Bladder/Prostate Rhabdomyosarcoma: Past, Present and Future

Fernando A. Ferrer,* Michael Isakoff and Martin A. Koyle

From the Departments of Pediatric Urology (FAF) and Oncology (FAF, MI), Connecticut Children's Medical Center, University of Connecticut, Hartford, Connecticut, and Division of Pediatric Urology, Denver Children's Hospital, University of Colorado (MAK), Denver, Colorado

Purpose: The last few decades have witnessed substantial improvement in outcomes in children with bladder/prostate rhabdomyosarcoma. We reviewed relevant historical aspects of treatment, current treatment strategies and new developments. Most importantly we identified areas of existing controversy, which will provide direction for future studies and continued improvements in therapy.

Materials and Methods: A database (PubMed, MEDLINE, etc) search was performed from 1966 through January 2005. Approximately 500 citations were identified. Relevant citations were reviewed in detail.

Results: While the reported cure rate has improved to approximately 70% to 80% and bladder preservation rates as high as 60% are reported, substantial controversy continues in certain areas. Specifically the long-term function of preserved bladders, the contribution of radiotherapy to bladder dysfunction, the timing of reconstruction and molecular markers of disease progression are among the areas that require further investigation.

Conclusions: Substantial progress has been made as a result of multi-institutional collaborative trials. Future combined studies are required to further the treatment of this childhood malignancy.

Key Words: bladder, prostate, rhabdomyosarcoma, pediatrics, outcome assessment (health care)

Outcomes in children with B/P RMS have improved significantly in the last few decades. Progress has largely been due to collaborative trials done by the IRS. Readers are referred to the COG website (www.childrensoncologygroup.org), where the complete IRS protocols as well as rapid reviews for surgeons are available for members. Nonmembers should consult their institutional COG primary investigator for information on protocols. We reviewed the history of IRS studies, pathological and molecular advances in RMS, current evaluation and treatment guidelines, areas of controversy and future directions.

PRIOR IRS TRIALS

RMS was first described in 1850 by Wiener.[1] However, little was published on the treatment of RMS until the 1950s. At that time others described a histological classification system that remains the basis of the system in use today.[2,3] Initially surgery was the preferred treatment but subsequently the effectiveness of combined multimodal therapy led to the formation of large multicenter trials performed by the IRS.[1,4,5]

During the first IRS study (IRS I) (1972 to 1978) up-front anterior exenteration was the primary therapy in patients with B/P tumors.[6,7] Surgery followed by chemotherapy with or without radiotherapy had a relatively favorable outcome with 78% overall survival. However, the bladder preservation rate at 3 years was only 23% in IRS I.[8] At that time the price for survival was radical exenterative surgery with its associated complications.[9,10] During the final years some patients began receiving a trial of primary chemotherapy directed toward bladder preservation. IRS I demonstrated that lymph node dissection and adjuvant therapy benefited patients with nodal disease.[11,12]

IRS II (1979 to 1984) established the routine use of chemotherapy and/or radiotherapy before surgery. It was hoped that by administering primary chemotherapy the number of patients requiring exenterative surgery or radiotherapy would decrease.[13] Ten percent of patients achieved relapse-free survival with chemotherapy alone. Overall survival remained approximately 80%. Disappointingly the rate of survival with an intact functional bladder was only 25%.[13,14]

IRS III was performed from 1985 to 1992.[14] This was the first study to achieve significant improvements in bladder preservation. Chemotherapy was standardized to include doxorubicin, cisplatin and etoposide in patients with B/P tumors. The timing of radiotherapy was fixed at 6 weeks after the induction of treatment. Surgically primary and secondary partial cystectomy was emphasized. Overall survival was approximately 83%. The proportion of patients who retained bladder function at 4 years after diagnosis increased to approximately 60%, although by today's standards bladder function was evaluated only superficially.[15,16]

Outcomes in patients with B/P RMS treated in IRS IV (1993 to 1997) were reported by Ardnt et al in this journal.[17] Data analysis identified 88 patients with B/P RMS. Of these tumors 70% arose from the bladder. Overall 6-year survival was 82%, although event-free survival was 77% at a mean 6.1-year followup. Of the patients 55 retained the bladder

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* Correspondence: Department of Urology, Suite 2G, Connecticut Children's Medical Center, Hartford, Connecticut 06106 (telephone: 860-545-9658; FAX: 860-545-9545; e-mail: Fferrer@ccmckids.org).

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without relapse but only 36 (40%) had normal bladder function. It is important to note that functional evaluation was limited, suggesting that the true extent of dysfunction may have been greater.[18] IRS IV was the first study to evaluate the use of a TNM pretreatment staging system. IRS IV also concluded that hyperfractionated radiation did not provide an advantage in terms of outcome over that of standard conformal RT.[19]

PATHOLOGICAL AND MOLECULAR ADVANCES

The original histological classification of Horne and Enterline has been modified into an international system, which includes embryonal (encompassing the less common botryoid and spindle cell variants) along with ARMS, pleomorphic and undifferentiated subtypes.[3,20] Embryonal sarcomas represented 73% of B/P RMSs documented in IRS studies from 1998 to 2004.[21,22] In previous years they represented more than 90% of tumors. Histologically ERMS resembles fetal striated muscle, correlating with a gestational age of 7 to 10 weeks.[23] The composition is mainly that of spindle-shaped cells with a central nucleus in an eosinophilic cytoplasm. Of specimens 30% show cross-striation. The diagnosis of ERMS rests on morphological identification of the tumor and spotty nuclear staining for myogenin or MyoD1. Diffuse nuclear staining of myogenin or MyoD1 is seen with ARMS.[24] Sarcoma botryoides represents a subtype of embryonal tumor and it typically has a favorable prognosis. The spindle cell variant of ERMS is most common in the paratesticular region and it typically carries an excellent prognosis.[20]

ARMS is the next most common subtype, representing approximately 15% to 20% of all RMSs. It is usually seen in older children and histologically it resembles striated muscle at gestational ages 10 to 21 weeks. Histological features include clusters of small round cells adhering to fibrosepta, giving the appearance of well-defined alveolar spaces. Unlike ERMS cross-striations are uncommon and the alveolar subtype is more common in the extremities and trunk. Additionally, ARMS typically has distinct molecular alterations, including a t(2;13) or t(1;13) translocation.[25] The more common t(2;13) translocation corresponds to a *PAX3-FKHR* gene fusion and the t(1;13) translocation corresponds to a *PAX7-FKHR* gene fusion. Recently Sorenson et al documented the importance of these gene fusions in patients with ARMS and noted that in those with metastatic disease *PAX3-FKHR* fusion resulted in a significantly higher rate of relapse and death.[25] Patients with *PAX3-FKHR* fusion also seemed to have a greater predisposition toward bone marrow metastasis.

Pleomorphic RMS is not typically found in the bladder or prostate of children. However, it may occasionally present in the bladder of adults.[26,27] The undifferentiated subtype is often difficult to identify due to a lack of antigenic markers and nonspecific large round cells with scant cytoplasm. This tumor can be confused with Ewing's sarcoma and in difficult cases the identification of t(2;13), t(1;13) translocations specific for RMS or t(11;22) specific for Ewing's sarcoma can be helpful.[28,29] Occasionally these tumors can be differentiated by immunohistochemical identification of specific muscle proteins, such as actin, myosin, desmin and myoD.[30,31] Rarely electron microscopy can be used to identify Z bands associated with actin-myosin bundles specific to RMS.[32]

Histological classification related to outcome

Histology	Prognosis	% 5-Yr Survival
Sarcoma botryoides spindle cell	Favorable	90
Embryonal pleomorphic	Intermediate	65–75
Alveolar undifferentiated	Unfavorable	40–55

Histological classification continues to be one of the strongest predictors of outcome in RMS (see table). RMS can spread by local infiltration, and by lymphatic and hematogenous routes. Spread to local or regional lymph nodes is present in approximately 20% of patients at diagnosis.[33] B/P tumors metastasize most commonly to the lung, bone marrow and bone. Omentum is sometimes involved, while metastases to other organs, such as the liver or brain, are rare.[34–36]

Genetic analysis of embryonal and alveolar subtypes of RMS has identified a number of common abnormalities, including the described *PAX-FKHR* gene fusions, aberrant expression of regulatory factors such as MYOD1 and myogenin, and retinoblastoma and p53 pathway mutations.[37] Until recently which individual or combined alterations could cause cell transformation was unknown. Sharp et al reported that mice with inactivated *INK4a/ARF* (cyclin-dependent kinase inhibitor/alternate reading frame) that over express hepatocyte growth factor/scatter factor were found to almost uniformly have RMS with high penetrance and short latency.[38] Although the similarity of this model to human RMS remains unclear, the investigators described a unique animal model for further study. Deletions of *INK4a/ARF* have an effect on the retinoblastoma and p53 pathways, which are suspected to be important in RMS.

EVALUATION AND STAGING

B/P RMS typically presents as urinary retention, urgency, frequency or incontinence.[35] Gross hematuria and infection may also be present. Occasionally patients present with systemic signs of malignancy.

The first study to identify a B/P mass is often ultrasound. Definitive CT or magnetic resonance imaging must be performed in an accurate, reproducible manner, so that serial imaging can be used to help assess the efficacy of primary chemotherapy. Radiography typically involves fine cut cross-sectional imaging with tumor measurements along 3 axes. In up to 20% of cases it is impossible to determine whether the site of origin was the bladder or prostate. One should note that even with a good histological tumor response to chemotherapy the residual mass may contain a large amount of stomal tissue. Therefore, the size of the residual mass may not indicate the degree of cancer burden.

Regional lymph nodes should be assessed by retroperitoneal thin cut CT (fig. 1). Chest CT is used to evaluate lung metastasis. Brain imaging is not required for tumors limited to the genitourinary system. More recently the use of positron emission tomography has been reported, although in patients with RMS its true usefulness remains to be proved (fig. 2).[39]

Endoscopic biopsy of the primary lesion may be attempted using a pediatric resectoscope or cold cup biopsy forceps. Because the loop size of the pediatric resectoscope is small, multiple samples may be needed to make an accurate