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An Update on Current Treatment Options for Pediatric Genitourinary Tract Tumors

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Opinion statement

Most of the success and advances made in the care of children with genitourinary (GU) cancer over the last 50 years are thanks in large part to the efforts of the cooperative pediatric oncology groups both in North America and Europe. Currently, children with tumors of the kidney, bladder, prostate, and testis/para-testis largely enjoy a good prognosis thanks to the outstanding research into these relatively rare diseases. Evidence-based and protocol-driven care has resulted in outstanding rates of cure. The future of the care for these children with GU malignancy is to preserve these outcomes while minimizing the morbidity of therapy. One area of great interest across these entities is risk stratification which holds the potential to reduce the burden of therapy in those who can afford to do so and reserve more aggressive treatments for those with risk factors for poor prognosis. From a surgical standpoint, there is an increasing interest in reducing morbidity as well. For renal tumors, this includes nephron-sparing and minimally invasive surgery when possible. For bladder and prostate tumors, there is an increasing emphasis on organ preservation and non-exenterative surgery. Regardless of these surgical advances, the future of pediatric GU cancer therapy likely rests more in tumor-biology-driven risk stratification and personalized therapy. Thus, from a surgical standpoint, there is motivation for surgeons to think beyond just the surgery and to be involved and be knowledgeable about all of the multidisciplinary aspects of pediatric cancer care.

Introduction

Pediatric genitourinary (GU) malignancies account for 6 to 7 % of all childhood cancers [1]. The primary focus of this review is to update the readership on recent developments in the realm of pediatric GU tumors and secondarily, to briefly review current management strategies for the most common pediatric tumors of the GU system. We have reviewed the recent literature from the last 3 years (2012–2015) specifically in the areas of pediatric renal and testicular malignancies and pelvic rhabdomyosarcoma. The aim was to focus on the care for pediatric GU tumors and discuss novel surgical techniques, trends for risk stratification, and genetic factors implicated in the development of these tumors, as well as controversies that exist in this evolving area. It should be noted that most of the management discussed in this review is based on the general approach of the Children's Oncology Group (COG).

Pediatric renal tumors

Wilms tumor (WT) is the most common solid renal malignancy in children [2]. Among all WT, synchronous bilateral Wilms tumor (bWT) accounts for 5 % of diagnoses [3]. The current standard of care for a unilateral Wilms tumor (uWT) is an open total nephrectomy (TN) with regional lymph node sampling, utilizing a trans-peritoneal approach [4]. Nephron-sparing surgery (NSS) following pre-surgical chemotherapy is recognized as standard in bWT, due to the importance of renal parenchymal preservation [5, 6]; however, its use in non-syndromic uWT is debated. A recent retrospective study of NSS versus TN for uWT observed that overall survival and local relapse rate were apparently equivalent between NSS and TN, in a carefully selected group of patients [7•]. Pertinent to the issue of renal function in these patients, a separate review of non-syndromic, stage-matched patients with uWT treated with NSS and TN, investigated the impact on estimated glomerular filtration rate (eGFR) and observed that NSS enabled superior renal function preservation compared to TN [8]. In an additional study of uWT patients with predisposing syndromes who underwent NSS, Romão et al. noted that no such patients suffered postoperative renal impairment and two thirds of patients experienced an increase in eGFR after NSS [9]. However, one major limitation of these studies of NSS in uWT is the low numbers of cases involved. In an effort to address this limitation, Wang et al. retrospectively reviewed an administrative database of 1832 patients who had undergone WT resection. While only 6.2 % of the patients studied had been managed with NSS, this review also demonstrated no significant difference in overall and disease-specific survival between NSS and TN [10]. It should be mentioned that each of these studies of NSS in uWT are highly biased towards lower-stage and smaller tumors. Thus, given the extremely good outcomes in uWT with the currently accepted general COG paradigm of TN followed by adjuvant chemotherapy, outside of a clinical trial setting, the use of NSS for non-syndromic uWT must be considered experimental.

The other major surgical development in the treatment of WT is the use of minimally invasive surgery (MIS). In prior studies, the use of MIS for WT has not been specifically included in the large cooperative group protocols. Therefore, the existing, published studies include only small numbers, and the literature lacks any prospective, randomized data to clearly define the optimal role of MIS in this clinical setting. A recent retrospective analysis from the International Society of Pediatric Oncology (SIOP) investigating the use of MIS (at the individual treating surgeon's discretion) for uWT found comparable outcomes compared to open surgery, but that in general, there was inadequate lymph node sampling [11]. Importantly, these were all MIS nephrectomies done after pre-surgical chemotherapy as is standard under SIOP protocols. Another study of MIS reported equivalent oncological outcomes and concluded that MIS could be an alternative to open surgery in selected WT cases with small tumors that were otherwise not amenable to NSS [12]. These authors also raised concerns about the adequacy of lymph node sampling with an MIS approach. One other development in this area was a recent case report of a robotic-assisted laparoscopic approach to a pre-chemotherapy TN for uWT, and these authors again highlighted the need for careful patient selection in MIS (for example, small, more central tumors with low risk of spill), maintaining a low threshold for open conversion and that specifically a robotic-assisted technique may afford more fine motor control during lymph node dissection [13].

Risk stratification in WT varies between the Children's Oncology Group's (COG) upfront nephrectomy and SIOP's post-chemotherapy nephrectomy approach. The COG risk stratification for WT includes patient age, tumor weight, stage, histology, loss of heterozygosity (LOH) at chromosomes 1p and 16q, and lung nodule response to the first 6 weeks of chemotherapy. On the other hand, SIOP risk stratification includes stage, histology, response to preoperative chemotherapy, and tumor volume [14]. Recent studies of cytogenetic aberrations influencing outcome of WT patients have been reported. Segers et al. compared follow-up data from WT patients with tumor cytogenetic analysis and found that gain of 1q with significantly associated with 16q and 1p loss. Their key finding was that 1q gain was independently associated with adverse event-free survival and overall survival [15]. Gratias et al. observed a similar relationship between gain of 1q and 1p/16q loss and found that patients' event-free survival at 8 years was significantly less for those with 1q gain. In addition, 1q gain was found to significantly increase the risk of disease recurrence, but disease stage was not found to be correlated with 1q gain [16•]. Incorporation of the gain of 1q into risk stratification protocols is likely if current trials confirm significance since gain of 1q affects up to one third of favorable histology WT patients as opposed to LOH at 1p/16q which is only involved in approximately 5 % of such cases.

In general, it is important to note the relative advantages to risk stratification between the COG and SIOP approaches. In the setting of pre-chemotherapy nephrectomy, COG stratification relies more heavily on analyzing the tumor biology which is unadulterated by chemotherapy. Conversely, the SIOP approach allows for a clinical assessment of

the tumor response to chemotherapy during the first 4 to 6 weeks prior to nephrectomy. Regardless, prior studies comparing outcomes between the two approaches demonstrate near equivalence.

Pediatric testicular tumors

Testicular tumors account for 2 % of all pediatric solid tumors and have an annual incidence of 0.5 to 2 cases per 100,000 boys [17]. A bimodal peak of age distribution exists with an early period in the first 2 years of life and another increase in adolescence and young adulthood [18]. Testicular tumors in prepubertal patients are most commonly benign, in contrast to those in adolescents and adults [19]. The role of testis-sparing surgery (TSS) as opposed to radical orchiectomy, in prepubertal males, can allow for Leydig and seminiferous cell preservation thus preserving necessary hormonal production and later fertility [17]. The recent literature on this topic is mostly from adult studies; Gentile et al. undertook a prospective study looking at testis-sparing surgery, with no disease recurrence in their small population, and concluded that in small masses, it may be safe to perform [20]. Shilo et al. undertook TSS only after intraoperative frozen section and if the tumor was found to be benign. These authors concluded that two thirds of tumors <25 mm were benign and would advocate TSS in small benign lesions [21]. A recent review on TSS in children and adolescents concluded that for prepubescent boys with a normal serum alpha-fetoprotein (AFP), TSS could be considered in most all tumor regardless of size; however, in adolescent boys, TSS may be considered in non-palpable masses (<25 mm) with normal preoperative serum tumor markers [22].

Surveillance and outcomes after initial orchiectomy for testicular germ cell tumors (T-GCTs) of pediatric and adolescent males has been an area of interest in recent published studies. Rescorla et al. reviewed the recent COG experience with pathologic prognostic factors in boys with stage I malignant T-GCTs. These authors observed that the overall survival is excellent in this group but that lymphovascular invasion (LVI) was an adverse prognostic indicator in all age groups and specifically that adolescents had lower event-free survival when LVI was present in the orchiectomy specimen [23•]. On this same topic, Cost et al. reviewed an institutional experience with stage I pubertal and adolescent patients with T-GCTs and noted that risk factors of +LVI or >40 % embryonal carcinoma in the orchiectomy specimen increased the risk of occult metastatic disease, similar to reports in adults with stage I testicular non-seminoma [24]. While adolescents with stage I T-GCTs appear more likely to suffer relapse, there is also concern that those adolescents of all stages experience worse outcomes. A recent retrospective review by Cost et al. compared outcomes of pediatric, adolescent, and adult patients with T-GCT and demonstrated that, after controlling for stage and risk, adolescent patients suffered lower event-free survival compared to either pre-pubertal children or older adults [25•]. The driver of this outcome disparity remains unclear. Another retrospective analysis of survival rates of pediatric T-GCTs found that in such patients with

testicular yolk sac tumors, survival rates were not significantly different whether retroperitoneal lymph node dissection (RPLND) was performed or not [26]. In general, there appears to be much less need for RPLND in pre-pubertal T-GCT compared to adolescents or adults likely due to the predominance of pure yolk sac histology and its exquisite sensitive to systemic chemotherapy.

Pediatric genitourinary rhabdomyosarcoma

Rhabdomyosarcoma (RMS) is the most common soft tissue tumor in childhood and accounts for 2.9 % of all pediatric malignancy [27]. RMS demonstrates a male predominance (1.5:1) and is thought to arise from primitive mesenchymal cells which maintain potential to differentiate into the skeletal muscle. Genitourinary (GU) RMS makes up approximately one quarter of all new RMS diagnoses. In general, there is a bimodal age distribution in RMS and within GU-RMS, and in terms of primary location, three-quarters of bladder and prostate RMS occur in children under 5 years old whereas paratesticular RMS is most common in older adolescents [28]. Risk stratification for RMS is based on the TNM pretreatment staging system and an assigned clinical grouping after the primary surgical procedure which is based on the extent of residual tumor after surgery and regional lymph node involvement [29]. The disease group and stage are closely tied to future prognosis (Table 1).

Tumor biology is also used to stratify risk, and histologically RMS has historically been divided into an embryonal subtype (ERMS) or alveolar subtype (ARMS). ARMS patients generally have a worse prognosis than ERMS patients [30] and if any portion of the tumor specimen demonstrates ARMS histology, this is considered sufficient evidence for a diagnosis of ARMS [31]. Patient age at diagnosis is also an important consideration for risk stratification; patients under 10 years of age are more likely to have the EMRS subtype and those 10 years of age or older are more likely to have the ARMS subtype [32]. In "extremes" of age, older children (≥10 years of age) and infants (<1 year of age), patients experience worse outcomes [33, 34]. The combined staging, disease group, and age at diagnosis are used to stratify RMS patients into low-, intermediate-, or high-risk groups [27]. Table 2 highlights this risk-grouping and the impact on outcomes.

Table 1. Intergroup rhabdomyosarcoma study group 3-year failure-free survival rates based on RMS group and stage [29]

Group	% Survival	Stage	% Survival
I	83	I	86
II	86	II	80
III	73	III	68
IV (metastatic)	<30		

Table 2. Children's Oncology Group RMS risk groupings and long-term event-free survival [35, 36]

Risk group	Stage	Group	Histology	Long-term EFS (%)
Low-subset A	1	I–II	ERMS	85–95
	2	I–II	ERMS	
Low-subset B	1	III	ERMS	70–85
	3	I–II	ERMS	
Intermediate	2–3	III	ERMS	73
	1–3	I–III	ARMS	65
High	4	IV	ERMS	35
	4	IV	ARMS	15

Current management strategy for paratesticular RMS involves radical inguinal orchiectomy at diagnosis. Children under 10 years old without demonstrable retroperitoneal disease on cross-sectional imaging do not require a staging, ipsilateral-template retroperitoneal lymph node dissection (RPLND); however, children ≥10 years old should undergo RPLND before starting adjuvant chemotherapy as dictated by the disease stage, group, and risk. In contrast, patients with bladder/prostate RMS generally undergo biopsy rather than excision of tumor, as a primary approach, followed by vincristine, actinomycin-d, and cyclophosphamide (VAC) chemotherapy. Radiation therapy is generally required for residual disease [37]. Such an approach is generally preferred because of an emphasis on organ preservation and the extent of radical surgery that would be needed to achieve a complete excision in these pelvic primary locations.

One recent study [38] looked specifically at outcome after conservative management of bladder and prostate RMS. Conservative surgery was defined as achieving local control of the tumor with preservation of bladder function. The patients studied all had localized, non-metastatic tumors, and were either treated with primary surgery or secondary surgery after assessing an initial response to systemic chemotherapy. The observed 5-year overall survival was 77 % and event-free survival 63 %. These data confirm the general paradigm of avoiding highly morbid exenterative surgery due to the sensitivity of RMS to chemotherapy and radiation.

Genetic risk stratification in RMS may be the most substantial contribution in the future to facilitate targeted approaches to therapy. Positive PAX3/FOXO1 fusion gene status in RMS has been significantly associated with poorer outcome in non-metastatic cases when compared with fusion-negative and PAX7/FOXO1-positive patients. When this gene status was incorporated into a risk-stratification scoring system, along with age and TNM status, it significantly outperformed the existing model [39]. However, not all cases of ARMS or ERMS demonstrate expression of these genes and up to 25 % of ARMS cases do not demonstrate gene fusion. ERMS patients may not demonstrate gene fusion but instead, show highly variable karyotypes and loss of

heterozygosity at chromosome 11p15.5 [40]. Regardless, the future of a tailored therapeutic approach in RMS will be based on individual patient and tumor biology and the current emphasis on less precise factors such as tumor size and histopathology will likely give way to more complex diagnostic markers.

Conclusion

Pediatric genitourinary tumors encompass a broad spectrum of disease. Advances in surgical techniques aim to maintain and improve current oncologic outcomes while seeking to decrease therapeutic morbidity. However, the future of therapy likely rests less in surgical advancement but in tumor-biology-driven risk stratification and personalized therapy.

Compliance with ethical standards

Conflict of interest
Katie E. Brodie and Nicholas G. Cost 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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