FROM THE GUEST EDITORS

Nicholas G. Cost, MD
Armando J. Lorenzo, MD

It is our honor and privilege to introduce this special collection of articles focused on a few of the important current topics in pediatric and adolescent urologic oncology. The contributors have provided an excellent summary of five pertinent topics in the field and should be mandatory reading for urologists focused on caring for this population. These articles represent a collaborative effort between the Pediatric Urologic Oncology Working Group (PUOWG) of the Society of Pediatric Urology (SPU) and Dialogues in Pediatric Urology. The goal of the PUOWG is to supporting oncology initiatives, including education and research, amongst pediatric urologists.

There is clear interest in our field to have pediatric urology become more clinically involved in the oncology care of children at their local institutions. In general, being able to offer expertise on current clinical issues is the first step in this process. These five articles highlight specific topics about which pediatric urologists should be particularly knowledgeable and skillful. It is important to note that these articles are not simply focused on how to find ways for more pediatric urologists to do more oncology surgeries. Rather, the goal is education to allow for better care and improvement in outcomes for this special population of children.

We strongly encourage you to read the following series of articles and incorporate these key educational components into your fund of knowledge. Thank you again to these authors for their intelligent and thoughtful contributions, we hope that these topics will be of interest to all pediatric urologists and particularly those who are especially interested in the area of pediatric, adolescent and young adult urologic oncology.

FROM THE EDITOR

Elizabeth B. Yerkes, MD

I am excited to introduce what I hope will be a recurring Dialogues in Pediatric Urology resource from our colleagues in the Pediatric Urologic Oncology Working Group (PUOWG). As indicated by guest editors Nick Cost and Armando Lorenzo, many among us are demonstrating commitment to advancing care of children with genitourinary malignancies. Our role of caring for these children in part reflects the confidence of the medical oncology team in the level of knowledge and commitment of the pediatric urologist and their team. This relationship includes not only surgical expertise but also communication and collaboration in the care of children with urologic complications of the treatment of non-GU malignancies.

Even before the organization existed formally, the founders of PUOWG and its leadership have generously served as virtual consultants for me and for many others on our large and small oncologic dilemmas. There may be limited collective experience on some cases but the power of drawing experience together is tremendous.

For this first edition, PUOWG explores common important questions they receive from among us. These are topics where you won’t find a clear answer in a textbook or literature search or in an oncology protocol. They are contemporary questions you may contemplate, and this Edition is your PUOWG consultation. The topics lead off with the buffet of potential tools one may use in treating hemorrhagic cystitis. Next there are two timely topics on Wilms Tumor, tools for RPLND, and lastly, decision-making for rhabdomyosarcoma of the bladder and prostate.

Thank you to all of the authors for their thoughtful contributions!
Pediatric Hemorrhagic Cystitis

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Hemorrhagic cystitis (HC) is challenging consult for the pediatric urologist. The spectrum is vast, from asymptomatic microscopic hematuria, to clot retention requiring cystoscopic evacuation, and even life-threatening bleeding. Treatment depends on the severity and etiology of the HC and must be tailored to the individual patient. This review explores the epidemiology, treatment options, and urologic outcomes of HC.

Epidemiology

In the pediatric population, HC is most often seen in immunosuppressed patients after transplantation, particularly with stem cell transplant (SCT). Immunosuppressed patients typically have infectious HC, with viral or bacterial pathogens. Non-infectious causes of HC include radiation therapy and chemotherapy, most notably cyclophosphamide. Ifosfamide and busulfan have also been implicated. Graft versus host disease (GVHD), another non-infectious cause, is thought to directly attack on the urothelial cells of the bladder.

Non-infectious HC can be caused by direct damage to the urothelium, as with acrolein, the toxic metabolite of cyclophosphamide. The direct cytotoxic effects of acrolein can be attenuated by aggressive diuresis and bladder emptying1. It may also result from an immunosuppressive state allowing opportunistic infectious agents, as with radiation. Radiation therapy may deplete T cells, allowing infectious agents to flourish. Infectious HC nearly always presents in patients with immunocompromise. The most common culprit is BK virus, a human polyomavirus. Latent in most, immunosuppression allows for activation of the virus in the urothelium, typically leading to late onset HC. Delayed HC has also been associated with GVHD2,3. Other viral causes include JC virus, cytomegalovirus, and adenovirus, exerting a cytopathogenic effect on the urothelium. In addition to common uropathogenic bacteria, uncommon pathogens, such as Ureaplasma urealyticum, have been reported in a patient receiving a SCT4.

Incidence of HC in the pediatric population varies widely and differs by etiology. A retrospective review of all cases of pediatric hemorrhagic cystitis at a quaternary care cancer center observed an incidence of 1.6%. Etiologies included chemotherapy, SCT, pelvic radiation, rhabdomyosarcoma, leukemia and aplastic anemia5. Overall, incidence of pediatric HC is thought to be less than then incidence in adults with similar disease processes and treatments. This may in part be due to preventative measures. An early study of cyclophosphamide-induced HC showed a decreased incidence of HC from 6.2% to 0.5% by maintaining urine output 150 – 200 mL/hr, and voiding every hour or placing a catheter for drainage1. Many children with HC have multiple etiologies. One series found that of 285 children with HC, 74% had SCT, 83% had cyclophosphamide or ifosfamide exposure, and 55% had radiation therapy6. As such, the relative contribution of each factor may be challenging to evaluate.

Though historically rates of HC in SCT have been quoted from 10 – 70%, modern data suggest a far lower incidence7. Long-term incidence of HC in children undergoing SCT is much higher than short-term follow-up would suggest8. Of 1218 children undergoing SCT, only 44 (3.6%) developed HC within the first two months9. Four year follow-up in those patients with BK virus undergoing allogeneic SCT showed 22% developed HC10. This highlights the ability of BK virus to lay latent in urothelial cells for years, only to become activated and virulent with future immunosuppression11. Similarly, another study included 106 SCT patients of whom 26 (25.5%) developed HC and all of whom had an identifiable viral load in their urine11. Of 74 consecutive children undergoing SCT, 19% developed HC12. The rate of HC after SCT in the modern era may be somewhere around 20-25%.

Grading systems for the severity of HC have been developed for research and comparative purposes. The most common classification was proposed in 1982 by Droller and colleagues, though a simplified version was suggested a few years later by Brugieres and colleagues (Table 1)13,14. Multiple studies have looked at risk factors for increasing severity of HC. Higher grades of HC are associated with radiation, SCT, cyclophosphamide exposure, and BK virus positivity7. One study found an increased severity in older patients (age > 5), late onset of HC, positive BK urine culture, and SCT5. A smaller study found age > 6 to be a significant risk factor12. Not all centers have reached the same conclusion; one group reported that age < 8 was a risk factor9.

BK virus is highly correlated with HC. BK viremia may be associated with increased risk of HC death14. While traditionally BK urine cultures are tested in cases of HC, some evidence suggests that plasma BK viral loads may be more highly predictive of HC risk15. In one small study, plasma BK viral loads of 1,000 copies per mL had a sensitivity of 100% and a specificity of 86% for HC; where as urine BK viral loads of 100,000,000 had a sensitivity of 86% and a specificity of 60% for HC15. Conflicting data have been reported, where urine

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BK viral load was statistically significantly associated with HC and plasma viral load was not. Viral infection with BK is associated with later onset HC and should be considered even years after SCT or solid organ transplant.

Treatment Options

Treatment of HC depends on underlying etiology and severity of disease. There are no accepted guidelines of treatment for severe disease, rather a collection of techniques, each with benefits and risks. (Table 2) Ideally, HC can be prevented before it starts. Chemotherapy regimens should include mesna and hyperhydration for bladder protection when cyclophosphamide or busulfan is used for optimal preventative efforts, depending on patient clinical condition.

For mild HC, initial treatment consists of hyperhydration and forced diuresis, to flush the bladder. For children with thrombocytopenia, platelet transfusions should be given, with a goal of 50,000 platelets/mL. When viral etiology is confirmed, treatment of BK viruria is often recommended either with low dose systemic cidofovir (1mg/kg dose, once weekly) or intravesical treatment (5mg/kg in 60ml saline x 1 hour). Intravesical treatment with cidofovir may have less nephrotoxicity and other side effects. Systemic ciprofloxacin has been suggested for bacterial prophylaxis and inhibition of BK large T antigen protein synthesis, therefore halting viral replication.

In children who present with obstructive symptoms from clot retention, irrigation of the prepubertal bladder and urethra presents a challenge, with limited ability to irrigate. Bladder irrigation may be started after clot burden cleared and continued until bleeding slows. Given the small size of the pediatric urethra, a suprapubic tube may be required for irrigation as the smallest three way catheters (16 Fr) are often too large for a younger child.

Intravesical therapies may be useful at this treatment step, prior to more aggressive surgical intervention. Some authors have suggested intravesical instillation of sodium hyaluronate (120mg/50mL x 1 hr), in an attempt to reconstitute the disrupted glucosaminoglycan layer. Oral pentosan polysulfate (Elmiron) may also rebuild the glycosaminoglycan layer, though efficacy in hemorrhagic cystitis is limited. Prostaglandins have some reported success in adult series (carboprost tromethamine 0.8-1.0mg/DL x 60 min, every 6 hours), with side effects of flushing and bladder spasms. Additional agents such as E-aminocaproic acid instillations have also shown success in case reports. Intravesical tacrolimus has reported success in adults, possibly due to severe vasoconstrictive side effects. Systemic therapies such as estrogens and pentosan polysulfate have also been utilized in refractory cases. Other agents have also been suggested, including leflunomide and choreito, a formulation used in Japanese traditional Kampo medicine.

If bladder irrigation and more conservative measures are unsuccessful, cystoscopy with clot evacuation are attempted. Limited visualization with heavy bleeding may limit therapeutic success. Repeated attempts at clot evacuation and/or fulguration are often unsuccessful in a small child, with narrow caliber instruments, prompting more invasive options. Fibrin glue application to the bladder has been reportedly successful in a small series, with use of temporary ureteral stents. In adults, laser coagulation may have a high success rate in patients refractory to monopolar or bipolar cautery, especially with use of 980-nm diode green light laser.

Supravesical diversion, with percutaneous nephrostomy tubes, prevents urine and urokinase from reaching the bladder, thereby assisting in clot formation. This is the preferred approach at some institutions, as they may be placed by ultrasound at the bedside. Vescicostomy may additionally be used for bladder drainage if catheterization is poorly tolerated or maximal drainage desired. Other authors have reported a modified cystotomy approach with the “Alexis” wound retractor if traditional vescicostomy is unsuccessful or not feasible due to patient condition, such as severe anasarca.

Management for severely refractory patients, who require multiple transfusions and have persistent heavy bleeding, includes selective embolization of the inferior vesical artery. Instillation of alum (1% solution) may reduce bleeding, but systemic absorption and neurotoxicity are severe risks. Formalin instillation is generally reserved for most refractory cases, with risk of bladder fibrosis and upper tract damage if vesicoureteral reflux is missed. Cystectomy remains an option for the most severe cases, but morbidity of the procedure and urinary diversion is extremely high.

Hyperbaric oxygen treatments are effective in adult and pediatric patients, however treatment is time-consuming and may take weeks. In addition, hyperbaric oxygen treatments should not be given to patients with active malignancy or acute infection, precluding use in more severely ill patients.

Table 2: Treatment Options

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<td>Diuresis</td>
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<td>Blood and/or platelet transfusion</td>
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<td>If severe irritative symptoms, consider anticholinergics</td>
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<th>Second Line Therapy</th>
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<tr>
<td>Catheter with hand irrigation and/or continuous bladder irrigation</td>
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<tr>
<td>BK-viruria: Consider antiviral therapy</td>
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<td>Cystoscopic clot evacuation</td>
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<td>Intravesical therapy</td>
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<th>Third Line Therapy</th>
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<tr>
<td>Supravesical diversion</td>
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<td>Hyperbaric oxygen</td>
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Experimental options have been described in patients with graft versus host disease and hemorrhagic cystitis including mesenchymal stem cells and decidual stromal (placental derived) stem cells. In limited patient trials, these treatments were deemed safe, though side effects described (pneumonia, fungal infections, post-transplant lymphoproliferative disease) may limit application to pediatric hemorrhagic cystitis.

Urologic Outcomes

HC is relatively common to hematologists and oncologists, particularly after SCT, with rates of 19-30% of children undergoing hematopoietic SCT developing hematuria. As such, urology is not always consulted. At Texas Children’s

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Hemorrhagic Cystitis (continued from previous page)

Hospital, urology was consulted for about 50% of the children with HC, of which over 70% required no urologic interventions beyond catheter placement [14]. Severity of hematuria predicts urologic morbidity. One study defines “significant GU morbidity” as requiring catheter irrigation, nephrostomy tubes, or other invasive procedures; 93.3% of patients with significant urologic morbidity had grade IV HC14.

Duration of hematuria is variable. Children with more severe hematuria can expect a greater duration14. Gross hematuria may last anywhere from 2 to 82 days3,5,27. It is difficult to quantify the impact of various treatment modalities on duration of hematuria, as most are presented as cases or small series. Furthermore, duration of supportive care before initiation of therapy is variable.

Intravenous and intravesical cidofovir reportedly decreases HC duration. A series of 12 patients, 75% of whom had clots, had a median HC duration of 25 days (range 9-73), with 83% of patients resolving after 4 weeks of therapy28. In one series of early intravesical hyaluronic acid intervention in seven grade III HC patients, three of whom were pediatric, a complete response was seen in 71% of patients at a median of 12 days29. A case series of 10 patients ages 6-10 undergoing hyperbaric oxygen achieved a 70% gross hematuria resolution rate within one week30. Leflunomide is an immunosuppressive agent with antiviral activity, which, when compared to historic controls, has been demonstrated to decrease duration of symptoms in patients with BK virus-associated HC (median 12 days versus 121 days, p<0.01)31. The Japanese traditional medication choreito was shown to decrease duration of gross hematuria (median 2 days versus 11 days, p=0.004), despite the choreito group having worse hematuria prior to intervention22.

Table 3 presents hematuria duration of case reports of single patients.

Placement of indwelling bladder catheters is variable. Children with more severe HC are more likely to require a catheter14. Some centers place catheters for all patients with gross hematuria and start irrigation28. Of 17 children with catheters in one series, 12 required multiple catheter changes and 6 had three-way catheters placed for continuous bladder irrigation. Catheters remained in place from range 2-23.5 days14. Impact of HC on renal function is variable. Up to 60% of patients may experience some degree of renal failure27. Au et al. report that patients with more significant urologic morbidity had a nadir eGFR of 29.3 ml/min/1.73 m², while those without nadired at 47.0 ml/min/1.73 m², but it is unclear if this difference was significant14. The more significant the hematuria, the greater the likelihood of acute renal failure. Riachy et al. reported acute renal failure in 6.5% of patients with grade III HC and 46.7% of patients with grade IV HC. In general, they found that patients with higher grades of HC had higher serum creatinine levels1.

Hydroureterosis and bladder injury are urologic sequelae to HC. In one series, presence of hydroureterosis was not directly associated with grade of HC. Around 30% of children with HC undergoing renal ultrasound had hydroureterosis, most typically SFU 1 or 2, but 18% did have SFU 3 hydroureterosis14. A series of 97 patients found that 9.7% of patients with grade III HC and 73.3% of patients with grade IV HC had hydroureterosis on imaging. They also reported bladder necrosis in 3.2% of patients with grade III HC and 6.7% of patients with grade IV HC. Bladder perforation was only seen in patients with grade IV HC (13.3%)1.

Urinary diversion via nephrostomy tubes is occasional required for recalcitrant hematuria. The decision to divert is provider-specific, with some large series reporting nephrostomy tubes in less than 1%6 and others nearly 12%14. In a series of children with severe HC, 27.5% underwent nephrostomy tube placement. Those undergoing nephrostomy tube placement were younger and had a longer duration of HC. Resolution followed nephrostomy placement for 62.5% of the surviving patients, while 25% experienced some improvement. When diversion worked, symptoms stabilized on average after 12.4 days. Nephrostomy tubes remained in place for a mean 8.8 weeks7.

The most common surgical intervention is cystoscopy and clot evacuation, with 2-5% of patients undergoing this procedure6,12,14. One center reported a cystoscopy rate of 35%, where approximately 61% of patients with grade III HC who did not respond to non-invasive measures and all patients with grade IV were taken to the operating room. Where possible, bleeding vessels were fulgurated, but when the bleeding was more diffuse, 2% formalin was administered in the absence of bladder perforation or vesicoureteral reflux5. Selective artery embolization halted gross hematuria about two weeks after intervention for one patient35. Cystectomy has been reported for a patient with grade IV HC and bladder perforation5.

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<tr>
<th>Series</th>
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<th>HC Grade</th>
<th>HC Duration Before Intervention</th>
<th>Number of Treatments</th>
<th>Gross Hematuria Duration After Initial Treatment</th>
<th>Microhematuria Duration After Initial Treatment</th>
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<td>Isik et al. 32</td>
<td>Intravesical Hyaluronic Acid</td>
<td>III</td>
<td>40 days</td>
<td>2</td>
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<td>&gt;7 days</td>
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<td>Gökçe et al. 33</td>
<td>HBO*</td>
<td>“painful gross”</td>
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<td>Kaur et al. 34</td>
<td>HBO*</td>
<td>III</td>
<td>92</td>
<td>20</td>
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* HBO – Hyperbaric oxygen.
Hemorrhagic Cystitis (continued from previous page)

Conclusion

In conclusion, while HC is an uncommon consultation for the pediatric urologist, it occurs relatively frequently following SCT. Fortunately, prophylactic treatment with mesna and hyperhydration with frequent bladder emptying has decreased its frequency following chemotherapy. Multiple therapeutic modalities have been suggested, as presented in Table 2. Duration of gross hematuria and irritative symptoms is highly variable and depends in part on severity of HC. As patients with the worse hematuria are more likely to require intervention, prospective comparative studies are difficult. Most patients will resolve with supportive care or non- or minimally invasive therapies, but few may require nephrostomy tube placement, arterial embolization, or even cystectomy.

References

Introduction

Wilms tumor (WT) is the most common primary renal malignancy in children, accounting for approximately 7% of all pediatric cancers. Survival has dramatically improved to 90% over the past few decades as a result of clinical trials performed by multiple pediatric cancer cooperative groups. With the high rate of overall survival, focus has shifted to improving patient morbidity without adversely affecting oncologic outcomes. Classically, the open approach has been the mainstay of surgical treatment. However, since the first description of laparoscopy for WT in 2004, there has been an increasing interest in utilizing minimally-invasive surgery (MIS) for the surgical treatment of WT. In this article we discuss the current state of MIS in WT, patient selection, and technical/oncologic factors when considering laparoscopic radical nephrectomy (LRN) for a unilateral renal mass concerning for Wilms tumor.

MIS has been widely accepted today as an effective and safe approach for surgical treatment of adults and children. Compared to open surgery, MIS has been shown to decrease postoperative pain, decrease narcotic use, reduce hospital stay, and allow for quicker return to normal activities. Laparoscopy also inherently utilizes smaller incisions than a conventional open approach for WT. Long-term data has shown that scarring from childhood surgical cancer treatment has been linked with future psychological distress and reduced quality of life in pediatric cancer survivors. While MIS has been widely adopted for the surgical excision of renal tumors in adults, the use of LRN for WT has been met with some skepticism due to concerns of risking tumor rupture/spillage, inadequate lymph node sampling, and local recurrence.

Surgical Principles

Standard surgical oncologic principles for WT include clearance of all local disease, adequate lymph node sampling for staging, thorough peritoneal exploration, and avoidance of tumor spillage/rupture to prevent upstaging. The gold standard surgical approach is open transperitoneal radical nephrectomy with ipsilateral lymph node sampling. Depending on the treatment protocol, chemotherapy is given either before or after surgery. There has been controversy regarding the optimal timing of chemotherapy for unilateral WT.

Long-term data has shown that scarring from childhood surgical cancer treatment has been linked with future psychological distress and reduced quality of life in pediatric cancer survivors. While MIS has been widely adopted for the surgical excision of renal tumors in adults, the use of LRN for WT has been met with some skepticism due to concerns of risking tumor rupture/spillage, inadequate lymph node sampling, and local recurrence.

Technique

Patients are positioned in a 30-degree modified flank position. Figure 1 illustrates an example of port placement for a left-sided tu-

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Laparoscopic Nephrectomy in Wilms (continued from previous page)

mor. There is a 10 mm trocar at the umbilicus for a camera port, a 10 mm trocar at the level of a Pfannenstiel incision in the anterior axillary line, a 5 mm port approximately 2-3 fingerbreadths medial to the anterior superior iliac spine (ASIS), a 5 mm port near the xyphoid process, and a 5 mm port between the xyphoid and umbilical ports. For a right-sided tumor, the surgeon can switch the ASIS and Pfannenstiel ports to the right side. A transperitoneal approach is performed to allow for thorough laparoscopic peritoneal exploration. The standard surgical steps for a radical nephrectomy are undertaken with the exception that the kidney and tumor should be handled with the utmost care to prevent rupture. Fibrotic tumoral changes from chemotherapy may create adherences to surrounding structures such as the lumbar muscles or liver\textsuperscript{21}. Dissection of these structures should be handled with great care to avoid injuries and/or rupture. The specimen should be extracted in a bag without morcellation to allow for accurate pathologic staging. The authors suggest introducing the bag through the Pfannenstiel port with removal of the specimen through a Pfannenstiel incision to allow for a cosmetic closure.

Patient Selection

The SIOP 2016 Umbrella protocol gave criteria for indications and contraindications for LRN\textsuperscript{29}. Patients who are candidates for LRN must have unilateral, small central tumors with a rim of normal surrounding parenchyma and must undergo neoadjuvant chemotherapy. Contraindications include presence of venous thrombus, tumors that may be amenable to partial nephrectomy, are peripherally located, involve extra-renal structures, or extend beyond the ipsilateral spinous process. While not included in the SIOP Umbrella protocol, we would also include pre-operative tumor rupture as a contraindication to LRN. Burnand et al presented a series of LRN patients that utilized the SIOP criteria except for 7 patients who underwent LRN for tumors that crossed the ipsilateral spinous process\textsuperscript{19}. None of these patients had intraoperative tumor rupture and the authors suggest that in institutions with highly experienced laparoscopic surgeons, the SIOP criteria can be extended. Duarte et al recommended that masses chosen for LRN should have a largest tumor diameter of less than 10% of the patient’s height\textsuperscript{11}. Cost et al suggested that it may be clinically useful to utilize MIS exploration with a low threshold for open conversion\textsuperscript{17}.

Future Directions

One of the contraindications to LRN in the SIOP 2016 Umbrella protocol is a lack of surgeon experience in LRN\textsuperscript{19,29}. In a study utilizing a combined survey for both pediatric surgeons and pediatric urologists, Cost et al found that renal tumor (RT) surgery was low among the respondents, with approximately 50% who reported performing one to two RT surgeries annually and approximately 17% who reported performing none\textsuperscript{30}. Multiple studies across the spectrum of surgical specialties in both adult and pediatric patients have shown that higher volume surgeons have improved patient outcomes\textsuperscript{13-15}. This data suggests the need for dedicated centers of excellence for LRN. How to define a “center of excellence” for LRN in WT is still to be determined. An alternative approach may be a group of dedicated experienced LRN surgeons who would be willing to travel to other centers to add their expertise. Further studies are needed to better identify which patients with WT are best suitable to an MIS surgical excision. In addition, robotic-assisted MIS in WT has been sparsely studied, with only a few case reports presented in the literature. Studies are needed to determine whether a robotic-assisted approach would allow for improved outcomes.

Conclusion

In patients with suspected WT, laparoscopic surgical excision appears to be a safe and feasible approach with comparable oncologic outcomes as the gold standard open approach in well-selected patients. The ideal patient should have a small unilateral, centrally-located mass without evidence of locally advanced disease or tumor thrombus. Neoadjuvant chemotherapy may aid in making surgery safer and reducing the risk of tumor rupture.

References


Figure 1: Example of port placement for a left-sided laparoscopic nephrectomy. (Big circles = 10 mm ports, small circles = 5 mm ports)
Laparoscopic Nephrectomy in Wilms (continued from previous page)

32. Xia, L., Pulido, J. E., Chelluri, R. R. et al.: Hospital volume and outcomes of robot-assisted partial nephrectomy: a multicentre study. BJU Int, 121: 916, 2018
Wilms tumor is the most common pediatric renal tumor, occurring in about 650 North American children annually. The multi-institutional collaborative data collection and analysis through the National Wilms Tumor Study (NWTS), Children’s Oncology Group (COG) and SIOP has resulted in survival rates currently exceeding 90% for nonsyndromic unilateral Wilms tumor (UWT). As survival rates have durably increased, research now emphasizes the optimization of quality of life for cancer survivors. Because the mean age at sporadic UWT diagnosis is 3 years, maximizing renal function and minimizing disruption to quality of life over the long term is of obvious interest. Presently, both COG and SIOP (Societe Internationale d’Oncologie Pediatrique) protocols endorse radical nephroureterectomy with lymph node sampling as the preferred surgical procedure for UWT.

Definitive treatment for UWT typically involves a multimodal approach comprised of surgical resection, multidrug chemotherapy, and possibly radiation therapy (for positive surgical margins, intra-abdominal spill or rupture, and/or histopathologic evidence of anaplasia). Treatment is further dictated by genetic markers (e.g. loss of heterozygosity at chromosome 1p or 16q), therapeutic response, and potential development of late effects. Despite refinements in upfront and adjuvant therapies, curative treatment of UWT remains primarily surgical. Surgeons operating on UWT must prioritize patient safety, while completely resecting the primary tumor intact, sampling lymph nodes, and surveying the operative field for evidence of disease that may not have been clinically or radiographically evident before surgery (Figure 1). Not only is complete tumor extirpation and accurate disease staging necessary to identify what (if any) additional therapy is needed, but incomplete resection, tumor spill, and inadequate assessment of residual tumor burden have all been independently associated with decreased event-free and overall survival.

The safety and efficacy of nephron-sparing surgery (NSS) for the management of UWT remain controversial. NSS has been utilized most frequently in the 5-6% of children with WT who have bilateral disease (Figure 2). While adequate clinical and oncologic outcomes have been reported after NSS for BWT, there are important differences in the UWT and BWT populations. Although both are usually sporadic, BWT is more likely than UWT to occur in children with predisposing syndromes including WAGR, Denys-Drash, or Beckwith-Wiedemann; children with these syndromes also tend to develop earlier, multifocal, and recurrent tumors, and are, like all children with BWT, more likely than children with UWT to develop renal failure (10% vs 0.7%); usually attributable to nephron loss rather than direct

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Partial Nephrectomy in Unilateral Wilms (continued from previous page)

effects of the disease or treatment).\(^8,9\) The timing of tumor development as well as the quality of the non-neoplastic renal parenchyma also appear to influence renal function, since children with metachronous BWT (usually treated with initial unilateral nephroureterectomy and later NSS of the remaining renal unit) develop renal failure much more often than children with synchronous BWT (typically treated with bilateral NSS; 19.3% vs 4%).\(^10\) Finally, patients with BWT typically receive 12 weeks of upfront chemotherapy prior to surgery, whereas children with UWT treated on COG-based protocols do not.

The use of NSS in UWT has not been formally prospectively studied in any COG- or SIOP-directed clinical trial or protocol. Barriers to instituting a prospective randomized trial comparing NSS with nephroureterectomy include concerns that the risks of tumor recurrence and of NSS-related complications exceed the potential benefits. The excellent clinical outcomes achieved with current WT protocols mandate that new studies must offer potential alternative treatment options with a high likelihood of achieving oncologic control, preservation of renal function, and overall survival equivalent to or exceeding contemporary standards of care. Surgeons considering NSS for patients with nonsyndromic UWT, even as part of a theoretical clinical trial, must carefully consider whether the potential advantage of nephron preservation in a population with an excellent oncologic outcome and a very low prevalence of long-term renal failure warrants the potential risk of inadequate tumor resection, spill, or tumor recurrence, or of complications related to NSS (e.g. urine leak, bleeding, arteriovenous fistula development). Patient selection, technical considerations, surgical risks, and an understanding of late effects following treatment for WT are all key factors in making the decision for or against NSS.

Most urologists and some pediatric surgeons are well-trained in the surgical technique of partial nephrectomy. Thus, the crux of the debate surrounding NSS is not whether NSS can be performed, but whether it offers patients clear benefits above nephroureterectomy in terms of oncologic control, perioperative complications, and overall survival. In other words, do the benefits of preserving renal parenchyma exceed the potential risks of additional nonsurgical therapies and of poorer cancer control with NSS? To date, those questions have not been definitively answered. The SIOP 2001 protocol did not explicitly endorse NSS, but did permit NSS for non-central tumors provided the surgeon could achieve complete tumor resection. Sixteen-year follow up of a small series of patients undergoing NSS for UWT at a single European institution reported no disease-related deaths and only one disease recurrence, suggesting that NSS is not detrimental in at least a small cohort of patients.\(^11\) However, in SIOP, only about 3% of patients underwent successful NSS for UWT, and two-thirds of these patients had positive margins (despite routine upfront chemotherapy), necessitating adjuvant therapies beyond what they would have received with negative surgical margins.\(^12\)

While the overall complication rates in patients with UWT undergoing NSS and nephroureterectomy were similar, findings from both this SIOP study and a subset of patients from COG study AREN03B2 who underwent NSS for renal cell carcinoma\(^13\) raise concern that the surgical technique in patients undergoing NSS may be substantively different from patients undergoing nephroureterectomy. Patients undergoing NSS for UWT had markedly lower likelihood of lymph node sampling (33% in one study had no nodes sampled)\(^14\) than patients undergoing nephroureterectomy. While the optimal number and location of lymph nodes to be sampled remains to be determined, failure to sample lymph nodes clearly portends poorer overall and oncologic prognosis. Although the rationale behind intraoperative decisions is unknown and cannot be assessed retrospectively, both the decision to pursue NSS and to sample lymph nodes are surgeon-driven; thus, this difference may reflect the surgeons’ perceptions that children with tumors suitable for NSS are “healthier” and therefore at lower oncologic and/or surgical risk than patients undergoing nephroureterectomy.

Surgeon factors should not be underestimated or discounted when evaluating nonrandomized studies of children undergoing NSS. One study found that fewer than 10% of small (<550 g) UWT were amenable to NSS based on preoperative, prechemotherapy cross-sectional imaging (Figure 3).\(^15\) Histopathologic assessment of pre-chemotherapy nephrectomy specimens showed that over 75% of UWT specimens had nephrogenic rests in addition to tumor. Although rests are non-neoplastic, they increase the odds of recurrent and multifocal tumors. Only 10% of patients had truly multifocal tumors in one series,\(^16\) and of these, half had at least one-third of the renal parenchyma unaffected by tumor.

Figure 3: Although many WT are quite large at initial diagnosis, chemotherapy often shrinks tumors, increasing the proportion of masses amenable to NSS. (Image courtesy of Andrew M. Davidoff, MD)
mor; overall, 1 in 4 patients were candidates for NSS based on retrospective pathologic analysis. These findings underscore the need for surgeons to assess the feasibility of NSS both pre- and intraoperatively; radiographic assessment alone underestimated how many kidneys were candidates for NSS for BWT.17,18 Similarly, postoperative pathologic analysis does not permit assessment of the tumor in situ, meaning that the relationship between the affected kidney and surrounding structures cannot be assessed.

Published outcomes must be evaluated in light of the chemotherapeutic approach, as patients will often receive chemotherapy during the evaluation phase, and may ultimately receive therapy with or without radiotherapy. Functional outcomes in children with UWT undergoing nephroureterectomy and subsequent chemotherapy with or without radiotherapy. Functional outcomes in the small group of children undergoing NSS for UWT have not been studied in detail. After NSS for BWT, survivors may be at increased risk of hypertension (though typically not proteinuria or alterations in glomerular filtration rate (GFR) or serum creatinine).12,19,20 However, the development and persistence of hypertension is often multifactorial (and in some cases tumor-related), and that renal function may not be best assessed using serum creatinine measurements and current GFR calculations.21-24

In summary, a small minority of patients with UWT have tumors that can be completely excised with NSS. While NSS may be feasible in some patients, it has not been extensively studied with regard to functional or oncologic outcomes. Surgeons are encouraged to weigh the risks and benefits of NSS compared with nephroureterectomy, and to carefully and comprehensively counsel patients and families regarding management options and expected outcomes.

### References


### Partial Nephrectomy in Unilateral Wilms (continued from previous page)
Indications for Primary Retroperitoneal Lymph Node Dissection in Pediatric, Adolescent and Young Adult Patients with Para-Testicular and Testicular Malignancy

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Introduction

The pediatric, adolescent and young adult (PAYA) population with cancer is a vulnerable group. Compared with older adults with cancer, survival patterns differ, there are insurance coverage issues, these patients are less likely to participate in clinical trials, are more likely to experience delays in diagnosis or treatment and are more likely to suffer psychosocial problems and decreased quality of life related to their diagnosis.

Retroperitoneal lymph node dissection (RPLND) remains a standard part of surgical therapy for testicular and para-testicular malignancy. However, its use is more common in adult practice than in pediatrics. For the purposes of this review on the PAYA population, primary RPLND refers to RPLND prior to chemotherapy or radiation, whether as part of initial treatment or staging, or after relapse on active surveillance. There are 3 situations specifically that will be reviewed for the pediatric urologist: para-testicular rhabdomyosarcoma (RMS), testicular non-seminomatous germ cell tumor (NSGCT), and testicular seminoma. Discussion of RPLND efficacy compared to other treatment options, as well as side effects and complications, is outside the scope of this article.

Paratesticular rhabdomyosarcoma

All males with suspected para-testicular RMS should undergo radical inguinal orchiectomy and computed tomography (CT) scan of the abdomen and pelvis with oral and intravenous contrast for staging. Regional lymph nodes (LN) include the ipsilateral iliac and retroperitoneal nodes up to the hilum of the ipsilateral kidney. Inguinal LNs are rarely involved with a para-testicular tumor and thus are not regional LNs (i.e. they are distantly metastatic lesions). The exception is made when tumors invade the scrotum, at which point the inguinal nodes should be pathologically assessed.

For patients ≥ 10 years of age without any suspicious nodal disease on staging imaging, RPLND is unnecessary. If there are suspicious nodes, RPLND with a unilateral template with resection of any additional grossly evident intra-operative disease should be performed for complete staging. If there is extensive gross nodal involvement which is deemed unresectable, biopsy can be performed to confirm diagnosis followed by chemotherapy. However, leaving gross disease in situ has therapeutic consequences. Any nodal disease that is not completely resected, either due to biopsy or positive margin, places the patient in clinical group III, which mandates therapy intensification and adjuvant radiation.

All males >10 years should undergo staging ipsilateral RPLND, regardless of staging imaging results, due to the high rates of LN metastases. As with patients <10 years, if there is extensive and unresectable gross nodal involvement, biopsy can be performed to confirm diagnosis and the patient should be treated as clinical group III with therapy intensification and adjuvant radiation.

During staging RPLND, the area inferior to the inferior mesenteric artery contralateral to the LN dissection should be avoided to preserve sympathetic fibers and ejaculatory function (akin to modified template for testicular germ cell tumors). Nerve-sparing strategies should be employed and can be achieved by tagging exposed post-ganglionic fibers with vessel loops. Nerve fibers coexist with lumbar vessels and must be meticulously identified, travelling from behind the vena cava to anterior to the aorta. The template for RPLND in this disease, per protocols, entails a nerve-sparing approach with resection of the ipsilateral spermatic cord and all nodal tissue up to the bilateral renal veins (Figure). Open or laparoscopic techniques can be employed, but the template remains the same regardless of approach. Oncologic control is paramount and should not be compromised in lieu of minimally-invasive techniques. While full bilateral templates can be performed due to the possibility of disease spread related to crossed lymphatic drainage, this carries a significant risk of retrograde ejaculation and should be avoided unless there is suspicion of disease outside the template. Importantly in this disease process, unlike testicular cancer, the superior-most lymph node must be marked for the pathologist as this carries prognostic information.

Figure. Staging RPLND template for paratesticular rhabdomyosarcoma. For right sided tumors, the ipsilateral spermatic cord and all nodal tissue inferior to the bilateral renal arteries, medial to the bilateral ureters and superior to where the ipsilateral ureter crosses the common iliac artery is resected. Inferior to the IMA the left lateral limit is the aorta to preserve sympathetic fibers. For left sided tumors, a similar, nerve-sparing approach is applied with the exception that the right lateral limit includes only paracaval nodes superior to the inferior mesenteric artery.
Primary Retroperitoneal Lymph Node Dissection (continued from previous page)

NSGCT

When compared to prepubertal patients and the older adult population with NSGCT, there are differences in histology (high incidence of embryonal component and rare seminomas) as well as more advanced disease at presentation for adolescents. NSGCT in prepubertal males are usually pure yolk sac tumors, which rarely metastasize, and pure teratoma, which is benign in this age group. NSGCT is most common in the AYA population and generally is of mixed histology (especially with embryonal components), more frequently involves metastatic disease at presentation, and has a higher rate of relapse compared to children or older adults. Similar to adult testis cancer, there are high risk features which are associated with an increased risk of occult metastases, albeit in a small sample population. Lymphovascular invasion and ≥ 40% embryonal component in pubertal and adolescent patients with NSGCT revealed that almost 60% harbored occult metastatic disease. In this study no patients without high risk features had metastatic disease. The same high-risk features for NSGCT in the adult population confer a similar risk for harboring occult metastatic disease in the AYA population. This may lend itself to counseling points for families and perhaps future incorporation into treatment strategies, however they are currently not part of any treatment guidelines.

Individual pubertal status must be determined before discussing any treatment of testicular cancer. Traditional COG regimens have been thought to undertreat adolescents with NSGCT and may contribute to worse outcomes in adolescents relative to adults. COG protocols generally target patients aged <15 years, with most post-pubertal patients (including AYAs) being treated per adult algorithms.

In general, testicular NSGCT is the most common situation where primary RPLND is offered. In the 2018 NCCN guidelines, there are specific general principles that should be mentioned. Nerve sparing or template RPLND for primary therapy should be performed, and consideration given to referral to high volume centers. Prior to primary RPLND, cross sectional imaging (CT scan) should be obtained within 4 weeks of surgery and tumor markers verified to be normal 7-10 days prior to surgery. Primary RPLND should not be performed when tumor markers are elevated, regardless of stage.

Primary RPLND is an option for those with stage I (clinically localized, N0M0S0) NSGCT. Generally, active surveillance is preferred over primary RPLND; however, all options should be discussed. For low volume stage IIA and IIB patients there is consideration between primary RPLND and chemotherapy. Importantly, stage IIA and IIB patients being considered for RPLND must have normal post-orchiectomy (S0) tumor markers.

Patients with recurrence during active surveillance should generally be treated with chemotherapy. However, if there is low-volume retroperitoneal-only disease and the serum markers are still normal, RPLND may be offered. It is important that the specific treatment plan must be made on a case-by-case basis.

Traditional COG regimens have been thought to undertreat adolescents with NSGCT and may contribute to worse outcomes in adolescents relative to adults. COG protocols generally target patients aged < 15 years, with most post-pubertal patients (including AYAs) being treated per adult algorithms.

Metastatic seminoma

Pure seminoma, while the most common histology of testicular cancer in adult men, is rare in pediatric patients. A recent review of the National Cancer Database compared AYAs to adult counterparts and showed that AYAs were more likely to have clinical stage I disease at presentation, receive care at a high-volume institution, and undergo surveillance over adjuvant therapy. Overall survival was significantly better for AYAs, even when controlling for other factors.

Extrapolating from adult guidelines, RPLND is rarely implemented in the treatment of seminoma, primarily being reserved for patients with a residual retroperitoneal mass post-chemotherapy. There are two small series (14 patients) that have shown no recurrence for stage IIA patients treated with primary RPLND (4-7 year follow up). There is interest in exploring RPLND in seminoma and a clinical trial open investigating its role in patients age e”16 years with low volume, stage II (retroperitoneum only) seminoma (SEMS – Surgery in Early-stage Metastatic Seminoma, https://www.clinicaltrials.gov/ct2/show/NCT02537548?cond=seminoma&rank=5) which may further expand the surgical treatment options for patients with this disease.

Other Considerations

It is important to discuss fertility preservation with all patients who undergo RPLND, specifically due to the risk of retrograde ejaculation and potential future exposure to chemotherapy. All adjunctive treatment strategies beyond radical orchiectomy (chemotherapy, RPLND, radiation) are associated with potential fertility issues, either transient or permanent. A recent survey of cancer survivors ranked fertility questions as the second most common concern behind mortality. Sperm cryopreservation is the most effective method to maintain fertility potential, but this must be initiated prior to treatment. There are a host of issues surrounding cryopreservation, including young age and collection methods, anxiety associated with cancer diagnosis, and high cost of preservation. PAYA patients and their families may not immediately think of fertility to be important given a diagnosis of malignancy and the patient’s current life stage, so it is the responsibility of the provider to address this issue head on, prior to treatment initiation. Early involvement of an onco-fertility specialist can help patients and families work through issues related to sperm-harvest and banking.

PAYA patients represent a unique population for study and it is encouraged that all patients enroll in available clinical trials. More than 90% of children participate in clinical trials, while approximately 10% of teenagers and even fewer young adults participate. Providers must educate patients and families about clinical trial opportunities that exist and should work to create trials that specifically target this unique population.

Conclusion

(continued on next page)
While the indications for primary RPLND discussed herein are rare in a pediatric urology practice, there are situations where discussion and implementation of primary RPLND for PAYA patients may be indicated. Discussion between oncology and urology, perhaps involving adult urologic oncologists as necessary, is imperative in the decision to offer and then pursue primary RPLND.

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Introduction

Rhabdomyosarcoma (RMS) is the most common soft tissue sarcoma in infants, children, and adolescents; there are approximately 350 new cases diagnosed in the United States each year. The median age of children presenting with bladder and prostate rhabdomyosarcoma (BP-RMS) is 5 years. Bladder and prostate are the most common genitourinary sites, accounting for ~5% of all RMS.

Over time, study of the clinical and pathologic features of RMS have progressively led to the development of uniform, international diagnostic criteria and staging systems. This system utilizes the factors predictive of outcome to “stage” the patients pre-surgically, “group” them based on completeness of resection, and “risk-stratify” them based on histology, stage, and group. 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.

The prognostic outlook for RMS has improved significantly with time, from an estimated survival of 25% in 1970 to over 70% now, mainly due to effective multimodal, risk-adapted therapy, and better supportive care. 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 disease

Table I - Pre-operative TNM and IRSG Staging

<table>
<thead>
<tr>
<th>T-stage</th>
<th>N-stage</th>
<th>M-stage</th>
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<tbody>
<tr>
<td>T1 Confined to anatomic site of origin</td>
<td>N1 Regional nodes clinically involved</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td>T1a ≤5cm in diameter in size</td>
<td>N0 Regional nodes not clinically involved</td>
<td>M1 Metastasis Present</td>
</tr>
<tr>
<td>T1b &gt;5cm in diameter in size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 Extension and/or fixed to surrounding tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a ≤5cm in diameter in size</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b &gt;5cm in diameter in size</td>
<td></td>
<td></td>
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<tr>
<td>N-stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0 Regional nodes not clinically involved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N1 Regional nodes clinically involved by neoplasm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nx Clinical status of regional nodes unknown (especially sites that preclude evaluation)</td>
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<table>
<thead>
<tr>
<th>Stage</th>
<th>Site</th>
<th>T</th>
<th>N</th>
<th>M</th>
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<tbody>
<tr>
<td>1</td>
<td>Vaginal and Paratesticular</td>
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<td>Any</td>
<td>M0</td>
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<td>2</td>
<td>Bladder/Prostate</td>
<td>T1a/T2a (≤5cm)</td>
<td>N0 or Nx</td>
<td>M0</td>
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<tr>
<td>3</td>
<td>Bladder/Prostate</td>
<td>T1a/T2a (≤5cm)</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>OR T1b/T2b (&gt;5cm)</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
</tr>
<tr>
<td>4</td>
<td>Any</td>
<td>Any</td>
<td>Any</td>
<td>M1</td>
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(continued on next page)
Bladder Preservation  *(continued from previous page)*

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 a sarcoma botryoides variants (i.e., intravesical BP-RMS) have 10-year survival rates of >90%.2,3

**General Treatment Paradigm**

**Initial Surgical Management**

Historically, the usual treatment of BP-RMS was surgical excision via radical cystoprostatectomy or pelvic exenteration.4 Beginning with the IRSG studies in the 1970s, 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.5 Currently, the major components of surgical management are an initial biopsy (ideally by endoscopic or percutaneous means), followed by chemotherapy and/or radiotherapy, and lastly, under special circumstances, exenterative surgery.

Diagnosis of BP-RMS obviously requires 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.6 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 postoperative bladder function and long-term secondary malignancy risk.5

**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 risk group is defined in part based on the pre-chemotherapy, 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,7 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 as potential candidates for this approach.

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<th>Group</th>
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<td>I</td>
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<td>Iic</td>
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<td>III</td>
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<tr>
<td>IIIa</td>
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<tr>
<td>IIIb</td>
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<tr>
<td>IV</td>
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</table>
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 which becomes resectable after initiating chemotherapy). 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. 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. 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.

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. 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. 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. Overall survival rates were similar between those who did and did not receive radiation. 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 patient questionnaire only, and only 1 child underwent formal urodynamics testing. 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. Among all children with BP-RMS in IRS-IV, only 40% were

Table III – Risk Group Classification

<table>
<thead>
<tr>
<th>IIa. RMS General</th>
<th>Histology</th>
<th>Post-Op Group</th>
<th>Pre-Op IRSG Stage</th>
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<td>I, II</td>
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<td>All</td>
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<tr>
<td>Intermediate</td>
<td>Embryonal</td>
<td>III</td>
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<td>Alveolar</td>
<td>I, II, III</td>
<td>1, 2, 3</td>
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<tr>
<td>High</td>
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<td>All</td>
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<tr>
<td></td>
<td>Alveolar</td>
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<td>All</td>
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</table>

<table>
<thead>
<tr>
<th>IIIb. BP-RMS Specific Risk Classifications</th>
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<tbody>
<tr>
<td>Pre-Op Stage</td>
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<td>--------------</td>
</tr>
<tr>
<td>2 or 3</td>
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<td>2 or 3</td>
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<tr>
<td>4</td>
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Bladder Preservation (continued from previous page)

event-free with “normal functioning bladders” – and as noted previ-
ously, this is likely an overestimate given the lack of formal urodynamic
assessments in these children.5

A small series of 3 patients plus an additional 15 from the litera-
ture 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 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 pro-
cedures.14,15

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. However, excellent quality of life can be restored to these
patients.16

Many authors advocate for the use of initial incontinent urinary
diversion, either by ileal or colonic conduits,17 although good outcomes
following an immediate orthotopic continent diversion have also been
reported.5,15 Initial continent urinary diversion bears a particular set of
challenges, however: first, any postoperative complication is likely to
delay chemotherapy, and continent diversion is generally accepted to
have a higher complication rate than incontinent diversions;16 second,
frozen section is unreliable at assessing the adequacy of surgical mar-
ters, including cystoprostatectomy. Careful patient selection is cru-
cially important, and further research is required to help define exactly
which patients will require aggressive surgery.

Conclusion

Most BP-RMS patients will survive beyond their initial diagnosis
and treatment, and most do well with organ-sparing approaches. How-
ever, an important minority will benefit from more aggressive exci-
sions, including cystoprostatectomy. Careful patient selection is cru-
cially important, and further research is required to help define exactly
which patients will require aggressive surgery.

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“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 experi-

cences parents and children

both report excellent quality

of life following the former;

..... given the age range in

which BP-RMS occurs, it

can be difficult to gauge whether

the child and/or family are

capable of long-term, ade-

quate maintenance of their

urinary diversion.”