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## Long term results of HDR brachytherapy in men older than 75 with localized carcinoma of the prostate

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### ABSTRACT

**Background:** Prostate cancer is an illness with a high incidence, especially among older men. The choice of a treatment option among men above 75 years is, however, not clear. Radical prostatectomy in this age group is connected with a relatively high morbidity. A further possibility of curative treatment is radiotherapy which can be administered in the form of external beam or in combination with high dose rate (HDR) brachytherapy.

**Aim:** The aim of our work was to evaluate how HDR brachytherapy is tolerated among men older than 75 and how associated diseases can influence the tolerance to this treatment. Of interest to us were the treatment results and mortality from other diseases.

**Materials and methods:** We analyzed a sample of 20 men above 75 years old (median 77 years) who were undergoing treatment by a combination of external radiotherapy and brachytherapy. Sixteen (80%) of them had prostate cancer with an intermediate and high risk of recurrence, four had low risk prostate cancer. Most patients, 14 (70%), had less than two comorbidities.

**Results:** The median observation period was 57 months. No perioperative complications were recorded. Acute genitourinary toxicity (GU) to a maximum grade of 1–2 manifested in 60% of cases. Acute gastrointestinal toxicity (GIT) was observed only at grade 1 and in 25% of cases. Late GU toxicity occurred in 35% of patients, with only one showing grade 3; late GIT toxicity was recorded at grade 1 only in 3 patients (15%). 70% of the men lived longer than 3 years after treatment, at present, 50% lived more than 5 years. Long-term biochemical remission was achieved in 18 patients (90%).

**Conclusions:** HDR BRT is possible and well-tolerated in older men above 75 years in good condition and without serious intercurrents.

Well-selected older patients with higher-risk tumours and without serious comorbidities undoubtedly benefit from radical treatment when compared with watchful waiting.

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## 1. Background

Prostate cancer occurs predominantly among older men, most often in the 70–74 age group, 75% of cases are detected in men older than 65, and 25% in men above 75 years.

Its incidence and early detection continues to increase due especially to preventive administration of the prostatic specific antigen (PSA) and to population aging. More than 60% of tumours are detected in stages I and II.

The fact that at present more forms of prostate cancer are being diagnosed more often, and also the occurrence of illness in patients with a long life expectancy is substantially changing approaches to treatment. Among curative treatment methods of localized prostate cancer are radical prostatectomy (RAPE), external radiotherapy, interstitial brachytherapy (BRT), and “watchful waiting”. This last method is being used more frequently due to the detection of clinically insignificant forms of the disease. It is, however, important to identify patients who have, on the basis of the clinical and pathological characteristics of the tumour, a low possibility of disease progression. Treatment strategy depends especially on the evaluation of the aggressiveness of the tumour, comorbidity and biological age. The approach to treatment of men older than 75 is not unequivocal.<sup>1</sup> It is always imperative to carefully consider life expectancy respective to intercurrent and the overall state of the patient.

Equal to radical prostatectomy is the possibility of curative treatment with radical radiotherapy. Radical prostatectomy in older men is not often indicated, because it is connected with a higher level of complications. A comparison of the complications of radiotherapy and RAPE among older men was made by Canadian authors. A higher degree of complications was found in the group treated surgically.<sup>2</sup> There is another work that confirms that higher age is connected with larger blood loss and higher incidence of further complications.<sup>3</sup> The most frequent and unpleasant postoperative complication after radical prostatectomy is urinary incontinence and it is precisely this which is much more likely to occur after operation with older men.<sup>4</sup> Evaluation of and work on continence one year post-operation has been undertaken by Shikanova.<sup>5</sup> The probability of incontinence among men of 75 years was the worst in comparison with those less than 70 and less than 65 (0.59 vs. 0.63 vs. 0.66). Similar results were also published after the use of laparoscopic RAPE in men over 75 years. Once again, urinary incontinence was more frequent than with younger men.<sup>6</sup> Comparison of perioperative morbidity in older men who had undergone open RAPE with those operated laparoscopically also showed a higher risk of haemorrhage and the appearance of urinary fistulae with open radical prostatectomy.<sup>7</sup>

The objective is then to find the best way of choosing patients for radical operation, for example on the basis of evaluation of intercurrent.<sup>8</sup>

A further possible treatment modality with curative potential is radical radiotherapy, often used especially with older patients. In the last two decades radiotherapy has made great advances. The escalation of irradiation dosage has significantly added to the improvement in treatment outcomes in localized prostate cancer, because it has been shown that

**Table 1 – Characteristics of patients and tumours.**

		No of pts.
PSA	≤10	6
	10–20	6
	>20	8
Gleason score	4–6	4
	≥7	16
T stage	T1c	12
	T2a–b	6
	T3a	2

**Table 2 – The most chronic comorbidities in our group of patients.**

Comorbidities	No of pts.
Hypertension	12
Ischaemic heart disease	4
Hyperlipidaemia	4

prostate cancer is dosage-dependent: the higher the irradiation dosage applied, the better results achieved.<sup>9–11</sup> The dosage required to ensure control over the illness should be greater than 72 Gy.<sup>12</sup> The ability of conventional radiotherapy to deliver such a dosage is limited by the high rate of gastrointestinal (GI) and genitourinary (GU) complications. For this reason, in order to increase dosage to the required volume, it is appropriate to use the new technologies of external radiotherapy (e.g. conformal; 3D CRT or intensively modulated radiotherapy: IMRT) or a combination of external radiotherapy and brachytherapy.

Each of the aforementioned methods has its advantages, disadvantages, limitations and indications. Rapid development has also been achieved in the field of brachytherapy (BRT) which is now also obtainable conformally, which allows for new planning systems and techniques implemented using transrectal ultrasonography (TRUS, the guided technique). In recent years, interstitial brachytherapy has been enjoying a revival especially as a result of new technologies (ultrasound navigation technology), which allows a more precise calculation of the position of the source. With the use of conformal brachytherapy, it is possible to achieve higher dosage in the target volume even to over 100 Gy. The main advantage of a combination of RT and HDR BRT, apart from dosage escalation, might also be the overall reduction in treatment time of 2–3 weeks, when compared with external RT alone.

## 2. Materials and methods

In our cancer centre, from 2004 to 2010, we treated 20 men over the age of 75 with a combination of external radiotherapy and HDR brachytherapy. At the start of the treatment, the average age of the group was 76.9 years (75–79, median 77 years). Nine of the men had prostate cancer with a high risk of recurrence, 7 had cancer of intermediate risk and 4 had low risk prostate cancer. Characteristics patients and tumours are listed in Table 1. The majority of patients (70%) had less than two comorbidities and the performance status of all was 0–1 according to WHO. Among the most frequent intercurrent was hypertension and ischaemic heart disease (Table 2).

**Table 3 – Treatment protocol for the external beam radiotherapy and brachytherapy combination.**

Risk of recurrence		3D CRT	BRT
<i>Low risk group</i>			
T1a-T2a	PTV	Prostate	Prostate
+GS ≤ 6		+base of seminal vesicles	+base of seminal vesicles
+PSA ≤ 10		+safety margin	+margin 3 mm
	Technique	6 isocentric fields – conformal RT	Interstitial temporary implantation
	Dose	45 Gy in 25 fractions 5 fractions/week	2 × 8 Gy (in 3rd and 5th week of 3D CRT)
<i>Intermediate risk group</i>			
T2b	PTV	Prostate	Prostate
or GS = 7		+seminal vesicles	+base of seminal vesicles
or PSA 10–20		+safety margin	+margin 3 mm
	Technique	6 isocentric fields – conformal RT	Interstitial temporary implantation
	Dose	50.4 Gy in 28 fractions 5 fractions/week	2 × 8 Gy (in 3rd and 5th week of 3D CRT)
<i>High risk group</i>			
GS > 7	PTV	Pelvis	Prostate
or PSA > 20			+base of seminal vesicles
or T2c			+margin 3 mm
	Technique	Box	Interstitial temporary implantation
	Dose	50.4 Gy in 28 fractions 5 fractions/week	2 × 8 Gy (in 3rd and 5th week of 3D CRT)
	+Hormonal manipulation		

All men underwent external radiotherapy in the pelvic region (in the patient group with high recurrence risk) in dose 45.0–50.4 Gy in 25–28 fractions or external irradiation of the prostate and parts of the seminal vesicles (intermediate and low risk) in dose 45.0 Gy in 25 fractions. External radiotherapy was supplemented with HDR brachytherapy in two fractions in dose 8.0 Gy per fraction, the interval between fractions was two weeks. HDR brachytherapy was conducted in the 3rd and 5th weeks of external RT. Treatment protocol is described in Table 3. On the day preceding brachytherapy, the patients were admitted to the department, where preparations were made which included introduction of a permanent urinary catheter. HDR BRT was performed under spinal anaesthesia, needles were applied to the prostate transperineally under the control of transrectal sonography. The operation time was between 120 and 150 min. The day after the surgery, the catheter was extracted and the patient was released and on the same day external radiation continued.

Hormonal treatment was added in the high risk group (four months before radiotherapy and concomitantly with RT total androgen deprivation and two years after RT bicalutamide alone). In patients with medium risk tumours hormonal treatment consisted of total androgen deprivation two months before and concomitantly with RT.

### 3. Results

The average observation period for our group was 50 months (10–80), and the median 57 months.

We evaluated perioperative, acute post-radiation and late post-radiation toxicity according to the RTOG criteria. No perioperative complications occurred, all men endured more than two-hours of surgery under spinal anaesthesia without any

difficulties. After needle extraction from the perineum, bleeding was minimal. The second day after surgery, the urinary catheter was removed and all patients were able to urinate naturally. Acute genitourinary toxicity (GU) occurred in 12 (60%), of whom 10 at G1 and two at G2. Most common was frequent urination and nycturia. Acute gastrointestinal toxicity (GIT), most frequently in the form of frequent stools and tenesmus, was recorded in 5 men (25%), but only at grade 1. Late GU toxicity, or that longer than 6 months, was observed in 7 patients (35%) (one patient at grade 3 and the others at grade 1), late GIT toxicity was recorded only in 3 patients (15%) (grade 1). Toxicity of radiotherapy is described in Table 4.

Fourteen men (70%) lived post treatment longer than 3 years, 10 (50%) longer than 5 years. During the observation period, only one patient died after 2 years of heart failure and only in one did the illness show progression, from which he died after 53 months.

Long-term biochemical remission was achieved in 18 patients (90%), in two patients there was biochemical failure (one died from progression of illness, the other from heart failure).

### 4. Discussion

As already stated, it is not clear which treatment option to choose in older men with localized prostate cancer. The recommendation of the International Society of Geriatric Oncology (ISGO) speaks of an individual approach, which is based mainly on the judgement of further additional diseases and the overall state of the patient, and not merely on the indications of eventual therapy according to chronological age. Patients should be classified into 4 groups: (1) the “healthy” patient, without uncontrollable comorbidity, fully capable

**Table 4 – Toxicity of radiotherapy.**

Toxicity	Grade 1 (No of pts.)	Grade 2 (No of pts.)	Grade 3 (No of pts.)
Acute GU	10	2	–
Acute GIT	5	–	–
Late GU	6	–	1
Late GIT	3	–	–

of daily activities, without malnutrition. He should receive the same treatment as a younger man; (2) the “vulnerable” patient, who should receive standard treatment after medical intervention; (3) the “frail” patient, who should receive adaptive treatment; (4) the very ill patient, who should receive symptomatic treatment.<sup>13</sup> Patients from our group should be incorporated into group 1, and maximally into group 2.

According to various population databases, treatment of older men tends to be more active, especially in patients with intermediate or high-risk prostate cancer.<sup>14</sup> It seems that neither further nor multiple comorbidity is taken into account. The choice of treatment used on patients with prostate cancer both younger and older than 75 years was the subject of a study undertaken with the multi-institutional database CapSURE.<sup>15</sup>

Well-selected older patients with higher-risk tumours and without serious comorbidities undoubtedly benefit from radical treatment when compared with watchful waiting. Conversely, older patients with lower-risk carcinoma should benefit rather from observation. Similar views were expressed in another study which concerned the quality of life.<sup>16</sup> In lower-risk carcinomas in older men, watchful waiting is appropriate as an alternative to active treatment. Nevertheless, individual preferences are always a decisive factor. Unfortunately, we always encounter the application of a stand-alone hormonal antiandrogen therapy in older men with prostate cancer without serious intercurrent. This palliative approach may cause a contrary effect of shortening life expectancy and worsening the quality of life. The risk of cardiovascular death in hormonal treatment lasting more than one year is up to 20% higher.<sup>17</sup> Androgen deprivation especially in low risk carcinoma may in fact decrease overall survival.

A meta-analysis of data from the current year from 4 major RTOG studies was undertaken to compare treatment results in men under and over 70 years with local advanced prostate cancer who had been treated by radiotherapy in combination with hormonal treatment. Overall survival was lower in the group of older men (10-year overall survival 55% vs. 41%,  $p < 0.0001$ ), higher was death from other causes and lower prostate-specific mortality; also lower was the occurrence of distant metastases.<sup>18</sup> A possible cause might have been the lower aggression of the tumours in the higher age group. Our patients in the group of intermediate and high risk were also treated with a combination of hormonal treatment and radiotherapy. A worsened tolerance to the hormonal treatment was not recorded. Only one man, who had been treated with antiandrogens after progression, died from cardiovascular disease which was already present in anamnesis before the start of the treatment (myocardial infarction).

Alibhai has questioned the benefit of curative treatment in older men.<sup>19</sup> Age should not be a hindrance to treatment especially in men with little comorbidity and moderately or

poorly differentiated carcinoma. Only one patient in our group died from associated diseases (median of observation in our group was almost 5 years). Therefore, if we had not chosen an active approach to treatment, patients with a risk of carcinoma would most likely have experienced a progression of the disease. Our patients had in 80% of cases an intermediate or high risk carcinoma. The remaining four men (20%) with low cancer risk preferred active treatment before the observation.

HDR brachytherapy has been in use for some decades in the treatment of prostate cancers but the studies relating to this form of treatment in men over 75 have not been much published. Chenov’s work evaluating morbidity of brachytherapy and its relationship with age showed a higher urinary (obstruction, incontinence, bleeding, fistulae) and even a higher intestinal morbidity (proctitis, bleeding) in men over 65.<sup>20</sup> Among other risk factors apart from age are intercurrents. In our study for HDR brachytherapy our patients were chosen appropriately. None of them had either perioperative complications or acute higher or later toxicity. Genitourinary toxicity was exceptionally grade 1 and only once was later GU recorded at a toxicity of grade 3, which manifested itself as bladder retention with the importance of the installation of a permanent urinary catheter. Thirteen of our patients (65%) had hypertension, 4 (20%) currently also have ischaemic heart disease. It is apparent that compensated chronic intercurrent illnesses such as ischaemic heart disease and hypertension do not worsen tolerance to HDR brachytherapy.

## 5. Conclusions

In spite of the low number of patients, we can state that the tolerance to the treatment was very good, toxicity low, and the survival of patients long, despite their advanced age.

In addition, using HDR BRT resulted in a shortened overall treatment period of up to 2 weeks without greater complications and without further influence on the quality of life.

HDR BRT is possible and well tolerated in men in good condition over 75 years of age and without serious intercurrent. Well-selected older patients with higher-risk tumours and without serious comorbidities undoubtedly benefit from radical treatment when compared with watchful waiting.

## Conflict of interest

None declared.

## Financial disclosure

None declared.

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