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Original Research Article

High-dose rate brachytherapy in localized penile cancer: 5-Year clinical outcome analysis

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ABSTRACT

Purpose: To analyze the oncological outcome and toxicity profile after conservative treatment based on multicatheter interstitial high-dose rate brachytherapy (MHB) for patients presenting a localized penile cancer.

Materials and methods: Patients with histologically proven, non-metastatic (T1-T2 N0-N2 M0) localized penile cancer were treated with MHB. Needles were placed under general anesthesia into the target volume using a dedicated template. Treatment planning was performed using a post-implant CT-scan to deliver 35 Gy or 39 Gy (9f, 5d) for adjuvant or definitive treatment respectively. Five-year oncological outcome was evaluated with local relapse-free (LRFS), regional relapse-free (RRFS), and metastasis-free survival (MFS), specific (SS) and overall survival (OS). In pre-treatment and follow-up consultations, skin, urinary and sexual toxicities were investigated using CTCAEv4.0 classification, International Prostate Symptom Score (IPSS) and International Index of Erectile Function 5-items (IIEF-5). Dosimetry data were also analyzed.

Results: From 03/2006 to 05/2020, with a median follow-up of 72.4 months [3–174], 29 pts, mainly T1 (75.9%) and N0 (89.7%), underwent MHB. Eleven (38%) and 18 pts (62%) received MHB as adjuvant or definitive treatment respectively. Five-year LRFS, RRFS, MFS, SS and OS were 82%, 82%, 89%, 88% and 73% respectively. Six patients (20.7%) experienced local relapse and underwent salvage penectomy leading to a penile preservation rate of 79.3%. Acute skin toxicity was reported 1 month after MHB, with 28% G1, 66% G2 and 6% G3. Late skin complications were telangiectasia for 5 pts (17%) and necrosis for 3 pts (10.3% requiring hyperbaric oxygen therapy). Comparing pre- and post-treatment status, no significant change was observed for skin appearance, IPSS and IIEF-5.

Conclusion: MHB represents an efficient first line conservative treatment option for early penile cancers. Oncological outcome and late toxicity profile appear encouraging. However, larger-scale cohorts with longer follow-up are needed to more accurately precise the features of the best candidate to MHB.

Abbreviations: ABS, American Brachytherapy Society; CCAFU, Cancer Committee of the French Association of Urology; CT, computerized tomography; CTCAE, common terminology criteria for adverse events; CTV, clinical target volume; DFS, disease-free survival; DNR, dose non-homogenity ratio; EAU, European Association of Urology; EBRT, external beam radiotherapy; EQD2, equivalent dose in 2Gy fractions; GC-SFRO, Groupe Curiethérapie/Société Française de Radiothérapie Oncologique; GEC-ESTRO, Groupe Européen de Curiethérapie/European Society for Therapeutic Radiation and Oncology; HDB, high-dose brachytherapy; IIEF, international index of erectile function; IPSS, international prostate symptom score; LC, local control; LDR, low-dose rate; MDFS, metastatic disease-free survival; MFU, median follow-up; MHB, multicatheter interstitial high-dose rate brachytherapy; MMS, Mohs micrographic surgery; MRI, magnetic resonance imaging; NCCN, national comprehensive cancer network; OS, overall survival; PDR, pulse-dose rate; PET, positron emission tomography; PP, penile preservation; RC, regional control; SCC, squamous cell carcinoma; SFRO, Société Française de Radiothérapie Oncologique; SS, specific survival; TNM, tumor node metastasis.

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1. Introduction

With a global incidence of 26,000 cases/year, penile cancer is a rare tumor [1]. In developed countries, the estimated incidence is approximately 1/100,000 men per year, most of them being squamous cell carcinomas (SCC) [2,3].

Given the rarity of the disease and the organ preservation challenge, there are currently no high-proof level guidelines for treatment recommendations. Penile cancer management is currently based only on retrospective and single institution studies while there is no recruiting prospective trial concurrently open (Clinicaltrials.gov access 10/22/20). Partial penectomy has mostly been the historical procedure. It is often the first and only treatment performed. It allows good local control (>90% at 5 years) [4] at the expense of urinary and significant psychosexual side effects [3,5,6]. Consequently, therapeutic strategies have been proposed towards organ preservation. A consensus between the American Brachytherapy Society (ABS) and Groupe Européen de Curiethérapie/European Society for Therapeutic Radiation and Oncology (GEC-ESTRO) has been proposed for the use of brachytherapy as first line management for early stage penile cancers [7]. Historically, low-dose rate (LDR) brachytherapy has been the standard treatment and provided excellent oncological outcome and toxicity profile [8,9]. However, since 2014, this technique has no longer been available while pulsed (PDR) and high-dose rate (HDR) brachytherapy techniques keep being used [10,11].

In this study, we updated the clinical results of a cohort of patients presenting a localized stage penile cancer who underwent multicatheter interstitial high-dose rate brachytherapy (MHB) [12].

2. Materials and methods

This is a single-institution, retrospective, observational study which evaluated the oncological outcome and long-term toxicities after conservative treatment consisting in MHB for patients with a localized penile cancer. Data were collected from patients' files. This study, as well as the ethical aspect of the protocol, were approved by the Urologic Institutional Review Board of Antoine Lacassagne Cancer Centre (n°MR-3616170920). The board waived the requirement for informed consents because of this study's retrospective design.

2.1. Patient and tumor characteristics

Patients with histologically proven non-metastatic penile cancer were offered conservative treatment based on MHB. Patients were treated in the Antoine Lacassagne Cancer Center (Nice, France) in collaboration with the Urology department of the Nice Academic Hospital. All the patients were offered partial penectomy or conservative treatment with extensive information in regard to oncological results and side effects of each procedure. MHB was considered either in an adjuvant setting after surgical procedure or as a definitive approach after biopsy. Each patient underwent a complete physical examination (tumor depth extension, inguinal lymph node involvement). In some cases, a penile Magnetic Resonance Imaging (MRI) was performed in order to distinguish contact/bulge from corpus carvernosum true invasion. As recommended by the European Association of Urology (EAU) guidelines, inguinal lymph node involvement and metastatic status were investigated by inguinal ultrasound (+/-biopsy) and abdomino-pelvic computerized tomography (CT), respectively [3]. Before MHB, all patients underwent circumcision.

2.2. Brachytherapy procedures

Implant procedure, planning and dose delivery were already described [12]. Briefly, after urethral catheterization, the penile was placed in a dedicated applicator (Fig. 1). Needle insertion allowed plastic catheters placement (Sharp Needles™; Elekta company, Stockholm, Sweden; Flexible Catheter Leader™ Eckert&Ziegler BEBIG, Berlin, Germany) through the templates in regard to the tumor volume in 1 to 3 plans (depending on the clinical target volume – CTV).

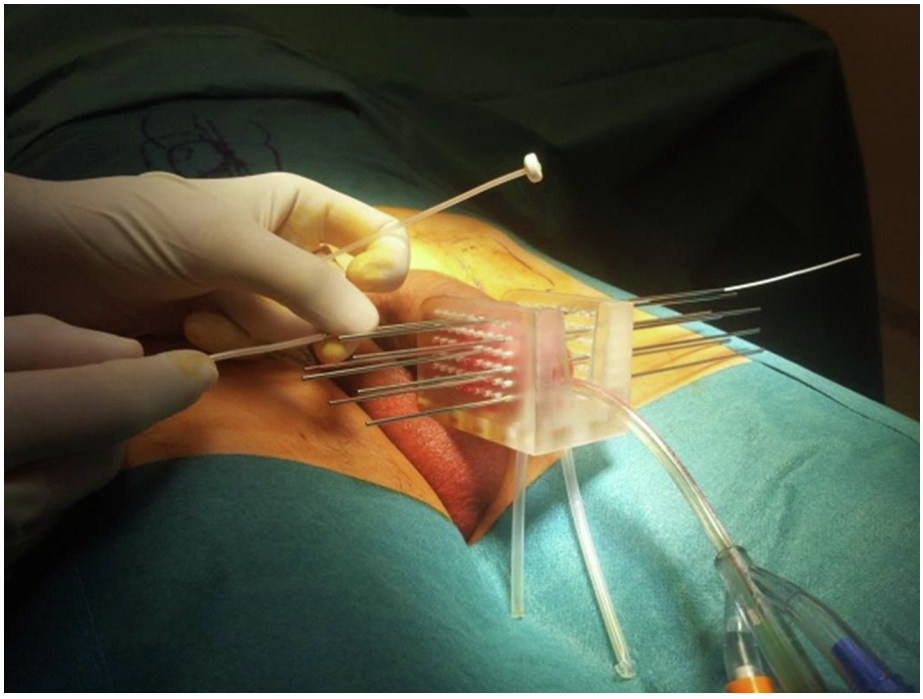

Fig. 1. Penile cancer multicatheter interstitial high-dose rate brachytherapy implant.

After patient recovery, CT-scan planning was performed for the dose distribution analysis and optimization. CTV included the macroscopic tumor plus a safety margin ranging from 5 to 10 mm. For patients without gross residual at the time of implant, CTV was based on imaging, surgical reports, and/or photographs. The prescribed dose was established according to MHB indication. For adjuvant MHB, the total dose was 35 Gy in 9 fractions over 5 consecutive days (7 Gy at day 1 then 3.5 Gy/f twice daily from day 2 to day 5), while for definitive treatment the prescribed dose was 39 Gy with the same fractionation (7 Gy at day 1 then 4 Gy/f twice daily from day 2 to day 5). Dose-volume adaptation was manually achieved by dwell location and time variation (graphical optimization) (Microselectron™; Elekta company, Stockholm, Sweden; Saginova™, Eckert&Ziegler BEBIG, Berlin, Germany). CTV dose constraints were: $V_{100\%} > 90\%$, $V_{150\%} < 35\%$. Confluence of two $V_{200\%}$ isodoses and $V_{200\%} > 10$ mm in diameter were avoided. For the urethra, dose constraints were $V_{115\%} < 1\%$. Dose non-homogeneity ratio (DNR), D_{10u} and D_{30u} were also reported.

The first fraction was delivered on the day of the implant (on Monday) then the remaining dose was delivered twice daily 6 h apart from Tuesday to Friday [13,14]. After the last irradiation session, catheters were removed, and the patient was discharge from the hospital with a medical prescription for acute radiodermatitis.

2.3. Oncological outcome and toxicities

After MHB, patients were systematically examined at 1, 3, 6 and 12 months then every 6 months during the 5 first years of the follow-up, then annually. Penile and inguinal areas clinical examinations were conducted and, if necessary, combined with an inguinal ultrasound exam, penile MRI or positron emission tomography (PET) using fluorine 18-labeled fluorodeoxyglucose. The analysis of the oncological outcome was based on local (LRFS) and regional lymph node (inguinal and/or iliac) recurrence-free survival (RRFS) rates and metastasis-free (MFS), disease-free (DFS), specific (SS) and overall survival (OS) rates.

In pre-treatment and follow-up consultations, urinary (International Prostate Symptom Score-IPSS), and sexual (International Index of Erectile Function 5-items-IIEF-5) functions as well as skin status were analyzed. IPSS was systematically rated in 3 grades according to the score: grade 1 for light (1 to 7), grade 2 for moderate (8 to 19) and grade 3 for severe urinary symptoms (20 to 35). IIEF-5 was rated in 4 grades: 1 for normal (21 to 25), 2 for light (16 to 20), 3 for moderate (11 to 15) and 4 for severe erectile dysfunction (5 to 10). Post-treatment skin toxicities were scored according to CTCAEv4.0 classification [15]. Because organ conservation represents a composite factor depending on local relapse and side effects, penile preservation rate at the end of follow-up was reported.

2.4. Statistical analysis

Qualitative data were presented as absolute frequencies, relative frequencies, 95% confidence intervals and percentages of missing data. Quantitative data were presented as medians, extremes, means, standard deviations and percentages of missing data. The normality of these parameters was assessed using the Shapiro test. Quantitative data were compared using Student's T-test or Mann-Withney's test in case of non-compliance with the conditions of Student's test. The censored data (survival data) were defined between the date of treatment start and the date of occurrence of the event: local relapse for LRFS, regional lymph node (inguinal and/or iliac) relapse for RRFS, metastasis for MFS, any oncological events for DFS, deaths due to penile cancer for SS and deaths due to any cause for OS. Patients lost to follow-up were censored at the date of last news. These data were graphically presented with Kaplan-Meier curves. The significance level was a p-value < 0.05. The median time to onset of relapse was calculated from the treatment date and the onset recurrence date. The penile preservation rate at the end of follow-up was calculated.

3. Results

3.1. Patient, tumor and treatment characteristics

From 2006 to 2020, 29 pts who underwent MHB for non-metastatic localized penile cancer were retrospectively analyzed. With a median age of 70 years [46–84], patients were mainly classified T1 (75.9%) and N0 (89.7%). Histological type was mainly SCC (93%) with a median tumor size of 15 mm [5.4–32] (Table 1).

The imaging work-up for disease extension before brachytherapy evolved upon time. From 2006 to 2013 patients were mostly explored with ultrasonography and CT scan (86%), while since 2014, MRI and PET scan were the standard work-up (73%).

Table 1
Patient, tumor and treatment characteristics.

Features	#	[min–max]/%
Median age (years)	70	[46–84]
Median Karnofsky Index (%)	90	[80–100]
Cardio-vascular comorbidities*		
yes	18	62.1
no	11	37.9
Histological type		
Squamous cell carcinoma	27	93.1
Bowen	2	6.9
Median tumor size (mm)	15	[5–32]
Clinical stages		
Tis	1	3.4
T1	22	75.9
T2	6	20.7
Lymph node status		
N0	26	89.7
N1	1	3.4
N2	2	6.9
Localization		
Glans/Coronal sulcus	17	58,6
Peri-urethral meatus	12	41.4
Brachytherapy indication		
Definitive treatment	18	62
Adjuvant	11	38
Median time interval between surgery/MHB (days)	76	[18–217]
Median total dose of brachytherapy (Gy)	36	[31–39]
Median number of fractions	9	[7–10]
Median number of needles	12	[3–19]
Median number of plans	3	[1–4]
Dosimetry Data		
CTV (cc)	16	[3–42]
D90 (%)	107	[73–118]
V100 (%)	95	[78–100]
V150 (%)	32	[12–57]
V200 (%)	12	[3–22]
DNR	0.35	[0.22–0.58]
Urethra		
$D_{0.1u}$ (cc)	132	[78–230]
D_{1u} (cc)	103	[11–149]
D_{10u} (%)	127	[59–217]
D_{30u} (%)	113	[27–177]

Cardio-vascular comorbidities*: smoking, alcohol, diabetes, high blood pressure, obesity and dyslipidemia
CTV: Clinical Target Volume; D90: dose delivered to 90% of CTV expressed in percentage of the prescribed dose; V100: CTV receiving 100% of the prescribed dose expressed in percentage; V150: CTV receiving 150% of the prescribed dose expressed in percentage; V200: CTV receiving 200% of the prescribed dose expressed in percentage; DNR: Dose Non-homogeneity Ratio = 1-[V100–V150]/V100; D0.1: dose delivered to 0.1 cc of the urethral volume; D1: dose delivered to 1 cc of the urethral volume; D10: dose delivered to 10 cc of the urethral volume expressed in percentage of the prescribed dose; D30: dose delivered to 30 cc of the urethral volume expressed in percentage of the prescribed dose.

MHB was performed as definitive treatment for 18 pts (62.1%: primary disease = 12 pts; local relapse after surgery = 6 pts) or as adjuvant treatment for 11 pts (37.9%). Median total dose was 36 Gy [31–39] with a median number of fractions of 9 [7–10] ($EQD2_{\alpha\beta10}$ = 43 Gy [38–53] and $EQD2_{\alpha\beta3}$ = 53 Gy [47–68]). Median $EQD2_{\alpha\beta10}$/$EQD2_{\alpha\beta3}$ were 41/50 Gy and 47/59 Gy for adjuvant and definitive MHB respectively.

4. Dosimetry characteristics

The median CTV was 16 cc [3–42]. The median D_{90} was 107% [73–118]. Median V_{100} and DNR were 95% [78–100] and 0.35 [0.22–0.58] respectively. For urethra, the median D_{10u} was 127% [59–217] and D_{30u} was 113% [27–177] (Table 1).

4.1. Oncological outcome and toxicities

4.1.1. Oncological outcome

The median follow-up (MFU) was 72 months [3–174]. Six pts (20.7%) experienced local relapse leading to a 5-year LRFS rate of 82%. The median local recurrence time was 29 months [6–77]. Salvage penectomy was performed only in case of local relapse resulting in a penile preservation (PP) rate of 79.3%. Fifty-percent of the local recurrences occurred within the first 24 months (Fig. 2A). Five-year RRFS and MFS rates were 82 and 89% respectively. No regional or distant recurrences was detected after the first two years of follow-up (Fig. 2B and 2C). Five-year DFS rate was 57%, while 5-year SS and OS rates were 88% and 73% respectively (Fig. 2-D-2F).

4.2. Toxicities

Acute skin toxicity observed at 1 month were mainly grade 2 radiodermatitis (83%) (Fig. 3A). Regarding late skin toxicity, 5 pts (17%) presented telangiectasia (Fig. 3B) and 3 pts (10%) presented grade 3 necrosis requiring hyperbaric oxygen therapy sessions allowing complete skin recover (Fig. 3C, Table 2). The skin appearance difference between pre- and post-treatment assessments were statistically significant at 1 ($p < 0.01$), 3 ($p = 0.01$), 6 ($p < 0.01$) and 12 months ($p = 0.01$) (Fig. 4A).

Urinary function evaluation compared pre versus post-therapeutic IPSS calculated at each post-treatment evaluation. Assuming that mild urinary symptoms were already observed before brachytherapy in 25 pts (86%), no statistical difference was observed (pNS) (Fig. 4B). However, 2 pts (7%) presented late urethral meatus stenosis requiring iterative dilatations. Ten pts (34%) presented late urinary complications without any grade 3 (Table 2). Mean V150 was statistically correlated with the risk of G2/3 acute urinary toxicity (G1 V150: 30% versus G2/3 V150: 42%; $p = 0.038$) but not with late urinary toxicity (G1 V150: 32% versus G2/3 V150: 35%; $p = 0.58$).

Regarding sexual function, while normal erectile activity was observed in 14 pts (54%) before brachytherapy, no statistical difference was found (pNS) between pre versus post-therapeutic period (Fig. 4C). Five pts (17%) presented sexual complications with 7% of grade ≥ 3 (Table 2).

5. Discussion

The psychological consequences of total penectomy, as well as urinary and sexual deleterious impact, have progressively oriented the management of patients towards conservative treatment.

The surgical alternative to penile preservation is Mohs micrographic surgery (MMS), which consists in making intraoperative cross-sections, examined in real time by the surgeon until a negative plane appears. NCCN suggests that MMS may be useful for superficial low-risk penile cancers of the proximal diaphysis, with 5-year local control ranging from 68 to 89% [16–20]. None of the patients had a urinary or sexual functional deficit [16]. Because of technical difficulties in implementation and the need of qualified surgeons, MMS has not achieved broad consensus.

Studies investigating the efficacy of external beam radiation therapy (EBRT) for penile cancer conservative treatment reported high relapse rates. Zouhair *et al.* presented the results of 41 pts treated with exclusive EBRT (56%) or surgery (+adjuvant radiotherapy 44%) for T1-T2 penile cancers. The authors reported a 5-year

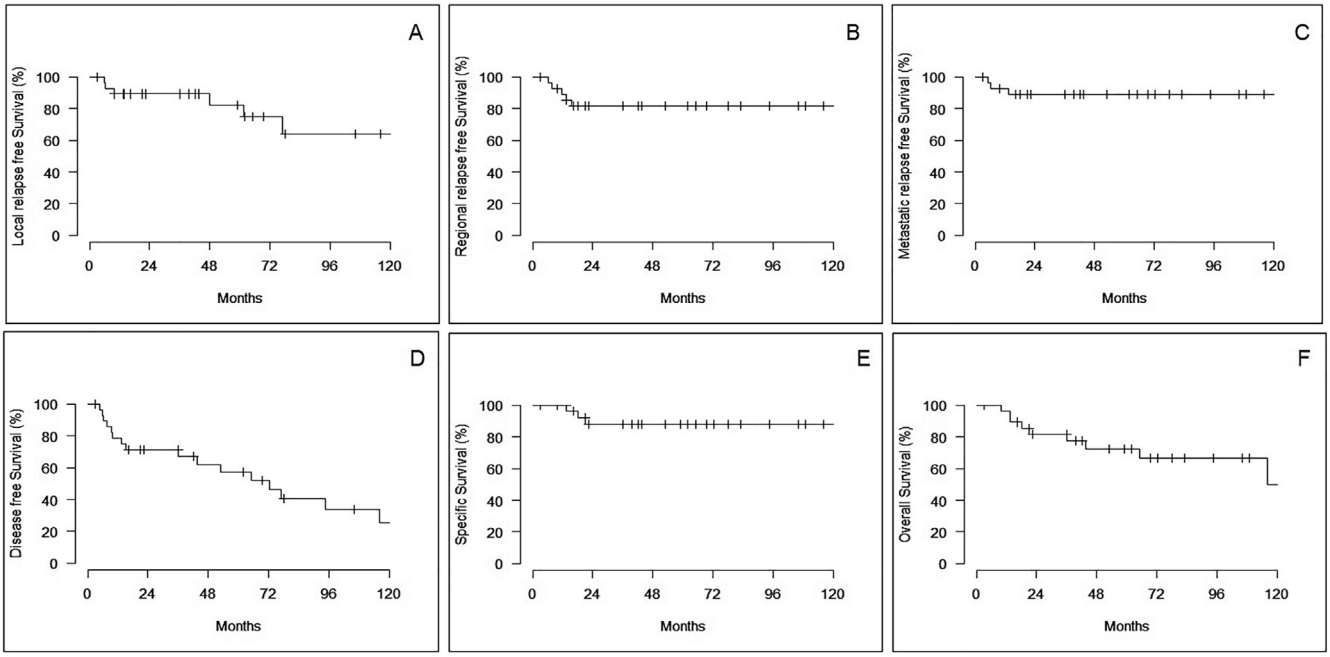

Fig. 2. Kaplan-Meier survival curves for local recurrence-free survival (A), regional recurrence free survival (B), Metastatic disease-free survival (C), Disease-free survival (D), Specific survival (E), Overall survival (F).

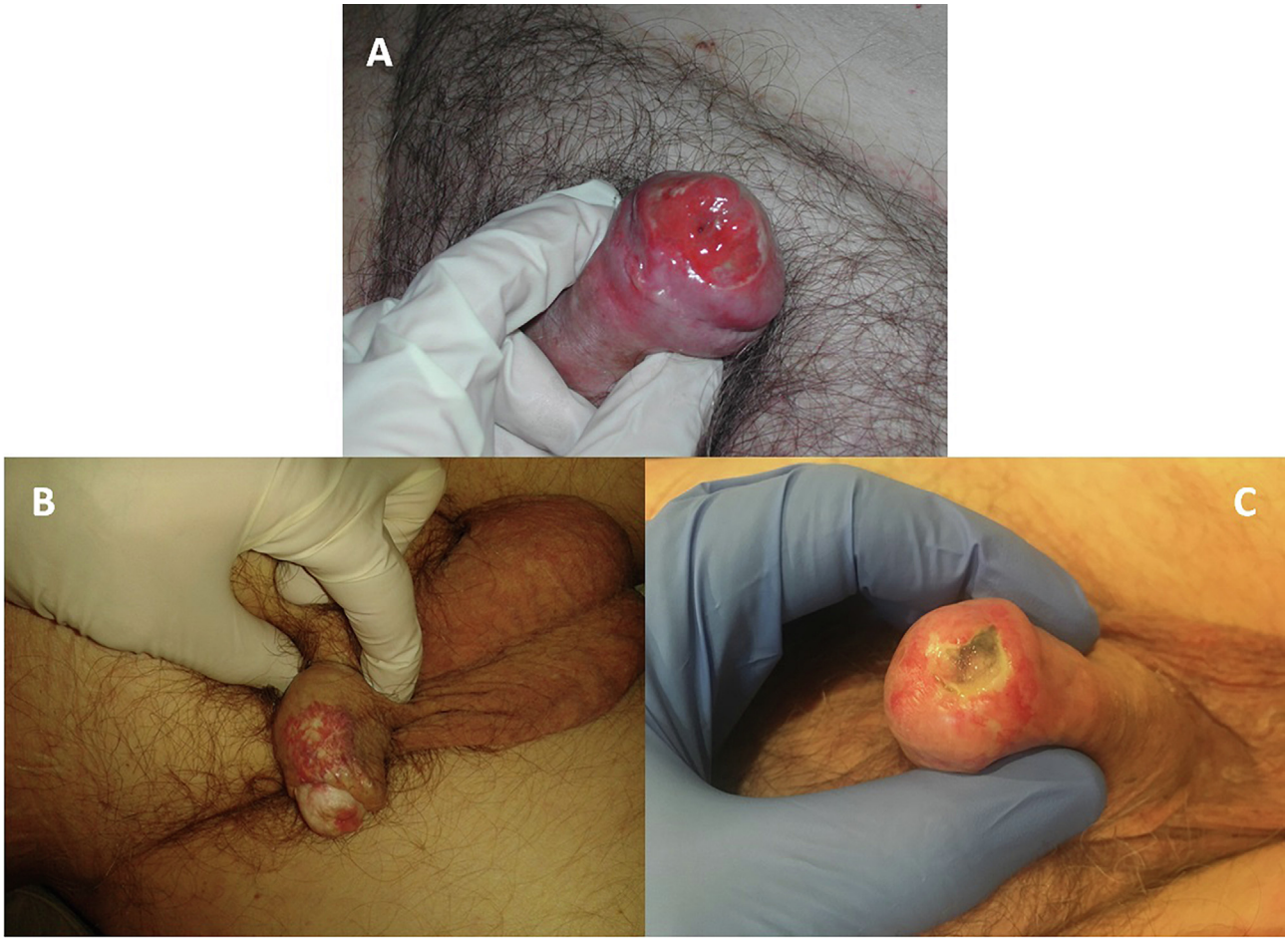

Fig. 3. Post MHB skin toxicities: acute radiodermatitis (A), telangiectasia (B), necrosis (C).

Table 2
Skin, urinary and sexual late complications.

Toxicities	Acute					Late				
	G1	G2	G3	G4	Total	G1	G2	G3	G4	Total
Skin	2 (7%)	24 (83%)	1 (3%)	0	27 (93%)	7 (24%)	5 (17%)	3 (10%)	0	15 (51%)
Urinary	11 (38%)	0	1 (3%)	NA	12 (41%)	7 (24%)	3 (10%)	0	NA	10 (34%)
Sexual	5 (17%)	0	0	0	5 (17%)	3 (10%)	0	2 (7%)	0	5 (17%)

NA: non-applicable for IPPS.

penile preservation rate of 36% [21]. Compared to EBRT, brachytherapy allows a significant improvement of local control, mainly due to a more accurate and precise dose delivery combined with a dose escalation. Consequently, brachytherapy appears as the best irradiation technique in order to avoid deleterious consequences of radical surgery.

The 5-year LRFS (82%) and PP (79.3%) rates reported in our cohort are consistent with those published in LDR/PDR brachytherapy series with 5-year LRFS rates about 80% [66–100] and PP rates around 76% [69–100] (Table 3). HDB clinical data are still limited. Petera *et al.* reported the results of a cohort of 10 pts with penile SCC. The total delivered dose was 54 Gy (3 Gy/Fr, twice daily over 9 days). With a MFU of 20 months, LRFS rate was 100% [22]. More recently, with a MFU was 76 months, Kellas-Sleczka *et al.* analyzed 76 pts treated with HDB (42.8 Gy or 48.2 Gy for adjuvant or definitive treatments respectively). Five-year LRFS rate was 66% with PP rate of 67% [11]. In our study, the median time to local recurrence onset was 29 months. Other studies report similar results, leading to consider that 50% of recurrences occur within the first two years [10,23]. It also suggests that the other half of relapses occur later and mostly during the five first years leading to consider a long surveillance [24].

In this study, 5-y RRFS rate was 82%. In LDR and PDR brachytherapy series, estimated RRFS rates were estimated at 87% [84–91] [9,25–28]. Sharma *et al.* presented a series of 14 pts treated with MHB (42–45 Gy in 14–15 fractions) (29). With a MFU of 22 months, the regional relapse rate was 14.3%, whereas Kellas-Sleczka *et al.* described only one patient (1.3%) with inguinal nodal metastases 64 months after MHB [11]. As we reported, Sharma *et al.* described 100% of events occurring within the first 24 months. Lymph node relapse could be considered as a progression of micrometastatic disease at the time of brachytherapy, highlighting the potential place of PET-CT in the initial work-up.

Five-year actuarial SS and OS rates were 88% and 73% respectively. Our results are superimposed on those described in the literature (Table 3). However, Petera *et al.* and Rouscoff *et al.*

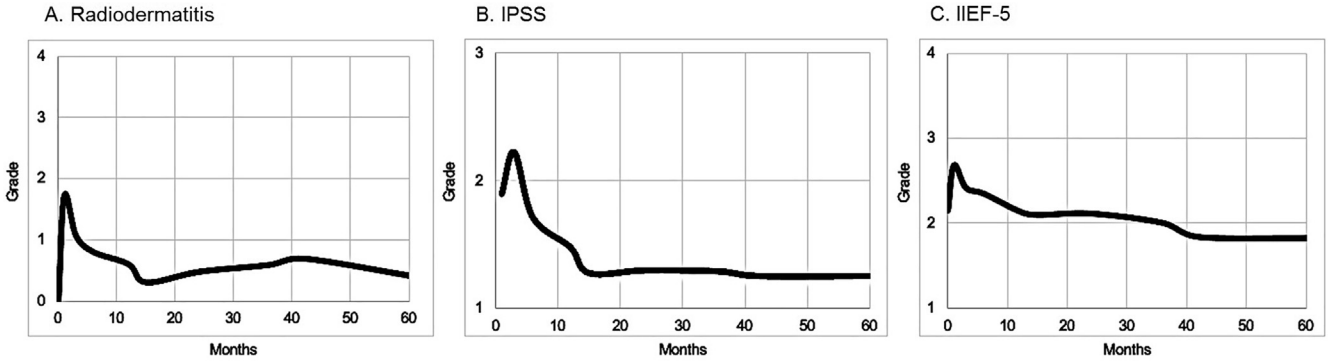

Fig. 4. Toxicity analysis evolution from pre-treatment (MHB) status for skin (A; radiodermatitis according to CTCAEv4.0 classification), urinary (B; IPSS: rated in 3 grades according to the score: grade 1 for light (1 to 7), grade 2 for moderate (8 to 19) and grade 3 for severe urinary symptoms (20 to 35)) and sexual (C; IIEF-5: rated in 4 grades: 1 = normal (21 to 25), 2 = light (16 to 20), 3 = moderate (11 to 15) and 4 = severe erectile dysfunction (5 to 10)) functions.

Table 3
Comparative clinical outcome analysis from brachytherapy series.

Authors	n	MFU (months)	Type	Dose (Gy)	5y-LRFS (%)	5y-OS (%)	Necrosis (%)	Stenosis (%)	PP (%)
Mazeron *et al.* [34]	50	36-96	LDR	60-70	78	63	6	19	74
Delannes *et al.* [28]	51	65	LDR	50-65	86	72	23	45	75
Rozan *et al.* [8]	184	139	LDR	63	86	66	21	45	78
Soria *et al.* [23]	102	111	LDR	61-70	77	63	1	1	72
Chaudhary *et al.* [27]	23	21	LDR	50	70	66	0	9	70
Kiltie *et al.* [33]	31	62	LDR	63.5	81	69	8	44	75
De Crevoisier *et al.* [9]	144	68	LDR	65	80		26	29	72
Cordoba *et al.* [25]	73	52	LDR	60	88	82	6.8	6.8	69.1
Crook *et al.* [26]	67	48	PDR/LDR	60	87		12	9	88
Escande *et al.* [10]	201	128	PDR/LDR	65	82	79	21.4	24.8	77.1
Makarewicz *et al.* [35]	33	60	PDR/HDR	51	78.8	85	9	-	84.8
Petera *et al.* [22]	10	20	HDR	54[(a)]	100		0	0	100
Rouscoff *et al.* [12]	12	27	HDR	36/39[(c)]	83	78	9	9	92
Sharma *et al.* [29]	14	22	HDR	42-45	86		0	0	93
Kellas-Sleczka *et al.* (11)	76	76	HDR	42.8/48.2[(b)]	66	77	2.6	1.3	69.5
Pohankova *et al.* [36]	26	85	HDR	51	83	92	4	4	73
Marban-Orejas *et al.* [30]	7	90	HDR	38.4/53[(d)]	86	100	43	43	86
Present study	29	72	HDR	35/38[(e)]	86	73	10	7	79

Type: modality of radiation therapy; LDR: Low-dose rate brachytherapy; PDR: Pulse-dose rate brachytherapy; HDR: High-dose rate brachytherapy; n: number of patients; LRFS: local relapse free survival; OS: overall survival; MFU: median follow-up in months; PP: Penile preservation
[(a)]54 Gy in 18 fractions over 9 days.
[(b)]42.8 Gy for adjuvant setting and 48.2 Gy in sole therapy, with a median fractionation dose of 3.2 Gy.
[(c)]36 Gy in 9 fractions over 5 days (in the adjuvant setting: 6 Gy day 1 + 2 x 3.75 Gy from day 2 to day 5) or 39 Gy in 9 fractions over 5 days (in sole therapy: 7 Gy day 1 + 2 x 4 Gy from day 2 to day 5).
[(d)]Prescribed dose ranged from 38.4 Gy in 6 days (3.2 Gy in 12 fractions) to 53 Gy in 9 days (3.12 Gy in 17 fractions).
[(e)]Median total dose of 35 Gy in 9 fractions over 5 days in the adjuvant setting or 38 Gy in 9 fractions over 5 days in sole therapy.

described 5-year actuarial SS rates of 100% [12,22]. This can be explained by the low sample size of those cohorts and a shorter follow-up.

After penile brachytherapy, acute skin complications are frequently described. In our series, 93% of patients had radiodermatitis (grade 2: 83%). Radiodermatitis is a well-documented acute complication after MHB which takes about 8 weeks to recover from [22]. The most serious late skin complication is necrosis. In our series, the rate of necrosis was 10.3%. In the literature, this rate varied from 0 to 26%. Kellas-Sleczka *et al.* did not find any post-therapeutic necrosis [11]. This could be explained by a median CTV 8.4 cc versus 15.1 cc in our series. Other late toxicities observed in the treated area were hyperpigmentation and telangiectasia. Kellas-Sleczka *et al.* described pigmentation changes in 35.5% and telangiectasias in 21% of cases [11]. Dose distribution must be homogeneous to limit the occurrence of acute and late skin toxicities. A spacing of 9–12 mm of the needles is recommended for obtaining optimal homogeneity and also limiting side effects [30].

Considering urinary function, urethra is the main organ to be considered for the evaluation of urinary function. At various follow-up visits, the IPSS measurement did not find any significant deterioration in urinary function after HDB. Various studies on LDR, PDR and HDR brachytherapy evaluated post-treatment urinary status as a function of the percentage of urethral stricture. In our cohort, 2 pts (7%) had urinary stenosis, corresponding to the interval ranged in the literature from 0 to 45% (Table 3). Stenosis is usually treated by dilatation or endoscopy. However, no significant correlation was observed between dosimetric parameters and the risk of self-reported urinary toxicity according to Gambachidze *et al* [31]. The challenge of brachytherapy is to limit the impact on urinary function while preserving the oncological outcome, by using dose distribution optimization to the urethra.

In our study, there was no significant deterioration in sexual function using IIEF-5 score evaluation. The treatment impact on quality of life is becoming a major issue in patient management. After radical penectomy, sexual function damage represents one of the main concerns, leading to higher anxiety level and depres-

sion [32]. Escande *et al.* shown that, after penile brachytherapy, 67% of patients declared having maintained a sexual activity after 3 years of follow-up [10]. Petera *et al.* reported a rate of 90% of patients who declared having maintained sexual function [22]. The impact of brachytherapy on QoL is thereby limited [31].

The main limitation of our retrospective observational study is represented by the small number of patients (29 pts) and a still short MFU (72 months). A low proof level is currently being observed from retrospective studies, while those aiming to randomize surgery versus brachytherapy seem ethically difficult to set up. Recently, the Groupe de Curiethérapie of the Société Française de Radiothérapie Oncologique (GC-SFRO) created a national database gathering all patients who underwent brachytherapy for penile cancer, in order to provide more consistent results.

6. Conclusion

For localized cancers penile (T1-2), brachytherapy after circumcision represents the treatment of choice aiming to offer both efficient and conservative approach. Because of its ability to optimize the dose distribution and its low constraints in terms of radiation protection, HDR brachytherapy gradually gains in popularity and respectability. For promoting penile cancer conservative treatment, MHB provides encouraging results in terms of oncological and functional results, while presenting a consistent alternative to the LDR/PDR brachytherapy series. Larger series with extended follow-up are warranted.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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