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CURRENT TOPIC / АКТУЕЛНА ТЕМА

Modern radiotherapy in the treatment of localized prostate cancer

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SUMMARY
Prostate cancer (PC) is one of the most prevalent cancers in men and the second leading cause of cancer-related deaths, after lung cancer. The incidence and mortality from PC worldwide are correlated with increasing age.
The treatment of patients is multidisciplinary, with radiotherapy being an integral part, whether applied as an independent method or in combination with surgery or systemic therapy. The technological progress in the middle of the last century, opened up new possibilities in the planning and conducting radiotherapy started the new era of radiotherapy called modern radiotherapy. Today, highly conformal external beam techniques such as intensity-modulated radiotherapy (IMRT) and volume-modulated arc therapy (VMAT) are used as the gold standard in PC radiotherapy. They enable the precise definition of tumor volume based on modern diagnostic procedures, with maximum sparing of the surrounding organs. Advanced conformal techniques have also led to an escalation of the tumor dose, thus achieving better local control of the disease with significant reduction of early and late complications of treatment, the quality of life of PC patients is preserved.
In addition to technological progress, modern radiotherapy includes monitoring the side effects of radiotherapy, and assessment of clinical and individual parameters that affect sensitivity and response to radiation. This should enable personalized radiotherapy with optimization of the treatment for each patient, which is one of the goals of modern oncology.
Keywords: prostate cancer; IMRT; VMAT

INTRODUCTION

In men, prostate cancer (PC) is the second most frequent cancer diagnosed, and the second leading cause of cancer-related deaths [1]. In Serbia, it ranks third in both incidence and mortality, behind lung and colorectal cancer [2]. The incidence rate is almost 60% in men over 65 years of age [3]. It is believed that global aging of population and prolonged life expectancy increase the incidence of PC in the future, and it is anticipated that by 2030 there will be 20.3 million new cases, with 13.2 million deaths [1, 4].

Multidisciplinary approach in the treatment of PC includes radiotherapy (RT) as an important treatment modality in both localized and metastatic disease. It can be applied as a stand-alone method or in combination with other forms of treatment – surgery, or systemic therapy [5, 6].

Since the clinical behavior of PC range from indolent to highly aggressive, it is important to know prognostic factors to determine the appropriate treatment as well as possible benefits and side effects of each of the therapeutic options. The main prognostic factors include prostate-specific antigen value (PSA), Gleason score (GS) and tumor stage. Based on these three factors, according to the European Association of Urology (EAU), patients are divided according to the risk of biochemical recurrence after local treatment in three risk categories (Table 1).

The optimal management for localized PC remains controversial due to various forms of therapy that have different and specific impact on the quality of life and sexual function of long-term PC survivors. When comparing treatment options for localized PC, there are no significant differences in biochemical recurrence-free survival and disease-free survival between the patients treated with active

Table 1. The European Association of Urology risk categories for biochemical recurrence of localized and locally advanced prostate cancer [6]

Low-risk	Intermediate-risk	High-risk	
PSA < 10 ng/ml	PSA 10–20 ng/ml	PSA > 20 ng/ml	any PSA
and GS < 7 (ISUP grade 1)	or GS 7 (ISUP grade 2/3)	or GS > 7 (ISUP grade 4/5)	any GS (any ISUP grade)
and cT1–2a	or cT2b	or cT2c	cT3–4 or cN+
Localized	Localized	Localized	Locally advanced

GS – Gleason score; ISUP – International Society for Urological Pathology; PSA – prostate-specific antigen

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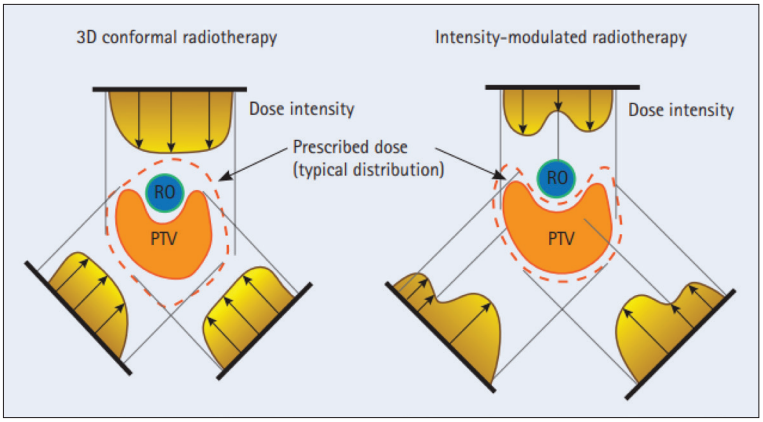

Figure 1. Intensity-modulated radiotherapy improves the conformity of the total dose delivered to the planning target volume (prostate and seminal vesicles) while reducing the dose to the risk organ – rectum, compared to conformal radiotherapy; the dotted line represents the applied dose delivered to the planning target volume [5];
RO – rectum; PTV – planning target volume

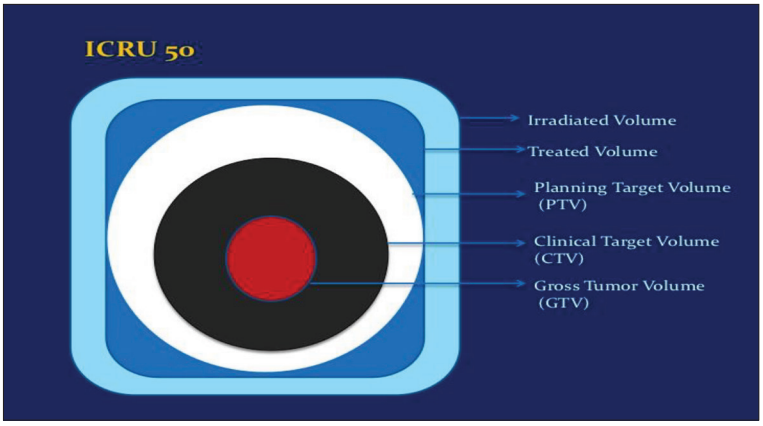

Figure 2. Schematic diagram of radiotherapy irradiation volumes – ICRU 50 [14]

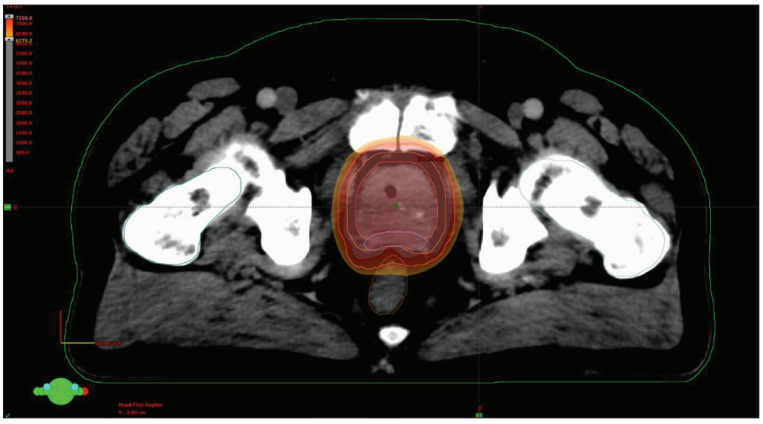

Figure 3. Isodose distribution in a patient with intermediate-risk prostate cancer (property of the Institute of Oncology and Radiology of Serbia)

surveillance, radical prostatectomy, or high-dose external beam radiotherapy (EBRT). In addition to the age of the patient, the presence of comorbidities, socioeconomic status of the patient, and trends in the personal practice of clinical centers play an important role in choosing the appropriate therapy [6, 7].

MODERN RADIOTHERAPY

The first reports of radiation usage in the treatment of PC appeared in the early 20th century. EBRT was initially used only as an addition to interstitial radium treatment because kilovoltage radiation systems were not adequate to allow definitive treatment of deeply localized tumors such as PC. With the discovery of androgen-deprivation therapy (ADT) in the early 1940s, radiotherapy lost its popularity in PC treatment. In the late 1950s, the pioneering work of an American radiologist, Malcolm Bagshaw, introduced the possibility of treating PC using megavoltage radiotherapy [8]. Today, more than one third of men with localized PC are treated with only EBRT [9].

Improved diagnostic data processing, such as computerized tomography (CT) and magnetic resonance imaging (MRI), have resulted in three-dimensional conformal radiotherapy treatment (3D-CRT) with accurate visualization of the geometric positions of tumor and normal tissue [10].

Today, highly conformal EBRT such as intensity-modulated radiotherapy (IMRT) and volume-modulated arc therapy (VMAT) are used as the gold standard in the treatment of PC. Both techniques provide a complex dose distribution within the target volume (TV) and enables:

1. dose-escalation
2. better sparing of surrounding healthy tissue
3. better local disease control
4. lower morbidity rate

Radiotherapy treatments require a careful balance between adequate therapeutic tumor doses but not causing irreparable damage to normal tissues. Known as the "therapeutic ratio", ongoing technological advances and research continue to develop techniques to maximize this balance [5, 11].

Intensity-modulated radiotherapy

Worldwide, IMRT is most commonly used in PC. IMRT is a more advanced form of 3D-CRT. It is a technologically complex radiotherapy option developed to deliver the appropriate radiation dose to irregular and inhomogeneous TV with maximum sparing of the surrounding organs. IMRT uses dynamic multileaf collimators, which automatically and continuously adjust to the TV. This is achieved by subdividing each radiation beam into smaller beamlets and varying the individual intensities of these beamlets [5, 11]. In the treatment of PC, IMRT uses five to seven beams which reduce the dose to adjacent structures. A

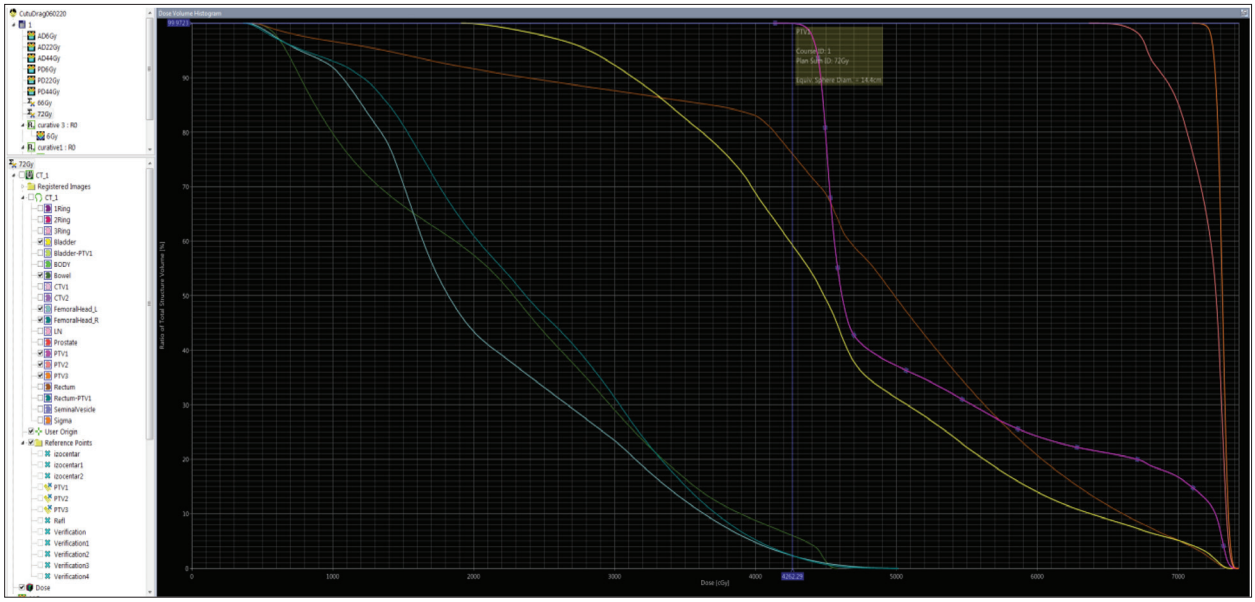

Figure 4. Dose Volume Histogram (graphical representation of target volumes and radiation doses, property of the Institute of Oncology and Radiology of Serbia)

standard IMRT plan often requires multiple fixed angle radiation beams, which can increase treatment delivery time. However, IMRT compared with 3D-CRT leading to a larger volume of normal tissue receiving low radiation doses which could be associated with an increased risk of secondary malignancies [11, 12].

Volumetric modulated arc therapy

In recent years, there has been a development of IMRT with the addition of rotating fields, to overcome a limit of IMRT with fixed fields. VMAT is a novel radiation technique which involves treatment of the whole TV using one or two arcs of beams from a machine that rotates around the patient continuously while delivering therapy. The main advantage over static fixed-gantry IMRT is reduced treatment delivery time and reduction of radiation dose to the rest of the body. With dose escalation using IMRT and VMAT, organ movement becomes a critical issue, in terms of both tumour control and treatment toxicity. Evolving techniques will therefore combine IMRT with some form of image-guided radiotherapy (IGRT), in which organ movement can be visualized and corrected in real time. IGRT involves the incorporation of imaging before and/or during treatment to enable more precise verification of treatment delivery and allow for adaptive strategies to improve the accuracy of treatment [6, 13].

Target volumes

Delineation of TV and organs at risk, in both IMRT and VMAT, is performed by using some imaging method (CT, MRI). Accurate determination of TV is the most important and most difficult part of PC radiotherapy. In the context of radiotherapy delivery, the International Commission on Radiation Units and Measurements (ICRU) has been developing guidelines for prescribing, recording and reporting dose for radiation therapy. TV is defined following the recommendations of ICRU, the most recent of which is ICRU 83.

TVs include:

- GTV (gross tumor volume) – represents the tumor mass visible on the planning CT scan. In PC, the tumor within the prostate itself is not visible on the CT image, thus entire prostate is defined as GTV.
- CTV (clinical target volume) – the volume around the visible tumor mass which includes possible microscopic zones of tumor spread such as seminal vesicles and pelvic lymph nodes. In postoperative setting, this volume includes the tumor bed and the surrounding zones of possible microscopic spread of malignant cells.
- PTV (planning target volume) – represents the TV to which the prescribed therapeutic dose is applied. They are obtained by the delineation of the appropriate margin on the CTV, which represents an additional safety zone, having in mind the inaccuracies of immobilization and physiological movements of organs.
- OAR (organs at risk) – represent organs receiving significant RT dose, such as intestine, rectum, bladder [11, 14].

Dose prescription

Up to now, using conventional RT, doses was in the range of 65–66Gy. Recent advances in RT, such as IMRT and VMAT, have significantly reduced irradiation-related toxicities, which makes dose intensification possible. Recommended treatment for the low-risk group of PC patients is in the range of 72Gy to over 80Gy, with a standard fractionation regiment (1.8–2Gy daily, five days a week). In the intermediate-risk group, doses are in the same range as in the low-risk group, with the addition of ADT for

4–6 months. Dose-escalation in this group leads to better treatment results, and by the EAU the lowest recommended dose is 76Gy. For the high-risk group for localized disease, dose-escalation and long-term use of ADT are recommended, usually 2–3 years [6, 11].

RADIATION TOXICITY

Modern radiotherapy includes monitoring of radiotherapy side effects. Side effects result from the damage of healthy tissues near the treatment area. Therefore, in assessing the overall effect of radiotherapy, it is necessary to assess the complications of the treatment. The side effects can be divided into:

a) Acute (early) complications – occur during radiation or a few weeks after it. These reactions are sometimes very severe, usually transient and less likely to lead to permanent damage.
b) Subacute complications – occur in the period from several weeks to several months after radiation.
c) Late complications – usually manifest after several months, even several years after the radiation. These changes are usually permanent (irreversible). Oncogenesis with the appearance of the so-called secondary malignancy caused by radiation is late damage.

With the use of modern RT (IMRT, VMAT), greater precision was achieved compared to the conventional RT, which results in less pronounced acute and late complications [15].

Small bowel and the rectum are two important dose-limiting structures in PC radiotherapy. Symptoms experienced during treatment include a change in bowel habits, bowel frequency, urgency, and fecal incontinence. The most commonly reported late toxicities were chronic diarrhea, proctitis, or rectal bleeding. Several factors have been associated with increased gastrointestinal toxicity and these include larger bowel volume receiving high doses of radiation, the patient's age, comorbidities such as diabetes, and concomitant use of ADT. Hemorrhoids, previous gastrointestinal diseases, and abdominal surgery, as well as the use of antiplatelet drugs, had a significant impact on the occurrence of acute toxicity grade ≥ 1 of the lower gastrointestinal tract [15, 16].

Bladder damage resulting from acute radiation toxicity is primarily manifested as radiation cystitis (frequent urination and dysuric disorders). Smoking, previous abdominopelvic surgeries and the use of diuretics significantly affect the occurrence of acute genitourinary toxicity grade ≥ 2. Risk factors for the development of late genitourinary complications (i.e., cystitis, hematuria, urethral stricture, or bladder contracture) are higher radiation dose, previous urinary problems, transurethral interventions, and acute genitourinary complications [15, 17].

The increased radiation dose for patients with localized PC has now become an established standard of practice. However, a few retrospective studies confirmed the increased risk of late complications when higher radiation doses are delivered using conventional RT. With IMRT the rectal and bladder volume receiving 95% of the prescribed dose was significantly reduced, by shaping the high-dose volume to the prostate, with an absolute reduction of 23% and 80%, respectively [15, 18].

In general, if IMRT with IGRT is used for dose escalation, rates of severe late side effects (≥ grade 3) for the rectum are 2–3% and for the genitourinary tract 2–5%. Several retrospective and prospective studies have shown that IMRT reduces the radiation dose in the OAR with diminished rates of acute and late toxicity, even with higher doses (> 74 Gy). Zelefsky et al. [18] compared treatment outcomes in two groups of patients, first treated with 3D-CRT, and the second treated with a higher dose using IMRT. The use of IMRT significantly reduced the risk of late gastrointestinal toxicities compared with conventional 3D-CRT yet the incidence of late urinary morbidity did not seem to be diminished [6, 18, 19].

CONCLUSION

Severe late complications significantly reduce the quality of life (QOL) of PC survivors. It is essential to strike a balance between the therapeutic benefits and radiotherapy side effects. Early detection and proper evaluation of complications as well as personalized therapy approach are especially important in increasing the patient's QOL. With the use of modern RT (IMRT, VMAT), greater precision achieved compared to conventional RT, allowing dose escalation, which has been shown to improve clinical outcomes while simultaneously reducing toxicity. This is particularly significant in long-term PC survivors.

Conflict of interest: None declared.

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Савремена радиотерапија у лечењу локализованог карцинома простате

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САЖЕТАК

Карцином простате један је од најчешћих малигнитета код мушкараца а други по смртности узроковане раком, одмах после карцинома плућа. Учесталост и морталитет од карцинома простате широм света су у корелацији са повећањем старосне доби.

Лечење болесника је мултидисциплинарно, при чему је радиотерапија његов неизоставан део, било да се примењује као самостална метода или у комбинацији са хирургијом или системском терапијом. Технолошки напредак средином прошлог века отворио је нове могућности у планирању и спровођењу радиотерапије и почетак нове ере радиотерапије, коју можемо назвати савремена радиотерапија. Данас се као златни стандард у радиотерапији карцинома простате користе висококонформалне транскутане технике као што су интензитетом модулисана радиотерапија (*IMRT*) и запремински модулисана ротациона терапија (*VMAT*). Оне омогућавају да се на основу савремених дијагностичких процедура прецизно дефинише волумен тумора уз максималну поштеду околних органа. Напредне конформалне технике довеле су и до ескалације туморске дозе, чиме је постигнута боља локална контрола болести. Овакав напредак је био услов да се знатно смање ране и касне компликације лечења и тиме очува квалитет живота онколошких болесника.

Дакле, савремена радиотерапија поред технолошког напретка подразумева и праћење нежељених ефеката радиотерапије и процену клиничких и индивидуалних параметара који утичу на осетљивост и реакцију на зрачење. Све ове активности треба да омогуће персонализовану радиотерапију са оптимизацијом плана лечења за сваког болесника понаособ, што представља један од циљева модерне онкологије.

Кључне речи: рак простате; *IMRT*; *VMAT*