

Brachytherapy

Anatomy-based inverse planning dose optimization in HDR prostate implant: A toxicity study

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Abstract

Background and purpose: The aim of this study is to evaluate the acute and late complications in patients who have received HDR implant boost using inverse planning, and to determine dose volume correlations.

Patients and methods: Between September 1999 and October 2002, 44 patients with locally advanced prostate cancer (PSA ≥ 10 ng/ml, and/or Gleason score ≥ 7 , and/or Stage T2c or higher) were treated with 40-45 Gy external pelvic field followed by 2-3 fraction of inverse-planned HDR implant boost (6-9.5 Gy /fraction). Median follow-up time was 1.7 years with 81.8% of patients who had at least 12 months of follow up (range 8.6-42.5). Acute and late morbidity data were collected and graded according to RTOG criteria. Questionnaires were used to collect prostate related measures of quality of life, and international prostate symptom score (IPSS) before and after treatment. Dose-volume histograms for prostate, urethra, bladder, penis bulb and rectum were analyzed.

Results: The median patient age was 64 years. Of these, 32% were in the high risk group, and 61% in the intermediate risk group. 3 patients (7%) had no adverse prognostic factors. A single grade 3 GU acute toxicity was reported but no grade 3-4 acute GI toxicity. No grade 3-4 late GU or GI toxicity was reported. Acute (late) grade 2 urinary and rectal symptoms were reported in 31.8 (11.4%) and 4.6% (4.6%) of patients, respectively. A trend for predicting acute GU toxicity is seen for total HDR dose of more than 18 Gy (OR = 3.6, 95%CI = [0.96-13.5], $P=0.058$). The evolution of toxicity is presented for acute and late GU/GI toxicity. Erectile dysfunction occurs in approximately 27% of patients who were not on hormonal deprivation, but may be taking sildenafil. The IPSS peaked on averaged 6 weeks post-implant and returned to the baseline at a median of 6 months.

Conclusions: Inverse-planned HDR brachytherapy is a viable option to deliver higher dose to the prostate as a boost without increasing GU or rectal complication. Further HDR dose escalation to the prostate is feasible.

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Worldwide, more than 650,000 men are diagnosed with prostate cancer every year, accounting for a tenth of all new male cancers [6]. There were an estimated 220,900 new cases of prostate cancer diagnosed in the United State in 2003 [16] and around 190,000 diagnosed each year in Europe [7]. Although the majority of these patients are being diagnosed with organ confined disease due to widespread availability of serum prostate specific antigen (PSA), there are still many patients who present with intermediate or high risk of extra prostatic extension.

Radiation therapy has been an alternative treatment for these locally advanced prostate cancer patients [25,28]. However, this has been limited due to prostate's proximity to critical organs such as the rectum and the bladder.

There have been different approaches to deliver higher doses to the prostate without increasing the acute and late morbidity. Three dimensional conformal treatments (3D-CRT) and Intensity modulated radiation therapy (IMRT) using anatomy based inverse planning algorithms have been an alternative form of external beam radiation therapy (EBRT). However, EBRT has its limitation due to the difficulty in measuring and correcting for daily internal organ motion [36]. To correct for this uncertainty, safety margins around the clinical tumor volume (CTV) are added to create planning tumor volume (PTV). Thus, when using EBRT, the dose is conformed to the PTV, with a consequent increase in field size and volume irradiated, therefore increasing the risk for acute and late morbidity. High Dose Rate (HDR)

brachytherapy as a sole mode of treatment of prostate cancer has been reported as a viable option with low toxicity profile [9,33].

Recent trials have also shown that local control is directly related to the dose of radiation [10,11,32]. The intermediate and unfavorable risk patients significantly benefited from increased dose, these include patients with one or more risk factors: Gleason score ≥ 7 , clinical stage T3 or higher, and PSA > 10 [1,37]. Patients with PSA ≤ 10 who had at least one adverse risk factor, including Gleason ≥ 7 , clinical stage T2b-T3, or perineural invasion, demonstrated a benefit with higher doses [13,27].

Among strategies to achieve dose escalation, there have been many reports of combining EBRT and HDR interstitial brachytherapy (BT) with encouraging results [3,22,24,26,33-35]. Recent long term outcome of this strategy was recently published, and showed excellent results in terms of biochemical control and disease free survival and cause specific survival [8].

In addition HDR BT has the ability to deliver a high dose of radiation within a well defined volume, but with rapid fall off the dose outside the implanted area. Trans rectal ultrasound guidance (TRUS) allows for accurate catheter placement [14]. The dwell times are determined after catheter implantation, thus providing good control on the resultant dose distribution [19]. These factors make HDR BT an ideal conformal treatment of prostate cancer. We have previously reported our computer planning program based on a simulated annealing algorithm which was first developed for permanent implant optimization [29]. We applied this concept of inverse planning to obtain an anatomy-based optimization of the dose distribution to deliver a highly conformal HDR prostate treatment. The details of an early version of this algorithm have been previously published [20]. The dosimetric superiority of this approach with respect to geometric optimization has been reported [17,19].

The objective of this paper is to report our acute/late toxicity with anatomy-based inverse planning HDR boost for adenocarcinoma of the prostate and to report on possible correlations with dose, prostate volume and other eventual predictors of toxicity.

Methods and materials

Between September 1999 and December 2002, 64 patients with unfavorable and/ or locally advanced prostate cancer (PSA ≥ 10 ng/ml, and/or Gleason score ≥ 7 , and/or Stage T2c or higher) were treated with 40-45 Gy of EBRT (2 Gy/fraction) to the whole pelvis via a 4 fields technique. Of these patients 44 had at least 8 months of follow up and are included in the present analysis. Median follow-up time was 1.7 years with 81.8% of patients having at least 12 months of follow up (range 8.6-42.5 months). All patients underwent pre-treatment pelvic CT for planning. Patients received EBRT prior to the HDR boost. Thirty-eight of the 44 patients received neo-adjuvant/adjuvant hormonal deprivation.

Our implant procedure has been previously described elsewhere [5,15,19,24]. Our current technique calls for

single implant and 2 HDR fractions. From September 1999 to December 2001 all patients received 3 HDR fractions; the dose was subsequently escalated from 6 Gy/fraction to 6.5 Gy/fraction on April 2001 (29 patients and 12 patients, respectively). After December 2001, 3 patients received 2 fractions of 9.5 Gy. Catheter placement was performed in the operation room, either under general or spinal anesthesia. During the implant procedure, 17-18 flexible catheters (25-cm Flexi-Needles) were inserted in the prostate gland through the perineum under transrectal ultrasound (TRUS). The prostate template was sutured to the perineum to maintain the catheters in place. Post-implant flexible cystoscopy was performed to ensure that the catheters were not perforating the urethra or the bladder wall and to verify that the catheters are positioned in the prostate base. Reference marks are drawn on each catheter at the template level with a waterproof pen once the CT is acquired. This is to ensure that all catheters can be repositioned in the cranio-caudal direction before each fraction if necessary.

Each patient underwent CT scan in the supine position with slice spacing of 2.5 mm after placement of temporary implant. The target volume (CTV), urethra, bladder, rectum and penis bulb was contoured from the CT scan. Our method for catheter reconstruction and patient data acquisition has evolved since the initiation of this HDR program. Detail of the various procedures has been reported [19].

All patients were planned using the CT data on a PLATO workstation, which includes a beta release of an inverse planning optimization based on the simulated annealing algorithm (IPSA) [20]. Once the anatomy and the catheters are digitized, the IPSA algorithm is called from a special button implemented in the Nucletron's Brachytherapy system. At the moment this feature is unique to Centre Hospitalier Universitaire de Québec, University of California at San Francisco and National Institute of Health Hospital in Bethesda. The algorithm selects the active dwell positions and determines the dwell time values to fulfill dose constraints applied on each target and organ at risk contoured. These dose constraints force the dose to drop and remain inside the acceptable zone between the minimum and the maximum dose preset. The dose constraints were chosen to minimize the dose to the rectum, bladder and urethra, while delivering the adequate coverage to the prostate and the urethra. A complete description of the dose constraints use for the patient cohort reported here can be found in Ref [19]. IPSA finds a solution in a short time (about 30 s) and transfers the optimized dwell times to the planning system [20,21].

After the completion of the treatments, the brachytherapy catheters were then removed as well as the PCA pump. The patients were discharged home once spontaneous voiding was accomplished, typically around 3-4 h after the last treatment.

Acute and late morbidity data from all patients were collected retrospectively, and graded according to European Organization for Research and Treatment of Cancer and Radiotherapy and Oncology group criteria (EORTC/RTOG) [31]. Self-administered questionnaires were used to collect prostate related measures of quality of life, and to determine the international prostate symptom score (IPSS) before and after treatment [18]. For all patients, an

alpha-blocker was initiated at time of implant and continued until IPSS returned close to the baseline. The dose-volume histogram for prostate, urethra, bladder, rectum and penis bulb was reviewed and analyzed for all patients.

Logistic regression analyses to predict for acute and late toxicity were performed. The age, stage, Gleason score, risk group, pre-treatment volume, EBRT dose, total HDR dose, urethra and rectal dose as predictors were all analyzed.

Results

The median follow-up of the 44 patients is 20.35 months (range 8.6-42.5 months). Thirty-six of 44 (81.8%) patients had at least 12 months of follow-up. Since the objective of this work is to report on the short term toxicity, this average follow up is sufficiently long to encompass most of their possible occurrences.

Patient characteristics

Table 1 lists various clinical, pathological and treatment related information. The median patient age was 64 years (range 39-76 years). The Pre-treatment PSA level was greater than 10.0 ng/ml in 50% of the cases. According to AJCC-98, stages T2b-T3a were seen in 32% of the patients. Patients are also listed as per their risk group in the Table 2. We have used MSKCC definition of risk group. Low risk group would consist as being without adverse prognostic factors (PSA \leq 10 ng/ml, Gleason score 2-6, clinical stage T1-2).

Table 1
Patients characteristics

		n	%	Mean
Age (yr)	\leq 60	17	38.6	64
	$>$ 60	27	61.4	
^a Clinical stage	T1c	12	27.3	47.04
	T2a	18	40.9	
	T2b	7	15.9	
	T2c	3	6.8	
	T3a	4	9.1	
PSA (ng/ml)	$<$ 10	22	50.0	10.49
	10-20	21	47.7	
	$>$ 20	1	2.3	
GS	$<$ 7	21	47.7	52.3
	\geq 7	23	52.3	
^b Risk group	Low	3	6.8	3.4 months
	Intermediate	27	61.4	
	High	14	31.8	
Pre-Treat-ment volume	$<$ 40	17	44.7	47.04
	40-60	12	31.6	
	\geq 60	9	23.7	
EBRT dose	40	20	45.5	54.5
	$>$ 40	24	54.5	
HA	No	6	13.6	3.4 months
	Yes	38	86.4	

Low risk, No risk factor; Intermediate risk, 1 risk factor; High risk, 2 or more risk factor.

^a AJCC(1998).

^b Risk factors; GS \geq 7, PSA \geq 10, Stage T3 \leq .

Table 2
Toxicity results

	Grade	n	(%)	Grade	n	(%)
GU acute	0	16	(36.4)	0	20	(45.5)
	1	13	(29.5)	late 1	19	(43.2)
	2	14	(31.8)	2	5	(11.4)
	3	1	(2.3)	3	0	(0.00)
GI acute	0	35	(79.5)	GI 0	36	(81.8)
	1	7	(15.9)	late 1	6	(13.6)
	2	2	(4.6)	2	2	(4.6)

Grade: RTOG acute radiation morbidity scoring criteria.

Intermediate risk patients had a single adverse factors (PSA $>$ 10, Gleason score \geq 7, or clinical stage $>$ T2), and a high risk patient had two or more adverse risk factors. Of the 44 patients, 32% were in the high risk group, and 61% in the intermediate risk group, and only 3 patients (7%) had no adverse prognostic factors. Thirty eight of 44 patients, had a volume study prior to the treatments, of these 55% had \geq 40 cc prostate. No implant was abandoned due to the pubic arch interference. Fifty-two percent of patients had Gleason score 7 or higher.

Toxicity analysis

Summary of genitourinary (GU) and gastrointestinal (GI) toxicity in the acute and late periods is found in Table 2. Only one patient developed a grade 3 GU toxicity, an occasional hematuria by the first follow up (6 weeks), which did not require any medication or intervention. No grades 3-4 acute GI toxicity was reported. Acute grade 2 GU and GI symptoms were reported in 31.8 and 4.6% of patients, respectively.

No grade 3-4 late GU/GI toxicity was observed. Only 5 patients (11.4%) developed grade 2 late GU toxicity, which consisted of urgency and was treated with flomax. Grade 2 late GI toxicity was observed in 2 patients (4.6%).

The evolution of toxicity was analyzed for acute and late GU/GI toxicity. As shown in the left portion of Table 3, 13 of the 44 patients (29.5%) have reported no acute/late GU toxicity and 15 patients (34.1%) had the same toxicity in both

Table 3
Evolution of toxicity

	Grade	0	1	2	3	Total
Late GU toxicity						
Acute GU toxicity	0	13	3	0	0	16
	1	3	10	0	0	13
	2	3	6	5	0	14
	3	1	0	0	0	1
Total	20	19	5	0	44	
Late GI toxicity						
Acute GI toxicity	0	32	3	0	0	35
	1	4	3	0	0	7
	2	0	0	2	0	2
	3	0	0	0	0	0
	Total	36	6	2	0	44

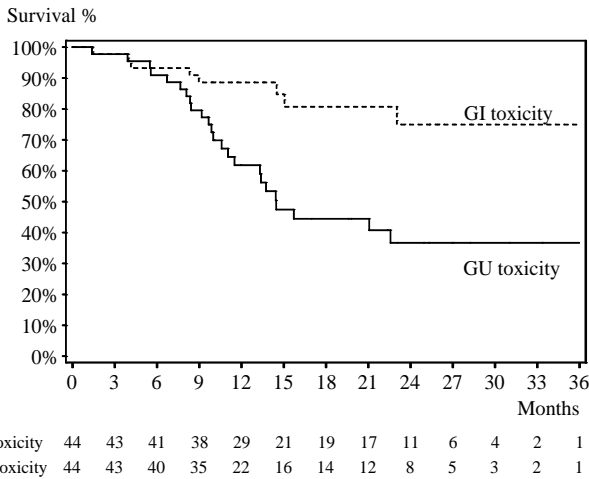


Fig. 1. The incidence of GI and GU toxicity of any grade in the form of toxicity survival free progression. The number of patients at risk are given below the figure.

periods. Of the 14 patients who had acute grade 2 GU toxicity, nine patients (64.3%) had lower (grade 0 or 1) late GU toxicity. 13 patients or 29.5% (corresponding to cases below the diagonal) experienced lower GU toxicity in the late period. Only 3 cases or 6.8% have shown a slightly higher GU toxicity in the late period, going from grade 0 to 1. In the right portion of Table 3, 32 of the 44 patients (72.7%) have reported no acute/late GI toxicity, 5 (11.4%) the same toxicity in both periods, 4 (9.1%) experienced lower toxicity in the late period and 3 (6.8%) had increased toxicity from acute GI grade 0 to late GI grade 1.

Pretreatment prostate volume, use of AD, or total dose either in the form HDR or external beam did not predict for GU/GI acute or late symptoms either in the univariate or multivariate logistic regression analysis. The logistic regression analysis showed that there was only a trend for acute GU toxicity if patients have received total HDR dose greater than 18 Gy (Odds Ratio=3.6, 95% CI=[0.96-13.5], P=0.058).

Following the approach of Bentzen et al. [2], actuarial estimates, using the Kaplan-Meier method, of GU and GI

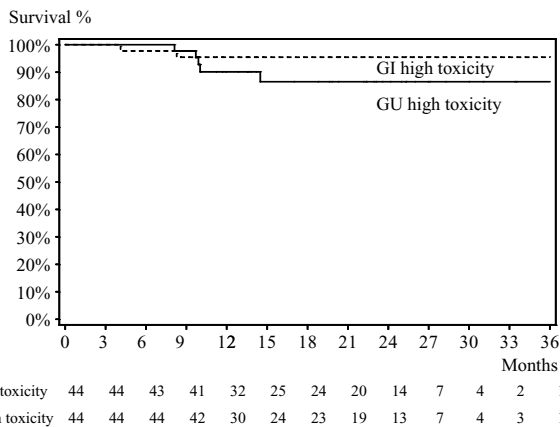


Fig. 2. The incidence of GI and GU toxicity of grade 2 or higher in the form of toxicity survival free progression. The number of patients at risk are given below the figure.

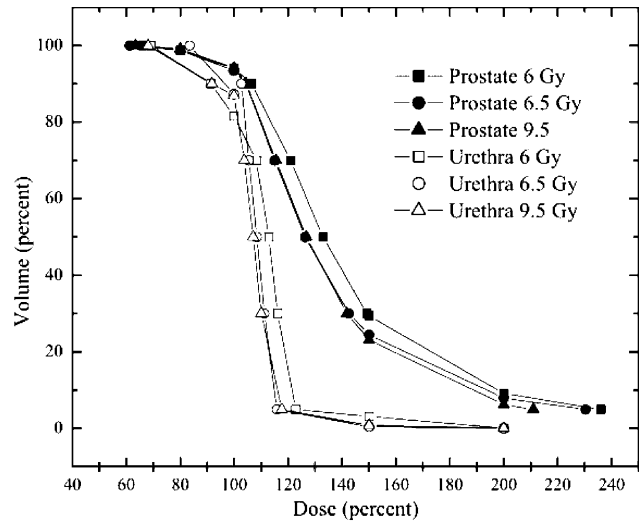


Fig. 3. DVH of the prostate and the urethra. Three fraction schemes are presented.

toxicities are also reported in Figs. 1 and 2 to adjust for censored observations, i.e. patients who did not report toxicity at the time of their last visit. It should be kept in mind that in this reporting approach newly occurring late toxicity and persistent toxicity are undistinguishable because the data are censored as soon as an event happen. The incidences of GU and GI toxicity of any grade are 3.56% and 1.04% per month, respectively. These numbers reduce to 0.60% (0.24%) per month for grade 2 or higher GU (GI) toxicity. The toxicity survival free at 36 months for all patients is 36.7% (74.9%) for GU (GI) toxicity. If only toxicity of grade 2 or higher is considered then the survival free fraction of the patients increases to 86.5% (95.5%) for GU (GI) late toxicity.

Dose-volume study

The dosimetric parameters for the prostate are shown in Fig. 3. For a prescription of 9.5 Gy, the average prostate volume receiving 100% of the prescribed dose (V100) was

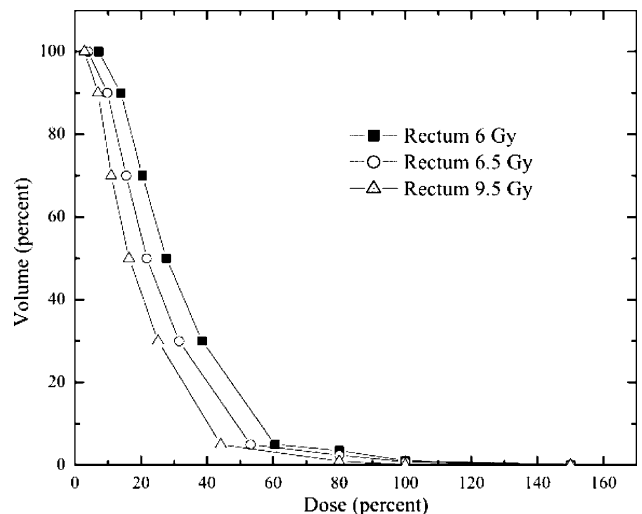


Fig. 4. DVH of the rectum with multiple dose fraction.

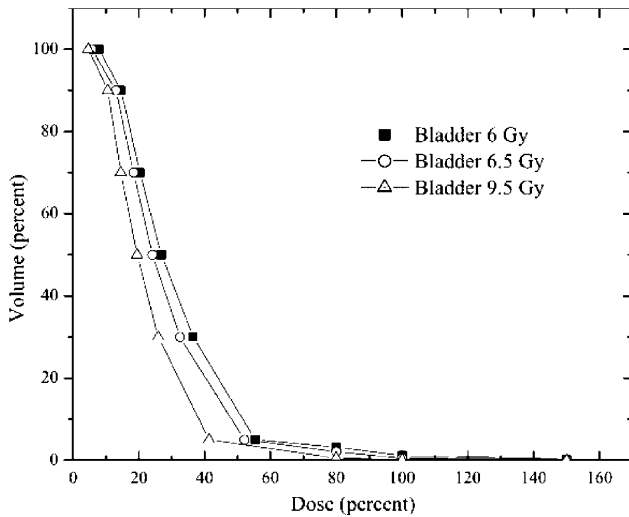


Fig. 5. DVH of the bladder with multiple dose fraction.

94%, and V150 and V200 was 27.7 and 6.2%, respectively. The mean urethral and rectal V150 value was 0.8 and 0.0%, and no urethral or rectum volume received 200% of the prescribed dose, as shown on Figs. 3 and 4. The average volume of the urethra receiving 100% of the prescribed dose was less than prostate, with 94% for the prostate compare to 87% for the urethra (Fig. 3). Fig. 5 shows that the bladder was well protected, and only 5% of the bladder received on average 50% of the dose prescribed.

Erectile dysfunction occurs in approximately 27% of patients who were not on hormonal deprivation, but may be taking sildenafil (Fig. 6). There is a trend of improving erectile function with time, this may be due to recovery from radiation or trauma and it peaks around 12 months. However, our follow-up is too short at this time to report on a final conclusion. Average D90 and D50 to Penis bulb via HDR BT was 2Gy and 2.7 Gy, respectively. The IPSS peaked on averaged 6 weeks post-implant and return to the baseline at

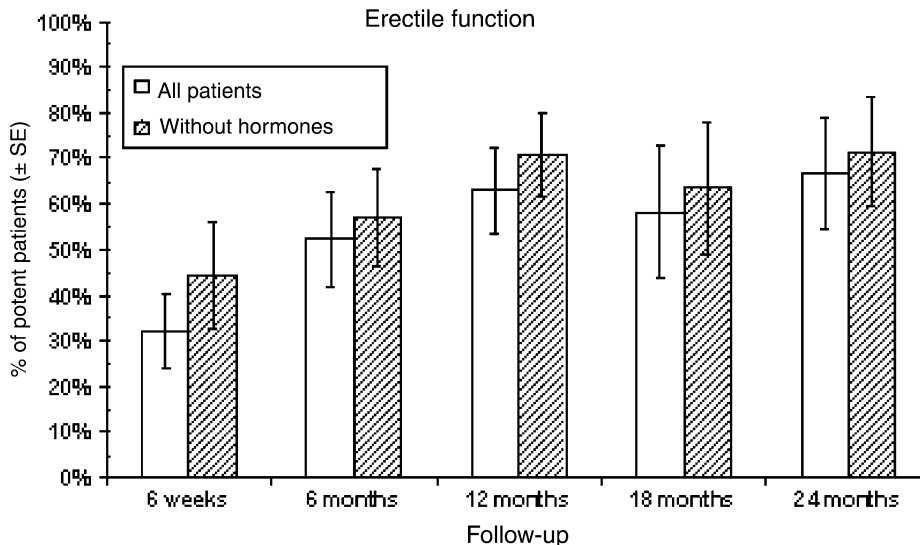


Fig. 6. Erectile function with time.

a median of 6 months as shown in Fig. 7. At 6 months and 12 months, 20.6 and 16.7% of patients, respectively, continued on an alpha-blocker.

Discussion

A treatment of locally advanced prostate cancer patients continues to be challenging. Local control has been shown to be directly related to the dose of radiation [10,11,32,37]. The study of dose escalation by Zelefsky et al., indicated a direct correlation between dose and prostate-specific antigen (PSA) relapse-free survival response for patients with intermediate and high-risk prognostic features [12,37]. The possible radiobiological advantage with using hypofractionation has also recently popularized HDR BT boost [4].

The dose-escalation trial using HDR BT boost by the William Beaumont group have demonstrated that patients who have received biological effective dose (BED) > 93 Gy had beneficial effect on biochemical and cause-specific survival [23]. The question remains on the appropriate dose and the number of fraction of the HDR BT boost.

Our HDR BT boost protocol calls on a single implant, 2-3 weeks following completion of EBRT. Patients received 3 fractions at 6-6.5 Gy per fraction during our initial phase. After reviewing our toxicity profile this was reduced to 2 fractions with increase dose to 9 Gy then escalated to 9.5 and very recently to 10 Gy. We applied the concept of anatomy-based inverse planning to deliver a highly conformal HDR boost to the prostate, while sparing organs at risk.

The dosimetric advantage of the inverse planning simulated annealing (IPSA) algorithm over the standard geometric optimization (GO) has been recently published by Lachance and colleague [19]. The IPSA algorithm was shown to provide better CTV coverage by prescription isodose and dose homogeneity. This was reflected by higher V100 values, 94.5-96 vs. 89-92.6% with IPSA compared to GO, respectively. This was achieved with a high conformity as no active dwell positions are used outside a narrow margin (typically 1 mm)

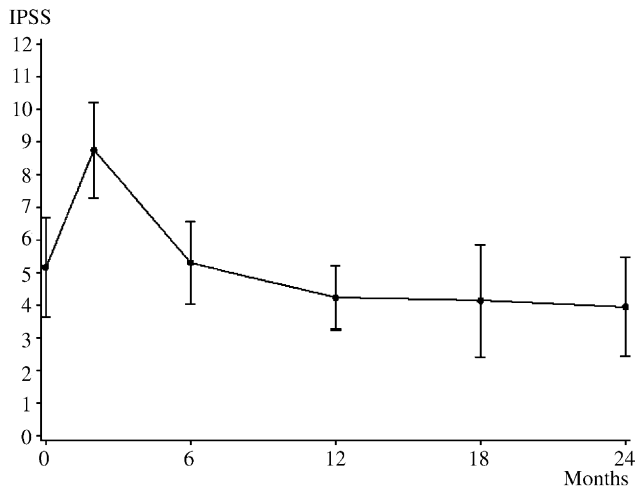


Fig. 7. International prostate symptom score (IPSS) over time. The black dots represent the mean IPSS and the error bars illustrate the 95% confidence interval.

outside the prostate contours. It is unclear if dose homogeneity is a necessity in those implants as long as target is well covered and that the organs at risks are protected. If further HDR dose escalation is envisaged, good dose homogeneity might become an advantage. However, in some situations it might be appropriate to introduce localized dose inhomogeneities to offer a boost-within-a-boost to an area of the prostate with confirmed lesions [30]. This is nonetheless the gain brought by inverse planning: versatility and flexibility in fixing the dose constraints.

The superiority of IPSA was also better appreciated when the V150 and V200 values were analyzed. The average of the V150 values of ranging from 25.2 to 29.4% for IPSA appeared as a significant improvement compared with the 50-58% values characteristic of geometric plans. The organ at risk protection was also noted when urethra V150 and V200 was analyzed.

Using this method we have shown the possibility of delivering $\geq 94\%$ of the prescribed dose to the prostate while maintaining 81-87% of the dose to the urethra (Fig. 3). The patients treated with 6 Gy per fraction were planned with the first version of the IPSA algorithm. The improved prostate dose homogeneity and urethra protection visible on Fig. 3 can be explained by the algorithm improvement. The average dose delivered was 83% with a standard deviation of 8%. The average urethra V150 was 0.42-3.17%. The DVH also shows excellent dose homogeneity within the prostate (V200 below 10%).

The conformity of dose distribution is also seen in dose volume correlation of the Rectum (Fig. 4). Rectum was spared quite effectively with IPSA as 5% of rectum volume received no more than 50% of the prescribe dose. Furthermore, the IPSS was observed to reach its maximum at 6 weeks post-implant and return to base line by 6 months (Fig. 7).

As we have shown our toxicity profile is very encouraging. No urethral stricture has been observed to this date. We had no incontinency or rectal bleeding. Only one patient (2.3%) reported grade 3 acute GU toxicity, but no grade 3 or 4 late GU/GI toxicity occurred. The GEC/ESTRO-Eau

recommendation is that grade 3 late toxicity should be below 5% [18]. Only 5 patients (11.4%) had grade 2 late GU toxicity and 2 patients (4.6%) late GI toxicity. Fig. 5 shows dose distribution to the bladder. We were able to keep less the 10% of bladder receiving 100% of the dose. Our limited number of patients prevents us to make any real conclusion of erectile dysfunction, taking in to fact that 86% of our patients received some kind of hormonal treatment.

Conclusion

HDR brachytherapy is a very viable option to deliver higher dose to the prostate for boost with out increasing GU or rectal complication. We have shown HDR implant boost using anatomy-based inverse planning dose optimization has provided a precise dose delivery system. Low V200 to the prostate shows overall good dose homogeneity within the target volume. Dose distribution to both rectum and urethra were excellent. Both organ at risk protection and minimal toxicity obtained should allow us to escalate the HDR dose to the prostate without increasing undesirable side effects. Furthermore, HDR boost with inversed planning dose optimization does not bear per se the uncertainty of organ motions that exist with 3D conformal or IMRT. It opens the possibility for safe and accurate local dose escalation within the prostate gland while keeping the doses to the critical structures (rectum, urethra and bladder) within their tolerance doses. HDR boost with IPSA is a very promising avenue to evaluate the potential benefit of hypofractionation, dose escalation and intensity modulation for localized prostate cancer.

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