Radiation treatment in prostate cancer: balancing between tumor control and toxicity

Heemsbergen, W.D.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: https://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 1

Introduction
1 Diagnosis of prostate cancer

Development of malignant cells in the prostate is a common process in elderly men in Western countries: about 30 % of the male population above 50 years has a -latent- prostate tumor at obduction. [1] The number of men diagnosed with prostate cancer has increased considerably in the past decades. A major cause of this increase is the clinical introduction of the biochemical PSA (prostate specific antigen) assay in the period 1980 -1990. With this assay part of the elderly male population with a symptom free prostate tumor could be diagnosed, whereas many of them would not have been diagnosed with prostate cancer (or at a higher age) before the “PSA era”. [2]

To determine the prognosis and the treatment options, the main diagnostic data are: the clinical stage according the American Joint Committee on Cancer guidelines (TNM stage), the PSA level in the blood and the pathological Gleason score of the tumor cells. The clinical stage indicates whether the cancer is confined to the prostate lobes (T2 tumor) or beyond the prostatic capsule and/or into the seminal vesicles (T3). If the tumor is not palpable or visible it is defined as a T1, and if the tumor invades adjacent structures it is defined as T4 (Fig. 1). From surgical series it is, however, known that the clinical staging (by digital rectal examination and/or echo) is not reliable. [3]

Whether regional nodes are positive (the N staging) can be determined by a laparoscopic nodal dissection but is often not established especially when the T stage and PSA level are relatively favorable. For the M staging a bone scan is used as the main diagnostic tool to find metastatic spread to the bones, when the patient is suspect for metastasis.

The PSA level indicates whether the prostatic gland cells produce more proteins than normal due to a benign or malign process. A slowly growing tumor is more often associated with low PSA levels than a fast growing tumor. The Gleason score (between 2 and 10) is a grading system which indicates the aggressive nature of the tumor. In general, a relatively
high Gleason score (poor differentiation) is correlated with a high PSA and a high clinical tumor stage, and vice versa. Also the volume of the tumor has a prognostic value and a large tumor volume often correlates with a poor differentiation grade. [3-4] Assessment of the tumor volume is however not a standard procedure in the current clinical practice. Another prognostic factor which is usually not assessed in standard clinical practice is the location of the tumor. The growth of prostate cancer cells starts in more than 80 % of the cases in the ‘peripheral zone’ of the prostate. This zone is located at the dorsal site of the prostate, close to the prostate capsule and the rectum which is unfavorable because of the high chance of extra capsular spread and beyond, like tumor infiltration into the neurovascular bundles. [5]

2 Treatment

Treatment options
Prostate cancer without extra-capsular, regional or metastatic spread can be cured by means of surgery removing the prostate (prostatectomy), local internal irradiation of the prostate (brachytherapy) or by external beam radiation therapy: radiotherapy (RT). For small tumors there is no evidence to date (from randomized trials) which is the best option of these three treatment types. [6] RT is, in general, the main treatment option when the tumor has invaded the prostatic capsule and/or the seminal vesicles. Also in for a T2 tumor in combination with a high PSA level and/or high Gleason score, RT is the main treatment option because the chance of invasion of surrounding structures is known to be high from surgical series. [7] The last decades RT is often combined with a hormonal treatment to improve outcome (survival) for prostate tumors with a relatively poor prognosis. Apart from the mentioned treatments, an alternative option can be a ‘wait-and-see’ policy, because the value of treatment is questioned for patients with a life expectancy below 10 years (i.e. patients of 80 years and older), for patients with a very slow rising PSA and for patients with a very limited tumor and good prognostic factors. [1,8]

Radiotherapy: current state of the art
Patients selected for radiotherapy are nowadays treated with conformal fields around the prostate. In earlier years it was common practice to treat the area of the pelvic bones with the pelvic nodes (elective treatment) and plan a boost to the prostate. This concept is still in use for a subgroup of patients with (a high risk for) tumor positive pelvic nodes.
The preparation of conformal RT for prostate cancer implies the delineation of the prostate (plus VS) on a multi-slice CT scan of the patient (the clinical target volume) and an expansion of this volume with a margin to a three-dimensional planning target volume (PTV). This margin is needed to cover for drawing uncertainties, patient setup variability, organ motion and other factors and is nowadays in the range of 5-10 mm. [9] With the use of a treatment planning system the required dose is planned with a good coverage of the PTV according to the guidelines of the ICRU. [10] Prescribed dose tot the PTV is in the range of 66-80 Gray (Gy) in daily fractions of 1.8 - 2.2 Gy. Based on established dose effect relations, dose constraints are used during treatment planning in order to minimize the risk for severe toxicity. These constraints limit especially the high dose area in the anorectal wall. [11]

For the execution of the RT (and the scan for planning purposes) the patient is often instructed with a drinking protocol and/or use of mild laxatives, in order to achieve a full bladder and an empty rectum for the planning CT and during irradiation. This is the most optimal situation, because the prostate can move several mm when there is a large variation in rectal filling. [12] A full bladder is associated with less small bowel in the treatment area. [13] During treatment the position of the patient is kept stable, often within specified limits of about 5 mm with respect to the bony anatomy close to the PTV (pelvic bones). The last decade also monitoring of the position of the prostate itself instead of the bones becomes more and more daily practice. [14]

3 Side effects of RT

Irradiation of the tumor cells by means of external RT, implies irradiation of surrounding tissues like the bladder, rectum, anal canal and the femur heads. Irradiation leads to cell damage which may lead to cell death, which eventually can lead to permanent damage. The radiosensitivity of tumor cells is higher than the sensitivity of normal tissue cells. Nevertheless, irradiation of the surrounding structures will lead to clinical side effects.

Dose limiting factors in RT for prostate cancer are toxicities concerning the anal canal and rectum, especially severe bleeding. These side effects are diverse and a result of functional loss. The RTOG/EORTC (Radiation Therapy Oncology Group / European Organization for Research and Treatment of Cancer) toxicity scoring system is a grading system for several organs, which describes in detail for the rectum (including anal region) several acute and late symptoms like bleeding, mucus loss,
increased stool frequency, cramping and diarrhea. [15] Also clinical interventions are incorporated in the scoring system, e.g. complaints needing laser treatment, blood transfusion and/or surgery. Reported maximum gastrointestinal toxicity grade 2 or more (moderate to severe complaints) are in the range of 30% - 50% for acute side effects (within 3-6 months after start RT) and 10% - 40% for late effects of RT (cumulative at 5 years). The scoring of these toxicities is however not well standardized. [16,17]

As mentioned earlier, in the last decades the irradiation fields in the pelvic area have become smaller due to the implementation of conformal radiotherapy. Several studies have shown that the incidence of (severe) toxicity dropped significantly using these smaller fields. [18, 19] As a consequence, the standard radiation dose has however increased considerably bringing toxicity levels back at a higher level.

4 Tumor control and disease specific survival

Tumor control in prostate cancer is defined as freedom from clinical failure and/or biochemical failure (i.e. a relevant rise in the PSA level). A “relevant” rise in PSA has been defined as a result of a consensus meeting in 1996 [20] and more recently, a meeting in 2005. [21] The first meeting resulted in a biochemical failure definition of 3 consecutive rises or any rise followed by an intervention with hormonal therapy, backdating the time of failure between the last non-rising value and the first rise. At the second meeting this definition was evaluated, drawbacks were discussed and an alternative definition was proposed (referred to as the “Phoenix definition”): a rise of 2 units (μg/L) above the nadir. The major drawbacks of the ASTRO definition were its sensitivity to the frequency of PSA determinations, the backdating (failure date was defined as midway between first rise and last non-rising value) and the risk of a false positive result in patients treated with adjuvant hormonal therapy.

Reported 5-year freedom from clinical and biochemical failure for patients with moderate to poor prognostic factors, after external radiotherapy with a dose of about 66-70 Gy, are in the range of 30% - 70%. [22] A number of randomized clinical trials demonstrated a significant improvement in tumor control for patients treated at higher doses of about 74-80 Gy (compared to 10 Gy less; about 64-70 Gy). [23] In contrast with the results for tumor control, there are to date no convincing data suggesting that these higher doses in localized prostate cancer lead to a relevant drop in prostate cancer related mortality, whereas there are many studies suggesting that
treatment of prostate cancer (in general) has only a marginal effect on mortality in the male population. [1-2,24] This can be explained by three important factors: 1) the prostate cancer patient is relatively old and therefore likely to die within 10-15 years anyway, 2) untreated localized prostate cancer (low and intermediate risk) will eventually lead to death but for many cases this will be only 10-20 years after the diagnosis because of the slowly progressive nature of the disease and 3) if the prostate cancer is an aggressive type leading to death in a short period, the chances for cure are relatively low. It is however broadly recognized that prevention of a painful progression of prostate cancer for a number of patients is a relevant reason to initiate an effective treatment for patients at risk.

5 This thesis

In this thesis different aspects of external beam irradiation for prostate cancer are studied and discussed, with the emphasis on dose effect relations with regard to tumor control and toxicity. Chapter 2-5 concern studies in which the relations between dose and acute & late anorectal toxicity were analyzed in two trial populations: the first trial was a randomized study in the Erasmus Medical Center in Rotterdam, evaluating rectangular versus conformal fields when prescribing 66 Gy (Chapter 2-3). The second trial concerned a multicenter study, initiated by the Erasmus Medical Center and the Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, comparing a standard dose of 68 Gy with a high dose of 78 Gy (Chapter 4-7).

The data used for the research in this thesis were obtained in two large randomized clinical trials and are therefore of a good quality: they were collected prospectively, by data managers according the applicable standards of good clinical practice, resulting in a database with a minimum of errors and missing data.

To determine the optimal treatment plan for a prostate cancer patient, underlying mechanisms of toxicity and tumor control have to be investigated carefully. In this thesis we address the question how to optimize the relationship between risks and benefits of radiotherapy in prostate cancer: how can we avoid risks of side effects as well as risks of underdosage of the tumor as much as possible.
References


