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Handbook for Children with Rhabdomyosarcoma

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from the
Cancer Committee

of the
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Attending physicians, residents, fellows, students and providers using this handbook in the treatment of pediatric patients should recognize that this text is not meant to be a replacement for discourse or consultations with the attending and consulting staff. Management strategies and styles discussed within this text are neither binding nor definitive and should not be treated as a collection of protocols.

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INTRODUCTION

This handbook intends to describe current management of children with rhabdomyosarcoma. It is based on current literature and accepted practice, and is managed and updated by the APSA Cancer Committee and reviewed by the surgical disease chair of COG. It is designed to consolidate the most current and up to date material you need to know when treating your patient. Rhabdomyosarcoma treatment is centered on risk stratification according to groupings for staging and assessment of resectability.

This handbook begins with A One Minute Review, is designed for use immediately before an operation and includes abbreviated staging, risk stratification, surgery guidelines and tissue handling. There follows more descriptive sections for staging and surgical management, including diagrams for retroperitoneal lymph node dissection. Enrollment on open Children's Oncology Group, both biology and clinical trials, is strongly encouraged.

Surgery Study members are listed below, and should be contacted for questions. Any and all suggestions for improvement are welcome.

APSA Pediatric Surgical Contacts for Questions on Soft tissue Sarcoma:

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ONE-MINUTE REVIEW

Rhabomyosarcoma (RMS) is staged pre-operatively and grouped post-operatively. Extent of surgical resection matters and is prognostic. Lymph node evaluation is essential and required in trunk and extremity tumors and para-testicular RMS patients aged >10 yrs.

STAGE (PREOPERATIVE)

I	Orbit, Head and Neck (not parameningeal) GU (not bladder/prostate) Biliary Tract	Any size, node
II	Bladder/Prostate Extremity Parameningeal Trunk, Retroperitoneal	< 5 cm, node (-)
III	Same as II	>5 cm and/or node (+)
IV	All	Metastasis

GROUP (INTRAOPERATIVE)

I Localized disease, completely resected
- a. confined to muscle of origin
- b. contiguous involvement

II Total gross resection
- a. microscopic residual, node (-)
- b. no microscopic residual, node (+)
- c. microscopic residual, node (+)

III Gross residual disease
- a. biopsy only
- b. gross resection (>50%)

IV Metastases

SURGICAL PRINCIPLES

Primary Tumor

Complete resection with confirmed adequate margin, (at least 0.5cm) mark margins clearly for pathology review, to guide possible re-excision. Obtain frozen section confirmation of clean margins. Consider biopsy only if there is unacceptable morbidity. Obtain enough tissue for all biological studies and cytogenetic studies. Core needle biopsy techniques may be used being careful adequate amount and quality of tissue is obtained, usually multiple cores are required.

<u>Pre-Treatment Re-excision (PRE)</u>

If a patient presents with biopsy and mass is felt to be resectable without undue morbidity, resection with negative margins should be done prior to chemotherapy and radiation. (Impacts group determination – same outcome as initial resection with negative margins.)

Delayed Primary Excision

Re-resection of residual disease at Week 12, prior to XRT. (complete gross resection allows reduction of XRT)

Lymph Nodes

Nodal biopsy indicated:

1. To confirm clinically positive nodes with sampling procedure (no dissection needed, sampling as open, needle, or sentinel biopsy)
2. If clinically negative, then site specific approach:
   -Trunk, Extremity- Sentinel Lymph node biopsy recommended
   -Paratesticular RMS for boys >10yrs or boys <10yrs with CT (+) nodes, then Staging Ipsilateral Retroperitoneal Lymph Node dissection required. (Description at end) Radical dissection not necessary, appropriate

Positive lymph nodes are not an indication for further lymph node dissections, however are important for risk stratification as affected nodal basin will be treated with radiation

Metastatic Disease

If primary tumor can be removed at diagnosis, then should consider primary resection of all metastatic disease.

Biopsy of suspected metastatic disease is important on initial presentation to confirm disease
Pulmonary mets can be resected if they persist following chemo/XRT.

Central Access

Placement of central venous access prior to initiation of chemotherapy recommended.
(double lumen broviac or port often required with sarcoma treatment regimens- insure pre-operative discussion with treating oncologist for specific request)

Tissue Handling

All tissue obtained in OR kept fresh, NO FORMALIN

DETAILS OF RMS MANAGEMENT

Rhabdomyosarcoma (RMS) is the most common form of pediatric soft tissue sarcoma accounting for 5% of all childhood cancers. It is the third most common pediatric extracranial solid tumor after Wilms tumor and neuroblastoma. 350 cases each year in the United States are diagnosed with a Caucasian male predominance and presents with a bimodal age of distribution with peaks between ages 2 to 6 years and again between 10 and 18 years. However more than 80% of cases are diagnosed before 14 years of age. Two major histologic subtypes of RMS: embryonal rhabdomyosarcoma (ERMS) for early childhood, which typically presents in the head, neck and genitourinary (GU) regions; and alveolar (ARMS) for the later childhood and adolescent years and is commonly located in the trunk and extremities. The overall incidence of the two subtypes is approximately 65-75% (ERMS) and 25-32% (ARMS). In terms of site, greater than one third (35%) of RMS occurs in the head and neck followed by GU and extremity presentations.

PRESENTATION

Symptoms of RMS will depend on the location and size of the primary disease; however, patients usually present with an asymptomatic mass. Patients may also have signs and symptoms secondary to mass effect on adjacent structures and complications due to compression.

ASSESSMENT

All patients with suspected RMS require a complete work up prior to initiation of treatment. Cross sectional imaging studies should be performed on the primary tumor with computed tomography (CT) or magnetic resonance imaging (MRI). For most patients, staging work up includes: bone marrow biopsy, whole body bone scan, CT of the brain, chest for lung evaluation, abdomen with triple phase contrast for liver assessment, and lumbar puncture for cerebrospinal fluid evaluation. Recent studies have shown that RMS without evidence of local invasion has a low rate of metastatic disease, and bone marrow biopsy and bone scan are unnecessary in these patients. The use of metabolic imaging with ^{18}F-Fluorodeoxyglucose positron emission tomography (FDG-PET) in the pediatric RMS population has limited experience and is not yet part of the first line imaging.

RISK STRATIFICATION

TNM PRE-TREATMENT STAGING CLASSIFICATION

This is a modification of the UICC-TNM staging system, which is based on site, size, clinical regional nodal status and distant spread. Staging prior to treatment requires thorough clinical examination, laboratory, imaging and examination. Biopsy is required to establish the histologic diagnosis. Pre-treatment size is determined by external measurement or MRI or CT depending on the anatomic location. For less accessible primary sites, CT will be employed as a means of lymph node assessment as well. Metastatic sites will require some form of imaging (but not histologic confirmation except for bone marrow examination) confirmation.
The staging is CLINICAL and should be based on PREOPERATIVE imaging and physical findings. Intraoperative and/or pathologic results should not affect the stage (but will affect

Clinical Group). For example, a regional lymph node that is clinically positive but pathologically negative is N1. A node that is clinically negative is N0 but if pathologically positive places the patient in Clinical Group II B. Size should reflect actual physical examination or imaging measurements. Site designation alters stage and, therefore, treatment assignment. Careful evaluation of clinical and/or imaging findings should precede site assignment. THE SURGEON IS GENERALLY BEST ABLE to designate site when choice is difficult.

Stage	**Sites**	**T**	**Size**	**N**	**M**
1	Orbit Head and neck excluding parameningeal) GU – non-bladder/ non-prostate Biliary Tract	T_1 or T_2	a or b	N_0 or N_1 or N_x	M_0
2	Bladder/Prostate Extremity, Cranial Parameningeal, Other(includes trunk,retroperitoneum, etc.) Except Biliary tract	T_1 or T_2	a	N_0 or N_x	M_0
3	Bladder/Prostate Extremity, CranialParameningeal, Other (includes trunk, retroperitoneum, etc.) Except Biliary tract	T_1 or T_2	a b	N_1 N_0 or N_1 or N_x	M_0 M_0
4	All	T_1 or T_2		N_0 or N_1	M_1

Tumor –

T(site)1 – confined to anatomic site of origin

a. < 5cm in diameter in size

b. ≥ 5 cm in diameter in size

T(site)2 – extension and/or fixative to surrounding tissue

a. < 5cm in diameter in size

b. ≥ 5 cm in diameter in size

Regional Nodes –

N_0 regional nodes not clinically involved

N_1 regional nodes clinically involved by neoplasm

N_x clinical status of regional nodes unknown (especially sites that preclude lymph node evaluation

Metastasis –

M_0 no distant metastasis

M_1 metastasis present

GROUPING CLASSIFICATION

One of the most important prognostic factors in RMS is the extent of residual disease after initial resection. After the surgery patients are assigned to a clinical group according to the pathologic evaluation of the specimen, which encompasses the completeness of excision (residual disease including margin status) and evidence of tumor metastasis to lymph nodes or distant sites prior to the initiation of systemic therapy. Clinical Group assignment is based on intraoperative findings and post-operative pathologic status and must include final pathologic verification of margins, node involvement and cytological examination of pleural and peritoneal fluid, and CSF, when applicable.

***It is important to note that the Clinical Group designation assigned at the time of diagnosis remains unchanged regardless of any second-look operation that may be performed after the initiation of chemotherapy. Clinical Group can only be changed by pre-treatment re-excision (PRE) before the initiation of chemotherapy.**

Group I: Localized disease, completely resected. Regional nodes not involved

a) Confined to muscle or organ of origin.
b) Contiguous involvement - infiltration outside the muscle or organ of origin, as through fascial planes.

NOTATION: This includes both gross inspection and microscopic confirmation of complete resection. Any nodes that may be inadvertently taken with the specimen must be negative.

Group II: Total gross resection with evidence of residual disease

a) Grossly resected tumor with microscopic residual disease such as positive margins or tumor that is removed piecemeal but is grossly removed.
b) No microscopic residual disease from primary tumor resection but with involved regional nodes.
c) Regional disease with involved nodes and evidence of microscopic residual disease.

Group III: Incomplete resection with gross residual disease this includes biopsy only

Group IV: Distant metastatic disease present at onset (Lung, liver, bones, bone marrow, brain, and distant muscle and nodes). This includes the presence of positive cytology in CSF, pleural or abdominal fluids as well as implants on pleural or peritoneal surfaces.

NOTATION: The above excludes regional nodes and adjacent organ infiltration which places the patient in a more favorable grouping (as noted above under Group II).

Risk stratification

Using components of Stage and Group a risk stratification schema has been developed to tailor disease outcomes to therapy intensity. Favorable primary sites include: orbit, genitourinary tract, biliary tract, non-parameningeal head and neck. All other sites are unfavorable. For initial resection Yes means Group I, No means Group II or III, Any means Group I, II, or III.

Risk group	Histology	Primary site	Initial resection	Distant metastases	Proportion of patients (%)	EFS (%)
Low	ERMS	Favorable	Any	None	32	70–95
		Unfavorable	Yes	None		
Intermediate	ERMS	Unfavorable	No	None	27	73
	ARMS	Any	Any	None	25	65
High	ERMS	Any	Any	Present	8	35
	ARMS	Any	Any	Present	8	15

ARMS, alveolar rhabdomyosarcoma; EFS, event-free survival; ERMS, embryonal rhabdomyosarcoma.

TREATMENT

Chemotherapy

All patients require chemotherapy the standard chemotherapy regimen include vincristine, actinomycin-D and cyclophosphamide (VAC). For the low risk group the duration of chemotherapy and the dosing of cyclophosphamide can both be decreased from the current regimen dosing while maintaining good outcomes, thereby limiting its toxicity. Irinotecan (I) was added to the regimen VAC/VI as it has shown significant benefit with metastatic and recurrent RMS. Although it didn't improve EFS, or overall survival (OS) compared to VAC alone, the lower rate of toxicity and cumulative dose of cyclophosphamide in the VAC/VI regimen supports its use as the current standard therapy for RMS. In high risk patients, slow progress has been made in ongoing prospective trials despite the use of new chemotherapeutic agents and molecular therapies. Currently a randomized phase III trial is comparing standard chemotherapy vs. standard chemotherapy and temsirolimus in treating patients with intermediate risk tumors hypothesizing that temsirolimus (m-tor inhibitor) may improve survival in conjunction with standard chemotherapy.

Radiation

RT along with surgical resection is an essential part of local control. The anatomic location, extent of residual disease after surgical resection, and lymph node involvement will dictate dosing and timing of therapy. RT is generally given between 6 to 12 weeks after the beginning of chemotherapy. RT dosing ranges between groups: Group I ARMS (36 Gy), Group II (41.4 Gy) and Group III (50.4 Gy).

Surgery

The basic principle of wide and complete resection of the primary tumor with a surrounding margin of normal tissue should be the primary goal as long as there is no major functional impairment or disfigurement. Adequate margins of 0.5 cm uninvolved tissue are suggested to

achieve local tumor control unless this involves an extensive operative procedure with sacrifice of normal tissue that would result in loss of function/cosmesis or is not technically feasible.

If resection of the primary site is carried out, the surgeon should mark all margins and orient the specimen at the operative field, so that margin evaluation is precise. Narrow margins are unavoidable in some sites such as in the head and neck. In these situations, the surgeon should take a number of separate biopsies of the "normal" tissue around the margins of resection and these should be marked and submitted separately for pathologic review. Communication with the pathologist is mandatory to assure accuracy of margin examination. The tumor should not be bisected or cut into separate specimens prior to this discussion. Any suspected microscopic or gross residual tumor that cannot be resected should be marked in the tumor bed with titanium clips to aid radiotherapy simulation.

Pre-treatment re-excision (PRE) of RMS should be considered in cases where the surgical margins are positive, a non-oncologic excision was performed, or when only a biopsy was taken, if the surgeon feels that complete resection with negative margins is feasible prior starting chemotherapy. It is most commonly performed in extremity and trunk RMS.

Patients who undergo PRE are then categorized as Group I, and have the same outcome as patients with negative margins following initial excision. PRE has shown to improve FFS and OS. Clinical Group assignment will be determined on the basis of pathology from the definitive operation prior to the start of multimodal therapy.

Delayed Primary Excision (DPE)

Response to therapy evaluated at week 12, pathologic response (amount of viable tissue) has a direct association with prognosis. A delayed primary excision (DPE) should be considered in patients with residual disease after chemotherapy, if a complete resection can be achieved without significant morbidity. The goal of DPE is to achieve local control, and reduce the required RT dose and the associated morbidity. Recent studies propose tailoring RT dosing based upon completeness of excision (36 Gy for complete R0 excision, 41.4 Gy for microscopic residual disease R1 excision, and 50.5 Gy for gross residual disease R2 excision).

Node Sampling or Node Dissection

Clinical and/or imaging evaluation of regional lymph nodes should be performed and is an important part of pretreatment staging. In those patients with clinically/radiographically enlarged nodes, treatment with chemotherapy and irradiation is recommended. However, it is preferable to avoid the need for radiotherapy. Therefore, the clinically or radiographically enlarged node(s) should be sampled histologically; patients with no tumor in the node(s) will not require radiation of the regional nodal bed. This is why pathologic confirmation of clinically positive nodes should be performed. Sentinel node biopsy with injection of blue dye and technetium 99 tracer at the site of the primary tumor can assist in identifying the node most likely to contain tumor deposits. Sentinel node biopsy should be performed with technetium 99m sulfur colloid based reagents. The use of isosulfan blue 1% dye is an accepted adjunct to technetium. Pathologic evaluation of clinically uninvolved nodes is site specific; it is required in extremity sites, trunk and in boys ⧫10 years with paratesticular primaries.

Prophylactic radical node dissection, as employed for some other malignancies, is not necessary in childhood RMS. However, staging ipsilateral retroperitoneal lymph node

dissection (SIRPLND) (see description below) is required for all boys 10 years of age and older with paratesticular RMS and for patients < 10 yrs. with positive nodes on CT exam.

IPSILATERAL STAGING RETROPERITONEAL NODE DISSECTION

Open Ipsilateral Node Dissection

A nerve sparing ipsilateral template modification to the standard bilateral RPLND is recommended. This is based on techniques described and modified by Narayan, Donohue, Jeweett and Ritchie. The approach can be transperitoneal or lateral extraperitoneal (i.e. used in renal transplant or spine fusion exposure) or laparoscopic. Figures 1 and 2 adapted from Ritchie are the templates for the dissection. In either right or left sided lesions the dissection boundaries above the inferior mesenteric artery are similar, but contralateral dissection below the IMA is avoided to assure preservation of the sympathetic fibers at L2 - 4 which are the most important fibers for ejaculatory function.

Right-Sided Lesions

The dissection for right-sided lesions begins at the level of both renal veins encompassing the aorta and cava and intra-aortocaval tissue across to the left gonadal vein / ureteral junction down to the inferior mesenteric artery and then down the right side to the level of the right common iliac artery where it is crossed by the ureter. The ipsilateral spermatic vessels are removed to the deep inguinal ring where the previously ligated stump of the cord is removed.

Left-Sided Lesions

A similar dissection for left-sided lesions is carried out with the exception of the right lateral margin, which is the vena cava rather than the right ureter. (This is due to a different pattern of nodal spread) The infra-IMA dissection is the mirror image of that described for right-sided lesions. The ipsilateral spermatic vessels are removed to the deep inguinal ring where the previously ligated stump of the cord is removed.

Laparoscopic Node Dissection

Ipsilateral retroperitoneal node dissection can be carried out effectively using laparoscopic techniques by experienced surgeons. If, in the opinion of the surgeon, surgical goals will be compromised by the laparoscopic approach for any reason after the start of a procedure, then conversion to an open node dissection is mandatory.

***The specimen should be marked so that the highest node(s) is identified,**

CENTRAL LINE

Central venous access (generally a venous port) is recommended for all patients

OUTCOMES

Overall, the patient's age, site, and size of primary tumor, clinical group, histopathology with fusion status, +/- regional lymph node involvement, and presence or absence of metastasis drive

the prognosis for RMS. Favorable characteristics include age < 10 years at diagnosis, tumor size less 5 cm, embryonal fusion negative tumor, orbit and non-parameningeal head/neck primary, tumor completely excised prior to initiation of chemotherapy, and the lack of metastatic disease at diagnosis.

Group I low risk patients have > 90% survival even with reduced chemotherapeutics dosing. Group II patients with microscopic residual disease have an 85% survival. Group III patients have increased FFS in patients with tumors < 5cm, in favorable sites, and without lymph node involvement.

Late effects

Due to the intensive treatment of RMS and increased survival of these patients with multi-modal treatment, late effects are prevalent in this patient population and often correlate with tumor site. Patients with head/neck tumors can present with late effects from therapy including pituitary or thyroid dysfunction and hearing loss from radiation. Some patients with extremity as their primary site can have function loss, fractures and impaired length growth from radiation. All patients have increased risk of secondary malignancies and have increased mortality compared to the general population. All children treated for RMS should be monitored regularly with physical examinations and imaging every 3-6 months for the first two years after completing treatment. All physicians should follow growth patterns, sexual maturity, fertility and signs and symptoms of recurrence including weakness, weight loss, neurological deficits, bone pain, bleeding and recurring infections.