Physica Medica xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Physica Medica

journal homepage: http://www.physicamedica.com

Review Paper

# Prostate cancer radiation therapy: A physician's perspective

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ARTICLE INFO

*Article history:*
Received 11 December 2015
Received in Revised form 27 January 2016
Accepted 17 February 2016
Available online xxxx

*Keywords:*
Prostate cancer
Radiotherapy
Image-guided radiotherapy
IMRT
3-D radiotherapy

ABSTRACT

Prostate cancer is the second most common cancer in men and a major cause of cancer deaths worldwide. Ionizing radiation has played a substantial role in the curative treatment of this disease. The historical evolution of radiotherapy techniques through 3D-conformal radiotherapy (3D-CRT), intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT) has allowed more accurate and precise treatments toward significant improvements in the therapeutic ratio. The addition of androgen deprivation therapy has significantly improved overall survival becoming the standard therapy for intermediate- and high-risk disease. Many randomized controlled trials have shown improved local control with dose escalation, and hypofractionated RT has been consolidated with proven efficacy and safe clinical results. However, several questions remain open in the radiotherapeutic management of prostate cancer patients and hopefully ongoing studies will shed light on these uncertainties. More individualized approaches are essential through better prognostic and novel predictive biomarkers of prostate radiotherapy response. Clinicians should critically interpret the evolving technologies in prostate cancer radiotherapy with important optimism but balancing the costs and the actual magnitude of clinical benefit. This article provides an overview of the basic aspects of radiotherapy treatment in localized prostate cancer from a physician's perspective.



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## An introduction to prostate cancer management

Prostate cancer (PCa) is the second most frequent cancer in men and a major cause of cancer deaths worldwide. Although the 5-year relative survival rates steadily increased from 73.4% in 1999–2001 to 83.4% in 2005–2007 [1], 250,000 patients die of PCa every year and the burden is expected to rise to 499,000 new deaths [2].

The increased PCa incidence is related to the implementation of serum-measured prostate-specific antigen (PSA) in the early 90', which has changed the landscape of PCa management. Lately the efficacy of PSA-based screening has been questioned due to the risk of over-diagnosis and over-treatment of clinically non-relevant or non-lethal disease and the associated morbidity of treatment [3].

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http://dx.doi.org/10.1016/j.ejmp.2016.02.012
1120-1797/

Currently, screening for PCa is one of the most controversial topics in the urological literature [4].

Patients with PCa seldom present clinical symptoms at diagnosis, unless the disease is locally advanced or metastatic. Usually an increase in the PSA level and/or an altered digital rectal examination (DRE) prompts further investigations with an ultrasound-guided biopsy for definitive diagnosis. The histologic diagnosis of PCa is then graded based in the architectural aspects of the cancer cells and is called the Gleason score. The Gleason score comprises the Gleason grades that are based upon the degree of differentiation and ranges from 1 (the most well-differentiated) to 5 (the least differentiated). The summation of the most extensive pattern (primary pattern) plus the second most common pattern (secondary pattern) gives the final Gleason score. The Gleason score ranges from 2 to 10, however Gleason score of 4 or less should not be reported (low grade malignancy), a Gleason score 5 or 6 is rarely associated with PCa death, while a Gleason score higher than 7 is associated with aggressive disease [5]. Additional histological information from biopsies can be important in the treatment decision (e.g. proportion of carcinoma-positive cores, extent of tumor involvement). Overall, depending on the PSA levels, Gleason score and the tumor size in the prostate (T category), staging of the disease should be supplemented with bone scanning and abdominopelvic computed tomography (CT) or multiparametric magnetic resonance imaging (mpMRI) [6].

In non-metastatic PCa patients, the most frequently used treatment modalities are radical prostatectomy, radiotherapy (RT) (plus or minus androgen ablation) and active surveillance. Focal ablative techniques, such as cryotherapy and highly focused ultrasound, are less commonly used [7]. Overall, approximately 50% of men with localized PCa undergo radical prostatectomy, and 25% RT (external beam RT and/or brachytherapy) [7]. Most attempts of randomized trials between treatment modalities have been unsuccessful due to slow and incomplete accrual related to patient or physician bias prior to randomization. Therefore, evidence is limited to allow a direct prospective comparison between outcomes with different treatment modalities [8,9].

The decision-making process regarding primary treatment often depends on many factors, including TNM classification, Gleason score (defined using an adequate number of core biopsies), baseline PSA, age of the patient, associated comorbidity, life expectancy, International Prostate Symptom Score (IPSS) plus uroflowmetry recordings, and the risk group classification (see Section "Risk grouping and radiotherapy recommendations"). Many men with localized PCa will not benefit from definitive treatment and about 45% of men with PSA-detected PCa are candidates for deferred management [10,11]. In men with comorbidity and limited life expectancy, treatment of localized PCa may be deferred to avoid loss of quality of life.

The potential side effects profile of surgery and RT varies enormously and this is usually a key factor in the treatment decision. Numerous clinical trials and other prospective studies, from both academic and community settings, have consistently demonstrated that prostatectomy causes more urinary incontinence and erectile dysfunction [12,13], with a 0.5% risk for perioperative mortality [14]; whereas radiation causes more urinary irritation and bowel/rectal symptoms [13,15], with a small risk of treatment-induced second malignancy [16]. The major limitations of the available data are the frequent retrospective nature of the studies and the use of different assessment tools preventing a proper comparison between treatment modalities and techniques. In the absence of prospective clinical trials, RT largely offers similar oncological outcomes as compared with radical prostatectomy, and is undoubtedly an established curative treatment for PCa.

## A brief history of prostate cancer radiotherapy

The first experience with RT in the treatment of PCa started with brachytherapy in the beginning of the twentieth century. Radium sources were implanted in the urethra and rectum as a palliative treatment [17–19]. This rudimentary approach paved the way, later on, to important developments in techniques for brachytherapy using radioactive sources inserted via the perineum, the rectum or an open bladder. Willet Whitmore and colleagues described an open implant technique using the $^{125}$I radioisotope of iodine in the 1970 s [20]. The isotope was sealed in miniature titanium cylinders and inserted into the prostate without the aid of any imaging device. Although the technique had great appeal, it frequently resulted in inconsistent dose distributions, with some areas receiving too much and others too little irradiation. This led to serious complications and a high rate of local failure.

The use of brachytherapy declined up to 1983 when Holm et al. reported a technique of implanting the prostate with radioactive 'seeds' under the guidance of a transrectal ultrasonography [21]. This new approach revived brachytherapy and it became again a commonly used therapeutic option for treating localized PCa [22]. Nowadays, advanced planning systems coupled with better imaging modalities (e.g. MRI) allow a safer and more precise treatment (the role of brachytherapy in PCa treatment is covered in details in a separate article in this journal issue).

In the early years of external beam radiation therapy (EBRT) for PCa, older equipment and techniques were unable to properly deliver optimal doses of radiation to deep-seated prostatic tumors because of unavoidable skin toxicity so EBRT was frequently used in combination with radium insertion. With the discovery of the castration treatment for PCa in the early 1940 s [23], RT lost popularity. However, in the 1950 s the higher-energy cobalt machines were implemented and RT started to be increasingly utilized again. One of the first reports of PCa patients treated with cobalt 60 ($^{60}$Co) therapy focused on patients with locally advanced, unresectable disease [24]. Afterward, Juan Del Regato published on a series of patients who were apparently cured following treatment with $^{60}$Co [25]. Of historical importance is the extensive work from Bagshaw and collaborators in the late 50's showing that higher-dose, small-field radiation could allow patients to undergo curative radiation treatment without the need for surgery and without exceeding the tolerance dose of normal structures. RT techniques and regimens devised by Bagshaw for localized PCa became standard of care in many centers [26,27]. Over the subsequent decades, higher-energy accelerators and the design of new RT machines have been developed and implemented. Improved imaging resources, such as computerized tomography, and data-processing capabilities, shifted radiation delivery from 2-dimensional into three-dimensional (3D) conformal treatment plans that allowed better dose distributions permitting the prostate to be treated to higher doses of radiation, while adequately sparing the surrounding normal tissues [28].

In the late 1970 s, androgen deprivation therapy (ADT) was added to RT to reduce tumor burden and provide a more favorable geometry for external irradiation. Several randomized trials have now proven the beneficial role of combining ADT with radiation and this is considered by many to be the current standard for unfavorable intermediate and high-risk disease [29].

## The evolution of radiotherapy techniques and its impact on the management of prostate cancer

The main goal of the radiation treatment is to deliver a high, tumoricidal dose to the tumor while keeping the dose to the surrounding normal structures below tolerance; thus the single most

Please cite this article in press as: Dal Pra A, Souhami L. Prostate cancer radiation therapy: A physician's perspective. Phys. Med. (2016), http://dx.doi.org/10.1016/j.ejmp.2016.02.012