Abstract. External beam radiotherapy (EBRT) for the treatment of loco-regional prostate cancer yields similar survival rates to radical prostatectomy (10-year survival: 90-95%, 60-70% and 50-60% in T1, T2 and T3-stages, respectively). Post-operative radiotherapy in high-risk prostate cancer may improve the local and distant disease-free survival of patients. Using the recently developed technology of the 3D-conformal RT and of the intensity-modulated RT (IMRT), the focalized administration of a higher radiation dose is allowed keeping exposure of surrounding normal tissues to low levels. Cytoprotection with amifostine administration before EBRT fractions may reduce the incidence of early and late radiation sequel from the bladder and rectum. The developments in radiobiology suggest that large radiotherapy fractions may be more efficacious than standard radiotherapy, so that hypofractionation of radiotherapy may further improve local control rates. The use of interstitial high-dose rate implants to boost the prostate after an initial course of EBRT has been applied successfully in various institutes, with further improvement of the results obtained with EBRT. Chemotherapeutic agents, such as docetaxel and liposomal doxorubicin, as well as novel biological agents introduced into clinical practice (i.e. anti-erbB, anti-angiogenic and apoptosis-modulating agents) have shown significant radiosensitizing activity and deserve clinical evaluation in conjunction with radiotherapy.

Cancer of the prostate is one of the most common tumors in men. It represents the second most common cause of death from neoplasia in men (1). In contrast to benign hypertrophy, prostatic adenocarcinoma arises from the peripheral glands of the prostate (2). Autopsy studies clearly show that subclinical prostatic adenocarcinoma precedes clinical evolution and this latent course of the disease may never reach the level of clinical manifestation (3).

Today, patients with prostate cancer can chose among a variety of highly effective surgical or non-surgical therapeutic approaches. Observation with hormonotherapy without local intervention is a widely accepted policy for low Gleason (score 2-4) early disease in elderly patients, as the 15-year mortality rate is lower than 10%. Such patients will be offered local therapy once biochemical recurrence is manifested. The necessity, however, of local or loco-regional therapy in patients with higher Gleason scores is clearly indicated by the 18–30% and 60-87% mortality rates in the Gleason scores 6 and 8–10, respectively (4).

Radiotherapy, whether external beam or interstitial, represents a principal curative therapeutic option, equivalent to radical prostatectomy in early stages. Post-operative external beam radiotherapy (EBRT) is also of value in cases with positive surgical margins or lymph node metastatic disease. In more advanced, inoperable local stages, hormono-radiotherapy, combined or not with brachytherapy, results in acceptable local control and survival rates. The present review presents the current position of radiotherapy in the management of prostate carcinomas and discusses important developments awaited to further improve the efficacy of radiation treatment.

External Beam Radiotherapy (EBRT)

The development of megavoltage irradiation (cobalt units and linear accelerators) 5 decades ago, brought forward radiotherapy as a principal therapy for early cancer, with cure rates above 70% in certain tumor types, such as nasopharyngeal and laryngeal cancer, cervical carcinomas, prostate and bladder carcinomas. The subsequent introduction of computerized tomography as a tool for
radiotherapy treatment planning further improved the accuracy of the radiation fields and the reduction of radiation toxicity. In the early ’80s, clinical studies on the 10-year control rates obtained with megavoltage irradiation in patients with prostate cancer were published (5-7).

Traditional radiotherapy techniques used anteroposterior large pelvic fields and cone down booster fields with lateral or oblique directions to deliver a total dose of 44-46 Gy to the pelvic nodes and 64-68 Gy to the prostate / seminal vesicle area. The irradiation of regional lymph nodes is justified in high-grade tumors (Gleason score >6) or bulky local disease, as laparoscopy studies show that the likelihood of metastasis to the nodes is as high as 45% (8-10). Low Gleason score A/B-stage cases can be effectively treated with localized irradiation of the prostate and seminal vesicles, as it is unclear whether pelvic radiotherapy contributes to the improvement of survival of these patients.

During the past decade, 3D-conformal radiotherapy technology appeared (11). This is based on the CT-simulation, on-line transfer of patient data to and elaboration by sophisticated computer packages, conformal beam-eye view-based establishment of the radiation fields and, finally, reproduction of the virtual planning by a linear accelerator endowed with a multi-leaf collimator. This technology allowed the substantially better shielding of normal tissues, so that the radiation dose can be escalated to 76-80 Gy without increasing rectal and bladder toxicities (12). One step forward was the development of computer logismics that recognize multiple targets in the same axial image and allow the modulation of the radiation dose within the same field of radiotherapy (13). This so-called “intensity modulated radiotherapy” (IMRT) allows for the safe administration of even higher doses, compared to conformal techniques with further reduction of acute and late radiation toxicity (15). The incorporation of PET (positron emission tomography) data in IMRT planning is a very recent development (14), with unknown clinical benefits, as yet.

Efficacy of EBRT in Early (Stage A/B) Prostate Cancer

The efficacy of EBRT depends on the local stage, the Gleason score and the pre-therapy PSA levels. Using these 3 parameters, patients can be divided in 3 prognostic groups: a) low-risk group (stage T1c / T2, PSA <10 μg/L, Gleason score <7), b) intermediate-risk group (only 1 of these features higher than the low-risk group) and c) high-risk group (at least 2 of these features higher than the low-risk group).

In 1979, Taylor et al., in a study on 36 stage-B carcinoma patients, reported a 68.8% 5-year survival following EBRT (16). In 1986, Perez et al. reported an analysis of a large series of 343 patients with prostate cancer treated with EBRT (60-70 Gy total dose) (6). The 5-year disease-free survival rates were 100% and 75% for stage-A2 and -B, respectively. A Canadian study by Hahn et al. included 151 patients with T1 and 346 patients with T2-stage disease, reporting a 10-year post-radiation (66 Gy) survival of 93% and 68%, respectively (17).

An analysis of 1469 patients with prostate cancer treated with EBRT, between 1972-1999 in the Massachusetts General Hospital, Boston, USA, provided important information (18). Overall, the 10-year disease-free survival was 74%, whereas a Gleason score >7 was linked with significantly poorer results. Local control was also important for the subsequent manifestation of distant metastasis, which often appeared immediately after local recurrences. Overall, the development of metastatic disease after EBRT occurred in 20% of stage-B patients (19,20).

An important question raised is whether the patient’s age defines the EBRT efficacy. In a study from the MD Anderson Cancer Center, Texas, USA, on 964 patients with prostate cancer treated with EBRT, the 7-year survival without biochemical recurrence was 47% in patients younger than 60 years and 59% in older patients (21). In contrast to this finding, in an analysis of 1018 patients treated with EBRT (without hormonotherapy) at the Naval Medical Center, San Diego, USA, age had no impact on the results of EBRT. Gleason score and pre-EBRT PSA levels were the only features defining survival (22). Similar results have been recently reported from the Memorial Sloan-Kettering Cancer Center, NY, USA, where the biochemical recurrence rate following EBRT rate was 22%, regardless of the age of the patients (23).

**EBRT vs. Radical Prostatectomy**

Radical prostatectomy is a popular method of early prostate cancer therapy with high cure rates. Special nerve sparing techniques contribute to the reduction of the incidence of sexual impotence, a complication of prostatectomy that affects 30-50% of patients (24, 25, 28). The efficacy of radical prostatectomy depends, similarly to EBRT, on the Gleason score, the local tumor burden and the preoperative PSA levels (24). Patients with small T1/T2-stage tumors with low PSA levels and Gleason scores <7 have an excellent post-operative prognosis. In a series of 610 patients with Gleason score 7-10, the 10-year survival without biochemical recurrence was 65%. This, however, dropped to 30% in cases with positive surgical margins or tumor invasion beyond the prostate capsule at pathology examination (26). In a study by Lau et al., on 407 patients with Gleason score 8-10, the cause-specific 10-year survival following radical prostatectomy was 85% (27). The 10-year survival without biochemical recurrence was 36%.
Overall, the efficacy of radical prostatectomy is equivalent to that of EBRT (29). The concurrent administration of hormonal therapy together with EBRT and the recent introduction of high-Tech radiotherapy techniques and protocols form a modern field of clinical research, so that randomized trials are warranted to define the superiority of surgery or of EBRT in specific subgroups of patients.

Prostatic Biopsy after EBRT

Following EBRT, the prostate undergoes fibrosis and regression of the glandular component, frequently accompanied by diffuse calcification. The disappearance of the tumor is slow, reaching a maximum at 18 months after the end of EBRT. Prostatic biopsies after EBRT are not indicative of the efficacy of radiotherapy and do not predict the clinical course of the disease. Nevertheless, persistent tumor at 18-24 months after EBRT is associated with high rates of local and distant relapse (30-32).

EBRT in Locally Advanced Prostate Cancer

EBRT combined with hormonotherapy is the treatment of choice for tumors with prostate capsule infiltration or extension to the seminal vesicles (stage T3/C) and in cases with tumor fixation to the adjacent anatomical structures (stage T4/D1). Hormonotherapy alone, postponing radiotherapy at the time-point when clinical symptomatology demands palliation, can also be used in selected cases.

Radiation portals include the pelvic nodes, the prostate and the seminal vesicles. The radiation dose to the lymph nodes is 50 Gy and the local dose to the tumor should reach 76 Gy with conformal techniques. Paraortic area irradiation is also applied in some centers, but the value of this technique is controversial.

The efficacy of EBRT in T3/C-stages is remarkable, as the 5-year and 10-year disease-free survival is 50% and 30%, respectively (33). In a study by Hahn et al., the 5-year survival of 92 patients with T3-stage was 87.3% and the 10-year survival was 54% (17). In a recent RTOG study on 1554 patients with locally advanced T2c-T4 stages, the concurrent use of hormonotherapy improved the efficacy of EBRT in cases with high Gleason scores (5-year survival 81% vs. 70%) (34).

In D1-stage, EBRT has rather a palliative position, aiming to prevent or treat hematuria, obstruction, pain or lymphedema. An important success of EBRT has been reported with 100% control rate of hematuria and 75% of obstruction (35, 36).

The Importance of the EBRT Dose

Retrospective studies stress the importance of the radiation dose in the local control achieved after EBRT (37-39). In a randomized study, the dose of 70 Gy was compared to escalated doses up to 78 Gy, showing a significant improvement of the 5-year biochemical relapse-free interval (BRFI) in the group of patients receiving a higher radiation dose (40). This positive effect was confirmed only for patients with T3-stage (5-year BRFI 61% vs. 36%) or with high pre-EBRT PSA levels (5-year BRFI 75% vs. 48%). In another prospective study on 743 patients treated with escalated doses of EBRT between 65-81 Gy, the 5-year survival improved by increasing the radiation dose in high-risk patients (advanced T-stage, high Gleason score or high PSA) (41). IMRT techniques, delivering a dose of up to 86 Gy seem promising even in low-risk patients, but have to be confirmed in randomized trials (42).

In a recent analysis of 4839 patients with T1,2-stage prostate carcinoma treated with EBRT without hormonotherapy in 4 American centers, the dose of radiotherapy was a decisive factor in the radiotherapy efficacy in cases with high Gleason score or high pre-treatment PSA levels (43). Cheung et al. analyzed 363 patients with T3-stage disease or with high Gleason score or PSA levels, suggesting that dose levels higher than 75 Gy are needed in order to substantiate an important clinical benefit (44). Zelefsky et al. also agreed that a radiation dose higher than 75.6 Gy is linked with improved 5-year survival in younger than 60-year-old patients, stressing the importance of considering high-dose conformal radiotherapy regimens for the treatment of prostate cancer (23).

Changing Concepts in the Radiobiology of Prostate Cancer

An important development in the field of radiotherapy research for prostate cancer came recently from radiobiological analysis of clinical data. Although cancer tissues are generally considered to behave similarly to early responding tissues (i.e. rapidly regenerating epithelia), having therefore an α/β ratio >10 Gy, this does not apply in many situations and very low α/β values have been reported in many tumors (45, 46). In 1999, Brenner and Hall reported an analysis of mature data from 2 series of patients treated with EBRT or low dose-rate brachytherapy with permanent implants (47). Using the linear/quadratic dose-effect analysis model, the authors concluded that the α/β ratio value for prostate cancer is very low, about 1.5 Gy (0.8-2.2 Gy). If this is true, large radiotherapy fractions (hypofractionation) may be more effective than standard (2 Gy per fraction) radiotherapy. In a subsequent analysis of 17 clinical studies, Fowler et al. confirmed very low α/β ratios for prostate cancer (1.49-1.9 Gy) (48). An additional analysis by Brenner et al., of the results obtained from a clinical protocol combining EBRT with high dose-rate brachytherapy provided, once again, an α/β ratio of 1.2 Gy (49).
These surprising radiobiological data show that prostate cancer, in contrast to what is believed for human malignancies, behave as late responding tissues (i.e., connective tissue) so that large responding tissues are more effective. The 1.5 Gy $\alpha/\beta$ value is, in fact, much lower than the 4 Gy value of the late radiotherapy sequel for rectum and bladder. In this way, hypofractionation, apart from being more effective in prostate cancer, is also expected to be less toxic for the adjacent normal tissues. Even if the low $\alpha/\beta$ value of prostate cancer is attributed to hypoxia and not to intrinsic factors, as suggested by Nahum et al. (50), the choice of hypofractionation is appealing for the treatment of prostate cancer.

On the other hand, the duration of radiotherapy may also affect the radiotherapy outcome in prostate cancer (51), as prolongation of the overall treatment time intensifies the adverse effect of clonogenic cancer cell repopulation on the efficacy of radiotherapy. In spite of the general assumption that prostate cancer is a slow growing tumor, experimental studies show that large prostate carcinomas contain cancer cell populations with a high mitotic index (52-54). In theory, hypofractionated and accelerated radiotherapy should be highly effective in prostate cancer as it targets cancer cell populations with low $\alpha/\beta$ ratio values (due to intrinsic factors or due to hypoxia) and tumors with highly proliferating activity of clonogenic cancer cells.

The efficacy and safety of hypofractionated radiotherapy in prostate cancer has been confirmed in retrospective studies (55, 56). In a study by Livsey et al., 705 prostate cancer patients received hypofractionated and accelerated radiotherapy (16 fractions of 3.13 Gy in 22 days for a total dose of 50 Gy), with radiation portals localized to the prostate and seminal vesicles (55). The efficacy was at least as high as expected from standard radiotherapy, while the low toxicity noted allowed the escalation of the dose to 60 Gy. We also reported preliminary results of a hypofractionated accelerated radiotherapy scheme, also treating the pelvic area, using 15 consecutive fractions of 3.4 Gy (total dose of 51 Gy in 19 days) (57). The support of the scheme with a high daily dose of amifostine, a potent cytoprotective agent, allowed for the administration of this aggressive radiotherapy scheme with minimal early and late radiation toxicity, and with promising efficacy.

**Combined EBRT and Hormonotherapy**

The introduction of hormonal therapy was an important clinical development in the treatment of metastatic prostate cancer as in that of breast cancer. Hormonotherapy alone can also be considered for the treatment of small, low Gleason score tumors in elderly patients. Androgen deprivation also results in a potentiation of the efficacy of radiotherapy. Bolla et al. reported a randomized study on 415 high-risk T1,2-stage or T3-stage patients treated with EBRT, with or without hormonal therapy (58, 59). The administration of cyproterone acetate for a month and with goserelin for 3 years together with EBRT improved the 5-year survival from 62% to 78% and the 5-year disease-free survival from 40% to 72%. In a meta-analysis from RTOG in 2200 patients, androgen deprivation improved the 8-year survival after EBRT in patients with high Gleason scores by 20% (60). An important benefit was also noted in patients with low Gleason scores but large local tumors.

Today, the combination of androgen ablation with EBRT is a standard procedure for the radiation treatment of prostate cancer. Generally, the duration of hormonotherapy recommended to achieve optimal results is 1-2 years.

**Integrating High-dose Rate Brachytherapy in EBRT**

Interstitial radiotherapy (brachytherapy) is a popular radiotherapy method in early T-stages. The implantation of low-dose rate radioactive seeds ($^{125}\text{I}$ or $^{103}\text{Pd}$) in low-risk patients is an excellent alternative to EBRT or to radical prostatectomy, offering a 10-year survival without biochemical relapse of 70-85% (61-71).

High dose rate brachytherapy (i.e. $^{192}\text{Ir}$) can be used after an initial course of pelvic EBRT to deliver a booster radiation dose to the prostate, with minimal exposure of the adjacent rectum and bladder. This technique which delivers 1 or 2 large radiotherapy fractions of 8 Gy within 1 day assumes an interesting position as a complement to EBRT, especially from the point of view of recent radiobiological revelations of prostate carcinoma indicating high sensitivity to large radiotherapy fractions (72). Administration of 2 fractions of 7 Gy (16 Gy) produces a biological equivalent of 34 Gy to tissues with an $\alpha/\beta$ ratio of 1.5 Gy (such as prostate cancer), while the equivalent to adjacent tissues ($\alpha/\beta$ ratio of 4 Gy) is 25 Gy. In this way, an initial course of 44 Gy of pelvic radiotherapy followed by 2 fractions of 7 Gy give a dose to the prostate of 78 Gy, with a maximum dose to the areas proximal to the prostate normal tissue of 69 Gy. Several clinical protocols have been applied using high dose-rate brachytherapy to boost prostate area after EBRT (73-78).

**Post-operative EBRT**

High-risk patients undergoing radical prostatectomy have a high-risk of developing loco-regional or distant metastasis, so that post-operative pelvic radiotherapy and hormonotherapy are recommended (26, 27). It is, however, unclear, whether post-operative radiotherapy improves the survival figures (79). Early results from the RTOG (94-13) trial show that post-operative radiotherapy improves the prognosis of high-risk patients who also receive hormonotherapy (80). Certainly, the rationale for adding...
post-operative radiotherapy is far clearer in cases with positive surgical margins or lymph node metastasis.

**Reducing Side-effects from EBRT**

The early toxicity from EBRT comprises diarrhea, abdominal discomfort and pain, urgency, tenesmus and proctitis. Patients with a known history of hemorrhoids often develop more severe painful proctitis and bleeding. Dysuria and frequency are also common, while dry or moist skin desquamation may appear at the perineal area. Late sequels include chronic colitis and cystitis in 5% of patients. Hemorrhagic cystitis is uncommon, while urethral stenosis appears in no more than 5% of patients. Impotence occurs in 35% of patients, which seems to be reduced with the use of interstitial radiotherapy (81-94).

Using conformal radiotherapy or IMRT the dose to the rectum and bladder is reduced, therefore lowering the complications from these organs. Storey et al. noted that inclusion of 30% of the rectum in the isodose of 70 Gy leads to grade 3-4 complications in 25% of patients (95). Zelefsky et al. observed that conformal radiotherapy is accompanied with a high complication rate when the dose to the prostate exceeds 76 Gy, while IMRT seems better to protect the rectum, but not the bladder (42).

Amifostine is a wide-spectrum cytoprotective agent with proven efficacy against radiation-induced mucositis and platinum-induced toxicities. The use of amifostine as a cytoprotector for patients receiving pelvic irradiation is currently under investigation in clinical trials. Encouraging results have been reported in several studies, with protection against rectal and bladder toxicity (96-99). Amifostine may prove of significant value as a protector against aggressive hypofractionated radiotherapy, a regimen expected to substantially improve the efficacy of radiation against prostate cancer (57).

**Combined Chemo-radiotherapy**

Several novel drugs have shown substantial activity against prostate cancer. In a phase III trial (TAX327) docetaxel demonstrated important activity against metastatic prostatic carcinoma leading to reduction of PSA, improved pain response and an overall improvement of survival and quality of life (100). The drug has been recently approved for the treatment of hormone-refractory metastatic cancer, in combination with prednisone. Similarly, liposomal doxorubicin yielded important responses in hormone-refractory metastatic prostate cancer (101). Both drugs have been tested in phase I/II studies in combination with radiotherapy with acceptable toxicity (102, 103). Whether the combination of these drugs with radiotherapy can prove of benefit in patients with high-risk or locally advanced disease needs thorough clinical investigation.

**Combined Radiotherapy with Targeted Therapies**

The erbB family of oncoproteins (c-erbB-2 and EGFR) is frequently overexpressed in prostatic cancer (104-106). Monoclonal antibodies (i.e., the trastuzumab anti-c-erbB-2 MoAb and the cetuximab anti-EGFR MoAb) and pharmacological inhibitors of the EGFR tyrosine kinase activity (i.e. ZD1839/Iressa) have already been introduced into clinical practice (107, 108). These agents have shown activity against prostate carcinoma cell lines (109-111). Experimental studies suggest a strong radiosensitizing activity following erbB-blockage (112-117). Concurrent administration of such agents with radiotherapy may prove of importance in enhancing the local control of prostatic cancer.

The blockage of tumor angiogenesis is also expected to improve the efficacy of radiotherapy (118, 119). Experimental studies by Hall et al. indicated that high angiogenic activity results in reduced radiotherapy efficacy in prostate cancer (120). In experimental animals, the addition of anti-angiogenic agents to radiotherapy improves local control without increasing normal tissue toxicity (121, 122). The anti-angiogenic agent thalidomide has shown activity against prostate cancer in clinical studies (123-124). An anti-VEGF monoclonal antibody (bevacizumab) has already been approved for the treatment of metastatic colorectal cancer (125), and trials are on-going to assess its activity in other carcinomas. The combination of anti-angiogenic agents in prostatic carcinomas with excess angiogenic activity may prove of significance in improving the local control rates and the distant metastasis-free survival in patients undergoing radiotherapy for prostate cancer (126).

Another interesting molecular approach is the administration of antisense oligonucleotides (i.e. oblimersen sodium), aiming to block the anti-apoptotic activity of the bel-2 protein (127). This therapeutic approach has already entered the clinical phase of experimentation in hormone-refractory prostate cancer (128, 129).

**Conclusion**

EBRT is a principal method of treatment of localized prostate cancer, yielding similar survival rates to those achieved with radical prostatectomy. Post-operative radiotherapy in high-risk prostate cancer treated with prostatectomy may improve the local and distant disease-free survival of patients. Novel techniques, such as 3D-conformal radiotherapy and IMRT, allow the focussed administration of a higher radiation dose without affecting the surrounding normal tissues. Similarly, the cytoprotective agent amifostine may prove of significance in preventing radiation-induced toxicities. Developments in radiobiology suggest that large radiotherapy fractions may be more efficacious than standard radiotherapy and such fractionation of radiotherapy may
further improve local control rates. The use of interstitial high-dose rate implants to boost the prostate after an initial course of EBRT has been applied successfully in various institutes, suggesting a further improvement of the results obtained with external irradiation. The concurrent use of chemotheraphy with docetaxel, liposomal doxorubicin or novel biological agents may prove of importance in enhancing the cure rates of prostate cancer patients treated by radiotherapy.

References


Received September 20, 2005
Accepted October 19, 2005