Acta Oncologica, 2007; 46: 909–917

informa
healthcare

ORIGINAL ARTICLE

Clinical outcome in patients with prostate cancer treated with external beam radiotherapy and high dose-rate iridium 192 brachytherapy boost: A 6-year follow-up

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Abstract

To report the long-term results for treatment of localized carcinoma of the prostate using high dose rate (HDR) brachytherapy, conformal external beam radiotherapy (3D EBRT) and neo-adjuvant hormonal therapy (TAB). From 1998 through 1999, 154 patients with localized prostate cancer were entered in the trial. Biologically no evidence of disease (bNED) was defined at PSA levels <2 μg/l. In order to compare the results of this treatment with other treatment modalities, the patient's pre-treatment data were used to calculate the estimated 5-year PSA relapse free survival using Kattan's nomograms for radical prostatectomy (RP) and 3D EBRT. After 6 years of follow-up, 129 patients remain alive. The actual 5-year relapse-free survival is 84%. None of the patients demonstrated clinical signs of local recurrence. The median PSA at follow-up among the relapse-free patients was 0.05 μg/l. Among the 80 patients who presented with clinical stage T3 tumours, 55 (68%) were relapse-free. The expected 5-year relapse-free survival using nomograms for RP and 3D EBRT was 54% and 70%, respectively. Late rectal toxicity RTOG grade 3 occurred in 1% of the patients. Late urinary tract toxicity RTOG grade 3 developed in 4% of the patients. Combined treatment, utilizing HDR, 3D EBRT and TAB, produces good clinical results. Rectal toxicity is acceptable. Urinary tract toxicity, most likely can be explained by the fact that during the first years of this treatment, no effort was made to localize the urethra, which was assumed to be in the middle of the prostate.

In Sweden, prostatic adenocarcinoma is the most common male cancer, with an annual incidence of 168/100 000 [1]. The optimal method of treatment for patients with localized prostate cancer remains to be defined, since there are several approaches to treatment such as radical prostatectomy, radiotherapy with curative intention or watchful waiting. Furthermore the optimal method of radiation therapy, external beam radiotherapy, brachytherapy (low dose rate or high dose rate), or a combination, remains in question. The currently accepted standard is that the curative dose of irradiation should be 70 Gy or greater, and several dose-escalating projects are currently investigating the optimal dose for cure and minimal side effects.

Known side effects when using external beam radiotherapy include symptoms from the rectum and/or the urinary bladder caused by the dose of irradiation to these organs which are in close proximity to the prostate.

The advantage of brachytherapy is the short range of its irradiation, leading to reduced doses of

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(Received 24 June 2006; accepted 4 December 2006)

ISSN 0284-186X print/ISSN 1651-226X online © 2007 Taylor & Francis
DOI: 10.1080/02841860601156140

irradiation to the rectum and bladder. However, this short range may also produce the problem of inhomogeneous dose-distributions and the risk of insufficient dose to parts of the target. Another problem is that the source must be accurately placed in the target or in very close proximity.

Since 1998, we have utilized a treatment method, which combines neo-adjuvant hormonal therapy, conformal external beam radiotherapy (EBRT), and two sessions of high dose rate (HDR) iridium 192 source brachytherapy for patients with localized prostate cancer. The principle of this treatment has been reported previously [2]. This combination delivers a normalized dose equivalent of 2 Gy per fraction (NTD) of more than 104 Gy (assuming a conservative tumour alpha/beta ratio = 3 Gy). Presently, the patient-reported toxicity and quality of life up to 3 years after treatment seem acceptable [3,4].

In this article, clinical outcome and side effects at a median follow-up of 6 years will be reported and compared with the calculated results using accepted nomograms for radical prostatectomy and dose escalated conformal external beam radiotherapy.

Material and methods

Patients

From May 1998 through December 1999, 154 patients with localized prostate cancer entered this trial. The patients had a biopsy proven prostatic adenocarcinoma. The Karolinska has a long tradition of fine needle aspiration cytology (FNAC). Ultrasound guided core needle biopsies in the diagnosis of prostate cancer was introduced relatively late at the hospital. Briefly, with FNAC dispersions of isolated or groups of cells are assessed according to the morphology of nuclei and cytoplasm whereas core biopsies provide tissue pieces suitable for histopathological examination. Consequently, in the initial period of the protocol most patients were diagnosed only with FNAC. The biopsies were reported according to the WHO grading system and later the Gleason system. The Gleason score was transformed to WHO high, middle or poor differentiation defining Gleason score ≤ 5 as denoting low grade cancer and Gleason score ≥ 7 (4+3) denoting high grade cancer. The T-stage was defined according to the 1997 TNM classification system.

A lymph node dissection was performed if the tumour was high grade or the prostate-specific antigen in serum (PSA) exceeded 20 μg/l. Only patients with negative lymph node sampling were included. In this report, 103 patients were surgically staged with negative biopsies of lymph nodes. A bone-scan was routinely performed if the PSA exceeded 10 μg/l, in order to exclude bone metastasis. All patients received neo-adjuvant hormonal (TAB) treatment for 6–9 months, consisting of anti testosterone (orally Bicalutamide 50 mgx1 or Flutamide 250 mg × 3) combined with subcutaneous implants of a gonadotropin releasing hormone analogue.

Patient characteristics at diagnosis are listed in Table I. Pre-treatment PSA was missing in one patient and T-stage was not assessed in one patient.

Poor prognostic risk factors were defined as follows: PSA >10 μg/l, T-stage 3 (TNM), and poorly differentiated prostate cancer (WHO grade III). 32 patients had no risk factors, 54 patients had one risk factor, 52 patients had two risk factors and 14 patients had all three risk factors.

All patients have been identified for follow-up and 24 have died, however, four patients have moved abroad, resulting in a follow-up period of 2.8–4.0 years for these patients. Routinely the follow-up consists of clinical visits every third month during the first year, every sixth month during the second year and annually, beginning the third year. The

Table I. Patient characteristics covering age at diagnosis, PSA levels, differentiation grade according to WHO, T-stage and N-stage.

	Mean	Range	Total
Age (years)	67	(46–79)	154
PSA (μg/L)	21	(2–116)	153⋆
	Number	Percent	
PSA <10 μg/l	56†	37	
PSA 10–20 μg/l	40	26	
PSA >20 μg/l	57	37	
Total	153⋆		
Histopathology	34†	22	
Cytology	120	78	
Total	154		
Differentiation (WHO)			
Grade I	44	29	
Grade II	82†	53	
Grade III	28	18	
Total	154		
T-stage (WHO)			
T1	20	13	
T2	52	34	
T3	81†	52	
T unknown	1	1	
Total	154		
N-stage			
N0	103	67	
NX	51†	33	
Total	154		

⋆ PSA at diagnose was missing in one patient.

† Denoting a 71 years old man with PSA 8 μg/l who violated the protocol and was excluded in the outcome analyses.

clinical visits included physical examination with digital rectal examination and blood studies including PSA.

Biologically no evidence of disease (bNED) was defined as PSA levels <2 μg/l, in order to exclude PSA-bounce. Time to PSA relapse was defined as the time from radiotherapy to the third raised PSA level that was above 2 μg/l. In 1998 when this study began there had been a recent consensus meeting of ASTRO defining PSA relapse as three consecutive increased PSA measurements [5]. This definition was not totally implemented in this trial since one of our laboratories did not titrate levels of PSA lower than 2 μg/l until 2000.

The side effects were assessed and recorded by the physicians according to the toxicity criteria of the USA Radiation Therapy Oncology Group (RTOG). Briefly, grade 0 corresponds to no symptoms, and grade 5 implies that the effects led to death. Grade 1–2 denotes increased amount of diarrhoea or frequency of voiding, grade 3 corresponds to severe symptoms in terms of frequency, bleeding, need of sanitary pads or requirement of surgery, grade 4 is equivalent to severe symptoms with requirement of blood transfusion or development of necrosis [6]. Grades 3 to 5 refer to "major toxicities".

The study has been approved by the ethical committee at the Karolinska Institute in Stockholm.

Treatment

In total 153 of 154 patients received neo-adjuvant hormonal therapy and external beam radiotherapy combined with 2 fractions of trans-perineal-approach HDR brachytherapy with transrectal ultrasound guidance. One patient received only two sessions of brachytherapy due to personal preferences, and developed a PSA relapse after 2.0 years. Prostate cancer cells were verified with cytology from the prostate. Since the patient violated the treatment protocol, this patient was excluded from the outcome analysis.

External beam radiotherapy

Patients received their external beam radiotherapy (EBRT) at Södersjukhuset or Radiumhemmet, Karolinska University Hospital, Stockholm. For EBRT, a computed tomography-based dose plan was established allowing a three-dimensional simulation of the radiotherapy. The planning target volume (PTV) of the EBRT included the prostate and the seminal vesicles with a 2 cm margin in all directions except posterior where the margin was reduced to 1.5 cm. The treatment units consisted of high voltage accelerators equipped with multi-leaf collimators (MLC) making the treatment a true 3D conformal therapy treatment. The patients were placed in a supine position. At Radiumhemmet the EBRT was performed with a four-field box technique. All fields were equally weighted. The dose planning system was TMS-Radix 3D® (Nucletron). At Södersjukhuset the EBRT was performed with a three-field technique, one anterior and two lateral fields. The lateral fields were weighted 50% compared to the anterior field and for the dose plans Pinnacle v. 6.2 (Philips) were used.

The target dose was 50 Gy in 2 Gy daily fractions 5 days a week. The brachytherapy was delivered after an external dose of 24 or 26 Gy, during a gap of 2 weeks. The remainder of the EBRT was delivered after the second brachytherapy session.

Brachytherapy

All patients received their brachytherapy at Radiumhemmet, Karolinska University Hospital, Stockholm. The dose-planning system (Nucletron Planning System®, Nucletron, The Netherlands) used images from transrectal ultrasound (TRUS), with images taken every 5 mm of the prostate gland. The PTV of brachytherapy included the prostate and the base of the seminal vesicles plus a 3 mm margin. The prescribed dose to the PTV was 10 Gy ($\times 2$ fractions). The HDR boost dose to the inner surface of the rectal wall was always kept below 60% of the prescribed dose of 10 Gy. The urethra was thought, during those years of treatment, to be centrally located and needles were placed so as to avoid the geometrical centre of the prostate.

The brachytherapy portion of the treatment was performed under spinal anaesthesia. The technique has previously been described in detail [2]. In general 10–18 needles were used, and the duration of the procedure was usually 2 hours in total.

Statistics

The survival analyses were calculated according to Kaplan-Meyer, and the Log Rank Test was used to demonstrate differences. The Cox proportional hazards model was used in order to quantify the relationships between PSA, WHO, T-stage and PSA relapse-free survival. Student t-test was used to compare means. Analyses of count and frequency data were performed with the χ^2 test. The tests were performed with the Statistica™ Release 4.1 software for Macintosh. P-values equal to or less than 0.05 were considered statistically significant.

Using the nomograms

The patients' pre-treatment data were used in the nomogram for radiotherapy according to Kattan et al. [7] and in the nomogram for surgery [8]. In the nomogram for radiotherapy the highest dose-escalated total dose of 86.8 Gy was chosen for comparison.

In cases where only cytology was available, a conversion to a Gleason score was performed as follows: Cytologically well differentiated tumours (WHO grade I) = Gleason score 4, cytologically moderately differentiated tumours (WHO grade II) = Gleason score 6, and poorly differentiated tumours (WHO grade III) = Gleason score 8.

The 5-year probability of PSA-free survival was defined for each patient and treatment modality. An average of the predicted 5-year probabilities was then calculated for all 154 patients using the nomograms, one set for radiotherapy and another set for surgery, to produce the third and fourth columns in Table III.

Results

Clinical outcome

In 129 living patients the median follow-up was 6.1 years (range 2.8–7.9 years). Death occurred in 24 (16%) patients, 9 (6%) of the deaths were caused by prostate cancer. The remaining 15 patients died from other causes (cardiac infarction, pancreatic neoplasm, cerebral infarction, accident) without any evidence of recurrence. Thirty-four (22%) patients developed a PSA relapse after a median follow-up time of 3.1 years (range 0.4–7.3 years). In 119 patients without a PSA relapse the median PSA value was 0.05 μg/l (range 0.02–1.9 μg/l) and 58% of the patients had a PSA value ≤0.05 μg/l at the latest follow-up. The majority of patients had at least one unfavourable prognostic factor. According to the number of risk factors, the observed 5-year PSA relapse-free survival was 0.97, 0.83, 0.83 and 0.51 for 0, 1, 2 and 3 risk factors, respectively. The PSA relapse-free survival according to number of risk factors is demonstrated in Figure 1. Forty-seven (85%) of 55 patients with PSA <10 μg/l at diagnosis were bNED and 72 (74%) of 97 patients with PSA ≥10 μg/l at diagnosis were bNED. The difference is not statistically significant using the Log Rank Test ($p = 0.11$). Fifty-five (69%) of the 80 patients presenting with a stage T3 tumour were bNED at their last follow-up. The relapse-free survival for patients with stage T3 tumour is demonstrated in Figure 2. Taking stage T1 and T2 together, 63 (88%) of the72 patients were bNED. When patients with stage T3 were compared with patients with stage T1-2 a statistically significant difference in relapse free survival was found (Log Rank Test $p = 0.003$) in favour of the lower stage patients. Seventeen (61%) of 28 patients with high grade tumours (WHO grade III) were bNED at their latest follow-up. Among the 125 patients with well or moderately differentiated tumours (WHO grade I–II), 102 (72%) were bNED. Using the Log-Rank test there was a statistically significantly difference between the patients with WHO grades I-II and grade III ($p = 0.005$).

Table II. Prognostic value of WHO grade, T-stage and PSA in PSA relapse-free survival. Tested by Cox regression multivariate analyses.

	Hazard ratios	95% confidence interval
WHO grade	2.46	1.44–4.18
T-stage	1.64	0.91–2.98
PSA	1.49	0.96–2.30

In a Cox regression univariate analyses, clinical features (PSA levels; <10, 10–20, >20 μg/l and T-stage) and histopathologic parameters (WHO grade) yielded statistically significant prognostic information regarding bNED. In multivariate analyses only the WHO grade remained independently statistically significant (Table II).

Side effects

Urinary tract symptoms. In 139, 142 and 131 patients with no relapse at 6 weeks, 6 months and last follow-up, respectively, the RTOG score for urinary tract symptoms was assessed. There was a decrease of symptoms over time and the proportion of different RTOG scores at 6 weeks, 6 months and last follow-up are summarised in Figure 3.

Rectal symptoms. In 139, 142 and 130 patients with no relapse at 6 weeks, 6 months and last follow-up, respectively, the RTOG score for symptoms from the lower intestinal tract were assessed. There was a decrease of symptoms over time and the proportion of different RTOG scores at 6 weeks, 6 months and last follow-up are summarised in Figure 4. Symptoms from the lower intestinal tract were less frequent than symptoms from the urinary tract.

Comparison with nomograms

The 153 patients, of whom 80 were T3, had an actual 5-year bNED survival of 84%. The predicted probability of a 5-year bNED survival was calculated using the pre-treatment data for each patient and the Kattan's nomogram for radiotherapy [7] assuming the total dose of 88 Gy and the use of neoadjuvant

Table III. The calculated values for the probability of 5-year PSA relapse-free survival using nomograms for surgery and dose-escalated radiotherapy are demonstrated. The patient characteristics in this study are used. The result is divided into the number of risk factors in terms of PSA, T-stage and WHO grade. The actual result from the present study is also demonstrated.

	Actual 5-year PSA relapse-free survival		Calculated 5-year PSA relapse-free survival	
Number of riskfactors	Number of patients	Present study (%)	Surgery (%)	Radiotherapy (%)
0	32	97	84	88
1	54	83	61	75
2	52	83	37	60
3	14	51	21	45
Total	152	84	54	70

hormonal treatment. The average probability estimated for a 5-year bNED survival following dose-escalated radiotherapy was 70%.

Regarding surgery, the probability of a 5-year bNED survival was calculated using the pre-treatment data for each patient and the nomogram for radical prostatectomy [8]. The average probability for a 5-year bNED survival following surgery was predicted to be 54%. The calculated values for patients with 0-3 risk factors are demonstrated in Table III together with the numbers from the present study.

Radiobiological consideration

Using the linear-quadratic formula and assuming that α/β is a conservative 3 Gy, the tumour effect is predicted to be equivalent to 102 Gy in 2 Gy fractions. The rectal dose, where it is possible to reduce the dose contribution from HDR brachytherapy to 60% of the prescribed dose in the prostate, will be equal to 72 Gy in 2 Gy per fractions (Table IV).

Regardless of the α/β ratio, a comparison with a multi-centre prostate tumour dose response curves passing through the 50% 5 year relapse-free rate produced by 66 Gy with a gamma-50 slope of 2.1 brings the apparent "Intermediate Risk" result here

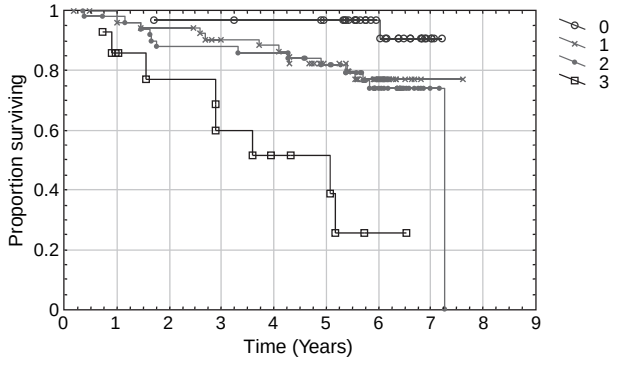

Figure 1. PSA relapse-free survival related to the number of risk factors. The risk factors are defined as PSA >10 μg/l, T-stage = 3 and high grade prostate cancer WHO = 3.

of 88% fitting that curve at 81 Gy NTD in 2 Gy fractions, instead of at 102 Gy NTD [9]. However this top end of the dose-response curve is very sensitive to uncertainties in the gamma-50 slope. If the slope were 1.4 as suggested if the "nadir + 2 μg/L" criterion [10] instead of ASTRO's criterion [5] was assumed, the matching dose would be close to 102 Gy NTD.

Discussion

Clinical outcome

In the effort to cure prostate cancer the radiation dose to the prostate should be equal to or exceed 70 Gy [11]. When doses below 70 Gy have been used, a lower percentage of a histopathologically tumour free state have been reported [12]. The use of the conformal EBRT technique has made it possible to increase the dose to 78–88 Gy [13,14], without increasing the rate of side effects in the rectum or bladder. Interstitial brachytherapy provides the option of decreasing the dose to the rectum while delivering an even higher NTD-equivalent dose to the prostate. A combination of external beam conformal radiotherapy and HDR brachytherapy delivers a tumour NTD exceeding 100 Gy in 2 Gy fractions to the prostate gland (assuming the alpha/beta ratio = 3) while the dose to the anterior wall of the rectum is kept below 72 Gy provided that during the HDR boost the rectal dose is below 6.0 Gy for each brachytherapy tumour-prescribed dose of 10 Gy application (Table IV). This high dose to the tumour will provide excellent tumour response results with acceptable side effects.

Long term clinical outcomes utilizing this transperineal transrectal ultrasound guided technique have been published in reports from nine centres [15–23]. Three of these centres have recently reported on the treatment results in more than 600 patients [24]. The results are summarized in Table V. In addition, centres have reported their experience using the Syed free-style template technique [25,26]. There has been increasing experience with the use of

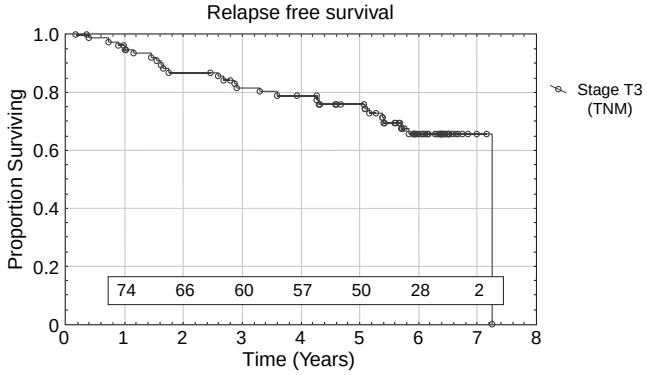

Figure 2. PSA-relapse free survival in stage T3 patients. The number of patients at risk each year is noted in the diagram.

HDR brachytherapy as a boost to external beam radiotherapy, and this has been evidenced in reports from a number of institutions of 5 years bNED survival in the range of 67–93%. These are encouraging results and our data is consistent with these earlier reports. There are surprisingly small differences in results despite the different NTD delivered to the prostate. However, no randomized trial has been conducted regarding the different fractionation schema. In addition, different selection criteria for recruiting patients, makes it difficult to compare the results.

All centres have reported the outcome data as bNED survival, however, different definitions of PSA relapse have been used, which complicates the interpretation. In an attempt to compare our results with outcome from conventional radiotherapy or surgery, we used the widely accepted nomograms according to Kattan et al. and the patient pre-treatment data from the present study. The results indicated that the outcome from surgery in this group of patients would be inferior to the outcome from combined radiotherapy. This is explained by the inclusion of a high proportion of patients with intermediate and high-risk tumours. These patients are usually not candidates for surgery due to the high risk of extra capsular extension of disease. The high rate of local control and PSA <0.05 μg/l in 58% of the patients treated by radiotherapy, would seem to indicate that extra capsular growth is manageable using the combined external beam and HDR brachytherapy radiotherapy**.** The predicted differences between the results from the nomogram regarding dose escalated external beam radiotherapy and the present study were small. Since no confidence interval was presented using the nomogram, it was not possible to make any statistically significant conclusions. Furthermore, in the present study, a majority of the patients had a diagnostic fine-needle aspiration cytology performed instead of core biopsies. This introduced an uncertainty regarding the tumour grading [27,28]. However, the WHO grading from cytology was converted to the lesser Gleason score in the respective interval when placed in the nomogram. For example, WHO Grade III was converted to Gleason score 8 and not 9 or 10 during

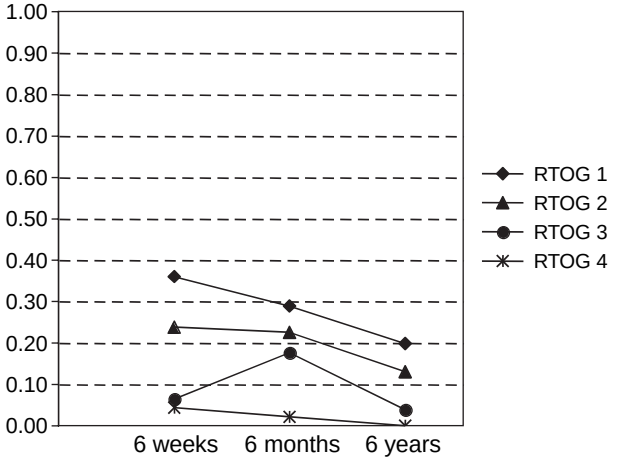

Figure 3. Side effects from urinary tract according to RTOG score and reported as proportion of patients at 6 weeks, 6 months and 6 years follow-up.

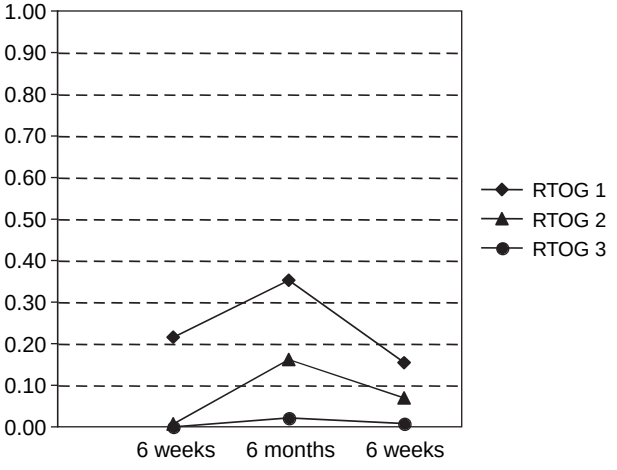

Figure 4. Side effects from lower intestinal tract according to RTOG score and reported as proportion of patients at 6 weeks, 6 months and 6 years follow-up.

Table IV. Radiobiological calculation for tumour tissue and the rectum: F = fractions, BED = biologically effective dose, Gy3 = assuming $\alpha/\beta = 3$, NTD = normalized dose to 2Gy per fraction.

	Total Dose × RE	BED	NTD @ 2 Gy Fractions
Tumour			
25 F × 2 Gy = 50 Gy	50 × 1.667	83.35 Gy3	50 Gy
2 F × 10 Gy = 20 Gy	20 × 4.333	86.66 Gy3	52 Gy
Total Tumor Dose		170.00 Gy3	102 Gy
Rectum			
25 F × 2 Gy 50 Hy	50 × 1.667	83.35 Gy3	50.0 Gy
60% = 6 Gy × 2F = 12 Gy	12 × 3	36.00 Gy3	21.6 Gy
Total rectum Dose		119.35 Gy3	71.6 Gy

calculation in the nomogram. This makes an overestimation of our results less probable.

One alternative way to report out come is to use core needle biopsy proven relapse as an end point. This has been reported in only two studies, probably because there is a risk of developing fistulae and rectal complications when performing trans-rectal biopsies of irradiated tissue. Borghede et al. reported that biopsy proven local control was found in 48 of 50 patients and only four patients demonstrated a PSA above 2 μg/l with a median follow-up of 45 months [29]. Dinges et al. reported the results from 82 evaluable patients, treated with external beam radiotherapy (45 Gy in 25 fractions) combined with two sessions of brachytherapy (9 Gy a week). Of these patients, 73% had negative biopsies at 2 years follow-up and 43 patients had a PSA < 1.0 μg/l after 24 months [30]. In our present study, patients with PSA relapse were examined with digital rectal examination and suspected pathological findings were investigated using fine-needle aspiration cytology. No local recurrence was found.

Side effects

Different methods for the evaluation of side-effects in patients with prostate cancer have been proposed using patients' self-assessed questionnaires covering local symptoms and disease specific quality of life [31] or criteria emanating from the Radiotherapy Oncology Group consensus meeting [32]. There is growing knowledge that self-assessed questionnaires are more sensitive when describing the presence of side effects compared to different methods where physician report the side effects [26,33,34]. However, the RTOG scores for acute and late radiation reactions have reached a consensus and a widespread use, which makes it practical when comparing different radiotherapy methods.

Differences in the rate of side effects between different centres should not in general be a result of patient selection; however, age and long-term diabetes are well-known risk factors for developing late rectal bleeding. Furthermore, there are differences in the actual delivered dose to the prostate according to the NTD. Some institutions have performed dose-escalation trials and it appears that NTD exceeding 100 Gy can be safely delivered with HDR brachytherapy boost but not using EBRT alone using delivered daily doses of 1.8 or 2 Gy fractions.

In accordance with previous studies the present trial reports a higher frequency of RTOG grade 3 symptoms from the urinary tract compared to the lower intestinal tract. The urethra is considered to be

Table V. Review of the literature. Abbreviations: 3D EBRT = Three dimensional conformal external beam radiotherapy, HDR = high dose rate brachytherapy, NTD ($\alpha/\beta = 3$) = Normalised dose to 2 Gy per fraction and alfa/beta ratio equal to 3, RFS = relapse free survival, RTOG GU = symptoms from the urogenital tract according to the Radiation Therapy Oncology Group, RTOG GI = symptoms from lower intestinal according to RTOG.

Centres	Number of patients	3D EBRT Dose (Gy)	HDR dose	NTDα/β = 3 (Gy)	Median Follow-up (months)	Outcome 5 years RFS	RTOG Uro	RTOG GI
Royal Oak USA [15]	207	46	5.5–11.5Gy × 3	74–146	56	74%	8%	0.5%
Seattle USA [16]	104	50	3–4Gy × 4	64–72	45	86%	10%	0%
Kiel Germany [17]	189	40	15Gy × 2	148	78	78%	NR	NR
Multi-Institutional [24]	611				60	67%	NR	NR
Sao Paulo Brasil [18]	119	45	4–5Gy × 4	66–76	41	75%	0%	0%
Kurashiki Japan [19]	71	42–45	5.5Gy × 3–4	70–81	44	93%	6%	0%
Sydney Australia [20]	82	45	5.5Gy × 3	72	36	92%	6%	1%
Berlin Germany [21]	230	40–50	9–10Gy × 2	83–102	40	82%	10%	2%
Offenbach am Main Germany [22]	102	40–45	5–7Gy × 4	72–100	31	82%	5%	1%
Gothenburg Sweden [23]	214	50	10Gy × 2	102	48	82%	10%	0%
Present trial	154	50	10Gy × 2	102	72	84%	4%	1%

rather resistant to irradiation. However, urethral strictures, urethral necrosis, urinary incontinence have been reported [30,35,36]. Galalae et al. have identified trans-urethral resection of the prostate (TUR-P) less then 6 months before irradiation as a risk factor, and they reduced the urinary tract toxicity by excluding patients with previous history of TUR-P [36]. Still, the number of patients with severe symptoms in each report is limited and caution about the dose delivered to the urethra should be emphasized.

One can speculate if different numbers of needles used during HDR could impact results. A higher number of needles would facilitate a homogenous dose distribution within the prostate, but would make the implantation more complex and it would thereby be necessary to identify the urethra throughout the whole length of the prostate. In the present study no effort was made to identify the urethra in the pre-planning situation, but a surrogate urethra was used making the assumption that the urethra was centrally located. Since 2001 we have identified the urethra with the use of a urinary catheter during the pre-planning process. Preliminary outcome data evaluation has demonstrated a reduction of urinary complications. Further studies will be performed to elucidate the maximum tolerable dose to the urethra.

Conclusion

In conclusion, this present report is the experience in treatment of localized prostate cancer in a single institution with long-term follow-up. We conclude that HDR boost to the prostate combined with external beam radiotherapy and neo-adjuvant hormonal blockade, delivering an NTD over 100 Gy, can be safely given provided that precautions are taken regarding the dose to the urethra and floor of the urinary bladder. The 5-year PSA relapse-free survival rate is encouraging especially in the group of patients with intermediate risk tumours where surgery appears to produce less favourable results.

Acknowledgements

This report was supported by grants from the Cancer society in Stockholm and King Gustav V Jubilee Foundation.

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