



Conservative surgery plus brachytherapy treatment for boys with prostate and/or bladder neck rhabdomyosarcoma: a single team experience

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Abstract

Purpose: The aim of this study is to report the results of a conservative surgery + brachytherapy treatment for boys with prostate and/or bladder-neck rhabdomyosarcoma avoiding total cystectomy or prostatectomy and external radiotherapy.

Patients: From 1991 to 2007, 26 boys were operated for a residual mass after chemotherapy (1 for local relapse). All patients underwent a conservative surgical procedure, with bladder-neck and urethra preservation. Surgery was never microscopically complete. Brachytherapy was systematically performed after tumor resection, as a perioperative procedure, consisting of 2 loops encompassing the prostate and the bladder-neck area. A dose of 60 Gy was delivered with low dose rate. Bladder function was evaluated clinically and with urodynamic study for boys with abnormal continence.

Results: Median age at operation was 23 months (9 months–11 years). Seventeen boys underwent a partial prostatectomy associated in 5 with a partial cystectomy. The remaining 9 patients underwent a partial cystectomy with no procedure at the level of the prostate. At a median follow-up of 4 years (10 months–14.5 years), 24 of 26 boys are alive. Only 1 patient relapsed locally out of the brachytherapy field and died. A second boy died from metastatic relapse. Only 1 patient with bladder dysfunction after treatment underwent a total cystectomy. Four patients are too young to be evaluated for bladder function (<4 years of age). Seven patients, aged 4 to 6 years, have daytime continence, 1 has diurnal dribbling. Among 11 boys older than 6 years, 9 (82%) are normally continent (3 after temporary dribbling), 2 have diurnal dribbling treated by bladder education.

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Conclusion: Even if very long-term sequelae of brachytherapy cannot be evaluated, this conservative combined treatment may allow normal continence in nearly all patients, even after temporary diurnal incontinence and should be discussed as an alternative to external radiotherapy or radical surgery.
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Outcome in children with bladder-prostate rhabdomyosarcoma (BP RMS) has improved significantly in the last few decades because of the international collaborative trials of the International Society of Paediatric Oncology and Intergroup Rhabdomyosarcoma Study (IRS) group. Children with BP RMS have a 5-year overall survival of 82% in IRS IV study [1] and of 80% in Malignant Mesenchymal Tumors (MMT) 89 study [2]. The concept of total burden of therapy with the major problem of late sequelae is particularly applicable to BP RMS in terms of local treatment [2]. Local treatment usually performed after chemotherapy (CT) is represented by surgery completed or not with radiotherapy.

Bladder preservation is a major goal in BP RMS, and the number of patients alive with their bladder increased over successive IRS studies from 23% in IRS I study [3] to 60% in IRS III study [4] and 83% in IRS IV study [1]. However, bladder preservation does not mean normal bladder function: only 40% of the 36 survivors had normal bladder function in IRS IV study [1]. Moreover, all but 4 patients received external radiotherapy, and bladder function may be affected by fibrosis as a late effect of radiotherapy. Total prostatectomy associated or not with bladder neck resection conveys a very high risk of incontinence where performed in very young children [5], and partial prostatectomy alone has a very high risk of local relapse [6]. Brachytherapy (BT) has been used for a long time in France in the multimodal treatment of BP RMS [7,8] to avoid external radiotherapy in very young children.

The purpose of this article is to report the results of a combined local treatment including a conservative surgical procedure completed with BT, aiming at preserving urinary and sexual function without jeopardizing survival.

1. Patients and methods

From 1991 to 2007, 26 boys with BP RMS were referred to our centers (Bicêtre Hospital for surgery and Institut Gustave Roussy for BT) for a conservative local treatment (1 patient was treated in 1991 and the others after 1995). Boys were coming from different hospitals and were treated according to International Society of Paediatric Oncology protocols (MMT 89, 95, and 98 protocols) and, more recently, the current European protocol RMS 2005.

All but 1 patient underwent initial biopsy for a mass arising from the prostate and/or the bladder (IRS III group). The other patient was referred for a local relapse after tumorectomy performed in another hospital. Pathological material was reviewed by the pathology committee of the French MMT group. Patients received a standard first line of CT according to their risk group of treatment: IVA (Ifosfamide, Vincristine, Actinomycin D) in MMT 89 study [2], IVA or a combination of 6 drugs (Ifosfamide, Vincristine, Actinomycin D, Carboplatin, Epirubicin, Etoposide) in MMT 95 and 98 protocol, and IVA or IVADO (IVA + Doxorubicine) in RMS 2005 protocol.

Possibility to perform a conservative combined treatment was assessed by imaging (ultrasound and magnetic resonance imaging [MRI]) at diagnosis and after CT. Cystoscopy with biopsies was recommended whenever feasible at diagnosis and after CT. Patients were not selected at diagnosis but according to their response to CT: All patients with prostate tumor (Fig. 1) were good candidates for this procedure assuming that BT could be performed after tumor resection even incomplete. As far as BP or bladder-urethra tumors are concerned (Fig. 2), the exact anatomical localization of the tumor was determining. One criteria were mandatory to

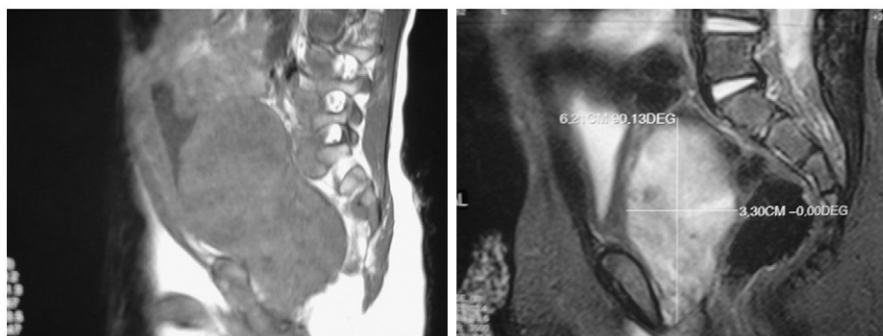


Fig. 1 The MRI of prostate RMS at diagnosis and after CT at time of local treatment.

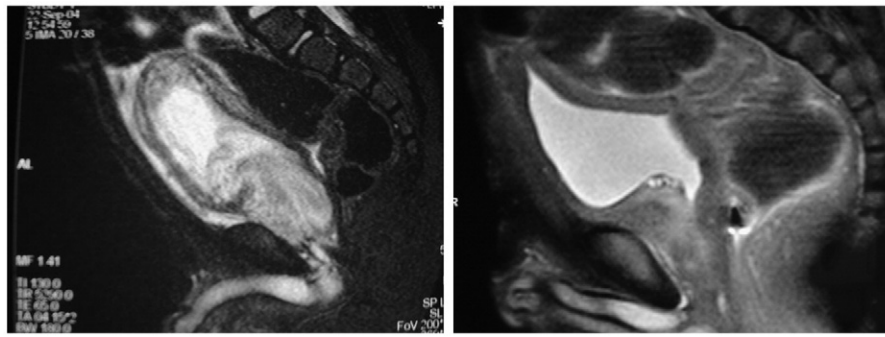


Fig. 2 The MRI of a bladder neck RMS before and after CT at time of local treatment.

decide this procedure: to have no extension in the bladder above the level of the trigona, assuming that BT could sterilize any residual tumor of the prostate and/or of the bladder neck but could not reach tumor cells at a higher level in the bladder wall. To try to avoid surgical sequelae (mainly urinary incontinence), the surgical procedure was a partial prostatectomy with urethra preservation and/or a partial cystectomy of the bladder neck or trigona associated, if necessary, with ureteral extravesical reimplantation.

When the tumor response to CT was estimated insufficient to perform a conservative procedure, the CT was continued for 2 to 3 courses, and a new evaluation was done afterward. Especially for bladder tumors, the parents and the child were always informed that the conservative procedure might be not feasible because of unexpected operative findings and/or results of frozen sections and that a total cystectomy might be finally decided and immediately performed.

Implantation of the plastic tubes for BT was always done during the surgical procedure (**Fig. 3**). The BT technique would depend on the tumor location. For bladder and prostate tumors, plastic tubes were implanted through a perineal approach consisting of 2 loops encompassing the prostate and the bladder neck. If necessary, plastic tubes were maintained by a suture at the level of the loop bridge to avoid plastic tube geographical modification. For bladder tumors, the technique consisted of 2 loops encompassing the partial cystectomy scar. After 5 to 7 days following the surgical procedure, children were transferred to the BT department of the IGR. X-rays were performed with dummy sources to decide upon radioactive source length, according to histopathological findings and application geometry. Iridium wires were manually loaded with dosimetry. Paris system rules were respected, and a total dose of 60 Gy was delivered with a dose rate of 10 Gy per day. Systematic x-rays were

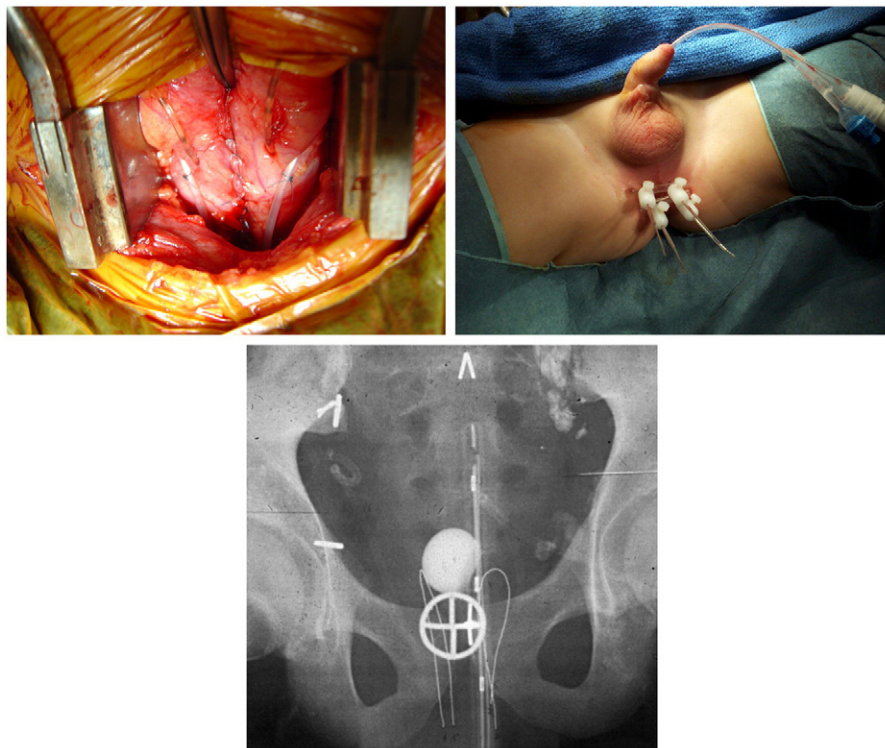


Fig. 3 Intraoperative insertion of BT tubes and x-ray of the pelvis showing the tubes.

performed during the BT procedure twice a week to detect a potential source displacement.

After local treatment, most patients received some additional courses of CT according to the protocols. Only 2 patients underwent additional external radiotherapy for nodal involvement of the aorto-iliac chain. In these cases, the BT dose was limited to 20 Gy with a dose of 45 Gy for external irradiation.

Follow-up was done by the oncology team, the surgeon, and the brachytherapist with usual tools (ultrasound, MRI, and cystoscopy for bladder tumors). Functional results were assessed by clinical examination until 6 years of age. After 6 years, all children with abnormal symptoms (diurnal incontinence, dribbling, etc) underwent urodynamic studies and were usually treated by bladder education and/or medical drugs. Parents and/or children were also questioned about erection and for the older boys about sexual function.

2. Results

2.1. Patients and tumor characteristics

They are indicated in Table 1. Median age at operation was 23 months (range, 9 months-11 years). Eighteen boys (70%) were less than 3 years of age at operation, and all but 1 were less than 10 at diagnosis. Eleven patients had a tumor limited to the prostate, 11 had a BP tumor or a bladder tumor with extension to the prostatic urethra, and 4 had a tumor limited to the bladder (trigona and/or bladder neck). Tumor size was larger than 5 cm in more than half of the patients at diagnosis. Only 3 patients had alveolar histology, and 4 patients had metastatic disease. A median number of 6 courses of CT (range, 4-10 courses) was administered before local treatment.

2.2. Surgery

The surgical procedure was always performed for a residual mass after CT. One patient underwent a tumor-ectomy for a pediculate lesion of the bladder neck with no resection of the bladder wall. Seventeen (65%) boys underwent a partial prostatectomy with preservation of the urethra associated in 5 with a partial cystectomy. The remaining 8 patients underwent a partial cystectomy with no procedure at the level of the prostate. Among them, 1 boy with involvement of the whole trigona underwent a mucosectomy of the trigona with no resection of the entire bladder wall, with bilateral extravesical reimplantation of the ureters, and introduction of 3 parallel plastic tubes through the posterior bladder wall. Partial cystectomy was performed either at the level of the bladder neck, removing less than half of the circumference of the anterior-lateral bladder neck in 8 patients, or at the level of the trigona removing half of the trigona in 4 patients. Partial

Table 1 Tumor characteristics

	n
Tumor site	
Prostate	11
Bladder	4
Bladder + Urethra	5
BP	6
Histology	
Botryoid	3
Embryonal	20
Alveolar	3
TNM stage	
2	21
3	2
4	3
Local relapse	1
IRS group	
III	21
IV	4
Local relapse	1
Tumor size	
<5 cm	12
>5 cm	14
T status (invasiveness)	
T1	12
T2	13
Not applicable	1

prostatectomy always left a wall of tissue around the urethra, accepting a macroscopic residual disease at this level. Surgery was never considered as complete at the level of the prostate, and a macroscopic residual disease was left behind in 10 patients.

2.3. Histology

Excision was never considered microscopically complete. Eleven patients had a microscopic residual disease, and 11 had a macroscopic residual disease (10 at the prostate/urethra level and 1 at the trigona level where no entire bladder wall resection was performed).

Twenty-two patients (85%) had viable immature, desmine positive, rhabdomyoblasts in the resected specimen. Only 4 patients had no viable tumor cells with only necrosis and fibrosis of whom 3 had a macroscopic residual disease and 1 a microscopic residual disease of an alveolar RMS. Interestingly, 3 of these 4 boys were metastatic. Finally, no patient was identified as having mature rhabdomyoblasts as defined by Ortega et al [9], neither in the resected specimen nor later in biopsies performed during follow-up.

2.4. Outcome

At a median follow-up of 4 years (range, 10 months-14 years), 24 boys are alive. Among them, 22 are in first

complete remission after induction treatment. The boy treated for a local relapse is in second complete remission 1 year after the local treatment. One boy developed nodal and bone relapse 16 months after the end of treatment and achieved second complete remission with CT alone. Only 2 boys died, 1 from a metastatic pulmonary relapse 22 months after diagnosis. The other boy who died was the youngest boy of this series (9 month old). He had a very large abdominopelvic tumor (12 cm) arising from the prostate, which did not respond to the first-line and second-line CT. He underwent a tumorectomy with prostatectomy. He relapsed 6 months after surgery and BT with local relapse out of the field of BT, nodes, and pulmonary relapse and died 2 months after relapse.

Among the 24 alive patients, only 1 lost his bladder secondarily because of severe dysfunction with bilateral ureterohydronephrosis. This patient was operated after initial CT (partial cystectomy) in another center. He had a macroscopic residual disease at the level of both the prostate and the bladder. He was then reoperated in our center (redo partial cystectomy + partial prostatectomy + ureteral extravesical reimplantation) and received BT. He had a post Ifosfamide tubulopathy and developed 6 months after the operation a severe pollakiuria with incontinence and bladder dysfunction with hydronephrosis. Urodynamic study demonstrated a decreased bladder compliance with detrusor sphincter dyssynergia. Drugs did not improve the bladder function leading to total cystectomy and urinary diversion 3 years after the local treatment.

2.5. Functional results of survivors

Four boys are too young to be evaluated in terms of bladder function (<4 years of age). Seven patients, aged 4 to 6 years, have nocturnal enuresis but normal daytime continence for 6 and diurnal dribbling for 1. Interestingly, this latter boy who was 4 years old at local treatment had normal diurnal continence during 10 months after the local treatment. The urodynamic studies demonstrated a subnormal bladder compliance with rather low urethral pressure. Night-time incontinence has recently completely disappeared, and the boy receives now anticholinergic drugs and bladder education.

Among 11 boys older than 6 years, 9 are normally continent and 2, aged 9 and 7, have still diurnal dribbling and nocturnal enuresis. One has a normal urodynamic study, and the other 1 has a detrusor sphincter dyssynergia. Both are treated by bladder education. Among the 9 boys normally continent, 2 presented a temporary diurnal dribbling between 6 and 10 years of age and 1 had a temporary stress incontinence. Urodynamic studies were performed for 2 of these 3 boys showing a decrease of urethral closing pressures in the latter boy and detrusor sphincter dyssynergia in the other. All these symptoms have disappeared with bladder education.

2.6. Sexual function

Most of the patients were too young to be evaluated. However, the 2 oldest boys (18 and 17 years old) consider themselves as normal in term of erection and ejaculation. Only 5 parents told us that they saw normal erections in their child, but this question was not always asked.

2.7. Other complications of local treatment

Most of the patients complained of temporary and mild rectal bleeding related to BT. This bleeding was not associated with pain, did not need any special therapy, and resolved. The boy who had mucosectomy of the trigona and BT of the posterior bladder wall developed, 2 years after local treatment, a bladder stone without any obstruction of bladder emptying. This lithiasis relapsed twice after removal. Finally, 1 boy developed a stenosis of a ureteral meatus after reimplantation and needed a JJ catheter for several months.

3. Discussion

Local treatment is a major challenge in BP RMS because most patients with this localization will survive. Consequently, the aim to reduce as much as possible the burden of therapy and long-term sequelae seems mandatory. Beyond bladder preservation, which was the main goal some years ago, the necessity to retain prostate and to preserve bladder function without jeopardizing survival has become the concern of all clinicians [10,11].

As far as surgery is concerned, total prostatectomy without urethra preservation should be considered as a procedure with a very high risk of incontinence where performed in very young boys. The consequences for continence are completely different in adolescents and young adults, where risk factors for urinary incontinence have been well established and who are usually continent when neurovascular bundles are preserved with absence of anastomotic stricture [12-14]. Partial prostatectomy alone in RMS has a very high risk of local relapse and should not be performed without radiotherapy [6]. It is also well established that partial cystectomy may have an impact on bladder function not only in terms of decreased storage but also by more subtle effects especially after extravesical ureteral reimplantation [15,16].

Finally, the impact of external radiotherapy on bladder function has been demonstrated [5] especially by IRS studies where most of the patients were irradiated [1,17]. In France, BT has been used for decades in the local treatment of RMS of the vagina and vulva with excellent results in terms of local control and function [18,19].

For all these reasons, an attempt was made to treat BP RMS with the combined surgery + BT procedure, and the

results of this series seems very encouraging not only in terms of local control (only 1 local relapse) but also in terms of functional results (only 1 secondary cystectomy and mild problems of diurnal dribbling in 3 patients).

One of the questions is whether our patients represent a selected population amenable to this procedure and how it can be compared to the whole population of children with BP RMS.

All but 1 boy were less than 10 years of age, but 4 had metastatic disease, 3 had alveolar histology, and 14 had a tumor size more than 5 cm. If our patients (except the boy treated for a local relapse) would have been classified according to the risk grouping factors of the current European RMS 2005 protocol, 9 patients would have been in the standard-risk group (tumor size <5 cm and age less than 10 with no alveolar histology), 11 would have been in the high-risk group (tumor size >5 cm and/or age more than 10 with nonalveolar histology) and 5 in the very-high-risk group (1 alveolar histology with nodal involvement and 4 with metastatic disease). Regarding IRS-Children Oncology Group (COG) risk groups, all but 2 patients would have been in the intermediate-risk group, the remaining 2 patients (metastatic alveolar RMS) being in the high-risk group.

Our patients represent a selected population because they were referred to our team especially for the BT procedure. We discussed some other patients with oncology teams and surgeons. When the bladder was completely involved by the tumor with no realistic possibility to preserve it, the patients were not referred to our team and were operated by the local surgeon. Only 2 total cystectomies were performed in our hospital during the same period.

A comparison was also performed with the 29 boys with BP RMS (localized or metastatic) enrolled in the MMT 95 study in France from 1995 to 2003. Nine of our patients are included in this study. Among the 25 survivors of this French group, 17 were not addressed to our team. Among these 17 boys, 7 underwent a radical surgery (4 total prostatectomy and 3 total prostatectomy with bladder preservation). We cannot assume that these last 3 patients could have received a conservative procedure instead of radical surgery because these patients were not referred to our team. The remaining 10 boys underwent a conservative surgery + BT procedure in 5 cases and a partial cystectomy alone for a bladder tumor in 5 cases.

The fact that 5 patients were cured without BT may be explained by the localization of the tumor (1 bladder dome, 2 lateral bladder wall, 1 trigona, 1 pediculate bladder neck tumor), which was completely resected with free margins in all cases and with no tumor cells in 3 specimen. This fact may be compared to the absence of tumor cells in 4 patients of our series. Because 3 of them had prostate RMS with residual disease left behind, we think that it was to risky in terms of local relapse to avoid BT.

Finally, all these results confirm that a conservative combined approach should be attempted after CT in most BP

RMS, except for a large tumor of the bladder surrounding the bladder neck with extension above the level of the trigona. The further question is whether the surgical resection could be decreased to minimize functional sequelae. Because no patient relapsed in the BT field, even those with macroscopic residual disease of the prostate, we could reasonably assume that the surgical procedure at this level could be only a simple biopsy after precise evaluation of the tumor volume by the brachytherapist. An attempt is also made to decrease the bladder neck resection because BT tubes can easily encompass this area.

Most BP RMS can now be treated with conservative procedures minimizing late sequelae without impacting survival. Because BT seems to be the key point of this improvement, it can be wished that most patients could have an access to this technique by developing BT centers in close relation with pediatric surgeons. The necessity of a approach in pediatric oncology is, once again, demonstrated.

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