In this issue of the Dialogues, an experienced panel from Children’s Hospital of Philadelphia and Stanford discusses some of the central issues and controversies regarding the management of children with bladder/prostate rhabdomyosarcoma (BP RMS). Since the majority of patients (>80%) with BP RMS will have localized embryonal tumors, one of the fundamental questions is how to best achieve local disease control? On this point our panelists’ recommendations are at odds with those of the COG, but in-line with that of our European colleagues who defer radiation therapy. Limited available data has suggested that the omission of radiotherapy resulted in inferior outcomes in COG patients. Therefore, current COG protocols call for early radiotherapy in intermediate risk patients, a source of much angst for some surgeons. An upcoming publication of pooled data including COG and European studies sheds more light on

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The management of bladder prostate rhabdomyosarcoma has undergone cyclic changes over the years. Starting with an extremely aggressive surgical approach, which unfortunately left many children with a debilitated urinary tract, it subsequently moved towards upfront radiation and chemotherapy with its attendant morbidities.

This issue of the Dialogues in Pediatric Urology evaluates the current controversy between COG recommendations and recommendations that are in Europe over management of these patients. One of the major controversies is where does this radiation therapy fit into the management protocol. So as we can see, the pendulum is still trying to reach a comfortable resting point.

This is a well organized and well thought out Dialogues. Dr. Ferrer asked pointed questions to his experienced panelist. These panelist clearly approach bladder prostate rhabdomyosarcoma with their eyes open, individualizing care.

I congratulate Dr. Ferrer and his contributors for a very informative and state of the art manuscript.
FROM THE GUEST EDITOR (continued from page one)

this subject, showing that while an increased number of local failures may occur as a result of delayed or omitted radiation, overall survival at 5 years was no worse in these patients. These findings suggest that patients who fail locally can be successfully salvaged (Rodeberg et al, Int. J. Ca in press). While preliminary, this information will be important in future discussions about the role and timing of radiotherapy.

Regardless of the approach to local control, on both sides of the ocean there is consensus on the goal of bladder preservation. This is evidenced by the fact that recent combined data shows only 14% of patients undergo an attempt at definitive resection up front (Rodeberg et al, Int. J. Ca. in press). The logical question is, “Does our therapeutic approach accomplish our goals?” Unfortunately, the answer to this fundamental question remains unclear. A recent comparison of COG and SIOP functional outcomes suggests that no difference exists in functional outcome despite different treatment strategies. However, this study utilized a relatively superficial assessment of bladder function.2 Ardnt and coworkers showed that only about 55% of patients had good bladder function in IRS IV. Again, bladder function assessment was cursory, and one could argue this study under-estimated dysfunction.1 The ideal way to answer this question would be to carefully monitor patients by doing serial assessments using voiding questionnaires, ultrasound evaluation of the upper/lower tracts and urodynamics. Recognition of the need for more thorough analysis exists among most experts in the field, yet some our non-urologic colleagues feel that urodynamics are too invasive to perform de rigueur on all patients. As such, it appears that when the next intermediate-risk sarcoma come online in about 2 years, the best we can hope for is that a non-invasive evaluation (standardized voiding function questionnaire and ultrasound) will be included in the protocols.

DIALOGUE

Fernando Ferrer (FF): Treatment of children with bladder prostate rhabdomyosarcoma (BP/RMS) has differed between the IRS (subsequently the COG) in North America, and our colleagues overseas in SIOP or the CWS. Can you comment on these differences and the rationale behind the different strategies?

Richard Womer (RW): The ultimate therapeutic goal is the same, which is to maximize overall survival. The COG studies reflect the philosophy that this is best done by maximizing progression-free survival, while the SIOP MMT studies are willing to tolerate some local progression in order to minimize the late effects from surgery and radiation. They accept that some patients will need more intense retrieval therapy. The German CWS studies have taken a middle path, trying to adjust radiation doses according to tumor response.

FF: How have outcomes compared relative to RMS in general and BP/RMS in specific?

Hsi-Yang Wu (HYW): It would seem that both approaches have achieved what they set out to do. For non-BP/RMS, both 5-year overall and event-free survival are the same in IRS-IV and SIOP MMT-89: 90% and 83% (IRS) vs. 94% and 82% (SIOP). The problem with BP/RMS is that while overall survival was similar, 86% (IRS) vs. 80% (SIOP), the event-free survival was markedly worse, 79% (IRS) vs. 64% (SIOP) using the SIOP approach.3

FF: Current COG protocols call for the use of early radiotherapy (4 weeks) in intermediate risk patients. This paradigm is quite different from that utilized by our European colleagues, what do you see as the principal advantages and disadvantages of this approach?

Howard M. Snyder (HMS): One of the main goals of this COG protocol is to study the effect of early radiotherapy, so until the current study is completed, it is going to be difficult to avoid it. I think we have much to learn from our colleagues in Europe in terms of being careful about local therapy. We, at the Children’s Hospital of Philadelphia, have taken the approach that radiotherapy should not be given until all local disease has been grossly resected. I can see one big disadvantage, that it makes it very hard for our pathologists to read the biopsy specimen afterwards. At the doses of radiation that are being given, we can’t be sure that we will have a functional bladder or outlet when the child is an adolescent. We have to remember that in previous protocols, second look surgery occurred at week 15, and even at that point, interpretation of intra-operative findings was difficult for patients with residual disease. In IRS-III, 36% of patients with no clinical radiographic response were in complete remission at second look surgery, after only chemotherapy.4

FF: Can you elaborate on the impact of radiotherapy on interpretation of pathologic specimens?

HMS: There are 3 important lessons we have learned over the years:
1. Chemotherapy cures microscopic disease; 2. Residual mass does not equal disease; and 3. Radiotherapy renders pathology very difficult to read. What this means is that most patients get chemotherapy, but we cannot rely on imaging to tell us if a persistent mass after treatment is malignant. If the mass has been radiated, it is even more difficult to tell if the mass is malignant. Benign stroma is slower to involute than tumor, so we need to be able to read the tissue specimens.

About 15 years ago, we had a teenager with prostatic RMS who was treated with the IRS protocol at that time. He had a biopsy, received chemotherapy, and because he had a residual mass, he underwent radiotherapy. I took him back multiple times for repeated biopsy, and each time the pathologist could not tell me whether there was viable tumor, or whether it was a tumor cell that was heading for senescence. By the time that we could see radiographically that the tumor was growing, I wound up performing an anterior exenteration on him. He then died of metastatic disease. Experiences like that explain why we feel so strongly that radiotherapy should only be used for microscopic residual disease.

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**FF: What are the available data suggesting that radiotherapy improves outcome and local control?**

**RW:** The data comes from a review of IRS data on the treatment of parameningeal RMS,\(^1\) as well as studies in breast and head and neck cancers,\(^6\) and medulloblastoma.\(^7\) They suggest that delay in radiotherapy leads to decreased event-free survival. There is not enough data on BP/RMS to know if this will hold true in this specific location. The other main goal of the current COG protocol is to see if irinotecan in conjunction with radiotherapy provides a potentiating effect. This is based on rectal and cervical cancer data, so we do have acceptable toxicity data for the pelvis, albeit from adult patients.

**FF: COG strategies have focused on organ (bladder) preservation, can you comment on the data available regarding our outcomes as it pertains to bladder function.**

**HYW:** The data is extremely limited. The most we can say is that half of the children treated with a bladder preservation technique will have normal bladder capacity later on, and that pelvic radiotherapy is a negative predictive factor.\(^8\) The experience in Philadelphia is that every patient that has had radiotherapy to the bladder has some degree of urinary incontinence. It will be interesting to see if new radiotherapy techniques such as intensity modulation can decrease this complication. These are all topics that the Late Effects Group of the COG, which you’re on, is planning on studying more systematically with urodynamics and questionnaires. About half of patients currently undergo biopsy and chemotherapy, 30% partial cystectomy, and 20% complete cystectomy. Of the males, about 25% undergo prostatectomy. It is a mixed population, but by questionnaire, 70% of patients who had biopsy and chemotherapy or partial cystectomy said that they had normal bladder function. Serum creatinine was abnormal in 40%, and bowel function assessed by questionnaire was abnormal in 13%.\(^2\)

**FF: What is the histologic appearance of rhabdomyoblasts? Does the presence of rhabdomyoblasts after chemotherapy require further therapy (surgery, chemo or radiation)?**

**HYW:** Typical rhabdomyosarcoma consists of small, blue, round cells, whereas rhabdomyoblasts are large, pink cells, so they look very different. From the experience in treating vaginal RMS, we’ve learned that rhabdomyoblasts are evidence of chemotherapy response. These patients receive additional chemotherapy to prevent metastases. If rhabdomyoblasts persist afterwards, and can be resected without destroying a functional bladder, patients undergo surgery. Otherwise, the patients have close radiologic follow-up.

**FF: Cystoscopic biopsy can be challenging due to the small diameter of pediatric scopes, do you have any tips or preferred techniques?**

**HMS:** The key thing is to get enough tissue for the pathologist to read, so I take a generous wedge with a resectoscope if it’s a broad based lesion, or I grasp the base of a frond with a cold cup biopsy forceps and avulse it, then go back to fulgurate. It’s important not to have thermal artifact in the specimen, and to minimize crush artifact. If it’s in the prostate, then a transperineal needle biopsy might need to be done.

**FF: Do patients enrolled in COG protocols undergoing initial cystoscopic biopsy require lymph node sampling or is radiologic imaging adequate?**

**HYW:** Soft tissue imaging with MRI is very accurate nowadays, so as long as the retroperitoneal and pelvic MR are negative for nodal disease, regional lymph node sampling is not required. It is unusual to have to perform an exploratory laparotomy to get tissue, but if it is necessary, a formal iliac and para-aortic node dissection should be carried out, along with removal of any enlarged lymph nodes seen on imaging. There is one population that urologists need to be aware of, which is very different. In paratesticular RMS, boys greater than 10 years of age require an RPLND regardless of imaging, because the biological behavior of that tumor is aggressive, like adult germ cell tumors.\(^10\)

**FF: What do you include in your staging workup; can you comment on the emerging role of positron emission tomography using fluorodeoxyglucose (FDG-PET) imaging for these patients?**

**RW:** We get a chest CT to look for lung metastases. For the metastatic workup, we obtain a bone scan, and a bone marrow aspirate and biopsy. FDG-PET may supplant bone scans in the future, since it gives us both location and biological activity, and there is some evidence that it is more sensitive and specific than bone scans for RMS. The real usefulness of FDG-PET hopefully will be to tell us whether a residual mass is viable tumor, necrosis, or scar. Currently, FDG-PET is optional, but if we find that changes in FDG-PET activity at 1, 4, and 15 weeks of chemotherapy are predictive of survival, then this will be a way out of the quandary of how to best manage a residual mass: to excise it, give more treatment, or observe it.

**FF: What are the current generation chemotherapy agents commonly used in COG protocols?**

**RW:** COG protocols use VAC (vincristine, dactinomycin, cyclophosphamide), whereas CWS (German) and ICG (Italian) protocols use IVA (ifosfamide, vincristine, and dactinomycin). IRS-IV found that VAC was as effective as two other regimens (VIE/IVA: ifosfamide, etoposide), so COG is not using ifosfamide. The use of vincristine, topotecan, and cyclophosphamide alternating with VAC in the IRS-V studies provided no benefit in progression-free or overall survival.\(^11\) COG is currently comparing VAC with VAC/vincristine-irinotecan in intermediate-risk patients, which include those with bladder-prostate tumors. The duration of chemotherapy is longer in COG studies than in European studies. For low, intermediate, and high risk COG patients, the duration is 22, 42, and 51 weeks, compared to 16, 36, and 46 weeks in SIOP patients.\(^12\) Second line chemotherapy is used more often (6-17%) in Europe in an attempt to avoid local therapy with surgery or radiotherapy, due to a higher rate of local recurrences.\(^13,14,15\)
**FF: What about dosing and timing of radiation?**

HYW: COG radiotherapy doses are based on the amount of tumor remaining after initial surgery, whereas SIOP allows for reduction in radiotherapy depending on the amount of tumor remaining after chemotherapy. Group II patients (microscopic residual) receive 36-41 Gray, and Group III patients (gross residual) receive 45-50 Gray. Hyperfractionated radiotherapy had no benefit over conventional radiotherapy in IRS-IV. In the German CWS-86 protocol, they eliminated radiotherapy for patients with a complete response, delivered 32 Gray if there was >2/3 volume regression, and 54 Gray if there was < 2/3 volume regression. There was no difference in total (local + systemic) relapse rates between Stage III patients who did or did not receive radiotherapy, but the local relapse rate was significantly lower (10% vs. 27%) in patients who received radiotherapy. The choice for improved local control may come down to surgery or radiotherapy. While radiotherapy reduces the number of patients who require radical excision, the lowest effective doses delivered to the bladder neck may still cause urinary incontinence, infertility, bowel injury, and bony pelvis deformity. It is unclear if these side effects cause more morbidity than surgical excision of the bladder or prostate.

**FF: Can you discuss the timing of definitive resection in COG studies and comment on the role of intraoperative biopsy to guide resection?**

HMS: Organ sparing resection is always the goal, whether that is a partial cystectomy or a prostatectomy with reconstruction of the urethra. Multiple biopsies around the tumor are obtained, usually at a preoperative staging cystoscopy. Since this is a non-encapsulated tumor, surgical planning for adequate margins is important. The retroperitoneum is examined for suspicious lymph nodes, and any enlarged lymph nodes are removed, although a formal lymphadenectomy is unnecessary. If it is possible to perform a partial cystectomy with a 2 to 3 cm margin of expendable tissue, then only the tumor is removed. Otherwise a cystectomy or prostatectomy is carried out. Pelvic enterectomy is reserved for local control when residual viable tumor (not mature rhabdomyoblasts) remains after chemotherapy and radiotherapy, and an organ sparing approach is not possible.

**FF: For patients undergoing exenterative surgery in general do you favor immediate or delayed reconstruction?**

HMS: Continent urinary reconstruction can be carried out after cystectomy, but should be limited to patients who are motivated and capable of performing clean intermittent catheterization afterwards. For patients who receive multimodal therapy and have no recurrence for 2 years, the likelihood of recurrence is very low, and you can proceed with continent reconstruction at that point. Interestingly, if you only receive chemotherapy, that’s not the case, we have seen recurrences 8 or 9 years out. Since a lot of the patients are young, and temporary incontinence is not a big issue, we generally perform delayed reconstruction. If the child is not ready for immediate reconstruction, we bring the remnant bladder plate out to the skin as a vesicostomy, or low end-cutaneous ureterostomies can be brought out as a single stoma. Frozen section at the time of cystectomy can be inaccurate, so if there is residual disease on the final pathology, the patient may face additional chemotherapy or radiation after continent urinary reconstruction. However, for teenagers I would consider an immediate continent reconstruction, because body image and urinary incontinence are much bigger issues at that age. John Duckett’s contribution of the Penn pouch, or other variations on ileocecal diversion using the Mitrofanoff principle are useful in these patients. The Abolenin technique of laying a dilated ureter into a serosal lined trough of bowel is also a great contribution.

**FF: What’s the future hold?**

RW: We need to do better in treating patients with metastatic RMS. This group continues to have poor outcomes despite aggressive chemotherapy. Three year overall and event-free survival remains at only 34% and 27%, with no difference between IRS and SIOP studies. Age < 1 year or > 10 years continues to be a risk factor for lower event-free survival (25% and 15%, vs. 36%). Understanding the differences in tumor biology that occur at different ages will hopefully open up new avenues for treatment, such as the inhibitors of the vascular endothelial growth factor and insulin-like growth factor pathways that are currently in Phase I and Phase II clinical trials.

**FF: How should we assess outcomes?**

HYW: Like all other pediatric tumors, we’re at the point of trying to better stratify treatment in order to limit long term morbidity. We can cure a fair number of children, now we need to make sure their quality of life as they reach adulthood is appropriate. More than half of the women surviving treatment for pelvic RMS have long-term endocrine, gastrointestinal, musculoskeletal, gynecologic, and urological complications, which often occur in the radiation field. They are more likely to require sex hormone replacement, are shorter than expected, and develop secondary malignancies at 6 times the expected rate. These patients develop acute myeloid leukemia, cutaneous melanoma, bone and soft tissue sarcomas, and breast cancer. As we accumulate the long-term outcomes on urodynamics, renal, endocrine, and gastrointestinal function, this data helps design the next trial, to see what minimum intensity of treatment is required to achieve a cure in childhood and a healthy adult.
REFERENCES


The First World Congress of Pediatric Urology: A Recap

Following on the footsteps of two very successful joint meetings between the European Society of Pediatric Urology (ESPU) and the AAP/Section on Urology (Tours, France organized by Dr. Henri Lottmann and Uppsala, Sweden organized by Dr. Goran Lackgren), several members of the Society for Pediatric Urology (Drs. Bill Cromie, Tony Caldamone, Marty Koyle, Doug Husmann and Marc Cendron) were inspired to expand the meetings to worldwide participation.

After five years of preparations, several organizational meetings, many conversations with members and leaders of various pediatric urology societies, the concept of a World Congress of Pediatric Urology came into being. The International Children’s Continence Society (ICCS) and the Asian Pacific Association of Paediatric Urologists (APAPU) were very early supporters of the idea and soon the Society for Fetal Urology (SFU), Sociedad Iberoamericana de Urologia Pediatrica (SIUP), Pediatric Urology Nurses Specialists (PUNS), Egyptian Urological Association/Pan African Urological Surgeons’ Association (EAU/PAUSA) and the European Society for Pediatric Urology (ESPU) were on board. Following very constructive discussions with the American Urological Association (AUA), it was felt, that, for logistical and educational reasons, the meeting should be held right before the AUA annual meeting in San Francisco to allow participants to also attend the educational portion of that meeting.

Recommendations for topics and speakers, as well as the call for abstracts, yielded results beyond expectations with over 600 abstracts and 35 videos, originating from 42 countries around the globe, afforded the Program Planning Committee (Marc Cendron, Chair, Douglas Husmann, William Hubert, Patrick Duffy, Anthony Herndon, Miguel Castellan, Soren Rittig, Stuart Bauer, Paul Austin, Ibrahim Mokhless, and Mohammed Eissa) the opportunity to assemble an outstanding program composed of state-of-the art lectures, panel discussions, podium presentations, moderated poster sessions, poster displays and video sessions.

The meeting started very auspiciously on May, 27, 2010 with the nurses and allied personnel meeting attended by over 120 participants, in addition to a Biofeedback Course for both allied health and physician participants.

During the next two days it was non-stop pediatric urology. Dr. Bloom presented a wonderfully erudite account of “The First 50 Years of Pediatric Urology.” Keynote speakers during the meeting included Mr. Christopher Woodhouse, who delivered the Meredith Campbell lecture devoted to adolescent urology; Dr. Bernard Churchill who provided new insights on nanotechnology and its potential use in pediatric UTIs. The role of the psychologist in the management of children with bladder and bowel elimination disorders was explored by Dr. William Warzak. The Kelm Hjalmas ICCS Memorial Lecture was given by Alyssa Lebel on the application of functional MRI with pediatric pain to neural circuits and micturition.

Dr. Craig Peters summarized some of the recent information on reflux and questioned whether antibiotic prophylaxis was necessary. Dr. Brock reviewed the status of prenatal diagnosis of GU anomalies and its impact on current practice. Several panels on hypospadias, varicocele, testicular maldescent, enuresis, regenerative medicine, minimally invasive surgery, voiding dysfunction, Wilms tumor management, and building pediatric urology in low resource countries, covered the gamut of pediatric urology topics. Master classes on genital reconstruction were also extremely well attended.

In total, 67 podium presentations were made, 67 posters were moderated, 79 posters were on display, and 18 videos were either shown or discussed. The total number of registered participants was a remarkable 1,006, with 562 urologists and 158 residents/fellows. Participants came from 75 countries, making the World Congress the best attended pediatric urology meeting ever.