Original article

HDR brachytherapy of prostate cancer – two years experience in Greater Poland Cancer Centre

Marek Kanikowski, MD, Janusz Skowronek, MD, PhD, Ass. Prof., Adam Chicheł, MD

Brachytherapy Department, Greater Poland Cancer Center, Poznań, Poland

Abstract

Purpose: The aim of this work was to analyze the results and complications of three treatment schemes of patients with initially localized prostate cancer after two years of observation time.

Material and methods: Sixty-three patients were enrolled into the study and divided into groups according to radiation schemes (I group – EBRT 50 Gy/BRT 15 Gy, II – EBRT 46 Gy/BRT 2 × 10 Gy, III group – BRT 3 × 15 Gy). Group I, II and III consisted of 46 (73%), 14 (22.2%), 3 (4.8%) patients, respectively. The low-, intermediate- and high risk groups consisted of 23 (36.5%), 18 (28.5%) and 22 (35%) men, respectively. Results and tolerance of the treatment and acute complications in analyzed groups were discussed.

Results: Median observation time was 24 months. Complete remission was observed in 43 patients (68.3%) out of the whole group. Locoregional and distal metastases progression were noted in 4 patients (6.4%). Partial remission was observed in low-, intermediate- and high risk group: 7.9%, 9.5% and 9.5% of all men. Nadir of PSA results were estimated as mean value of 0.094 ng/ml, average 0.0-0.63. The mean value for the complete group decreased from 0.98 ng/ml (range 0.0-9.7) in the third months to 0.32 ng/ml after one year (0.0-3.34) of the end of treatment time. Urologic and gastrointenstinal side effects were noted in different rates according to 1 month observation (dysuria – 22.2%, urinary incontinence – 7.9%, frequency – 58.7%, weak stream – 68.3%, rectal bleeding – 15.9%).

Conclusions: 1. HDR brachytherapy of prostate cancer can be used as a boost after or before the external beam radiation therapy in different treatment schemes. 2. In selected groups under investigation trials, sole HDR-BRT is a suitable method of treatment. 3. To confirm superiority of analyzed modality treatment a prospective investigation with larger groups of patients would be required.

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Key words: HDR brachytherapy, prostate cancer, radiotherapy, complications.

Purpose

Since the last ten years, the number of patients suffering from prostate cancer is constantly increasing. Such a large group has a choice of different treatments such as surgery, cryotherapy, radiation, hormonotherapy as well as watchful waiting. The choice of treatment depends on initial risk group, general patient condition and modality treatments available in particular oncology center. Each year an increased amount of patients is treated by radiation modalities without the necessity for invasive surgical treatment. Radiation oncologists in the United States and Western Europe tend to use interstitial, low dose rate brachytherapy (LDR-BT) while the other specialists prefer an external beam radiotherapy due to lower cost of the procedure [1, 2]. Concurrent hormonotherapy applied during radiation course seems to be an advantage in high risk group of patients [3].

The role of interstitial high dose rate brachytherapy (HDR-BT) in prostate cancer treatment is well estimated. High risk group with significant threat of nodal and distant spread is the appropriate group of patients for a combined treatment of external beam radiotherapy (EBRT) preceded or followed by brachytherapy as a boost. Monotherapy of HDR-BT can be applied in low risk group of patients (Gleason score below 6 and initial PSA value below 10 ng/ml) and consisted of two or three single modality fractions [4, 5].

The most important aim of brachytherapy is to deliver prescribed dose to prostate gland and sparing healthy

Address for correspondence: Marek Kanikowski, MD, Brachytherapy Department, Greater Poland Cancer Center, 15 Garbary Street, 61-866 Poznań, Poland, phone +48 61 885 09 18, fax +48 61 885 08 34, ✉ e-mail: marekk0@poczta.onet.pl

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tissues that should not be irradiated during treatment, basing on seminal vesicles. Ability to deliver high dose to the inside of well-defined area with rapid fall-off outside this volume allows brachytherapists to treat patients with higher fraction and higher biological effective doses (BED). Insertion of applicators during real time HDR-BT procedures guided by transrectal ultrasound (TRUS) eliminates every day set-up errors (EBRT treatment) and increases the concentration of high dose within the previously planned area. The chance to cure the cancer with low rate of serious complications (rectum and urethra) seems to be higher after applying brachytherapy [6]. The most frequent urologic complications noticed after interstitial HDR-BRT procedure are: proctitis, dysuria, frequency, haematuria and inability to empty the bladder completely. Transrectal resection of the prostate (TURP) followed by brachytherapy may increase the risk of urinary incontinence [7]. Rectal complications in most of the cases include painful bowel movements, urge and diarrhea, bleeding and rarely prostatorectal fistulas [8].

There is no clear consensus between brachytherapists about radiation doses that should be applied in combined EBRT and HDR-BRT treatment. The main problem regarding the accuracy of doses in exact risk groups or even individual patients is the impossibility to estimate the one α/β ratio for prostate cancer in BED calculation. Apart from that, many publications from all over the world concerning combined treatment and monotherapy, shows similar outcomes in independence of radiations schedules [9, 10]. In our center we have established the α/β ratio for early radiation reactions as 1.5 and for late reactions as 3 in volume. Since the beginning of practicing the prostate brachytherapy procedure in our centre, we have started to use two schedules for combined treatment and one for monotherapy. 50 Gy in EBRT and 15 Gy in HDR-BRT were reserved for patients with cardiac incidence where single general anasthesia was possible in the mediate and high risk group (higher radiation doses necessary). The rest of patients were able to receive smaller amount of total dose with better dose coverage of prostate gland and healthy organs surrounding (46 Gy in EBRT, 2 × 10 Gy in HDR-BRT). We decided to treat low risk group with good general condition in three HDR-BRT monotherapy fractions with total dose of 45 Gy (3 × 15 Gy). Different biologically effective doses (BED) and 2 Gy equivalent of external beam radiation therapy doses (EQD2) in different schemes are presented in Table 1. It also shows the difference in calculated doses relating to accepted α/β ratio.

Table 1. Comparison of biological and equivalent doses in different radiation schemes for prostate tumor

Radiation schedule	BED – α/β 1.5	EQD2 – α/β 1.5
EBRT/HDR-BRT 50/15 Gy	281	120.7
EBRT/HDR-BRT 46/2 × 10 Gy	260	111.7
EBRT/HDR-BRT 40/2 × 10 Gy	246	105.7
EBRT/HDR-BRT 40/15 Gy	258	110.7
EBRT/HDR-BRT 54/15 Gy	291	124
EBRT/HDR-BRT 54/10 Gy	202.7	86.9
EBRT 70 Gy	163.3	70
HDR-BRT 3 × 15 Gy	495	212.1

EBRT – external beam radiation therapy, HDR-BRT – high dose rate brachytherapy, BED – biologically effective dose, EQD2 – equivalent 2 Gy dose of EBRT

The aim of this paper is to present our results as well as complications after 2 years of the end of treatment of prostate cancer brachytherapy, combined with EBRT or as a single modality treatment.

Material and methods

Since June 2006 till April 2007, 63 men with prostate cancer were treated in Greater Poland Cancer Centre with the use of HDR-BT and all of them were qualified for radiotherapy. Radical brachytherapy of prostate glands cancer was proposed as a boost after external beam radiotherapy or as a sole modality treatment. The group consists of patients with at least two years of observation time in regular follow up.

The median age of men was 70.3 years (ranged from 59 to 80). They were divided into three groups according to radiation schedules – 46 (73%) of patients were treated with combined method of external beam radiotherapy/ /brachytherapy in scheme 50/15 Gy, respectively. The other group of patients consisted of 14 men (22.2%) also treated with EBRT/HDR-BRT with dose proportion of 46/2 × 10 Gy, respectively. Three patients (4.7%) received BRT-HDR monotherapy (3 × 15 Gy), one of them as a result of tumor relapse after prostatectomy. The intensity modulated radiotherapy (IMRT) or 3-dimentional conformal radiotherapy (3D-CRT) techniques were used. The mean interval time between EBRT and HDR-BT fractions was 2 to 4 weeks.

Before brachytherapy, chest X-ray, transrectal ultrasound examination and CT of pelvis with nodal state estimation were performed in all of patients. In all of the cases, HDR-BRT was applied under general anesthesia in order to make the procedure more comfortable for patients.

During real-time brachytherapy intraoperative planning process target and organ at risk (OAR) doses were estimated using SWIFT and Oncentra Prostate System (Nucletron B.V.). Cooperation between computer planning system (CPS) and transrectal ultrasound real-time visualisation enabled the exact placement of a needle followed by CPS generating the dose volume parameters of prostate gland, urethra and rectum with dose volume histogram (DVH).

The average number of metal needles used in HDR-BRT procedure was 14 (range 7-18). The mean prostate gland volume observed was 28.5 cm^3, with 66 cm^3 volume as the largest and 14 cm^3 the smallest. Generated doses and volume parameters of target (prostate) were estimated as follow: D_{min} (minimal dose), D_{max} (maximal dose), D_{90} (dose delivered to 90% of treated volume), V_{100}, V_{150}, V_{200} (volume receiving 100, 150, 200% of reference dose). For description of urethral and rectal doses parameters D_{min}, D_{max}, D_{mean}, D_{10} (dose delivered to 10%

of OAR's volume), V_{100} were used. Parameter D_{90} (D_{90} > 90%) was taken into account as a minimal target dose limitation in planning process. For urethra and rectum, the D_{10} parameter was the most important and values < 120% and < 75%, respectively, were the limitations for plan acceptance. The largest mean treatment volume was observed in 50/15 Gy group – 34 cm^3, the smallest in BRT monotherapy (21 cm^3). Radiation part of brachytherapy procedure was accomplished by Ir192 source from microSelectron HDR unit (Nucletron B.V.).

Low, intermediate and high risk groups represented 23 (36.5%), 18 (28.5%) and 22 (35%) men, respectively. Pathologically, in every case adenocarcinoma in all differentiation stages was diagnosed. During the initial investigation, an average Gleason score value was observed as 6, ranged from 2 to 9. The mean lavel of initial PSA (iPSA) was settled on 23.13 ng/ml ranged from 0.12 till 132 ng/ml. The majority of cases in TNM clinical stage diagnosis belonged to T2 group (n = 33; 52.4%), T1 and T3 consists of 26 (41.3%) and 4 (6.3%) patients, respectively.

No case with rectum or bladder infiltration by prostate cancer (T4) were noted. One patient developed nodal metastases (1.6%), four patients (6.3%) experienced distant metastases in vertebral column, ribs and bones of pelvis.

In most of the cases the treatment of prostate cancer was preceded by hormonal therapy – 29 of patients (46%) received maximal androgen blockade (MAB), 18 of patients (28.6%) received analogs LH-RH. The antiandrogen blockade was applied in 2 persons (3.2%). Radiation without neoadiuvant or concurrent hormonal treatment was applied in 14 cases (22.2%).

Duration of hormonal therapy in all groups was different and ranged from 3 to 32 months. The mean MAB treatment time was established at 17.6 months, analog LH-RH at 21 months and antiandrogen – 26 months. Transurethral resection procedure was received by 7 patients as a minimum 6 months before brachytherapy.

According to mean age data of our group (70.3 years), the majority of men suffered from cardiovascular diseases (49.2%). Angina, myocardial infarction, hypertension, cardiac arrythmia and thrombosis were the most frequent complications. Seven patients (11.1%) developed diabetes and chronic obstructive pulmonary disease was noted in 4 (6.4%) cases even before brachytherapy. Gastrointestinal problems were noted in 11 cases (17.5%), however stomach and duodenum ulceration were the common complaints. Six patients (9.5%) developed second malignant tumor such a skin, lips, bladder and testis carcinoma. Hyperthyreosis and nephrolithiasis were observed in two men within this group.

After brachytherapy, patients were examined in regular period of time (1, 3, 6, 9, 12, 18, 24 months). Remission stage was estimated after phisical examination and blood test (value of PSA). In case of increased PSA value, imaging techniques such a TRUS, magnetic resonance, bone scan were applied. Basic clinical patients data are presented in Table 2.

Results

The mean observation time was estimated as at least two years. During this time none of our patients died from prostate cancer or other medical causes. Complete remission (decreasing or stabile PSA value) was observed at 68.3% (n = 43) of men in the whole group. Instabile PSA without any signs of cancer spread (partial remission) was noted in 27% of patients and progression was observed in 4 cases (6.4%). Prostate tumor spread was found in skeletal bones and pelvis nodes mainly in the intermediate and high risk group (1 and 3 patients, respectively). The best results in correlation between CR/PR and progression ratio

Table 2. Clinical data of 63 patients

Clinical data	Number of patients
Radiation schedules:	
EBRT/HDR-BRT 50/15 Gy	46 (73%)
EBRT/HDR-BRT 46/2 × 10 Gy	14 (22.2%)
HDR-BRT 3 × 15 Gy	3 (4.8%)
Age:	
range	59-80 years
mean	70.3 years
Risk groups:	
low	23 (36.5%)
intermediate	18 (28.5%)
high	22 (35%)
Hormonotherapy:	
antiandrogen treatment	2 (3.2%)
analog LH-RH treatment	18 (28.6%)
maximum androgen blockade (MAB)	29 (46%)
no hormonal treatment	14 (22.2%)
Gleason score:	
mean value	6
range	2-9
PSA (ng/ml):	
mean value	23.13
range	0.12-132
Number of metal needles (per application):	
mean	14
range	7-18
TNM:	
T1	26 (41.3%)
T2	33 (52.4%)
T3	4 (6.3%)
T4	0
N1	1 (1.6%)
M1	4 (6.4%)
Prostate gland volume:	
mean	28.5 cm^3
range	14-66 cm^3
Concurrent diseases:	
cardiovascular	31 (49.2%)
gastrointenstinal	11 (17.5%)
pulmonary	4 (6.4%)
diabetes	7 (11.1%)
degenerative bone desease	11 (17.5%)

was achieved in men from low risk group. One patient was treated because of a relapse of cancer after 2 years of observation time and was free from any signs of tumor in prostate gland and metastases. Partial remission was observed in low, intermediate and high risk groups as follow: 7.9%, 9.5% and 9.5%, respectively. Particular clinical results according to all risk groups and radiation scheme are summarized in Table 3 and 4.

PSA value was estimated after 1, 3, 6, 9, 12, 18 and 24 months after brachytherapy. The mean value for whole group decreased from 0.98 ng/ml (range 0.0-9.7) in the third month to 0.32 after one year (0.0-3.34). During the end of observation time (2 years) the mean PSA level has increased to 0.51 ng/ml, mainly due to metastases reveal. Progression group (recognized on the ASTRO definition) received maximal androgen blockade with analog LH-RH and antiandrogen treatment. After failure of treatment the mean time of hormonotherapy was estimated at 4 months. Nadir of PSA results (lowest PSA observed) was estimated as a mean value of 0.094 ng/ml, average 0.0-0.63.

The mean time of nadir was 14 months (range from 3 to 24 months). Durability of PSA nadir was noted in 40 patients (63.5%) and in 23 of patients (36.5%) the prostate cancer marker changed during follow up. In 6 patients (9.5%) short term increase of PSA (bounces) were recognized, however it disappeared in most of the cases within 12 months after completion of irradiation. HDR brachytherapy alone with high radiation doses was applied in 3 cases where a short term increase of PSA occurred (see Table 3). The correlation between results and radiation scheme application was not clearly revealed. All patients from HDR-BRT monotherapy group had a complete remission (all in low risk group), all men with progression and metastases underwent combined EBRT/HDR-BRT treatment in 50/15 Gy schedule. Patients with two brachytherapy procedures (2 × 10 Gy) presented complete and partial remissions in 50% for each group after two years.

Table 3. Stage of remission according to risk groups

	Complete remission (CR)	Partial remission (PR)	Progression
Low risk group 22 (34.9%)	17 (27%)	5 (7.9%)	0
Intermediate risk group 18 (28.6%)	11 (17.5%)	6 (9.5%)	1 (1.6%)
High risk group 22 (34.9%)	13 (20.6%)	6 (9.5%)	3 (4.8%)
Tumor relapse group 1 (1.6%)	1 (1.6%)	0	0

Table 4. Stage of remission according to radiation scheme

Treatment scheme	Complete remission (CR)	Partial remission (PR)	Progression
EBRT 50 Gy/ /HDR-BRT 1 × 15 Gy *n* = 46 (73%)	34 (53.9%)	9 (14.3%)	3 (4.6%)
EBRT 46 Gy/ /HDR-BRT 2 × 10 Gy *n* = 14 (22.2%)	5 (7.9%)	8 (12.7%)	1 (1.6%)
HDR-BRT 3 × 15 Gy *n* = 3 (4.8%)	3 (4.8%)	0	0

Complications rates in 1, 3, 6, 12 and 24 months after the end of brachytherapy procedure were noted, in addition to PSA value results. Weak stream (43 pts – 68.3%) was the most frequent symptom observed after 1 months of follow-up. During this time, the complication rate decreased and only 25 patients experienced the weak stream problem after 1 year (39.7%) and 31 of patients (49.2%) complained after 2 years. Nocturia was observed in all men enrolled to our study and the mean value was estimated at 2.8 points in 1 months (international prostate symptom score – IPSS scale) to 2.26 points in 24 months. Nocturia was 5 points in IPSS achieved in 1, 3, and 24 months with a range 0-5. Frequency symptom noted in 58.7%, 55.6%, 50.8%, 42.9% and 36.5% of patients during follow up respectively from 1 to 24 months. To a certain extent, urinary bleeding was a rare symptom and in most of the cases observed in acute rate during the first month (5 patients – 7.9%). After 2 years, only 2 men (3.2%) complained from occasional bleeding without the necessity of serious urological procedure. Because of urinary tract infections, at 22.2% of patients an antibiotic therapy was applied. The more time we spent on observations the less number of patients experienced clinical symptoms of bacterial infections (3 months – 17.5%, 6 – 4.8%, 24 – 1.6%). Only 3 patients (4.8%) had acute obstruction of urinary tract after HDR-BRT with prolonged cathaterization (7-28 days). Incontinence was a serious problem for 5 patients (7.9%) and it was relieved in most cases after 1 months. The mean value of IPSS score according to each examination time decreased from 12.55 points in the first month to 10.11 after 2 years (range 3-25 and 0-19, respectively). Between 12 and 24 months the change of the mean value score was not so obvious as earlier estimated and ranged from 10.16 points to 10.11.

Rectal bleeding was a frequent symptom (10 patients – 15.9%) in connection with a group of patients treated with combined EBRT/HDR with higher biological effective dose (50/15 Gy). Diarrhea were rare (7.9%) and observed in patients with antiandrogen hormonotherapy and previous gastrointenstinal history. General correlation between treatment volume applied and rectal bleeding complication was observed and it should be confirmed in statistical tests. All data of the results and complication rates are presented in Table 5. Complication rates according to risk groups in first months after BRT are summarized in Table 6.

Discussion

Prostate cancer is one of the most frequent tumors to be detected all over the world. Since 2002 the incidence rate has increased from 189 000 to 234 500 men per year in the United States alone [11]. Adenocarcinoma of prostate gland seems to be a tumor of elderly men. Out of 100 000

Table 5. Results and complication rates during follow-up

	1 month	3 months	6 months	12 months	24 months
Mean PSA range	X X	0.983 ng/ml (0.00-9.7)	0.537 ng/ml (0.00-7.20)	0.316 ng/ml (0.00-3.34)	0.508 ng/ml (0.00-12.24)
Weak stream	*n* = 43 68.25%	*n* = 37 58.73%	*n* = 31 49.21%	*n* = 25 39.68%	*n* = 31 49.21%
Frequency	*n* = 37 58.73%	*n* = 35 55.55%	*n* = 32 50.79%	*n* = 27 42.86%	*n* = 23 36.51%
Nocturia (IPSS scale)	2.8 points (range 0-7)	2.52 points (range 0-7)	2.14 points (range 0-5)	2.19 points (range 0-5)	2.26 points (range 0-7)
Urinary bleeding	*n* = 5 7.93%	*n* = 2 3.17%	*n* = 3 4.76%	*n* = 3 4.76%	*n* = 2 3.17%
Infections of urinary tract	*n* = 14 22.22%	*n* = 11 17.46%	*n* = 4 6.35%	*n* = 4 6.35%	*n* = 1 1.59%
Mean score in IPSS scale	12.55 points (range 3-25)	11.54 points (range 1-23)	10.48 (range 0-20)	10.16 (range 1-20)	10.11 (range 0-19)

of men population, 966.4 is over 65 years old and only 51.7 is under this age [11]. In 2005 in Poland the mortality rate of prostate carcinoma was 11.1% (III place after pulmonary and intestine tumors) [12].

For these patients we can offer radical treatment as prostatectomy (surgical procedure) or radiation therapy according to prognostic factors, general condition as well as patients will and awareness. The difference between these two modalities is generally estimated on complications and post procedure quality of life, not focused on clinical outcomes [13]. During the last few years more and more patients were treated with brachytherapy after external beam radiation treatment or as a monotherapy.

All published data confirmed good results and acceptable complication rate independently to combined or sole treatment modality applied with different schemes. The observation time of more than 5 years is the most reliable data. Department of Radiation Oncology in Karolinska University in Sweden presented results of 6 years of external beam radiotherapy and high dose-rate iridium 192 brachytherapy as a boost with neo-adjuvant hormonal therapy [14]. Since 1998 through 1999, the amount of 154 patients with localized prostate cancer were entered into a trial. Comparison between the results of this treatment with other treatment modalities (prostatectomy and 3D EBRT) were made using Kattans nomograms. After 6 years of follow-up, none of the patients demonstrated clinical signs of local recurrence and 129 patients remain alive. 5-year relapse-free survival is 84%, the median PSA at follow-up among the relapse-free patients was 0.05 µg/l. Using nomograms for prostatectomy and 3D EBRT, the expected 5-year relapse-free survival was 54% and 70%, respectively. Among 80 patients who presented clinical stage T3 tumors, 55 (68%) were relapse-free. Authors concluded that combined treatment, utilizing HDR, 3D EBRT and hormonal therapy, produces good clinical results with acceptable rectal toxicity rate (grade 3 of RTOG occurred in 1%) and late urinary tract toxicity (RTOG grade 3 developed in 4%) [14].

Table 6. Complication rates according to risk groups in first months after BRT

	Low risk group	Intermediate risk group	High risk group
Weak stream *N* = 43	*n* = 15 34.9%	*n* = 20 46.5%	*n* = 8 18.6%
Frequency *N* = 37	*n* = 10 27.03%	*n* = 12 32.4%	*n* = 15 40.5%
Incontinence *N* = 5	*n* = 2 40%	*n* = 2 40%	*n* = 1 20%
Urinary bleeding *N* = 5	*n* = 1 20%	*n* = 2 40%	*n* = 2 40%
Infections of urinary tract *N* = 14	*n* = 6 42.9%	*n* = 1 7.1%	*n* = 7 50%

The long-term outcome (10 years) and morbidity in high-dose-rate brachytherapy (HDR-BT) treatment combined with external beam radiotherapy (EBRT) for localized prostate cancer were presented by Demanes *et al.* from California Endocurietherapy Cancer Center, Oakland [15]. 209 consecutive patients with no prior androgen suppression were treated with combined radiation treatment. The patients were stratified into three risk groups, the median follow-up was 7.25 years (range 5-12 years). The overall survival rate was estimated as 79%, the cause-specific survival rate was 97% and the PSA progression-free survival rate (according to ASTRO definition) was 90%, 87%, and 69% for the low-, intermediate-, and high-risk groups, respectively [15]. Regarding the occurrence of complications, rectal morbidity developed grade 3 or 4. The rate of grade 3 and 4 late urinary morbidity was 6.7% and 1%, respectively, mostly in patients who underwent the post-RT transurethral prostate resection. The sexual potency preservation rate was 67%. In conclusion, authors underlined that HDR-BT plus EBRT is a proven treatment

for all stages of localized prostate cancer with low complications rates, however emphasizing to avoid post-RT transurethral resection [15].

In 2008 Sato *et al*. published data of high-dose-rate (HDR) brachytherapy of a single implant with two fractions and external beam radiotherapy (EBRT) for hormone-naive prostate cancer [16]. Between March 2000 and September 2003, 53 patients with tumor stage T1c-T3b N0 M0 prostate cancer were treated with HDR brachytherapy boost doses (7.5 Gy/fraction) and 50-Gy EBRT during 5.5-week period. Patients were divided into groups with localized (T1c-T2b) and advanced disease (T3a-T3b) with median follow-up 61 months. Estimated and presented overall survival rate was 88.1% and cause-specific survival was 100%. In 3th year of the localized and advanced groups biochemical failure-free control rates were 100% and 42%, respectively [16]. Authors concluded that brachytherapy boost applied in two fractions as a single implant is an effective way in treating patients with localized hormone-naive prostate cancer, with the least genitourinary and gastrointestinal toxicities (grade 2 late genitourinary and gastrointestinal toxicity rates were 0% and 3.8%, respectively). They have also found rather low erectile preservation rate (25% at 5 years) [16].

In 2003 Pellizzon and others presented biochemical control rate (bNED), acute and late gastro-intestinal (GI) and urological (GU) morbidity of initial and locally advanced prostate cancer treated with fractionated transrectal ultrasound-guided (TRUS) high dose rate afterloading brachytherapy (HDR-B) as a boost to conventional external beam radiation therapy (EBRT) [17]. From March 1997 to February 2000, 119 patients, prior to HDR-B received a course of EBRT 6 MV photons as a median dose of 45 Gy in 1.8 Gy fractions to the prostate and seminal vesicles only. Low risk group (LR) encompassed patients who presented GS < 6, T1 or T2a and or initial PSA < 10 ng/ml, who were treated with 16 Gy (4 Gy fractions) HDR-BT. The remained amount of patients was assembled into high risk (HR) group with or without androgen deprivation (HR ± AD) and received 20 Gy (5 Gy/fractions) HDR-BT. Median observation time of this group was estimated at 41 months (range 18-48). The crude and actuarial biochemical controls (bNED) in 48 months for all patients were 69.5 and 75.3%, respectively. At the time of dividing into LR, HR and HR + AD the actuarial bNED was 78.2 in LR, 76 in HR and 72.3% in HR + AD. Acute genitourinal (GI) and gastrointenstinal morbidity (GU) grade 1-2 were noted in 18.5% (20/108) and 10.2% (11/108) of patients with spontaneous regression. Late GI and GU morbidity grade 1-2 were seen in 12% (13/108) and 4.6 (5/108) of patients, with no need of intervention. No acute or late grade 3-4 U or GI morbidity was seen [17].

Four years of patients follow-up after prostate cancer treatment was presented by Shigehara *et al*. from Department of Urology, Kanazawa University Hospital in Japan [18]. Between February 1999 and December 2003, ninety-seven patients underwent 192Ir HDR brachytherapy combined with EBRT. 192Ir was delivered three times during 2 days, 6 Gy per time with total dose of 18 Gy. Several patients received additional hormonal therapy according to risk of nodal metastases. Interstitial application was followed by EBRT at a dose of 44 Gy. The 4-year overall survival of all patients, the nonadjuvant hormone therapy group (NAHT) and the adjuvant hormone therapy group (AHT) was estimated at 87.2%, 100%, and 70.1%, respectively [18]. The PSA progression-free survival rate of all patients was 82.6%. According to the T stage classification, PSA progression-free survival rates of T1c, T2, T3, and T4 were 100%, 82.8%, 100%, and 12.1% and for groups PSA < 20 and PSA ≥ 20 PSA progression-free survival ratio presented were 100%, and 46.8%, respectively. There was no significant intraoperative or postoperative complications that required an urgent treatment [18].

Among all available HDR-BT publications in prostate cancer treatment, monotherapy datas are the minority. In 2009 Ghadiar and coworkers presented acute and late genitourinary and gastrointestinal toxicity and short-term biochemical with no evidence of disease rates (bNED) [19]. Between October 2003 and June 2006, 36 patients with low and intermediate risk of prostate cancer were treated with monotherapy schedule receiving one implant and four fractions of 9.5 Gy within 48 h for a total prescribed dose of 38 Gy. Median follow-up was 3 years (range: 0.4-4 years) and during this time bNED survival rate was estimated at 100% [19]. Acute and late grade 3 GU toxicity was observed in 1 (3%) and 4 (11%) patients, respectively. Grade 3 GI toxicity was absent. Late grade 3 GU toxicity was associated with the planning target volume (PTV) V(100), D(90) and the urethral V(120). The sexual preservation rate in patients without HT was 75%. Another publication about HDR brachytherapy as a sole modality treatment was presented by Yoshioka and coworkers from Radiotherapy Center in Osaka [20]. The aim of the study was to improve results for localized prostate cancer, a prospective clinical trial of hyperfractionated Iridium-192 high-dose-rate brachytherapy. Between May 1995 and September 1998, 22 implants were performed on 22 patients with localized desease. Nineteen of patients with T3-T4 tumors or pretreatment PSA ≥ 20.0 ng/mL, received hormone therapy. Patients were irradiated twice a day, with a interval time of more than 6 h. The total dose was 48 Gy/8 fractions/5 days or 54 Gy/9 fractions/5 days [19]. Obtained results showed (median follow-up 31 months) four-year clinical and biochemical relapse-free rates were 95% and 55%, respectively. PSA levels normalized in 95% of patients within 20 months after irradiation. No significant intra- or peri-operative complications occurred, no patient experienced acute toxicity of grade 3 or more. In conclusion authors apart from satisfactory results, underlined the necessity of longer follow-up in order to compare the modality of other treatment techniques [20]. Several other results from different Cancer Centers are presented in Table 7 [21].

Conclusions

The results presented above do not significantly differ from other papers. The largest group was 50/15 Gy scheme

Table 7. Results of combined prostate cancer treatment in different cancer centers [20]

	Number of patients	Clinical stage	Treatment	Follow-up in months	Results (bNED)
University of Kiel	*n* = 171	T1-T2 G1-G2	EBRT 50 Gy + + BRT 15 Gy × 2	55	78%
Swedish Tumor Institute	*n* = 104	T1-T3 mPSA = 12.9 G1-G3	EBRT 50.4 Gy + + BRT 3-4 Gy × 4	46	84%
University of Gothenburg	*n* = 214	T1-T3 G1-G3	EBRT 50 Gy + + BRT 10 Gy × 2 + HT	60	82%
William Beaumont Hospital	*n* = 142	T2b-T3 GS = 7	EBRT 46 Gy + + BRT 5.5-6.6 Gy × 3 or 8.25-9.5 Gy × 2	26	89%
University of Berlin	*n* = 82	T1-T3 N0 G1-G3	EBRT 40-45 Gy + + BRT 9-10 Gy × 2	24	52.9%
AC Camargo Hospital Sao Paulo	*n* = 119	T1, T3	EBRT 45 Gy + + BRT 4 Gy × 4 (T1) 4Gy × 5 + HT (T3)	41	75.3% (T1) 69.5% (T3)

EBRT/HDR-BRT, respectively. This combined radiation schedule was pointing into the highest biological dose application with shortest treatment time available in prostate tumor treatment. Two brachytherapy fractions was introduced in order to maximally preserve organs at risk (OAR) with decreased volume of total external beam radiation dose in low and intermediate risk group. Monotherapy was applied in more than 3 patients, however the minimum 2 years observation time was achieved by no more than 3 patients in regular follow-up. Presented results do not show superiority one scheme over another due to short time of observation and small groups of patients enrolled into study. It is not possible to point out which radiation schedule is the most suitable for each risk groups. However, dividing brachytherapy procedure into two fractions with lower EBRT dose seems to be more adequate for younger patients with a good general condition. Prostate cancer HDR-BRT monotherapy is still under a study and at the present time can be applied in low risk group of patients without any serious threat of nodal and distant metastases. Further study of statistical correlation between diagnostic and optimization plan parameters could possibly help to find the best way to treat patients with prostate tumors in exact radiation scheme. Moreover, in order to confirm the advantage of a modality treatment, a prospective investigation with much larger groups of patients is also needed.

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