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Current Approaches in Prostate Cancer Radiotherapy

Prostat Kanseri Radyoterapisinde Güncel Yaklaşımlar

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Abstract

Prostate cancer is one of the most common tumor in males. Radical prostatectomy, radiotherapy and watchful waiting are the main treatment options in localized disease. Radiotherapy together with hormonotherapy is accepted as the standard of care in patients with advanced stages. Surgery or radiotherapy has comparable local control and survival outcomes in localized disease. During recent years a significant reduction in the rate of serious side effects has been achieved due to the development of modern radiotherapy techniques. With the use of these techniques such as Intensity-modulated radiotherapy (IMRT), Image-guided radiotherapy (IGRT), Stereotactic body radiotherapy (SBRT), high doses can be given safely and the rates of serious short-or long-term side effects have not exceeded 1 percent. Modern radiotherapy techniques allow dose escalation for the target volume, and due to its achievement of sharp dose gradient around the target volume and enable to increase radiation doses homogeneously within the target volume without exceeding the tolerance doses in organs at risk. In the last few years hypofractionation has gained popularity in the curative radiotherapy of prostate cancer.

Keywords: prostate cancer, radiotherapy, intensity-modulated radiotherapy, stereotactic body radiotherapy, hypofraction

Öz

Prostat kanseri erkeklerde en sık görülen tümörlerdendir. Lokalize hastalıkta radikal prostatektomi, radyoterapi ve aktif izlem ana tedavi seçenekleri olup, ileri evrelerde radyoterapi ile birlikte hormonoterapi kullanımı standart tedavi olarak kabul edilmektedir. Lokalize hastalıkta cerrahi ve radyoterapi birbirine eşdeğer lokal kontrol ve sağkalım sonuçları sunmaktadır. Son yıllarda modern radyoterapi tekniklerindeki gelişmeler ciddi yan etki oranlarında belirgin azalmaya neden olmuştur. Günümüzde kullanılan Yoğunluk ayarlı radyoterapi (IMRT), Görüntü kılavuzlu radyoterapi (IGRT), Stereotaktik vücut radyoterapisi (SBRT) gibi modern radyoterapi teknikleri ile yüksek dozlar uygulanabilmekte ve ciddi erken ve geç yan etki oranları %1'leri geçmemektedir. Prostat kanserlerinde yüksek teknoloji radyoterapi uygulaması, hedef volüme yüksek doz verilmesini sağlarken hedef volüm dışında keskin doz düşüşü özelliği ile çevre kritik organların tolerans dozlarını aşmaksızın, hedef volümün aldığı radyasyon dozlarını homojen bir şekilde arttırılmasına imkân verir. Son yıllarda lokalize prostat kanserinin küratif radyoterapisinde hipofraksiyone rejimlere ilgi giderek artmıştır.

Anahtar Kelimeler: prostat kanseri, radyoterapi, yoğunluk ayarlı radyoterapi, stereotaktik vücut radyoterapisi, hipofraksiyone

Introduction

Prostate cancer is one of the most common cancers in men, and in the treatment of prostate cancer; active surveillance, radical prostatectomy, radiotherapy, hormonotherapy and chemotherapy are the treatment modalities used according to the stage and risk group of the disease. Intensity-modulated radiotherapy (IMRT), Volumetric modulated arc therapy (VMAT), Stereotactic body radiotherapy (SBRT), brachytherapy (BT), proton therapy are used in radiotherapy treatment as a result of developments in recent years [1].

Among these options, multiple treatment modalities can be equally effective with desirable clinical outcomes [2,3]. Clinical results obtained with intensive modulated and image-guided radiotherapy (IG-IMRT) used in the treatment of prostate cancer are also being achieved in our clinical practice.

The National Comprehensive Cancer Network (NCCN) prostat cancer guidelines include a variety of radiation therapy modalities as part of the standard of care for the definitive treatment of prostat cancer [4]:

Very low risk patients (T1c, Gleason score ≤ 6, PSA <10 ng/ mL, fewer than 3 positive prostate biopsy cores, ≤ 50% cancer in each core, PSA density <0.15 ng/mL/g) with a life expectancy of ≥ 20 years, external beam radiation therapy (EBRT) or (BT);

Low risk patients (T1-T2a, Gleason score ≤ 6, PSA <10 ng/ mL) with a life expectancy of ≥ 10 years, EBRT or BT;

Intermediate risk patients (T2b-T2c or Gleason score 7 or PSA 10 – 20 ng/mL), EBRT ± 4 to 6 months of androgen deprivation therapy (ADT) ± BT or BT alone;

High-risk patients (T3a or Gleason score 8 – 10 or PSA> 20ng/ mL) EBRT + 2 to 3 years of ADT, or EBRT + BT ± 2 to 3 years of ADT.

Indications for adjuvant EBRT following prostatectomy are: extracapsular tumor extension or invasion into the seminal vesicles (pT3), positive margins, Gleason score 8-10, seminal vesicle involvement, or detectable PSA.

Patients who have an undetectable PSA after prostatectomy with a subsequent detectable PSA that increases on two or more occasions without detectable distant metastases should be offered salvage EBRT [4,5].

Over the past decade radiation techniques have been improved to allow better coverage of tumor volumes with better sparing of adjacent normal structures. A smaller margin around the target means less radiation dose to the rectum, bladder and penile structures means a lower incidence of bowel, urinary and sexual side effects.

3D Conformal Radiotherapy (3D CRT)

Computed tomography (CT)-based EBRT planning was introduced in the 1980s. CT planning allows the radiation oncologist to delineate the anatomical structure of the prostate and organs at risk in axial images. It also enables multiple-shaped beams to be oriented and shaped around the target to reduce high doses to organs at risk. The 3D conformal radiotherapy, homogeneous in PTV while providing dose distribution in dose limiting organs (bladder, rectum and femoral head) is a highly protective treatment method.

Intensity-modulated Radiation Therapy (IMRT)

There are a large number of dose escalation studies in prostate cancer radiotherapy. These studies have confirmed that 74- to 81-Gy doses provided a 15-20% improvement in biochemical control compared with conventional doses of <70 Gy [6]. IMRT is an improved version of three-dimensional CRT. It can be described as its shape. IMRT provides a sharp dose reduction outside the target volume. It is possible to increase the doses (up to 86 Gy) delivered to the target volume without exceeding the tolerance doses of critical organs **(Figure 1)**.

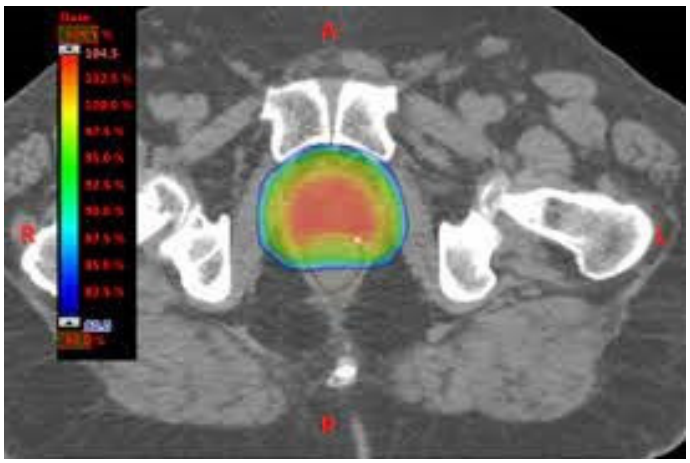

Figure 1. IMRT plan treating the prostate

One of the most important advantages of prostate IMRT, is a reduction in rectal toxicity. In IMRT applications, multi-leaf collimators continuously adapt to the target volume and thus the dose density of concave shaped areas (such as the rectum) is optimum.

Volumetric Modulated Arc Therapy (VMAT)

Volumetric modulated arc therapy (VMAT) has attracted increasing attention because of its greatly improved delivery efficiency over fixed-field IMRT. VMAT is a novel form of IMRT optimization that allows the radiation dose to be delivered in a single gantry rotation of up to 360 degrees **(Figure 2)**. VMAT is not expected to be superior to standard IMRT in terms of

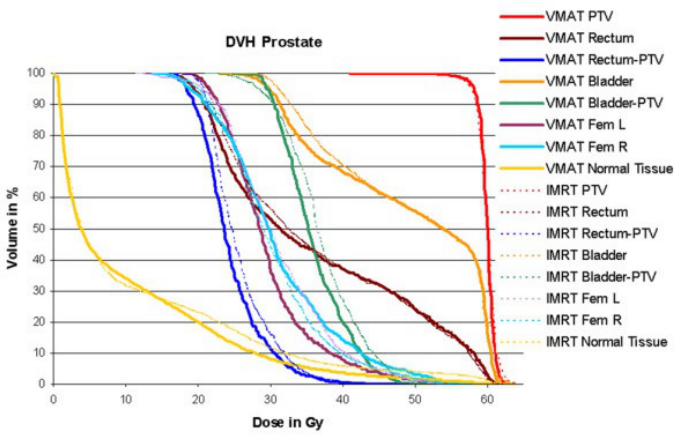

Figure 2. Dose volume histograms for prostate cancer

prostate cancer control, but is widely used because it can deliver each fraction in a shorter time (2–5 minutes). This technique is more convenient for the patient, and reduces the risk of mobility of tumour and organs at risk during treatment [7,8].

Hypofractionated Radiotherapy

Hypofractionation has gained popularity in the curative radiotherapy of prostate cancer. The rationale for hypofractionation is the low α/β ratio for prostate cancer which is even lower than that of the surrounding organs at risk. By hypofractionation isoeffective doses can be delivered to prostate in much shorter treatment time without increasing the side effects thus providing therapeutic gain. Hypofractionated EBRT delivers equivalent or greater total doses in a shorter overall treatment time than conventional fractionation, which delivers higher doses per fraction. Prostate cancer is more sensitive to hypofractionation and it allows patients to complete treatment more quickly. Data from randomised trials assessing this approach for localised disease shows that hypofractionation will be well tolerated [9]. There are two types of hypofractionation: moderate (daily delivery of 2.4–4.0 Gy per fraction, over 4–6 weeks) and extreme (the delivery of >4-10 Gy per fraction, ≤5 fractions to a total dose of 35-50 Gy).

Stereotactic Body Radiation Therapy (SBRT)

SBRT is a highly conformal method of delivering ultra-high dose radiation therapy. Also called Stereotactic Ablative Radiation Therapy (SABR), this technique will ablate malignant tissue in just few treatments delivered over 1-2 weeks. [7]. This accelerated scheduling is appealing to patients due to its convenience to patients over the traditional course of radiation that takes 5 to 8 weeks of daily treatments [10]. Extreme hypofractionation is delivered using SBRT. Randomized trials showed that moderate hypofractionation gives similar clinical and biochemical failure- free survival and toxicity rates as conventional fractionation. Although the results of phase I/II SBRT studies produced similar biochemical control and toxicity rates long term results must be evaluated. Phase III randomized trials will provide clear evidence **(Figure 3)**.

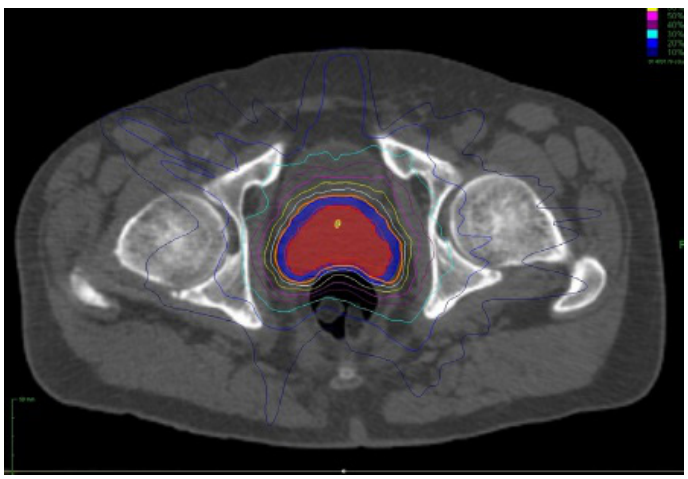

Figure 3. Prostate SRBT treatment

Brachytherapy (BT)

An alternative to EBRT with either X-rays or protons is the use of radioactive sources implanted directly into the prostate gland (BT) [11]. This technique was introduced at Washington University. There are two general approaches to prostate BT, low-dose rate (LDR) permanent radioactive seed implant and highdose rate (HDR) temporary radioactive seed implant [12]. Both approaches utilize real time ultrasound image guidance to assure accurate implantation of sources into the prostate while avoiding delivering high doses to the rectum, urethra and bladder. In addition, CT or MR imaging of the implant is performed following the procedure. This imaging allows quality assessment of the implant. In some cases of high risk prostate cancer, a combination of external beam radiation therapy and brachytherapy will be recommended. A recent Canadian study, the ASCENDERT trial, has reported superior biochemical control compared to external beam radiation alone. Of the 398 participants, 200 were assigned to the EBRT and 198 to the LDR boost. Compared with the 78 Gy EBRT boost, men randomized to the LDR boost were twice as likely to be free of biochemical failure at a median follow-up of 6.5 years (P=.004). The 5-, 7-, and 9-year Kaplan-Meier biochemical progression-free survival estimates were 89%, 86%, and 83% for the LDR boost versus 84%, 75%, and 62% for the EBRT boost (p=0.124). The 5-year prevalence of grade 3 gastrointestinal toxicity was lower than the cumulative incidence for both arms (1.0% vs 2.2%, respectively). Because of the improved biochemical progression-free survival, there is an increased interest in the radiotherapy community to boost intermediate- and high- risk patients with brachytherapy. Brachytherapy also has the advantage of shortening the treatment duration [13].

Proton Beam Radiation Therapy

Proton therapy provides advantages compared to photon radiotherapy. High- energy protons generated from a cyclotron are used in radiotherapy. The accelerated charged particles goes at a constant dose until it reaches a certain depth limit and most of its energy is discharged iat a distance of 0.5-1 cm (Bragg peak). The normal tissue outside this area is preserved **(Figure 4)**. This modality is especially attractive when

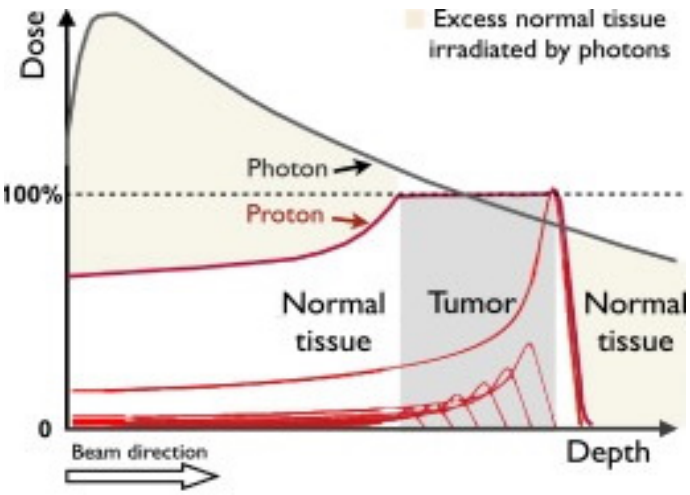

Figure 4. Proton therapy for prostate cancer

tumors are in close proximity to organs at risk. Massachusetts General Hospital and the Harvard Medical School reserchers are conducting a randomized clinical trial of IG-IMRT versus proton beam radiation in men with low- and intermediate- risk prostate cancer. The PARTIQoL trial is seeking to measure and compare relative impact of the two modalities on patient quality of life after treatment [14].

Conclusion

Radiotherapy is an integral part of the modern multidisciplinary management of prostate cancer. There have been advances in prostate cancer radiotherapy in recent years due to technological developments which enable achievement of higher doses in tumor volume while providing lower doses in organ at risk (OARs) Image-guided IMRT or VMAT is now the standard treatment modality that maximises the dose delivered to the target while sparing normal tissues.

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