Feasibility study combining low dose rate ^{192}Ir brachytherapy and external beam radiotherapy aiming at delivering 80–85 Gy to prostatic adenocarcinoma

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Abstract

Background: Increasing the radiation dose to prostatic adenocarcinoma has provided higher local control rates. A total of 80 Gy seem necessary to achieve this goal but patient set-up and prostate motion remain difficult problems to solve in conformal radiotherapy. Brachytherapy which overcomes these points could be an alternative way to external beam boost fields. We wanted to transpose the irradiation models largely used in cervix cancer treatment combining external beam radiotherapy and low dose rate brachytherapy.

Materials and methods: In 71 patients with 19.5 and 13 ng/ml mean and median PSA levels, respectively, a dose escalation from 74 to 85 Gy was performed in four groups.

Results: Shifting from intraoperative placement of sources vectors (Group I) to positioning under ultrasound controls (groups II–IV), improving the implantation shape and optimizing radiation delivery to urethral bed have reduced the total dose to rectal wall under 65 Gy and to urethra under 100 Gy. Rectal/prostate dose ratio was lowered from 0.7 (Groups I–II) to 0.58 (Groups III–IV) while avoiding problems resulting from pelvic bone arch interference, prostate volume or seminal vesicles location. The mean and median follow-up periods are 28 and 18 months. In Groups III and IV 85% of patients without hormonotherapy treated with 80–85 Gy normalized PSA under 1 ng/ml within 6 months. No severe late effect has been noted for patients implanted under echographic control.

Conclusions: The method described allows to deliver 85 Gy. Longer follow-up is however needed but the levels of dose delivered are not expected to induce prohibitive side effects. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

Keywords: Prostate; Brachytherapy; Dose; Escalation; ^{192}Ir

1. Introduction

Efficacy of external beam radiotherapy (EBT) in the treatment of prostatic carcinoma was recognized in the 1980s. Bagshaw reported results on 1119 patients in 1992 [2]. At 15 years follow-up local control rates were 55% for T1–T3 tumors. By that time Hilaris was developing a free hand implantation brachytherapy (BT) technique of iodine 125 (^{125}I) seeds in the prostate. At 15 years follow-up 46% local control rates on 679 patients were published with particular low morbidity [9]. A clear dose efficacy relationship was established. Tumors receiving at least 140 Gy dose to total decay recurred significantly less, with lower rate of

dissemination. Since that time considerable efforts have been made to improve the local control rates by increasing the delivered dose or by using high LET particles. Neutron therapy has been investigated in two randomized trials [13,19]. The local control rates were significantly improved from 62 to 68% for control photons arms to 85–89% with possible increase of survival rates. However the rates of severe late effects were particularly high (8.4–11%). More recently photons conformal radiotherapy intended to reach the 75 Gy level of dose [11,17,21]. For cases with PSA superior to 4 ng/ml, the failures decreased significantly from 33 to 10% by increasing the dose from 65 to 77 Gy [17], the higher the pre-treatment PSA value, the higher the benefit resulting from dose increase. Moreover, high conformal therapy doses have been recently correlated with lower

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rate of dissemination [10]. However, the results obtained with doses superior to 75–76 Gy remain scarce (only 10% of the population of recent publications) and the 60–80% biochemical NED rates are not entirely satisfactory for intermediate or unfavorable risk groups [11,17,21]. EBT alone might possibly be insufficient or should radiation oncologists try to increase the dose to the gross tumor volume (GTV) up to 80–90 Gy with improvement of present conformal radiation techniques? In this way efforts have been made to rise the dose while sparing the rectal wall above 72 Gy because of unacceptable toxicity [11]. These attempts are however impaired by the risk of underdosing the prostate peripheral zone which is invaded in 70% of cases and located not further than 5 mm from the anterior rectal wall [7,20]. Mean day to day prostate motion and patient set up variations around 2–5 mm each could preclude the interest of increasing the delivered dose above 72–75 Gy unless particularly expensive and time consuming checks are performed before each radiotherapy session [3,14]. Theoretically BT overcomes these points and should be able to deliver higher doses to the target volume. There is no problem of patient set-up nor prostate motion as the organ and the radioactive sources placed into are moving together. Vectors of radioactive sources are now inserted under echographic control, this method being with magnetic resonance imaging (MRI) the most suitable for prostate imaging and prostatic contours delineation. Like the uterine cervix, the prostate is located between the rectum and the bladder and there should be no reason why interstitial BT could not deliver 80–85 Gy to the prostate in comparison to endocavitary treatments for cervix carcinoma. As the only critical organ going through the prostate urethra has been shown to tolerate particularly high doses (up to 90–100 Gy) [8,16]. Appropriate techniques of implantation should prevent an overdose in the central region of the prostate where urethra lays. We report our preliminary results with a BT protocol extensively confirmed in cervix cancer treatment and combining low dose rate (LDR) and EBT in order to increase the delivered dose to 85 Gy.

2. Materials and methods

2.1. Patients general characteristics

From 1991 to 1998, 71 patients have been treated for prostate adenocarcinoma with a combination of EBT and BT. Their mean and median ages at diagnosis were 69.4 and 69.7 years (range 49–78 years). The mean and median PSA values were 19.5 and 13 ng/ml. The tumors were well, moderately and poorly differentiated in, respectively, 35, 47 and 18% (Grade I–III). T1b–T2b were present in 36.6% and T2c–T3 in 63.4% of cases. Twenty-four percent of patients presented major medical problems such as pronounced obesity (>100 kg), diabetes, severe cardiac or arteritic conditions. Twenty-four patients were referred to the department with a 6-month course of hormonotherapy initiated by the urologist and stopped within 3 months after radiation treatment. The median and mean follow-up periods are respectively 18 and 28 months.

2.2. Treatment groups

Four treatment groups have been investigated during this study. Their particular characteristics are listed in Tables 1 and 2.

2.2.1. Group I

Seventeen patients were included from 1991 to 1992. The median follow-up is 55 months. Three plastic loops were placed in the prostate under laparotomy with the aid of the MUPITT template hoping to improve the parallelism between the lines. Two rows of three needles in a rectangular shape were chosen. In case of pelvic bone arch interference a triangular implant was decided (Fig. 1). A cystotomy was performed to allow the loops to cover the base of the prostate. The reference isodose chosen to overlay the prostatic capsule was 70 or 85% of the mean central dose (MCD). A total of 50 Gy were delivered in low dose rate (LDR). Two weeks apart from BT, EBT delivered 26 Gy

Table 1
Patients characteristics among the different treatment groups

Patients characteristics	Group I (EBT + BT)	Group II (EBT + BT)	Group III (EBT + BT)	Group IV (BT only)
A				
Number (n)	17	13	28	13
Mean/median PSA (ng/ml)	29.7/21	11.5/11	21.9/16.5	8.9/8
%T1bT2b/T2cT3	12%/88%	23%/77%	32%/68%	92%/8%
% grade I–II/III	82%/18%	100%/0%	68%/32%	100%/0%
Neoadjuvant hormonotherapy	5/17(29%)	3/13(23%)	16/28(57%)	0/13(0%)
Period of study	1991–1992	1992–1996	1996–1998	1996–1998
B				
Diabetes, severe obesity, arteritic problems	3/17(18%)	4/13(31%)	9/28(32%)	1/13(8%)
US control	No	Yes	Yes	Yes
Template use during implant	Yes	Yes	No	No

Table 2
BT, EBT, total prostatic and rectal BT doses (Gy)[a]

Group	Prostate BT dose	Prostate EBT dose	Prostate total dose	Rectal BT dose	RPDR BT ratio	Urethral BT dose
I ($n = 17$)	50 (± 9)	26	76	33.9 (± 17.9)	0.68 (± 0.27)	Not available
II ($n = 13$)	48 (± 13.7)	26	74	31.3 (± 12.7)	0.72 (± 0.27)	Not available
III ($n = 28$)	43 (± 3.6)	42	85	24 (± 3.57)	0.56 (± 0.09)	60.9 (± 12)
IV ($n = 13$)	81 (± 2.8)	0	81	47.4 (± 5.37)	0.59 (± 0.08)	105.6 (± 22)

[a] Rectal/prostate dose ratio (RPDR) values and urethral BT dose. 1 SD of values is between the parenthesis.

(ICRU point) with a box technique, 2 Gy/fr, 5 × /week. The PTV included prostate, seminal vesicles and pelvic nodes until the S2 sacral bone level.

2.2.2. Group II

Thirteen patients were included from 1992 to 1996. The median follow-up is 37 months. End blinded plastic catheters (Cook® Rads 5.5.20) were inserted inside the prostate through a perineal template under ultrasound (US) control with the same shapes as in group I. The laparotomy was disused. BT and EBT doses were similar to those described in Group I.

2.2.3. Groups III and IV

Forty-one patients were included from 1996 to June 1998. Median follow-up is 11 months. At the difference from Groups I and II we did not implant the anteromedian part of the prostate which contains urethra at basal and apical levels. The end blinded catheters were inserted manually under US control without the aid of a perineal template. This method allowed to modify the course of the needle in case of pelvic bone arch interference particularly for high sized prostate >55–60 cm^3 or while implanting the seminal vesicles. U-trapezoidal design which conforms ideally to the shape of the prostate and seminal vesicles was considered first (Fig. 2). In the case of small prostatic volume (<20 cm^3) or prostatic width <4 cm only four needles were implanted in a square geometry (Fig. 3). When urethra was coming too close to the posterior in the median region a square geometry was chosen with optional lateral tubes in case of prostatic width larger than 4 cm(Fig. 3). In these situations however only two tubes are placed in the seminal vesicles.

The tubes were implanted 1.8–2.4 cm apart, at 5–7 mm distance from the capsula. The posterior row of tubes was maintained at a constant 5–7 mm distance from the posterior side of the prostate and from urethra.

Under rachi or general anesthesia patients were placed in lithotomy position. To localize urethra and bladder neck a Foley catheter was inserted and left until CT Scan simulation and ^{192}Ir loading. The balloon was filled with 7 cm^3 contrast agent (Urografin®). A suprapubic bladder catheter was placed for the whole duration of the hospitalization. A prostatic echography was performed and the implantation scheme decided according to the volume of the prostate, the sites of both tumor and urethra and the rules described above. Under US control, while endorectal Kretz® probe
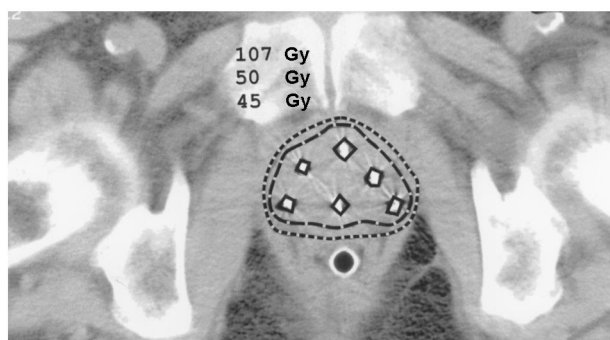

Fig. 1. A triangular arrangement in Group I. BT has delivered 50 Gy and EBT 26 Gy. Isodoses 107, 50 and 45 Gy are represented. The mean central dose (MCD) is 71 Gy. The HDV (high dose volume) isodose is107 Gy and 50 Gy is the isodose on which the dose was prescribed (=70% of the MCD). The rectal wall receives 90% of the prescribed dose at this level. Urethral dose was not measured at that time. The Kerma rate of the sources is 9.8 μGy.h^{-1}.cm^{-1}.m^2 and the total reference air Kerma (TRAK) is 51254 μGy.
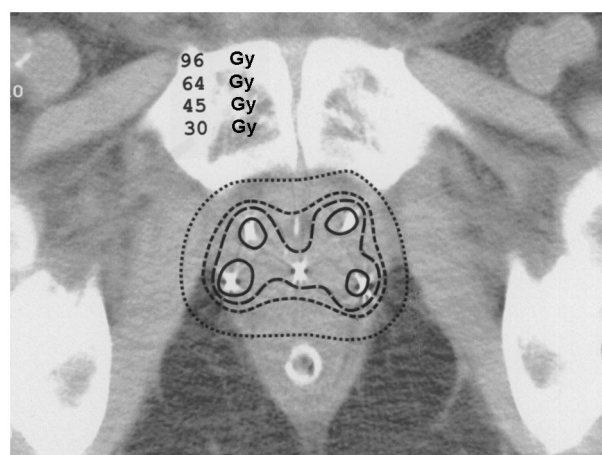

Fig. 2. A U-trapezoidal implant in Group III. BT is used as a boost to EBT. Isodoses 96, 64, 45 and 30 Gy are represented. The MCD is 64 Gy, it avoids urethra. The HDV isodose is 96 Gy and 45 Gy is the isodose on which the dose was prescribed (=70% of the MCD). The rectal wall receives 66% of the prescribed dose at this level. Urethra is at least 5 mm far from the active sources and will not be included in the hyperdosage sleeves. The posteromedian catheter has been loaded with a lower Kerma rate ^{192}Ir source (3.5 instead of 10,12 μGy.h^{-1}.cm^{-1}.m^2 for the other sources) to avoid prohibitive doses to urethra (>100 Gy) and rectum. The TRAK of the application is 19343 μGy.
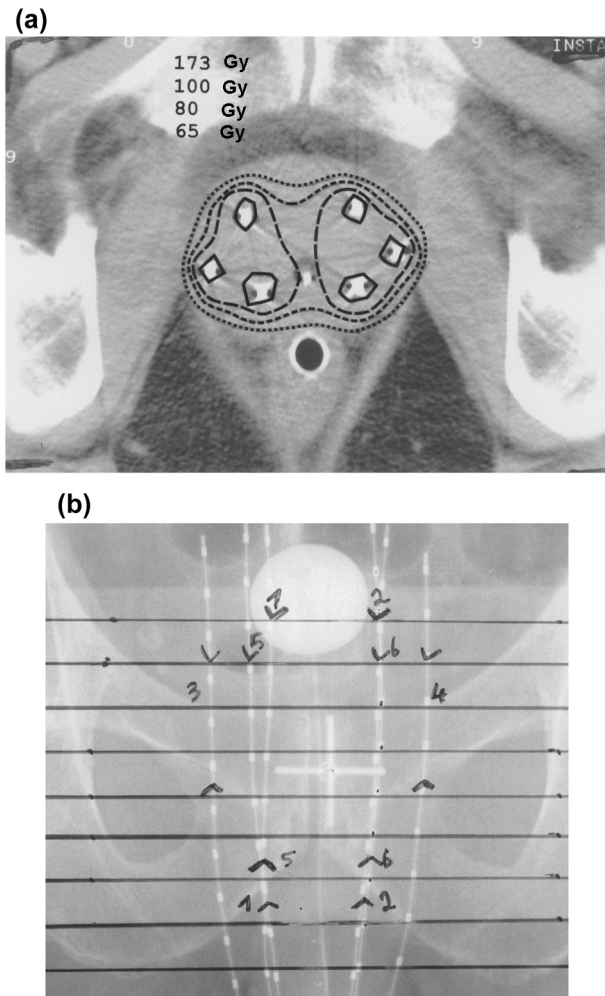
(a)

(b)

Fig. 3. (a) A square implant in Group IV. Exclusive BT delivers 80 Gy (70% of the MCD). A square implant has been chosen because the urethra was positioned posteriorly. Due to the size of the prostate two lateral tubes have been added. Isodoses 173, 100, 80 and 65 Gy are represented. The MCD is 115 Gy. The HDV isodose is 173 Gy. The isodose 100 Gy does not cover the urethra. The isodose 65 Gy is just before the rectum. The Kerma rate of the source is 9.92 $\mu Gy.h^{-1}.cm^{-1}.m^2$. The TRAK of the application is 38388 μGy. (b) Orthogonal X-rays of the same patient. Selective loading of the tubes has been designed to homogenize the dose inside the CTV while not overdosing the critical organs. The loaded region of the different tubes has been represented between arrows. Tubes 1 and 2 are inserted in seminal vesicles while the differential loading at apical level was designed to prevent overdosage to urethra which is positioned anteriorly.

was moved on a stepping device, the point of penetration of prostatic apex was searched with a small 14 gauge metallic needle itself replaced by the plastic catheter advanced manually by 0.5 cm increments to the base of the organ. A grid overlaid on US image was necessary to make the placement of catheters easier according to the shape of implant initially decided. To avoid problems due to prostate motion, a posteromedian needle was implanted first, followed by the anterior and finally by the other needles. The posterior tubes were inserted 2 cm in the lower half of the seminal vesicles (Fig. 4) while the tip of the two anterior
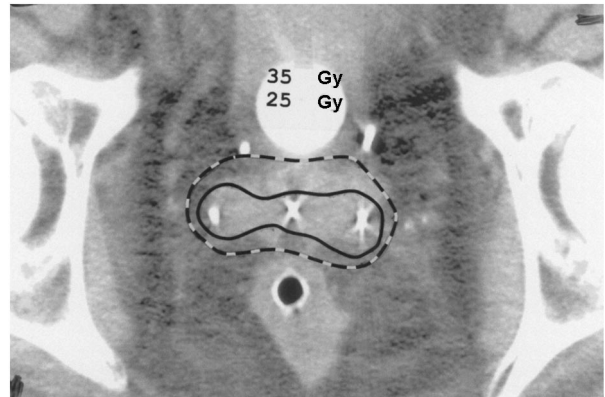

Fig. 4. BT isodoses at the level of seminal vesicles where the three posterior tubes have been loaded. This patient belongs to Group III. Isodoses 25 and 35 Gy are represented. The isodose 25 Gy surrounds the seminal vesicles which receive with EBT a total dose of 67 Gy.

tubes was stopped 1.5 cm beyond the bladder neck (top of the bladder balloon pulled into the bladder neck). The plastic tubes were finally sutured to the perineal skin through a simple metallic button device. The implantation of plastic tubes lasted no more than 30–45 min while the total duration of the procedure was shorter than 1.5 h.

In the less favorable prognosis Group III (PSA > 10 ng/ ml and/or T > 2b and/or undifferentiated adenocarcinoma) BT delivered 43 Gy in LDR according to ICRU Report 58 (Fig. 2). The EBT dose was increased to 42 Gy according to the same techniques and modalities as those described in Groups I and II. In the other cases (favorable prognosis Group IV) exclusive BT delivered 80 Gy.

2.3. Dosimetry and ^{192}Ir loading procedures

On the day of the implant, patients underwent orthogonal X-rays as well as CT scan for dosimetry purposes. Five to eight slices were analyzed. On each slice the dose was recorded to urethra, to the anterior third of the rectum, to the anterior and peripheral prostatic capsule as well as to seminal vesicles when visualized. Mean rectal and urethral doses were defined as the mean of the values recorded on the different slices while maximum urethral dose was the maximum value obtained. A total of 43 Gy in Group III (or 80 Gy in group IV) were delivered with a 12–15 Gy/day dose rate and prescribed on the isodose 70 or 85% of the MCD which overlays the prostatic capsule. Dosimetry time spent by both physicist and physician did not exceed 2 working hours. The plastic tubes were loaded manually with ^{192}Ir wires 3.5–8 cm long and mean 11 $\mu Gy.h^{-1}.m^2.cm^{-1}$ Kerma rate in air. The anterior tubes were loaded 1 cm above the base of the prostate (lower extremity of the bladder balloon) to 0.5 cm below the apex to avoid any contact with urethra at this level (Fig. 5). The posterior tubes were loaded from the lower half of the seminal vesicles to 1.5 cm below the apex. Differential loading of the tubes could be chosen according to the shape and size of the prostate as well as to the localization of
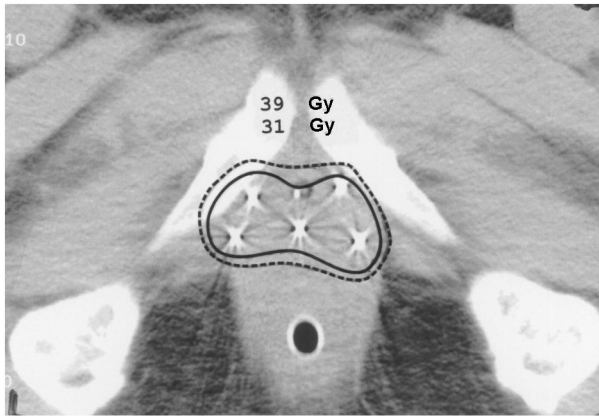
Fig. 5. BT isodoses below the apex. This patient belongs to Group III. Due to convergence of catheters at the pelvic bone arch which causes narrowing, the two anterior plastic catheters have not been loaded at this level, located 0.5 cm below the prostatic apex. Isodoses 31 and 39 Gy are represented. This region receives with EBT a total of 73 Gy.

the urethra to cover the whole CTV while avoiding hot spots to critical organs (Fig. 3). In the case of higher distance between the two anterior catheters (e.g. 2.4–2.8 cm to avoid a non median urethra) cold spots could be allowed in a non-macroscopically invaded transitional zone which still receives more than 66% of the prescribed dose for a total dose >70 Gy (EBT + BT). For the last patients treated with a U-trapezoidal implant the posteromedian catheter was loaded with a 4–5 $\mu Gy.h^{-1}.m^{2}.cm^{-1}$ Kerma rate wire to contribute to optimize the urethral dose under 100 Gy in accordance with the selective loading principles mentioned above (Fig. 2). The total dose (EBT and BT) was delivered in less than 7 weeks in groups I–III and less than 1 week in group IV.

2.4. Hospitalization time

Patients were encouraged to walk inside their room during the irradiation time or to sit down on a night commode to avoid pressure on the perineal aperture of the tubes. Every 2 days the position of the wires was checked under pelvic fluoroscopy. Any visible displacement was corrected. Patients were discharged on the day of plastic tubes as well as suprapubic bladder catheter removal and prophylactic antibiotherapy was maintained for 2 days afterwards. No particular care to perineal skin was advised in the next days nor to skin location of the suprapubic catheter. Total hospitalization time averaged 5 days for Group III and 7 days for Group IV.

2.5. Statistics

Anova test was used to study the difference in rectal sparing between the different groups treated and Chi-square test was used to ascertain the difference in side effects between the groups.

3. Results

Table 2 presents doses to prostatic capsula, to the anterior 1/3 of rectal wall and to urethra for the four groups of patients. In group III, a mean dose of 85 Gy (EBT + BT) was achieved while maintaining dose around 65 Gy to the anterior 1/3 of the rectum. Rectal wall protection indicated by the rectal/prostate doses ratio (RPDR) is significantly better in groups III and IV in comparison to groups I–II initially treated (ANOVA test significant at $\alpha < 0.05$). Moreover the standard deviations of the RPDR values are lower in groups III and IV. In these last groups, the BT dose rates were, respectively, 13.5 (± 2.94) and 15.6 (± 3.2) Gy/day. Dose rates calculated in the anterior rectal wall were 7.53 (± 1.84) and 9.27 (± 2.7) Gy/day.

Irradiation homogeneity criteria are reported in Table 3 with maximal urethral dose (UMAX)/prostate dose ratio and seminal vesicles/prostate dose ratio. UMAX were observed in the apex and are due to vectors convergence at the pelvic bone arch level (Fig. 5). Doses delivered to the lower half of the seminal vesicles exceed 65 and 60 Gy in groups III and IV, respectively (Fig. 4).

At 55 months 53% of Group I patients are free from biochemical failure according to ASTRO criteria and 71% are free from local recurrence. No biochemical failure has been reported in Group II with a 37 months median follow-up. In Groups II, III, IV, 85% of the 35 patients without previous hormonotherapy normalized the PSA level under 1 ng/ml within 6 months.

In Group I only severe complications were observed (one gastrointestinal and two genitourinary). They appeared within 2 years and necessitated surgical treatment. Use of US control during implantation reduced significantly the severe morbidity in Groups II–IV in comparison to Group I (χ^2 test significant with $\alpha < 0.005$). However 66% of patients treated in Groups III and IV with 80–85 Gy presented moderate acute dysuric symptoms which resumed easily within one to three months with Terazosine (Hytrin[R]) administration. Five of 41 (12.2%) developed grade II urethral late effect according to Lent genitourinary sequelae [11,18] (four of them had received urethral dose >110 Gy). In view of these results, we decided to optimize the treatment by maintaining the total urethral dose under 100 Gy

Table 3
Homogeneity rates inside the treated area[a]

Group	U_{max}/Prostate dose ratio	Seminal vesicles/prostate dose ratio
III	1.55 (± 0.025)	0.86 (± 0.15)
IV	1.42 (± 0.36)	0.77 (± 0.24)

[a] The ratio of maximal urethral dose (U_{max}) on prostate dose indicates the hot spots in the apex region due to the convergence of the radioactive lines when no optimization is used. The seminal vesicles/prostate dose ratio underlines the lower dose delivered in the lower third of the seminal vesicles. Standard deviations of values are between parenthesis.

and a selective loading in the apex region (Fig. 5) was used for the last 15 patients treated. None of these presented a grade II urethral late effect at the time of analysis.

4. Discussion

In this feasibility study total doses delivered to prostatic tumors were increased from 74 Gy to 80–85 Gy according to recent data concerning EBT conformal therapy alone [11,17,21]. Implantation of catheters under US control avoided urethra and rectal wall to be included in the hyperdosage sleeves of irradiation. Total rectal dose (EBT + BT) was maintained below 65 Gy. Optimization allowed the maximal urethral dose to remain below 100 Gy (EBT + BT). The 70 or 85% isodose of the MCD was systematically overlaying the prostatic capsule. U-trapezoidal or square implants with or without additional lateral tubes and differential loading of the tubes were chosen depending on the shape and size of the prostate as well as on the localization of critical organs. U-trapezoidal shape was considered first as it covers more of the seminal vesicles. When the urethra was running too posteriorly in the apex, not loading the posteromedian catheter at the contact with urethra, using lower kerma rates for this wire or using square implants were alternative solutions. A higher distance chosen between the two anterior lines due to a non-median urethra (uncommon presentation) might induce small cold spots on the anteromedian region but the total dose (EBT and BT) remained above 70 Gy. This region is by far the less important to be boosted [18] unless macroscopic invasion has been diagnosed. The 53% biochemical control rates obtained in unfavorable prognosis group I patients with a median follow-up of 55 months are in accordance to those published after conformal EBT at the same levels of dose [11,17,21]. Despite the short follow-up normalization of PSA values under 1 ng/ml within 6 months in 85% of cases in Groups II, III and IV is encouraging and is also in accordance to conformal EBT data [21]. This method of analysis has been published among the most powerful prognostic factors of cure and can be considered as an end point for early evaluation of the efficacy of radiotherapy protocols [1,4,21–22]. These preliminary results however have to be confirmed on a higher number of patients with longer follow-up times. Due to 12% grade II late urethral effects in Groups III and IV treated with doses between 80 and 85 Gy, we decided to optimize the total urethral dose below 100 Gy in the last 15 patients treated according to literature data [8,16].

Using plastic tubes instead of metallic needles has made the technique more comfortable for the patient and allowed to use LDR BT associated to EBT. Such a combination indeed has been largely confirmed in cervix cancer treatment in regard to efficacy as well as tolerance. Moreover, the absence of template during treatment allowed patients to walk inside their room without any significant problems of wire displacement that made the procedure safer. Irradiation of the rectal wall at low dose rate confers a selective biolo-gical protection on these old male population (among which 24% presented severe diabetes or arteritic problems) in comparison to EBT or high dose rate (HDR) BT procedures. Like in the highly conformal permanent implants techniques however urethra is still receiving 110–120% of the prescribed dose even after optimization. From a radiobiological point of view, arguments have been advanced in favor of LDR in situations where critical organs receive more than 2/3 of the prescribed dose particularly in the range of toxic doses [5]. Nevertheless preliminary results from fractionated HDR BT studies have not reported prohibitive grade III or IV toxicity provided that particular attention was paid to not overdosing the urethra [8,12,15–16].

Implanting manually 4–6 tubes spaced 1.4–2.4 cm under US control enabled to overcome the problems due to pelvic bone arch narrowing, large prostate volumes and seminal vesicles location. Previous TURP was not a contra-indication to the method. This technique is thus totally different from those used for ^{125}I or ^{103}Pd permanent implants which are mainly recommended for good prognosis tumors with prostate size <60 cm^3 and without pubic bone arch interference [6]. Exclusive ^{192}Ir BT however was feasible in our favorable prognosis group IV but necessitated hospitalization. Nevertheless the method seems particularly suitable to boost less favorable prognosis tumors with higher probability of capsular penetration [12,15–16]. The higher energy of ^{192}Ir rays in comparison to ^{125}I or ^{103}Pd reduces the risks of cold spots inside the CTV. Optimization of dose delivery is planned using CT Scan data on a postoperative setting avoiding discrepancies between theoretical pre-implant and real dosimetry. Moreover at the difference from US device which pushes the rectal wall anteriorly, CT Scan is more appropriate for evaluating the width of the prostatorectal fascia and calculating the rectal dose. These features are particularly important when delivering high levels of dose or using HDR. Finally, the technique described is performed in one fraction at the difference from most HDR techniques requiring two anesthesia. These are however realized in the 1-day clinic.

This BT technique does not require expensive equipment or long training to be mastered. We now plan to investigate pulsed dose rates (PDR) which improve radiation protection safety and could make easier the optimization principles developed above. However PDR will oblige patients to be in bed most of the time at the difference from ^{192}Ir LDR.

Conformal EBT followed by boost BT to 85 Gy total dose could be a valuable alternative to the hypersophisticated techniques developed to achieve the same goal with EBT alone.

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