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Radical irradiation of the prostate. Combination of percutaneous irradiation and irradiation with LDR Ir-192 implants

Borut Kragelj, France Guna, Janez Burger

Institute of Oncology, Ljubljana

Background. *The irradiation of the carcinomas of the prostate with the doses above the tolerable ones of standard radiotherapy improves the local control of the disease. The aim of this study is to determine the acute toxicity and tolerability of the high-dose prostate irradiation combining external beam radiotherapy (EBRT) and interstitial low dose rate (LDR) brachyradiotherapy (BRT) with Ir-192 of the prostate.*

Material and methods. *We examined medical records of 8 patients with localized carcinoma of the prostate (T2-T3 No-x Mo) treated from August 1999 until February 2000. The initial PSA was 2.7-37.5 ng/ml (median 13.7) and Gleason score 4-9 (median 7). Radiotherapy consisted of 48.6 - 50.4 Gy of EBRT to the prostate and seminal vesicles (4 patients) or the whole pelvis (4 patients) and 20.0-28.0 Gy of interstitial LDR Ir-192 BRT given as a single fraction, fluoroscopic guided transperineal implantation of the prostate. The cumulative doses of percutaneous and interstitial irraditations to the prostate were 68.6 - 79.1 Gy.*

Results. *Acute toxic effects of irradiation though observed in all patients were of only mild intensity. According to the RTOG criteria, 20/30 toxicities were assessed as grade 1, 9/30 as grade 2, and 1/30 as grade 3. In none of the patients, toxic effects required any specific modification of the treatment regimen.*

Conclusions. *The very first experiences indicate moderate toxicity and optimal tolerance of the treatment by patients. An improvement of implantation techniques may be expected with regular CT controls of the implants and extra attentive care of the implants in the urethra region.*

Key words: prostatic neoplasms - radiotherapy; radiotherapy dosage; brachytherapy; radiotherapy - adverse effects

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Correspondence to: Borut Kragelj, MD, MSc, Institute of Oncology, Zaloška 2, 1000 Ljubljana, Slovenia; Phone: +386 01 323063 Fax: +386 01 4314180; E-mail. bkragelj@onko-i.si

Introduction

The aim of any local therapy has always been to obtain local control of the disease. A better local control over the localized carcinomas of the prostate and the locally advanced tumors invading to the seminal vesicles, periprostatic tissue or urinary bladder can improve also the systemic control of the disease - better local control is associated with better biochemical, distant metastasis-free and cancer specific survival rates.[1-3]

The probability of local recurrence after standard irradiation with the doses not exceeding 70 Gy is 20-60 % in locally advanced tumors (T3,T4),[4] and 8-27 % in T1 and T2 tumors.[2,5-7] However, the effectiveness of standard radiation in terms of local disease control might be even lower. As suggested by the PSA-based follow-up, the rate of local disease control assumed from the digitorectal and imaging examinations of the prostate is perhaps overestimated.[6]

One of the factors that influence local disease control is the radiation dose. Even within the range of conventional external beam radiotherapy (EBRT), the dose increase improves the local control of disease. In conformal radiotherapy; a better biochemical control of disease, at least temporarily, within five-year projection, is obtained with a dose increase up to 81 Gy. In view of the treatment modality, this is due to a better local control. The effectiveness of conformal radiotherapy may be observed in particular in the group of patients with the initial PSA between 10 and 20 ng/ml or with high tumor grade (Gleason score 8-10) in whom standard radiation is often unsuccessful.[8,9]

Tumor dose depends upon the tolerance of surrounding organs to radiation. In conformal radiotherapy, higher tolerance may be obtained with a more precise adjustment of radiation fields to target volume, thereby reducing the involvement of the surrounding organs that are not affected with tumor mass.[9-11] Similarly, the increase of a tumor dose not exceeding the level of admissible impairment of the surrounding organs can be obtained with the combination of percutaneous radiation and brachyradiotherapy (BRT) using J-131, Pd-103[12,13] seeds or Ir-192 wires[14-17] as permanent or temporary implants, respectively. The article describes our experiences with the combination of percutaneous irradiation and interstitial low dose rate (LDR) BRT with Ir-192.

Material and methods

From August 1999 to February 2000, 8 patients with localized carcinoma of the prostate received combined therapy of percutaneous irradiation and interstitial brachyradiotherapy with Ir-192.

In all patients, transrectal ultrasonography was carried out before treatment. In seven patients, the US guided biopsy from six typical sites was performed, whereas in 1 patient only the biopsy of tumor mass was made. In all patients, the PSA concentration in the serum was measured. In all of them, the carcinoma of the prostate was histologically confirmed and its grade assessed according to Gleason score. They also underwent the CT scan of the pelvis, bone scintigraphy, X-ray of the thorax and renography.

The treatment indications were given with the histological confirmation of the adenocarcinoma of the prostate, stage T1-T3 No Mo, while the contraindication was earlier transurethral resection of the prostate. Some restrictions were imposed by the expected survival rate - 5 years in patents with high tumor grades (Gleason over 7), and 10 years in the rest of the patients, all with PSA concentration in the serum not exceeding 30 ng/ml.

The recruitment of the patients was based on negative selection, i.e. unsuitability of the patients for a radical surgery due to the risk factors, such as high tumor grade, tumor

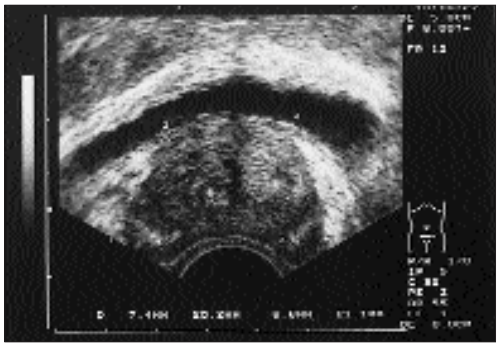

Figure 1. US-guided implantation of metal implants. The implants are marked with arrows.

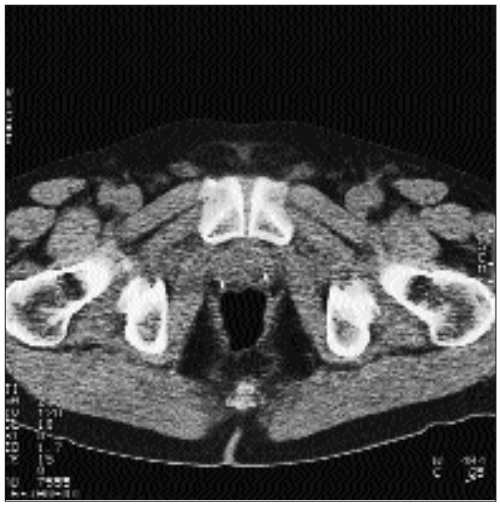

Figure 2. Metal implants viewed by CT scan. The implants are marked with arrows. The distance between the implants and the prostate margins on CT and US images is used in assessing the target volume and implantation planning.

spread into seminal vesicles, tumor overlapping the capsule, PSA over 10 ng/ml, or accompanying diseases that may add on doubts to the fitness of the patients for surgical treatment.

The patients' characteristics are presented in Table 1.

The preparations for brachytherapy started with the US-guided insertion of 3 to 4 permanent metal implants into the prostate (Figure 1). CT scans were used for the planning of radiation delivery and metal implants served as markers. The location of markers in the prostate, especially with respect to the prostate margins, was determined from the CT scans (Figure 2). The planned target volume encompassed at least 0.5 cm margin around the outer border of prostate or any extracapsular tumor extension. The needles were implanted under digital and fluoroscopic control using metal implants as orienters. A proper needle positioning was achieved by a template with 1 to 1.5 cm spacing between the needles. The contrast in the urinary bladder served for a proper positioning of needles' points into the bladder wall in order to assure a satisfactory radiation of the base of the prostate. In planning the implantation as well as carrying it out, we were careful to avoid the urethra. During the implantation, the

Table 1. A survey of patients with regard to their age, tumor stage, initial PSA concentration and tumor grade (Gleason score)

No. of patients	Age (years)	T stage	PSA (ng/ml)	Grade
1	68	T2c	24.4	7
2	68	T3	7,2	4
3	71	T2a	18,9	7
4	68	T3	37,5	7
5	72	T2b	12,5	5
6	72	T3	14,3	9
7	73	T3	2,7	5
8	68	T3	13,2	7

position of the urethra was marked by the contrast contained in the urinary catheter. With regard to the size of the prostate and activity of Ir wires, the number of implanted needles varied from 11 to 16. Following the tradition of the house, we applied, in 7 patients, metal needles, which were later replaced by plastic ones, to provide higher comfort to patients and also to facilitate the subsequent determination of the location of the needles with CT scan. We used 20 cm long needles with a diameter of 1.9 mm.

A single implantation was planned before starting with of EBRT. The prescribed dose was defined as the dose applied to the peripheral isodose area involving the planned target volume and, at the same time, assuring a minimal exposure of the rectal wall and urethra (the so-called *100 % isodose*) (Figure 3). The dose calculation was made according to the Paris dosimetry system. The reference dose was 15 % lower than the minimum dose within the implant. The calculations of the prescribed dose also took account of biological correction factor with respect to the dose rate. The so-calculated radiation dose ranged from 2000 cGy to 2800 cGy.

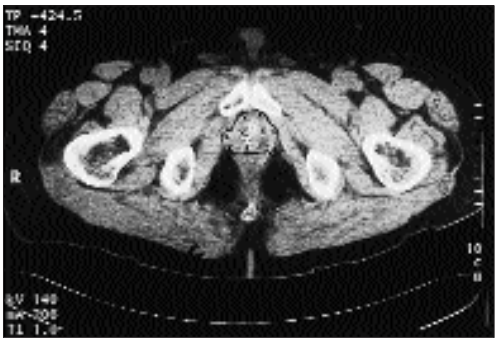

Figure 3. CT image of the implant with reference isodose.

Brachyradiotherapy was followed by EBRT. The patients were irradiated with the linear accelerator of the energy of 10 MV using the technique of four fields and individual shieldings. The standard fractionation was applied. The prescribed target dose was 50.4 Gy given in daily doses of 1.8 Gy. With regard to the probability of lymphogenic spread that was calculated from Roach's equation, the radiation was targeted exclusively to the prostate and seminal vesicles if the estimated risk was lower than 15 %; otherwise the regional lymph nodes were also involved.[17] In these cases, standard, pelvic fields were applied. In EBRT, limited to the prostate and seminal vesicles, target volume included also a 2.5 cm wide surrounding margin.

The details of radiation therapy are presented in Table 2.

All patients received complete androgen

Table 2. A survey of patients with regard to the external beam radiotherapy (EBRT) field and dose, dose delivered by brachiradiotherapy, total dose delivered to the prostate and treatment time

No. of patients	EBRT field	EBRT dose (Gy)	EBRT dose (cGy) dose (cGy)	Dose to (Gy) the prostate	Treatment) time (days
1	pelvis	48,6	2000	68,6-78,6	54
2	P+SV	48,6	2000	68,6-72,3	48
3	P+SV	48,6	2000	68,6-69,5	42
4	pelvis	48,6	2500	73,6-78,9	47
5	P+SV	50,4	2500	75,4-80,6	53
6	pelvis	50,4	2000	70,4-74,4	48
7	P+ SV	50,4	2400	74,4-79,6	45
8	pelvis	50,4	2800	79,1-84,1	56

P+SV: prostate and seminal vesicles; Dose to the prostate: total dose including the mean minimal dose within the implant.

blockade for a period of at least three months before irradiation.

Toxic effects of irradiation were evaluated according to the RTOG criteria.

Results

In all patients, the treatment was completed within the expected period. The treatment time ranged from 42 to 56 days (median 48 days). The differences in treatment time are due to different time intervals between brachy- and teleradiotherapy, which could not be avoided because the treatment facilities are overcrowded. In no one of the patients, the toxic effects of radiation were so severe that they would require discontinuation of the therapy.

In most patients (7/8 patients) the treatment was completed without major complications. In one patient, the position of the implant changed. The implant was therefore prematurely removed and reimplanted after the completed percutaneous irradiation.

The toxic side effects of the irradiation of the urinary bladder, urethra and rectum occurred in all patients. They were generally mild and did not radically affect the quality of life. According to the RTOG criteria, 20/30 side effects were categorized as morbidity grade 1, 9/30 as grade 2, and 1/30 as morbidity grade 3.

The side effects arising from the radiation toxic effects on the urinary organs were evaluated in 6 patients. In one patient, this evaluation could not be made because the urinary catheter had been inserted permanently before treatment. The most often side effects were more frequent urinations, urge to urinate (7/7 patients), stranguria (6/7 patients), dysuria (4/7 patients), and hematuria (1/7 patient). This single case of hematuria, which occurred immediately after the removal of the implant and required the whole day rinsing of the bladder, was the only morbidity grade 3.

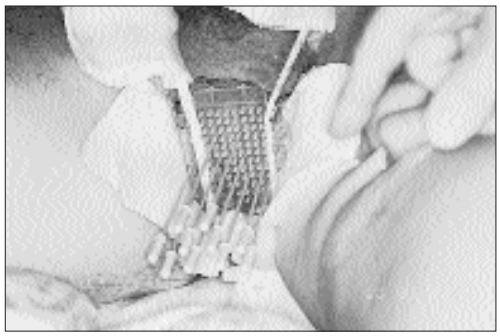

Figure 4. A patient with the inserted implant: a clear view of plastic guides and perineal template.

Table 3. Acute toxic effects of percutaneous irradiation combined with low dose rate brachyradiotherapy (LDR BRT) Ir-192: urinary toxicity with regard to the pain, frequency of mictions, decreased stream, and hematuria. The grade of these complications is evaluated according to RTOG criteria

No of patients	Pain (grade)	Frequency (grade)	Decreased stream (grade)	Hematuria (grade)
1	2	1	+	0
2	2	1	0	0
3	1	1	+	0
4	0	1	+	3
5	0	1	+	0
6				
7	1	1	+	0
8	0	1	+	0

Table 4. Acute toxic effects of percutaneous irradiation combined with LDR BRT Ir-192: intestinal toxicity with regard to stool frequency, painful defecation, tenesmuses and bleeding. The grade of these complications is evaluted according to RTOG criteria

No. of patients	Stool frequency (grade)	Pain (grade)	Tenesmuses (grade)	Bleeding (grade)
1 2	1	0	0	
2 0	0	0	0	
3 0	1	0	0	
4 1	1		2(*)	0
5 0	0		2(*)	0
6 2	2	0	0	
7 1	0		2(*)	0
8 0	2	0	0	

(*) concurrent miction, evacuation of winds and mucinous rectal discharge

Painful defecation was the most often toxic effect of the rectal irradiation (5/8 patients), followed by more frequent defecation (4/8 patients), and tenesmuses (3/8 patients). No hemorrhage from the colon was observed.

The complications in the urinary organs occurred in all patients immediately after the completion of BRT. During percutaneous irradiation, these complications were intensified in 3/7 patients: in 2 patients, the urge of frequent urination further increased, whereas in one patient, stuttering urination became more disturbing. Radiation proctitis was noted in 3/8 patients after the removal of the implant: in one patient, it was manifested as more frequent tenesmuses, in the second as tenesmuses and more frequent defecations, and in the third as painful defecations.

The occurrence of side effects was higher with higher BRT doses. They were mostly related to more intensive proctitic complications. All patients who had proctitic complications after brachyradiotherapy received a dose exceeding 2000 cGy. In all these patients, the complications persisted also during the percutaneous irradiation. The cystitic symptoms were also more pronounced and long lasting in the treatment with higher doses, while with lower doses, this complications disappeared in the first two or three weeks of percutaneous irradiation.

Within the short follow up, no biochemical recurrence was observed in the patients with the PSA concentration that was at the beginning of radiotherapy lower than 1 ng/ml.

Discussion

The technique of transperineal biopsy of the prostate with the US-guided needle was introduced by Holm in the 1980s. The technique was then used primarily for diagnostic purposes, and after unsuccessful retropubic implantations of J-125 seeds into the prostate, also for therapeutic purposes in the treatment of the carcinoma of the prostate. The findings of some radiobiological facts on the unsuitability of the treatment with J-125 and the development of high dose rate (HDR) BRT urged the application of permanent Pd-103 implants and temporary HDR Ir-192 implants in the treatment of the carcinoma of the prostate. At the same time, new data and knowledge on the value of particular tumor characteristics in prognosticating the natural progression of very different tumor types were being gathered.

The prognostic factors, such as PSA concentration, local spread of the disease, and histological tumor grade, allow the categorization of the patients with localized disease into the groups with respect to the assumed disease progress. This also facilitates a better analogy of different treatment modalities and, consequently, also the selection of the most suitable one. In view of radical radiotherapy, the patients may be classified into three groups; the first group, termed as 'prognostically favorable', includes the patients with the tumor stages T1 and T2, PSA level below 10 ng/ml and Gleason score grade lower than 8. In this group, the conventional teleradiotherapy, implantation of J-125 or Pd-103 seeds [8,18-20] and radical prostatectomy18 are all considered as effective treatment modalities. The second group comprises the patients in whom high dose radiation therapy,[8,9] eventually with the irradiation of the regional lymph nodes,[13,20] seemed to be more effective than standard radiotherapy. The patients falling into this group have the serum PSA levels ranging between 10 and 20 ng/ml,[8,9,13,21] tumor stage T3,[8,14] and Gleason score grade above 7[8] or 8.[22] The patients with more of the above mentioned unfavorable prognostic factors[8,23,24] or PSA level exceeding 20 ng/m[l8,9,13,22] may be defined as 'high risk group', at least in view of the curability with only local or locoregional treatment - however, in these patients the local control, relapse-free and overall survivals[25,26] can be improved by an adjuvant hormonal therapy. With regard to the above prognostic factors, our patients were consistent with the mean and the high-risk group. The decision on treatment modality was therefore focused on three main issues: the use of high dose irradiation of the prostate,[8,9,14-17] elective irradiation of the seminal vesicles[27] or regional lymph nodes[24] and instantaneous medicamentous androgen blockade.[25,26] These issues were resolved by applying the combination of EBRT to the prostate and seminal vesicles or to the pelvic region and the LDR Ir-192 BRT to the prostate, together with an instantaneous application of LH-RH agonists and blockers of androgen receptors.

Our brachyradiotherapy technique was based on the CT and transrectal ultrasound (TRUS) determinations of the target volume, the introduction of the needles with respect to the position of implanted metal markers, fluoroscopic control of the position of the needles, and choice of LDR Ir-192 as the radiation source. The main reasons for this specific technique were the in-house experiences with LDR BRT Ir-192 method, limited possibilities of US-guided implantation of the needles and unavailability of technical devices for HDR. These are also the basic differences between our technique and more advanced ones.

The advantage of the HDR BRT Ir-192 technique is the possibility of more accurate adjustment of irradiated field to the prostate, thereby reducing the exposure of the surrounding tissue to irradiation; it is also possible to avoid hot spots that may occur because of the improper geometry of the implant. This may be obtained by planning the treatment after the needles have been in place, and by precise placing of a single movable high intensity Ir-192 source anywhere in a after loading needle, and by varying the time spent at a particular location to control the dose deposition. By choosing different lengths of active Ir-192 wires and by varying the time of insertion of a particular active wire into the after loading needle it is possible to adjust to a certain point also the dose in LDR BRT; but this is only a rough approximation to the possibilities of HDR BRT.

An important advantage of the US-guided implantation is higher accuracy in positioning the needles. Besides, in the determination of target volume, our technique can hardly assure the same accuracy as that achieved in TRUS-guided implantation.[15] However, the accuracy of TRUS has certain limitations: the accuracy of the TRUS measurements of the

tumor volume is 62-92 %.[28] Moreover, in the determination of the prostate volume, there is a discrepancy between CT scan and TRUS - the target volume determined by CT scan may exceed the volume determined by TRUS by 25-40 %.[17] TRUS is also unreliable in predicting the invasion into the capsule and periprostatic tissue. This is particularly important in bilateral tumors in which as high as 72 % probability of the invasion into the capsule has been recorded. In view of the possibility of underestimation of the tumor volume by TRUS, especially in T2B, T3 tumors, a larger treatment volume determined by CT scan from the target volume and wider safety margin, due to a lesser accuracy of needle placement, may contribute to a more reliable implantation.

The limited follow-up of our patients has not allowed any comparison of the late sequels of the LDR and HDR BRT Ir-192 treatment modalities. The only components of the two modalities that could be compared were acute toxicity of the treatment and tolerance of the patients to the treatment. Both treatment modalities are comparable as regards the non-occurrence of serious toxicity and 100 % tolerance of the patients to the planned therapy. Perhaps, an exception was a patient with hematuria. It was classified as RTOG toxicity grade 3, but it was short and transitory and did not affect the physical condition of the patient. Similar complications were observed also in US-guided implantations and were classified as low degree toxic effects (15). A higher toxicity, due in particular to proctitic complications, was observed with the doses escalating up to 2500 cGy. Nevertheless, even in these dose ranges, the toxicity remained within low to median limits.

The factors that may influence the toxicity, such as the accuracy of irradiated volume to fit the prostate, and the quality of treatment planning are not in favor of our technique - the main advantages of more accurate adjustment of irradiated to the target volume by US-guided HDR BRT Ir-192 are lower exposure of the surrounding organs to radiation and lesser possibilities of hot spots inducing acute and late sequels of treatment. The dose, another factor influencing the occurrence of toxic effects is, at least nominally, comparable or even higher than 36-50 Gy of EBRT and 12- 30 Gy of BRT in HDR 192-Ir treatments (14,15,22). Hence, one can speculate that the comparability of the least acute toxicity may be due to better biologic tolerance of LDR BRT.

The possibilities to improve our technique lie in the use of TRUS during the implantation without the help of a fixed template, and in the routine use of CT scan after the implantation. The determination of the actual position of needles allows more adequate calculation of the dose. Another advantage is the possibility to irradiate different areas of the implant with different doses, i.e. increasing the dose in the tumor area and decreasing it in the area of the urethra and of the wall of the rectum - i.e. the organs most at risk for the development of late irradiation injury.[21] With further technical improvements, we expect to decrease toxicity or, at least, preserve the existing tolerance with increasing the tumor dose.

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