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Prostate brachytherapy

^{192}Ir or ^{125}I prostate brachytherapy as a boost to external beam radiotherapy in locally advanced prostatic cancer: A dosimetric point of view

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Abstract

***Purpose*: This work aims at comparing the dosimetric possibilities of ^{125}I or ^{192}Ir prostate brachytherapy (Bt) as a boost to external beam radiotherapy in the treatment of locally advanced adenocarcinoma.**

***Methods and materials*: From 1/1997 to 12/2002, 260 patients were treated. Until 12/2001 a low dose rate (LDR) treatment with ^{192}Ir wires was used, later replaced by a high dose rate (HDR) delivered with an ^{192}Ir stepping source technology. For the present work, we selected 40 patients including the last 20 treated, respectively, by LDR and HDR. The planning CT Scans of all these 40 patients were transferred into the 3D Prowess^{R} system for ^{125}I permanent implants design according to the Seattle method. The reference data for dosimetric comparisons were the V100 and the prescribed dose for ^{192}Ir as well as the dose delivered with ^{125}I techniques to the ^{192}Ir V100. We compared V100-150 data as well as doses to the organs at risks (OR) and cold spots (CS).**

***Results*: The V100 is 85.3 ± 8% for ^{192}Ir LDR and 96 ± 2% for HDR techniques ($P < 0.0001$). In comparison with ^{125}I, the ^{192}Ir LDR mode induces higher hyperdosage volumes inside the CTV but also more CS, while maximal doses to urethra and rectum are, respectively, 17 and 39% less with ^{125}I ($P < 0.0001$). In comparison with the ^{192}Ir HDR mode, ^{125}I Bt induces higher hyperdosage volumes and slightly more CS deliberately planned around the bladder neck. If delivered doses to urethra are identical, those to the 20% anterior part of the rectum are 33% less with ^{125}I ($P < 0,0001$).**

The ^{125}I Bt technique was only possible in 24 out of the 40 patients studied due to pelvic bone arch interference.

***Conclusions*: At the present time, there is no evident dosimetric superiority of one Bt method when all the criteria are taken into account. However, improving Bt techniques to implant any prostatic size could found the superiority of the ^{125}I or permanent implants. ^{125}I indeed allows large hyperdosage volumes inside the CTV in comparison with ^{192}Ir HDR techniques while lowering doses to OR and minimizing CS.**

Keywords: Prostate; Brachytherapy; Dosimetry; Selectivity; ^{125}I; ^{192}Ir

This work aims at comparing the dosimetric properties of ^{125}I or ^{192}Ir prostatic brachytherapy (Bt) as a boost to external beam radiotherapy (EBRT) in the treatment of locally advanced prostatic cancer. It also analyses the feasibility of ^{125}I methods when ^{192}Ir Bt techniques were possible.

The success of prostatic Bt is continuously growing. In the USA, it is now included in 36% of prostate radiation treatments [14]. It is indeed a highly conformal treatment allowing to easily spare the rectal mucosa while delivering doses 1.2–1.5 times higher than the prescribed dose (PD) to 50–70% of the clinical target volume (CTV) and mainly to the peripheral zone.

Exclusive Bt is one of the treatments of choice for good prognosis prostate tumours. It is however less satisfactory for intermediate or unfavourable prognosis cancers, offering 5 years biochemical no evidence of disease of 60% or less [1,3]. Combinations with EBRT are thus mandatory, leading to rates between 70 and 90% [4,5,9,17,21].

EBRT and Bt associations are numerous [4,5,9,17,21]. ^{192}Ir high dose rate (HDR) Bt use has been encouraged as it takes benefits from the low α/β ratio of 1.5 Grays (Gy) of prostate tumours [7]. Severe late toxicity rates of 3–6% are reported [8,16]. Techniques using the very low dose rate [12] provided by ^{125}I or ^{103}Pd seem to induce the same percentages of 5 years biochemical no evidence of disease with severe late side effects of 1–2% [10,22]. One possible explanation consists in the high selectivity of Bt delivering particularly high doses to the CTV while minimizing the importance of the α/β factor. We wanted to test this hypothesis by comparing the dosimetric characteristics of both ^{192}Ir and permanent implants techniques.

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Methods and materials

From January 1997 to December 2002, 260 patients with locally advanced prostatic adenocarcinoma were treated with ^{192}Ir Bt as a boost to EBRT.

Until December 2001, a low dose rate (LDR) treatment by ^{192}Ir wires was used [19]. The treatment planning was calculated in 2D with the Isis^{R} system (Curie Institute, Paris, France). The LDR was later replaced by a HDR delivered by a unique ^{192}Ir source, using stepping source technologies. The treatment planning was calculated in 3D with the Theraplan 3.6 ^{R} system now integrated in the Brachyvision^{R} module (Varian Medical Systems, Haan, Germany).

During the whole evaluated period, the method of vector implantation remained unchanged and has been previously described [19]. In summary, 4–6 and sometimes eight lines were implanted according to the principles of the Paris system [6]. The majority of implants included a central square of 20–22 mm side at the centre of which ran the urethra at mid prostate (Fig. 1). At the base and apex, the urethra had to remain at equal distance from the two anterior lines. In case of large prostate sizes, 2–4 additional lines were implanted laterally in triangular shapes. Catheters were inserted manually without template, under endorectal echographic control to overcome problems of pelvic bone arch interference, to diverge slightly at the base of the prostate when the size increases and to modify the vectors travelling posteriorly to include the seminal vesicles at least in their caudal half (Fig. 2). The optimisation of the delivered dose was based on the rules of the Paris system assuming a homogeneous distribution of catheters inside the CTV. For the whole study the CTV was defined as the prostate with a security margin of 2 mm posteriorly, 5 mm from the postero lateral border of the prostate and 3 mm from the remaining border, the caudal part of the seminal vesicles as well as from the prostatic base and apex.

With regard to LDR Bt, a selective loading of ^{192}Ir wires with a linear activity of 10 $\mu Gy\ h^{-1}\ cm^{-1}\ m^{2}$ was used as an additional mode of optimising the delivered dose. The prescription isodose, evaluated in a 2D mode, was considered as the mean of the different isodoses surrounding the CTV on all CT Scan slices, 5 mm apart. The prescription isodose had to surround as homogeneously as possible the CTV but no more than 130% of the PD was tolerated to 20% of the urethra and no more than 75 and 50% to, respectively, 20 and 33% of the rectum.

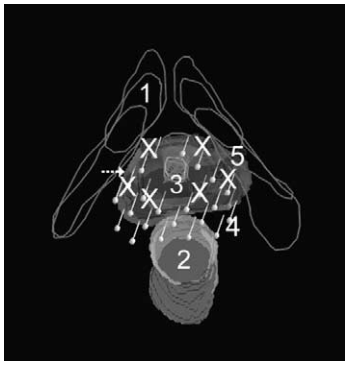

Fig. 1. A perineal view of the prostate. The Clinical Target Volume (CTV) contour is indicated with the arrow. 1, 2 and 3 point out, respectively, the pelvic bone arch, the rectum and the urethra. The ^{125}I technique includes 24 lines (4) distributed homogenously inside the CTV while avoiding the central region with the urethra. The ^{192}Ir technique is represented by six lines implanted in a central square and two lateral triangles (5).

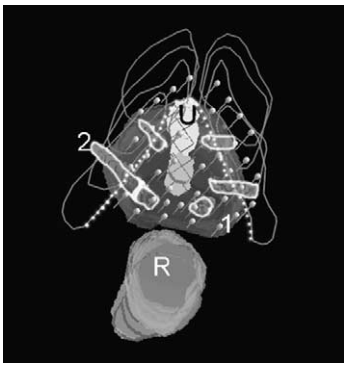

Fig. 2. The interference of the pelvic bone arch. All the lines designed for I^{125} brachytherapy (Bt) (1) cannot be implanted due to an important bone arch interference delineated by the dotted line. The six lines for Ir^{192} Bt (2) diverge slightly from the apex to the base, allowing to overcome this dosimetric problem.

Regarding the HDR, an inverse treatment planning philosophy was used as an additional way of dose optimisation [20]. Constraints for doses to CTV and organs at risk (OR) were similar to tolerance limits established for the LDR mode.

The last 20 patients treated in the LDR mode as well as the last 20 patients treated in the HDR mode were selected for the present work.

At first, the CT Scan data of the 20 patients treated in LDR with ^{192}Ir wires were transferred in the Theraplan 3.6^{R} module to calculate the delivered dose in 3D. This LDR was simulated by using equal dwell times all over the travelling of the ^{192}Ir source.

Afterwards the CT Scan of the 20 patients treated in the LDR mode and of the 20 patients treated in the HDR mode, including also the contours of the CTV and OR delineated in the Theraplan3.6 ^{R} treatment planning, were transferred in the 3D Prowess ^{R} system (Prowess Inc, Chico, USA) for ^{125}I dosimetry. The design of a homogeneous seeds arrangement inside the CTV was performed according to the modified uniform Seattle approach [11] usually applied in our department for good prognosis tumours while ignoring deliberately any situation of pelvic bone arch interference. These problems were considered in a separate analysis. The seeds intended to deliver a theoretical PD to the CTV while sparing the rectal wall posteriorly [18]. A relative sparing of the bladder neck was also planned. Like for ^{192}Ir techniques no more than 130% of the PD was tolerated to 20% of the urethra and no more than 75 and 50% to, respectively, 20 and 33% of the rectum.

Dose volume histograms were calculated for LDR and HDR ^{192}Ir and for ^{125}I Bt. The percentage of CTV having really received the PD with LDR and HDR ^{192}Ir Bt (V100) [18] was determined as well as the corresponding dose delivered to this V100 with simulated ^{125}I Bt. The latter dose was called 'normalised prescription dose' for ^{125}I (^{125}I NPD) as a reference to allow comparisons between ^{192}Ir and ^{125}I Bt

Table 1
Ratio of the UD20-50 on the PD or ^{125}INPD, $n=20$

Ratio	*Ir^{192}LDR*	*I^{125}*	*P*
UD20/PD or UD20/^{125}INPD	1.33±0.15	1.1±0.08	<0.0001
UD33/PD or UD33/^{125}INPD	1.28±0.15	1.03±0.13	<0.0001
UD50/PD or UD50/^{125}INPD	1.08±0.14	0.89±0.16	=0.002

Paired Student *t*-test.

methods. The volumes of CTV receiving 110–150% of the PD and ^{125}INPD were also calculated (V110 to V150).

The cold spots (CS) were evaluated by the ratio of the minimal dose delivered to 99% of the CTV (D99) on the PD or ^{125}INPD (D99/PD or D99/^{125}INPD). This ratio thus increases with D99. The doses delivered to 20, 33 and 50% of the urethra and rectum were also calculated. We defined the UD20-33-50/PD, RD20-33-50/PD and UD20-33-50/^{125}INPD, RD20-33-50/^{125}INPD values corresponding, respectively, to the ratio of the minimal doses delivered to the hottest 20, 33 and 50% of the urethra and rectum on the PD or the ^{125}INPD.

We finally looked if the seed arrangement designed in ^{125}I Bt techniques was compatible with the pelvic bone arch, making the procedure technically feasible or not. Interference was searched by overlaying the treatment lines and the bone arch on 3D views (Fig. 2).

Paired Student *t*-test was used to compare the different dosimetric data obtained from LDR and HDR ^{192}Ir and from ^{125}I treatment plans of the same patients. The unpaired Student *t*-test was used in the other situations.

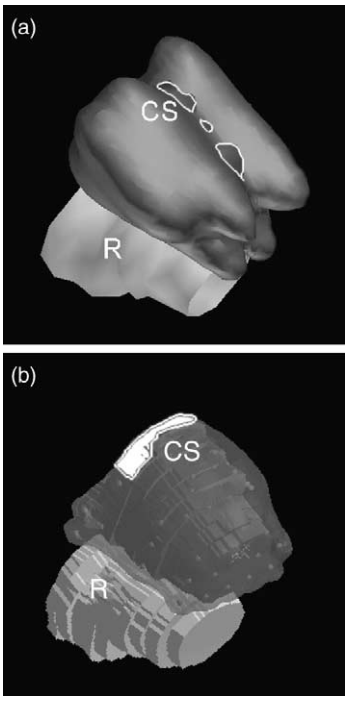

Fig. 3. For the same patient, the cold spots (CS) are presented for the high dose rate (HDR) ^{192}Ir (Fig. 3(a)) and I^{125} (Fig. 3(b)) treatment plans. With ^{192}Ir, the CS are located anteriorly on the whole length of the CTV. With I^{125}, they are located near the bladder neck only. The I^{125} CS are less in comparison with HDR ^{192}Ir treatment as the D99/^{125}I NPD or D99/PD ratios are, respectively, 0.89 and 0.74. Unlike for HDR ^{192}Ir, the I^{125} CS were deliberately designed near the bladder neck and could have been avoided by increasing the number of seeds at this level.

Results

The V100 is 85.3±8% in the ^{192}Ir LDR mode against 96±2% for the HDR mode ($P<0.0001$). The V110 to V150 are 78.2±9% to 41.8±10,3% for ^{192}Ir in the LDR mode and 89.1±3.7% to 38.8±6.7% in the HDR mode. These differences are significant ($P<0.001$) except for the V130 and V150. The CS expressed by the D99/PD ratios are, respectively, 0.71±0.2 and 0.89±0.1 for ^{192}Ir in the LDR and HDR modes ($P<0.0001$). The UD20/PD to UD50/PD ratios decrease from 1.33±0.15 to 1.08±0.14 for ^{192}Ir in the LDR mode (Table 1) and from 1.24±0.09 to 1.06±0.06 in the HDR mode (Table 3). The differences are significant ($P<0.05$) except for the UD50/PD. The RD20/PD to RD50/PD ratios between ^{192}Ir in the LDR and HDR modes are not different (Tables 2 and 4). For both techniques, the RD20/PD ratio is less than 0.55.

When ^{192}Ir in the LDR mode and ^{125}I Bt techniques are compared for the same V100, the ^{125}I V110-150 are 1 to 20% less than those obtained with ^{192}Ir ($P\leq0.004$). However, the D99/PD ratio is 0.71±0.2 against 0.77±0.1 for the D99/^{125}INPD ($P=0.03$). The CS are thus more important with ^{192}Ir. The delivered doses by ^{125}I Bt to the urethra and rectum are weak, with RD20/^{125}INPD and UD20/^{125}INPD ratios of 39 and 17% less ($P<0.0001$) (Tables 1 and 2).

When ^{192}Ir in the HDR mode and ^{125}I Bt techniques are compared for the same V100, the ^{125}I V110-150 are 2.5% ($P=0.02$) to 36% ($P=0.003$) greater than those obtained with ^{192}Ir. The D99/PD ratio is 0.89±0.1 against 0.84±0.1 for the D99/^{125}INPD ($P=0.004$) meaning that CS are slightly more prominent with ^{125}I. The latter however have been deliberately planned around the bladder neck only (Fig. 3). If the UD20/PD-^{125}INPD, UD33/PD-^{125}INPD and UD50/PD-^{125}INPD are not different (Table 3), the RD20/^{125}INPD to RD50/^{125}INPD ratios are 33–53% less than the values obtained with ^{192}Ir Bt ($P<0.0001$) (Table 4).

Table 2
Ratio of the RD20-50 on the PD or ^{125}INPD, $n=20$

Ratio	*Ir^{192}LDR*	*I^{125}*	*P*
RD20/PD or RD20/^{125}INPD	0.51±0.1	0.31±0.04	<0.0001
RD33/PD or RD33/^{125}INPD	0.37±0.07	0.2±0.03	<0.0001
RD50/PD or RD50/^{125}INPD	0.27±0.05	0.13±0.03	<0.0001

Paired Student *t*-test.

Table 3
Ratio of the UD20-50 on the PD or ^{125}INPD, $n=20$

Ratio	*Ir^{192}HDR*	*I^{125}*	*P*
UD20/PD or UD20/^{125}INPD	1.24±0.09	1.29±0.15	=0.23
UD33/PD or UD20/^{125}INPD	1.20±0.07	1.25±0.15	=0.31
UD50/PD or UD20/^{125}INPD	1.06±0.06	1.09±0.13	=0.48

Paired Student *t*-test.

Table 4
Ratio of the RD20-50 on the PD or ^{125}INPD, $n=20$

Ratio	*$Ir^{192}HDR$*	*I^{125}*	*P*
RD20/PD or RD20/^{125}INPD	0.54±0.07	0.36±0.08	<0.0001
RD33/PD or RD33/^{125}INPD	0.40±0.06	0.23±0.06	<0.0001
RD50/PD or RD50/^{125}INPD	0.3±0.05	0.14±0.04	<0.0001

Paired Student *t*-test.

The ^{125}I technique is only possible in 24 out of the 40 patients due to pelvic bone arch interference (Fig. 2). The mean prostatic volume is then 48±8 cc in comparison with 56±17 cc when Bt is technically unfeasible ($P=0.002$).

Discussion

The methodology

The dosimetric selectivity of ^{192}Ir and ^{125}I prostate Bt is proposed as an alternative explanation of the particular efficacy of prostate Bt. Performed on the same patient, a comparison between ^{192}Ir and ^{125}I techniques remains however a difficult task as the real dosimetry of a Bt technique can only be compared to the theoretical dosimetric data obtained from the other. We compared ^{192}Ir Bt to pre plans designed for ^{125}I Bt. The latter are never implemented perfectly in practice and are very often slightly degraded dosimetrically depending on the skill of the brachytherapist. We postulate however that the theoretical plans could be translated correctly in practice by a well trained team. An inverse methodology, comparing ^{125}I Bt post plans to theoretical pre plans designed for ^{192}Ir techniques would have suffered from similar limitations.

The ^{125}I Bt plans were performed using the same CTV as those delineated for ^{192}Ir techniques, according to the Seattle method [11] usually applied for good prognosis prostatic tumours in our department, while ignoring the ^{192}Ir treatment plans formerly calculated. The goal of the work was indeed to compare two different Bt methods performed in daily practice by a same well trained team.

Whatever the radioisotope or Bt technique used, the treatment plans intended to surround the CTV with the reference isodose while maintaining the UD/PD and RD/PD ratios below similar pre established levels and avoiding as much as possible CS represented by the D99/PD or D99/^{125}INPD data. For a same V100, the dosimetric comparisons were made between V110 and V150, CS and OR treatment data. They were thus based on dose (D99/PD or D99/^{125}INPD ratio) and volume (V100-150) parameters.

To facilitate dosimetric comparisons between ^{192}Ir and ^{125}I Bt methods, we introduced the concept of 'normalised prescription dose' for ^{125}I (^{125}INPD), corresponding to the dose delivered to the V100 established for ^{192}Ir. When comparing the V110-V150 values of both techniques we wanted thus to refer to an identical initial V100 value. We did not pay attention to absolute delivered doses but only to dose ratios.

The CS were evaluated by the ratio of the minimal dose delivered to 99% of the CTV (D99) on the PD or ^{125}INPD (D99/PD or D99/^{125}INPD).

The dosimetric selectivity of LDR and HDR ^{192}Ir Bt

The V100 are 85% for LDR ^{192}Ir Bt against 96% for the HDR mode ($P<0.0001$). The D99/PD values are greater with HDR Bt ($P<0.0001$). The delivered doses to urethra are less with the HDR mode as the UD20/ PD ratio is 1.24 against 1.33 for the LDR mode ($P=0.025$). For both LDR and HDR Bt, the RD20/PD values are less than 0.55 and considered safe.

The dosimetric selectivity of ^{192}Ir LDR techniques can be thus improved by the HDR mode using stepping source technology and 3D treatment plans.

The dosimetric selectivity of ^{125}I Bt in comparison with the ^{192}Ir techniques

When ^{192}Ir in the LDR mode and ^{125}I Bt techniques are compared, the ^{125}I V110-150 are 1–20% ($P\leq0.004$) less than the values obtained with ^{192}Ir. However, the volume of CS is smaller with ^{125}I as the D99/^{125}INPD ratio is 0.77 against 0.71 for ^{192}Ir ($P=0.03$). Moreover, the RD20/^{125}INPD and UD20/^{125}INPD ratios are, respectively, 39 and 17% less than with ^{192}Ir ($P<0.0001$).

The dose homogeneity inside the CTV is thus greater with ^{125}I as V110-150 and CS are of less importance in comparison with ^{192}Ir in the LDR mode. Likewise, OR are better spared with ^{125}.

When ^{192}Ir in the HDR mode and ^{125}I Bt techniques are compared, the ^{125}I V110-150 are, respectively, 2.5% ($P=0.02$) to 36% ($P=0.003$) greater than the values obtained with ^{192}Ir. The D99/^{125}INPD ratio of 0.84 against 0.89 for ^{192}Ir underlines the increase of CS with ^{125}I ($P=0.004$). These are however only located around the bladder neck and have been deliberately planned (Fig. 3(b)). They could have been avoided by increasing the number of seeds at this level. Finally, if the UD/PD and UD/^{125}INPD values are identical, the RD20/^{125}INPD are 33% less than with ^{192}Ir ($P<0.0001$).

The V110-150 and CS deliberately planned are thus of greater importance with ^{125}I. Furthermore, the rectal wall is better spared with ^{125}I.

All these differences are in favour of ^{125}I use provided that designed plans can be really transposed in practice.

The pelvic bone arch interference

The present ^{125}I Bt was only possible in 60% of patients as the pelvic bone arch did not allow to place the most anterior required needles (Fig. 2). We could argue that a more appropriate angulation of the template would have solved some of these problems. However, the mean CTV volume in these situations was 56 cc versus 48 cc without interference ($P=0.002$). Due to pelvic bone arch limitations, 50 cc is in general the maximal authorized prostatic volume in the literature for permanent implants and 60 cc for temporary ^{192}Ir methods [13].

According to ^{192}Ir techniques developed in the present work, the manual implantation of a small number of plastic vectors [19] permitted in each case to overcome the pelvic bone arch in order to implant prostatic sizes as high as 70–80 cc

(Fig. 2). No selection of patients on the basis of prostatic size was thus induced, which probably explains the high rate of pelvic bone arch interference with ^{125}I Bt techniques.

The number of catheters

Would a higher number of catheters in the ^{192}Ir techniques have reduced the dosimetric advantage of ^{125}I Bt [2]? The hypothesis cannot be refuted but the use of a higher number of sources delivering low energy beams increases the dosimetric capabilities and should remain in favour of ^{125}I Bt or permanent implants in general. So much of the difference in dosimetric parameters observed is probably a predictable consequence of the radial dose function of the two different radioisotopes. Moreover, one of the goals of modern radiotherapy techniques is to increase the V100-150 for boosting the more radioresistant zones [15] favouring thus permanent implants use.

The dosimetric selectivity and radiobiologic data

Can the dosimetric selectivity of Bt techniques be an alternative explanation of treatment efficacy in comparison with the radiobiologic data? Prostate tumours have a low α/β ratio, favouring theoretically HDR use. In the literature however, EBRT and permanent implants boost have given similar encouraging results as those reported after HDR boost [4,5,9,17,21]. One possible explanation consists in the particularly high selectivity of both the most modern ^{192}Ir and ^{125}I Bt, allowing the delivery of very high V100-150. This could be also explained by other radiobiologic factors than the α/β ratio, such as the continuous mode of irradiation and its role in the reoxygenation and the repopulation of clonogens which are playing a major role in the efficiency of Bt [23].

Hence, if some rectal toxicity remains considering the present Bt methods, a higher degree of rectal sparing and a very low dose rate should favour permanent implants use. However, the bone arch interference remained a significant problem, only with permanent implants in the present work. New efforts should be made to overcome the unfavourable situations through treatment planning innovations like the 'beam eye view concept' used in EBRT to find the most appropriate angulations of penetrating needles and why not through partially automated procedures with robotic assistance to implant diverging needles like in the present ^{192}Ir Bt technique.

Conclusions

There is no evident superiority of one Bt method when all the dosimetric criteria are taken into account. However, improbing Bt capabilities to implant any prostatic size by overcoming systematically the pelvic bone arch could found the superiority of the ^{125}I or permanent implant techniques. The latter indeed induce the highest V110-150 in comparison with ^{192}Ir HDR techniques while reducing the doses to OR and minimizing CS.

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