INTRODUCTION AND RESULTS OF LOW AND HIGH DOSE RATE BRACHYTHERAPY IN THE DEFINITIVE RADIATION TREATMENT OF PROSTATE CANCER

Ph.D. thesis
(short version)

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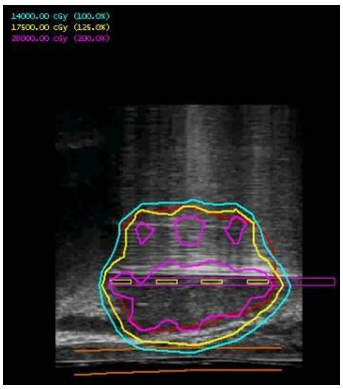

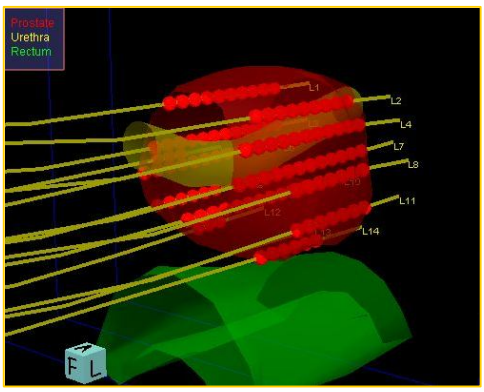

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Pécs
2013.

A. INTRODUCTION

Prostate cancer (PC) is the fourth most common cancer in Hungarian men according to the Hungarian National Registry of Cancer (1). Treatment of prostate cancer depends on the life expectancy, the stadium of the tumour and the prognostic group (2).

Non-metastatic PC can be treated by radical prostatectomy or radiotherapy. Androgen deprivation therapy (ADT) can be added to both procedures. Radiotherapy can be performed by external beam therapy (EBRT) or by interstitial brachytherapy (BT).

During prostate BT procedure, radioactive sources are placed into the prostate gland directly by needles through the perineum. Due to the introduction of transrectal ultrasound (TRUS) and radiotherapy treatment planning systems, the application of prostate BT has spread over worldwide in the last three decades. TRUS guided needle insertion and dosimetry calculated by treatment planning systems made the assessment of the dose to the prostate and the critical organs more exact.

According to the dose rate of the applied radioactive source low dose rate (LDR) and high dose rate (HDR) BT can be distinguished. For properly selected patients with early stage, localized prostate cancer the clinical results with permanent implant brachytherapy of the prostate (PIBP) are as good as with radical prostatectomy (3). HDR-BT using Ir-192 source is mainly applied for dose escalation (boost) added to external beam radiotherapy (4). Regards to the clinical results of the last two decades (5) the higher the dose to the prostate the better the biochemical and local relapse free survival (bRFS and LRFS) can be achieved.

The HDR-BT and the LDR-BT are two advanced radiotherapy methods. The former is used to escalate the dose in treating intermediate and high risk prostate cancer; the latter is to give an alternative to radical prostatectomy in early, localized cases with low morbidity rate and short hospital stay (6). Realizing these facts a prostate brachytherapy working group was organized in our department in 2000 with the aim of implementation of these methods into the practice in Hungary.

In the thesis, we describe the introduction of the HDR-BT as a boost treatment in Hungary added to three-dimensional conformal external beam radiotherapy (3D-CRT). Five-year clinical outcome of the first hundred patients treated in a prospective protocol is presented. We also report the introduction of PIBP in the country and our early experience with the treatment of the first consecutive 75 patients.

B. AIMS

1. To implement HDR-BT of the prostate for patients with clinically localized, intermediate and high risk or locally advanced PC.

2. To present the five-year results of patient treated with 3D-CRT and HDR-BT boost.

3. To compare dose-volume parameters of BT and clinical results.

4. To implement PIBP for patients with organ confined localized, low- and selected intermediate risk prostate cancer.

5. To review the early toxicity of PIBP.

6. To assess the late toxicity of PIBP in patients followed for at least one year.

C. SCIENTIFIC BACKGROUND

C.1. HDR-BT

In the last two decades, there were two main strategies to improve the result of radiotherapy for PC. The first was to add ADT to radiotherapy and the second was to escalate the dose to the prostate. Dose escalation can be achieved either by EBRT (7) or by BT (8). If BT is used for this purpose, organ movement and set up errors can be omitted.

First, Bertermann et al. (9) applied HDR-BT to escalate the dose in Kiel in 1985. Martinez et al (10) published their phase I-II dose escalation trial using HDR-BT in 1995. The method has become generally used worldwide after feasibility reports.

3D-CRT has been used for dose escalation to treat PC patients at our institute since 1995 (11). HDR-BT was introduced in our department in 2001 (12).

Pieters et al (13) compared EBRT +HDR-BT to sole EBRT and to EBRT + PIBP boost, and reviewed the literature. The hazard ratio (HR) of clinical relapse with sole EBRT and PIBP boost were 1.4 and 1.37 compared to HDR-BT boost. HDR-BT achieved the best overall survival rates too. HR for overall survival with sole EBRT and PIBP compared to HDR-BT boost were 1.5 and 2.33, respectively.

Nowadays a promising technique of dose escalation is the HDR-BT boost. Among all procedures, the highest biological effective dose (BED), 110-130 Gy can be achieved with this technique.

C.2. Permanent implant brachytherapy of the prostate (PIBP)

In LDR-BT or PIBP, low dose rate, small size (4.5 x 0.8 mm) capsulated radioactive sources are placed into the prostate permanently. Sources are also called seeds and the procedure is called seed implantation. According to their half-life, sources give the prescribed dose to the prostate in a prolonged time. Advantages of the method are the short hospital stay, and the low rate of side effects, such as incontinence and impotence (14).

The most frequently used isotope for PIBP is iodine-125 (half-life: 59.4 days, mean energy: 28 keV). Type of seeds can be loose, stranded or linked seeds. Herbert et al. (15) published retrospective data of implantation of 1500 patients in which 327 were implanted with loose and 1173 with stranded seeds. The biochemical no evidence of disease (bNED) were comparable after loose and stranded seed implantation (93.5% and 94%; p=0.85). Saibishkumar et al. (16) compared the dosimetry of postimplant treatment plans of 20 loose seed and 20 stranded seed implantation. Rectal and urethral doses were smaller with loose seeds. Seed migration can occur more frequently with loose seed technique.

Result with sole PIBP

Sylvester et al. (18) published their results after 11.7 year follow up with sole PIBP. Two hundred fifteen patients were treated with clinically localized PC and the 15-year bRFS was 85.9%. 15-year bRFS in low-, intermediate, and high risk cases were 85.9%, 79.9%, and 62.2% respectively. Others published excellent long-term results with sole PIBP (19, 20). The local control achieved by the sole PIBP was between 90-95% for low- and intermediate risk PC.

D. PATIENTS AND METHODS

D.1. HDR-BT

Patients treated with HDR-BT

As a new method of dose escalation, HDR-BT boost was introduced in the Radiotherapy Centre of the National Institute of Oncology in December 2001. Between December 2001, and October 2010, two hundred eighty patients with intermediate and high risk localized or locally advanced non-metastatic PC (T1-3 N0 M0) were treated with this

method. During or after the 3D-CRT one or two fractions of HDR-BT boost were carried out. In the thesis, we analyzed the outcome and side effects of the first 100 consecutively treated patients between 2001, and 2005. All these patients received one fraction of HDR-BT. Patients were classified into intermediate and high risk group according to D'Amico's risk group categories (21). Patients' clinical characteristics are shown in Table 1.

Table 1. : Clinical characteristics of patients with prostate cancer (n=100) treated by external beam radiotherapy and one fraction of HDR-BT

Feature	**n**
T status*	
T1	43
T2a-c	25
T3a-b	32
Initial PSA (ng/ml)	
<10	35
10-20	36
>20-60	29
Histological WHO grade	
I	42
II	35
III	19
Prognostic group	
Intermediate risk	39
High risk	61

PSA = prostate specific antigen; *AJCC 2002 = American Joint Committee on Cancer staging, 2002, 6. Edition

Patients' mean age was 65 years (range: 50-80 years), the mean initial PSA (prostate specific antigen) value was 18 ng/ml (range: 4-58 ng/ml). Patients with initial PSA >60 ng/ml were excluded from this analysis as they have a very high-risk of relapse after treatment, and their results will be reported separately. TNM status was defined by staging examinations. The World Health Organization (WHO) classification system was used for histological

grading, because Gleason score was not available for all patients. If Gleason score or grade was given, it was corresponded to WHO grade.

Institutional protocol for endocrine therapy included neoadjuvant and concurrent (3 to 6 months) ADT for intermediate risk patients. For high risk patients endocrine treatment was suggested to be continued for 2 to 3 years after the completion of radiotherapy. Sixteen patients were not given ADT, because either they refused it, or they could not get it due to their severe comorbidity. Mean duration of ADT was 17.7 months (range: 4-60 months). The duration of ADT was less than 12 months in 38 patients. For the other 46 patients long-term (>12 months) ADT was given. The median follow-up after the end of ADT was 50 months (range: 0 to 88 months).

External beam radiotherapy (EBRT)

EBRT was performed in supine position; the patients were immobilized with knee and ankle support system. Daily one fraction of 2 Gy was given, five times a week. Patients in high risk group received a four-field whole pelvic RT to a median dose of 46 Gy (range: 27 to 50 Gy), which was followed by a conformal irradiation via reduced beams to the prostate and vesicles up to a median dose of 60 Gy (range: 40 to 61 Gy). In intermediate risk patients, the pelvic lymph nodes were not irradiated. Prostate and vesicles were given a median dose of 60 Gy (range: 40 to 61Gy).

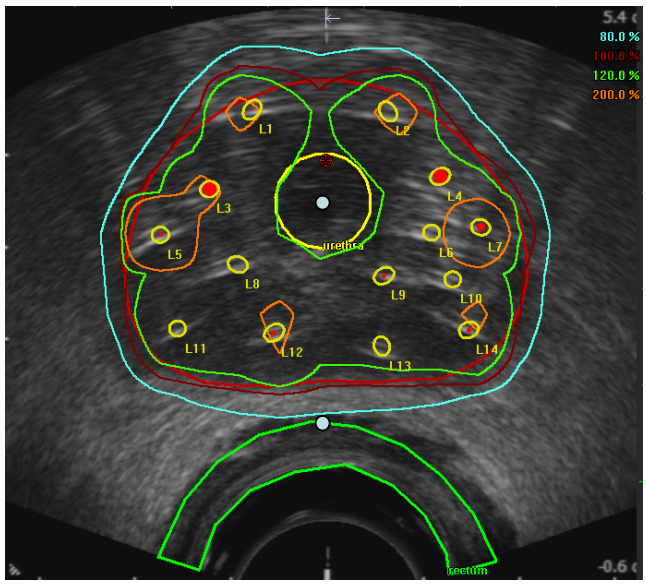
Technique of the HDR-BT

TRUS-guided transperineal conformal interstitial HDR Ir-192 implants were performed during the EBRT course. A single fraction HDR-BT boost was given during the first four weeks of EBRT. The implant procedure was performed under spinal anaesthesia with patient in the lithotomic position with extreme pelvic flexion. The prostate gland was scanned at 5-mm intervals from 2.0 cm above the base to 2.0 cm below the apex of the prostate. The UH detector was moved longitudinally with a special stepping device. Images were transferred into the treatment planning system. The target volume was the prostate gland with the visible extension of the tumour. Urethral reference points were placed into the centre of the urethral catheter and rectal reference points were placed at 0.5 cm from the outer surface of the US probe in anterior direction on each transversal TRUS image. After scanning the prostate with TRUS, a virtual preimplant treatment plan was generated. Geometrical

optimization followed by graphical optimization was used, and the prescribed dose (PD) was 8 Gy in six and 10 Gy in ninety-four patients given to the surface of the prostate. Treatment plan was accepted, if the whole prostate volume received at least 95% of the PD and the maximum of the reference point dose of the urethra and rectum was below 125% and 80% of the PD, respectively. Metal needles were inserted into the prostate through a template under TRUS-guidance, according to their positions on the virtual plan. During insertion, positions of the needles were updated on the reference plane (real-time dosimetry). Insertion depth of needles was adjusted one by one using longitudinal images of the US. Optimization on source dwell times was used again (22) in order to obtain the final dose distribution (Figure 1).

Patients were treated with HDR remote after-loading equipment, using a ^{192}Ir stepping source with 370 GBq initial activity.

Figure 1. Dose distribution of HDR–BT of the prostate on the transversal ultrasound image.



Red dots: needles; red line: contour of the prostate; yellow circle: urethra; green line: rectum; light blue circles: urethral and rectal reference points; blue, claret, green, orange lines: isodose lines of the 80, 100, 120, and 200% of the prescribed dose.

Follow up after HDR-BT boost treatment

All 100 patients were eligible for evaluation of biochemical and clinical outcome, toxicity and implant quality. Local tumour control (LC), regional tumour control (RC), overall survival (OS), cause-specific survival (CSS), clinical relapse free survival (cRFS), distant metastasis free survival (DMFS), biochemical relapse free survival (bRFS) and the side effect free survival was calculated from the last day of radiotherapy. Biochemical failure was

defined according to the Phoenix consensus criteria (23): PSA nadir + 2 ng/ml. Acute and late side effects were prospectively followed and recorded using the Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer (RTOG/EORTC) acute and late toxicity scales (24).

Statistics

All time intervals were calculated from the last day of RT to failure, death, or to the last follow-up visit. The actuarial rates of OS, CSS, DFS, local recurrence free survival (LRFS), DMFS, biochemical no evidence of disease (bNED) and complication rates were estimated according to the Kaplan–Meier method (25). Univariate Cox regression analysis was used to evaluate the possible prognostic factors for different end-points including death from any cause, cause-specific death, biochemical and clinical failure (26). A p-value of ≤ 0.05 was considered statistically significant. A trend to significance was established at $0.05 < p \leq 0.10$. The SOLO software (Department of Biometrics, University of California, Los Angeles, USA) was used for statistical analysis. The time-to-event curves were compared using the two-sided log-rank test (27).

Permanent implant brachytherapy of the prostate (PIBP)

After having seven year of experience with HDR-BT, technical, professional and official authorization of loose seed LDR-BT was implemented. The first PIBP was performed in our centre at the end of 2008 (28). In the thesis, the procedure of the PIBP is described and the outcome, gastrointestinal (GI) and genitourinal (GU) toxicity of the first 75 consecutively treated patients are reported. Dosimetric parameters of implantations are also presented.

Patients treated with PIBP

Between December 2008, and September 2011, seventy-five patients with low- and selected intermediate PC were treated by sole PIBP in a prospective protocol. Inclusion criteria, presented in Table 2, were defined according to international treatment guidelines (29, 30).

Table 2. Inclusion criteria for sole permanent implant brachytherapy of the prostate.

Factor	Criteria
Life expectancy	> 10 year
ECOG	0-1
IPSS	≤ 15
Prognostic factors	T1-2a N0 M0 and PSA ≤ 15 ng/ml and Gleason score ≤ 6
Biopsy cores	At least 6 cores, 50% positive at the most
Prostate volume	< 50 cm^3 (measured on TRUS or MRI)
Anatomy	No pubic arch interference or asymmetrical large loge after TURP
TURP before PIBP	No or more than 6 months prior to PIBP

ECOG: Eastern Cooperative Oncology Group; IPSS: International Prostate Symptom Score; TRUS: transrectal ultrasound; MRI: magnetic resonance imaging; PIBP: permanent implant brachytherapy of the prostate; TURP: transurethral resection of the prostate

Patients classified according to clinical prognostic factors and risk groups are shown in Table 3. Patients' mean age was 66 years (range: 51-80 years), the mean initial PSA value was 9 ng/ml (range: 3.2-15 ng/ml). Thirty-one patients (41.3%) were given ADT before the implantation for a mean period, of 6.4 months (range: 2-48 months). PIBP was sole treatment for forty-four patients (58.6%).

Table 3. Prognostic characteristics of patients treated by sole permanent implant brachytherapy of the prostate

Factor	N (%)
T status	
T1	33 (44)
T2	42 (56)
Initial PSA (ng/ml)	
< 10	53 (71)
10-15	22 (29)
Biopsy Gleason score	
2-4	9 (12)
5-6	65 (87)
7	1 (1)
Prognostic group	
Low risk	51 (68)
Intermediate risk	24 (32)

Technique PIBP

The implant procedure was performed under spinal anaesthesia with patient in the lithotomic position with extreme pelvic flexion. Longitudinal TRUS images were acquired by automatic rotation of the detector, and then they were transferred to the treatment planning system. After contouring the whole prostate as the target volume, rectum and urethra were delineated. Preplan was created using an inverse optimization algorithm. Dose–volume constraints were defined to the target and the critical organs according to treatment guideline recommendations (Table 4.). The dose prescribed to the prostate was 145 Gy. Preplan was accepted, when dose–volume constraints fulfilled the criteria (Table 4).

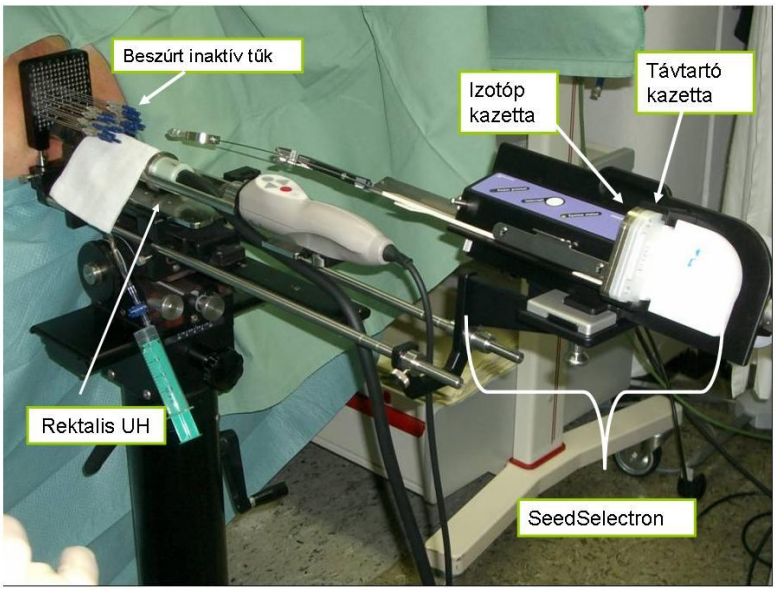
Table 4. Dose-volume criteria for permanent implant brachytherapy of the prostate.

Organ	Dose-volume parameter	Constraint
Prostate	V100	≥ 95 %
	D90	≥ 100 %
Urethra	Du10	≤ 150 %
	Du30	≤ 130 %
Rectum	$Dr_{0,1cm^3}$	< 200 Gy
	Dr_{2cm^3}	≤ 145 Gy

V100: percent volume of the target volume receiving 100 % of the PD; D90: maximum dose covering the 90% of the target volume in percent of the PD (145 Gy); Du10 and Du30: maximum dose of the 10% and 30 % of the urethra; $Dr_{0.1cm3}$ and Dr_{2cm3}: maximum dose of the 0.1 cm^3 of the rectum and 2 cm^3 of the rectum.

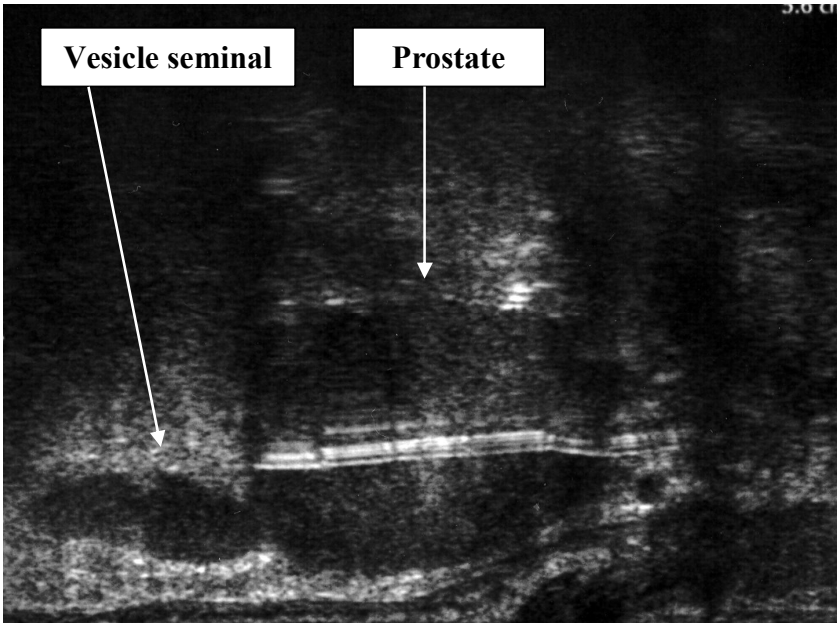
Needles were inserted to the prostate through the perineum with TRUS guidance. Planned needle positions were updated according to the real needle positions. All the updates were followed by modification of the plan immediately (intraoperative, real time planning). After all modifications the final treatment plan was accepted. Seed implantation was carried out by “SeedSelectron” equipment (Nucletron, Veenendaal, The Netherlands) with real-time longitudinal TRUS visualization. Figure 2 shows the „SeedSelectron” mounted to the TRUS detector device just before seed loading.

Figure 2. „SeedSelectron", mounted to the transrectal ultrasound stand that loads seeds into the prostate through connected needles.



The equipment automatically makes seed–spacer chain before loading and this is pushed into the prostate with a metal wire. Seed loading is visible on live longitudinal ultrasound image (Figure 3). After seed loading an x-ray verification image is taken to check the number and the position of the seeds.

Figure 3. Longitudinal TRUS image of the seed deposition into the prostate.



Echo dense line: loaded source-spacer chain; low echo area around the seeds: the prostate and one vesicle.

Perioperative care

Patients were discharged with sufficient urinating function on the day following the implantation. Alfa blockers and anti-inflammatory drugs were prescribed. Radiation exposure of the caring staff remained well below the 1mSv yearly threshold value (31). For precautionary reason holding a child or hugging a pregnant woman is prohibited for two months for the patient. Condom is also mandatory for two months during sex. Four weeks after the PIBP postplan is calculated on MRI/CT fused images.

Follow up after implantation

Regular visits three monthly for six months, six monthly for five years, then annually was recommended. PSA values were registered on each follow up visit. Urogenital and gastrointestinal toxicity were measured according to the RTOG/EORTC scoring system. Quality of life were documented by validated questionnaires (EORTC QLQ-30, IIEF) filled by the patients. Urinary function was assessed by the IPSS scoring system.

E. RESULTS

E.1. Results with HDR-BT boost

At a median follow-up of 61.5 months four local recurrences (4%), one regional recurrence (1%) and 12 distant metastases (12%) occurred. Fifteen patients (15%) developed biochemical failure. Among these, six patients (6%) had a PSA-relapse without clinical failure. To date, only four patients (4%) died of prostate cancer. Actuarial 5-year estimates of different end-points for intermediate- and high-risk patients are shown in Table 5.

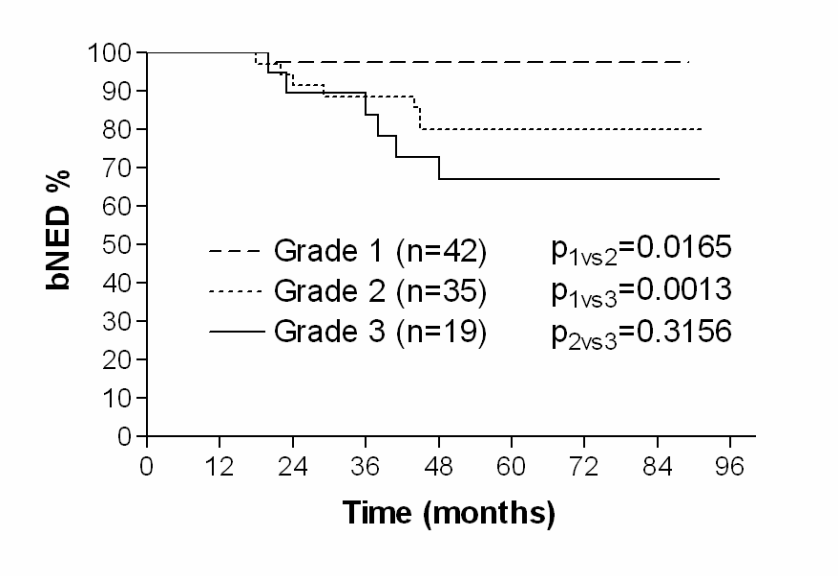
Univariate Cox regression analysis showed correlation between WHO grade and bRFS (Figure 4). Seven-year rate of bRFS were 97.5%, 80.0% and 67.1% for grade 1, 2, and 3 tumours, respectively.

Table 5. Five-year results in patients treated with HDR-BT boost (n=100) according to risk groups.

Endpoint	All patients %	High risk group %	Intermediate risk group %	Log-rank p-value
OS	93.3	92.8	94.2	NS
CSS	99.0	98.3	100	NS
RFS	89.3	86.2	94.0	NS
LC	97.7	98.3	96.6	NS
RC	100	100	100	NS
DMFS	89.3	86.2	93.9	NS
bRFS (Phoenix)	85.5	86.4	84.2	NS

OS = overall survival; CSS = cause-specific survival; RFS = clinical relapse free survival; LC = local tumour control; RC = regional tumour control; DMFS = distant metastasis free survival; bRFS = biochemical relapse free survival; NS = non-significant.

Figure 4. Time to biochemical failure according to grade by Kaplan-Meier estimates.



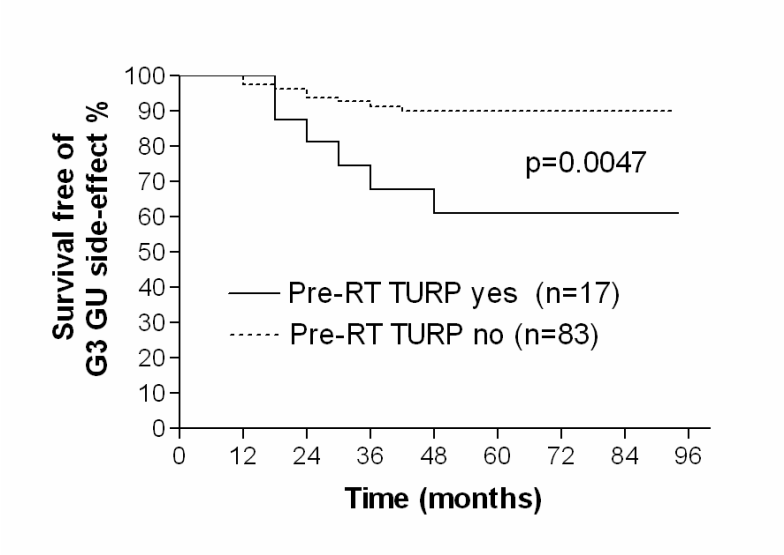
bNED: biochemical no evidence of disease

Interestingly, hormonally untreated patients had a trend for a better 5-year biochemical control rate compared to men receiving ADT (100% vs. 83.4%; p=0.0682). On the other hand, the 5-year probability for bNED following long-term (>12 months) ADT was significantly higher than after shorter (<12 months) duration of endocrine treatment (92.9% vs. 72.2%; p=0.024).

Patients' toxicity

Early complications were rare and reversible in all cases. Only few (n=2) severe late rectal complications were observed with a 5-year actuarial rate of 2.1%. Grade 3 late GU side effects occurred in 14 patients with a 5-year actuarial rate of 14.4%. The most frequent Grade 3 GU complication was urethral stricture (n=12) and hemorrhagic cystitis (n=2). These patients required endourethral incision or TURP after RT. Incontinence after postirradiation TURP occurred in four patients (4%). The 5-year probability of developing grade 3 late GU side effect with or without pre-RT TURP was 29.1% and 8.8% (p=0.0047), respectively (Figure 5).

Figure 5. Time to G3 GU side effect according to pre-RT TURP by Kaplan-Meier estimates.

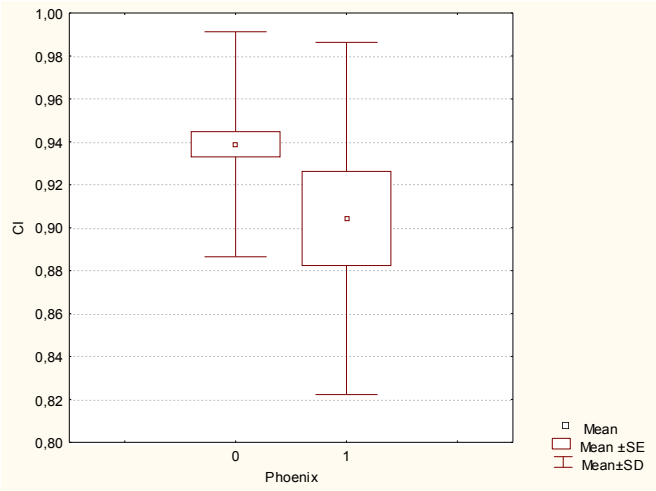


G3 = grade 3; GU = genitourinary; RT = radiotherapy; TURP = transurethral resection of prostate.

Result of patients treated with HDR-BT boost according to dosimetric parameters

Rate of biochemical relapse was significantly in correlation with the dose coverage of the target volume in HDR-BT (p=0.04). The better the coverage the lower the biochemical relapse rate (Figure 6.). Neither the number of applied needles, nor the volume of the prostate correlated to late GU or UG side effects. Dr_{max} and Dr_{2cm^3} values were not predictors of late GI or UG toxicity, neither Du1% and Du_{1cm^3} parameters of HDR-BT were correlated to the rate of late GI or UG toxicity.

Figure 6. Correlation between dose coverage of the target volume and biochemical control.



X-axis: biochemical relapses using the Phoenix definition no: 0, yes: 1 value.
Y axis: dose coverage of the target volume (CI; „coverage index")

E.2. Results with PIBP

Between December 2008 and September 2011, in a prospective phase II trial seventy-five patients were treated by PIBP monotherapy. Median follow up was 15 months (range: 5-38 months).

One man developed biochemical relapse (1.3%) and later clinical relapse (1.3%). No other relapse has been detected. All the patients are alive. In three patients (4%), temporary catheterization was performed due to grade 3 acute dysuria in three months after the implantation.

Dosimetry of PIBP

The mean volume of the treated prostate gland was 33.2 cm^3 (range: 12.2- 57.8 cm^3), the mean number of applied needles was 17 (range: 12-24), the mean number of the implanted sources was 55 (range: 30-78). In all, 3876 radioactive sources were implanted. The mean activity of sources was 0.5 mCi (0.41-0.52 mCi). The final plans satisfied the dose-volume constraints for the target, rectum and urethra in 68 (90.6%), 75 (100%) and 71 (94.7%) cases, respectively. The largest deviation from the predefined dose-volume constraint was 3.2% for the target and 2.3 % for the urethra.

Biochemical and clinical control after PIBP

In one patient (1.3%) biochemical relapse developed 14 months after the implantation. In this case, despite that ADT was introduced again, pelvis MRI showed lymph node metastases 30 months followed the implantation, as a clinical relapse (1.3%). The patient is now given chemotherapy. All patients are alive.

Toxicity after PIBP

The treatment was well tolerated, the mean hospital stay was 2 day (range: 1-5 day). No acute grade 3 or 4 toxicity was detected. Grade 1 acute proctitis developed only in five patients (6.9%) and in seventy patients proctitis did not occurred. In seven patients (9%) no urological acute side effect was detected. In twenty-eight patients (37%) grade 1, in thirty-seven patients (49%) grade 2 acute cystitis developed. In three patients (4%) grade 3 acute urethrocystitis and dysuria was observed. In these cases temporary bladder catheterization was necessary for 3-6 months to due to urge urination or severe dysuria.

Assessment of late toxicity was limited by the short follow up time, therefore late side effects were reported in only the first forty three patients whose follow up time was at least twelve months. In nine patients (20.9%) grade 1 late proctitis developed. More severe late gastrointestinal toxicity was not detected. In fourteen cases (32.6%) grade 1, 26 patients (60.5%) grade 2, in one patient (2.3%) grade 3 late urological side effects were registered. In this latter case, temporary percutan cystostoma was placed and later as the complaints had not disappeared, transurethral resection was performed one year after the implantation. After that urination was settled, continence remained perfect. The mean IPSS value increased temporarily after the implantation but returned to baseline at one year after the PIBP.

F. Discussion

F.1. HDR-BT for patients with prostate cancer

Dose escalation can be performed with HDR BT boost. With this method both the planning and treatment are very precise, since with optimizing the dwell position and time of the sources in the implanted needles the dosimetry can be properly adapted to the shape of the

target volume and the surrounded healthy organs (32). Critical organs like the rectum and the bladder can be protected better with HDR-BT boost than with EBRT.

Recently, it has been postulated that the alpha/beta ratio for prostate cancer is around 1.5 Gy, much lower than 10 Gy, the value normally assumed for tumour (33). If the alpha/beta ratio for prostate cancer was really lower than that for the rectum, hypofractionation treatments would be preferable for better tumour control. Supposed that alpha/beta value for prostate cancer is 1.5 Gy, then our treatment schedule of 60 Gy EBRT+ 1x10 Gy HDR-BT boost equals to 94 Gy biologically equivalent dose (BED) given in 2 Gy / fraction (34). Such a large dose cannot be given even by very sophisticated external beam techniques. Comparing our protocol to other groups' treatment protocols using HDR-BT, we use a moderate dose escalation. Although, BED of our EBRT +1x10 Gy HDR-BT boost is 16 Gy higher than dose given if we perform EBRT only (78 Gy in 2 Gy / fraction, 5 times a week) for this group of patients with intermediate or high risk prostate cancer.

In the theses, the first 100 patients treated by EBRT and one fraction of HDR-BT boost with a median follow up of more than five years were analysed. Results are promising. Despite the high rate (61%) of high risk patients, the 5-year bRFS rate was 85%. Our results can be compared to other groups' published results using HDR-BT boost in the literature. Galalae et al. (35) published their result in a group of patients with PC where 61% were in the high risk (61%). In their 611 patient, the 5-year bRFS was 77%. The Catalan Centre of Oncology report the results of 114 patients in whom 86% had high risk PC (36). Their treatment protocol was similar to ours (60 Gy KST + 1 x 9 Gy HDR-BT). The 4-year probability of bRFS was 97.4%.

In our study we did not find significant difference between 5-year bNED for intermediate- and high-risk patients (84.2 % vs. 86.4%). %). This can be partially attributed to our clinical practice using routine long-term AD for high-risk patients. Furthermore, pelvic lymph node irradiation was given more often to high-risk patients compared to intermediate-risk patients (96.7% vs. 2.6%).

Rare and reversible severe acute toxicity was found. Late GI toxicity is low and comparable to that of reported by others. The 5-year actuarial rate (14.4%) of late GU side effects in our series is somewhat higher compared to other series. Fortunately, six out 14 patients (43%) developing grade 3 GU complications were treated efficiently by minor surgical intervention. Therefore, the ultimate rate of late grade 3 GU complications at last follow-up was decreased to 8%, which is comparable to that of reported by others. Four patients (4%) suffered from moderate or severe incontinence during their follow up. This rate

is still comparable to the best toxicity data reported from laparoscopic radical prostatectomy series (3). In our series the incidence of developing grade 3 late GU side effect was significantly higher for patients having pre-RT TURP (29.1%) compared to those without pre-RT intervention (8.8%; p=0.0047). This observation corresponds with others' experience.

F.2. Permanent implant brachytherapy for prostate

PIBP monotherapy is equally effective treatment method to radical prostatectomy or EBRT for patients with low and selected intermediate risk of PC according to international treatment guidelines (37). In low risk, the 10–year bRFS is between 80-90% (18-20, 37) with mono PIBP. In our practice iodine-125 sources were used with a loose seed technique. In our experience, patients can be discharged from the ward 1-2 days after the implantation. This has an advantage compared to 7-8 week of EBRT. Further advantage to EBRT, that gastrointestinal toxicity is negligible with this method. Disadvantage of the seed implantation is its high cost, although as a definitive, curative monotherapy, long-term use of ADT, which is also expensive, can be omitted for the implanted patients.

More than ten years ago in 2001, in the Radiotherapy Centre of the National Institute of Oncology, requirements of the prostate brachytherapy were established. Since December 2001, HDR-BT has been performed for patients with locally advanced or localized intermediate and high risk PC. PIBP for patients with low- and selected intermediate risk PC was started in 2008. Introduction of PIBP was supported by the College of Radiotherapy and Oncology and by the College of Urology. This method became the part of the National Program against Cancer (38). The National Health Insurance Fund Administration (OEP) had reimbursed the procedure on individual base since 2009 for two years. Since 2011 this procedure is fully reimbursed contributing to an advanced, tolerable, curative treatment option for patient with early, organ confined PC.

G. Conclusions:

1. We introduced HDR-BT boost for PC in Hungary.
2. According to our experience, the 5-year results (LC, DFS and bRFS) for patients with intermediate and high risk PC treated with 3D-CRT and 1x10 Gy HDR-BT boost are encouraging and comparable to other series in the literature. Histological grade was a significant predictor of bRFS. There were no significant difference in outcome between the intermediate and high risk patients. Rate of late GI and GU side effects

was low and comparable to other series. In our patients' cohort, TURP prior to HDR-BT increased significantly the rate of late grade 3 GU toxicity.

3. In case of HDR-BT, significant correlation was found between V100 and bRFS. The higher the V100, the lower the biochemical relapse. No significant correlation was found between the dose-volume parameters of HDR-BT and the grade 3 GI and UG side effects.
4. We implemented PIBP for patients with low- and selected intermediate risk PC.
5. PIBP was well tolerated, with a few days of hospital stay. Early GI toxicity was negligible. Grade 3, early GU toxicity that needed catheterization occurred rarely. The mean IPSS value increased temporarily after the implantation but returned to baseline at one year after the PIBP.
6. At patients followed at for least one year after PIBP, moderate or severe GI toxicity has not been detected. Two third of our patients needed anti-inflammatory or alpha blocker drugs for a period of time due to late grade 2 urological toxicity. Grade 3 dysuria requiring TURP occurred in only one case.

List of publications served as a base of the theses

I. ***Ágoston P.,*** *Major T., Fröhlich G., Szabó Z., Lövey J., Fodor J., Kásler M., Polgár C.:* Moderate dose escalation with single-fraction high-dose-rate brachytherapy „boost" for clinically localized intermediate- and high-risk prostate cancer: 5-year outcome of the first 100 consecutively treated patients. *Brachytherapy 10:376-84, 2011.*
IF: **1,964**

II. *Fröhlich G.,* ***Ágoston P.,*** *Lövey J., Somogyi A., Fodor J., Polgár C., Major T.:* Dosimetric evaluation of high-dose-rate interstitial brachytherapy „boost" treatments for localized prostate cancer. *Strahlenther Onkol 186:388-95, 2010.*
IF: **3,567**

III. *Fröhlich G.,* ***Ágoston P.,*** *Lövey J., Polgár C., Major T.:* The effect of needle number on the quality of high-dose-rate prostate brachytherapy implants. *Pathol Oncol Res 16:593-9, 2010.*
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IF: **3,567**

Impact factor of publications related to the theses: 10,581

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I. ***Ágoston P.,*** *Major T., Fröhlich G., Baricza K., Szabó Z., Lövey J., Varjas G., Kásler M., Fodor J., Polgár Cs.:* Permanens implantációs prosztata brachyterápia korai, szervre lokalizált prosztatarák kezelésére. A módszer magyarországi bevezetése és első tapasztalataink. *Magyar Onkológia 55:170-7, 2011.*

II. ***Ágoston P.:*** A prosztatarák kezelésének jelenlegi és jövőbeni lehetőségei. *Orvostovábbképző Szemle 12:123-123, 2011.*

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V. ***Ágoston P.,*** *Major T., Somogyi A., Szûcs M., Danczig Á., Lövey J., Polgár Cs., Fodor J., Németh Gy., Kásler M.:* Brachyterápiás „boost" besugárzás nagy kockázatú, lokalizált prosztatarák kezelésében: első hazai tapasztalatok. *Magyar Onkológia 48:81-8, 2004.*

VI. ***Ágoston P.,*** *Kisbenedek L., Kiss T., Forgács Gy., Takács T., Poller I., Németh Gy.:* Lokális prosztata tumorok konformális besugárzása 3 dimenziós besugárzástervezés alapján. *Magyar Onkológia 42:151-154, 1998.*

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I. ***Ágoston P.,*** *Major T., Fröhlich G., Szabó Z., Lövey J., Fodor J., Kásler M., Polgár Cs.:* Moderate dose escalation with single-fraction high-dose rate brachytherapy „boost" forclinically localized intermediate- and high-risk prostate cancer: 5-year outcome of the first 100 consecutively treated patients. *Radiother Oncol 99(Suppl.1): S88, 2011.*

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All impact factors: 24,046

I. Acknowledgements

First of all, I wish to thank prof. Csaba Polgár, the current head of our centre, for his continuous support and encouragement throughout my PhD work. I learned the assiduous high quality scientific work without compromise from him. I'd like to thank prof. Miklós Kásler, the director general of our institute, his personal attention and encouragement to my PhD and scientific work. I also thank him that he supported us and helped us to settle the requirements of prostate brachytherapy in the institute. I wish to thank prof. János Fodor, the former head of our centre, that he taught me the exacting way of scientific work and the need of high standard, bolted and creative use of the Hungarian language in publications.

I also gratefully thank prof. György Németh, my first head of the department, that he directed me to the uro-oncology field, and provided me all his support to build my carrier. He helped us to make the first steps in prostate brachytherapy and encouraged us to start the treatment in 2001.

I gratefully thank prof. György Kovács, for inviting us to the University Kiel, where we could learn prostate brachytherapy in practice from a well experienced group leaded by him. He has been always supportive and open to help us in any practical questions arisen during brachytherapy work.

I recall and thank my former colleague dr. András Somogyi, whom we are missing for a few years now, as he passed away. I learned the principles of brachytherapy and the sincere affection of patients from him †.

I honestly give my great appreciation to my colleague dr. habil. Tibor Major physicist. His indispensable help ensured the continuous development in prostate BT, and the high quality physics background. He also gave me a lot of help in correcting my publications.

I grateful to dr. Géza Varjas for his careful pioneer work in safety of prostate brachytherapy procedures., to dr. Georgina Fröhlich physicist, for her deliberate work in daily practice, data collection and statistics.

I wish to thank dr. med. habil. József Lövey, dr. Zoltán Szabó and dr. Kliton Jorgo colleagues for the help in treating patients in the prostate brachytherapy working group.

I greatly acknowledge to several member of the urological society – prof. Imre Romics and prof. Péter Nyirády, dr. Miklós Szűcs, dr. László Kisbenedek and prof. Péter Tenke – for their multidisciplinary cooperation and scientific partnership.

I thank all the member of the anaesthesiology department for their smooth and helpful cooperation, brachytherapy and ward nurses in our Centre for their devoted work at our patients' bed.

I'd like to thank prof. József Bódis, that I could join the PhD program at the University of Pécs.

I also thank prof. Péter Örs Horváth, my program leader that I took part in his program and he gave me all support to reach my PhD degree.

And last but not least, I especially thank to my wife for her long lasting patience and that she provided me a blissful family life background. Without her courage and support this work could not have been born.

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