Modern external beam radiotherapy of prostate cancer

Nowoczesne metody leczenia wiązkami zewnętrznymi pacjentów z nowotworem gruczołu krokowego

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Introduction

Prostate cancer is the one of the most commonly diagnosed cancers. There are two main methods of prostate cancer treatment: surgery and radiotherapy (either external radiotherapy or brachytherapy). Because prostate cancer often progress slowly for some patients the so called active surveillance (monitoring) is carried out. A comparison of efficacy of prostatectomy, radiotherapy and active monitoring revealed that at 10 years horizon prostate-cancer-specific mortality for low risk group of patients did not differ statistically [1]. In this group, however, the rate of disease progression is lower in the surgery and radiotherapy group than in the active monitoring one. In the intermediate risk group of patients, the trials' results demonstrated that prostatectomy leads to slightly better statistics concerning overall and cancer specific survival [2]. However, surgery is associated with a higher decline in sexual function and a higher frequency of urinary incontinence. Therefore both treatments, surgery and radiotherapy alike, can be considered as a sound option for treatment. Decision on which type of treatment to choose depends on the personal patient's preferences.

Clinical evidence of dependence of treatment outcome on the total dose has been provided by several randomized trials [3,4]. In these trials, the prescription dose for external beam radiotherapy has increased even to 84 Gy (2 Gy per fraction) [5]. The control of prostate cancer has a high sensitivity to the size of the dose per fraction. Brenner and Hall estimated that the α/β value of the linear-quadratic model for prostate cancer is 1.5 Gy. This findings has been confirmed by Vogelius and co-workers in a systematic analysis of randomized trials of radiation therapy for prostate

174

Abstract

Prostate cancer is the most commonly diagnosed cancer in modern societies. There are three methods of prostate cancer treatment: surgery and radiotherapy (either external radiotherapy or brachytherapy). Last 10 years radiotherapy developed very much. New methods of treatment allow for diminishing the total treatment time, making the irradiation almost fully safe. The results treatment of surgery and radiotherapy are very similar. The choice of treatment method dependence on the decision of a patient. In this paper new achievements in external radiotherapy are presented.

Key words: prostate, external beam radiotherapy, modern techniques of irradiation

Streszczenie

Nowotwór gruczołu krokowego jest najczęściej diagnozowanym nowotworem w populacji mężczyzn w krajach rozwiniętych. Obecnie u pacjentów z nowotworem gruczołu krokowego można zastosować chirurgię, radioterapię wiązkami zewnętrznymi i brachyterapię. W ciągu ostatnich 10 lat nastąpił bardzo szybki rozwój leczenia z użyciem promieniowania jonizującego. Najnowsze metody umożliwiają skrócenie całkowitego czasu leczenia i zapewniają niemal w pełni bezpieczne leczenie. Wyniki chirurgii i radioterapii są bardzo podobne. Wybór metody leczenia zależy od preferencji pacjenta. W tym artykule zostały przedstawione osiągnięcia radioterapii wiązkami zewnętrznymi w zastosowaniu u pacjentów z nowotworem gruczołu krokowego.

Słowa kluczowe: gruczoł krokowy, terapia wiązkami zewnętrznymi, nowoczesne techniki napromieniania

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cancer [6]. The estimated α/β ratios were 2.7 Gy (95% CI 1.6-3.8) and 1.2 Gy (95% CI 0.8-1.7), in the case when the overall treatment time was and was not taken into account respectively. These findings have changed the fractionation policy used for prostate cancer patients. In many radiotherapy centers, moderate hypofractionation regimes with dose per fraction of 2.6 – 4 Gy are used [7,8]. Stereotactic Body Irradiation with a very high dose per fraction, of about 7 Gy per fraction are used [9]. High Dose Rate brachytherapy should also be considered as the hypofractionated radiotherapy. The American Brachytherapy Society Prostate High Dose Rate Task Group recommends three different fractionations, namely 3 fractions of 10.5 Gy, 4 fractions of 8.5 – 9.5 Gy or 6 fractions of 6.0 – 7.5 Gy [10]. The dose escalation requires special protection of critical structures, the rectum and the bladder. The accurate delineation of the CTV and precise irradiation are thus extremely important. More and more frequently, prostate delineation is supported by MRI images [11,12]. Multi-parametic MRI is well established for detection of dominant prostatic lesion in order to escalate the dose delivered to this region [13]. Depending on the image guidance and the method of prostate position localization used during irradiation different CTV-PTV margins are used. The smaller the margin is, the more precise treatment is needed [14]. The selection of the smaller CTV-PTV margin is critical for safe irradiation, especially in case of dose escalation protocols. There are two organs that limit the dose delivered to prostate: rectum and bladder. Minimizing the dose delivered to these critical organs can be achieved by better dose conformity of dose distribution to PTV. This may be achieved by implementation of the newest Volumetric Modulated Arc Radiation Techniques [15]. Additional protection of rectum can be achieved by using a tissue spacer to move the rectum out of the high dose region [16,17].

The aim of the paper is to describe the modern technique of external beam radiotherapy of prostate cancer.

Patient preparation

In many radiotherapy departments before any step of radiotherapy chain patients are instructed to have a filled bladder and an empty rectum. The aim is to ensure as reproducible anatomical scenario as possible.

Positioning

A patient should be placed supine with legs slightly bended and kept on the supporting wedge. The angle of the wedge should be individually chosen. The prone position is not recommended. Bayley showed that in prone position there are larger movements of the prostate what requires larger CTV-PTV margin [18]. It is widely accepted to aligned patient's position using the skin marks (tattoos) and lasers. Our experience revealed that during simulation to define the reliable position of lateral skin marks after placing a patient on the table top one need to wait for some time (approximately 5 minutes). This time is needed to reach the stable, comfortable position for a patient. There are many different immobilization devices. Published data on the use of these devices did not lead to unambiguous conclusions concerning which one is the best [19].

Ensuring precise irradiation

The state of the art precise prostate radiotherapy is based on implanted fiducial markers that are used as surrogates of prostate gland position. There are a few types of fiducial markers, made from gold and polymer based [20]. Fiducial markers may be visualized with Megavoltage or kilovolatage images. They can also be visualized with Cone-Beam Computed Tomography. Using fiducial markers enables daily localization of the prostate immediately before irradiation. This method is not convenient for every day assessment of the intrafraction movement of prostate. Intrafraction motion can be assessed by real-time motion tracking systems such as Calypso [21]. However, this system is not widely used due to its high price. Kotte showed that in 28% of treatment fractions motions larger than 2 mm were observed [22]. Whichever system is used daily on-line verification should be performed. According to Skarsgaard if this procedure is followed the CTV-PTV margin of 0.4 cm is required to ensure 95% probability of complete CTV coverage in each treatment session [23]. To limit the intrafraction movement of the prostate both localization and irradiation should be as fast as possible [24]. Therefore imaging with two orthogonal portals is preferably. It is best if they are taken simultaneously.

Prostate contouring

Contouring the prostate is not an easy task. Gao demonstrated that prostate delineated on CT images was almost always larger than the anatomically defined prostate [25]. Unfortunately significant portions of the prostate were systematically excluded from the Clinical Target Volume. The underestimation was observed more frequently in the posterior part of the prostate. This might significantly influence on the increase of local failure as the most clonogenic cells occur in the peripheral zone of prostate (dorsal and dorso-lateral side of the prostate) [27]. McLaughlin in his excellent paper describes how to avoid errors in prostate delineation [28]. Certainly in modern era of prostate radiotherapy incorporating MRI images, and elastic image registration, may help in precise gland contouring [29,30]. Contouring with the support of radiologist should be considered and recommended.

Protection of the critical structures and ensuring prostate localization

Rectum and bladder are the two most important organs at risk in prostate patients. These two organs are in close physical contact with prostate what makes sparing of them very challenging. There are traditional approaches to optimization of dose distribution based on dose–volume histograms and the qualitative one. In the latter the NTCP for each side effect and each organ is calculated.

Rectum

To describe the late gastrointestinal toxicity three end points are used: rectal bleeding, high stool frequency and fecal incontinence. For rectum several dose-volume constraints are proposed [31,32,33]. According to RTOG dose escalation protocol (www.rtog.org) 0126 following dose-volume constraints were proposed:

Table 1 *Dose-volume constraints for rectum*

Rectum	
V75	<15%
V70	<25%
V65	<35%
V60	<50%

VX <D means the volume of the organ receiving more than D dose

It should be noted that in this protocol the fraction dose was 1.8 Gy. For moderate hypofractionation with fraction doses < 4 Gy dose-volume constraints should be converted to equivalente doses of 2 Gy fraction dose with the Linear Quadratic model using α/β value of 3 Gy [34,35]. For clinical practice to calculate the NTCP for rectum Defraene and co-workes recommend to use the LKB model with the Equivalent Uniform Dose as the indicator. They emphasized that several clinical factors (abdominal surgery, cardiovascular history, diabetes mellitus, smoking) taken into account significantly improved the predictive power of their model. Pathophysiology of late anorectal dysfunction following radiotherapy is complicated. Doses delivered to specific anatomical substructures of anorectum and close to anorectum play an important role in formation of rectum side effects. It might be that more detailed contouring of anorectum substructures will be introduced in the nearest future. Dose distribution will be optimized with regard to these subregions. Schaake and others revealed that the rectal bleeding, incontinence, and increase in stool frequency are associated with high doses to the anorectum, low doses to the external anal sphincter and iliococcygeal muscles, intermediate doses to the levator muscles respectively [36].

On the other hand introduction of perirectal spacing between the prostate and rectum changed the modern radiotherapy very much. There are two different rectal spacers available today. SpaceOAR™ System (Augmenix Inc.) and ProSpace™ Balloon (BioProtect Inc.) [37,38]. The first one is a polymethylene glycol gel that polymerizes in seconds creating a hydrogel space. The second one is is composed of biogradeable polymers balloon filled with warm saline. The effectiveness of rectal spacers in decreasing the dose delivered to anorectum region have been demonstrated in numerous studies and trials [39]. The distance between the posterior prostate capsule and anterior rectal wall after spacer insertion was increased of more than 1 cm. The absolute rectal surface encompassed by the isodes > 80% are decreased very much. The incidence of rectal toxicity higher than grade 2 was statistically significantly lower in the spacer group than control group [40]. It is very likely that introducing spacers will limit the role of the rectum as dose limiting organ at risk in prostate radiotherapy.

Bladder

The base of the bladder is always placed in the Planning Target Volume. It will receive the same dose as the prostate. To spare remaining part of bladder patients should be irradiated with full bladder. In the literature there is no reliable, well documented data on the constraints for bladder to reduce late genitourinary late toxicity. This is partly because bladder is highly distensible organ what leads large inter-fractional variations of the shape and size of the it [41]. Contouring the bladder as a solid organ may also deteriorate the analysis of results. It is worth to notice that in the Quantitative Analysis of Normal Tissue Effects in the Clinic the urinary bladder was the only organ for which dose-volume guidelines were not described. Dose-volume constraints for urinary bladder proposed by RTOG for dose escalation protocol 0126, and by Pederson are shown in Table 2.

Table 2 *Dose-volume constraints for bladder and rectum*

Bladder	RTOG	Pedersen
V80	<15%	NA
V75	<25%	NA
V70	<35%	<15%
V65	<50%	<30%
V40	NA	<60%

NA – not available
For moderate hypofractionation with fraction doses <4 Gy dose-volume constraints should be converted to equivalente doses at 2 Gy fraction dose with the Linear Quadratic model using α/β value of 3 Gy [43]
Source: [42].

Penile bulb

In the RTOG protocol 0126 it is recommended to keep the mean dose to penile bulb below 52.5 Gy what should lowered incidence of erectile dysfunction.

Femoral heads

Usually femoral heads are listed as organs at risk. However, modern radiotherapy techniques allow for quite substantial reduction of dose delivered to femoral heads. It is widely accepted that for doses < 50 Gy to entire femoral head the risk of femoral head necrosis and femoral head fracture is << 5%. [44] For all modern radiotherapy techniques this aim is easy to achieve.

Treatment planning

There are four modern treatment techniques of prostate cancer carried out with photons: Intensity Modulated Radiation Therapy, Volumetric Arc Therapy, Tomotherapy and Stereotactic Body Radiation Therapy. The published results of the dose distribution comparisons are ambiguous. [45,46] There is one clear advantage of VMAT technique which is the shorter time required to deliver plan. It creates a chance to reduce the dose to rectum and bladder. For longer time of irradiation larger CTV-PTV margin must be used due to intrafractional movement of the prostate. Curtis analysed the movement of the prostate with the help of the real tracking system. He showed that for 3 mm margin the irradiation time should be shorter than 240 sec if full prescribed dose to CTV is to be delivered for 95% of irradiation time [47]. The most precise positioning of a patient is achieved with internal fiducial markers or real time tracking systems. According to Badakhshi the CTV-PTV set-up margin may be 2.7, 4.3 and 4.4 mm for left-right, superior-inferior and anterior-posterior directions respectively. If intrafractional repositioning is implemented these margins may be decreased to 1.8, 2.9 2.8 mm [48]. Taking into account the uncertainty of contouring the smallest reliable margin should be at least 4 mm. The 5 mm is a good choice between safety of critical organs and delivery the full prescribed dose to prostate. However, it should be noticed that in some centers smaller margins are used. Posteriorly the margin might be even 3 mm only [49].

Dose prescription

There is an improvement in freedom from biochemical failure with dose escalation. Due to a low α/β value of the prostate cancer estimated to 1.5 Gy the prescribed dose is often described in terms of the biologically equivalent dose (BED1.5). A meta-analysis performed by Zaorsky and coworkers revealed that increased the BED up to 200 Gy was associated with improvements in the percentage of patients with freedom from biochemical failure. For larger doses no further dose response was evident [50]. These findings should be treated with caution. Data analyzed by the authors comprise also High Dose Rate and Low Dose Rate treatment either as boost or monotherapy. Dose distribution for brachytherapy treatments is quite inhomogeneous so the dose delivered for these techniques is not prescribed precisely.

Recently irradiation with a few very large fraction doses met a great interest. Much shorter treatment time and fewer visits to the hospital is very convenient for patients [52]. In SBRT the most often fraction doses of 7 to 10 Gy and total dose between 35 and 50 Gy is prescribed. [51] The majority of clinics for SBRT use the CyberKnife robotic radiosurgery. Seldom conventional accelerators are used [49,53].

New trends

Because the local recurrence after radiotherapy is mainly present in or close to dominant cancer foci (DCF) to increase the efficacy of treatment it is proposed to irradiate the whole gland to the full dose associated with boost to the dominant cancer foci. In the majority of studies the DCF was defined with MRI. The dose was escalated even to 95 Gy in 35 fractions [FLAME trail] or to 50 Gy delivered in 5 fractions (NCT01409473 trial). The results of FLAME trial showed no increase in GU and GI toxicity. The follow-up of all clinical attempts with boosting is too short to make any reliable conclusions concerning the improvement of tumour control. The idea of boosting is used for salvage prostate re-irradiation. It seems promising method of treatment in case of failure.

Summary

The external beam therapy of prostate cancer has certain advantages over alternative methods. It is less invasive than brachytherapy and much less invasive than surgery. Moreover, the surgery very depends on the skills of the surgeon. It has be noted than even the most experienced and skilled surgeon may encounter unexpected difficult anatomical conditions for the surgery which might affect the treatment outcome (personal communication).

The modern external radiotherapy of prostate cancer with photon beams requires: very careful preparation of patients for treatment and precise, image-guided irradiation. The following steps should be followed to prepare a patient for such modern external radiotherapy:

a) implantation the 3-4 fiducial markers into prostate gland,
b) injection of spacer into perirectal fat today hydro-gel or polymer balloon),
c) MRI and CT imaging in the treatment position (one week after implantation and injection),
d) contouring the prostate with the help of radiologist,
e) contouring the organs at risk,
f) preparation a VMAT plan,
g) irradiation with on-line verification of the prostate position (verification of the position of markers); in case of longer irradiation intrafraction verification may be considered.

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