved the quality of life of our treated patients is the reason IMRT has become the standard mode of treatment delivery for prostate cancer at Memorial Sloan Kettering Cancer Center.

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Cancer gene discovery

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A major application for the human genome sequence in elucidating oncogenesis will be as a template subserving genome-wide searches for somatic mutations in cancer cell genomes. A full description of changes at the DNA level in cancer cells will require information on all types of abnormality; copy number changes, rearrangements, point mutations and methylation. Currently, however, there is no single technology that practically can address this diversity of mutation class simultaneously. To begin the process of using a whole genome sequence, we have embarked upon systematic genome-wide searches for small intragenic mutations (base substitutions and small insertions / deletions) and homozygous deletions in cancer cell lines. These searches are beginning to yield fruits in terms of newly identified somatically mutated cancer genes. The first fruit of this process has been the discovery of mutations in the BRAF gene in human cancer. BRAF is a member of a family of three serine / threonine kinases that also includes RAF-1 (also known as CRAF) and ARAF. RAF proteins are recruited to the cell membrane and activated by RAS proteins in the RAS-RAF-MEK-ERK-MAPkinase signal transduction pathway. Mutations of BRAF were found in 70% of melanomas and in a lower proportion of other cancers. Over

80% of the mutations cause a single amino acid change (V599E). We have subsequently shown that BRAF mutations cause activation of the BRAF kinase activity, are transforming in NIH3T3 cells and often (but not always) render the cell independent of signalling through RAS proteins. The patterns of BRAF mutation and their associated biology have revealed new insights into kinase function, pathway function and have generated a plausible new target for drug development. In the future as systematic genome wide mutational screens progress they will reveal insights into global patterns of mutation that differ between individual cancers and cancer types and will provide information on fundamental parameters of human cancers: how many genes are mutated and implicated in the genesis of a single human cancer and how many different cancer genes are there?

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Predicting breast cancer behaviour by genetic analysis

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In the treatment of breast cancer, patient tailored therapy is becoming increasingly important. Decisions on optimal treatment include the choice between mastectomy and breast conserving treatment; dose of radiotherapy; and decisions on adjuvant chemotherapy and hormonal therapy.

Specific DNA alterations, most notably amplification of oncogenes and inactivation of tumour suppressor genes, will have an influence on tumour cell behaviour and may therefore be clinically useful. The assessment of germline alterations in the BRCA1 and BRCA2 genes are already used to identify women with a genetically determined increased risk to develop breast cancer. It has been shown that breast carcinomas with an amplified HER2 gene respond to optimal dosed anthracyclin based therapy and may be less sensitive to tamoxifen. The unravelling of other associations between genetic alterations and tumour behaviour can be expected to impact on the clinical management of breast cancer patients.

Gene expression profiling by micro-array analysis allows the study of the level of expression of large numbers of mRNA's in a single experiment. Gene expression analysis can be used to subclassify tumors on the basis of hierarchical cluster analysis in specific subgroups; supervised cluster analysis can be used to directly link gene expression profiles to clinical characteristics, including prognosis and response to various forms of treatment.

We have used microarray analysis, first on a series of 117 breast carcinomas and more recently on a series of 295 breast carcinomas.

We have defined a gene expression profile of 70 genes that is predictive for a short interval to distant metastases (<5 yrs) in lymph node negative (LN0) patients. We have validated the prognostic value of this gene expression profile in lymph node negative patients; and also in premenopausal lymph node positive patients. The profile outperforms all currently used clinical parameters in predicting outcome of disease.

At present, we are employing gene expression profiling to identify patients at high risk of local recurrence after breast conserving therapy and to predict the responsiveness of primary and metastatic disease to systemic treatment.

As a result, we expect that in the future, gene expression profiling of breast cancer will be used to guide optimal therapy.

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Expression and CGH analysis in soft tissue sarcomas, bladder cancer, and prostate cancer

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We have performed Expression and Comparative Genomic Hybridization studies onto cDNA arrays for a variety of cancer types including sarcomas, prostate cancer and bladder cancer. Expression profiles were obtained for 37 leiomyosarcomas. The dataset was first filtered to select a set of 335 genes whose expression varied most widely between primary and metastatic tumours. Clustering analysis of non-metastatic tumours using this gene set revealed that the tumours could be divided into two distinct groups. The metatstatic potential of primary tumours in the two groups were dramatically different (log-rank test p=0.001). We concluded that expression profile could predict metastatic potential of human sarcomas and that the ability to metastasis was a bulk property of the tumour. Expression studies have also been performed on primary prostate cancer with the objective of identifying new potential prostate markers. In this study we used microarrays randomly selected from a prostate LNCaP cDNA library. Several novel potential prostate cancer markers have been identified. CGH onto Geneset microarrays studies were performed usingh prostate and bladder DNA to identify regions of genetic gain and loss. Several novel classes of genetic alteration have been identified. Acknowledgements: We thank the National Cancer Research Institute, Cancer Research UK and the Medical Research Council for funding this work.

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Proteomic pattern analysis serum for early detection of ovarian cancer

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Diagnosis and management of cancer requires tools with both high sensitivity and specificity. The minimally invasive cervical smear has demonstrated how such a test can change the public health profile of a cancer from deadly to cured. Neither a robust test, nor reliable or specific early symptoms are available for ovarian cancer and other solid tumors. Current approaches testing one protein or gene at a time will not address this expeditiously. New high throughput cost-efficient technologies are needed. These should focus on available patient resources, blood or urine, or minimally invasive approaches such as cervical smears. Proteomics, the study of the expressed proteins and protein fragments, has been applied experimentally to cancer diagnostics. Ovarian cancer is a rare disease with 1:2500 postmenopausal women affected in their lifetime. It is diagnosed in advanced stage in over 70% of women with similar trends for pancreatic, gastric, and other cancers. A specificity of 99.6% on a background of 100% sensitivity is the target requirement for an ovarian cancer biomarker to yield positive predictive value of 10% but is not powered for the detection of early stage cancer, occurring in 15% of ovarian cancer cases. Early detection of ovarian cancer can increase frequency of long term survival to over 90%. The goal of proteomic monitoring is development of a reliable screen to identify stage I/II disease and to allow rapid and optimal patient intervention. We have applied mass spectroscopy (MS)-based proteomic screening of serum with bioinformatic pattern analysis for ovarian cancer biomarker development under the hypothesis that circulating blood contains information from organ-confined disease. Surface-enhanced or matrix-assisted laser desorption and ionization MS has been used to detect low molecular weight proteins, an untapped information reserve. Small serum samples yield datastreams containing over a hundred thousand features. A protein separation on a solid-phase capture matrix directs the view of the proteome. Advanced bioinformatics algorithms mine the MS datastreams for diagnostic patterns of information. The algorithm is trained with data from known samples to define the signature pattern. This pattern is tested with blinded unknowns for validation. The weak cation exchange matrix analysis yielded a experimental diagnostic signature pattern 99-100% sensitive and 99-100% specific when queried with blinded unknown samples (n=250). All 36 early stage cases were correctly identified as cancer. The features comprising the diagnostic pattern can soon be isolated and identified with newer. We are initiating a large scale prospective blinded study to determine the robustness of these early findings and to form the basis for prospective randomized testing. Application of MS coupled with bioinformatic techniques has promise for identification of discriminating protein signature patterns in the blood of organ-confined ovarian and other cancers.

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Early colorectal cancer - treatment choice

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Early colorectal cancer unfortunately is a seldom diagnosis in symptomatic patients. The proportion of 10% however may be increased to 45%, provided that screening for colorectal cancer (CRC) with fecal occult blood test programs are accepted in average risk persons above 50 years of age and positive stool tests are followed by a complete colonoscopy.

The pT-stage may be defined, when the resection margin is free of tumour tissue. Before treatment it is possible to define the T-stage by intraluminal ultrasound examination with a high accuracy; and local excision (endoscopic polypectomy, peranal excision Transanal Endoscopic Microsurgery) of a TI