TITLE PAGE

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Long-term urological complications after conservative local treatment in children with bladder-prostate rhabdomyosarcoma. A single team experience.

The complete affiliations of all authors:

Rezkalla Akkary: Department of paediatric surgery, Bicêtre Hospital, Assistance Publique –Hôpitaux de Paris, Paris-Saclay University, Le Kremlin-Bicêtre, France.

Florent Guérin: Department of paediatric surgery, Bicêtre Hospital, Assistance Publique –Hôpitaux de Paris, Paris-Saclay University, Le Kremlin-Bicêtre, France.

Cyrus Chargari: Brachytherapy Unit, Department of Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France.

Loic Jauchult: Department of Biostatistics, Hôpitaux Civils, Colmar, France.

Georges Audry: Department of paediatric surgery, Armand Trousseau Hospital, Assistance Publique-Hôpitaux de Paris, Sorbonne University, Paris, France

Luca Pio: Department of paediatric surgery, Bicêtre Hospital, Assistance Publique – Hôpitaux de Paris, Paris-Saclay University, Le Kremlin-Bicêtre, France.

Veronique Minard-Colin: Department of Paediatrics, Gustave Roussy Cancer Campus, Villejuif, France.

Christine Haie-Meder: Brachytherapy Unit, Department of Radiation Oncology, Gustave Roussy Cancer Campus, Villejuif, France.

Hélène Martelli: Department of paediatric surgery, Bicêtre Hospital, Assistance Publique –Hôpitaux de Paris, Paris-Saclay University, Le Kremlin-Bicêtre, France.

-The name, address, phone, fax and email contact for the corresponding author:

Name: Pr Hélène MARTELLI

Adress: Department of Paediatric surgery, Bicêtre Hospital, Assistance Publique-Hôpitaux de Paris, Paris-Saclay University, 78 rue du Général Leclerc, 95275 Le Kremlin-Bicêtre Cedex, France

Tel: +33678463337 Fax: +33145213189

Email: helene.martelli@aphp.fr

hemartelli@gmail.com

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-An abbreviations key in a table:

abbreviation	full term
RMS	Rhabdomyosarcoma
GU	Genitourinary
BP RMS	Bladder prostate rhabdomyosarcoma
SIOP	International Society of Pediatric Oncology
IRS	Intergroup Rhabdomyosarcoma Studies
MMT	Malignant Mesenchymal Tumors
EFS	Event Free Survival
OS	Overall Survival
COG	Children Oncology Group
CWS	Cooperative Weichteilsarkom Studiengruppe
LDR	Low Dose Rate
PDR	Pulse Dose Rate
MRI	Magnetic Resonance Imaging
CTCAE	Common Terminology Criteria for Adverse Events
AE	Adverse Events
ICCS	International Children's Continence Society
UDS	UroDynamic Studies
UTI	Urinary Tract Infection

This paper was presented at SIOP 2020 virtual meeting in the Best of IPSO session with the same title: Long-term urological complications after conservative local treatment in children with bladder-prostate rhabdomyosarcoma. A single team experience.

ABSTRACT

Background:

Outcome of children with bladder-prostate rhabdomyosarcoma has improved with multimodal therapies, including surgery and/or radiotherapy for local treatment. Our aim was

to report the long-term urological complications after a conservative approach combining conservative surgery and brachytherapy.

Patients and methods:

Eighty-six patients, free of disease, were retrospectively reviewed. Symptoms related to urinary tract obstruction, incontinence, infection and lithiasis were reported and graded according to CTCAE classification. Only symptomatic patients underwent urodynamic studies. Risk factors for complications were analyzed.

Results:

There were 76 males and 10 females. The median follow-up was 6.3 years (18 months-24 years). Complications occurred after a median follow up 5 years (0-21).

Twenty-two patients had long-term urological complications. Urinary tract obstruction was found in 15 patients, urinary incontinence in 14 patients. Recurrent urinary tract infection and urinary lithiasis were found in 5 patients respectively. Beyond symptom, 3 etiologies were identified: bladder dysfunction in 15 patients, urethral stenosis in 6 and uretero-vesical junction stenosis in 5. Posterior bladder wall dissection used in large prostatic tumors, operation at age less than 2 years and partial prostatectomy were identified as risk factors for these complications.

Conclusion:

The conservative surgical approach combined with brachytherapy for BPRMS leads to long-term urological complications in 22% of patients free of their disease. Optimizing brachytherapy doses for young children and establishing a clear and long term follow-up protocol, could help to reduce these complications.

INTRODUCTION:

Rhabdomyosarcoma (RMS) is the third most common soft tissue, extra cranial, non-hematologic pediatric tumor. It accounts for around 50% of soft tissue sarcomas in children. Genitourinary (GU) RMS represents 25% of pediatric RMS [1], and the bladder and the prostate represent around 50% of GU localization[2].

Historically, the standard treatment of pediatric bladder-prostate RMS (BP RMS) was radical cystectomy/cysto-prostatectomy associated with chemotherapy and radiotherapy[2].

The severe sexual and urinary sequelae of this radical approach have changed the treatment towards a more conservative one with bladder preservation, and radiotherapy, knowing that rhabdomyoblasts are highly radiosensitive[3].

According to IRS-IV and MMT studies, the current management includes systemic control by chemotherapy and local control by a conservative surgery, whenever feasible, and/or radiotherapy. In comparison to IRS I, this approach provides a better event free survival (EFS), overall survival (OS), and a higher bladder preservation rate[1, 4].

The late effects of external beam radiation therapy on pelvic bones[5] and on the urinary tract are important[6]. Scoliosis, epiphyseal slipping, avascular necrosis and bone growth impairment have been reported[5]. Hemorrhagic cystitis, bladder fibrosis, neurogenic bladder and the development of secondary malignancies were also reported[6, 7].

An attempt was made in France to combine conservative surgery and brachytherapy, in order to decrease long term sequelae without jeopardizing survival[8], for a selected subset of patients. The first 100 patients treated with this combined local treatment from 1991 to 2015 and according to the ongoing European protocols were published with a good outcome. The five-year disease-free rate was 84% and the overall survival rate was 91%.[9].

The aim of this study was to analyze the long term urological complications observed in survivors of this latest population and to assess the risk factors for these complications. Genital complications, concerning gonads and internal genital ducts (vagina, deferens) were excluded of this study.

PATIENTS and METHODS:

Inclusion criteria:

We retrospectively documented all children referred to our department between 1991 and 2015 and treated for a histologically confirmed BP RMS according to a multimodal approach including neoadjuvant chemotherapy (all patients had biopsy at diagnosis – IRS III), conservative surgery and brachytherapy. The patients were treated according to different protocols (RMS 2005, MMT 95, COG, MMT 98, MMT 89 and CWS 2006). Patients' response to chemotherapy was evaluated with cross sectional imaging. Fifty percent of the patients came from abroad. Selection criteria were all discussed before[10].

Exclusion criteria:

Among the 100 patients, we excluded 8 patients who died before functional outcome was eligible for analysis and 2 patients who underwent a total cystectomy for tumor relapse at an age younger than 1 year. Moreover, 4 patients were excluded because of insufficient follow-up (i.e. less than 1 year).

Surgery

Surgical modalities had evolved, trending to progressively decrease the extent of resections. With time, instead of full-thickness bladder wall resection, only mucosal resections were done, whenever possible. Therefore, the bladder neck was spared. For anterior bladder wall tumors, an anterior partial cystectomy was performed. For tumors involving the prostate, a partial prostatectomy was performed with urethral preservation. Trigone-bladder neck

dissection was done in order to reach the prostatic tumors. For all tumors extending behind the bladder higher than the trigone, posterior bladder wall dissection was performed followed by resection of higher part of the tumor, preserving the bladder neck and urethra. Macroscopic residuum was accepted at the level of the prostate as it was estimated to be in the brachytherapy field. When the trigone and ureteral orifices were estimated to be in the irradiated zone, a bilateral ureteral reimplantation was performed. An extra-vesical dissection of the ureters was done. The ureters were resected as distally as possible. Higher ureteral entry orifices were made as in the classic Leadbetter Politano technique. Then, the submucosal tunnel was created in the transverse plane -as in Cohen technique- but at a supra-hiatal level. So, crossing ureterocystotomies were made.

Brachytherapy

The description of brachytherapy treatment protocols was detailed in a previous paper[10]. We switched from low-dose rate (LDR) brachytherapy (two loops encompassing the prostate/urethra and/or the bladder neck) to pulse-dose rate (PDR) brachytherapy in 2014 with 4 single leads plastic tubes. The PDR tubes encompassed the macroscopic residuum and were sutured under direct vision to the bladder wall in order to optimize the brachytherapy field around the residual tumor (Figs 1A and 1B). Sixty Gy were delivered in 6 days, starting from day 5 postoperatively. External beam radiotherapy (41Gy) was associated with brachytherapy (20 Gy) for patients with nodal disease.

Follow-up:

Follow-up was done by the referring oncologist. Patients were followed regularly by clinical examination, ultrasound, MRI with or without cystoscopy. Radiologic investigations (except ultrasound) and urodynamic studies were performed when indicated clinically. Only the significant permanent urological postoperative complications were studied. Transitory

complications with spontaneous favorable evolution were not studied. Complications were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. A single patient could have multiple symptoms [i.e. multiple adverse events (AE)] and each one had its own CTCAE grading.

We reported the incidence of urinary incontinence, urinary tract obstruction, febrile urinary tract infections and urinary lithiasis.

Urinary incontinence was studied in patients aged more than 5 years and was defined according to the International Children's Continence Society (ICCS) criteria. It was defined as involuntary leakage of urine. It was subdivided into continuous, intermittent, daytime incontinence and enuresis[11].

Urinary tract obstruction was reported at any level, urethra, bladder outlet, or uretero-vesical junction. The symptoms of urinary tract obstruction like retention, straining, upper tract dilatation and chronic flank pain were equally reported.

Urodynamic studies (UDS) were performed in the presence of symptoms like straining, dysuria, urinary lithiasis, repetitive urinary tract infections and incontinence, or when abnormal findings were found at ultrasounds such as increased bladder wall thickness of more than 3mm for the full bladder[12], significant post voiding residual volume (>10-15% of estimated bladder capacity)[13], and upper tract dilatation. During UDS, detrusor pressures, volume, compliance, bladder-sphincter dyssynergia, bladder over activity were evaluated. All bladder functional abnormalities like decreased compliance, bladder-sphincter dyssynergia and detrusor overactivity were grouped under "bladder dysfunction". On ultrasounds, ureteral dilatation was considered to be significant if it was symptomatic and/or if it was more than 7-8 mm. Renal pelvic dilatation was considered significant if it was symptomatic and/ or if the antero-posterior diameter was more than 10 mm with progressive increase**.** Then, we plotted

each complication versus several factors that we hypothesized they might represent “Risk factors”.

All the complications were studied according to gender, age at surgery, tumor localization, (prostate, bladder or bladder-prostate), tumor size at diagnosis, type of surgery and type of brachytherapy (LDR vs. PDR). The different surgical procedures studied were: partial prostatectomy, anterior cystectomy, mucosectomy/biopsy, posterior bladder wall dissection, trigone-bladder neck dissection and ureteral reimplantation. Then, patients with CTCAE grade 3 symptoms and higher, were analyzed in the same manner as mentioned above.

Statistical analysis:

The statistical analysis was done using univariate and multivariate logistic regression. The variables retained for the multivariate analysis are those having obtained a p value less than or equal to 0.25 in univariate analysis. The sex variable was systematically forced in the multivariate model. For multivariate analysis, a descending stepwise logistic regression was performed in order to respect the parsimony principle. The software used is Rsutdio software. (Version 1.2.1335,© 2009-2019 RStudio, Inc.)

RESULTS:

Eighty-six patients were included, 76 males and 10 females. Patients’ age at the operation ranged from 6 months to 14 years with a median age of 29 months. Median follow-up was 6.3 years (18 months-24 years). Median follow-up of the patients treated by PDR brachytherapy was 4.2 years (2-6.3 years). Patients received a median number of 6 courses (3-13) of neoadjuvant chemotherapy. Three patients received brachytherapy (20 Gy) and external beam radiotherapy (41 Gy) for nodal disease.

Patients' and treatments' characteristics are summarized in Table 1. Two patients had alveolar (FOXO1 status was not studied) and all others had embryonal RMS. At last follow-up, all patients were aged more than 7 years, 83 patients (96.5%) kept their bladder and all kept their prostate/urethra.

Thirty-one (36%) patients had been symptomatic. Of them, 9 patients were temporarily symptomatic with a spontaneous favorable evolution and the remaining 22 patients (26% of our cohort), were symptomatic at last follow-up and hence considered with permanent urological sequelae.

Symptoms:

Only one patient had a grade 4 AE, all the others had grade 3 or less AE. The repartition of AE was summarized in Table 2.

Fifteen patients (17%) had symptoms of urinary tract obstruction. Seven of them had retention, 6 patients had straining and 10 patients had an upper tract dilatation. In 7 of them, the dilatation was bilateral. The median delay of apparition of the urinary tract obstruction was 5 years (1-21 years) postoperatively.

Fourteen patients (16%) had incontinence. Twelve of them had a continuous urinary incontinence. Stress urinary incontinence was found in 2 patients. The median delay of apparition was 5 years (1-12 years) postoperatively.

Recurrent febrile urinary tract infections and urinary lithiasis were found in 5 patients (6%) respectively. The median delay of apparition of the UTI and urinary lithiasis were respectively 3 years (0-18 years) and 14 years (0-18 years) postoperatively.

Three etiologies were considered underlying urologic symptoms: bladder dysfunction, urethral stenosis and uretero-vesical junction stenosis. Fifteen patients (17%) had bladder

dysfunction. Twelve of them underwent urodynamic studies: 10 patients had a small non-compliant bladder and 2 patients had a bladder sphincter dyssynergia with normal bladder compliance. Three patients did not undergo urodynamic studies; however, they had a significant post voiding residual volume. The median age of apparition was 5 years (0-9 years) postoperatively. Seven of those patients had severe bladder dysfunction with secondary high intra-vesical pressure, resistant to conservative management (intermittent bladder catheterism) in 6. Three of those underwent bladder augmentation with enterocystoplasty. Three others had secondary renal dysfunction contra-indicating bladder augmentation and underwent a secondary total cystectomy. Six patients (7%) had urethral stenosis. Three of them had a prostatic tumor, 2 had a bladder tumor, and one had a bladder-prostate tumor. Two had an initial tumor size greater than 5 cm. The delay of apparition was 2 years (1-16 years) postoperatively.

Five patients (6%) had a uretero-vesical junction stenosis. They all had either a bladder or a bladder /prostate tumor. Initial tumor size was greater than 5 cm in 2 of them. All underwent a bilateral ureteral re-implantation. Three of them had bilateral stenosis. The median age of apparition was 3 years (2-11 years) postoperatively. Patients who had no ureteral reimplantation, did not develop any uretero-vesical junction stenosis.

When analyzing all the symptomatic patients, as seen in Table 3, posterior bladder wall dissection was associated with a higher incidence of complications with an OR= 5.15 (1.29-22.79, p=0.022). On multivariate analysis, patients who had only mucosectomy, did not develop less complications that those who had a more invasive surgical procedure with p = 0.77.

Regarding factors associated with postoperative bladder dysfunction (Table 4), patients operated on at less than 2 years were found to have significantly more bladder dysfunction on multivariate analysis. Posterior bladder wall dissection was equally associated with an

augmented risk with on multivariate analysis. Bladder neck -trigone dissection and partial prostatectomy were significantly associated with an increased risk, only on univariate analysis.

Urethral stenosis and uretero-vesical junction stenosis were not correlated with any determining factor. Both were not found in patients who had only mucosectomy. All patients with urethral stenosis had LDR brachytherapy.

Grade 3 and above complications were not correlated with any determining factor.

DISCUSSION:

In our study, the long-term urological complication rate was 26%. Symptoms consisted mainly of urinary tract obstruction and incontinence. The underlying causes of these symptoms were mainly bladder dysfunction and urethral stenosis. These complications were associated with extensive posterior bladder wall dissection (Figs. 2A and 2B) which was performed for large prostatic tumors developing higher than the level of trigone. This is to our knowledge, the first large series studying the long term outcome of a combination of BT and surgery for a conservative treatment of BP-RMS. When analyzing the IRS IV results, despite the conservative surgical approach, 9 patients (10%) underwent mutilating surgery (cystectomy/ prostatectomy/ or cystoprostatectomy). In this last study, the number of patients who received brachytherapy was not clearly specified. Out of their 88 patients, only 40% had normal functioning bladders, although urodynamic studies were performed in only one patient compared to 12 patients in our series. In their analysis, dribbling, incontinence, hydronephrosis and enuresis, were considered abnormal after the age of 10[14] whereas in our series these symptoms were regarded abnormal after the age of 5. In another study, late effects in 164 patients, survivors of a BPRMS, were analyzed in an international workshop[15]. The incidence of urinary incontinence for patients who did not have a partial cystectomy was

31%. As in our study, partial cystectomy did not increase the incidence of incontinence. In their series, the incidence of urinary incontinence for patients who had a partial cystectomy was 27%. Half of their patients had repetitive febrile urinary tract infections, compared to 6% in our series. Moreover, in our series, 77 patients were free of symptoms at last follow-up, therefore were regarded as normal. These were the lowest rates of complications reported with a bladder preservation technique. In our study, we could identify risk factors for developing complications: age less than two years at operation was a significant risk factor for developing a bladder dysfunction, which was not reported in the existing literature. This effect might be due to the brachytherapy's fibrosis effect, which could have a greater impact in young patients than in older ones. Moreover, partial prostatectomy, bladder neck- trigone dissection and posterior bladder wall dissection were also associated with a higher incidence of bladder dysfunction suggesting a combining effect of both bladder innervation injury after extensive pelvic surgeries and biologic effects of brachytherapy. Moreover, the rate of bladder dysfunction was similar between the patients who had a conservative surgery combined with brachytherapy and those who had only conservative surgery, though the follow-up period was of a median of 1 year[16]. This highlights the possibility of bladder dysfunction secondary to the tumor mass effect.

The rate of ureteric stenosis after reimplantation is low, but should question the benefits of systematic reimplantation in these patients submitted to renal impairment due to the use of Ifosfamide[17].

Regarding urethral stenosis and ureterovesical junction stenosis, we could not find any associated factors. This could be a statistical effect due to the small sample of patients with these complications.

In our study, the combination of conservative surgery with brachytherapy was associated with a low incidence of urological complications. These complications may however be

severe, sometimes leading to enterocystoplasties or cystectomies, moreover they may appear after a long follow-up. We could aim at decreasing the rate of complications by reducing the extent of surgery in the brachytherapy field. However, in our study, the advantage of this approach was not statistically significant when we compared mucosectomy vs. more extensive surgeries. The rate of complications might be also related to the size of the tumor itself, and the hypothetical chronic outlet obstruction lasting between induction chemotherapy and surgery. In our study, we could not analyze the effect of preoperative tumor size as it was not consistently available in our records. But this effect could be studied in the future and by also performing pre-operative urodynamic studies in these patients. Brachytherapy is the backbone of the conservative treatment[16]. One important next step will be to better identify dose/volume parameters associated with probability of complication, and potentially better tailored brachytherapy parameters to patients and tumor specificities, keeping in mind that recurrence is a possible drawback[18]. Recent dose/volume parameters were found predictive of rectal complication[19]. The impact of the dose to relevant anatomic structures (e.g. the bladder neck, as shown in adults) remains uncertain in children, with the difficulty that in this disease, the bladder neck is usually both an organ at risk and the target volume[20]. It should be highlighted that most patients included in this study were treated at time of low dose rate brachytherapy, with treatment planning based on radiographs. The integration of 3D imaging to guide brachytherapy delivery may lead to increase the therapeutic index with long term follow-up in these patients[21, 22].

In Conclusion, we assume it is mandatory to standardize a long-term follow-up for patients with BP-RMS, with a questionnaire[23] and systematic urodynamic studies even for asymptomatic patients as they can have a possible, although underdiagnosed, reduced bladder compliance. This approach is supported by long delay between symptoms and surgery in our study. We could also question the use of preoperative urodynamic studies, for

high-risk patients (i.e. patients younger than 2 years, with large prostatic tumors on preoperative imaging) which could help to understand the mechanism of long-term bladder dysfunction for a subgroup of procedures.

COONFLICT OF INTEREST STATEMENT: The authors have no conflict of interest to declare

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LEGENDS:

Figure 1
Peroperative view of anterior plastic tubes sutured to the bladder wall (1A)
and picture showing the catheters going through the perineum (1B).

Figure 2
Preoperative MRI, * the urinary bladder compressed by the prostatic tumor ** (2A).
Intraoperative finding, total dissection of posterior bladder wall **, posterior trigonal wall, reaching bladder neck. The rectum: *, the prostatic fossa: + (2B).