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Genitourinary Rhabdomyosarcomas

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Introduction

Rhabdomyosarcoma is the most common soft tissue sarcoma in children and young adults.[1,2] RMS accounts for approximately 4%-6 % of all pediatric cancers and 50 % of soft tissue sarcomas. The annual incidence is 4.3 cases per one million children, and approximately 350 new cases are diagnosed in the United States each year. There is a predilection for males (Male:Female = 1.4:1), and it is more often seen in Caucasians.[1,2,3] More than 2/3rd of patients are diagnosed before the age of 6 years. Approximately 30% of RMS tumors arise from the genitourinary area. There are two main subtypes of RMS, embryonal (ERMS), which is the more commonly encountered subtype, and the alveolar (ARMS) subtype, which is clinically more aggressive.

In 1972, the Intergroup Rhabdomyosarcoma Study Group (IRSG) was formed to study the biology and treatment of RMS patients in the United States.[4] The results from the IRSG clinical trials have reinforced the concept that RMS is a disease that requires coordinated multidisciplinary care between the surgical, pathology, medical oncology, and radiation oncology services.[4,6,5,7] This chapter will review the clinical characteristics, evaluation, treatment, and post-therapy considerations for patients with genitourinary RMS (GU RMS).

Pathology

Arising from the striated muscle, RMS is one of the "small round blue cell tumors of childhood", which also includes neuroblastoma, Ewings sarcoma, and lymphoblastic lymphoma. Under light microscopy, cross-striations or characteristic rhabdomyoblasts can be identified. Immunohistochemical studies for RMS include stains for muscle-specific myosin, actin, desmin, myoglobin, myogenin, and Myo-D[8].

As previously mentioned, there are two main subtypes of RMS. ERMS is the most common, accounting for 75% of all RMS cases. Sarcoma botryoides, or botryoid variant, is a specific subtype of ERMS that mainly is found in patients with vaginal RMS during infancy and early childhood. This sarcoma generally presents as soft nodules that fill and sometimes protrude from the vagina, resembling a bunch of grapes. Another ERMS variant is the spindle cell variant, which has been described in paratesticular RMS cases.[9] ARMS accounts for approximately 20% of cases. In 80% of ARMS cases, there is a characteristic translocation involving fusion between the forkhead transcription factor (FOXO) gene, located on chromosome 13, with either the PAX3 or the PAX7 transcription factor genes, located on chromosomes 2 and 1 respectively.[10,11]

Clinical Presentation

a. Bladder/Prostate RMS

Children with bladder RMS usually present clinically at a mean age of 4.5 years with symptoms of urinary tract obstruction, hematuria, dysuria, polyuria, or abdominal mass.[5,12] Some children present with obstructive uropathy, which requires urgent decompression using either percutaneous or endoscopic techniques. Bladder RMS is most commonly located in the trigone and base of the bladder and is more likely to be embryonal in histology. Spread of the tumor is superficial beneath the mucosa and may infiltrate surrounding structures, such as the urethra, vagina, cervix, and perivesical tissues. Loco-regional lymph node metastasis is seen in 10%-20% of cases.[13]

RMS of the prostate presents with similar symptoms as that of bladder tumors, but in addition, some children may also have difficulty in defecation. Histology is similar to bladder tumors and since tumors in this site can be large or protrude into the bladder, it becomes challenging to ascertain the exact location of the primary site.[12]

b. Paratesticular

Paratesticular RMS usually arises as a painless mass in the scrotum. Median age of presentation is approximately 6 years of age.[14] Histology is ERMS in more than 90% of cases, but a spindle cell variant has been noted in some cases.[9] It arises from mesenchymal elements of the spermatic cord, epididymis, or tunica.

Lymph node metastasis is seen in about 35% of patients with embryonal histology and around 15% for spindle cell variant cases.[9]

c. Uterus and Cervix

RMS in the uterus and cervix tend to occur in adolescent girls (median age = 15 years).[15,16] Bleeding is a common symptom, and a pelvic mass in the form of a pedunculated polyp may be seen on examination. Uterine tumors tend to be large at time of diagnosis while cervical tumors are usually less than 5 cm at diagnosis. Nodal involvement is uncommon. Tumors are usually of the ERMS or botryoid subtype.[16]

d. Vagina and Vulva

RMS in the vulva and vagina tends to occur in younger children (median age= 21 months).[15] Clinically vaginal tumors can present with bleeding, introital mass, urinary and/or bowel obstruction, while vulval lesions can also present as a firm nodule in the labia or in the periclitoric region.[15] Vaginal tumors tend to be of the ERMS or botryoid subtypes, while tumors of the vulva tend to be ARMS.[17] Lymph node involvement is also more likely with vulval RMS.[16]

Evaluation and Staging

Initial imaging of the primary site can be performed with either ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) scans. For paratesticular and pelvic RMS, serum â-human chorionic gonadotropin and á-fetoprotein levels should be assessed since malignant germ cell tumors are in the differential diagnosis. Metastatic evaluation should include CT or MRI imaging with contrast of the abdomen and pelvis to assess for lymph node metastasis, CT scan of the chest, radionuclide bone scan, and bilateral bone marrow biopsies and aspirates of the iliac crests since RMS can metastasize to the bone marrow (Table 1). 18F-fluorodeoxyglucose positron emission tomography (FDG PET) scans are increasingly being used to aid in assessment for metastases, but their utility is still being studied.[18]

Special consideration should be given to patients with paratesticular tumors. Patients at least 10 years of age should undergo an ipsilateral retroperitoneal lymph node dissection due to the increased risk of lymph node involvement that may escape the detection by CT scans.[14] However, patients less than 10 years of age may be evaluated with CT scans. If there is radiographic evidence of suspicious lymph nodes, then nodal exploration is recommended.

Based on the results of previous IRSG clinical trials, the current RMS staging system has evolved into a combined stage and group system which takes into account various factors that are known to affect clinical outcome, such as histology, site of primary tumor, and lymph node involvement. The current stage and group categories are detailed in (Table 2) and (Table3).

Table 1. Recommended Evaluation Studies

Complete blood count with differential, serum creatinine, glutamic pyruvic transaminase(SGPT), glutamic oxaloacetic transaminase(SGOT), total bilirubin, and urinalysis
Bilateral bone marrow biopsy and aspirate
Chest radiograph
Computed tomography (CT) of chest
Magnetic resonance imaging (MRI) or CT scan of primary site with contrast, including draining lymph node regions. For paratesticular tumors, thin cut CT scan is recommended to evaluate ipsilateral retroperitoneal lymph node region
Radionuclide bone scan
Ipsilateral retroperitoneal lymph node dissection for patients with paratesticular tumors and age = 10 years or < 10 years and with radiologic evidence of lymph node involvement

Table 2. Stage - TNM staging system for genitourinary rhabdomyosarcoma

Stage	Sites	Tumor stage invasiveness	T stage size	N	M
1	Genitourinary	T_1 or T_2	a or b	Any N	M_0
2	Bladder/prostate	T_1 or T_2	a	N_0 or N_X	M_0
3	Bladder/prostate	T_1 or T_2	a	N1	M_0
			b	Any N	
4	All	T_1 or T_2	a or b	N_0 or N_1	M_1

T: Tumor stage
N: Regional nodes
M: Metastases

T_1: Confined to anatomic site of origin
T_2: Extension
a: 5 cm in diameter
b: >5 cm in diameter

N_0: Not clinically involved
N_1: Clinically involved
N_X: Clinical status unknown

M_0: No distant metastases
M_1: Distant metastases present

Ref: *Lawrence, W, Gehan, EA, Hays, DM, et al. Prognostic significance of staging factors of the UICC staging system in childhood rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study (IRS-II). J Clin Oncol 1987;5:46; and Lawrence, W, Anderson, JR, Gehan, EA, et al. Pretreatment TNM staging of childhood rhabdomyosarcoma: a report of the Intergroup Rhabdomyosarcoma Study Group. Cancer 1997;80:1165*

Table 3. Clinical group system by the Intergroup Rhabdomyosarcoma Study Group (IRSG)

Clinical group	Extent of disease/surgical result
I	a. Localized tumor, confined to site of origin, completely resected b. Localized tumor, infiltrating beyond site of origin, completely resected
II	a. Localized tumor, gross total resection, but with microscopic residual disease b. Locally extensive tumor (spread to regional lymph nodes), completely resected c. Locally extensive tumor (spread to regional lymph nodes), gross total resection, but microscopic residual disease
III	a. Localized or locally extensive tumor, gross residual disease after biopsy only b. Localized or locally extensive tumor, gross residual disease after major resection (50% debulking)
IV	Any size primary tumor, with or without regional lymph node involvement, with distant metastases, irrespective of surgical approach to primary tumor

Ref : *Crist, W, Gehan, EA, Ragab, AH, et al. The Third Intergroup Rhabdomyosarcoma Study. J Clin Oncol 1995;13:610; and Crist, W, Garnsey, L, Beltangady, M, et al. Prognosis in children with rhabdomyosarcoma: A report of the intergroup rhabdomyosarcoma studies I and II. Intergroup Rhabdomyosarcoma Committee. J Clin Oncol 1990;8:443*

Treatment

RMS therapy requires a coordinated multidisciplinary management plan that includes chemotherapy, surgery and/or radiation therapy. Successive clinical trials by collaborative groups, such as the IRSG (now known as the Soft Tissue Sarcoma Committee of the Children's Oncology Group), the Study for Malignant Mesenchymal Tumors of the Societe´ Internationale d'Oncologie Pediatrique (SIOP-MMT) in Europe, and the Cooperative

Weichteilsarkom-Studie (CWS) in Germany, have demonstrated that successful treatment of RMS is dependent upon a variety of clinicopathologic factors, such as tumor histology, primary site of disease, extent of disease, and extent of disease resection. Thus, careful coordination between the surgical, pathology, medical oncology, and radiation oncology services is paramount for the care of RMS patients, and each subspecialty has its own special considerations that will be reviewed in this section.

a. Surgery

Since most bladder/prostate RMS tumors are initially unresectable, a biopsy is usually performed by cystoscope with cold-cup biopsy forceps making sure that the amount of tissue obtained is sufficient.[18] However, if a laparotomy is performed for initial evaluation, then the iliac and paraaortic lymph node chains should also be evaluated. The first IRSG trial utilized exenterative surgical procedures, however, subsequent clinical trials have focused on bladder salvage with approximately 50%-60% of patients achieving bladder preservation.[16] For those few patients with bladder RMS localized to the dome of the bladder, then a partial cystectomy can be performed.

Paratesticular RMS is typically assessed by radical inguinal orchidectomy with complete removal of the spermatic cord and making sure that the proximal cord has no residual tumor on frozen section analysis. Approach through a scrotal incision is generally not recommended since there is a risk of tumor seeding, which may lead to need for hemiscrotectomy.[18,19,20] Patients at least 10 years of age or younger patients with radiographic evidence of lymph node involvement require an ipsilateral nerve-sparing retroperitoneal lymph node dissection with the superior margin being at the level of the renal vein. One previous IRSG study demonstrated that older patients were at increased risk of lymph node involvement despite having "normal" appearing CT scans.[14] Establishment of lymph node involvement is vital since radiation therapy is required for areas with positive lymph node involvement.

Initial complete resection of vaginal tumors is often difficult. Location is relevant since proximal vaginal tumors would likely require a hysterectomy with vaginectomy. Partial vaginectomy or local excision of certain vaginal or cervical tumors is possible if the tumor is pedunculated or polypoid and attached via a stalk. Uterine tumors are difficult since they tend to be large at diagnosis and have an increased likelihood of being ARMS. Also, since female patients who receive pelvic radiation are at increased risk of pubertal delay and infertility, hysterectomy is often necessary for uterine RMS.

b. Chemotherapy

Vincristine, actinomycin-D, and cyclophosphamide (VAC) is currently the standard of care chemotherapy for non-metastatic RMS in the Unites States. However, the SIOP group utilizes several different chemotherapy regimens using a risk-based schema that is also based on initial response to chemotherapy.[21] The SIOP-MMT regimens vary with patients who have completely resected low risk disease receiving only vincristine and actinomycin-D (VA), while patients with nodal involvement receiving a six drug combination including VA, ifosfamide, carboplatin, epirubicin, and etoposide. Given the different treatment strategies by the different collaborative groups, comparing efficacy of treatment regimens has been difficult.

Currently the focus has been on development of chemotherapy regimens that decrease the risk of late-effects, yet remain clinically effective in producing treatment response. The current clinical trials by the Children's Oncology Group have decreased the amount of cumulative alkylator exposure in an effort to decrease the risk of infertility and second malignancy.

c. Radiotherapy

Radiation therapy remains an important tool in the treatment of RMS, especially for cases of surgically unresectable disease. However, since most RMS patients are prepubertal at time of diagnosis, there has been much investigation into decreasing the radiation dose for certain groups of patients in order to decrease the risk of side effects, such as infertility, delayed puberty, and delayed bone growth. The field of treatment is determined by treating all areas of gross tumor involvement, including regions of nodal involvement. Total radiation dose is determined by extent of disease, tumor histology, and extent of tumor resection. While ERMS patients with completely resected disease and without nodal involvement can avoid radiation therapy, all ARMS patients are recommended to receive radiation therapy irregardless of surgical resection status. In general for ERMS and ARMS patients with grossly resected tumor with microscopic residual disease and no nodal involvement, then these patients may receive a reduced dose of 36 Gray (Gy), while patients with microscopic

residual disease with nodal involvement would receive 41.4 Gy. Patients with gross residual disease (IRSG Group III) would receive 50.4 Gy.

The most common modality of radiation therapy is conventional photon delivery. However, there has been interest in utilizing different modalities that deliver more directed doses to special sites. Brachytherapy has been used for female genital-tract RMS, and recent reports from Europe have indicated that brachytherapy can provide safe and effective local control.[22,23] Proton beam therapy (PBT) has also been investigated for use in sites such as the prostate, and the hope is that PBT may prevent the need for radical surgery such as total cystectomy and/or prostatectomy. However, long-term follow up of efficacy is still being investigated.[24]

d. Outcome

Improvements in the delivery of multidisciplinary care have improved the outcome for most patients with RMS. Resectability of disease plays an important role, and patients with gross residual disease (IRSG Group III) have historically had a worse outcome than patients with grossly or completely resected disease (Fig. 1). However, other factors, such as patient age, tumor histology, primary site of disease, and extent of disease, play a role in patient outcome.

In general the outcome for most patients with nonmetastatic GU RMS is quite good. Patients with paratesticular RMS have an excellent prognosis with expected overall survival (OS) rates of greater than 90%.[14,21] For patients with bladder/prostate RMS, there is an increasing awareness for bladder preservation and maintenance of bladder function. In the IRS-IV clinical trial, 82% of patients with nonmetastatic bladder or prostate tumors survived 6 years, but only 40% of patients had normal functioning bladders.[20]

For female patients with genital-tract RMS, the combination of chemotherapy and conservative surgery with or without radiation therapy have resulted in excellent survival outcomes along with organ preservation. Hysterectomy rates decreased from 48% to 22% from the early IRS-I/II clinical trials compared to the IRS-III/IV trials.[25] The 5-year OS has been reported to be 82%-91%.[15, 20]

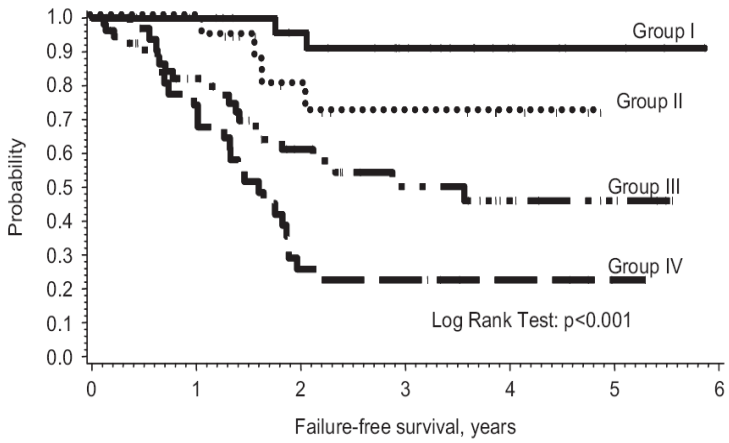

Fig. 1. Effect of clinical group on survival in IRS-IV:

Conclusion

Advances in multimodal care have led to improvements in the diagnosis, staging evaluation, and treatment of patients with GU RMS. Although the overall prognosis for most patients with GU RMS is excellent, further collaborative study is needed to further refine the treatment in order to improve the rate of organ preservation and to decrease the incidence of long-term morbidities in this challenging group of patients.

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