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Surgical Management of Paratesticular Rhabdomyosarcoma: A Consensus Opinion from the Children's Oncology Group, European paediatric Soft tissue sarcoma Study Group, and the Cooperative Weichteilsarkom Studiengruppe

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Abstract

The treatment of para-testicular rhabdomyosarcoma (PT-RMS) has varied over time and by cooperative group. The International Soft Tissue Sarcoma Database Consortium (INSTRuCT) is a collaboration of the Children's Oncology Group Soft Tissue Sarcoma Committee (COG), European pediatric Soft Tissue sarcoma Study Group (EpSSG), and the Cooperative

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Weichteilsarkom Studiengruppe (CWS). The INSTRuCT surgical committee has been charged with development of internationally applicable consensus guidelines for the surgical treatment of rhabdomyosarcoma. This clinical consensus opinion document addresses accepted principles and areas of controversy, such as scrotal violation and retroperitoneal nodal evaluation, providing an evidenced based guideline for the surgical treatment for PT-RMS.

Keywords

Pediatric; International; Para-testicular; Rhabdomyosarcoma

Introduction

The prognosis for patients with localized paratesticular rhabdomyosarcoma (PT-RMS) is excellent, potentially due to early detection of the tumor and a predominance of PAX-fusion negative RMS [1 2]. PT-RMS with classic alveolar histology are typically PAX-fusion negative and also have a more favorable prognosis [3 4]. Patients with PT-RMS comprise about 7% of patients with RMS, presenting at a median age of 5-8 years [5 6]. In boys <10 yrs of age most tumors are ≤ 5 cm (56-74%), are completely resected (IRS Group I) (68-72%) and have no radiographic or clinical nodal involvement (>90%) [4 7]. In contrast, patients ≥10 years old are more likely to have tumors >5 cm (62%), have microscopic positive margins or positive nodes (IRS Group II) (42%), are locally invasive (16%), have clinically/radiographically enlarged regional nodes (17%), have pathologically positive regional nodal involvement (32%), and pathologically positive nodes that are not enlarged (19%). An international pooled data analysis from the Soft Tissue Sarcoma Committee of the Children's Oncology Group (COG), Cooperative Weichteilsarkom Studiengruppe" (CWS), European paediatric Soft tissue sarcoma Study Group (EpSSG), the Italian Soft Tissue Sarcoma Committee (STSC), and The International Society of Paediatric Oncology (SIOP) trials concluded that the outcomes for these tumors are excellent where 5-year event-free survival (EFS) and overall survival (OS) were 87.7% and 94.8%, respectively [7]. A proportional hazards regression model selected era of enrollment, age, tumor size, and surgical assessment of regional nodes as significant ($P \leq .05$ each) in the EFS model, and era of enrollment, age, tumor size, and histology ($P \leq .05$ each) in the OS model. Multiple other independent studies have identified age ≥10 years, tumor size >5 cm, involvement of regional retroperitoneal lymph nodes, and tumors that are invasive and unresectable (Group III) as having unfavorable prognostic features [4 7 8 9 10 11 12 13 14 15].

Three pediatric oncology cooperative groups (COG, EpSSG & CWS) have initiated the development of a combined database (International Soft Tissue Sarcoma Consortium (INSTRuCT) similar to the International Neuroblastoma Risk Group (INRG) [16 17]. A component of the INSTRuCT mission is to develop consensus opinion documents for local control of primary tumors that could be utilized across all of the cooperative groups. The consensus opinion document for surgical treatment of PT-RMS presented here represents one such consensus document. The process and methodology to achieve this included a review of the current literature combined with recommendations of the treatment protocols

of the appropriate clinical trials. Additionally, opinions of international PT-RMS experts were incorporated into recommendations.

This consensus opinion document provides treatment guidelines for the surgical management of PT-RMS, including: including primary inguinal orchidectomy, pretreatment re-excision (PRE), management of large tumors, trans-scrotal excision, scrotal violation, hemi-scrotectomy (HS), testicular transposition and retroperitoneal lymph node assessment and management. Recommended guidelines are followed by summation of scientific evidence and consensus expert opinion. At the beginning of each evidence section the National Cancer Institute level of evidence is provided to indicate the general quality of the data presented in the evidence section (Table 1) (https:www.cancer.gov/publications/pdq/levels-evidence/treatment).

Consensus Surgical Opinion

Primary Inguinal Orchidectomy

Guideline: Tumors in the paratesticular/spermatic cord region should be removed by radical orchidectomy through an inguinal approach. Care is taken not to breach the tunica vaginalis when the tumor, testis, and the entire cord up to the internal ring are removed as a single specimen. The cord should be clamped at the internal ring before mobilization of the tumor. The cord is ligated using a non-absorbable suture and left as a long (>2 cm) tag in order to be easily identified in case a retroperitoneal lymph node dissection (RPLND) or re-excision of the cord is required. When scrotal skin is fixed or grossly invaded by tumor, it should be resected en-bloc with the specimen. Testicle preserving approaches should be avoided in PT-RMS.

Evidence **[Level of evidence: 2A]—**This treatment paradigm has been the standard of care since the beginning of cooperative randomized trials. The majority of patients with PT-RMS undergo a complete tumor resection (IRS Group I, 75%) or gross tumor resection but with microscopically positive margins (IRS Group II, 16%) [7]. IRS Group has consistently been identified as a major prognostic factor in patients [4 7 8 9 10 11 12]. However, this appears to be most pronounced for IRS Group III patients (gross residual disease after resection or biopsy). The recent pooled international data analysis by Walterhouse et al. reported a 5 year EFS and OS of 88% and 96% for Group I, 89% and 93% for Group II, compared to a 61% and 68% for Group III patients [7]. Therefore, effort should be made to perform an initial non-mutilating (without loss of function) complete gross tumor resection.

Pretreatment Re-Excision

Guideline: Pretreatment re-excision (PRE) is a wide, non-mutilating re-excision of the operative site to obtain a complete tumor resection with microscopically clear margins, that is performed when the initial procedure did not include en-bloc complete gross resection of the tumor, testis and spermatic cord up to the internal ring and therefore is classified as IRS Group III. As with other primary tumor sites, when PRE is indicated, it needs to be done before other adjuvant therapies begin and as soon as possible after the primary resection. Expert consensus is that patients with PT-RMS and microscopic residual disease after initial

resection (IRS Group II) may undergo PRE when there is microscopic disease at tunica margin and should when at the cord margin.

Evidence: **[Level of evidence: 2A]—**In general, PRE has been shown to improve outcome when it can convert Group II or III tumors to Group I when performed before the initiation of adjuvant chemotherapy [18 19]. Recent studies of PT-RMS would suggest that microscopic positive margins (Group II) at the tunica may not warrant PRE, HS, increased chemotherapy or radiation (RT) of the scrotum, since outcomes (recurrences and death) appear to be equivalent regardless of intervention (chemotherapy, RT or HS) [7 20]. Other trials have shown that EFS was maintained when patients with PT-RMS and microscopically positive margins received intensified chemotherapy without the addition of RT [4 9]. Therefore, given this conflicting information, we have elected to stay with the recommendation of PRE for PT-RMS with microscopically positive margins. The indication for HS during PRE is addressed later. Unlike the tunica, there is no conflicting evidence regarding microscopic residual disease at the cord margin and therefore the current recommendation to excise the cord should be followed. The optimal adjuvant therapy for patients with Group II resections is not the focus of this manuscript and is debatable.

Management of Large Tumors

Guideline: For large tumors that are difficult to excise through a standard inguinal incision, it is better to extend the inguinal incision down into the scrotum to facilitate a complete gross total tumor resection.

In rare cases, the tumor may not be primarily resectable if there is proximal extension of the tumor through the inguinal canal, or extension into the urethra and base of the penis. In these patients an inguinal approach for tumor biopsy (incisional or needle) is appropriate, followed by induction chemotherapy. These patients would be IRS Group III and historically comprise <3% of patients.

Patients receive chemotherapy and radiotherapy as specified for Group III disease with or without delayed primary resection. After 3-4 cycles of induction therapy delayed primary excision (DPE) should occur if it is anticipated the tumor can be grossly excised (R0/R1) since this may allow for a reduction in RT dose. Unlike Group III tumors at other sites PT-RMS tumors can almost always be resected allowing a potential decrease in adjuvant RT dosing.

Evidence: **[Level of evidence: Expert opinion]—**Given the extreme rarity of this presentation there is no direct evidence to support this guideline. However, it does adhere to standard oncologic principles and has been used in previous surgical guidelines for the treatment of PT-RMS.

Trans-scrotal excision, scrotal violation, & hemi-scrotectomy (HS)

Guideline: A trans-scrotal approach to tumor resection should be avoided since it makes complete resection more difficult, especially obtaining a negative cord resection margin.

A trans-scrotal biopsy should also be avoided as this will result in the need for a second incision as well as a potential increased risk of tumor spill.

HS is indicated if the tumor invades into the scrotal skin or if there is macroscopic disease at the scrotal skin, then the scrotal skin should be removed en bloc during tumor excision. Failure to remove this clinically apparent invading disease would result in the patient being classified as Clinical group III with a resulting worse outcome. However, HS is not indicated if patients have a scrotal violation or microscopic residual disease (Clinical group II) present in the scrotum.

Evidence: **[Level of evidence: 2Di]—**There are conflicting data whether tumors undergoing trans-scrotal excision have a worse prognosis compared to an inguinal approach [21 20]. After initial trans-scrotal tumorectomy or trans-scrotal orchidectomy, subsequent PRE specimens contained residual tumor in 56% and 30% respectively, and all required more than one procedure [22]. This compares with inguinal orchidectomy that achieves complete resection (Group I) in 75% of primary procedures. Therefore, the consensus is that these tumors should be resected through an inguinal incision adhering to established guidelines whenever an intra-scrotal mass is the pre-operative diagnosis.

Previous best evidence suggested that HS should be performed in instances of scrotal contamination after trans-scrotal resection or biopsy, direct scrotal tumor invasion, as well as gross or microscopic residual disease present after initial resection [23 24 21] [Level of evidence:3iiiDiii]. However, data from CWS and EpSSG cooperative studies would suggest that HS may not be indicated if the patient receives at least 3 drug chemotherapy [25 5 4 22] [Level of evidence: 3iiiDi]. In these studies patients had similar outcomes with or without HS after trans-scrotal violation. In addition, none of the pathology specimens after HS contained any viable tumor. The limitation of these studies is the low number of patients in each arm of the retrospective evaluation (12-16 patients). In addition, data from the COG would suggest that neither RT, PRE, or modification of standard chemotherapy are required in patients with a trans-scrotal approach when microscopic tumor is present at the tunica vaginalis margin [20] [Level of evidence: 2Di]. Again, the optimal adjuvant therapy for patients with Group II resections is not the focus of this manuscript.

In summary, after an inappropriate trans-scrotal approach, PRE is indicated for residual macroscopic disease and includes HS when tumor invades the scrotal skin; a microscopically involved cord should be resected. PRE for microscopic residual at the tunica vaginalis may be performed.

Testicular Transposition

Guideline: If scrotal RT, including Intensity-Modulated RT (IMRT), is required due to Clinical group III disease, then temporary transposition of the remaining normal testis should be done to preserve function. The cord and testis can be placed in a custom-made silastic bag to simplify the subsequent repositioning orchidopexy. In instances when preservation of testicular function is questionable, due to combined RT and chemotherapy, then the treating physicians should offer established methods of fertility preservation (eg,

semen cryopreservation) for postpubertal children. For prepubertal children, the only fertility preservation option is investigational testicular cryopreservation.

Evidence: **[Level of evidence: 3iiiC]—**Testicular tissue is exquisitely sensitive to radiation-induced damage, so the proximity of the normal contralateral testis would place it at risk of radiation damage if not moved out of the RT field [26] . Several small case studies including 11pre-pubertal or post-pubertal patients have reported a normal-sized testis, normal testosterone levels (4 of 5 evaluated) and fertility (1 reported) after temporary testicular transposition [27 28]. A recent study of 12 children undergoing testicular transposition before scrotal external radiotherapy reported that 6 of 9 children evaluated had normal testosterone levels for their age, while more follow-up would be needed to assess their fertility[29]. Specific operative techniques and alternative fertility preserving strategies are used to try and mitigate the toxic effects of both RT and chemotherapy [30 31 32].

Retroperitoneal Lymph Node (RPLN) Assessment and Management

Guideline (Table 2): All patients should undergo cross-sectional imaging (either by computed tomography (CT) or magnetic resonance imaging (MRI)) of the retroperitoneum to identify patients with enlarged (diameter >1cm) RPLN at initial staging. Patients with enlarged nodes have a significant risk of having pathologic disease and therefore one or more representative nodes should be biopsied (needle or excisional) to assure disease presence otherwise disease presence should be presumed (Group III) and the patients treated accordingly with adjuvant therapy.

All patients ≥ 10 years old should undergo nerve-sparing retroperitoneal lymph node evaluation, to identify patients with pathologic disease. Patients <10 years old with no nodal enlargement should not undergo surgical RPLN evaluation given the low rate of nodal relapse in this age group. Patients who have alveolar histopathology, irrespective of age or tumor size, should undergo surgical nodal staging procedure.

Patients undergoing surgical nodal evaluation should have either an open or laparoscopic operation using the surgical template for regional RPLN sampling shown in Figure 1, and excision of the remainder of the spermatic cord. In addition, the RPLN boundaries should be marked with titanium clips for future RT if needed. This is not a nodal clearance operation as is done for other histology testicular tumors, but a sampling procedure done for the purposes of staging. Nodal sampling should be of 7-12 nodes from multiple areas within the template area, especially near the ipsilateral renal vein. Alternatively, sentinel nodal evaluation, which can be performed by injecting radioisotope tracer and blue dye at the tumor or at the spermatic cord stump, may be used to help identify the positive node. The patient should still have additional nodes sampled to achieve at least 7 RPLN. Evolving technologies, such as indocyanine green injection and [F-18]-fluorodeoxy-D-glucose positron emission tomography (PET), may find a role in staging retroperitoneal nodes, but currently these techniques should be considered investigational.

Open laparotomy to perform the RPLN surgical evaluation is the most common approach. The procedure requires a thorough knowledge of retroperitoneal anatomy and common variations, excellent exposure, and early identification of important structures to minimize

inadvertent injury to vital structures (major vessels, accessory renal vessels, pancreas, ureters). Meticulous ligation of lymphatic vessels will minimize lymphatic complications [33].

A laparoscopic approach is technically demanding and should only be considered by surgeons with extensive laparoscopic experience or a surgeon proficient with the procedure. The laparoscopic approach should sample the same area described for the open approach [34]. Robotic-assisted laparoscopic retroperitoneal lymph node dissection is an emerging approach but current evidence does not indicate great advantages using this over the laparoscopic approach [35]. As with laparoscopic approaches, robotic-assisted approaches should only be attempted by experienced surgeons.

Patients with PT-RMS rarely have inguinal lymph nodes involved, except when there is scrotal invasion by the tumor. With scrotal involvement, inguinal nodes should be biopsied when clinically enlarged or the patient is ≥ 10 years.

Evidence: **[Level of evidence: 2A]—**PT-RMS drain into regional lymph nodes that ascend from the spermatic cord into the ipsilateral retroperitoneum up to the renal vessels. The epididymis drains into the external iliac nodes and ipsilateral pelvic nodes, while the scrotum drains into the inguinal nodes. Nodes at these sites are also considered regional nodes. Lymph node metastases above the renal vessels are considered metastases.

Accurate assessment of regional nodal disease is clinically important since tumor involvement of RPLN is a major prognostic indicator [7] [Level of evidence: 2Di]. All patients should have cross-sectional imaging of the RPLN. However, the predictive value of lymph node evaluation based solely on cross-sectional imaging for patients with PT-RMS, has been questioned based initially upon reports from the COG. The Intergroup Rhabdomyosarcoma Study (IRS)-IV that followed IRS-III, did not systematically perform surgical staging of RPLN in patients ≥10 years old (as IRS-III did), but relied on CT evaluation of RPLN; IRS-IV identified fewer patients with nodal involvement at diagnosis but then observed higher nodal relapses (43% in IRS-IV vs. 18% in IRS-III) [13]. [Level of evidence :2A]. In addition, approximately 90% of patients with PT-RMS do not have enlarged RPLN and imaging alone will miss 51% of pathologically positive nodes [20]. Therefore, COG studies have recommended surgical staging of RPLN for patients ≥10 years of age since 2001[13 2 14 36].

In contrast to COG, other co-operative groups including; SIOP and STSC (now combined into EpSSG), and CWS had traditionally based staging on lymph node enlargement identified by radiographic imaging, and surgical assessment reserved for those with indeterminate nodes [12 37 4 9]. The reliance on imaging, as opposed to surgical/pathologic assessment, was due to concerns regarding the potential morbidity associated with surgical resection of retroperitoneal lymph nodes. However, a recent SIOP review of PT-RMS patients on MMT-89 and 95 showed a significant risk for lymph node relapse in patients ≥10 years of age using a nonsurgical (imaging only) strategy for lymph node staging [4]. Thirty-one percent of Stage N-0 (imaging node negative) patients ≥10 years developed node relapse, compared with 8% of Stage N-0 patients <10 years (P = .0005). In these patients

78% of relapses occurred in regional nodes with a median time to relapse of 13 months. Similar to other reports of RMS relapse, salvage of these patients was poor and 38% of relapsed patients died.

The importance of performing a RPLN surgical lymph node evaluation was confirmed analyzing patients with PT-RMS pooled from North America and Europe [7]. Estimated nodal involvement was significantly dependent on age and tumor size. For patients <10 years old and ≤5cm positivity was 3%, but for patients <10 years with tumors >5cm it increased to 32%. For patients ≥10 years nodal involvement was present in approximately 32-35% regardless of tumor size. Disease failures were more likely to be regional (RPLN) than local (42% vs. 17% respectively). Surgical evaluation of RPLN was associated with improved EFS, however age and tumor size were the major patient tumor characteristics associated with improved EFS and OS. For patients ≥10 years old with tumors >5 cm, receiving RT was also associated with improved EFS. These findings suggest that surgical assessment of nodal disease to identify patients who should receive RT is important for improving patient outcomes.

The recommendation all patients ≥10 years old irrespective of tumor size undergo surgical evaluation of RPLN is supported by an EpSSG publication that showed the risk of nodal relapse in patients ≥10 years with normal nodes on diagnostic imaging was not statistically different for those with tumors ≤5cm versus >5cm (P= .28) [22].

The importance of surgical evaluation of RPLN has also been validated through several studies utilizing large population cancer databases [38 39 40][Level of evidence: 3iiiA]. These studies, using the Surveillance, Epidemiology, and End Results (SEER) database, identified two important observations. First, only half of the patients for whom a RPLN dissection (RPLND) was required underwent the procedure. Second, patients that had a RPLND had significantly better outcomes. Patients aged ≥ 10 years had improved OS (64% to 86%) when they underwent RPLND followed by appropriate adjuvant therapy with RT [40]. The improved survival with RPLND did not hold true for patients <10 years (97% to 100%). The incidence of lymph node involvement was higher in patients ≥10 years compared to patients <10 years (40% vs 8%). RT was shown to significantly improve OS in patients with nodal disease from 36% to 90%.

Surgical RPLN evaluation is for staging, to identify patients at high risk for regional nodal relapse, so that appropriate adjuvant therapy can be administered to improve outcomes, although CWS have advocated removal of persistent lymphadenopathy after induction chemotherapy[9]. COG and EpSSG have not, but rather have advocated for adjuvant therapy alone[20 22].

There are groups of patients who do not require surgical lymph node staging. Boys < 10 years with normal RPLN by imaging do not require surgical staging, as malignant nodal spread is rare in those with tumors ≤5cm and nodal relapse is rare in this age group [8 4 7]. In contrast, patients with fusion positive PT-RMS should always have RPLN surgical evaluation given the poor prognosis for fusion positive patients with regional nodal disease [41].

Given the high incidence of positive pathologic nodes when RPLN are enlarged, surgical confirmation may not be required, and the assumption can be made that they are positive (Group III) and therefore require RT and possibly intensified chemotherapy.

The risk for potential morbidity has resulted in a reluctance to do staging template RPLN dissection [12 13]. The morbidity associated with performing RPLN dissection is related to damage to the sympathetic nerves in the lower retroperitoneum. These sympathetic nerves from T12-L3 are responsible for emission and bladder neck closure during ejaculation. Much of the literature concerning operative morbidity is based on publications of patients with testicular tumors. Surgical complications following RPLN dissection for testis cancer occur in 5- 20% of patients and can include sexual dysfunction, infertility, chylous ascites, small bowel obstruction and hydronephrosis [42 43 44]. Nerve-sparing techniques whereby the sympathetic chains, the postganglionic sympathetic fibers, and the hypogastric plexus are prospectively identified and preserved have been shown to minimize sexual dysfunction and improve post-operative recovery [45].

Previously COG has advocated a complete nerve-sparing RPLN dissection of the entire template. However, nodal sampling may allow pathologic determination of nodal disease while minimizing operative morbidity. There is controversy regarding the optimal number of nodes that should be resected in order to accurately determine pathologic involvement. Data from a recent COG review of PT-RMS, shown in Figure 2, suggests that sampling 7-12 RPLN is sufficient for accurately identifying pathologic disease in 26-33% of patients, provided the sampling includes nodes up to the renal vessels [20]. In addition, SEER data would suggest that 82% of patients had fewer than 10 nodes excised during RPLND and proposed that 10 nodes was sufficient [40]. Given these data, and the concerns regarding the morbidity of RPLND, our consensus is that to accurately stage nodal disease the number of RPLN surgically sampled with a nerve-sparing technique must be at least 7 and optimally 12 from the template area (especially in the region of the renal vein).

It is possible that future technical improvements in cross sectional imaging or functional imaging may obviate the need for surgical evaluation of RPLN. Physiologic imaging using PET-CT is increasingly being used to assess tumor spread and may improve staging for many cancers. The surgical morbidity of RPLN dissection or sampling could be avoided if PET accurately determined nodal disease. However, the sensitivity and specificity of PET imaging to determine RPLN tumor spread in RMS is unclear [46]. A recent evaluation of sarcoma patients showed poor sensitivity (57%) and specificity (52%) of PET-CT for detection of histologically confirmed nodal metastases [47]. In addition, most staging PET scans would be done after primary surgical resection, making interpretation of the scan difficult as post-surgical changes may lead to a false-positive result. Therefore, we cannot recommend PET only as a replacement for surgical nodal evaluation at this time, especially if PET is performed after primary tumor resection.

In COG studies RT to the regional RPLN basin has routinely been administered to patients with either pathologic nodal involvement or radiographically enlarged nodes. RT was beneficial for patients ≥ 10 years with tumors > 5 cm^7. In EpSSG and CWS protocols

patients with radiographically enlarged lymph nodes received intensified adjuvant therapy including RT and possibly additional chemotherapy for positive nodes [4 9 22].

Guideline Summary (Table 3)

The aggregate evidence quality and strength of the recommendations are summarized in Table 3 according to the GRADE approach [48].

Tumors in the paratesticular/spermatic cord region should be removed by radical orchidectomy through an inguinal approach. Care is taken not to breach the tunica vaginalis when the tumor, testis, and the entire cord up to the internal ring are removed as a single specimen. The cord should be clamped at the internal ring before mobilization of the tumor, and then ligated by a non-absorbable suture. When scrotal skin is fixed or invaded by tumor, it should be resected en-bloc with the specimen. Testicle preserving approaches should be avoided at all times. PRE is indicated when the initial procedure did not include en-bloc complete gross resection of the tumor, testis and spermatic cord up to the internal ring. PRE is only applicable when performed before the initiation of adjuvant chemotherapy. Microscopic disease at the cord margin does warrant PRE. The recommendation to perform PRE for microscopic disease at the tunica vaginalis margin remains, but conflicting data suggests that PRE may not be indicated.

A trans-scrotal approach to tumor resection should be avoided. A trans-scrotal biopsy should also be avoided as this will result in the need for a second incision as well as a potential increased risk of tumor spill. HS is not indicated for patients with scrotal violation or microscopic residual disease.

All patients should undergo cross-sectional imaging of the retroperitoneum to identify patients with enlarged RPLN at initial staging. Patients with enlarged nodes have a significant risk of having pathologic disease and therefore should be biopsied or disease presence assumed and treated accordingly. All patients ≥ 10 years old should undergo ipsilateral infrarenal nerve-sparing surgical RPLN evaluation, regardless of imaging results, to identify patients with pathologic disease. Patients <10 years old with no radiographic nodal enlargement should not have surgical RPLN evaluation given the low rate of nodal relapse in this age group. Patients undergoing surgical nodal evaluation should have either an open or laparoscopic infrarenal ipsilateral nerve-sparing RPLN evaluation. Nodal sampling of 7-12 nodes from within the template area is sufficient to identify disease presence. The sampling should be from multiple areas especially in the region of the ipsilateral renal vein. Alternatively, sentinel node evaluation can be performed by injecting tracer and dye at the tumor or at the spermatic cord stump. The patient should still have additional nodes sampled to achieve a total of at least 7.

The prognosis of patients with PT-RMS is excellent. The primary tumor resection and appropriate surgical RPLN staging play a major role in determining the subsequent treatment and chance of cure.

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Abbreviations:

PT-RMS	Paratesticular Rhabdomyosarcoma
ERMS	Embryonal RMS
COG	Children's Oncology Group
CWS	Cooperative Weichteilsarkom Studiengruppe
CT	Computered Tomography
STSC	Italian Soft Tissue Sarcoma Committee
SIOP	The International Society of Paediatric Oncology
EpSSG	European paediatric Soft tissue sarcoma Study Group
INSTRuCT	International Soft Tissue Sarcoma Consortium
PRE	Pretreatment (Primary) re-excision
HS	Hemi-Scrotectomy
EFS	Event Free Survival
OS	Overall Survival
PAX	Paired box gene
RT	Radiation Therapy
IMRT	Intensity-Modulated Radiation Therapy
DPE	Delayed Primary Excision
RPLN	Retroperitoneal Lymph Node
RPLND	Retroperitoneal Lymph Node Dissection
PET	Positron Emission Tomography

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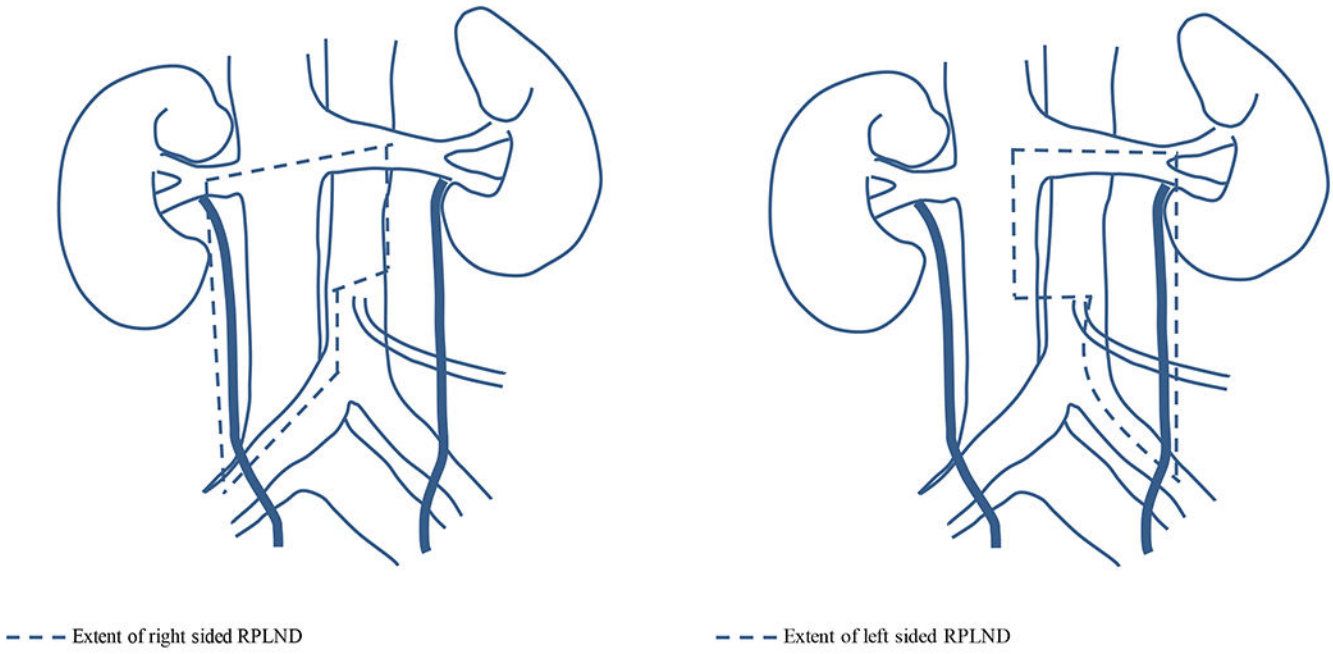

Figure 1.

Borders of the retroperitoneal lymph node sampling area. For right-sided tumors: the right ureter laterally, the anterior aspect of the infra-renal abdominal aorta medially, the anterior aspect of the right common iliac artery all the way to its bifurcation caudally, the renal vessels in the cephalad direction. For left-sided tumor: the left ureter laterally, the medial aspect of the infra-renal inferior vena cava medially, the anterior aspect of the left common iliac artery all the way to its bifurcation caudally, the renal vessels in the cephalad direction

# LN	3	4	5	6	7	8	9	10	11	12	13	14
% Pos.	17	20	19	22	26	28	26	25	32	31	33	34
# LN	15	16	17	18	25	30	37	42	47	50		
% Pos.	33	34	33	33	32	33	35	35	36	38		

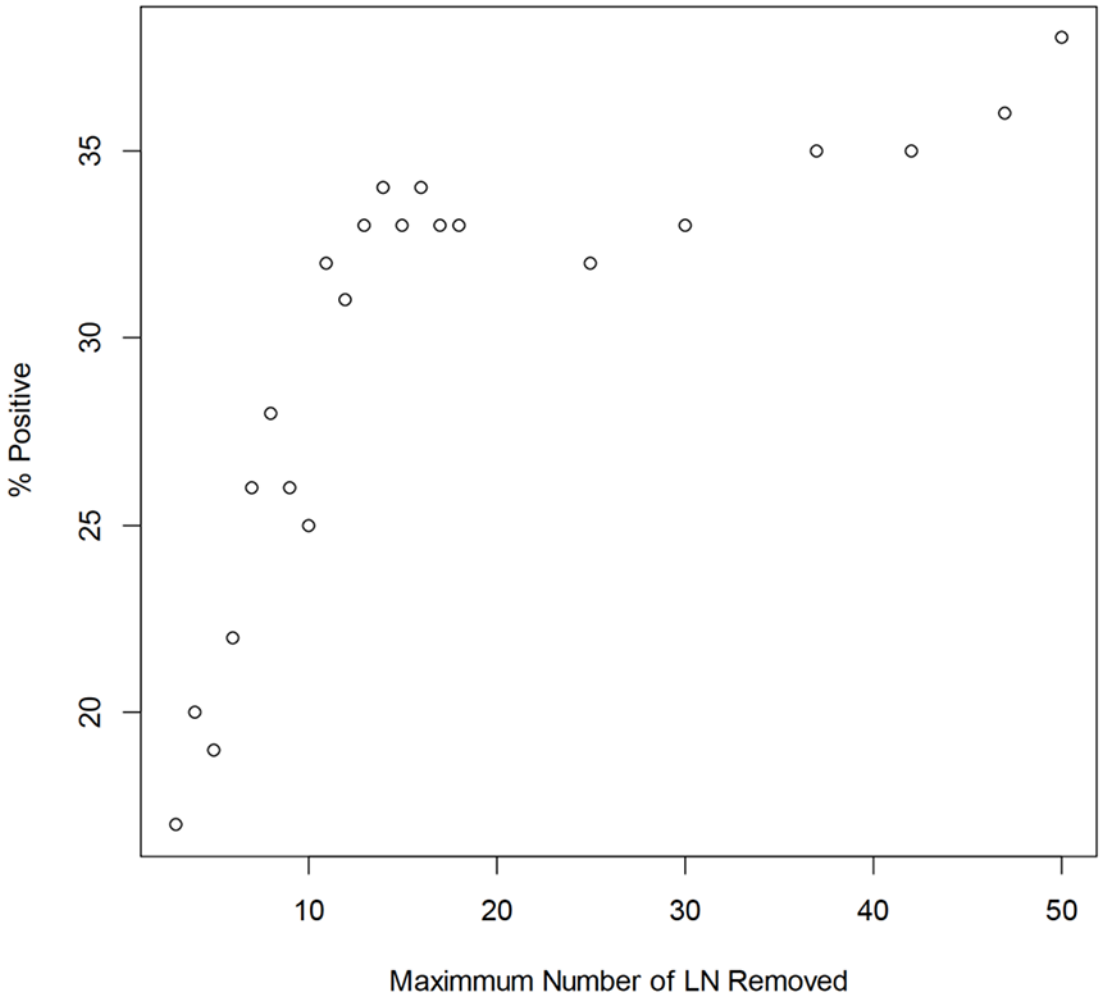

Figure 2.
COG review corelating number of retroperitoneal lymph nodes removed versus lymph node positivity

TABLE 1

Levels of Evidence for Adult and Pediatric Cancer Treatment Studies

Strength of study design	
1	Randomized, controlled, clinical trials i. Double-blinded. ii. Non-blinded treatment delivery
2	Nonrandomized, controlled, clinical trials
3	Case series or other observational study designs i. Population-based, consecutive series ii. Consecutive cases (not population-based) iii. Non-consecutive cases or other observational study designs (e.g., cohort or case-control studies)
Strength of endpoints	
A	Total mortality (or overall survival from a defined time)
B	Cause-specific mortality (or cause-specific mortality from a defined time)
C	Carefully assessed quality of life
D	Indirect surrogates. i. Event-free survival ii. Disease-free survival iii. Progression-free survival iv. Tumor response rate

TABLE 2

Recommendations for retroperitoneal lymph nodes biopsy at diagnosis

Lymph nodes	Action
ERMS, Nodes enlarged on imaging *	May biopsy to confirm pathological status, but if no biopsy performed then treat as involved
ERMS, Imaging negative	Patients ≥10 years old all should be biopsied
ERMS, Imaging negative	Patients < 10 yrs old no biopsy needed
ARMS	All patients receive biopsy regardless of imaging

* PET positive is not an absolute indication of nodal involvement, especially if PET is performed after surgery

Abbreviations: ERMS, embryonal rhabdomyosarcoma; ARMS, alveolar rhabdomyosarcoma

TABLE 3

Summary for surgical management of paratesticular rhabdomyosarcoma: INSTRuCT consensus opinion document

Item	Recommendation	Quality	Strength
Primary Inguinal Orchidectomy	Remove paratesticular RMS by radical inguinal orchidectomy	Moderate	Strong
	Remove the tumor as a single specimen incorporating the entire cord up to the internal ring and without breaching the tunica vaginalis	High	Strong
	The cord should be clamped at the internal ring before mobilization of the tumor	Low	Weak
	The cord is ligated using a non-absorbable suture	Low	Weak
	When scrotal skin is fixed or grossly invaded by tumor, it should be resected en-bloc with the specimen	High	Strong
	Testicle preserving approaches should be avoided	High	Strong
Primary Re-Excision	Primary re-excision (PRE) is indicated when the initial procedure did not include en-bloc complete gross resection of the tumor, testis and spermatic cord up to the internal ring	Moderate	Strong
	Patients with microscopic residual disease after initial resection (IRS Group II) may undergo PRE when there is microscopic disease at the cord margin	Moderate	Strong
Management of Large Tumors	For large tumors that are difficult to excise through a standard inguinal incision, it is better to extend the inguinal incision down to the scrotum or use a combined inguinal and scrotal approach to facilitate a complete gross total tumor resection	Moderate	Strong
	If there is proximal extension of the tumor through the inguinal canal, or extension into the urethra and base of the penis, the tumor is primarily irresectable and should be biopsied through an inguinal approach	Low	Strong
Trans-scrotal excision, scrotal violation, hemi-scrotectomy, scrotal RT	A trans-scrotal approach to tumor resection should be avoided since it makes complete resection more difficult	Moderate	Strong
	A trans-scrotal biopsy should be avoided since it may result in a potential increased risk of tumor spill	Low	Weak
	Hemi-scrotectomy is not indicated if patients have a scrotal violation or microscopic residual disease (Clinical group II) present in the scrotum after gross tumor resection	Low	Weak
	Scrotal skin should be removed en-bloc with the tumor excision if the tumor invades or extends into the scrotal skin	High	Strong
	If scrotal RT is required due to Clinical group III disease, then temporary transposition of the remaining normal testis should be done to preserve function	Moderate	Strong
Retroperitoneal Lymph Node (RPLN) Assessment and Management	All patients ≥ 10 years old should undergo ipsilateral infrarenal surgical lymph node evaluation, regardless of imaging results, to identify patients with pathologic disease	Moderate	Strong
	Patients <10 years old with no nodal enlargement should not undergo surgical RPLN evaluation given the low rate of pathologic nodal involvement	High	Strong
	The rare patients who have alveolar histopathology, irrespective of age or tumor size, should undergo surgical nodal staging procedure	Low	Weak
	Nodal sampling of 7-12 nodes from within the template area appears to be sufficient to identify disease presence	Moderate	Strong
	Sentinel nodal evaluation, may be used to help identify the positive node. The patient should still have additional nodes sampled to achieve at least 7 RPLN	Low	Weak