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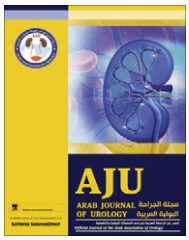

PEDIATRIC UROLOGY

REVIEW

The surgical management of paediatric bladder and prostate rhabdomyosarcoma

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KEYWORDS

Rhabdomyosarcoma;
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ABBREVIATIONS

B/P, bladder/prostate; RMS, rhabdomyosarcoma; EFS, event-free survival; OS, overall survival; COG, Children's Oncology Group; SIOP, International Society of Paediatric Oncology; FDG-PET, F-18

Abstract ***Background:*** The surgical management of paediatric bladder/prostate rhabdomyosarcoma (B/P RMS) continues to develop, with the goal of maximising organ preservation while achieving successful cancer control. The timing of radiotherapy and surgical excision to improve event-free survival (EFS) and overall survival (OS) remains controversial.

Methods: Previous reports in English on B/P RMS over the past 15 years were identified and reviewed, focusing on studies comparing the effects of radiotherapy and surgery for local control, the effect of local control on OS, and improved means of diagnosing viable tumour after chemotherapy.

Results: The concept of lowering the 'cost of cure' drives current protocols. Bladder-sparing surgery is possible for 80% of patients after initial chemotherapy, with a mean 5-year OS of 85%. Overall, half of the patients are continent of urine, and adding radiotherapy might increase the risk of incontinence. Previous studies suggesting that early radiotherapy achieved better EFS than delayed radiotherapy did not control for stage and size of the tumour, which are the primary determinants of EFS. Improved local control does not automatically translate into improved OS.

Conclusions: The current role for the surgical management in B/P RMS is to achieve local control of tumours that do not respond to chemotherapy and

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fluorodeoxyglucose positron-emission tomography; VAC, vincristine, dactinomycin and cyclophosphamide; IVA, ifosfomide; VAIA, IVA with or without an anthracycline; IRSG, Intergroup Rhabdomyosarcoma Study Group

radiotherapy. An improved means of detecting viable tumour after initial chemotherapy would improve the ability to decide when local therapy is necessary. The continuing challenge for urologists managing these children is knowing when bladder-sparing surgery would be the best therapy.

Introduction

The treatment of bladder and prostate rhabdomyosarcoma (B/P RMS) in children continues to develop away from radical cystectomy or prostatectomy to a combination of biopsy, chemotherapy, radiotherapy and/or surgical resection. The timing and method of local control continues to be controversial, as the side-effects of surgical excision or radiotherapy in the pelvis of the young child can have devastating effects on urinary continence and sexual function later in life. While the chemotherapy regimens for B/P RMS achieve good overall survival (OS) and event-free survival (EFS) rates, the ability to determine whether a residual mass that remains after chemotherapy and radiotherapy represents tumour remains a major problem. The pathological interpretation of RMS treated with radiotherapy is extremely difficult [1]. Therefore, a residual mass can subject patients to more local therapy than is necessary, whereas in other cases, a prolonged delay in local treatment can result in death.

There has been a philosophical difference between Children's Oncology Group (COG) studies which emphasised improved EFS by using early radiotherapy, and International Society of Paediatric Oncology (SIOP) MMT studies, which accepted more secondary chemotherapy and radiotherapy to minimise the late effects from surgery and radiation. While the OS rate was similar for B/P RMS between these approaches (86% for COG vs. 80% for SIOP), the EFS was markedly worse (79% for COG vs. 64% for SIOP) using the SIOP approach [2]. These findings have been questioned by recent data analysing the effect of stage and size of the tumour on EFS [3], suggesting that the COG and SIOP approaches achieve equivalent EFS when tumours are appropriately matched.

The current controversies in managing B/P RMS lie in the timing and order of surgical or radiotherapy treatment of residual disease after initial chemotherapy, and the method for determining if a residual mass after chemotherapy and radiotherapy is a viable tumour or stroma. This review analyses the current reports to determine if one approach is clearly superior.

Methods

Reports in English on B/P RMS were reviewed for articles published within the past 15 years, focusing on those comparing the effects of radiotherapy and surgery for local control, the effect of local control on OS, and radiographic means of detecting viable tumour after therapy.

Diagnosis

About 20% of RMS arises from the genitourinary tract, affecting children aged 2–4 and 15–19 years old [4]. RMS is a small blue-cell tumour with spindle cells, resembling skeletal muscle. Embryonal histology accounts for 90% of genitourinary RMS, and has a more favourable prognosis (82% 5-year EFS) than alveolar pathology (65% 5-year EFS) [5]. RMS is an unencapsulated tumour, requiring a wide margin of resection to achieve cure. Within the bladder, it forms sarcoma boytroides, which resembles a bunch of grapes, and usually arises from the trigone [4]. One of the problems in the pathological evaluation of RMS is the development of mature rhabdomyoblasts, which indicate a response to chemotherapy. They have a questionable malignant potential, so the choice of whether to observe with imaging vs. partial cystectomy depends on whether the bladder could be preserved during resection [6–8]. An age at presentation of <1 and >10 years is associated with a worse EFS (53% and 51%) than for patients aged 1–9 years (71%) [9].

B/P RMS presents with symptoms of gross haematuria, difficulty in voiding, urinary retention, or urgency. Ultrasonography of the bladder is used to make the diagnosis, and is followed by CT or MRI of the abdomen and pelvis to determine the extent of the tumour [4,8]. It is unusual to be able to completely resect the tumour while maintaining adequate bladder capacity. In most cases a biopsy is the initial procedure, which can be carried out cystoscopically, perineally or suprapubically. If the initial biopsy is done through an abdominal incision there is no need to remove lymph nodes unless

Table 1 TNM staging of RMS.

Staging	Definition
T1	Confined to organ of origin: (a) ⩽5 cm, (b) > 5 cm
T2	Extension to surrounding tissue: (a) ⩽5 cm, (b) > 5 cm
N0	Regional nodes clinically negative
N1	Regional nodes clinically positive
Nx	Unknown
M0	No distant metastasis
M1	Metastasis present
SIOP staging	
Stage I	T1, N0, M0
Stage II	T2, N0, M0
Stage III	T1 or T2, N1, M0
Stage IV	T1 or T2, N1, M1
COG staging and grouping	
Stage 1	Favourable site, N0
Stage 2	Unfavourable site, ⩽5 cm, N0, M0
Stage 3	Unfavourable site, > 5 cm or N1, M0
Stage 4	Any site, M1
Group 1	Completely excised local disease, no microscopic residual
A	Confined to organ of origin
B	Infiltrating to adjacent organ
Group II	Total gross resection
A	Microscopic local residual
B	Regional lymph nodes positive, no microscopic residual
C	Microscopic residual disease
Group III	Incomplete resection (> 50% of tumour remains) or biopsy only
Group IV	Distant metastasis

they are enlarged on CT or MRI. CT of the chest to look for lung metastases, a bone scan, bone marrow aspirate and biopsy complete the metastatic evaluation [4]. The use of F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) is optional in the current COG protocol, and it is hoped that it will perform better than a bone scan and offer additional information about the biological activity of the residual tumour [10].

Staging systems vary between the COG and SIOP [4,11]. Both use a TNM system (Table 1) but the COG also assigns patients to low-, intermediate- and high-risk groups. B/P RMS always falls into the intermediate-risk group, as the bladder and prostate are unfavourable genitourinary sites, and most patients have gross residual disease after initial biopsy, which places them into COG Group III [4]. This difference in the clinical staging systems has made direct comparisons of COG and SIOP studies challenging, and it can be argued that placing all patients with B/P RMS into the Group III category might make the interpretation of chemotherapy and radiotherapy effects on small (⩽5 cm) tumours vs. large (> 5 cm) tumours more difficult to detect.

Chemotherapy

The COG uses vincristine, dactinomycin and cyclophosphamide (VAC) as the standard chemotherapy regimen, whereas SIOP studies use ifosfomide (IVA) with or without an anthracycline (VAIA). In the current COG protocol, five cycles of chemotherapy (15 weeks) are given, radiographic re-staging is carried out, followed by another five cycles (30 weeks), another re-staging, followed by the final four cycles of chemotherapy (43 weeks). Progression of disease during chemotherapy allows patients to receive off-protocol treatment [10].

History of treatment

North America

The initial treatment of B/P RMS was radical surgical excision followed by chemotherapy, which achieved a 78% OS rate [12]. Beginning in the 1970s, studies by the Intergroup Rhabdomyosarcoma Study Group (IRSG, the precursor to the COG) and SIOP focused on the use of chemotherapy and radiotherapy as a means of avoiding radical surgical excision and maintaining bladder function. Primary chemotherapy before surgical excision or radiotherapy at 16 weeks maintained a 70% OS rate in IRS-II, but the bladder preservation rate remained at 22% and most disappointingly, the EFS rate decreased from 70% to 52% [12]. The radiotherapy dosing was initially 25 Gy, but was increased during the course of the trial to 40–45 Gy, due to a poor clinical response [12]. There was an improvement in the bladder preservation rate to 60% by intensified chemotherapy in IRS-III for stage III tumours. Radiotherapy was moved back to 20 weeks [13]. IRS-IV showed an improved 3-year EFS rate (72–92%) in genitourinary non-B/P sites with intensified cyclophosphamide dosing, but there was no improvement in B/P patients, who continued to have an EFS rate of 75%. IRS-IV compared hyperfractionated and conventional radiotherapy, starting at 9 weeks. A total of 50–59 Gy was delivered, and no difference was found between the methods of radiotherapy delivery [14–16].

Europe

The German CWS-86 study used VAIA as the main chemotherapy regimen, and adjusted the radiotherapy dosing based on the tumour response to chemotherapy. Radiotherapy was given at 10 weeks: 32 Gy was delivered if the tumour shrank by more than two-thirds of its volume, compared to 54 Gy if it shrank between a third and two-thirds of its volume [17]. The 5-year EFS for stage III B/P RMS was 66%, and for stages I-III the EFS was 70%. Stage III patients with tumours of < 5 cm and a good response to chemotherapy (⩾2/3 reduction) had a 77% EFS, compared to 54% for those with tumours of > 5 cm and a good response [17]. The SIOP MMT84 protocol achieved a 79% 5-year OS rate and 64% 5-year EFS rate using IVA chemotherapy, and

waited to administer radiotherapy until six courses of chemotherapy were completed [18]. The SIOP MMT89 protocol also used IVA, and surgery was carried out if there was < 50% response after two courses of chemotherapy. This study also achieved an 80% OS and 64% EFS rate for B/P RMS. It was felt that the additional secondary chemotherapy was outweighed by the ability to avoid significant radiotherapy or surgical excision in 58% of patients [19]. The recently completed MMT95 study found no difference when a six-drug regimen (IVA, carboplatin, epirubicin, and etoposide) was used, compared to IVA. The 5-year OS rate was 82%, and the EFS rate was 67% for B/P RMS [20]. It appears that new chemotherapy agents need to be developed to improve EFS rates to the level achieved by surgery or radiotherapy.

Currently, 50% (78/161) of patients are treated with biopsy, chemotherapy, and possibly radiotherapy, 30% (49/161) undergo partial cystectomy, and 20% (34/161) radical cystectomy [21]. Prostatectomy is generally not recommended due to the difficulty in obtaining a clear surgical margin [22]. In such situations radiotherapy can be given for local control. While both the COG and SIOP approaches try to minimise the 'cost of cure', the balance between primary chemotherapy and radiotherapy, which leads to less relapse but higher risk of late effects, vs. chemotherapy alone, with a higher risk of relapse but which can be salvaged at a later date, remains unclear [23].

Surgical technique

Radical excision is reserved for residual viable tumour after chemotherapy and radiotherapy, when an organ-sparing approach is not possible. However, early treatment failure and progression of disease despite chemotherapy and radiotherapy are indications for radical surgery, if a partial cystectomy cannot be completed [22]. If imaging at 15 or 30 weeks shows that the tumour is growing, the decision to proceed to radical cystectomy can then be made. During radical cystectomy any enlarged retroperitoneal lymph nodes are removed, although a formal lymphadenectomy is not required. Several biopsies are taken from around the tumour. If it is possible to perform a partial cystectomy with a 2–3 cm margin of expendable tissue, only the tumour is removed. Otherwise, a radical cystectomy is carried out, along with continent urinary reconstruction in those patients who are motivated and capable of performing clean intermittent catheterisation afterwards. The choice of the bowel segment to use for the continent reconstruction will depend on the radiation field and the viability of the tissues. If the child is not ready for immediate reconstruction, the remnant bladder plate can be brought out to the skin as a vesicostomy, or low end-cutaneous ureterostomies can be brought out as a single stoma [24].

Local control: surgery or radiotherapy?

The major difference between the COG and European studies is in the use of radiotherapy. SIOP studies have allowed for dose reduction or even elimination of radiotherapy, depending on the tumour response to chemotherapy. COG studies have based the radiotherapy dose on the tumour volume before chemotherapy. This results in higher radiotherapy doses in COG studies, with associated differences in cure rates and complications. In the current COG protocol, radiotherapy is started at 4 weeks. For COG Group II patients with microscopic residual disease, 36–41 Gy is delivered. For Group III patients with gross residual disease, 45–50 Gy is given. In MMT-89, radiotherapy was not given if there was a chemotherapy response and there was a full surgical excision. Patients who only had a partial response received 45 Gy [11].

A combined analysis of the IRS-IV, SIOP MMT-84, SIOP MMT-89, Italian Cooperative Group ICG RMS-79, ICG RMS-88, German Cooperative Soft Tissue Sarcoma Study CWS-91 studies suggested that: (i) EFS was primarily driven by tumour stage, size, and histology; and (ii) The lack of initial radiotherapy led to decreased EFS rates, without affecting OS [3]. The overall 5-year OS rate was 84%, and EFS was 75%. Of the IRS/CWS patients, 85% received initial radiotherapy, compared to 48% of SIOP/ICG patients. Of the failures, 88% occurred within 3 years; local recurrence accounted for 60%, regional lymph nodes 9%, distant metastases 25%, and the remaining 6% were unknown [3].

Tumour stage and tumour size were independently predictive of EFS, whereas only tumour size was predictive of OS. The EFS rate in patients with T1 (noninvasive tumours) was 81%, compared to 69% for T2 (invasive tumours; $P = 0.006$). Tumours of < 5 cm had an 85% EFS rate compared to 70% for those of > 5 cm. A tumour of > 5 cm had a relative risk of 2.4 for a worse OS ($P = 0.002$) compared to smaller tumours. This risk stratification is significant, because the previously published differences in EFS for IRS/ICG and SIOP/CWS approaches is no longer significant when tumour stage and size are considered. The SIOP and CWS studies had significantly more patients with T2 tumours, of > 5 cm, whereas the IRS and ICG studies had more patients with T1 tumours, of < 5 cm. The OS rate between groups was not significantly different, suggesting that the lack of initial radiotherapy in SIOP/ICG patients did not affect the eventual OS [3].

The most recent German CWS-96 study administered ifosfamide, vincristine, dactinomycin to standard-risk patients with B/P RMS, and added either doxorubicin or carboplatin and etoposide for high-risk patients [25]. Patients aged < 1 year did not receive radiotherapy, those aged < 3 years were limited to 32 Gy, and patients with a poor radiographic response received 45 Gy. This

radiotherapy dosing is 18–27 Gy lower than that used in the IRS-IV protocol. The 5-year EFS was higher in those patients receiving chemotherapy and surgery (84%), radiotherapy and chemotherapy followed by surgery (82.3%), and radiotherapy and chemotherapy (75%), than in those undergoing an incomplete resection followed by chemotherapy and radiotherapy (38.5%, $P = 0.031$). The 5-year OS rate was likewise better for those patients undergoing chemotherapy and surgery (84%), radiotherapy and chemotherapy followed by surgery (87.8%) and radiotherapy and chemotherapy (87.5%), than in those who had an incomplete resection (39.9%, $P = 0.027$) [25].

While the study was not designed to compare the efficacy of radiotherapy vs. surgery for local control, the poor performance of those patients who had an initial incomplete resection suggested that postoperative radiotherapy at this dose cannot substitute for adequate surgical excision. It is unclear whether a higher radiotherapy dose or more aggressive early surgical excision could have obtained an OS rate in the 80% range for these patients.

Brachytherapy alone for B/P RMS has not been used extensively, due to concerns about inadequate dosing. It has been used in addition to external beam radiotherapy, and in conjunction with partial prostatectomy. A series from France treated a highly selected group of 26 boys after initial chemotherapy with urethra-preserving partial prostatectomy or partial cystectomy, in conjunction with the implantation of brachytherapy catheters. A dose of 60 Gy was delivered at 10 Gy/day. Of the 26 patients, 24 were alive at a mean follow-up of 4 years, with daytime incontinence in one of seven boys who were aged 4–6 years, and two of 11 who were aged >6 years. Most of the boys with daytime incontinence had only minor urodynamic abnormalities. The boys were too young to assess their sexual function [26].

Complications of local control

Reports on bladder function after surgery, chemotherapy and radiotherapy are limited [21,22,27–30], but half of patients with B/P RMS will have normal bladder capacities, and radiotherapy usually results in some degree of urinary incontinence. There are only two studies that used a urodynamic evaluation of bladder function in B/P RMS; the remainder rely on questionnaire data. The initial study from Great Ormond Street showed that four of 11 patients who were managed with surgical excision alone had normal bladder capacities and flow rates, whereas the remaining seven patients who received radiotherapy had either day or night-time incontinence associated with a decreased bladder capacity, at a mean of 6.6 years after completing therapy [27]. The second study from Sao Paulo, Brazil, showed that four of eight patients who were treated with chemotherapy and radiotherapy had mild symptoms of frequency of dysuria, while one had a continent diversion, at a mean follow-up of 2.2 years after therapy [28]. The difference in the duration of follow-up might account for the difference in urinary incontinence, as radiotherapy effects might be progressive over time.

The effect of radiotherapy on bladder function was not immediately apparent in the IRS-I and IRS-II studies. Of the patients with urinary incontinence, 13 of 14 had received 20–50 Gy of radiotherapy, while 30 of 38 with normal bladder function had also received 8–80 Gy [29]. In IRS I-III, patients who had a partial cystectomy had a similar chance of incontinence if they received more or less than 40 Gy of radiotherapy (eight of 13 vs. one of six, $P = 0.14$) [30].

Of 55 patients who were successfully treated in IRS-IV with chemotherapy and radiotherapy, 36 of 55 (65%) of those who maintained their bladders had normal bladder function, representing 41% (36/88) of the entire group [22]. An analysis of IRS-IV, SIOP (MMT-84, MMT-89), Italian (RMS-79, RMS-88), and German (CWS-91, DWS-96) studies showed that at a median 8 years of follow-up, 43 of 62 (69%) patients who were managed with biopsy, chemotherapy, and possibly radiotherapy, had no problems with urinary continence. Of 44 patients who had a partial cystectomy, 32 (73%) were continent of urine [21].

Although sexual dysfunction after radical cystectomy or radiotherapy is a major concern, assessing sexual function in children is difficult. Of those patients who were mature enough to assess sexual function, erections were normal in 25 of 27 males, ejaculation was normal in 16 of 20 males, and five of seven females had normal menses. Fertility was confirmed in eight males and one female out of 60 patients [21].

Diagnosing residual tumour

In IRS-III, 'second-look' surgery was performed at 15 weeks to decide if a residual mass was viable tumour or stroma [13]. Second-look surgery has been replaced by radiographic staging in both the COG and SIOP studies. IRS-IV recommended a second-look procedure at 46–47 weeks for a persistent mass after chemotherapy. In the B/P RMS group, 67% (18/27) had no viable tumour found at a second-look procedure [31]. The 5-year OS rate was 89%, and patients with B/P RMS were more likely to undergo second-look procedures than were those with RMS in other locations. In the entire group of 73 patients the 5-year EFS rate was 81% and the OS was 89% for those without viable tumour, compared to an EFS of 53% and OS of 67% for those with viable tumour. The difference in EFS was marginally significant ($P = 0.05$, 95% CI 0.15–0.99) but there was no difference in OS ($P = 0.2$, 95% CI 0.12–1.41). Similarly, there was no difference in EFS or OS rates in the

patients who had second-look operations compared to those who did not [31].

A small series of 13 patients comparing FDG-PET/CT with conventional imaging (MRI, CT, and bone scan) at the diagnosis of RMS found that FDG-PET was more sensitive than conventional imaging for detecting both primary tumours and lymph nodes, but it was less sensitive for detecting small lung nodules [32]. Only three patients had a genitourinary primary tumour. FDG-PET was able to detect an additional prostate RMS primary, 19 lymph nodes, and 11 bone metastases, compared to 12 lymph nodes and three bone metastases with conventional imaging [32]. This initial study shows that FDG-PET is more sensitive for diagnosing RMS at presentation. If it has a similar ability for differentiating the biological activity of a residual mass (i.e. is the mass tumour, stroma, or necrosis?) then the ability to decide whether radical surgical excision should be carried out will be much improved.

Discussion

There is no clearly superior approach between the COG and SIOP approaches. Chemotherapy can achieve an 80% OS rate, but the previous three MMT studies have not been able to achieve an EFS rate of $>70\%$. Clearly, new chemotherapy agents are necessary if improvements in EFS by chemotherapy alone are to be expected [33]. The more recent studies might indicate a way to more efficiently use chemotherapy, radiotherapy and surgery. The assignment of most patients with B/P RMS to chemotherapy regimens is usually stage II or stage III in SIOP and stage III in COG, yet the biological behaviour of the tumour in terms of EFS and OS is clearly worse for those tumours of >5 cm at presentation. Studies focusing on decreasing chemotherapy dosing should focus on small B/P tumours, so that the minimal amount of chemotherapy necessary to achieve a complete response can be determined. For the large B/P tumours, they are known to be more aggressive, have worse EFS and OS, and require more local therapy to achieve a cure. From a surgical perspective, the ability to perform a partial cystectomy vs. a radical cystectomy is determined by the site where the tumour originates in the bladder, not the size of the tumour. Even if a tumour arising from the trigone decreases to less than a third of its initial volume in response to chemotherapy, radiotherapy or surgical excision remains technically challenging and urinary continence is not predictable. Prolonged courses of chemotherapy will achieve a successful EFS only if the patient can be treated by partial cystectomy or a combined surgical/brachytherapy approach. Decreasing the proportion of patients who undergo radical cystectomy to $<20\%$ would also require a breakthrough in chemotherapy. While there is no reason to return to aggressive surgical resection for all patients with B/P RMS, the threshold for proceeding to radical cystectomy in a patient who has a large tumour at the bladder neck and minimal response to chemotherapy perhaps should be lower than for a patient with a small tumour which is responding well. The CWS-96 study [25] indicates the danger of delaying definitive local surgical therapy while waiting for chemotherapy and radiotherapy to take effect. As determining whether a residual mass is tumour or stroma is not easily achieved by second-look surgery or pathological examination, improvements in FDG-PET or other imaging studies might help in understanding the behaviour of this rare tumour. Urologists can contribute to the treatment of B/P RMS by documenting the urodynamic effects of both surgical excision and radiotherapy on bladder function. If the bladder is not functional after treatment, was it worth preserving?

Conclusions

Tumour invasiveness and tumour size are powerful predictors of EFS in the treatment of B/P RMS. The appropriate use of surgery, chemotherapy and radiotherapy remains the cornerstone of management. While local failures can be salvaged with subsequent chemotherapy, radiotherapy or surgical excision without affecting OS in most cases, the best combination of all three methods of treatment to lower the overall burden of therapy remains to be defined.

Conflict of interest

None.

Source of funding

None.

References

[1] Womer RB, Synder HM. Bladder/prostate rhabdomyosarcoma: miles to go before we sleep. *J Urol* 2006;**176**:1278–9.

[2] Donaldson SS, Anderson JR. Rhabdomyosarcoma: many similarities, a few philosophical differences. *J Clin Oncol* 2005;**23**: 2586–7.

[3] Rodeberg DA, Anderson JR, Arndt CA, Ferrer FA, Raney RB, Jenney ME, et al. Comparison of outcomes based on treatment algorithms for rhabdomyosarcoma of the bladder/prostate: combined results for the Children's Oncology Group, German Cooperative Soft Tissue Sarcoma Study, Italian Cooperative Group, and International Society of Pediatric Oncology Malignant Mesenchymal Tumors Committee. *Int J Cancer* 2011;**128**: 1232–9.

[4] Ritchey ML, Shamberger RC. Pediatric Urologic Oncology. In: Wein AJ, editor. *Campbell-Walsh Urology*. 10th ed. Philadelphia: Elsevier Saunders; 2012. p. 3704–9.

[5] Meza JL, Anderson J, Pappo AS, Meyer WH. Analysis of prognostic factors in patients with nonmetastatic rhabdomyosarcoma treated on Intergroup Rhabdomyosarcoma Studies III and

IV. The Children's Oncology Group. *J Clin Oncol* 2006;**24**: 3844–51.
[6] Ortega JA, Rowland J, Monforte H, Malogolowkin M, Triche T. Presence of well-differentiated rhabdomyoblasts at the end of therapy for pelvic rhabdomyosarcoma: implications for outcome. *J Pediatr Hematol Oncol* 2000;**22**:106–11.
[7] Arndt CAS, Hammond S, Rodeberg D, Qualman S. Significance of persistent mature rhabdomyoblasts in bladder/prostate rhabdomyosarcoma. Results from IRS IV. *J Pediatr Hematol Oncol* 2006;**28**:563–7.
[8] Ferrer FA, Isakoff M, Koyle MA. Bladder/prostate rhabdomyosarcoma. Past, present, and future. *J Urol* 2006;**176**:1283–91.
[9] Joshi D, Anderson JR, Paidas C, Breneman J, Parham DM, Crist W. Age is an independent prognostic factor in rhabdomyosarcoma. A report from the Soft Tissue Sarcoma committee of the Children's Oncology Group. *Pediatr Blood Cancer* 2004;**42**:64–73.
[10] Children's Oncology Group ARST0531.
[11] Walterhouse D, Watson A. Optimal management strategies for rhabdomyosarcoma in children. *Pediatr Drugs* 2007;**9**:391–400.
[12] Raney Jr RB, Gehan EA, Hays DM, Tefft M, Newton Jr WA, Haeberlen V, et al. Primary chemotherapy with or without radiation therapy and/or surgery for children with localized sarcoma of the bladder, prostate, vagina, uterus, and cervix. A comparison of the results in Intergroup Rhabdomyosarcom Studies I and II. *Cancer* 1990;2072–81.
[13] Crist W, Gehan EA, Ragab AH, Dickman PS, Donaldson SS, Fryer C, et al. The Third Intergroup Rhabdomyosarcoma Study. *J Clin Oncol* 1995;**13**:610–30.
[14] Baker KS, Anderson JR, Link MP, Grier HE, Qualman SJ, Maurer HM, et al. Benefit of intensified therapy for patients with local or regional embryonal rhabdomyosarcoma: results from the Intergroup Rhabdomyosarcoma Study IV. *J Clin Oncol* 2000;**18**: 2427–34.
[15] Crist WM, Anderon JR, Meza JL, Fryer C, Raney RB, Ruymann FB, et al. Intergroup Rhabdomyosarcoma Study-IV. Results for patients with nonmetastatic disease. *J Clin Oncol* 2001;**19**: 3091–102.
[16] Donaldson SS, Meza J, Breneman JC, Crist WM, Laurie F, Qualman SJ, et al. Results from the IRS-IV randomized trial of hyperfractionated radiotherapy in children with rhabdomyosarcoma – a report from the IRSG. *Int J Radiat Oncol Biol Phys* 2001;**51**:718–28.
[17] Koscielniak E, Harms D, Henze G, Jurgens H, Gadner H, Herbst H, et al. Results of treatment for soft tissue sarcoma in childhood and adolescence: a final report of the German Cooperative Soft Tissue Sarcoma Study CWS-86. *J Clin Oncol* 1999;**12**:3706–19.
[18] Flamant F, Rodary C, Rey A, Praquin MT, Sommelet D, Quintana E, et al. Treatment of non-metastatic rhabdomyosarcomas in childhood and adolescence. Results of the second study of the International Society of Paediatric Oncology MMT 84. *Eur J Cancer* 1998;**34**:1050–62.
[19] Stevens MCG, Rey A, Bouvet N, Ellershaw C, Flamant F, Habrand JL, et al. Treatment of nonmetastatic rhabdomyosarcoma in childhood and adolescence: third study of the International Society of Paediatric Oncology – SIOP Malignant Mesenchymal Tumor 89. *J Clin Oncol* 2005;**23**:2618–28.
[20] Oberlin O, Rey A, de Toledo JS, Martelli H, Jenney MEM, Scopinaro M, et al. Randomized comparison of intensified six-drug versus standard three-drug chemotherapy for high-risk nonmetastatic rhabdomyosarcoma and other chemotherapy-sensitive childhood soft tissue sarcomas: long-term results from the International Society of Pediatric Oncology MMT95 study. *J Clin Oncol* 2012;**20**:2457–65.
[21] Raney B, Anderson J, Jenney M, Arndt C, Brecht I, Carli M, et al. Late effects in 164 patients with rhabdomyosarcoma of the bladder/prostate region: a report from the International Workshop. *J Urol* 2006;**176**:2190–5.
[22] Arndt C, Rodeberg D, Breitfeld PP, Raney RB, Ullrich F, Donaldson S. Does bladder preservation (as a surgical principle) lead to retaining bladder function in bladder/prostate rhabdomyosarcoma? Results from Intergroup Rhabdomyosarcoma Study IV. *J Urol* 2004;**171**:2396–403.
[23] Stevens MCG. Treatment for childhood rhabdomyosarcoma: the cost of cure. *Lancet Oncol* 2005;**6**:77–84.
[24] Wu HY, Snyder HM, Womer RB. Genitourinary rhabdomyosarcoma: which treatment, how much, and when? *J Pediatr Urol* 2009;**5**:501–6.
[25] Seitz G, Dantonello TM, Int-Veen C, Blumenstock G, Godzinski T, Klingebiel T, et al. Treatment efficiency, outcome and surgical treatment problems in patients suffering from localized embryonal bladder/prostate rhabdomyosarcoma: a report from the Cooperative Soft Tissue Sarcoma Trial CWS-96. *Pediatr Blood Cancer* 2011;**56**:718–24.
[26] Martelli H, Maie-Meder C, Branchereau S, Franchi-Abella S, Ghigna M-R, Dumas I, et al. Conservative therapy plus brachytherapy for boys with prostate and/or bladder neck rhabdomyosarcoma: a single team experience. *J Pediatr Surg* 2009;**44**: 190–6.
[27] Yeung CK, Ward HC, Ransley PG, Duffy PG, Pritchard J. Bladder and kidney function after cure of pelvic rhabdomyosarcoma in childhood. *Br J Cancer* 1994;**70**:1000–3.
[28] Soler R, Macedo Jr A, Bruschini H, Puty F, Caran E, Petrilli A, et al. Does the less aggressive multimodal approach of treating bladder-prostate rhabdomyosarcoma preserve bladder function? *J Urol* 2006;**174**:2343–6.
[29] Raney Jr B, Heyn R, Hays DM, Tefft M, Newton WA, Wharam M, et al. Sequelae of treatment in 109 patients followed for 5–15 years after diagnosis of sarcoma of the bladder and prostate. *Cancer* 1993;**71**:2387–94.
[30] Hays DM, Raney RB, Wharam MD, Wiener E, Lobe TE, Andrassy RJ, et al. Children with vesical rhabdomyosarcoma (RMS) treated by partial cystectomy with neoadjuvant or adjuvant chemotherapy, with of without radiotherapy. *J Pediatr Hematol Oncol* 1995;**17**:46–52.
[31] Raney B, Stoner J, Anderson J, Andrassy R, Arndt C, Brown K, et al. Impact of tumor viability at second-look procedure before completing treatment on the Intergroup Rhabdomyosarcoma Study Group protocol IRS-IV 1991–97: a report from the Children's Oncology Group. *J Pediatr Surg* 2010;**45**:2160–8.
[32] Ricard F, Cimarelli S, Deshayes E, Mognetti T, Thiesse P, Giammarile F. Additional benefit of F-18 FDG PET/CT in the staging and follow-up of pediatric rhabdomyosarcoma. *Clin Nucl Med* 2011;**36**:672–7.
[33] Meyer WH. Playing bad cards properly: challenges to improving cure rates in rhabdomyosarcoma. *J Clin Oncol* 2012;**20**:2431–3.

Editorial comment

At The Children's Hospital of Philadelphia we have had an extensive experience with this rare tumour, as oncology referrals are received widely in this centre. As a result we have identified several points that are worth reiterating. The first is that this is a rare tumour that is complex in management and unlike any other malignancy seen in children. Accordingly, this is a malignancy that cannot be managed by a simple 'cook-book' approach and should be managed in a centre of excellence that has abundant experience with this tumour.