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Phase II trial

^{192}Ir low dose rate brachytherapy for boosting locally advanced prostate cancers after external beam radiotherapy: A phase II trial

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Abstract

***Background and purpose*: To evaluate on 201 locally advanced prostatic cancers prospectively treated in a phase II trial, the efficacy of a combination of external beam radiotherapy (39.6 Gy) and ^{192}Ir low dose rate brachytherapy (Bt) (40–45 Gy).**

***Patients and methods*: Sixty-four patients were included in the intermediate prognosis group with only one of the following adverse factors (PSA $>$ 10 ng/ml, Gleason score $\geq$ 7 or clinical stage $\geq$ T2b) and 137 in the unfavourable group when at least two of these factors were present.**

***Results*: The actuarial 4 years biochemical no evidence of disease is 82.8% for the entire population. It is, respectively, 97 and 76% in the intermediate and unfavourable prognosis groups ($P < 0.0001$). Grade $\geq$ 3 late urinary complications occurred in 13 patients (6.5%). Eight patients (4%) presented late grade 2 rectal complications but no grades 3–5 was observed.**

***Conclusions*: Even if an α/β of 1.5–3 Gy theoretically favours the use of a high dose rate mode of irradiation, the early results presented here are as good as those reported for similar groups of patients with high dose rate treatments. Late toxicity is identical but our urinary toxicity is within the less favourable and rectal toxicity within the most favourable results.**

We can postulate that while inducing very high hyperdosage regions (V150) mainly focused on the peripheral zone, most of the Bt techniques consist of a more ablative treatment. Many of the radiobiological studies on Bt did not in fact take into account the heterogeneity of irradiation inside the CTV. This study highlights the need to explore pulsed dose rate therapies, permanent implant and new available radioisotopes such as ^{169}Ytterbium that will offer the safety of low and lower dose rates. The actual late toxicity of the different Bt techniques is not yet inexistent indeed.

Keywords: Prostate; Brachytherapy; Low dose rate; Iridium192

Prostatic brachytherapy (Bt) is widely used in the USA where it is now included in 36% of prostate radiation treatments [19].

It is a highly conformal treatment easily able to spare the rectal mucosa, the bladder neck and urethra while delivering at 50–70% of the clinical target volume (CTV) doses 1.2–1.5 times greater than the prescribed dose (PD). Well targeted on more radioresistant regions these boosted zones should increase the probability of local control [17,20,29]. At the present time, new imaging modalities such as magnetic resonance spectroscopic imaging (MRSI) have become available to visualize the bulky region of the tumour, thus allowing these theoretical concepts to be translated into clinical practice [30]. Pilot studies with Bt have already been initiated [24].

While exclusive Bt is one of the treatments of choice for good prognosis prostate tumours, it is less satisfactory for intermediate or unfavourable prognosis cancers with 5 years biochemical no evidence of disease (5 y bned) of 60% or less [1,5]. For locally advanced tumours, combinations with external beam radiation therapy (EBRT) are therefore mandatory to obtain 5 y bned between 70 and 90% [11,25]. ^{192}Ir high dose rate (HDR) Bt use has been encouraged as it takes advantage of the low α/β ratio of 1.5–3 Gy of prostate tumours [38]. Severe late toxicity rates of 2–6% are reported [10,22]. The permanent implant (PI) techniques delivering a very low dose rate (VLDR) [15] provided by ^{125}I or ^{103}Pd would thus be inappropriate. However, encouraging results have also been reported after PI as a boost to EBRT [25].

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Although PI delivers a VLDR, in the 1980s some papers analysed the efficacy of a real low dose rate (LDR) [15] from 10 to 22 Gy/day, delivered by an ^{192}Ir source [21,33]. After a pilot study at the beginning of the nineties, from January 1997 to December 2001 we routinely used an LDR ^{192}Ir boost in the treatment of nonfavourable tumours with the most modern techniques of catheter implantation [26]. We want to report our experience and analyse the contribution of the results obtained with a view to understanding the particular efficacy of prostate Bt.

Materials and methods

Patient selection

Between January 1997 and December 2001, 201 patients with a life expectancy of at least 5 years and locally advanced adenocarcinoma were prospectively and consecutively treated with EBRT first followed by a ^{192}Ir Bt boost in a phase II trial. The endpoints were overall survival, disease specific survival, biochemical failure and toxicity. Patients with any of the following criteria were eligible for this treatment: Prostate specific antigen (PSA)$>$10 ng/ml, Gleason score$\geq$7 or clinical stage T2b or higher. They were included in the intermediate prognosis group if they presented only one of these three adverse factors and in the unfavourable group if at least two of these factors were present. The clinical stages are reported according the 2002 classification of the International Union Against Cancer, similar to that adopted by the American Joint Committee on Cancer. We did not make any patient selection on the basis of the following criteria: gland volume, prostate length, previous transurethral resection of the prostate (TURP) or hormonal treatment. A pelvic CT scan and bone scan were also required to exclude metastasis.

The clinical characteristics of the patients are listed in Table 1. Nineteen percent had T1c–T2a while 81% had bulky stages ($\geq$T2b). The median and mean pre-treatment PSA values were 14 ng/ml and 21.1$\pm$22.7 ng/ml. In 35% of cases, the gleason score was $\geq$7 but could not be obtained for two patients. Sixty-four patients had only one of the adverse prognosis factors and were diagnosed with intermediate risk tumours. One hundred and thirty-seven patients had at least two of these factors and were classified in the unfavourable category. Of those, 95 and 42 had two and three adverse factors, respectively.

The median age of the patients was 70.3 years with minimal and maximal values of 47 and 80 years.

Table 1
Clinical and pathologic characteristics

Characteristics	n=201
2002 T stage	
1c	30 (15)
2a	9 (5)
2b	56 (28)
2c	47 (24)
3a	51 (25)
3b	8 (4)
Gleason score[a]	
$\leq$4	32 (16)
5	31 (16)
6	67 (34)
7	39 (20)
8	22 (11)
9	6 (3)
10	2 (1)
PSA (ng/ml)	
$\leq$10	52 (26)
$>$10 and $\leq$30	106 (53)
$>$30	43 (21)

Abbreviation: PSA, prostate-specific antigen. Data presented as the number of patients with the percentage in parentheses.
[a] Data missing for two patients.

EBRT and Bt techniques

EBRT included a 4-field conformal technique. Twenty-three megavolt beams were used to deliver an isocentric dose of 39.6 Gy in fractions of 1.8 Gy in a maximum of 32 days. Bt was performed within the 2 weeks following EBRT. During the whole period, the method of plastic needle implantation remained unchanged and has been described previously [26]. In brief, four to six and sometimes eight lines were implanted according to the rules of the Paris system [8]. Catheters were inserted manually without template, under endorectal echographic guidance, to overcome any situation involving pelvic bone arch interference and diverge slightly from the apex to the base when the size of the prostate increases. The route of the posterior needles was modified to include the seminal vesicles at least in their caudal half. All these procedures are more difficult while using a template [7,26]. Finally, the needles were sutured to the skin. The treatment planning was performed in 2D and dose distribution projected on CT scan slices, 0.5 cm apart [26]. The CTV was fixed as a 2D expansion from prostate contours to include the prostate with a security margin of 2 mm posteriorly, 5 mm from the posterolateral border and 3 mm from the remaining border. Five millimetre expansions from the posterolateral border seem sufficient to cope with situations up to T3 [35]. The reference isodose was defined as the mean value of the isodoses surrounding the CTV on every evaluated slice and represented 70–85% of the mean central dose (MCD). From treatment planning slices, the mean value of the minimal doses to the anterior third of the rectum circumference on every evaluated slice was called the rectal dose (RD) while the minimal dose delivered to the anterior 1/5 of the organ circumference was reported as the maximal rectal dose (RD max). The mean urethral dose (UD) was evaluated as the mean of the different values obtained on every slice while the highest dose delivered to 1 cm of the organ was called UD max. Needle loading was designed to comply with specific rules. With a linear activity of 10 μGy h^{-1} cm^{-1} m^2 the ^{192}Ir wires delivered 40–45 Gy with a dose rate of 12–15 Gy/day to the reference isodose. The maximal tolerated rectal doses were 25 Gy as RD and 32 Gy as RD max. Ideally the UD max had to remain below 52 Gy. The ^{192}Ir wires were loaded the next day to avoid the caudal translation of the plastic needles mainly present the first day after the implant. The cranial tip of the wires was fixed in relation to the position of the bladder balloon inserted in the bladder neck during the CT scan and the loading procedure. If the duration of irradiation lasted more than 3 days, the

position of the wires was checked again [26] with the position of the wires possibly being readjusted in relation to the bladder balloon.

The patients were discharged the day after the end of treatment. The follow up included a visit at 2 weeks, then at 2 months, then every 6 months. Patients alternated visits to the radiation oncologist and urologist. A PSA analysis was performed within the 4 first months and every 4 months thereafter to register prospectively PSA kinetics after this high radiation dose delivery.

Androgen deprivation therapy

One hundred and four patients received neoadjuvant androgen deprivation therapy at the discretion of the referring urologists. The treatment was initiated 1–2 months before the radiation treatment, for a 3–6 months period.

Data collection and statistical analyses

Tumour recurrence was defined as any case of clinical recurrence or biochemical recurrence according to the American Society for Therapeutic Radiology and Oncology (ASTRO) criteria [2]. Three consecutive rises in PSA after reaching a nadir constituted a biochemical failure. Overall survival reflected all deaths while cause-specific survival was based on events attributed to prostate cancer alone. The late side effects were recorded according to the Radiation Therapy Oncology Group (RTOG) glossary expanded to brachytherapy [22]. The actuarial rates were calculated using the Kaplan–Meier method [16]. The statistical significance between actuarial curves was calculated with the log-rank test. Multiple regression analysis was performed with the Cox proportional hazards model [3]. A P-value of ≤ 0.05 was considered statistically significant. The intervals were calculated from the date of Bt completion as published for HDR Bt procedures [22].

Results

The median follow up time is 3.5 years (range 1.4–7). A total of 73 patients (36%) have been followed for a minimum of 4 years.

The mean Bt dose delivered to the CTV was 42 ± 3.4 Gy in 3.6 ± 2.3 days. The mean UD and UD max were 44.7 ± 11.4 and 52.1 ± 9.9 Gy, respectively. The mean RD was 21 ± 4.8 Gy. Due to the particular technique of catheter implantation, we were not faced with problems of pelvic bone arch interference. At the check up, the displacement of ^{192}Ir wires was in excess of 0.5 cm in three patients and required a significant readjustment of position.

The actuarial cause specific survival at 4 years was 100% in the intermediate prognosis group but 88.5 and 84.4% when two and three adverse prognosis factors were present ($P<0.03$). The actuarial 4 y bned was 82.8% for the entire population. It was 97 and 76% in the intermediate and unfavourable prognosis groups, respectively, ($P<0.0001$) and 80.8 and 65% at 4 years when two or three adverse factors were present (Fig. 1). A significant difference remained between groups including two and three adverse factors ($P=0.026$). The bned was not impaired by androgen deprivation therapy whatever the prognosis group considered (Table 2). Thirty-three patients presented recurrence but only 15 patients were diagnosed with bone metastases. The median time to recurrence was 1.2 years (range 0.4–3.7). One patient with an initial gleason score of eight presented a local recurrence at 2.2 years.

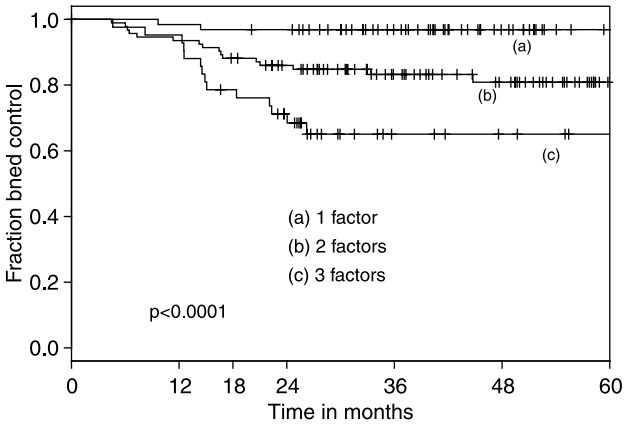

Fig. 1. Actuarial analysis of biochemical no evidence of disease (bned). The three different curves correspond to patients diagnosed with one, two and three adverse prognosis factors.

The parameters used for the univariate and multiple regression analyses to correlate with bned were T stage, gleason score, pre-treatment PSA and androgen deprivation therapy. Table 2 shows the univariate analysis and multivariate regression analysis with the Cox proportional hazards. In univariate analysis, a higher gleason score or T stage or pre-treatment PSA value were significantly correlated with lower bned but androgen deprivation therapy was not. In multivariate analysis, the pre-treatment PSA value shifted to borderline significance.

We repeated the same univariate and multivariate analysis on the 97 patients without androgen deprivation therapy, including the PSA nadir to 1 ng/ml as an additional variable. In univariate analysis, the T stage, gleason score, pre-treatment PSA and PSA nadir to 1 ng/ml were all highly significant ($P<0.0001$). In the multivariate analysis, the PSA nadir to 1 ng/ml ($P=0.0069$) and pre-treatment PSA ($P=0.02$) alone remained significant.

Grade 2 late urinary side effects occurred in 13 patients (6.5%). Grade 3 late urethral complications occurred in 12 patients (5.9%). The median time to appear was 1.2 years

Table 2
Univariate and multivariate analysis for bned

Variable	Univariate P-value	Multivariate P-value	Hazard ratio	95% CI
T stage	<0.01	0.0069	1.60	1.14–2.26
Pre-treatment PSA	<0.001	0.0761	1.01	0.99–1.10
Gleason score	<0.0001	0.0038	1.49	1.14–1.95
Androgen deprivation therapy	0.6	0.1383	0.56	0.26–1.21

Cox proportional hazards regression. Abbreviations: bned, biochemical no evidence of disease: CI, confidence interval.

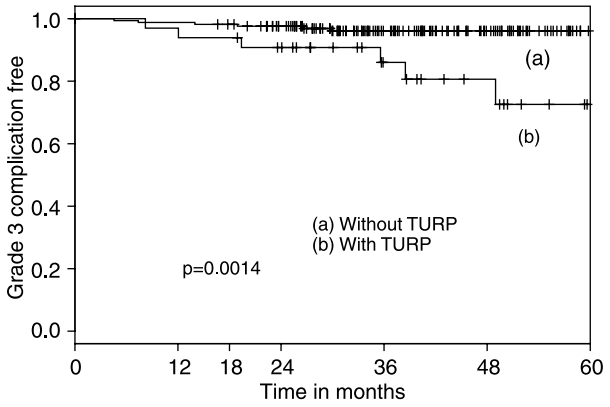

Fig. 2. Actuarial analysis of grade III urinary toxicity for patients who have and have not previously received treatment with transurethral resection of the prostate (TURP).

(range 0.38–4). One bladder grade 4 appeared in a heavy smoker suffering from severe arteritis problems. No grade 5 was encountered. Consequently, we observed 6.5% late severe urinary toxicity. Previous TURP and doses delivered to urethra were associated with late effects as we obtained 21.4% of grade II or more urethral late side effects for only 9.2% without TURP ($P<0.0001$). The rate of grade III decreased from 18.2 to 3.6% whether or not TURP was performed ($P<0.0001$) (Fig. 2). UD max >52 Gy were associated with 17% grade 2 or more urinary side effects in comparison with 8% for doses ≤ 52 Gy ($P<0.0001$). UD >47 Gy induced 19% grade II or more urethral toxicity rates in comparison with 7.9% for doses below ($P<0.0001$). However when these data were compared in a multivariate analysis, only previous TURP remained a significant factor of toxicity ($P<0.01$).

Eight patients (4%) presented late grade 2 rectal complications but no grade 3–5 complication was observed.

Discussion

This work reports data on 201 patients with locally advanced prostate cancer. They were prospectively and consecutively treated in a phase II study with EBRT followed by an ^{192}Ir Bt boost at a dose rate from 12 to15 Gy/day. The latter is called LDR, in contrast to VLDR, involving less than 10 Gy/day [15] provided by ^{25}I or ^{103}Pd. A small number of catheters were implanted manually in the most homogenous way possible, without template, according to the dosimetric criteria of the Paris system, which was used to automatically design an optimal dosimetry in 82% of patients initially [27]. The most conformal solutions can be designed in this way, allowing nonuniform dose distribution inside the CTV. When needles are left in tissues, local oedema heightened by the presence of a template can induce caudal displacements [6,14]. Mainly present the first 24 h, the latter were circumvented by loading the catheters on the next day. New plastic needles have now been developed with an umbrella mechanism at their tip, reducing the risk of displacement [31]. The method is thus comfortable for the patient and combines particularly well with multifraction HDR, LDR or pulsed dose rate therapies [9,26,31].

We obtained 97% 4 y bned for intermediate prognosis tumours. Seventy-six percent was achieved for unfavourable tumours with rates of 80.8 and 65% when two or three adverse factors were present ($P<0.0001$). The actuarial cause specific survival at 4 years was 100% in the intermediate prognosis group but 88.5 and 84.4% when two or three adverse prognosis factors, respectively, were present. All these curves in fact reached a plateau at 4 years even if we may expect more events after a longer follow up period.

Numerous papers have been reported on Bt as a boost to EBRT in the treatment of locally advanced prostatic cancer [11,25,36]. Most of the recent works presented the 5 y bned according to the ASTRO criteria and the different groups of intermediate or unfavourable prognosis based on three adverse criteria (PSA >10 ng/ml, Gleason score ≥ 7 and clinical stage $\geq$T2b). Such a policy allows the various data to be compared in a more relevant way.

Our results are among the best published in this category of locally advanced prostate cancers [11,25,36]. They also compare favourably with exclusive EBRT data published by Zelefsky et al. [39,40].

Contrary to the observation published for exclusive EBRT of 70–72 Gy [34], a short course of neoadjuvant androgen deprivation therapy did not change the bned rates in the present work. Similar conclusions have been reported when particularly high radiation doses are delivered [11,25].

We report 5.9% of grade III and 6.5% of grade II urethral late side effects. One grade IV late bladder complication was observed in a heavy smoker suffering form severe arteritis. Consequently we observed 6.5% late severe urinary toxicity. Late grade III rectal toxicity was not encountered but grade II was present in 4%. Our results are thus in the range of those found in literature [10,12,13,22,23,32], even if our urinary toxicity was within the less favourable and rectal toxicity within the most favourable results. We did not in fact exclude patients previously treated with TURP and obtained similar toxicity rates as those reporting on similar selection criteria [10]. Until now, no consensus states that TURP is a contra-indication to prostate Bt if the period between surgery and radiotherapy is at least 6 months [18]. However, in a multivariate analysis, TURP compared with UD and UD max remained the only significant factor at the origin of severe toxicity. Moreover, our selection policy, which was suitable for implantation with any prostatic size probably contributed to slightly increase general toxicity in comparison with studies limiting the implantation to prostatic volumes below 50–65 cm^3 [12,22]. Finally, in any case urethra remains near the V150 zone and receives very high doses. This observation probably contributes to maintain urethral late toxicity at a greater level mostly for patients with previous TURP.

Rectal toxicity was particularly low. These encouraging rates are probably related to the very low doses delivered to rectal mucosa with Bt and to the LDR mode of irradiation.

An α/β of 1.5–3 Gy theoretically favours the use of HDR. However while delivering very high doses (around 150 Gy$_3$ as

in most of HDR studies) [4], our LDR Bt method also achieved good results with similar severe toxicity rates. Moreover, authors investigating a VLDR boost with PI also published good results [25] if ASTRO recurrence criteria were used. For all these Bt methods, very high V150 (30–50%) are mainly focused on the peripheral zone which is at the origin of 70% of tumours but many of the radiobiological studies on Bt did not in fact take into account the heterogeneity of irradiation inside the CTV [37]. New biologic concepts such as the equivalent uniform dose (EUD) should be considered to integrate the high degree of dose heterogeneity inside the CTV in Bt [29,38].

In view of these data, Bt is more likely to consist of an ablative treatment, minimizing the importance of the α/β ratio of prostatic cancer [28]. In such an hypothesis, using lower dose rates should contribute to decrease at least the rectal toxicity as urethra remains most often near the V150 zone. This study highlights the need to explore pulsed dose rate therapies, new radioisotopes available for low dose rate use such as ^{169}Ytterbium that greatly facilitate radioprotection and also permanent implant possibilities. The actual late toxicity of the different Bt techniques is not yet inexistent indeed.

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