

Brachytherapy is a curative alternative to radical prostatectomy or external beam radiation [i.e. 3D conformal external beam radiation therapy (CRT), intensity-modulated radiation therapy (IMRT)] with comparable long-term survival and biochemical control and the most favorable toxicity. HDR brachytherapy (HDR-BT) in treatment of prostate cancer is most frequently used together with external beam radiation therapy (EBRT) as a boost (increasing the treatment dose precisely to the tumor). In the early stages of the disease (low, sometimes intermediate risk group), HDR-BT is more often used as monotherapy. There are no significant differences in treatment results (overall survival rate – OS, local recurrence rate – LC) between radical prostatectomy, EBRT and HDR-BT. Low-dose-rate brachytherapy (LDR-BT) is a radiation method that has been known for several years in treatment of localized prostate cancer. The LDR-BT is applied as a monotherapy and also used along with EBRT as a boost. It is used as a sole radical treatment modality, but not as a palliative treatment. The use of brachytherapy as monotherapy in treatment of prostate cancer enables many patients to keep their sexual functions in order and causes a lower rate of urinary incontinence. Due to progress in medical and technical knowledge in brachytherapy (“real-time” computer planning systems, new radioisotopes and remote afterloading systems), it has been possible to make treatment time significantly shorter in comparison with other methods. This also enables better protection of healthy organs in the pelvis. The aim of this publication is to describe both brachytherapy methods.

Key words: HDR brachytherapy, LDR brachytherapy, prostate cancer, seeds.

Contemp Oncol (Pozn) 2013; 17 (5): 407–412
DOI: 10.5114/wo.2013.38557

Brachytherapy in the therapy of prostate cancer – an interesting choice

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Introduction

All the observations indicate a steady increase in prostate cancer incidence rate worldwide and in Poland. In 2000 a total of 5049 new cases were diagnosed in Poland, while in 2009 it was already 9142, which means a 55.2% increase in 9 years [1]. In Poland this is the second (after lung cancer) most often diagnosed type of cancer in men. In many countries of the world it is the most frequently diagnosed type of cancer, e.g. in the USA in 2010 a total of 217,730 new prostate cancer cases were recorded (28%) and 116,750 cases of lung cancer. A similar tendency is evident in many countries in Western Europe [2, 3]. More and more patients are diagnosed at the early stage of the disease, which enables effective treatment. This is further enhanced by the increasing popularity of the prostate-specific antigen (PSA) test.

The choice of the treatment modality of prostate cancer patients depends mainly on the stage of the disease and the prognostic factors [4]. A highly precise diagnosis of the progression of the disease is possible by means of imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), and transrectal ultrasonography (TRUS), in parallel with clinical assessment (digital rectal examination – DRE) and PSA test results [5–8]. Knowledge of the TNM classification and results of pathology grading of the cancer makes it possible to select the appropriate treatment option. It is recommended to use the guidelines of ABS, GEC-ESTRO/EUA, NCCN and ASTRO [9–12].

There are many treatment options for cases of prostate cancer limited to the organ itself, as per the recommendations of most associations dealing with the treatment of such cases [9–15]. Treatment options include radical treatment (surgery, external beam radiation therapy, brachytherapy), active surveillance and in individual cases hormone therapy alone. Some physicians suggest that radical treatment methods should be offered to patients with an estimated survival time longer than 5–10 years [11]. Most physicians, however, tend to initiate treatment just because of the lack of possibilities to forecast the progression of cancer. It has also been observed that a younger age of incidence is usually associated with a higher risk of increased tumor malignancy. Brachytherapy of prostate cancer as monotherapy [this concerns both techniques – high-dose-rate (HDR-BT) and low-dose-rate (LDR-BT)] is used more frequently, as it is associated with a smaller risk of potency disorders and urination disorders [16–21]. It is moreover better tolerated by patients burdened with different concomitant diseases, especially cardiological diseases, which disqualify the patient from surgical treatment. This method is also used in the case of patients who do not consent to surgery. For many men, an increasingly more important factor is the faster return to daily activities (including employment).

The aim of this paper is to describe both brachytherapy techniques used in the treatment of prostate cancer.

Brachytherapy – general rules

Brachytherapy (Greek *brachy* – from a small distance) is a method which employs the energy of photons and/or particles created by the decay of radioac-

tive isotopes. Brachytherapy of prostate cancer is an interstitial brachytherapy (a source of radiation is put directly into the gland using applicators). The principle of brachytherapy is rapid decrease of the radiation dose (inversely proportional to the square of the distance) with increasing distance from the radioactive isotope. Compared to EBRT, brachytherapy increases the concentration of the dose within the tumor area, and enables the administration of increased fractionated doses and higher biological equivalent doses, while significantly reducing the time of treatment. Hospitals which use brachytherapy may benefit from the significant cost reduction associated with one-time anesthesia and application of isotopes (shorter in-patient treatment time). Obtaining good prostate cancer treatment results depends on selecting the right patients for treatment [4, 9–11].

According to the method of application and the power of the source dose in the target volume (prostatic gland), brachytherapy is divided into high-dose-rate brachytherapy (HDR-BT) and low-dose-rate brachytherapy (LDR-BT). Low-dose-rate brachytherapy is the implantation of low-dose-rate radioactive sources (seeds) into the prostatic gland, which stay inside until the end of the patient's life. This is usually done using iodine-125 (^{125}I), palladium-103 (^{103}Pd) and cesium-131 (^{131}Cs) isotopes. High-dose-rate brachytherapy is a temporary type of brachytherapy where the high-dose-rate radioactive source [usually iridium 192 (^{192}Ir) or cobalt 60 (^{60}Co)] is inserted into the prostate from an afterloading machine during the temporary applicators implantation procedure.

Brachytherapy is used as the sole treatment method mainly in the low risk group. A large number of individual LDR-BT procedures are performed in this group of patients worldwide. This is supported by the very good treatment results reported in various publications, the relatively small number of side effects and the short time of treatment [22–27]. The procedure in which permanent implants are used is safe and does not require the use of special rooms with radiation shields, as is the case for HDR-BT. Moreover, due to the large competition between radiation source manufacturers in the

USA and the number of procedures performed, the cost of the procedure is relatively low and these procedures are commonly available [9, 14, 28]. The situation in Europe is different, as for at least 30 years HDR-BT has been developing in parallel [29–32]. High-dose-rate equipment is commonly available and the radioactive source used for treatment is the same as in the case of other neoplasms. The dwell-time position of the source in the applicators may be freely programmed during the procedure. The dwell times may be adapted to the requirements of treatment. In the course of treatment and the real-time planning procedure, the possibility of imprecise indication of the applicators' position in relation to the treated gland is minimal, which ensures high precision of the treatment.

Initially HDR-BT was introduced as a high-dose-rate supplement for EBRT and proved to be an effective and safe method of treatment [21, 22, 33, 34]. Treatment of patients from the low and intermediate risk groups with HDR-BT monotherapy was initiated at the end of the previous decade [9, 10, 26, 35–39].

Patient selection for brachytherapy

Selection of the method of brachytherapy for prostate cancer depends mainly on the stage of the disease, recommendations of the societies and the treatment capabilities of the center [4, 9–12]. Patients are usually divided into risk groups (Table 1) and selection criteria for treatment are usually based on the risk groups (Table 2). When analyzing the division of patients into risk groups for prostate cancer it is evident that the indications in the low risk group are clearly determined, whereas for the groups with a worse prognosis they differ. Patients who are appropriate candidates for HDR or LDR monotherapy usually belong to the low or sometimes intermediate risk group according to ABS [9, 43]. The National Comprehensive Cancer Network (NCCN) [11] recommends brachytherapy alone for the low risk group. These are patients with iPSA ≤ 10 , Gleason 2–6, T1–2a. International leading interstitial brachytherapy centers, which treat

Table 1. Comparison of prostate cancer patient risk groups

Risk group	Very low risk	Low risk	Intermediate risk	High risk	Very high risk
Seattle/MSKCC [40]	–	iPSA ≤ 10.0 and Gleason 2–6 and T1–2b	iPSA > 10 or Gleason ≥ 7 or T $\geq 2c$	2 from 3 risk factors from intermediate risk	–
Mt. Sinai [41]	–	iPSA ≤ 10 and Gleason 2–6 and T1–2a	iPSA 10–20 or Gleason 7 or T = 2b	2 from 3 risk factors from intermediate risk or iPSA > 20 ng/ml or Gleason 8–10 or T $\geq 2c$	–
D'Amico [42]	–	iPSA ≤ 10.0 and Gleason 2–6 and T1–2a	iPSA = 10–20 and/or Gleason 7 and/or T = 2b	iPSA > 20 ng/ml or Gleason 8–10 or T $\geq 2c$	–
NCCN [11]	T1a and Gleason ≤ 6 PSA < 10 ng/ml fewer than 3 biopsy cores positive, \leq cancer in each one, PSA density < 0.15 ng/ml/g	iPSA ≤ 10.0 Gleason 2–6 T1–2a	iPSA 10–20 or Gleason 7 or T2b–2c	2 from 3 risk factors from intermediate risk or iPSA > 20 ng/ml or Gleason 8–10 or T3a	2 from 3 risk factors from high risk or T3b–T42

MSKCC – Memorial Sloan-Kettering Cancer Center; NCCN – National Comprehensive Cancer Network; *in NCCN recommendations there are two groups which are not mentioned in other classifications

Table 2. Patient selection criteria for HDR-BT and LDR-BT according to ABS and GEC-ESTRO [4, 9, 10, 43]

ABS Prostate High-Dose-Rate Task Group	ABS Prostate Low-Dose-Rate Task Group	GEC-ESTRO – High-Dose-Rate, Low-Dose-Rate
Monotherapy Clinical T1b–T2b and Gleason score ≤ 7 and PSA ≤ 10 ng/ml	Clinical stage T1b–T2b and Gleason score ≤ 6 and PSA ≤ 10 ng/ml, select higher risk patients, salvage of select radiation therapy failures	Clinical stage T1b–T2a iPSA < 10 ng/ml, Gleason max. 6
Boost Patients with high risk features such as T3–T4, Gleason score 7–10, and/or PSA > 10 ng/ml Selected patients with “bulky” T1–2b tumor (inadequate information exists to clearly define bulky tumor based on DRE, TRUS, percentage positive biopsies)	≥ Clinical stage T2c and/or Gleason score ≥ 7 and/or PSA > 10 ng/ml	Stages T1b–T3b Any Gleason score Any iPSA without distant metastases
Special clinical situations: Inadequate information exists to recommend supplemental EBRT based on perineural invasion, percent positive biopsies and/or MRI-detected extracapsular penetration		

DRE – digital rectal examination; TRUS – transrectal ultrasound; EBRT – external beam radiation therapy; MRI – magnetic resonance imaging

patients with prostate cancer in the low risk group and sometimes patients in the intermediate risk group (T2b or iPSA < 15 ng/ml or Gleason = 7) have a 95% cure rate [35, 44–46].

Patients suffering from prostate cancer in the intermediate risk group are the most heterogeneous group as far as possible methods of treatment are concerned. Patients in this group may be treated in accordance with several different protocols: combination therapy EBRT + HDR-BT boost, EBRT alone, or HDR-BT alone – all approaches together with short-term hormone therapy (usually 6 months). In the USA, patients in this group also undergo EBRT with LDR-BT.

In the low risk group the most often used method of treatment is HDR-BT (isotopes ¹⁹²Ir, ⁶⁰Co) or LDR-BT alone (isotopes ¹²⁵I, ¹⁰³Pd, ¹³¹Cs) and also EBRT alone or combined with HDR-BT. Some of the patients are operated on using different surgical techniques. Patients in this group do not usually require additional hormone therapy.

Prostate cancer in the high risk group without distant metastases and especially with a high value of the PSA test and a T ≥ 2c should be treated with EBRT, possibly with irradiation of lymph nodes in the pelvis and boosting the local dose by means of brachytherapy together with long-term hormone therapy (contradicting recommendations include a treatment period of 2–3 years).

Contraindications for brachytherapy [4]

The most frequently cited contraindications for brachytherapy are: life expectancy of less than 5 years, distant metastases, history of transurethral resection of the prostate (TURP) with chronic, significant damage to the gland (in a period of 3 months before brachytherapy), and recurrent hematuria. Regular anticoagulation treatment should be interrupted at least 7 days prior to the implantation of radiation sources.

The volume of the gland should not exceed 60 cm³ (part of the gland lies closer to the pubic symphysis, which makes it harder to position the sources appropriately). It is possible to reduce the volume of the gland by administering hormone therapy for 3–6 months, which will enable a reduction of the volume of the gland in approximately 30% of patients [22, 31, 47]. Transurethral resection of the prostate (TURP) is a relative contraindication for brachytherapy and is associated with a higher rate (~50%) of urinary incontinence after the procedure. Nevertheless, several publications did not confirm these data and proved that risk of this kind of complication is less than 10% [48]. Contraindications for HDR-BT and LDR-BT according to ABS and GEC-ESTRO are presented in Table 3.

Brachytherapy techniques [49]

Low-dose-rate brachytherapy

Low-dose-rate brachytherapy is a radiation method that has been known for almost 30 years in treatment of localized prostate cancer. The main idea of this method is to implant small radioactive seeds as a source of radiation, directly into the prostate gland. Low-dose-rate brachytherapy is applied as a monotherapy and also used along with EBRT as a boost. It is used as a sole radical treatment modality, but not as a palliative treatment. The application of permanent seed implants is a curative treatment alternative in patients with organ-confined cancer, without extracapsular extension of the tumor [13, 14, 50–54]. Low-dose-rate brachytherapy represents the most conformal radiation therapy [55] and the number of patients referred for this radical treatment has grown rapidly in the last 15 years, especially in the United States [4, 14, 16, 34]. There are several reasons why LDR-BT has achieved such popularity. Better toxicity profile with

Table 3. Contraindications for HDR-BT and LDR-BT according to ABS and GEC-ESTRO [4, 9, 10, 43, 49]

ABS Prostate High-Dose-Rate Task Group	ABS Prostate Low-Dose-Rate Task Group	GEC-ESTRO – High-Dose-Rate, Low-Dose-Rate
Relative contraindications		
Severe urinary obstructive symptoms Extensive TURP defect or TURP within 6 months Collagen vascular disease	Severe urinary irritative/obstructive symptomatology Extensive TURP defect Substantial median lobe hyperplasia Prostate dimensions larger than the grid (i.e., > 60 mm in width and > 50 mm in height) Severe pubic arch interference Gross seminal vesicle involvement Prior pelvic radiotherapy Inflammatory bowel disease Pathologic involvement of pelvic lymph nodes	Volume > 60 cm ³ TURP within 6 months Infiltration of the external sphincter of the bladder neck Significant urinary obstructive symptoms Pubic arch interference Rectum-prostate distance on TRUS < 5 mm Lithotomy position or anesthesia not possible
Absolute contraindications		
Unable to undergo anesthesia (general, spinal, epidural, or local) Unable to lie flat	Distant metastases Life expectancy < 5 years	

Table 4. Doses for HDR-BT and LDR-BT according to ABS and ESTRO/EAU/EORTC [9, 43, 49, 53]

ABS Prostate High-Dose-Rate Task Group	ABS Prostate Low-Dose-Rate Task Group and ESTRO/EAU/EORTC Low-Dose-Rate
Monotherapy	
10.5 Gy × 3 8.5–9.5 Gy × 4 6.0–7.5 Gy × 6	¹⁰³ Pd – median 125 Gy (110–120 Gy) ¹²⁵ I – median 145 Gy (140–160 Gy) ¹³¹ Cs – 115 Gy
BT + EBRT	
15 Gy × 1 (with 36–40 Gy EBRT) 9.5–10.5 Gy × 2 (with 40–50 Gy EBRT) 5.5–7.5 Gy × 3 (with 40–50 Gy EBRT) 4.0–6.0 Gy × 4 (with 36–50 Gy EBRT)	¹⁰³ Pd Boost (with 41.4–50.4 Gy EBRT) 90–100 Gy ¹²⁵ I Boost (with 41.4–50.4 Gy EBRT) 108–110 Gy

BT – brachytherapy; EBRT – external beam radiation therapy

a higher dose applied to the prostate gland are the main advantages for brachytherapy in comparison with EBRT. Compared with radical prostatectomy, permanent seed implantation is a short, one-day therapy with a lower complication rate during and after the procedure (bleeding, urinary incontinence, impotence) [27]. Specific selection of radioactive isotopes and their correct localization allow a high dose to be deposited into the prostate tumor with a rapid fall-off of the dose outside the area of treatment and – at the same time – allows preservation of organs at risk (OaRs) [56, 57].

High-dose-rate brachytherapy

High-dose-rate brachytherapy is a temporary type of brachytherapy where the high-dose-rate radioactive source [usually iridium 192 (¹⁹²Ir) or cobalt 60 (⁶⁰Co)] is inserted into the gland during the applicators implantation procedure. In Europe, since at least 30 years ago, HDR-BT has been developed in parallel to LDR-BT [10, 22, 29, 32, 58] and, during the last years, also it is being used in the USA with growing interest. HDR equipment is commonly available and the radioac-

tive source used for treatment is the same as in the case of other neoplasms. The dwell-time position of the source in the applicators may be freely programmed during the procedure. The dwell-time may be adapted to the requirements of treatment [59]. In the course of treatment and the real-time planning procedure the possibility of imprecise indication of the applicators' position in relation to the treated gland is minimal, which ensures high precision of the treatment.

Brachytherapy doses [49]

According to ABS recommendations, patients with organ-confined prostate cancer are to be treated with monotherapy, and others with combined treatment [EBRT in 40–50 Gy dose with BT boost of 110 Gy and 100 Gy depending on which EBRT dose was administered (LDR-BT) or different HDR-BT schemas]. The HDR-BT procedure is performed once or repeated several times, depending on the fractionating schema assumed. The ABS proposes three fractionating schemas for HDR-BT monotherapy and four schemas for combined treatment [9], although other schemas are also applied (Table 4). Depending on the mode of fractionation, the fractionated doses are administered in one session at time intervals (e.g. every 6 hours) or are repeated in the course of subsequent procedures. Some centers use the 3 × 10.5–11 Gy fractionation scheme with a 1–2-week interval between fractions. Many different fractionation schemes make it difficult to compare treatment results. LDR-BT doses have been used for years and do not undergo significant changes. Perhaps our knowledge about appropriate dose rate will expand after confirming the importance of the introduction of molecular tests during histopathological examination [60, 61].

In conclusion, radiobiological models support the current clinical evidence for equivalent outcomes in localized prostate cancer with either LDR or HDR brachytherapy using current dose regimens. At present, the available clinical data with these two techniques suggest that they are equally effective, stage by stage, in providing high tumor control rates. High-dose-rate brachytherapy has an important role in the treatment of prostate cancer in combination therapy (EBRT

+ HDR-BT). The HDR-BT monotherapy has been used for more than ten years and its benefits ensure a certain advantage over other methods of treatment. This is a method which allows a high dose to be deposited in a very fast and precise manner in the immobilized organ, minimizing the irradiation of neighboring organs, personnel and the patient's family. Several hundred thousand patients have been treated with LDR-BT, with experience over 15 years and more in major centers in the US and Europe. Results are mature and well established, and mainly related to the risk group of the patient. LDR-BT has been a gold standard for prostate brachytherapy in low risk patients for many years in a lot of countries. It is a convenient technique for a patient. On the other hand, HDR-BT is more cost effective, with reimbursement in many countries, and results for HDR-BT monotherapy are very promising.

The author declares no conflict of interests.

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Submitted: 27.09.2013

Accepted: 18.10.2013