Acute toxicity of conformal high dose interstitial brachytherapy boost in prostate cancer

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Over the past few years, brachytherapy has become more and more common in the treatment of prostate cancer, largely thanks to the reduced amount of acute and chronic side effects. At the same time, brachytherapy also allows dose escalation, resulting in significant improvements in the treatment results.

From August 2004 to June 2005, we irradiated 40 patients suffering from T1c–T3a prostate cancer. All of the patients underwent external beam radiotherapy with a median dose of 45–50.4 Gy and a conformal high dose interstitial brachytherapy boost (two fractions, 8 Gy per fraction). The patients were divided into three groups: low risk of recurrence (11 patients – 27.5%), intermediate risk (14 patients – 35%) and high risk (15 patients – 37.5%). The medium age of the patients was 68.7 years (between 55 and 77). Hormonal treatment was carried out 17 patients (42.5%). We evaluated the quality of each implantation, including the maximum urethral and rectal dose. The calculated doses were compared with measurements by *in vivo* dosimetry. Acute toxicity was evaluated in all of the patients according to the Radiation Therapy Oncology Group (RTOG) scale. Each of the patients completed an International Prostatic Symptom Score (IPSS) questionnaire.

Acute genitourinary morbidity grade 1 was recorded in 37.5% of patients; grade 2 in 15% of patients. Urine retention in one of the patients resulted in the need to perform an epicystostomy. According to the IPSS score, the majority of patients (90%) experienced an improvement in symptoms related to quality of life. Grade 1 acute gastrointestinal toxicity was recorded in 40% of the patients. Grades 2–4 were not recorded.

Here, we show that the combination of external beam radiotherapy and high dose rate (HDR) brachytherapy in the treatment of early prostate cancer to be feasible and well tolerated. Acute toxicity was low and scarcely influenced the quality of life. Among the risk factors of genitourinary toxicity was the volume of the prostate. For gastrointestinal toxicity, risk factors included the combination of HDR brachytherapy and external beam radiotherapy to the pelvis, as well as hormonal treatment.

Key words: high dose rate interstitial brachytherapy, organ-confined prostate cancer, acute toxicity

Prostate cancer is affecting more and more men, and represents a serious social problem all over the world. With most patients, the option of choice for treating organ-confined prostate cancer is either a radical prostatectomy or radical radiotherapy. At the ASTRO 1999 (American Society for Therapeutic Radiology and Oncology) Conference, MARTINEZ described the percentage of treatment modalities for localized prostate cancer in the USA. The number of patients treated in 1996 for early prostate cancer was 10 000, of which 65% underwent radical prostatectomy, 30% external beam radiotherapy (EBRT), and only 5% brachytherapy. Based on recent trends, it is thought that that number of patients will rise in 2005 to 120 000, of which 33% could be treated by surgery, 31% by EBRT, and 36% by brachytherapy [1]. The reason for the increase in brachytherapy is the low rate of acute and late morbidity with similar treatment results [2, 3]. Many patients prefer non-surgical treatment for fear of impotence and incontinence as a result of a radical prostatectomy.

In order to be successful in radiotherapy treatment of prostate cancer, a significantly high dose must be delivered [4]. The advantage of brachytherapy is the possibility of applying high dose radiation to the target volume, with a sharply lowered dose to the surrounding tissue, especially to the rectal wall. The advantages of higher-dose radiation on biochemical control and cause-specific survival has already been illustrated in studies with longer follow-up [5]. In brachytherapy

for prostate cancer, it is possible to use permanent implants with iodine I^{125} or palladium Pd^{103} (low dose rate brachytherapy – LDR), or temporary interstitial implants with iridium Ir^{192} (high dose rate brachytherapy).

It is possible to use brachytherapy either alone or in combination with external beam radiotherapy [6, 7]. A comparison of non-combined LDR and HDR implantations was presented by GRILLS et al [8]. Toxicity was lower in patients with HDR brachytherapy. The advantages of combined HDR brachytherapy and external beam radiotherapy compared to HDR brachytherapy alone allowed for greater homogeneity of dose distribution and a wider margin [9, 10].

There are radiobiological reasons behind the choice of combined external beam radiotherapy and brachytherapy. The prostate and the surrounding healthy tissue have a similar α/β ratio [11]. This means that the tumour and the surrounding slow-reacting tissue are similarly sensitive to changes in fractionation and that the therapeutic ratio between local control and later changes cannot be significantly influenced by fractionation. Because of the internal movement of the organs, and the risk of imprecise patient placement, external beam radiotherapy, including conformal techniques and intensity-modulated radiotherapy, must take into consideration a greater margin (from clinical target volume (CTV) to planning target volume (PTV)). Because of this, the anterior wall of the rectum receives higher doses [12]. On the other hand, a potential disadvantage of brachytherapy is the possible under-dosing of the microscopic spreading of the tumour outside the implanted volume. The combination of external beam radiotherapy, especially in intermediate and high risk patients, removes this disadvantage.

The need for dose escalation and higher conformal dose distribution in the tumour, without damage to the surrounding healthy tissue, can be resolved with a combination of HDR brachytherapy and new techniques in external beam therapy, such as intensity-modulated radiotherapy [13].

Material and method

Characteristics of patients. In our department, we use a combination of the three-dimensional conformal external beam radiotherapy (CRT) with temporary interstitial HDR brachytherapy for the treatment of localized prostate cancer. Inclusion criteria for brachytherapy are: histologically confirmed adenocarcinoma of the prostate T1b–T3b, any Gleason score whatsoever, a PSA <100 ng/ml, no metastasis in the lymph nodes and no distant metastasis. Among the exclusion criteria belong: a prostate volume >60 cm^3, transurethral resection of the prostate (TURP) within the previous six months, obstruction symptoms, a distance between the rectum and the prostate <5 mm in the transversal section, the inability of the patient to be placed in the lithotomic position, or contra-indications for spinal anaesthesia.

Between August 2004 and June 2005, 40 patients with localized carcinoma of the prostate were treated in accordance with our protocol (Tab. 1). All patients underwent a staging examination (medical history, physical examination, PSA, Gleason score, transrectal ultrasonography, pelvis CT, chest x-ray, skeletal scintiscan in cases where PSA >10 ng/ml, IPSS questionnaire). On the basis of this examination, patients were divided into three groups: Low risk of recurrence (11 patients – 27.5%), intermediate risk (14 patients – 35%), and high risk (15 patients – 37.5%). The medium age of the patients was 68.7 years (from 55–77). Hormonal treatment was carried out in 17 patients – 42.5% (15 in the high risk group and 2 from the intermediate risk group). The characteristics of the patients are presented in Table 2.

Each of the patients underwent a combination of external beam radiotherapy and transperineal HDR implant under spinal anaesthesia. An average of 12 needles was used (6–18).

Real time TRUS-guided brachytherapy technique.

- One day before the operation, patients were placed in the dorsolithotomy position with a catheter and a transrectal ultrasound (TRUS) probe was introduced into the rectum. The probe was placed in the stepping unit. The prostate was imaged from the base to the apex in 5 mm transverse sections.
- Delineation of the target volume – prostate with a 3 mm safety margin + the base of the seminal vesicles, critical structures – the urethra, rectum, skeletal structures.
- Pre-planning – planning of dose distribution according to the shape and size of the target volume – distribution of the needles.

Table 1. Treatment protocol

Risk of recurrence		CRT	BRT
Low risk T1a – T2a + GS ≤ 6 + PSA ≤ 10	PTV	prostate + base of seminal vesicles + safety margin	prostate + base of seminal vesicles + margin 3 mm
	technique	6 iso-centric fields conformal radiotherapy	Temporary interstitial implant
	dose	45 Gy in 25 fractions 5 fractions/ week	2 x 8 Gy (in 3rd and 5th week of EBRT)
Intermediate risk T 2b or GS = 7 or PSA 10 – 20	PTV	prostate + base of seminal vesicles + safety margin	prostate + base of seminal vesicles + margin 3 mm
	technique	6 iso-centric fields conformal radiotherapy	Temporary interstitial implant
	dose	50.4 Gy in 28 fractions 5 fractions/ week	2 x 8 Gy (in 3rd and 5th week of EBRT)
High risk GS > 7 or PSA > 20	PTV	pelvis	prostate + base of seminal vesicles + margin 3 mm
	technique	box	temporary interstitial implant
	dose	50.4 Gy in 28 fractions 5 fractions/ week	2 x 8 Gy (in 3rd and 5th week of EBRT)
	+ hormonal treatment		

Table 2. Characteristics of the patient group

		n	%
Age	≤60	2	5
	61 – 70	20	50
	>70	18	45
PSA	≤10	14	35
	10 – 20	13	32.5
	>20	13	32.5
Gleason score	<4	10	25
	4 – 6	26	65
	≥7	4	10
T stage	T1c	11	27.5
	T2a – b	27	67.5
	T3a	2	5
IPSS score before RT	<15	38	95
	≥15	2	5
IPSS score after RT	<15	31	77.5
	≥15	9	22.5

• Operation day: spinal anaesthesia

• Application of the TRUS in the dorsolithotomy position as mentioned above.

• Delineation of the target volume, urethra, rectum, skeletal structures.

• Implementation of the pre-planning to the real target volume, geometric optimisation, correction of the needle positions, calculation of dose distribution.

• Under TRUS control, the needles are inserted to the prostate with the help of a perineal template (Fig. 1).

• The distal ends of the needles are placed into the base of the bladder under fluoroscopic control.

• Correction of the position of the needles is done with respect to their real position in relation to the transversal ultrasound slice. We tolerated a deviation of up to 3 mm.

• Calculation of dose distribution (geometric optimisation) and dose volume analysis.

• Irradiation with high dose rate afterloading (source: Ir^{192}), *in vivo* dosimetry in the urethra and in the rectum.

• Extraction of the needles.

With each application we evaluated quality parameters – maximal dose in the urethra, maximal dose on the ventral wall of the rectum, D90 (dose that received 90% of the volume of the prostate), V100 (volume covered by 100% isodoses), V150 (volume covered by 150% isodoses). Each implant was performed using a dose volume histogram (DVH).

The calculated values were verified with the help of in vivo dosimetry in the urethra and rectum (Fig. 2). For the urethra we set a maximal dose of 125% of the prescribed dose on the reference isodose, and 85% for the ventral wall of the rectum. A three dimensional image of the 125% isodose is presented in Figure 3.

Patients with a high risk of recurrence were treated with external beam irradiation to the pelvis with doses of 50.4 Gy (1.8 Gy per fraction) to the reference point, in accordance with our protocol. We used a four field technique (box technique with multileaf colimator). With intermediate and low risk patients, the prostate and base of the seminal vesicles were irradiated with doses of 45–50.4 Gy through a six field conformal technique.

Brachytherapy was applied in two fractions (8 Gy per fraction) in the third and fifth weeks of external beam radiotherapy. This dose was calculated to the planning target volume – prostate and base of the seminal vesicles with a 3 mm safety margin (Fig. 4). The treatment time between each fraction was two weeks. When we calculated α/β 1.5 for a prostate tumor, the biologically equivalent dose was 89.5 Gy, and for late effects with α/β 3, the biologically equivalent dose was 65.6 Gy. In the peripheral zone of the prostate, where 75% of tumors were located, the dose was between 150–200% of the reference dose, the biologically equivalent dose was more than 200 Gy.

Patients in groups with high risk of recurrence underwent neoadjuvant and concomitant hormonal treatment with gosereline and flutamide.

After treatment, each patient was regularly examined by a urologist and an oncologist. Acute genitourinary (GU) and gastrointestinal (GI) toxicity were evaluated through RTOG criteria (Tab. 3) [14] and on the basis of the International Prostate Symptom Score (IPSS survey). Symptoms discovered during treatment, or within 6 months of the treatment being completed, were considered to be acute.

Table 3. Acute toxicity criteria of the Radiation Therapy Oncology Group

	G1	G2	G3	G4
GI	Increased frequency or change in quality of bowel habits not requiring medication/ rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs/ mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics	Diarrhoea requiring parenteral support/ severe mucous or blood discharge necessitating sanitary pads/ abdominal distension (flat plate radiograph demonstrates distended bowel loops)	
GU	Frequency of urination or nocturia twice pre-treatment habit/ dysuria, urgency not requiring medication	Frequency of urination or nocturia that is less frequent than every hour; dysuria, urgency, bladder spasm requiring local anaesthetic	Frequency with urgency and nocturia hourly or more frequently/ dysuria, pelvic pain, or bladder spasm requiring regular, frequent narcotic/ gross haematuria with/without clot passage	Haematuria requiring transfusion/ acute bladder obstruction not secondary to clot passage, ulceration, or necrosis

Grade 5 – death directly related to radiation effects

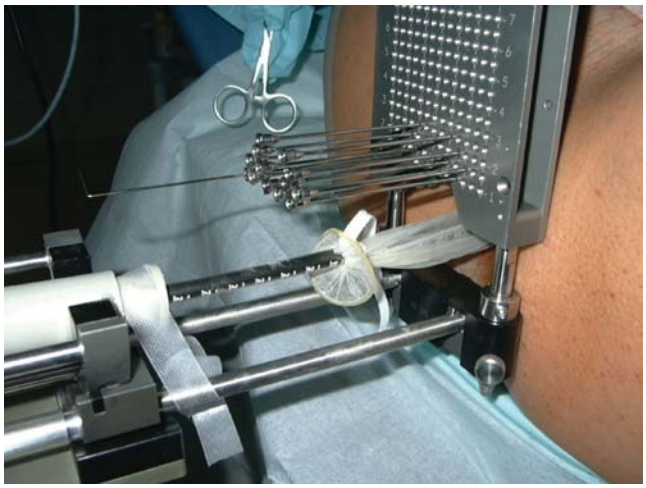

Figure 1. Transperineal implantations of the needles to the prostate under transrectal ultra-sonography.

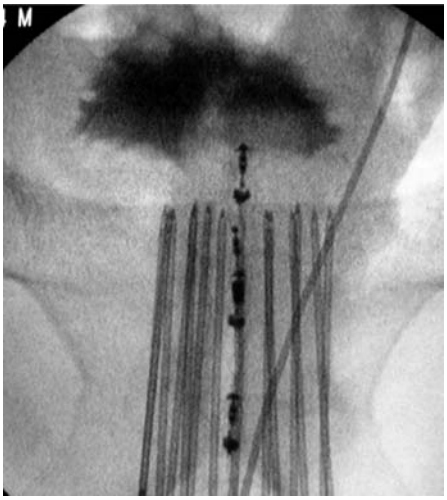

Figure 2. *In vivo* dosimeters located in the urethra and rectum.

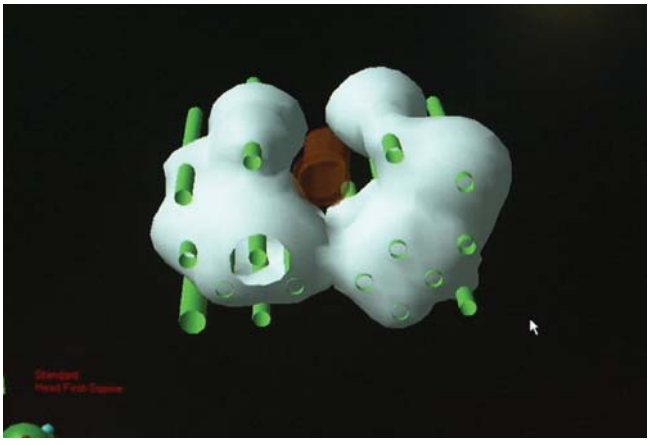

Figure 3. 3D image of distribution of 125% isodoses (white), urethra (red).

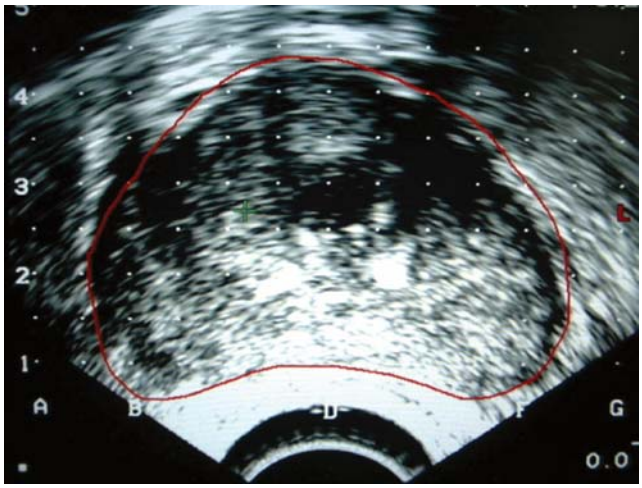

Figure 4. Target volume for brachytherapy planning in ultrasonography transversal section.

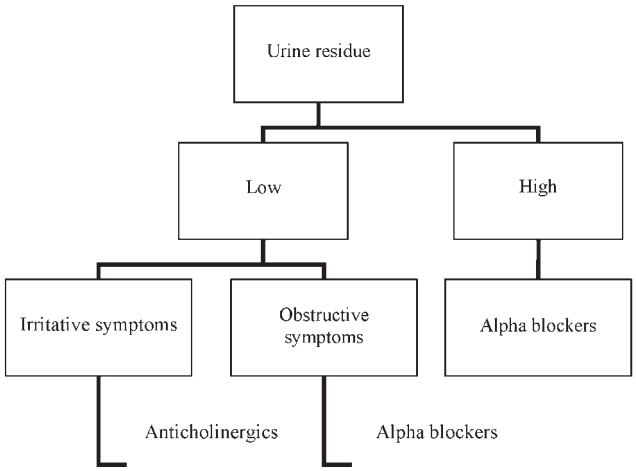

Figure 5. Management of side effects after ultasonography evaluation of the bladder.

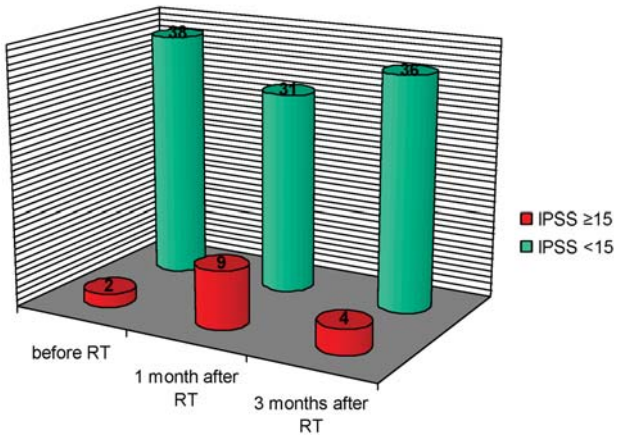

Figure 6. IPSS evaluation before treatment, 1 month after finishing radiotherapy, 3 months after finishing radiotherapy.

When symptoms were discovered in the area around the lower urinal tract, ultrasound examinations of the bladder were carried out. Further steps in managing patients with urinal residue are shown Figure 5.

Results

Quality parameters. In each of the patients, we evaluated doses which obtained 90% of the prostate volume (D90). In our group, D90 had an average of 7.24 Gy (median 7.22 Gy). The mean volume of the planning target volume (PTV – prostate + 3 mm) was 38.3 cm^3 (median 34.7 cm^3). The median volume, with 100% isodoses was 32.0 cm^3 (median 29.4 cm^3). Volumes with 150% isodoses were on average 15.6 cm^3 (median 14.3 cm^3).

The maximum dose in the urethra calculated in accordance with the planning system was, on average, 9.8 Gy (median 9.9 Gy) – 122.5%. The average *in vivo* urethra dose was 9.1 Gy (median 9.4 Gy) – 113.7%. The maximum rectal dose in accordance with the planning system – mean 6.2 Gy (median 6.3 Gy) – 78.7%. Quality parameters are shown in Table 4.

Average operating time was 128 minutes (70–270).

Toxicity. Side effects and complications can be divided into perioperative, acute, and late. To a large extent, they are dependent upon the proper choice of patient for brachytherapy.

Before beginning treatment, the patients filled in an IPSS survey. 95% of the patients had a score of less than 15 (38 men), meaning that obstructive urinary symptoms were minimal. One month after completing the treatment, 77.5% of the patients (31 men) had a score of less than 15. Within 6 months, almost all of the patients had returned to a score of less than 15 (Fig. 6).

Perioperative complications, including pain, seldom call for strong analgesics; significant bleeding from the perineum was not recorded in our group.

Acute gastrointestinal and genitourinary toxicity were evaluated according to RTOG criteria.

Grade 1 of genitourinary toxicity was recorded in 15 patients (37.5%); grade two, primarily in the form of nocturia, in 6 patients (15%). One man had to undergo epicystostomy for urinal retention (because it was not possible to apply a permanent catheter) two days after the first fraction of brachytherapy (toxicity grading 3–4). After two weeks, the epicystostomy was cancelled and the patient could urinate *per vias naturales*. In 45% of the patients (18), no toxicity in the area around the genitourinary tract was registered.

After implant, the Folley catheter was removed on average within 24–48 hours. In two cases, it was necessary to re-implant the catheter, because of a larger prostate volume (60 cm^3 and 48.5 cm^3, according to the planning system). The average PTV volume in patients with genitourinary toxicity of 2 or more was 48.0 cm^3 in comparison with patients with a genitourinary toxicity of grade 1 or 0, with an average PTV volume of 34.0 cm^3.

Gastrointestinal toxicity, most commonly in the form of diarrhoea, was registered at grade 1 in 16 patients (40%), and not at all in grades 2–4. In 24 of the patients (60%), no gastrointestinal symptoms were registered either during or after radiotherapy. To lower gastrointestinal toxicity, we use a water stand off between the rectum and the prostate, which is released after the needle is removed.

One patient suffered deep leg thrombosis after the first fraction of brachytherapy. The second fraction was therefore not carried out. Rather, the dose was complemented with external radiotherapy.

Acute toxicity is shown in Table 5.

Discussion

The treatment of localized prostate cancer is a controversial issue between urologists and radiation oncologists. Until recently, the equipment available in Radiotherapy Departments did not allow the application of high doses of radiation, which led to the failure of radiotherapy as a treatment for prostate cancer. A conventional radiotherapy dose, without increased morbidity, is about 69 Gy, but this dose is insufficient for the treatment of prostate tumors [15].

Another reason to view conventional radiotherapy negatively was the high grade of acute and late gastrointestinal

Table 4. Quality parameters

	Mean	Median	% of D_{ref}
PTV Volume	38.34 cm^3	34.70 cm^3	
D 90	7.24 Gy	7.22 Gy	
V 100	32.00 cm^3	29.40 cm^3	
V 150	15.64 cm^3	14.34 cm^3	
D_{max} urethra – planning system	9.81 Gy	9.90 Gy	122.5
D_{max} urethra – in vivo	9.13 Gy	9.42 Gy	113.7
D_{max} rectum – planning system	6.18 Gy	6.30 Gy	78.7

Table 5. Frequency of toxicity in our group of 40 patients

	Grade 1 number of pts in %	Grade 2	Grade 3	Grade 4
GU toxicity	15 / 37.5	6 / 15		1 / 2.5
dysuria	7	2		0
nocturia	4	6		0
incontinence	0	0		0
retention	5	1		1
haematuria	7	2		0
GI toxicity	16 / 40			
nausea	0			
vomiting	0			
diarrhoea	16			
Rectal discomfort	10			
pain	0			
Other				
thrombosis	1 / 2.5			

toxicity, despite relatively low doses. This was caused by the limited possibilities of radiotherapy, which was usually carried out on cobalt units with relatively low energy photons. Simple radiation techniques were used, particularly two opposed fields (AP/PA), which led to high doses upon the surrounding normal tissue (bladder, rectum). Shielding blocks were not even used in the four fields technique (BOX technique). Side effects – proctitis, cystitis, fibrosis, were therefore very common. On the other hand, it wasn't possible to deliver a sufficient dose of radiation to the target volume.

The results of many trials have shown statistically significant differences in 5 year local control between tumors irradiated by doses of less or more than 70 Gy [16–20].

Over the past two decades, huge technological gains have been made in radiation treatment – from conventional radiotherapy to conformal radiotherapy, or intensity modulated radiotherapy. This progress has permitted dose escalation to 80 Gy without increased toxicity [20, 21]. Nevertheless, it is very important to respect limits for radiation dosage in the rectum, which in some cases can prove difficult, or even impossible. The recommended limits for external beam use in our department are described in Table 6.

Table 6. Recommended dose limits in the urethra and rectum in patients treated by external beam radiotherapy

1. Contours of the rectal wall in sections 1 cm above and 1 cm below the target volume (PTV).
2. DVH evaluation 75 Gy < 15% rectal volume – V15 70 Gy < 25% rectal volume – V25 ! 65 Gy < 35% rectal volume – V35 60 Gy < 50% rectal volume – V50 For the development of late effects, an irradiated rectal volume of 70 Gy and 75 Gy is very important.
3. 2D image controlling in also very important – the maximal dose must be located outside of the rectum – A dose of 70 Gy should not be applied to more than 1/3 of the circumference of the rectal wall in any of the sections.

Progress has also been made in brachytherapy. The process of planning and imaging is more and more precise and conformal. In brachytherapy, it is possible to increase the dose to more than 100 Gy. Radiobiological data support brachytherapy too. In carcinoma of the prostate, a low α/β ratio (1.5 Gy) seems to indicate the greater efficiency of higher dose per fraction [22].

In our group, 72.5% of the patients were at an intermediate or high risk of recurrence. This is the group that should benefit most from increased doses [19]. We will have to wait for the treatment results over the long term.

One of the most common side effects of brachytherapy for prostate cancer is urethral toxicity. RUBIN et al analyzed 1220 samples of radical prostatectomy and evaluated the spread of tumors to periprostatic tissue. In 20% of the patients, the tumor was found near the urethra. So, it was necessary to deliver a dose of radiation to this area [23]. A dose of 100–140% of the prescribed dose should be tolerated by all of the segments of the prostatic urethra [24]. Our method of interstitial brachytherapy includes the application of a Foley catheter one day before the operation, during preparation of the radiation plan (preplanning). The Foley catheter allows the imaging of the urethra with the help of transrectal ultrasonography and the correct calculation of the dose in this area, which during radiation, is verified by *in vivo* dosimetry. Our limit for the maximal urethral dose is 125% of the prescribed dose. After the operation, the Foley catheter is extracted, on average, within 24–48 hours. Only 2 of our patients needed the catheter to be reintroduced, due to the larger volume of the prostate: 60 cm^3 and 48.5 cm^3. Some risk factors for urinal retention include: large prostate volume, pre-implant obstruction symptoms, or a higher urethral dose [25, 26].

Urinal retention is usually discovered within 24–48 hours, but can also be present in between 2–10% of patients for days or even months. In low dose rate (LDR) implants, urinal retention is found in 4–14% of patients [27]. Data from high dose rate (HDR) implants are limited and frequently distorted depending on the patient group. In our group, 17.5% of the patients reported various levels of urinal retention. For the majority, this condition was resolved immediately after taking alpha-blockers. Only two of the patients required the reintroduction of the Foley catheter, and one had to undergo an epicystostomy (7.5%). The treatment of urinal retention is based upon the application of alpha-blockers, the application of the Foley catheter, or the trans-urethral resection of the prostate (TURP). Some departments apply alpha-blockers through prophylactics [28].

Other side effects include dysuria, nocturia and frequency. Nocturia was the most frequent cause of grade two genitourinary toxicity among our patients.

Gastrointestinal toxicity is fairly well documented in patients with external beam radiotherapy. Less work has been done for such evaluations in brachytherapy [29]. Incidence of gastrointestinal toxicity vary from 17% to 30%. Among the risk factors is the combination of brachytherapy with external irradiation and advanced age. Most common are grade 1 and 2 [30]. In our group, only grade 1 gastrointestinal toxicity was registered, and that in 40% of the patients (16 men). Among the risk factors we must include the combination of radiotherapy and hormonal treatment (flutamide), present in about half of our group (17 patients – 42.5%). The benefits of combined hormonal and radiation therapy in local advanced tumors are shown in the randomized study [31]. Neoadjuvant hormonal treatment should help in reducing the volume of the prostate, and with it, the amount of irradiated healthy tissue [32].

According to data already published, escalated doses, in combination with hormonal treatment should improve results in patients at high risk of recurrence [18]. In our department,

patients at high risk of recurrence receive neoadjuvant and concomitant hormonal treatment.

Another risk factor for gastrointestinal toxicity is the irradiated volume of the bowel. According to our protocol, patients at a high risk of recurrence are indicated for irradiation of the pelvis (Tab. 1).

Low acute and late toxicity are among the great advantages of combined external beam and brachytherapy for prostate cancer [33].

Conclusion

The combination of external beam radiotherapy and high dose rate brachytherapy allows for optimal conformity, dose escalation, with low acute and late toxicity. The advantages of combination brachytherapy with external beam radiotherapy, in comparison with brachytherapy alone, are better dose homogenity and more safety margins. The disadvantages are the longer treatment and the higher incidence of gastrointestinal morbidity (proctitis).

Our paper illustrates the good tolerance level of this treatment method. Acute gastrointestinal toxicity grade 1 in 40% of our patients was caused by the combination of brachytherapy and external beam radiation of the pelvis and concomitant hormonal treatment. Acute genitourinal toxicity grade 1 and 2 (according RTOG criteria) was recorded in 52.5% of our patients, grade 4 only in one patient.

Contraindications of brachytherapy (for example large volume of the prostate) and dose limits in the urethra and rectum with *in vivo* dosimetry can help to decrease the side effects of this method.

To evaluate the late toxicity and local control of the disease, long term follow up is required.

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