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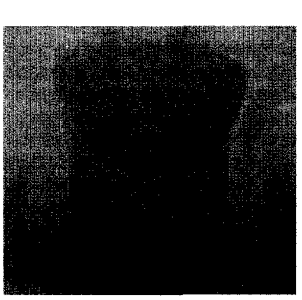
Introduction: Brachytherapy for prostate cancer could be applied as monotherapy or as a boost in combination with external beam irradiation.

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