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EDITORIAL

The evolution of radiotherapy techniques in the management of prostate cancer

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Acta Oncologica has a long tradition for publishing important papers focusing on radiotherapy (RT) for prostate cancer, covering aspects from planning and delivery techniques (1–4) to outcomes of clinical trials (5–10). Following-up on this tradition, the present issue brings no less than ten papers on RT of prostate cancer.

New and promising RT techniques and strategies are often initially tested in treatment planning studies as these are strong instruments to explore new treatments before bringing them into clinical practice, although such studies are not providing hard clinical evidence for the new and experimental treatment alternative. Several of the papers in this issue are of that nature, addressing the potential value of proton therapy, stereotactic body radiation therapy (SBRT) with the Cyberknife, focal therapy by use of I-125 brachytherapy, and integrated volumetric arc therapy (VMAT) of the prostate and pelvic metastases.

Proton therapy for prostate cancer goes back to the mid-1970s when Shipley and co-workers (11) at the Massachusetts General Hospital (MGH) conducted a pilot study on proton boost added on top of photon radiotherapy for prostate cancer. The total dose was 75.6 Cobalt-gray Equivalent (CGE) which was a very high dose at that time – long before the introduction of intensity-modulated and image-guided RT – and the reported morbidity was quite acceptable. In the years that have followed, until the end of 2013 more than 100,000 patients have received proton therapy and a large number of these were for prostate cancer (12). Ideally the early experience at MGH could have been the beginning of a process aiming at establishing a high level of evidence for treatment of prostate cancer with protons, but this has unfortunately not been the case; its use is therefore still debated (13). The recently presented PARTIQoL trial lead by the MGH is testing protons versus photons with morbidity (bowel morbidity) as the primary endpoint in therapy of low to intermediate risk prostate cancer (NCT01617161). There are many reasons for the late arrival of this trial. First of all, the clinical equipoise; is it ethical to assign a patient to photons in a randomized trial if we know that protons compared to photons have a favorable physical dose distribution with less low-dose bath to the patient? The comparison of photons and protons should not only be based on costs of the treatments (14, 15). We are awaiting the MGH initiative to provide stronger clinical evidence than we presently have, whether protons are sufficiently better or not.

In another strategy to improve treatment outcome and efficacy, Kole et al (16) have compared passive scattering protons with Gammaknife SBRT in ultra-fractionated RT of prostate cancer. There were only minor differences in the normal tissue radiation doses, although the penile bulb received a somewhat lower dose with protons compared to photon SBRT; the clinical significance of this reduction is not known. In another paper by Kole et al (17), the temporal patterns of PSA-changes after ultra-fractionated SBRT (36.24 Gy/5frx) for low to intermediate risk prostate cancer was investigated. Compared to conventional radiotherapy, the changes in PSA seem characterized by an initial steep decline and a benign bounce observed in more than one third of the patients. The steep drop has been used as an argument for the high efficacy

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of SBRT. SBRT for prostate cancer is now being introduced in many centers, but without sufficient evidence. Extreme hypo-fractionation of prostate cancer is still controversial (18). Fortunately, the HYPO-RT-PC study by Anders Widmark et al in Umeå, Sweden has succeeded to recruit 1100 patients and it will be one of the largest studies carried out in RT for prostate cancer (ISRCTN45905321). The HYPO-RT-PC will be the first and so far largest randomized study testing the efficacy and morbidity of extreme hypo-fractionation and it will thus provide valuable information on the fractionation sensitivity in this disease.

Polders et al (19) describes the result of a treatment planning study where they simulate focal therapy based on low-dose rate I-125 seed therapy of dominant intra-prostatic lesions. The study elegantly demonstrates the feasibility of this technique; it is possible to deliver accurate high brachytherapy doses to well defined volumes of the prostate as it is also possible for external beam RT (20). However, there are also a number of other important issues to consider within the concept of focal therapy for prostate cancer, including how to select the patients and subsequently how to define these dominant intra-prostatic volumes (21). Tissue-preserving focal ablation can be achieved also with a number of alterative techniques, including cryotherapy, high-intensity focused ultrasound and photodynamic therapy. It aims to target dominant cancer lesions rather than the whole prostate. Focal cryosurgery has been utilized for years by urologists, but it is now recommended by the Prostate Cancer RTC Consensus Group that these tissue-preserving therapies, including focal brachytherapy, should be tested in randomized trials (22).

In a study reported by Kiljunen et al (23), fourteen patients with locally advanced prostate cancer and metastases in the pelvic bones received volumetric modulated arc therapy (VMAT) with ablative doses to the prostate and the metastases in the pelvis. They found that it was feasible to deliver 42-76 Gy to the targets in these patients. Adding the pelvic metastases to the PTV resulted in increased radiation exposure to the organs at risk, but the morbidity was acceptable and it is notable that they did not observe any grade 2 or higher gastrointestinal toxicity. With only 2-years follow-up, survival outcomes were not reported. Overall there is an increasing use of ablative RT of prostate cancer metastases, driven by new treatment techniques that allow delivery of highly conformal radiation doses to the metastases either by hypo-fractionated SBRT or by normo-fractionated VMAT as in the present study. Oligometastases from colorectal cancer are frequently treated with ablation with various techniques, but it is based on low level of evidence (24, 25). Initial experiences with SBRT of prostate cancer metastases are on an even lower level, but indicates favorable outcomes (26, 27).

This issue also contains publications by Fonteyne et al (28) who shows that tightening up the constraints to the pelvic organs at risk resulted in decreased risk of rectal morbidity, by Carl and Sander (29) showing a favorable morbidity profile after image-guided RT using a removable nickel-titanium urethral stent and by Cahlon et al (30) showing the feasibility of anterior-oblique fields in proton beam RT.

As practice is changing by introducing more conformal techniques, including advanced photon-based RT and maybe even intensity-modulated proton therapy, combined with functional-imaging defined targets and image-guided treatment adaptation, it becomes of outmost importance that we keep an eye on the changes in pattern of the outcomes in terms of tumor control and morbidity. The movement from conformal to IMRT technique was not based on clinical trial results and the story is repeated in the change from photons to protons. The re-distribution of low doses to large patient volumes as seen with e.g. photon-based arc therapies is one example of a development whose long-term consequences are largely unknown.

The RT community is starting to accept that a very useful alternative – and indeed often the only realistic possibility – is to establish evidence through the use of large databases that includes relevant endpoints on disease control and morbidity (31). As in other parts of oncology, we have a tradition of using physician-administered morbidity scoring systems. They often give the highest priority to symptoms or items with the highest reproducibility such as diarrhea and rectal hemorrhage. However, these items are not necessarily the ones that are most important for patients and their wellbeing. Patient reported outcome measures (PROMs) have higher sensitivity in scoring of the patients' morbidity and PROM data should in future trials and data collection protocols have a higher priority than the conventional physician-administered morbidity scoring systems (32,33). PROM was also used in a small Swedish randomized study comparing radical prostatectomy with high dose irradiation, also published in this issue (34). Further, PROM data and not physician-administrated scoring systems should be used as the input morbidity endpoint for determining the constraints for treatment planning studies to further explore the potential of new, and potentially better, treatment techniques. This is an important avenue of research for the coming years of RT where joint efforts are instrumental.

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