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EDUCATIONAL ARTICLE

Genitourinary rhabdomyosarcoma: Which treatment, how much, and when?

Hsi-Yang Wu [a,*], **Howard M. Snyder III** [b], **Richard B. Womer** [c]

[a] *Department of Urology, Stanford University, 300 Pasteur Drive, S-287, Stanford, CA 94305-5118, USA*
[b] *Division of Pediatric Urology, Children's Hospital of Philadelphia, 34th & Civic Center Blvd., Philadelphia, PA 19104, USA*
[c] *Division of Oncology, Children's Hospital of Philadelphia, 34th & Civic Center Blvd., Philadelphia, PA 19104, USA*

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Abstract *Objective:* To review the current management of pediatric genitourinary rhabdomyosarcoma (RMS).
Methods: Studies performed by the Intergroup Rhabdomyosarcoma Study Group, Children's Oncology Group (COG), International Society of Paediatric Oncology (SIOP) and others over the past 10 years were reviewed to compare the use of surgery, chemotherapy, and radiotherapy for treatment of RMS and their associated outcomes.
Results: Equivalent overall survival rates were reported in the last COG and SIOP trials, with worse event-free survival rates for bladder/prostate RMS in SIOP trials. The use of radiotherapy for local control was the main difference between current COG and SIOP protocols. Surgery is used to diagnose RMS, and for local control after chemotherapy. Chemotherapy is used for systemic control of RMS, but metastatic RMS will require new approaches.
Conclusion: Risk stratification and risk-based therapy are being studied to decrease morbidity from treatment of RMS. The proper role of surgery vs radiotherapy for local control and whether additional treatment with second-line chemotherapy outweighs the avoidance of radiotherapy remain to be defined.

Introduction

The appropriate timing, extent, and intensity of surgery, chemotherapy, and radiotherapy for pediatric genitourinary rhabdomyosarcoma (RMS) remain controversial. Studies sponsored by the Children's Oncology Group (COG) in North America, International Society of Paediatric Oncology (SIOP) in Europe, Cooperativen Weichteilsarkom Studie (CWS) in

* Corresponding author. Tel.: +1 650 724 7608; fax: +1 650 498 5346.
E-mail addresses: hwu2@stanford.edu (H.-Y. Wu), snyderh@email.chop.edu (H.M. Snyder III), rwomer@mail.med.upenn.edu (R.B. Womer).

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Germany, and Italian Cooperative Group (ICG), are attempting to minimize treatment morbidity while maintaining event-free survival. (The COG studies are the successor to the Intergroup Rhabdomyosarcoma Study Group (IRS) studies.) With over 80% of genitourinary RMS patients being long-term survivors, there is increasing attention being paid to improved patient stratification, risk-based therapy, and functional organ preservation in order to prevent long-term complications. As there are important differences between the more aggressive COG approach of giving more chemotherapy and applying radiotherapy based on post-resection tumor volume vs the SIOP approach of minimizing radiotherapy based on chemotherapy response [1], we will review the reasons underlying these approaches so that the results of future studies can be appropriately interpreted.

Twenty per cent of RMS cases involve the bladder, prostate, vagina, or paratesticular area, and usually present at the ages of 2–4 years and 15–19 years. RMS consists of small, blue, round cells, with varying numbers of spindle cells resembling fetal skeletal muscle [2]. Three-year overall and event-free survival for non-metastatic RMS was 86% and 77% in IRS-IV using VAC chemotherapy (vincristine, dactinomycin, cyclophosphamide) [3]. Event-free survival is defined as no relapse, secondary malignancy, or death from a non-tumor cause. Tumor stage correlates with event-free survival (Stage I, 86%; Stage II, 80%; Stage III, 68%) [3]. Embryonal histology, which is favorable (82% 5-year event-free survival), accounts for 90% of genitourinary RMS. Sarcoma botyroides ('bunch of grapes') is a polypoid form of embryonal histology, which is often seen in bladder and vaginal RMS. Alveolar histology, which accounts for the remaining 10% of genitourinary RMS, has a 65% 5-year event-free survival rate [4]. Patients who are $<$1 year and $>$10 years old have a worse event-free survival rate compared to those aged between 1 and 9 years (53% and 51%, vs 71%) [5].

The key question is: if overall survival is similar, is adding radiotherapy to achieve improved local control (COG approach) a better choice than chemotherapy alone, with an increased need for salvage therapy and lower event-free survival (SIOP approach) [6,7]? For non-bladder/prostate genitourinary RMS, 5-year overall and event-free survival are essentially the same in IRS-IV and SIOP MMT-89: 90% and 83% (IRS) vs 94% and 82% (SIOP). For bladder/prostate RMS, overall survival was similar, 86% (IRS) vs 80% (SIOP), but event-free survival was worse in SIOP trials, 79% (IRS) vs 64% (SIOP) [7]. The outcome reflects different therapeutic goals: to maximize event-free survival in IRS studies, vs maximizing overall survival in SIOP studies [8].

Diagnosis

Bladder and prostate primaries can present with urinary retention, urgency, or gross hematuria. Vaginal primaries present with vaginal bleeding or an introital mass, and paratesticular primaries present as a painless scrotal mass. Imaging of the primary mass and retroperitoneum should be carried out with MRI. Chest CT is used to detect lung metastases. Bone scan, bone marrow aspirate and biopsy complete the metastatic work up. Positron emission tomography using fluorodeoxyglucose may supplant bone scans in the future [9]. For paratesticular RMS, serum β-human chorionic gonadotropin and α-fetoprotein will confirm that the mass is not a testicular germ cell tumor. The initial surgical approach is to obtain adequate tissue for a definitive diagnosis. One should attempt to remove the entire tumor without adversely affecting organ function, except in the case of paratesticular RMS, where the testis is removed with the spermatic cord using an inguinal approach. If full resection is not possible, primary chemotherapy is given after the biopsy is obtained.

Staging

Both COG and SIOP staging use a TNM system (Tables 1 and 2). However, IRS studies also used a clinical grouping system (Table 1) which is dependent on completeness of surgical excision. Since most patients are managed with initial biopsy and chemotherapy, they are placed in Group III. The grouping system is listed for the interpretation of IRS studies. Patients are assigned to low, intermediate, or high risk groups according to stage, group, and histology. Low risk patients include those with paratesticular RMS with embryonal pathology, with complete resection or microscopic residual, and those with vaginal primaries (including those with Group III disease). Intermediate risk patients include bladder/prostate RMS, and those with gross residual disease. High risk patients are those with metastatic disease [10].

Table 1 COG staging and clinical groups.

COG staging
T_1: Confined to Organ of Origin, a: $\leq$5 cm, b: $>$5 cm
T_2: Extension or Fixed to Surrounding Tissue, a: $\leq$5 cm, b: $>$5 cm
N_o: Regional Nodes Clinically Negative
N_1: Regional Nodes Clinically Positive
N_x: Unknown
M_o: No Distant Metastasis
M_1: Metastasis Present
Stage I: Vaginal and Paratesticular RMS, any T, any N, M_o
Stage II: Bladder/Prostate RMS, T_{1a} or T_{2a}, N_o or N_x, M_o
Stage III: Bladder/Prostate RMS (T_{1a} or T_{2a}) and N_1, M_o, OR (T_{1b} or T_{2b}), any N, M_o
Stage IV: Any Tumor with M_1
IRS/COG clinical groups
Group I: Localized Disease, Completely Excised, No Microscopic Residual
A: Confined to Site of Origin, Completely Resected
B: Infiltrating Beyond Site of Origin, Completely Resected
Group II: Total Gross Resection
A: Gross Resection with Microscopic Local Residual
B: Regional Disease with Involved Lymph Nodes, Completely Resected with No Microscopic Residual
C: Microscopic Local and/or Nodal Residual
Group III: Incomplete Resection or Biopsy with Gross Residual
Group IV: Distant Metastases