

# Low-dose-rate or high-dose-rate brachytherapy in treatment of prostate cancer – between options

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## Abstract

**Purpose:** Permanent low-dose-rate (LDR-BT) and temporary high-dose-rate (HDR-BT) brachytherapy are competitive techniques for clinically localized prostate radiotherapy. Although a randomized trial will likely never be conducted comparing these two forms of brachytherapy, a comparative analysis proves useful in understanding some of their intrinsic differences, several of which could be exploited to improve outcomes. The aim of this paper is to look for possible similarities and differences between both brachytherapy modalities. Indications and contraindications for monotherapy and for brachytherapy as a boost to external beam radiation therapy (EBRT) are presented. It is suggested that each of these techniques has attributes that advocates for one or the other. First, they represent the extreme ends of the spectrum with respect to dose rate and fractionation, and therefore have inherently different radiobiological properties. Low-dose-rate brachytherapy has the great advantage of being practically a one-time procedure, and enjoys a long-term follow-up database supporting its excellent outcomes and low morbidity. Low-dose-rate brachytherapy has been a gold standard for prostate brachytherapy in low risk patients since many years. On the other hand, HDR is a fairly invasive procedure requiring several sessions associated with a brief hospital stay. Although lacking in significant long-term data, it possesses the technical advantage of control over its postimplant dosimetry (by modulating the source dwell time and position), which is absent in LDR brachytherapy. This important difference in dosimetric control allows HDR doses to be escalated safely, a flexibility that does not exist for LDR brachytherapy.

**Conclusions:** 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, all available clinical data regarding these two techniques suggests that they are equally effective, stage for stage, in providing high tumor control rates.

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

## Purpose

Patients with organ-confined prostate cancer are the appropriate candidates for curative treatment. There are several modalities that can be performed in order to treat this kind of cancer, such as: external beam radiation therapy (EBRT), prostatectomy, cryotherapy or interstitial brachytherapy (BT). Brachytherapy is one of the oldest methods and means implantation of radioactive sources directly into the prostate.

### *Low-dose-rate brachytherapy*

Low-dose-rate brachytherapy is one of the radiation methods that is 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, however, not as a palliative treatment. The application of permanent seeds implants is a curative treatment alternative in patients with organ-confined cancer, without extracapsular extension of the tumour [1-7]. Recommendations are based on risk groups which are confirmed by several societies (Tables 1 and 2) [1,4,8]. This technique is particular favorite in United States, Japan, Netherlands, Spain. In Eastern European countries, however, high-dose rate brachytherapy method (HDR-BT) is still more popular in early staged prostate cancer treatment. As a monotherapy, LDR-BT seems to be a reliable choice for early stage prostate cancer, according to low morbidity rate good results and short hospitalization. It is curative alternative of radical prostatectomy or EBRT (i.e. 3D CRT, IMRT) with comparable long-term survival and biochemical control, and most favorable toxicity [9-14]. Low-dose-rate brachytherapy represents the most conformal radiation therapy, and the num-

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**Table 1.** American Brachytherapy Society recommendations for LDR-BT of prostate cancer [1]

Selection criteria	BT recommended, do well	BT optional, fair	BT investigational, poorly
PSA (ng/ml)	< 10	10-20	> 20
Gleason score	5-6	7	8-10
Stage	T1c-T2a	T2b-T2c	T3
IPSS	0-8	9-19	> 20
Prostate volume (cm <sup>3</sup> )	< 40	40-60	> 60
Q max (ml/s)	> 15	15-10	< 10
Residual volume (cm <sup>3</sup> )			> 200
TURP ±			+

IPSS – International Prostate Symptom Score, Q – maximum urinary flow rate in ml/s, TURP – transurethral resection of the prostate

**Table 2.** Indications and contraindications for LDR-BT monotherapy according to ABS and GEC-ESTRO recommendations [1,4]

Selection criteria	ABS (low risk group)	GEC-ESTRO
<b>Indications</b>		
PSA (ng/ml)	< 10	< 10
Gleason score	2-6	5-6
Stage	T1-T2a	T1c-T2a
AUA/IPSS	Low (1-7)	0-8
Prostate volume (cm <sup>3</sup> )	< 60	< 50
Q max (ml/s)	–	> 15
Residual volume (cm <sup>3</sup> )	–	< 200
TURP ±	–	–
<b>Contraindications</b>		
Life expectancy	< 5 years	< 5 years
TURP	Large and poorly healed defect	Exclusion criteria
Distant metastases	+	+
Gland size (cm <sup>3</sup> )	> 60	> 50
BPH	– (relative contraindication)	–
Pubic arch interference	+ (relative contraindication)	+ (relative contraindication)
Bleeding disorder	–	+
Positive seminal vesicles	– (relative contraindication)	

IPSS – International Prostate Symptom Score, Q – maximum urinary flow rate in ml/s, TURP – transurethral resection of the prostate, BPH – benign prostate hypertrophy

ber of patients referred to this radical treatment has grown rapidly in last 15 years, especially in the United States. In 1995, brachytherapy has taken a part in prostate cancer treatment only in ~5% (surgery ~65% procedures). Development of new techniques with new computer planning systems caused raising popularity of brachytherapy to about 40% in 2006. There are several reasons why LDR-BT achieved such popularity. Better toxicity profile with higher dose applying to prostate gland are the main points for brachytherapy in comparison with EBRT. Comparing with radical

prostatectomy, permanent seed's implantation is a short, one day therapy with lower complication rate during and after the procedure (bleeding, urinary incontinence, impotence). Specific selection of radioactive isotopes and their correct localization, allows to deposit high dose into the prostate tumor with rapid fall off the dose outside the area of treatment, and – at the same time – allows to preserve organs at risk (OaRs). Low-dose-rate brachytherapy has been a gold standard for prostate brachytherapy in low risk patients for many years.

#### High-dose-rate brachytherapy

High-dose-rate brachytherapy is a temporary type of brachytherapy where the high-dose rate radioactive source (usually iridium 192 [<sup>192</sup>Ir] or cobalt 60 [<sup>60</sup>Co]) is placed in the gland during the applicator implantation procedure. In Europe, since at least 30 years, HDR-BT has been developed parallel to LDR-BT [15-20], and in the last years with growing interest in the USA. 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 time may be adapted to the requirements of treatment. In the course of treatment and real-time planning, 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 [21-25]. Treatment of patients from the low and intermediate risk groups with HDR-BT monotherapy was initiated at the end of the previous decade [15,26-32].

The presence of both brachytherapy techniques in many countries is interesting to compare. The aim of this publication is to describe indications, similarities and differences of both brachytherapy techniques used in prostate cancer treatment.

#### Indications for brachytherapy

The American Brachytherapy Society (ABS) and the Groupe Européen de Curietherapie–European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) has

formed recommendations on consensus panel through clinical experience of experts and their analysis of published data. According to their publications, the appropriate candidates for LDR and HDR monotherapy are patients with a high probability of organ-confined disease (Tables 1 and 3). It is a general agreement not to apply LDR-BT or HDR-BT alone on patients with significant risk of extra prostatic extension. Most of physicians defines this group by the presence of at least two main risk factors such as PSA level greater than 20 ng/ml, stage higher than T2b and/or Gleason score greater than 7. It is to note that inclusions for HDR-BT include selected T4 cases (in combined therapy). In general intermediate risk group (at least one of the risk factors mentioned above) is not an absolute contraindication of a single BT modality treatment. Good results published by several authors change the physicians preferences to monotherapy combined with androgen deprivation [34]. However, to confirm these prospective observations, comprehensive studies are inevitable. In Table 4 inclusions for LDR-BT and HDR-BT monotherapy and combined therapy are presented.

### Contraindications

ABS and GEC-ESTRO recommends LDR-BT and HDR-BT in patients with at least 5 years of expected survival rate, what seems to be rather relative contraindication [1,14,15]. It is not included in HDR-BT Task Group recommendations (Table 5) [26,33]. According to their publications, neoadjuvant androgen deprivation can decrease volume of the gland before brachytherapy [1]. No nodal involvement and absence of distant metastases are basic points in definition of organ-confined prostate cancer. Patients with disseminated disease can not be cured by radical treatment with both techniques, which is not clearly mentioned in Hsu I-C *et al.* recommendations [26]. Transurethral resection of the prostate (TURP) is another relative contraindication for brachytherapy, and is associated with higher rate (~50%) of urinary incontinence after procedure. Nevertheless, several publications did not confirmed these data and proved that risk of this kind of complication is less than 10% [35]. Pubic arch interference as a result of large prostate may preclude adequate placement of seeds, which is the reason why

**Table 3.** General inclusion criteria for HDR-BT and LDR-BT according to ABS and GEC-ESTRO [15,26,33]

ABS Prostate High-Dose Rate Task Group	ABS Prostate Low-Dose Rate Task Group	GEC-ESTRO High-Dose-Rate
<b>Clinical stage</b>		
T1-T3b and selected T4	T1b-T2c and selected T3	T1b-T3b
<b>Gleason score</b>		
2-10	2-10	Any Gleason score
<b>PSA</b>		
No upper limit, but in almost all cases, patient does not have documented distant metastasis (TxNOMO)	In almost all cases, a PSA ≤ 50 ng/ml, NO, MO	Any iPSA without distant metastases

**Table 4.** Patient selection criteria for HDR-BT and LDR-BT according to ABS and GEC-ESTRO [4,15,26,33]

ABS Prostate High-Dose Rate Task Group	ABS Prostate Low-Dose Rate Task Group	GEC-ESTRO High-Dose-Rate, Low-Dose-Rate
<b>Monotherapy</b>		
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 score max. 6.
<b>Boost</b>		
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.
<b>Special clinical situations</b>		
	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

**Table 5.** Exclusion criteria for HDR-BT and LDR-BT according to ABS and GEC-ESTRO [4,15,26,33]

ABS Prostate High-Dose-Rate Task Group	ABS Prostate Low-Dose-Rate Task Group	GEC-ESTRO High-Dose-Rate, Low-Dose-Rate
<b>Relative contraindications</b>		
Severe urinary obstructive symptoms. Extensive TURP defect or TURP within 6 month. 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 <sup>3</sup> . 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. Lithotomic position or anesthesia not possible.
<b>Absolute contraindications</b>		
Unable to undergo anesthesia (general, spinal, epidural, or local). Unable to lay flat.	Distant metastases. Life expectancy < 5 years.	

TURP – transurethral resection of the prostate

volume of prostate higher than 60 ml seems to be relative contraindication. Potential solution of this difficulty in most cases is hormonal ablation for 3 months before the procedure. Neoadjuvant hormone deprivation can also reduce significant preoperative obstructive symptom, which is again a possible serious contraindication for brachytherapy, which decreases the probability of postoperative acute urinary retention. Several authors reported that downsizing of the prostate gland by 25-40% enables BT procedure, and reduces the risk of obstructive complication in patients with large glands [36]. It is worth to note that contraindications are defined in different mode in LDR-BT Task Group and GEC-ESTRO recommendations (Table 5).

### Implantation techniques

Most of both brachytherapy technical steps are similar. Many centers has improved and introduced their own techniques. Preoperative workup before brachytherapy insertion includes mechanical bowel preparation, prophylactic intravenous antibiotics, continued per os for several days afterwards (in some centers). Before the procedure, patients with history of deep vein thrombosis are being given heparin subcutaneously to prevent any complications in connection with these blood condition. Because of significant risk of perineal hemorrhage, the rest of the procedure candidates are to stop receiving anticoagulants, including aspirin, nonsteroidal anti-inflammatory drugs or warfarin. In the operating room, a patient is placed under general or spinal anesthesia in dorsal lithotomic position. After catheterization of contrast or air filled gel that are usually used to visualize the urethra, and to differentiate the bladder from the prostate. First step of the procedure is the necessity to determine the shape and size of the gland by initial transrectal ultrasound examination (TRUS) - before needles insertion. It can be done a few days before seeds (needles) insertion (preimplant treatment planning, preplanning) or can

be performed on the day of the procedure (intraoperative treatment planning). A biplanar probe at 5, 6, or 7.5 MHz of frequency, gather ultrasound visualization of prostate localization at 0.5 cm intervals, compared with the one after needles insertion. Treatment plan should contain several information such as needle location, number and strength of seeds (or number and position of HDR needles), and shape and volume of the target. To achieve the exact dose inside the prostate it is essential to use nomograms (inadequate amount activity per volume) combined with real-time TRUS and treatment planning system [37]. Transrectal ultrasound equipment is combined with special template, and by guiding creates stepping unit. Before proper procedure it is important to measure the distance from bladder base to template. Only then two stabilizing needles are being inserted through the template just posterior to the urethra on either side of the midline. Because of movement of the prostate, during the procedure a pre-plan can be created in order to minimize the risk of positioning errors. The loading pattern indicate coordinates in the computer planning system in connection with the templates stepping unit. That gives the physicians exact points to insert each needle. In this step brachytherapy techniques differ one from other. When the pre-plan is done, 20 cm long needles are inserted, and after consulting two plans (before and after insertion), radioactive seeds (in case of LDR-BT) are placed into the prostate gland. Withdrawing each needle should be done very carefully to avoid source migration inside the gland (LDR-BT). LDR-BT: once the procedure has been completed, the position of seeds must be observed under fluoroscopy and ultrasonography. Usually there is no possibility of removing seeds after insertion and if a "cold spots" are observed, a few extra seeds can be added to cover them. Performing a final CT scan of the prostate and postimplant dosimetry ends up the whole procedure of LDR seeds implantation in prostate cancer treatment. The patient leaves the theatre catheterized, and after removing it, can be dis-

charged home the next day. In LDR-BT there is another advanced technique of seeds implantation worth of mentioning. In stranded seeds technique, the point is to implant radioactive sources embedded in a polymer strand of glycolide, lactide and polydioxanone spaced from 5 mm to over 50 mm apart, and placed in 18-gauge needle. The main advantages of this technique is significant improvement in  $D_{90}$  parameter without increasing of toxicity rate and less number of seeds migration incidences.

**Doses**

According to ABS recommendations, patients with organ-confined prostate cancer are to be treated with monotherapy, 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 [26], however, other schemas are also applied (Table 6). Depending on the mode of fractioning, 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 centres use the 3 x 10.5-11 Gy fractioning schema with a 1-2 week interval between fractions [15,16,21]. Many different fractionations schema make difficult to compare treatment results. Using radiobiological models we noted also different BEDs (biologically effective doses), comparing to LDR-BT and HDR-BT – differences are sometimes significant [38].

**Treatment planning**

Describing of planning target volume (PTV) for HDR-BT and LDR-BT was published by both Task Groups [26,33]. The definition of volumes is based on ICRU Report 58. HDR Task Group recommendations are more specific and differs significantly from the recommendations of LDR Task Group (Table 7). There is a difference between recommended evaluated postoperative dosimetric parameters for HDR and LDR brachytherapy, according to ABS and GEC-ESTRO/EAU/EORTC [4,15,26,33] (Table 8).

**Dosimetry after LDR-BT**

Apart from dosimetric planning of the implant before or during seed insertion, ABS and GEC-ESTRO recommend postimplant dosimetry in all patients after LDR-BT for the best optimal care [1,4]. According to availability, cost and exact way to visualize a prostate with implanted seeds, CT-based dosimetry is in the world-wide use nowadays. CT scanning has to be determined by each center at a consistent postoperative intervals to check the evaluation of implanted seeds position and this intervals should be reported [1,4,7]. On every digital examination, physicians with physicist should obtain isodoses overlapping the gland at 50%, 80%, 90%, 100%, 150% and 200% of the prescribed dose, and compared with dose-volume-histograms (DVH) on previous CT scans. Nevertheless, ABS recommends for all centers to perform DVH and report the  $D_{90}$  value (dose received by 90% of the target volume) and the  $V_{100}$  (volume received 100% of the prescribed dose). To prevent any serious complication of organs at risk (OaR), the rectal and the urethral

**Table 6.** Doses for HDR-BT and LDR-BT according to ABS and ESTRO/EAU/EORTC [4,26,33]

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

BT – brachytherapy, EBRT – external beam radiation therapy

**Table 7.** Describing of planning target volume (PTV) for HDR-BT and LDR-BT [26,33]

ABS Prostate High-Dose-Rate Task Group	ABS Prostate Low-Dose-Rate Task Group
The definition of volumes will be in accordance with ICRU Report 58: - dose and volume specification for reporting interstitial therapy, - clinical target volume (CTV) is defined by the physician on the treatment planning scan, - for T1c-T2b the brachytherapy CTV includes the prostate only, - for T3a-T3b the brachytherapy CTV includes the prostate and extra-capsular extension, - PTV = CTV.	Prostate with margin. Seminal vesicles. Prostate minus non-cancerous regions of the gland (e.g., anterior base). Image-guided target volumes such as indium-111 or MR spectroscopy.

**Table 8.** Recommended evaluated postoperative dosimetric parameters for HDR and LDR brachytherapy according to ABS and GEC-ESTRO/EAU/EORTC [4,15,26,33]

ABS Prostate High-Dose-Rate Task Group	ABS Prostate Low-Dose-Rate Task Group	GEC-ESTRO/EAU High-Dose-Rate	ESTRO/EAU/EORTC Low-Dose-Rate
The prescription dose will be given only to the PTV.	V <sub>100</sub>	Dose rate and dose per fraction of the target dose	The volume implanted.
The goal is to deliver the prescription dose to at least 90% of the PTV (V <sub>100</sub> prostate > 90%).	V <sub>150</sub> V <sub>200</sub> D <sub>90</sub>	(D <sub>100</sub> , D <sub>90</sub> ) for CTV 1, CTV 2 and CTV 3.	The number of seeds.
The volume of bladder and rectum receiving 75% of the prescription dose should be kept to less than 1 cm <sup>3</sup> (V <sub>75</sub> rectum and V <sub>75</sub> bladder < 1 cm <sup>3</sup> ).	Urethral doses – should include: UV <sub>125</sub> , UV <sub>150</sub> , UD <sub>50</sub> , UD <sub>30</sub> , UD <sub>5</sub> and/or maximum and minimum dose.	Number and duration of the fractions.	The number of needles used.
The volume of urethra receiving 125% of the prescription dose should be kept to less than 1 cm <sup>3</sup> (V <sub>125</sub> urethra < 1 cm <sup>3</sup> ).	Rectal doses – cubic centimeters of rectum which received ≥ prescription dose (RV <sub>100</sub> ).	Time interval between fractions and the overall time.	The total activity implanted.
			The prescribed dose.
			The D <sub>90</sub> , that is the dose that covers 90% of the prostate volume as defined from post implant imaging.
			The V <sub>100</sub> , that is the percentage of the prostate volume that has received the prescribed dose.
			V <sub>150</sub> , the volume that has received 50% more than the prescribed dose.

GEC-ESTRO – The Groupe Europeen de Curietherapie – European Society for Therapeutic Radiology and Oncology, EAU – European Association of Urology, EORTC – European Organization for Research and Treatment of Cancer, PTV – Planning Target Volume, CTV – Clinical Target Volume, V – volume, D – doses, UV – urethral volume, UD – urethral doses, RV – rectal volume

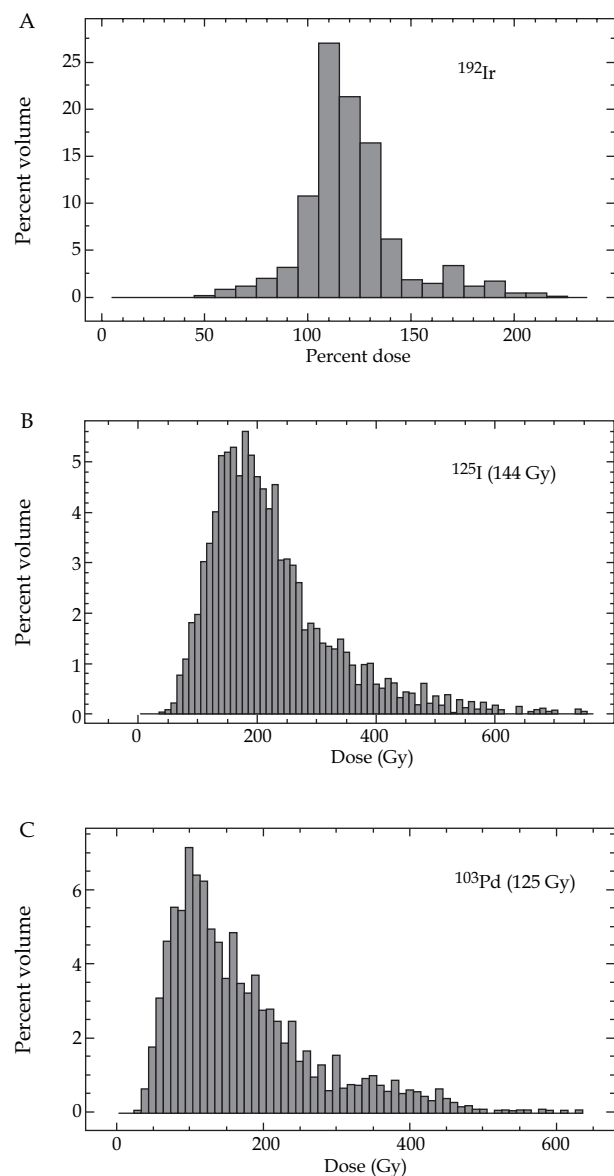
**Table 9.** Comparison of high-dose-rate temporary implants and low-dose-rate permanent seed implants. The following table was compiled by the HDR Prostate Working Group and presented to radiation oncologists at the American Society of Therapeutic Radiology and Oncology (ASTRO) meeting in Phoenix, October 1998

	High-dose-rate	Low-dose-rate
Conformal treatment	++++	++++
Target accuracy	++++	++++
Ability to treat extracapsular extension	++++	+
Ability to treat seminal vesicles	++++	++
Ease of control of radiation	++++	++
Lack of cold/hot spots	++++	++
Control of critical organ dose	++++	++
Modify dose distribution	++++	+
Need for external beam	Yes/Sometimes	No/Sometimes
Monotherapy	+	+++
Experience of physician	Crucial	Crucial
Pre-planning dosimetry	Not needed	Extensive (TRUS)
Post implant dosimetry	Not needed	Extensive (CT)
Stages treated	All, T1-T3	T1-T2
Gland volume > 60 cc at time of implant	Less difficulty	More difficulty
Pubic arch interference at time of implant	Less of a problem	Can't be done
Prior TURP	Less of a problem	Can't always be done
Final Dose Verification	Pre-treatment	Post treatment
Symptom duration	Weeks	Months
Implant cost	Higher	Lower

doses should be reported and correlated with patient ailments during the interview. In addition to the treatment, post implant radiographs can be performed to verify the seeds location and their number. The dose is usually prescribed at the periphery of the target volume and for  $^{125}\text{I}$ ,  $^{103}\text{Pd}$  - it equals to 145, 125 Gy, respectively. The prescribed dose in the centre of radiated volume should not be higher than 150%, what can be achieved by decreasing the number of seeds from potential “hot-spots” [3]. Oedema of the gland after implantation procedure is the last point worth of mention in this paragraph. Higher volume of prostate causes worse value of therapeutic dose cover. The use of treatment margin value (TM) in treatment planning should help to cover exact volume of the gland. Anyway, the role of treatment margin around the prostate is to cure possible microscopic disease spread outside the capsule. TM in most cases should be equal not less than 3-5 mm as seen in many publications [39]. The  $V_{100}$  indicator is used for assessment of the HDR-BT treatment plan for prostatic carcinoma – it provides a percentage value of the treated volume covered by the isodose of the fractionated dose. The American Brachytherapy Society recommends that the fractionated dose should cover > 90% of the planning target volume (PTV), i.e.  $V_{100} > 90\%$ . In the urinary bladder and rectum, the volume which receives 75% of the reference dose should be less than  $1\text{ cm}^3$  ( $V_{75}$  of the rectum and  $V_{75}$  of the urinary bladder <  $1\text{ cm}^3$ ). The volume of the urethra covered by 125% of the reference dose should be smaller than  $1\text{ cm}^3$  [1]. GEC/ESTRO-EUA-EORTC recommends the median target dose (MTD) in the urethra at a level of less than 120% per fraction, and below 50 Gy of the total dose on the bulb of the penis in combination therapy with EBRT + HDR-BT in order to reduce the risk of impotency [4].

### The comparison of temporary and permanent implants

Two brachytherapy treatment modalities (LDR-BT and HDR-BT) can be only compared in monotherapy in patients with low risk tumors. In most cases, LDR-BT is administrated as a monotherapy in early detected prostate cancer. HDR-BT is usually applied along with external beam irradiation to patients with prostate tumors non qualified by strict stage terms. HDR-BT is relatively new as a monotherapy, and at the moment there are limited data about the results and the complication rates in longer follow-up [16,21,38,40]. In some publications HDR as a radiation modality has ability to deposit higher dose to the tumor and lower dose to organs at risk [38]. It produces more inhomogeneous dose distribution in the target (higher  $V_{150}$  and  $V_{200}$  parameters), but due to flexibility of planning, inhomogeneity can be used to keep the dose of organs at risk low while increase the dose on the periphery of the gland. Inhomogeneity is a cost of preserving conformality, and differs in both HDR-BT and LD-BT techniques. Figure 1 presents differential dose volume histograms for  $^{125}\text{I}$ ,  $^{103}\text{Pd}$  and  $^{192}\text{Ir}$  from average patient-derived data. We observed heterogeneous and ‘hot’ DVH, particularly for  $^{125}\text{I}$  and  $^{103}\text{Pd}$  [38] (Fig. 1). Because of impossibility to remove or adjust permanent seeds, there is no way to compensate isodose by computer planning system after implantation. Moreover, it is advisable to use high-dose rate brachytherapy in pro-



**Fig. 1.** Differential dose volume histograms (dDVH) for  $^{125}\text{I}$ ,  $^{103}\text{Pd}$  and  $^{192}\text{Ir}$  from average patient-derived data. Note that for the  $^{192}\text{Ir}$  HDR brachytherapy DVH, the dose scale is ‘percent dose’, because different dose fraction sizes can be prescribed (A). Note how heterogeneous and ‘hot’ these DVH are, particularly for  $^{125}\text{I}$  and  $^{103}\text{Pd}$  [38]

state cancer, suspected of extracapsular spread, in order to achieve better coverage of this area, if compared with gland only targeted seeds therapy, since the seed migration can be significant problem in this case. Apart from the dosimetry, the larger dose per fraction seems to respond better in local control of prostate cancer treatment. According to radiobiological considerations, the use of HDR-BT in these kind of tumors is far more practical. After temporary HDR-BT there are no restrictions about patients radioactivity, and possibility of seeds migration through the bloodstream outside the gland. Oedema’s therapeutic dose coverage trouble does not exist in temporary implantation procedure, because of real time planning and short treatment time.

There are also some positive aspects about using LDR-BT in radiation oncology. Patients with cancers at early stage are able to attend one day procedure in surgery with all cost profits, according to this fact. In United States, single LDR-BT costs much less than EBRT along with HDR-BT. The comparison of time duration in these two modality treatments is another serious plus point of using seeds therapy (one day versus 4-5 weeks). This technique has yet another strong argument - many cancer centers has a lot of experience in performing permanent implants, usually about 5 years longer than modern HDR-BT. Wide availability of this treatment and its frequent performing, give rise to increased number of publishing data with generally good results in treatment of organ confined prostate cancer. Seeds implants therapy, performed by experienced brachytherapist, gives almost the same quality of glands dose coverage as the temporary implants technique. One of the earliest summarized comparison of both brachytherapy techniques was presented at ASTRO Meeting in Phoenix, 1998 (Table 9).

## Conclusions

For the radiation treatment of prostate cancer high dose should be delivered for optimal biochemical control. 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 suggests that they are equally effective, stage for stage, in providing high tumor control rates. Several hundred of thousands of 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 Eastern Europe and results for HDR monotherapy are very promising.

Concluding, brachytherapy is a high, effective method of radiation dose, with higher concentration of the dose within the prostate, which affects the reduction in the risk of complications in OaRs and reduction in the frequency of complications such as impotence (5-15%) and urinary incontinence (< 5%). It is also the most cost-sparing technique of all prostate cancer treatment counting all costs including diagnostic, treatment and social costs after treatment.

## References

- Nag S, Beyer D, Friedland J et al. American Brachytherapy Society (ABS) recommendations for transperineal permanent brachytherapy of prostate cancer. *Int J Radiat Oncol Biol Phys* 1999; 44: 789-799.
- Porter AT, Blasko JC, Grimm PD et al. Brachytherapy for Prostate Cancer. *Cancer J Clin* 1995; 45: 165-178.
- Garbaulet A, Potter R, Mazon JJ et al. The GEC ESTRO Handbook of Brachytherapy. Brussels 2002; chapter 20, pp. 473-480.
- Ash D, Flynn A, Battermann J, de Reijke T et al. ESTRO/EAU/EORTC recommendations on permanent seed implantation for localized prostate cancer. *Radioth Oncol* 2000; 57: 315-321.
- Thompson I, Thrasher JB, Aus G et al. Guidelines for the management of clinically localized prostate cancer: 2007 update. *J Urol* 2007; 177: 2106-2131.
- Horwich A, Parker C, Bangma C et al. ESMO Guidelines Working Group. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; Suppl 5: 129-133.
- Skowronek J, Kanikowski M, Zwierzchowski G et al. Brachyterapia LDR w leczeniu raka gruczołu krokowego. *Wspolczesna Onkol* 2009; 13: 316-329 [In Polish].
- Mohler J, Bahnson RR, Boston B et al. NCCN clinical practice guidelines in oncology: prostate cancer. *J Natl Compr Canc Netw* 2010; 8: 162-200.
- Grimm P, Billiet I, Bostwick D et al. Comparative analysis of prostate-specific antigen free survival outcomes for patients with low, intermediate and high risk prostate cancer treatment by radical therapy. Results from the Prostate Cancer Results Study Group. *BJU Int* 2012; 109 Suppl 1: 22-29.
- Crook JM, Gomez-Iturriaga A, Wallace K et al. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. *J Clin Oncol* 2011; 29: 362-368.
- Ferrer M, Suarez JF, Guedea F et al. Health-related quality of life 2 years after treatment with radical prostatectomy, prostate brachytherapy, or external beam radiotherapy in patients with clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; 72: 421-432.
- Sylvester JE, Grimm PD, Wong J et al. Fifteen-Year Biochemical Relapse-Free Survival, Cause-Specific Survival, and Overall Survival following I-125 Prostate Brachytherapy in Clinically Localized Prostate Cancer: Seattle Experience. *Int J Radiat Oncol Biol Phys* 2011; 81: 376-381.
- Polascik TJ, Pound CR, DeWeese TL et al. Comparison of radical prostatectomy and iodine 125 interstitial radiotherapy for the treatment of clinically localized prostate cancer: a 7-year biochemical (PSA) progression analysis. *Urology* 1998; 51: 884-889; discussion 889-90.
- Machtens S, Baumann R, Hagemann J et al. Long-term results of interstitial brachytherapy (LDR-Brachytherapy) in the treatment of patients with prostate cancer. *World J Urol* 2006; 24: 289-295.
- Kovacs G, Potter R, Tillmann L et al. GEC/ESTRO-EAU recommendations on temporary brachytherapy using stepping sources for localized prostate cancer. *Radiother Oncol* 2005; 74: 137-148.
- Burchardt W, Skowronek J, Łyczek J. Samodzielna brachyterapia HDR raka gruczołu krokowego – alternatywa we wczesnym stopniu zaawansowania. *Przeegl Urol* 2012; 4: 33-38 [in Polish].
- Chicheł A, Kanikowski M, Skowronek J et al. Correlation between treatment plan parameters and particular prognostic factors in prostate cancer treated with high-dose-rate brachytherapy (HDR-BT) as a boost. *J Contemp Brachytherapy* 2009; 1: 11-17.
- Seppenwoolde Y, Kolkman-Deurloo I-K, Sipkema D et al. HDR prostate monotherapy – dosimetric effects of implant deformation due to posture change between TRUS- and CT-imagining. *Radiother Oncol* 2008; 86: 114-119.
- Martin T, Baltas D, Kurek R et al. 3-D conformal HDR brachytherapy as monotherapy for localized prostate cancer. A pilot study. *Strahlenther Onkol* 2004; 180: 225-232.
- Galalae RM, Kovacs G, Schultze J et al. Long-term outcome after elective irradiation of the pelvic lymphatics and local dose escalation using high-dose-rate brachytherapy for locally advanced prostate cancer. *Int J Radiat Oncol Biol Phys* 2002; 52: 81-90.



21. Kanikowski M, Skowronek J, Milecki P et al. Brachyterapia HDR raka gruczołu krokowego. *Urologia Polska* 2007; 2: 5-11 [in Polish].
22. Chicheł A, Kanikowski M, Skowronek J et al. Correlation between treatment plan parameters and particular prognostic factors in prostate cancer treated with high-dose-rate brachytherapy (HDR-BT) as a boost. *J Contemp Brachytherapy* 2009; 1: 11-17.
23. Martinez AA, Gustafson G, Gonzalez J et al. Dose escalation using conformal high-dose-rate brachytherapy improves outcome in unfavorable prostate cancer. *Int J Radiat Oncol Biol Phys* 2002; 53: 316-327.
24. Demanes DJ, Rodriguez RR, Altieri GA. High dose rate prostate brachytherapy: the California Endocurietherapy (CET) Method. *Radiother Oncol* 2000; 57: 289-296.
25. Demanes DJ, Rodriguez RR, Schour L et al. High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California Endocurietherapy's 10-year results. *Int J Radiat Oncol Biol Phys* 2005; 61: 1306-1316.
26. Hsu I-C, Yamada Y, Vigneault E et al. American Brachytherapy Society Prostate High-Dose Rate Task Group." Retrieved 15-03-2010, 2010, from <http://www.americanbrachytherapy.org/guidelines/index.cfm>.
27. Demanes DJ, Martinez AA, Ghilezan M et al. High-Dose-Rate monotherapy: safe and effective brachytherapy for patients with localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2011; 81: 1286-1292.
28. Martinez AA, Demanes J, Vargas C et al. High-dose-rate prostate brachytherapy: an excellent accelerated-hypofractionated treatment for favorable prostate cancer. *Am J Clin Oncol* 2010; 33: 481-488.
29. Rogers L, Rogers LI. Extended follow up of high-dose-rate brachytherapy as monotherapy for intermediate- risk prostate cancer. *Brachytherapy* 2010; 9 (Suppl. 1): S55-S56.
30. Yoshioka Y, Konishi K, Oh RJ et al. High-dose-rate brachytherapy without external beam irradiation for locally advanced prostate cancer. *Radiother Oncol* 2006; 80: 62-68.
31. Yoshioka Y, Konishi K, Sumida I et al. Monotherapeutic High-Dose-Rate brachytherapy for prostate cancer: five-year results of an extreme hypofractionation regimen with 54 Gy in nine fractions. *Int J Radiat Oncol Biol Phys* 2011; 80: 469-475.
32. Martinez AA, Pataki I, Edmundson G et al. Phase II prospective study of the use of conformal high-dose-rate brachytherapy as monotherapy for the treatment of favorable stage prostate cancer: a feasibility report. *Int J Radiat Oncol Biol Phys* 2001; 49: 61-69.
33. Merrick GS, Zelefsky M, Sylvester K et al. American Brachytherapy Society Prostate Low-Dose Rate Task Group. [http://www.americanbrachytherapy.org/guidelines/prostate\\_low-doseratetaskgroup.pdf](http://www.americanbrachytherapy.org/guidelines/prostate_low-doseratetaskgroup.pdf)
34. Merrick GS, Butler WM, Galbreath RW et al. Biochemical outcome for hormone-naïve patients with Gleason score 3+4 versus 4+3 prostate cancer undergoing permanent prostate brachytherapy. *Urology* 2002; 60: 98-103.
35. Wallner K, Lee H, Wasserman S et al. Low risk of urinary incontinence following prostate brachytherapy in patients with a prior transurethral prostate resection. *Int J Radiat Oncol Biol Phys* 1997; 37: 565-569.
36. Lee WR. The role of androgen deprivation therapy combined with prostate brachytherapy. *Urology* 2002; 60 (3 Suppl 1): 39-44; discussion 44.
37. Pujades MaC, Camacho C, Perez-Calatayud J et al. The use of nomograms in LDR-HDR prostate brachytherapy. *J Contemp Brachytherapy* 2011; 3: 121-124.
38. King CR. LDR vs HDR brachytherapy for localized prostate cancer- the view from radiobiological models. *Brachytherapy* 2002; 1: 219-228.
39. Leibel SA, Phillips TL. Textbook of Radiation Oncology, Second Edition 2004, Chapter 45, 988-1000.
40. Grills IS, Martinez AA, Hollander M et al. High dose rate brachytherapy as prostate cancer monotherapy reduces toxicity compared to low dose rate palladium seeds. *J Urol* 2004; 171: 1098-1104.