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PEDIATRIC BLADDER DYSFUNCTION (J THOMAS AND D CLAYTON, SECTION EDITORS)

Outcomes of Bladder Preservation Following Treatment for Rhabdomyosarcoma

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Abstract

Purpose of Review Genitourinary rhabdomyosarcoma (RMS) is a relatively uncommon pediatric urologic oncologic condition with significant implications for both short- and long-term bladder functions. It is important for both pediatric and adult urologists to be aware of the pathophysiology, treatment, and long-term prognosis of this tumor and its potential impact on bladder function in both pediatric and adult survivors.

Recent Findings Abnormalities in bladder function may arise secondary to surgical or medical management. Typical presenting complaints include lower urinary tract symptoms, which may be more common in pediatric RMS survivors than in survivors of other childhood cancers. Post-treatment evaluation of urinary function should include a baseline urodynamics study and an assessment of symptom severity and bother using validated, age-appropriate questionnaires. Upper tract monitoring should include renal/bladder ultrasound and serum creatinine. Hemorrhagic cystitis, which often develops acutely in patients receiving alkylating agents, may also present as a late effect. Lastly, urinary diversion may be required in patients with bladder/prostate (BP)-RMS either due to initial or delayed cystectomy or due to radiation-related loss of bladder function. Recent data suggest that diversion can maintain excellent quality of life in these patients.

Summary Both BP-RMS and its treatments have the potential for profound impacts on long-term bladder function. Most BP-RMS patients will survive beyond their initial diagnosis and treatment, and it is therefore important for both pediatric and adult urologists to be aware of the pathophysiology, treatment, and long-term prognosis of this tumor and its potential impact on bladder function in both pediatric and adult survivors.

Keywords Pediatrics · Urology · Rhabdomyosarcoma · Bladder dysfunction

Introduction

Genitourinary rhabdomyosarcoma (RMS) is a relatively uncommon pediatric urologic oncologic condition with significant implications for both short- and long-term bladder functions. Because most RMS patients will survive beyond their initial diagnosis and treatment, it is important for both pediatric and adult urologists to be aware of the pathophysiology, treatment, and long-term prognosis of this tumor and its potential impact on bladder function in both pediatric and adult survivors.

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Epidemiology

RMS is the most common soft tissue sarcoma in infants, children, and adolescents; there are approximately 350 new cases diagnosed in the USA each year. It is the third most common solid tumor in children after neuroblastoma and Wilms tumor, making up 10–15% of all solid pediatric tumors. RMS incidence follows a bimodal age pattern. The first peak, and the majority of cases, occurs in the first decade of life with peak incidence at a median of 2 years of age. The second epidemiologic peak occurs during adolescence [1••]. Nearly 75% of GU-RMS cases are diagnosed before the age of 5 years, with a roughly 3:1 male predominance [2••]. Age of diagnosis impacts prognosis independently of tumor histology; patients who are < 1 year and > 10 years old have a worse prognosis

than those between 1 and 9 years of age (event-free survival (EFS) of 53% and 51% vs. 71%, respectively) [3].

Of particular relevance to the topic of this review, the bladder and prostate are the most common genitourinary sites for RMS (BP-RMS), accounting for ~ 5% of all RMS. RMS is the most common bladder neoplasm in children under 10 years of age. The median age of children presenting with BP-RMS is 5 years [4].

Pathophysiology

RMS is a sarcoma with skeletal muscle differentiation; interestingly, RMS can arise from sites where skeletal muscle is not found. This suggests that RMS may be of primitive mesenchymal skeletal muscle origin [5]. Younger RMS patients typically have embryonal RMS, which coincidentally is the pathologic subtype found in the overwhelming majority of genitourinary RMS. In adolescent and older patients, alveolar RMS is more frequently seen.

In addition to variation by age at presentation, the histopathologic variants of RMS (embryonal, alveolar, and pleomorphic) are also associated with different patterns of primary presentation and subsequent outcomes. Embryonal RMS is the most common pathologic subtype seen in the genitourinary tract; embryonal RMS also conveys a better prognosis than other subtypes. Alveolar RMS is more often seen in the extremities and is associated with a worse prognosis [6]. Pleomorphic or undifferentiated RMS has a particularly aggressive clinical course, is rarely seen in genitourinary sites, and as such will not be further addressed in this review.

Importantly, all alveolar RMS tumors are not created equal; alveolar RMS tumors that express certain fusion proteins are associated with a significantly worse prognosis. Roughly 60% of alveolar RMS tumors express PAX3-FOXO1, ~ 20% express PAX7-FOXO1, and the remainder express neither [7, 8]. PAX3-FOXO1 expression conveys a worse prognosis than that of PAX7-FOXO1, whereas "fusion-negative" tumors that do not express these fusion proteins are similar to embryonal RMS in terms of their long-term prognosis.

Multiple syndromes are noted to carry an increased risk of RMS development. Neurofibromatosis, Li–Fraumeni syndrome, Costello syndrome, Gorlin's basal cell nevus syndrome, Rubinstein–Taybi syndrome, trisomy 21, Beckwith–Wiedemann syndrome, and fetal alcohol syndrome have all been associated with RMS [9–11].

Staging

Over time, studies of the clinical and pathologic features of RMS have progressively led to the development of uniform, international diagnostic criteria and staging systems. This approach to classifying patients with RMS can seem complicated. However, by utilizing the important factors predictive of outcome, these systems attempt to logically "stage" the patients presurgically, "group" them based on the completeness of resection, and "risk-stratify" them based on histology, stage, and group (Tables 1, 2, 3). Favorable GU sites include paratesticular and vaginal/cervical/uterine regions. Unfavorable GU sites are the bladder and prostate. The presence of distant metastases at diagnosis, involved regional lymph nodes (LNs), and large primary tumors (> 5 cm) at unfavorable sites is relatively unfavorable prognostic signs. When assessing individual patients, it is important to note that the post-surgical grouping is dependent to a large extent on the completeness of surgical excision. As the treatment of GU-RMS has evolved, more patients with bladder/prostate RMS undergo biopsy only at the initial surgical procedure, leaving gross residual disease. This results in the shifting of more patients from group I to group III. Therefore, theoretically equivalent tumors could end up in different groups, depending on the aggressiveness of the initial surgical resection. IRSG and current COG RMS studies group patients into low-, intermediate-, and high-risk groups. This risk classification combines both the clinical grouping and tumor-node-metastasis (TNM) systems with the addition of histology or fusion protein expression. The system classifies patients based on the various prognostic variables known to predict outcomes.

Prognosis

The prognostic outlook for RMS has improved significantly with time, from an estimated survival of 25% in 1970 to over 70% now [1••]. This success is due to effective multimodal, risk-adapted therapy and better supportive care. Emerging information on tumor biology has afforded new insights into the pathogenesis of this tumor and has allowed advances in risk-based management.

Unlike other GU sites, BP is considered to be an unfavorable site for RMS. As such, BP thus carries a worse prognosis than other sites and under the IRSG staging system is—at best—considered to be stage 2 before treatment. The event-free survival for BP-RMS in the IRS-IV trial was 77%; patients with locoregional (not metastatic) disease had an overall survival of 82% at 6 years. However, there are groups with particularly good prognoses after a diagnosis of BP-RMS; children with sarcoma botryoides variants (i.e., intravesical BP-RMS) have 10-year survival rates of > 90% [1••, 12].

General Treatment Paradigm

The treatment of GU-RMS has evolved away from radical surgical excision towards organ sparing approaches when possible. Once it was demonstrated that most patients would survive the disease, investigators turned towards primary chemotherapy and radiation therapy to avoid the surgical exenteration generally employed for GU-RMS. The most recent studies have thus

Table 1 Preoperative TNM and IRSG staging

TNM staging				
T stage				
T1	Confined to an anatomic site of origin			
T1a	≤ 5 cm in diameter in size			
T1b	> 5 cm in diameter in size			
T2	Extension and/or fixed to surrounding tissue			
T2a	≤ 5 cm in diameter in size			
T2b	> 5 cm in diameter in size			
N stage				
N0	Regional nodes not clinically involved			
N1	Regional nodes clinically involved by neoplasm			
Nx	Clinical status of regional nodes unknown (especially sites that preclude evaluation)			
M stage				
M0	No distant metastasis			
M1	Metastasis present			
IRSG staging				
Stage	Site	T	N	M
1	Vaginal and paratesticular	Any	Any	M0
2	Bladder/prostate	T1a/T2a (≤ 5 cm)	N0 or Nx	M0
3	Bladder/prostate	T1a/T2a (≤ 5 cm)	N1	M0
		T1b/T2b (> 5 cm)	Any	M0
4	Any	Any	Any	M1

focused on further morbidity and therapy reduction for low- and intermediate-risk RMS, while high-risk studies have instead focused on therapeutic intensification for patients who experienced poor outcomes in prior studies [1••, 2••, 9, 13]. Overall, the current mantra in RMS therapy is to increase or maintain survival and decrease late effects by avoiding local control strategies (e.g., radical cystectomy) which would result in unacceptable loss of function or form. However, as will be detailed in short order, whether this shift away from aggressive surgical management has improved patients outlook and quality of life remains controversial [2••, 14••].

Clinical Presentation and Initial Evaluation BP-RMS typically presents with hematuria, stranguria (i.e., straining with urination), urinary frequency, and/or acute urinary retention [15]. As a general rule, a preschool-aged boy with acute urinary retention should be considered to be at high risk of RMS and should be worked up accordingly. In girls with an intraluminal sarcoma botryoides RMS, the tumor may be visibly prolapsing at the urethral meatus.

On physical exam, a palpable lower abdominal mass is often present, representing the mass itself, a distended bladder, or both. Prostatic RMS in particular is typically palpable on rectal examination.

Differentiating between the bladder and prostate as the primary site of origin from which a large RMS arose can be challenging. In general, prostatic primaries are more likely to be large, solid masses. By contrast, bladder RMS primaries tend to occur as intraluminal sarcoma botryoides variants; these tumors frequently arise from the trigone or bladder neck [16]. These are general rules of thumb; however, exceptions to these rules abound.

The initial evaluation of a child with suspected BP-RMS should consist of ultrasound if an abdominal mass is not palpable. If a tumor or a distended bladder can be palpated, or if an initial ultrasound reveals a suspicious mass, then cross-sectional imaging with CT or MRI should be performed in order to determine the extent of the local tumor. In addition, these modalities can evaluate the retroperitoneum for evidence of lymphatic or distant metastatic spread.

Treatment

Initial Surgical Management

Historically, the usual treatment of BP-RMS was surgical excision via radical cystoprostatectomy or, more commonly, pelvic exenteration [17]. Beginning with the IRSG studies in the 1970s, however, chemotherapy and radiation began to supplant surgery as the mainstay of treatment. Indeed, a major goal of IRS-II (1978–1984) was to preserve a functional urinary tract. This focus has sharpened in more recent years [14••]. Currently, the major components of surgical management are an initial biopsy (ideally by endoscopic or percutaneous means), followed by

Table 2 Post-surgical clinical grouping

Group	
I	Localized disease, completely resected (microscopically negative margins), and regional nodes not involved
	Lymph node biopsy or sampling is highly advised
Ia	Confined to an organ of origin
Ib	Contiguous involvement—infiltration outside the muscle or organ of origin, as through fascial planes
II	Total gross resection with evidence of regional spread
IIa	Grossly resected tumor with microscopic residual disease, but no regional nodal involvement
IIb	Regional disease with involved nodes, but completely resected with no microscopic residual disease
IIc	Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node in the dissection
III	Incomplete resection with gross residual disease
IIIa	After biopsy only
IIIb	After gross major resection of the primary (> 50%)
IV	Distant metastatic disease present at onset

chemotherapy and/or radiotherapy, and lastly, under special circumstances, exenterative surgery.

Diagnosis of BP-RMS obviously requires a pathological review of an adequate sample of tumor tissue. Depending on the size and location of the tumor, this should be accomplished by minimally invasive means such as transurethral resection (the preferred method if feasible), percutaneous needle biopsy, or ultrasound-guided transrectal or transperineal biopsy. These methods minimize patient morbidity while also minimizing tumor spread and seeding. Occasionally, these methods are not feasible, in which case an open biopsy may be necessary via a low midline or Pfannenstiel incision; if that is needed, an attempt at lymph node sampling (such as the iliac or obturator nodes) is strongly recommended in order to improve staging accuracy.

In cases when the tumor can be completely excised with minimal morbidity—for example, in a patient with a small RMS at the dome of the bladder—then consideration should be given to partial cystectomy with wide local margins [18]. A significant advantage to this approach is that, if completed with negative margins, the patient may be able to avoid radiation and retain a relatively normal-functioning bladder. In IRS-IV, this strategy was successfully applied in a number of patients, with 13 of 17 children undergoing initial partial cystectomy having no evidence of disease at long-term follow-up. Radiation therapy was required in 10 of these patients, however, with implications for post-operative bladder function and long-term secondary malignancy risk [14••].

Table 3 Risk group classification

RMS general

Risk	Histology	Post-op group	Pre-op IRSG stage	Age
Low	Embryonal	I, II, III	1	All
	Embryonal	I, II	2, 3	All
Intermediate	Embryonal	III	2, 3	All
	Alveolar	I, II, III	1, 2, 3	All
High	Embryonal	IV	4	All
	Alveolar	IV	4	All

BP-RMS-specific risk classifications

Pre-op stage	Initial surgical approach	Post-op group	Histology	Age	Risk
2 or 3	Resection	I or II	Embryonal	All	Low
2 or 3	Resection	III	Embryonal	All	Intermediate
2 or 3	Biopsy	III	Embryonal	All	Intermediate
2 or 3	Resection	I, II, III	Alveolar	All	Intermediate
2 or 3	Biopsy	III	Alveolar	All	Intermediate
4	Resection or Biopsy	IV	Embryonal	All	High
4	Resection or Biopsy	IV	Alveolar	All	High

If the tumor is sufficiently large to obstruct the ureter(s) and/or bladder drainage, then temporary urinary diversion should be performed via a JJ ureteral stent, percutaneous nephrostomy tube, and/or a Foley catheter as appropriate [19].

Pretreatment Re-excision (PRE)

Pretreatment re-excision (PRE) is a second surgical procedure *prior to initiation of chemotherapy* with the goal of complete surgical extirpation of the tumor. As noted above, the first procedure patients with BP-RMS undergo is typically a tumor biopsy. In rare cases, PRE—often by partial cystectomy, cystectomy, or cystoprostatectomy—may be considered if a complete excision is feasible. Because the risk group is defined in part based on the prechemotherapy, post-surgical tumor burden, a successful PRE can potentially reduce the overall treatment burden for a particular patient (e.g., by reducing a patient from intermediate-risk to low-risk tumor, then the dose of chemotherapy will be reduced and radiation can be avoided altogether). Although pretreatment re-excision may be necessary in non-RMS tumors [20], this treatment is not typically employed in BP-RMS, primarily due to the fact that BP-RMS tumors are not typically amenable to an R0 resection (i.e., one that results in complete extirpation with negative margins). That said, patients who were initially managed with an unplanned or incomplete excision in whom PRE can render the patient disease-free should be considered potential candidates for this approach.

Delayed Primary Excision (DPE)

Delayed primary excision (DPE) is a second surgical procedure *after initiation of chemotherapy* with the goal of complete surgical extirpation of the tumor. In contrast to PRE, DPE does not change a patient's risk group, and for the grand majority of BP-RMS, performing DPE typically does not result in a reduction in chemotherapy nor radiation therapy dose or intensity. There are infrequent situations where DPE can be helpful (e.g., a bladder dome tumor which is initially unresectable, but becomes resectable after initiating chemotherapy) [21]. In general, however, most current protocols do not encourage the use of DPE.

Second-Look Operation (SLO)

Following chemotherapy and/or radiation therapy, residual masses may be present; management of these residual masses is controversial [22]. A second-look operation (SLO) is occasionally performed in some cases, including cystoscopy, biopsy, exploration, partial cystectomy, or even exenterative surgery such as prostatectomy or cystectomy. In IRS-IV, 53 of 88 BP-RMS patients underwent at least 1 second-look operation [14••]. Assessing the completeness of therapeutic response, however, can be quite challenging. Mature rhabdomyoblasts are frequently present on post-treatment biopsies, and these can be easily confused with active disease (particularly on frozen section biopsy). For most patients, it is the authors' opinion that the risks of performing SLO most likely outweigh the benefits. These procedures are discouraged on current COG protocols [22].

Post-treatment Bladder Function

Post-treatment bladder function is a crucial aspect of long-term patient survivorship, and urologists are uniquely positioned to provide this care. Abnormalities in bladder function may arise secondary to surgical (e.g., nerve damage, partial cystectomy) or medical management [23, 24]. Typical presenting complaints include lower urinary tract symptoms, including enuresis; the latter may be more common in children with a history of genitourinary RMS than in survivors of other childhood cancers [25]. Radiation therapy, in particular, has a particularly important role in BP-RMS algorithms. In both IRS-IV and the SIOP MMT89 protocol, higher local recurrence rates were noted in patients who did not receive radiation [14••, 26]. However, overall survival rates were similar between those who did and did not receive radiation [26]. However, radiation therapy can have a substantial impact on bladder function. In IRS-IV, 55% of survivors were reported to have "preserved" bladder function. However, this figure was determined based on a patient questionnaire only, and only 1 child underwent formal urodynamics testing [14••]. In a smaller series reported by Yeung et al., all patients who received pelvic irradiation had markedly abnormal urodynamic profiles, specifically reduced functional capacity and atypical voiding curves [25]. Among all children with BP-RMS in IRS-IV, only 40% were event-free with "normal-functioning bladders"—and as noted previously, this is likely an overestimate given the lack of formal urodynamic assessments in these children [14••].

A small series of 3 patients plus an additional 15 from the literature were combined to assess functional urinary outcomes after radical prostatectomy for RMS localized to the prostate, postulating whether bladder preservation would allow for preserved continence. Though objective data obtained via a validated questionnaire and/or urodynamics testing was not described in the review, 8 of 18 patients (44%) were identified to have persistent incontinence requiring reconstructive procedures [27, 28].

Post-treatment evaluation of urinary function should include an assessment of symptom severity and bother using validated, age-appropriate questionnaires [29]. A baseline urodynamics study, including a freestanding uroflow with ultrasound post-void residual in toilet-trained children, should be obtained. In another pediatric population at risk of bladder dysfunction (myelodysplasia), risk of damage to the upper urinary tracts has historically been defined by leak point pressures greater than 40 cmH_2O [30–32]. It is imperative to note

that these changes can be silent, as elevated pressures can be present in completely asymptomatic children. As such, abnormalities on baseline and subsequent post-RMS treatment urodynamic evaluation may direct intervention in the form of medications (anticholinergics) and/or clean intermittent catheterization.

Routine follow-up evaluations should also assess the integrity of the upper tracts, as abnormal elimination habits (whether in the storage or voiding phase or in both) may place renal units already exposed to chemotherapy and/or radiation at risk. Upper tract monitoring should include renal and bladder ultrasound to evaluate for development of hydronephrosis as well as serum creatinine and estimated GFR. Those with renal scarring and/or chronic kidney disease should also have urinalysis to assess for proteinuria. In children who demonstrate renal scarring or dysfunction, a pediatric nephrologist should be consulted. Importantly, potential long-term sequelae of the urinary tract following RMS treatment must be discussed at the outset of initiation of therapy, with routine surveillance crucial to identifying changes that may warrant intervention in order to prevent or delay bladder and ultimately renal deterioration.

Hemorrhagic Cystitis

Hemorrhagic cystitis, which often develops acutely in patients receiving chemotherapy with alkylating agents, may also present as a late effect, with a widely variable presentation [33••]. Radiation- and chemotherapy-induced cystitis is correlated histologically with local tissue hypoxia, ischemia, and necrosis. Cyclophosphamide and its metabolite acrolein are considered the classic etiologic agents, but other chemotherapeutic agents (e.g., dactinomycin and doxorubicin) may act synergistically to increase the risk of hemorrhagic cystitis [15, 34, 35]. Furthermore, agents acting to decrease the toxicity of chemotherapeutic agents (e.g., MESNA and N-acetylcysteine) do not entirely eliminate the risk of hemorrhagic cystitis. Patients receiving pelvic radiation appear to be at increased risk of hemorrhagic cystitis, particularly when doses exceed 3000 cGy for whole bladder exposure and 6000 cGy for partial bladder exposure. Doses exceeding 4500 cGy are associated with more consistent development of radiation cystitis [36]. Even when the acute presentation is successfully managed (i.e., acute hemorrhage is stopped), decreased bladder compliance may result in late effects including lower urinary tract symptoms and altered lower tract function [37].

Urinary Diversion for BP-RMS

Despite the current focus on organ preservation, urinary diversion may be required in patients with BP-RMS. This may be due either to initial or delayed cystectomy or to radiation-related loss of bladder function. Importantly, excellent quality of life is frequently maintained in BP-RMS patients with urinary diversion [38, 39].

Many authors advocate for the use of initial incontinent urinary diversion, by either ileal or colonic conduits [40], although good outcomes following an immediate orthotopic continent diversion have also been reported [18, 28]. However, initial continent urinary diversion bears a particular set of challenges: first, any post-operative complication is likely to delay chemotherapy, and continent diversion is generally accepted to have a higher complication rate than incontinent diversions [41]; second, a frozen section is unreliable at assessing the adequacy of surgical margins, implying that there is potentially an increased risk of local recurrence (as has been reported) [12, 18]; third, if local recurrence does occur, a continent diversion makes adequate treatment even more challenging than it would otherwise be [42•]; fourth, it is unknown whether post-operative quality of life is improved in children with RMS after urinary diversion or continent reconstruction, but in our anecdotal experience, parents and children both report excellent quality of life following the former; and fifth, given the age range in which BP-RMS occurs, it can be difficult to gauge whether the child and family are capable of long-term, adequate maintenance of their urinary diversion. Because of these specific challenges, many authors, ourselves included, recommend against immediate reconstruction unless further therapy is highly unlikely and both the treating center and surgeon have extensive experience with continent reconstructions.

Patients with intestinal substitutions (neobladder, conduit, or augmentation cystoplasty) are at increased risk for metabolic abnormalities (hypochloremic and hypokalemic metabolic acidosis with ileal and colon conduits), calculi, and perforation. The use of bowel in the genitourinary tract is also associated with an increased risk of development of secondary malignancies, with the risk typically increasing between 5 and 10 years after surgery [43]. Patients with urinary diversions should be assessed at least annually with upper tract imaging and labs (electrolytes, BUN, and creatinine); given the time course for the development of secondary malignancies in this population, some urologists initiate annual cystoscopy and urine cytology 5–7 years after diversion, though this has been shown to not be cost-effective nor clinically effective [44–46].

Conclusion

Both BP-RMS and its treatments have the potential for profound impacts on long-term bladder function. Most BP-RMS patients will survive beyond their initial diagnosis and treatment, and it is therefore important for both pediatric and adult urologists to be aware of the pathophysiology, treatment, and long-term prognosis of this tumor and its potential impact on bladder function in both pediatric and adult survivors.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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