HANDBOOK FOR CHILDREN WITH RHABDOMYOSARCOMA

Updated Spring 2014

This handbook represents a synthesis of all guidelines and surgically relevant information from recent COG protocols for rhabdomyosarcoma. There is a Biology Protocol, D9902 which is open, but there are no open clinical protocols. This handbook is organized to eliminate redundancy and provide you with specific data you will need in treating your patient. The closed COG clinical protocols are ARST 0331 Low Risk (Aug 2012), ARST 0531 Intermediate Risk (May 2013), and ARST 0431 High Risk (Jan 2010).

There is a One Minute Review at the beginning of this handbook that outlines the bare minimum facts for surgeons going to the OR. It includes assessment of stage and group, classification into risk groups for placement into the appropriate protocol, surgical guidelines, and tissue handling.

There follow several sections, including abstracts, objectives and scientific aims from the three clinical protocols, Pre-Treatment Staging Classification, Designation of Primary Site, Anatomic Definitions, Grouping Classification, Surgical Guidelines, Pathology Requirements, and Treatment plans. The clinical protocols share similar surgical guidelines, so this handbook cites a unified outline of surgically relevant information. (citations are in parenthesis) The summary of surgeon responsibilities, along with the surgical checklist to be completed after each case, conclude the handbook

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This document is intended to facilitate compliance with protocol guidelines by providing relevant information in an easy format. This website will be updated as new clinical protocols are opened. Any and all suggestions for improvement are welcome.

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ONE MINUTE REVIEW

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

RISK GROUPS

Low Risk ARST 0331	Stage I-II, Group I-II embryonal Stage I, Group III orbit
Intermediate Risk, ARST 0531	Stage II-III, Group III embryonal Stage I-III, Group I-III, alveolar
High Risk, ARST 0431	Stage IV, Group IV

SURGICAL PRINCIPLES

-Complete resection with confirmed adequate margin with frozen section. (Unless unacceptable morbidity) Biopsy surrounding if concerned, and mark suspected residual tumor with small titanium clips. If somatic muscle, excision of entire compartment may not be required.

-Lymph Nodes: Confirm pathology of nodes if

-clinically positive, with sampling biopsy- open, needle, or sentinel ok.
-clinically negative, but site specific. (i.e extremity)

For boys >10 years or boys < 10 years with CT (+) nodes and paratesticular RMS, Staging Ipsilateral Retroperitoneal lymph node dissection required.
Radical Dissection not necessary or appropriate.

For intermediate risk tumors, radical debulking of clinically (+) nodes useful to get regional control. Attempt to sample highest node.

-Placement central venous access prior to initiation of chemotherapy recommended.

PreTreatment Reexcision (PRE)- establish clean margins if possible. PRE determines group if done prior to chemo/XRT.

Second Look- assess for complete resection of primary tumor at Week 12. (Prior to XRT, determines if XRT necessary)

For metastatic disease (High Risk), resect pulmonary mets if persist following chemo/XRT, biopsy nonregional clinically positive nodes, biopsy other sites (bone, liver)

TISSUE HANDLING

All tissue obtained in OR kept fresh, NO FORMALIN

ABSTRACTS

Low Risk, ARST 0331: (low risk, pg 7)

Therapy for low-risk rhabdomyosarcoma (RMS) patients requires further refinement in order to maximize long-term failure-free survival and minimize short and long-term toxicity. Two Subsets of low-risk patients have been defined for this protocol; these Subsets have had excellent outcomes following treatment on IRS-III or IRS-IV. Therapies for these Subsets consisted of either vincristine plus dactinomycin and radiation therapy to areas of residual tumor on IRS-III or IRS-IV (Subset 1), or vincristine, dactinomycin plus cyclophosphamide (26.4 g/m^2 total cumulative dose) and radiation therapy to areas of residual tumor on IRS-IV (Subset 2). In the present study, a more modest dose of cyclophosphamide (4.8 g/m^2 total cumulative dose) will be given with vincristine plus dactinomycin and radiation therapy to areas of residual tumor to patients in each of the two Subsets. In this manner we hope to improve outcome without significant acute or long-term toxicity for the majority of Subset 1 patients and to maintain the excellent outcome and reduce acute and long-term toxicity for patients in Subset 2. The durations of therapy will be 22 weeks for patients in Subset 1 and 46 weeks in Subset 2.

Intermediate Risk, ARST 0531: (int risk, pg 8)

Intermediate-risk rhabdomyosarcoma (RMS) is defined as non-metastatic (Group I-III) alveolar (RMS) arising at any site (Stage 1-3) and incompletely excised (Group III) embryonal RMS arising in an unfavorable site (Stage 2,3). The long-term failure-free survival (FFS) for intermediate-risk RMS is 65%. To improve long-term survival, ARST0531 will compare the outcome of patients randomly assigned to either standard vincristine, dactinomycin, and cyclophosphamide (VAC) chemotherapy or VAC alternating with vincristine and irinotecan (VI). Radiotherapy will start at Week 4 of therapy for all patients (with rare exceptions discussed in the protocol). The local control and FFS for patients receiving early (Week 4) radiotherapy and VAC chemotherapy will be compared to similar patients treated with delayed (Week 10) radiotherapy and VAC on IRS-IV. In addition, patients will be eligible for optional studies, including fluoro-deoxy-glucose positron emission tomography assessment of response, pharmacogenomic correlations with VAC and VI toxicity, and gene expression profiles correlation with FFS

High Risk, ARST 0431: (high risk, pg 7)

Patients with metastatic rhabdomyosarcoma have a poor prognosis with an overall survival rate of approximately 30%. To improve this outcome, ARST0431 will evaluate intensification of therapy using vincristine/docorubicin/cyclophosphamide (VAC) alternating with ifosfamide/etoposide (IE) using interval dose compression, comparing outcome to patients treated on D9802. As local control is critical for optimal management of rhabdomyosarcoma, ARST0431 will also evaluate the feasibility and toxicity of combining vincristine/irinotecan (VI) with radiation therapy. Patients will be eligible for optional studies evaluating the pharmacogenomic correlations with VI toxicity and radiation therapy.

OBJECTIVES AND SCIENTIFIC AIMS

Low Risk, ARST 0331: (low, pg 9)

Primary Objectives:

To estimate the failure-free survival (FFS) for patients with low-risk rhabdomyosarcoma in Subset 1 (Stage 1, Clinical Group I/II or orbital Clinical Group III, or Stage 2, Clinical Group I/II) when treated with four courses of VAC with reduced dose cyclophosphamide followed by four courses of VA plus radiation therapy (reduction in length of therapy to 22 weeks).

To specifically estimate the FFS for patients with Stage 1, Clinical Group IIB or C (node positive) or Stage 2, Clinical Group II low-risk rhabdomyosarcoma (a subgroup treated on D9602 with 45 weeks of intensive VAC) when treated as Subset 1 patients using four courses of VAC with reduced dose cyclophosphamide followed by four courses of VA plus radiation therapy (reduction in length of therapy to 22 weeks).

To estimate the FFS for patients with low-risk rhabdomyosarcoma in Subset 2 (Stage 1, non-orbital Clinical Group III or Stage 3, Clinical Group I/II) when treated with four courses of VAC with reduced dose cyclophosphamide followed by 12 courses of VA plus radiation therapy.

Secondary Objectives:

To estimate local control rates for patients with low-risk rhabdomyosarcoma when treated with reduced radiation doses (as compared to IRS-IV), including patients with microscopic residual disease and no regional lymph node involvement who receive 36 Gy, and those with gross residual orbital tumors who receive 45 Gy.

To determine the rate of second-look surgery in patients with bulk residual tumor at diagnosis (Clinical Group III) and the proportion of second-look surgeries that render the patient tumor free or with microscopic tumor only, and to evaluate the pathologic significance of such residual tumor.

To estimate the local control rates for patients with Clinical Group III disease when the radiation dose is response-adjusted after second look surgical resection.

INTERMEDIATE RISK, 0531: (int, pg 10)

Primary objective

To compare the early response rates, failure-free survival (FFS), and survival of patients with intermediate-risk RMS treated with surgery, radiotherapy, and vincristine, dactinomycin and cyclophosphamide (VAC) or VAC alternating with vincristine, irinotecan (VI).

Secondary objectives

To compare FFS, local control, and survival of patients with intermediate-risk RMS treated with VAC and early (Week 4) radiotherapy compared to delayed (Week 10) radiotherapy, using IRS-IV for historic comparison.

To compare the acute and late effects of VAC to VAC alternating with VI, including the toxicity associated with concurrent VI and radiotherapy.

To compare the acute and late effects of VAC as delivered on this study to D9803 VAC.

To correlate change in FDG PET maximum standard uptake value (SUVmax) from Week 1 to Week 4 and 15 with FFS.

For VI treated patients, to correlate patient UGT1A1 genotype with VI toxicity.

To correlate patient CYP2B6, CYP2C9 and GSTA1 genotypes with VAC toxicity.

To prospectively evaluate and validate gene expression values with the intent to define the best diagnostic predictors and more powerful prognostic classifiers.

HIGH RISK, 0431: (high, pg 9)

Primary Objectives:

To improve the early disease control interval for patients with high-risk rhabdomyosarcoma using an intensive, interval compression therapy that permits maximal early exposure to known effective agents

To determine the feasibility and assess immediate and short term side effects of delivery of concurrent irinotecan with irradiation.

Secondary Objectives

To expand the available data for response to irinotecan/vincristine in previously untreated high-risk rhabdomyosarcoma

To prospectively evaluate and validate gene expression values with the intent to define the best diagnostic predictors and more powerful prognostic classifiers

STAGING (Low, pg 74)

TNM PRE-TREATMENT STAGING CLASSIFICATION

Staging prior to treatment requires thorough clinical examination, laboratory and imaging examinations. 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.

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 Cranial Parameningeal, Other (includes trunk,	T_1 or T_2	a	N_1	M_0
			b	N_0 or N_1 or N_x	M_0

retroperitoneum, etc.)

Except Biliary tract

4	All	T_1 or T_2	a or b	N_0 or N_1	M_1

Definitions – See Appendix IV for anatomic definitions of parameningeal, orbit and other head and neck sites

Tumor –

$T(site)_1$ – confined to anatomic site of origin

a. ≤ 5 cm in diameter in size

b. > 5 cm in diameter in size

$T(site)_2$ – extension and/or fixative to surrounding tissue

a. ≤ 5 cm 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

DESIGNATION OF PRIMARY SITE (High, pg 100)

FOR USE IN PRE-TREATMENT STAGING
(Selection of "Site Category" for Patient Entry)

NOTE: This will extend to other areas the guidelines prepared to aid in the identification of head and neck sites (Appendix II). Some of the distinctions made below are largely semantic. Although they do not change therapy, they may be important in reviewing results for specific sites. Others are vital as they would make a change in stage and therapy in IRS-V. It is astonishing how frequently data forms on the same patient from the same institution list quite different primary sites. This can only be determined in retrospect, but it should make one cautious regarding accepting a confusing or illogical site designation at the time of registration.

I. Comment on the Terms Used to Designate Primary Site in the IRS

A. The Dictated Operative Note

If the patient has undergone an initial major operative procedure, the "post-operative diagnosis: listed on the operative note that should be dictated following the procedure will ordinarily include reference to site. In such cases, this is usually the most accurate source document for site designation.

B. Larger Site Categories

Most of the terms used follow common usage. As you are aware, we consider an "extremity" to include the total forequarter or total hindquarter. This extends the extremity area on the posterior, but not the anterior, aspect of the body. The muscles over the scapula are included in the upper extremity and the muscles making up the buttocks in the lower extremity. This confines the trunk area posteriorly to that which is paraspinal and chest wall; and anteriorly, chest wall and abdominal wall. The retroperitoneal and perineal sites are listed separately in the IRS.

C. Primary Site vs. Areas of Extension

Primary sites rather than areas of extension ordinarily determine the site category. In the case of the parameningeal tumors, however, the primary site is incidental, and the approach to the meninges is the important factor in site determination in the IRS.

D. Large Tumors Involving Multiple Organs and/or Structure

Our aim in these cases is to attempt to select the most likely site of original involvement or origin. The terms "abdominal", "thoracic" and "unknown" are the least helpful in analysis.

E. "Bones"

When the designated site on the institutional forms is a word indicating a bone, i.e. "tibia", "scapula", etc., try for something more accurate or at least make it an adjective.

II. Specific Sites Within Major Categories

The following is a glossary of site designations. They are almost entirely taken from IRS I-III forms reviewed by the Committee. Some of them should not be used and others would appear to need definition. In some cases we have simply provided an explanation of what a surgeon would ordinarily mean by a given term. Site designations in data collection sheets and even operative notes may be worded in terms, which are not inaccurate but not appropriate for site designation in the IRS, where consistency is required.

1. **Abdominal Wall**

   This refers to the anterior abdominal wall from the inferior costal margins superiorly to the inguinal ligaments and symphysis pubis, inferiorly, and extends laterally between the costal margin and iliac crests to the paraspinal region. From a practical point of view, this posterior extension is so narrow in a child that it is probably insignificant as a primary site.

2. **Arm**

   Refers to the area from the shoulder joint to the elbow joint.

3. **Bile Ducts**

   Bile duct is a specific site and can be recognized as such at surgery. This might also be called "choledochus" or "biliary tract". There is probably no way one can distinguish an intrahepatic bile duct site from a primary liver site except by examining the excised specimen.

4. **Bladder**

   Our criteria for identifying the bladder as a primary site has included the appearance of tumor within the bladder cavity, which can be biopsied through an endoscope or occasionally at laparotomy. We do not recognize as primary bladder tumors those that simply displace the bladder or distort its shape. The latter are ordinarily primary pelvic sites, unless otherwise specified.

5. **Bladder/Prostate**

   In approximately 20% of males with bladder or prostatic tumors, the precise site cannot be determined even at autopsy. The histologic features are similar. Although it is desirable to have an indication of the "most probable: site from the institution, and one should strive to get this, it may not be possible.

6. **Buttocks -** These are extremity lesions.

7. **Inguinal Canal** (See paratesticular).

8. **Liver -** See "bile ducts".

9. **Paraspinal**

When tumors are described as adjacent to the vertebral column, this designation is preferable to "trunk" or "neck".

10. **Paratesticular (testicular)**

Rhabdomyosarcomas rarely arise from testicular tissue. These tumors are almost always "paratesticular" arising either adjacent to the testes within the scrotum or in the inguinal canal, i.e., "groin" or lower abdominal wall. In either case they are classified in the G. U. major site category and called paratesticular.

11. **Pelvis**

This site must be distinguished from the previously designated "special pelvic" category used in prior IRS studies. It may be regarded as a tumor within the pelvis when no more specific site is appropriate.

12. **Perianal (often called "anus" or "rectum")**

These sites are ordinarily "perirectal" or "perianal". They are distinguished with difficulty from perineal and vulval sites; but the latter distinction is important.

13. **Perineum**

This should include the sites that appear anterior to the anus and posterior to the scrotum in males and posterior to the labia in females. It extends anteriorly to the base of the scrotum in males and to the introitus in females. It must be distinguished from labial and vaginal sites.

14. **Peritoneum**

This primary site is imprecise as it extends from the diaphragm to the pelvis. One should try for specific site.

15. **Prostate -**

(See Bladder/Prostate)

16. **Retroperitoneal - (often called "psoas muscle")**

We reserve the term retroperitoneal for those posteriorly situated abdominal tumors in which there does not seem to be a more specific site. If the tumor arose in an abdominal viscus, such as the pancreas, liver, etc., this would be a preferable site designation, to "retroperitoneal". Tumors in a retroperitoneal site are in the posterior aspect of the abdomen and/or pelvis. The term "psoas" as a site is not very specific, as this muscle extends through the posterior lower abdomen, pelvis, and into the leg.

17. **Shoulder**

The posterior aspect of the shoulder, i.e., the scapular area, is an extremity site.

18. **Testes –**

See Paratesticular

19. **Uterus**

A tumor in this primary site may be difficult to differentiate from a primary vaginal site, because a tumor originating in the uterus may fill the vagina. After a therapeutic response, the distinction is usually clear. In general, there is wide separation of age ranges between these two groups with the vaginal cases occurring in infancy or early childhood and the uterine primaries in adolescents or young adults. One should be skeptical regarding a patient with a designated "vaginal" site who is over five years of age, or a patient with a designated uterine site in a patient who is under 10 years of age. Fortunately, this is not a therapy-related distinction.

20. **Vagina**

For the purpose of our study the patient with a primary vaginal lesion must have evidence of a visible tumor on the vaginal surface which can be biopsied through the vagina. Displacement or distortion of the vagina is not sufficient.

21. **Vulva**

Primary lesions in this site arise in the labial minor or majora, and these terms are often used, and are acceptable.

ANATOMIC DEFINITIONS (Low, pg 76)

ANATOMIC DEFINITIONS OF PARAMENINGEAL, ORBIT AND OTHER HEAD AND NECK SITES FOR USE IN PRE-TREATMENT STAGING

Introduction

There are three groupings of sites in the head and neck: parameningeal; orbit; and all others ("head and neck")

PARAMENINGEAL

1. Middle Ear

   This refers to a primary that begins medial to the tympanic membrane. This tumor is often advanced at presentation and because of extension laterally may present with a mass in front of or under the ear suggesting a parotid origin. It may also extend through the tympanic membrane and appear to be arising in the ear canal. When there is doubt about the site of origin, the "middle ear" designation should be picked as it implies the more aggressive therapy required.

2. Nasal Cavity and Paranasal Sinuses

   The three paranasal sinuses are the maxillary sinuses, the ethmoid sinuses, and the sphenoid sinus. These surround the nasal cavity and primary in one will frequently extend to another. It can be difficult to determine the exact site of origin but the choice is academic as the randomization is not affected. The site designation will have a bearing on the design of radiotherapy portals. Tumor arising in the maxillary or the ethmoid sinuses may invade the orbit. This is much more likely than a primary in the orbit invading one of the sinuses. When the distinction between orbit and paranasal sinus is unclear, the site selected should be paranasal sinus as it is the more likely primary site and requires appropriately more aggressive therapy. A primary arising in the sphenoid sinus (rare) may extend inferiorly to involve the nasopharynx. Again the choice of site is academic as the therapy is not different.

3. Nasopharynx

   This refers to the superior portion of the pharynx which is bounded anteriorly by the back of the nasal septum, superiorly by the sphenoid sinus, inferiorly by a level corresponding to the soft palate, and laterally and posteriorly by the pharyngeal walls.

4. Infratemporal Fossa/Pterygopalatine and Parapharyngeal Area

   This refers to the tissues bounded laterally by the medial lobe of the parotid gland and medially by the pharynx. Large tumors in this region may extend through the parotid gland and present as a mass of the lateral face, sometimes extending even to the cheek. Where there is doubt as to the primary, the parameningeal designation should be chosen as it confers appropriately more aggressive treatment. The superior

boundary of this tissue volume is the base of skull just under the temporal lobe, hence the term "infratemporal". The distinction between this and the "parapharyngeal" area is academic.

ORBIT

1. Eyelid

   This site is sometimes erroneously designated as "eye". Although there may occasionally be a case arising from the conjunctiva of the eye, the globe itself is not a primary site. The eyelid is much less frequent than the orbit itself.

2. Orbit

   This refers to the bony cavity, which contains the globe, nerve and vessels, and the extra ocular muscles. Tumor in this site will only rarely invade the bony walls and extend into the adjacent sinuses. This is why this tumor which is clearly adjacent to the skull base and it meninges is not by its natural history appropriate to include in the parameningeal sites unless there is invasion of the bone.

HEAD AND NECK

1. Scalp

   This site includes primaries arising apparently in or just below the skin of all the tissues of the face and head that are not otherwise specified below. This usually means the scalp, external ear and pinna, the nose and forehead, but not the eyelids or cheek.

2. Parotid Region
   The parotid gland lies just in front of and under the ear and may surround both sides of the posterior aspect of the ascending ramus of the mandible. Tumors in the parotid region may not arise in the parotid gland itself. As noted above, large primaries in the infratemporal fossa may erode through the parotid. A true parotid region primary should not, on radiographic studies, reveal a mass in the infratemporal fossa.

3. Oral Cavity
   This includes the floor of the mouth, the buccal mucosa, the upper and lower gum, the hard palate, and the oral tongue (that portion of the tongue anterior to the circumvallate papillae). A primary arising in the buccal mucosa can be impossible to distinguish from one arising in the cheek but the distinction is academic. This would also include those lesions arising in and near the lips.

4. Larynx

   This refers to the primaries arising in the subglottic, glottic, or supraglottic tissues. Tumors of the aryepiglottic folds can be difficult to distinguish from the hypopharynx but the distinction is academic.

5. Oropharynx

This includes tumors arising from the anterior tonsillar pillars, the soft palate, the base of the tongue, the tonsillar fossa, and oropharyngeal walls. Tumors arising in the parapharyngeal space may indent the oropharyngeal wall. In this circumstance, the primary should be considered parameningeal. If the mucosa of the oropharynx actually contains visible tumor as opposed to being bulged by it, the primary would be oropharynx. Primaries arising in the tongue base, soft palate, or tonsillar region may extend into the oral cavity. The oropharynx designation is preferred.

6. Cheek

This refers to the soft tissues of the face that surround the oral cavity. Tumors arising in the parotid may invade the cheek. As noted above, the distinction between this and the buccal mucosa is academic.

7. Hypopharynx

This refers to the pyriform sinus and may be difficult to distinguish from larynx although the designation is academic with regard to randomization.

8. Thyroid and Parathyroid

Primaries arising in these two sites are exceedingly rare, if they exist at all, and should those structures be involved, it would more likely be from a primary arising in an adjacent structure such as the trachea.

9. Neck

This refers to the soft tissues of the lateral neck between the mastoid tip and the clavicle. It does not include those medial structures such as hypopharynx and larynx noted above. Unfortunately this site overlaps with the designation “paraspinal” included under the site group “trunk”. Primaries arising in the neck can and frequently do behave as a paraspinal primary with direct invasion into the spinal extra dural space.

GROUPING (High, pg 103)

APPENDIX V: IRS CLINICAL GROUPING CLASSIFICATION

Group I: Localized disease, completely resected

(Regional nodes not involved - lymph node biopsy or dissection is required except for head and neck lesions)

(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. If the latter should be involved microscopically, then the patient is placed in the Group IIb or IIc (See below).

Group II: Total gross resection with evidence of regional spread

(a) Grossly resected tumor with microscopic residual disease

(Surgeon believes that he has removed all of the tumor, but the pathologist finds tumor at the margin of resection and additional resection to achieve clean margin is not feasible). No evidence of gross residual tumor. No evidence of regional node involvement. Once radiotherapy and/or chemotherapy have been started, re-exploration and removal of the area of microscopic residual does not change the patient's group.

(b) Regional disease with involved nodes, completely resected with no microscopic residual.

NOTATION: Complete resection with microscopic confirmation of no residual disease makes this different from Groups IIa and IIc. Additionally, in contrast to Group IIa, regional nodes (which are completely resected, however) are involved, but the most distal node is histologically negative.

(c) Regional disease with involved nodes, grossly resected, but with evidence of microscopic residual and/or histologic involvement of the most distal regional node (from the primary site) in the dissection.

NOTATION: The presence of microscopic residual disease makes this group different from 2b, and nodal involvement makes this group different from Group 2a.

Group III: Incomplete resection with gross residual disease

(a) After biopsy only

(b) After gross or major resection of the primary (>50%)

Group IV: Distant metastatic disease present at onset

(Lung, liver, bones, bone marrow, brain, and distant muscle and nodes)

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).

The presence of positive cytology in CSF, pleural or abdominal fluids as well as implants on pleural or peritoneal surfaces are regarded as indications for placing the patient in Group IV.

SURGICAL GUIDELINES

Data Submission Section (High, pg 71)

All pretreatment staging forms, operative notes, and other surgical check sheets should be completed by the responsible surgeon and reviewed where applicable by the hospital surgical representative for accuracy, completeness, and protocol compliance to include final pathologic verification of residual and/or metastatic disease, and cytological examination of pleural and peritoneal fluid. The Surgical Committee of the STS Committee will evaluate the pretreatment stage assigned, the Clinical Group assignment, the anatomic site designation, and the adherence by the surgeon(s) to these surgical guidelines for quality assurance reporting.

Pretreatment Clinical Staging (Int, pg 87)

This is a modification of the UICC-TNM staging system and is based on site, size, clinical regional nodal status and distant spread. The staging is CLINICAL and should be done BY THE RESPONSIBLE SURGEON 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 N_1. A node that is clinically negative but pathologically positive places the patient in Clinical Group II B. However, patients with metastatic disease discovered at surgery would be classified as Stage 4 (Clinical Group IV).

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 multidisciplinary site assignment. THE SURGEON IS GENERALLY BEST ABLE to designate site when choice is difficult. See Appendices II, III, IV, and V for Staging/Clinical Grouping Criteria and Site Classification.

Surgical-pathologic (Clinical) Group (Int, pg 87)

Clinical Group assignment is based on intraoperative findings and post-operative pathologic status and must include final pathologic verification of margins, residual, node involvement, and cytological examination of pleural and peritoneal fluid, and CSF, when applicable. See Appendix III for Clinical Grouping Criteria.

***It is important to note that the Clinical Group designation assigned at the time of enrollment on study remains unchanged regardless of any second-look operation that may be performed. Clinical Group can be changed**

SURGICAL PRINCIPLES: (High, pg 72)

The basic principle of wide and complete resection of the primary tumor with a surrounding "envelope" of normal tissue should still be attempted as an initial procedure even in the presence of metastatic disease. This approach is generally more applicable to sites in the extremities or trunk than in the head and neck, but adequate margins of uninvolved tissue are still 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. There are several exceptions to this principle including primary tumors in the orbit, paramemingeal, or genitourinary system. Adequate margins of normal tissue are preferable to leaving gross or microscopic tumor in situ. For tumors that are too large to be resected without causing significant damage to the patient then an initial biopsy of the primary tumor and any involved lymph nodes should be performed. A subsequent delayed resection can then be performed following chemotherapy and radiation if the tumor has diminished enough to make resection of the tumor feasible.

Margins. (High, pg 72)

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.

Node Sampling or Node Dissection (Int, pg 88)

Clinical and/or imaging evaluation of regional lymph nodes should be performed pretreatment and preoperatively by the responsible surgeon and is an important part of pretreatment staging. Identification of the sentinel node by injection of methylene blue dye and technetium 99m at the site of the primary tumor can assist in identifying the node most likely to contain tumor deposits. Pathologic confirmation of clinically positive nodes should be performed. 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. Open biopsy is recommended, but needle aspiration may be appropriate, based on the surgeon's judgment and pathologist's recommendations. Pathologic evaluation of clinically uninvolved nodes is site specific; it is required in extremity sites and in boys ≥ 10 years with paratesticular primaries. Aggressive regional lymph node sampling is the most appropriate method of surgical evaluation for most sites. 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 Appendix VI) 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.

Pretreatment Re-excision (PRE) (Int, pg 88)
The initial surgical procedure (a biopsy or excision as employed for benign tumor) may have been performed prior to establishing the diagnosis and/or the involvement of the oncology team and may result in a situation in which there is: 1) gross residual tumor, 2)

microscopically involved margins, or 3) uncertainty as to margins or residual. This applies even if the microscopic margin is thought to be clear, if the operation and pathologic study were not done as described in 14.4.1.

Under these circumstances the concept of Pretreatment Re-excision (PRE) is advisable and should be applied wherever feasible, unless the resulting disability is considered unacceptable, i.e., resulting in loss of function or an unacceptable cosmetic result. This means wide re-excision of the previous operative site, including an adequate "envelope" of normal tissue, with careful marking and examination of all margins. This approach is particularly applicable to extremity and trunk lesions although it should be applied wherever possible. This procedure must be done prior to administration of chemotherapy or radiation.

Clinical Group assignment will be determined on the basis of pathology from the definitive operation prior to the start of multimodal therapy. The prior procedure(s) will be considered as an excisional biopsy. The conclusion that such re-operation is not advisable or feasible must be reached by multidisciplinary discussion and the reasons are to be listed on the surgical check sheet.

Second Look Operation(SLO) or Delayed Primary Resection (Int, pg 88)

Residual persistent mass after local radiotherapy is common, and in previous analyses is not correlated with patient outcome. Second look surgery is not recommended after irradiation, particularly before Week 15. Should the local treating institution elect to perform a second look surgery, justification for this decision must be discussed with the one of the ARST0531 surgical representatives. Such patients may remain on study if approved in writing by the ARST0531 surgical representative

CENTRAL LINE (Low, pg 44)

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

IPSILATERAL STAGING RETROPERITONEAL NODE DISSECTION: RECOMMENDED TECHNIQUE: (LOW RISK, APPENDIX VII, PG 93)

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. Before beginning the dissection, the postganglionic nerve fibers overlying the aorta should be identified. It should be pointed out

that the right-sided fibers arise behind the vena cava and pass anteriorly between the cava and aorta. The sympathetic chains are then identified just above the common iliac arteries. As each branch is exposed it is freed and tagged with a vessel loop. The loop can be used to manipulate the fibers atraumatically as the lymphatics are dissected from behind them. The lumber arteries and veins are either preserved or carefully dissected so as to preserve the closely adherent nerve fibers.

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.

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

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.

Preoperative colon cleansing is helpful and the bladder should be decompressed. The patient should be positioned in lateral decubitus position, facing the surgeon, with his abdomen near the edge of the table the primary tumor. The side ipsilateral to the tumor should be toward the ceiling. It is important to be able to tilt the table to a Trendelenburg position to gain access to the pelvis.

The initial cannula (for the telescope) can be inserted in the umbilicus, but may be better placed lateral to the rectus muscle at the level of the umbilicus, particularly in obese or muscular boys. Two additional working ports should be placed, one superior and the other inferior to the cannula, lateral to the rectus muscle.

An incision should be made in the peritoneum lateral to the colon to reflect the colon sufficiently medially to expose the aorta and the vena cava, and sufficiently superiorly to display the renal vessels. Care should be taken so as not to reflect the ureter with the colon. The dissection can begin either at the inguinal ring or the renal vessels .The same template described for the open technique should be followed. Nerve preservation should also be similar. Hemostasis can be secured using any energy device with which the surgeon is comfortable (e.g.: hook cautery, harmonic scalpel, Ligasure®, etc.) or using endoscopic clips. The specimen should be marked for location identification and removed using a laparascopic retrieval bag so as not to drag potentially involved tissue directly through the trocar sites.

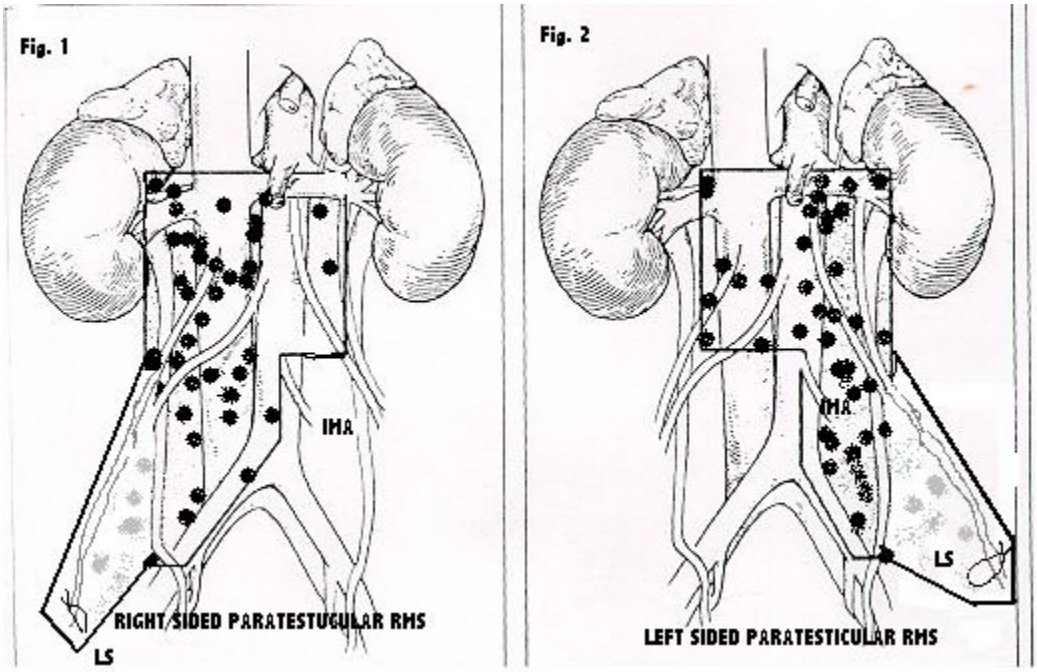

Figure 1: Right sided template: the dissection begins at the level of both renal veins encompassing the aorta and cava and intra-aortocaval tissue across to the left gonadal vein / ureteral junction down to the inferior mesenteric artery (IMA) and then down the right side to the level of the right common 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 (LS) of the cord is removed. Figure 2: Left sided template: a similar dissection is carried out with the exception of the right lateral margin, which is the vena cava rather than the right ureter. 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 (LS) of the cord is removed.

PATHOLOGY

D9902, BIOLOGY PROTOCOL:
PROCEDURE FOR PROCUREMENT, PREPARATION AND SHIPMENT OF MATERIALS

Diagnostic material may be obtained via incisional biopsy or multiple core needle (tru-cut or like) biopsies. Fine needle aspiration biopsy is not acceptable to establish the diagnosis. Core needle biopsies are prone to sampling error, which may make histologic subclassification difficult and may result in an underestimate of the tumor grade. Thus, sufficient tissue must be obtained. Incisional biopsy is the preferred approach at all anatomic sites, particularly in the extremities, chest wall, and abdominal wall. Within the thoracic and pelvic cavities, and in the head and neck, multiple core needle biopsies are acceptable. The minimum recommended sampling is 8 core biopsies of 2 cm in length. The surgeon should sample each of the 4 quadrants of the tumor. Care should be taken to prevent penetration of the needle through the tumor into unaffected soft tissues.

Procurement

Specimens can be submitted at multiple time points without re-enrollment on D9902.

Surgical Tissue

Whenever possible, tumor specimens should be obtained fresh from the operating room to allow optimal specimen triage, which includes (in order of importance):

- Formalin-fixed, paraffin-embedded tissue for histology and immunohistochemistry
- Tissue for biology studies and banking

Upon removal, the tumor specimen should be submitted immediately to the pathologist. It should not be bisected or cut into pieces prior to pathologic evaluation. The tissue should not be placed in formalin, as fresh and snap frozen tissue may be helpful in establishing the diagnosis and providing materials for biology studies and banking. Frozen section may be helpful in some cases to confirm that diagnostic tissue has been obtained.

It is not generally recommended that excision be attempted on initial biopsy material, but if the lesion is small and in an optimal location, this decision may be made at the time of operation. In these cases, the lesion should be carefully inked to avoid contamination of the submitted biology materials. Conversely, material for biologic studies should be carefully obtained so as not to contaminate the surgical margin. The evaluation of margins determines surgical stage and subsequent therapy.

After the necessary tissues for diagnosis and local institutional research are met, the remaining tissue may be submitted to the BPC.

It may be desirable to discuss with operating room and pathology personnel why tissue is being procured and the necessity for prompt and accurate processing, labeling and handling.

Tumor specimens obtained prior to treatment should be submitted. Submission of viable post-therapeutic tumor tissue is encouraged and may be a requirement of the therapeutic study on which the patient is enrolled.

Operating Room personnel should not put the tissue into fixative. The specimen should be brought to the Pathology Department quickly, by special messenger if necessary.

Tissues for submission to the BPC should be as sterile as possible.

Preparation

For Central Pathology Review

Promptly following removal, tumor tissue and slides for central pathology review should be prepared as described below. All supplies are provided by the Biopathology Center.

Representative formalin-fixed paraffin blocks of tumor material: If blocks absolutely cannot be sent, then send 1 H&E section from each available blocks and 10 (RMS) or 20 (NRSTS) plus-charged (polarized) unstained slides for immunoperoxidase studies from 1-2 representative blocks and 1-2 H&E slides from the same blocks. Be sure to include the Pathology Report, the Pathology Checklist, Operative Report and the COG Specimen Transmittal form with the samples. Label all materials with the patient's COG patient ID number and the surgical pathology identification (SPID) number.

This material can be sent along with the biology specimens or under separate cover.

Specimens for Biology Studies

Label all biology specimens with the patient's BPC number, specimen type and collection date.

Tissue Frozen in OCT (1^{st} priority)

Two truncated molds are provided for tumor (primary tumor and metastatic, if available). Use a CryoMarker or Securline Superfrost Marker to label the mold with the BPC specimen number. Cover the bottom of the mold with OCT embedding medium. Using forceps, place the mold over (not in) liquid nitrogen until the OCT appears to lose its transparency. Place up to 1 gm of tissue in this thickened gel, pushing the specimen to the bottom of the mold. Add additional OCT to completely cover the tumor and fill until approximately three-fourths full. Gradually immerse the entire mold into liquid nitrogen until completely solid. Store the mold with the snap frozen specimens at -80°C until shipment.

Snap-Frozen Tissue (2^{nd} Priority)

At least one specimen from the primary (if present) and metastatic areas (if present) should be cut into 2-3 mm slices (send as much tissue as available in 1cc aliquots) wrapped in foil and snap frozen in liquid nitrogen or cold isopentane. Mark foils as "primary" or "metastatic" if both are being submitted.

Some normal tissue should be submitted in addition to the tumor tissue, if available. This can be any normal tissue, e.g., muscle, skin, etc. Send as much normal tissue as possible but not to exceed the amount of tumor tissue provided. Wrap normal tissue in foil, snap freeze, and mark "normal". Store snap frozen tissue at -80°C until shipment.

Formalin-Fixed Tissue/Needle Cores

Tissue sections (a "cassette sized" piece), adjacent to both the submitted tumor and to the submitted normal specimens, should be sent. The tissue sections should be placed in the labeled formalin jars ("T" for tumor and "N" for normal). Stretch the Parafilm around the caps. If formalin fixed tissue is not available then, for tissue microarrays, a representative paraffin block of tumor from the pathology workup can be sent to the BPC. The BPC can core the blocks for the institutions and return them (upon request). As an alternative, the BPC can provide a coring kit to the institution so that the institution can core their own blocks and send two to three 1 mm core biopsies of the block to BPC.

Bone Marrow and Blood

Specimens should be submitted to the BPC whenever bone marrow aspirates are collected. Three to six mL of the bone marrow aspirate and five to ten mL of whole blood anticoagulated with EDTA (purple top tubes) should be collected and kept at room temperature.

Serum

Prior to therapy, collect 4-6 mL of blood in a red top tube (2 mL for children 5 years of age or less). Spin blood for 10 minutes at 2500 rpm at 4ºC. Transfer serum into tubes provided in the specimen procurement kit. Using a waterproof marker, label the tubes with the patient's BPC number and the date obtained. Store serum at -80ºC until shipment.

Banking

If consent for banking is signed, all specimens leftover from central review and biology studies will be banked for future research.

Shipment

BPC Number

Patients will receive a BPC number when they are registered with the COG Cancer Registry. This anonymous number will be used to label the specimens and all paperwork sent to the BPC. Please label the fresh tissue sent to Dr. Bridge with the patient's COG Patient ID number.

Specimen Transmittal Form

A Specimen Transmittal Form (one copy) must accompany each shipment of specimens. The form is available on the COG website.

Mailing Kits

Mailing kits are provided by the BPC upon request. The kits include foil for frozen tissue, plastic zip lock baggies, truncated embedding molds for tumor frozen in OCT and formalin containers for fixed tissue. Also included with each kit are instructions, mailing labels, and a Federal Express air bill.

Packing

The snap frozen tissue, OCT block, and sera must be sent on dry ice. Using approximately 4 lbs. total, layer ½ the dry ice on the bottom of the compartment, add the specimens, then fill with the remaining dry ice and replace the Styrofoam top.

Place the formalin containers, bone marrow, and blood samples with the Specimen Transmittal Form in the second (room temperature) compartment.

Seal the kit securely with filament or other durable sealing tape. Complete the pre-printed Federal Express air bill, insert it into the plastic pouch and attach the pouch to the top of the kit. Complete the dry ice label (UN 1845) and stick both this label and the UN3373 label to the side of the box. Be sure to mark only on the lines provided and send the kit to:

Biopathology Center

Columbus Children's Hospital

700 Children's Drive, Rm. WA1340

Columbus, Ohio 43205

(614) 722-2810

Shipping

Arrange for Federal Express pick-up per your usual institutional procedure or by calling 1-800-238-5355. When requesting pick-up, be sure to give the account number but stress that pick-up is at your institutional address.

Specimens should be shipped Monday through Thursday for delivery Tuesday through Friday. If the specimen is collected on Friday, please store frozen tissue in a -80°C freezer. Refrigerate blood and bone marrow, at 4°C for shipping on Monday. Fresh tissue can be shipped any day of the week, and should be sent without delay.

ADDITIONAL PATHOLOGY GUIDELINES AND SPECIMEN REQUIREMENTS FROM CLINICAL PROTOCOLS (LOW, PG 61)

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Patients who do not enroll on D9902 prior to starting therapy are not eligible for this protocol.

If there is clinical urgency to start therapy, treatment assignment will occur at study entry based on institutional pathology prior to completion of Rapid Central Review. The diagnosis will be confirmed/corrected within 14 days after D9902 study enrollment. If patient therapy needs to be changed because of a change of the histologic diagnosis based on rapid central review, the patient should be switched to an appropriate treatment regimen before Week 4 therapy is started.

The STS Pathology Center will notify the institution with the rapid review results via fax or overnight mail with a copy of the report being submitted to the STS Data Management Center for tracking.

If Pathology Center and institutional diagnosis agree, treatment should continue based on the institutional histologic subtype.

-FOR LOW RISK PATIENTS:

If the results of the rapid review make a patient previously enrolled on another STS protocol eligible for ARST0331, the patient must be switched, enrolled on, and begin therapy according to ARST0331 by Week 4. Consent for ARST0331 Therapy must be signed prior to start of therapy.

-FOR INTERMEDIATE RISK PATIENTS:

If the results of the rapid review make a patient previously enrolled on another STS protocol eligible for ARST0531, the patient must be switched, enrolled on, and begin therapy according to ARST0531 by Week 4. Consent for ARST0531 Therapy must be signed prior to start of therapy.

15.2.2 Pathology Review at Time of Second Look Surgery

A second pathology review will be required at the time of second look surgery. This is not a rapid review, so materials do not need to be submitted overnight. Results of pathology review of second look surgeries are not reviewed rapidly and results are not returned to the referring institution.

Materials to send:

Send at the time of Second Look surgery:	**Label all materials with the patient's COG patient identification number and the surgical pathology identification (SPID) number from the corresponding pathology report.**
Representative formalin-fixed paraffin blocks of tumor material (If patient did not consent to banking on D9902 then paraffin blocks will be returned after sectioning). If blocks absolutely cannot be sent, then send 1 H&E section	Please call the STS Pathology Center at 614-722-2898 to notify them of the shipment.

of all available blocks **and**

10 plus-charged (polarized) unstained sections for immunoperoxidase studies from 1-2 representative blocks and 1-2 H&E slides from the same blocks.

Label the parcel "**STS Second Look Review**".

Please use the phone number listed below, which is for the central receiving area, on all packages shipped to the STS Pathology Center.

Send all pathology central rapid review materials to:

Documentation including:

Institutional Pathology Report *

Pathology Checklist

Institutional Operative Report

COG Specimen Transmittal form

COG Soft Tissue Sarcoma

Columbus Children's Hospital

700 Children's Drive WA1340

Columbus, OH 43205

Phone: (614) 722-2810

FAX: (614) 722-2897

**a preliminary report may be sent with the review material, but please fax the final report when available*

The Study review pathologists are:

Review Pathologist:
Stephen Qualman, M.D.
Children's Research Institute
700 Children's Drive WA5011
Columbus, OH 43205
Phone (614) 722-5302
Qualmans@pediatrics.ohio-state.edu

Review Pathologist:
David Parham, M.D.
Department of Pathology
Arkansas Children's Hospital
800 Marshall Street, Slot 820
Little Rock, AR 72202-3591
parhamdavidm@uams.edu

Do not send specimens directly to the review pathologists. All specimens must be sent to the Biopathology Center (BPC).

TREATMENT

LOW RISK, 0331

Once enrolled and assigned to Regimen A (Subset 1) or B (Subset 2), patients will start therapy with one cycle of VAC. Patients with embryonal or the botryoid or spindle cell variants of embryonal RMS confirmed by enrollment on D9902 will continue on ARST0331. Patients whose tumors are alveolar RMS will transfer to the intermediate risk RMS protocol. Alternatively, patients who start on the intermediate risk protocol and are found to have embryonal or botryoid/spindle cell RMS may transfer to ARST0331 by Week 4 of treatment if they can be assigned to Subset 1 or 2.

Patients with recurrent or progressive disease at any site during any evaluation will be taken off protocol therapy and followed at six-month intervals for survival. These patients may be eligible for a COG recurrent rhabdomyosarcoma study. Some patients may have a residual imaging abnormality at the end of therapy. Such patients may be observed without intervention. Biopsies are often difficult to interpret in this setting and expert pathology consultation is strongly encouraged should the treating institution elect to perform a biopsy to assess response to therapy. If a patient undergoes biopsy/surgery during follow-up or at recurrence, specimens should be sent as specified in D9902.

General Therapy Guidelines

Regimen A (Subset 1) patients will have 22 weeks of therapy and evaluation at weeks 12 and 24.

Regimen B (Subset 2) patients will have 46 weeks of therapy and evaluations at weeks 12, 24, 36 and 48.

Central review of pathology (on D9902) must be accomplished by the start of Week 4 therapy.

Local Control: Radiation therapy begins at Week 13 for most patients (except Clinical Group I disease or node-negative Clinical Group III uterine/cervix primaries that are completely resected at Week 13, and patients with node negative vaginal primaries who begin radiation if necessary, following surgery at Week 24). Week 28 dactinomycin should be omitted for patients with vaginal primaries who are receiving radiation therapy at that time.

Patients with Clinical Group III disease may undergo second look surgery at Week 13 (based on Week 12 evaluation) followed by response-adjusted radiation therapy dosing. Radiation therapy should begin and chemotherapy should resume as soon as possible following surgery.

INTERMEDIATE RISK, 0531

Both regimen A and B patients will have 42 weeks of therapy.

Confirmation of pathology must be accomplished by the start of Week 3 therapy.

Local control will be provided according to the local control pathways (See Appendix VII).

Radiation therapy begins at Week 4 for all patients (with the exceptions of alveolar RMS rendered Group I by amputation, Week 1 emergency radiotherapy for symptomatic spinal cord compression, or individualized local control for children ≤ 24 months as outlined below).

Special Note for Patients ≤ 24 Months Old:

The long-term morbidity of radiotherapy or aggressive surgery for very young (≤ 24 months old) children makes appropriate local control challenging. Many clinicians are unwilling to follow standardized local control guidelines for very young children. This study encourages adherence to standardized local control guidelines for children ≤ 24 months old but permits deviations at the discretion of the treating clinicians. Deviation from protocol-mandated radiotherapy must be included in the QA documentation submitted to QARC. For patients ≤ 24 months only, deviations from the standardized local control guidelines will not be considered protocol violations.

Second Look Operations (SLO) or Delayed Primary Resections (DPR):

Residual persistent mass after local radiotherapy is common, and in previous analyses is not correlated with patient outcome. Second look surgery is not recommended after irradiation, particularly before Week 15. Should the local treating institution elect to perform a second look surgery, patients will remain on study.

HIGH RISK, 0431

- Patients whose tumor histology on Central Review is found not to be RMS will be removed from study.
- Patients with recurrent or progressive disease at any site during any evaluation will be taken off protocol therapy but remain on study, and followed at six-month intervals for survival. These patients should be treated aggressively using active agents and may be eligible for a COG recurrent RMS study.
- Some patients may have residual imaging abnormality at the end of therapy. Such patients should be observed without intervention. Biopsies are often difficult to interpret in this setting and expert pathology consultation is strongly encouraged should the treating institution elect to perform a biopsy.

General Therapy Guidelines

Patients with parameningeal (without intracranial extension) and paraspinal tumors should receive chemotherapy beginning Week 1 and begin radiotherapy at Week 20

Patients requiring emergency radiation therapy (for intracranial extension or spinal cord impingement) should begin chemotherapy Week 1 (irinotecan/vincristine) concurrently with radiation therapy.

SURGEON RESPONSIBILITIES

FOR PROTOCOLS ARST 0331, 0531, AND 0431, SURGERY CONTACTS INCLUDE:

Low Risk, 0331:	Charles Paidas	cpaidas@health.usf.edu
	Richard Andrassy	Richard.andrassy@uth.tmc.edu
Intermediate Risk, 0531	David Rodeberg	rodeberg.david@chp.edu
	Kenneth Brown	kbrown@interchange.ubc.ca
	Andrea Hayes-Jordan	andrea.hayes-jordan@uth.tmc.edu
	Charles Paidas	cpaidas@health.usf.edu
High Risk, 0431	David Rodeberg	rodeberg.david@chp.edu

As stated in the Data Submission section, All pretreatment staging forms, operative notes, and other surgical check sheets should be completed by the responsible surgeon and reviewed where applicable by the hospital surgical representative for accuracy, completeness, and protocol
Compliance. These materials should then be forwarded to the Data Management Center in a timely fashion through the institution's RDE system. . The Data Management Center will collate the data for the Soft Tissue Sarcoma Committee of the COG, which will evaluate the pretreatment stage assigned, the Clinical Group assignment, the anatomic site designation, and the adherence by the surgeon(s) to these surgical guidelines for quality assurance reporting.

Staging is CLINICAL and should be done BY THE RESPONSIBLE SURGEON based on PREOPERATIVE imaging and physical findings.

Intraoperative and/or pathologic results should not affect the stage, but will affect Clinical Group.

Site designation alters stage and, therefore, treatment assignment. Careful evaluation of clinical and/or imaging findings should precede multidisciplinary site assignment. THE SURGEON IS GENERALLY BEST ABLE to designate site when choice is difficult.

SURGICAL CHECKLIST

(link to https://members.childrensoncologygroup.org/_files/irsg_forms/srgcheck.pdf)