Evidence-Based Surgical Guidelines for Treating Children with Rhabdomyosarcoma

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Abstract

Background: Surgery remains the cornerstone of treatment for rhabdomyosarcoma (RMS) in children. However, there is considerable variation in surgical management practices worldwide, highlighting the need for standardized clinical practice guidelines (CPG). **Methods:** The CPG development involved assembling a multidisciplinary group, prioritizing ten key topic areas, conducting evidence searches, and synthesizing findings. Recommendations were voted on using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) methodology. **Recommendations:** The panel recommended regional lymph node evaluation for patients with paratesticular RMS who are more than 10 years old and extremity RMS. Other suggestions included pre-treatment re-excision for incompletely resected RMS, preoperative radiation therapy for unresectable tumors, maintaining a 0.5 cm resection margin, and tumor bed marking with surgical clips. The panel also suggests resection of residual metastatic disease following chemotherapy, resection of relapsed disease, and the least invasive approach for managing patients presenting with obstruction. **Conclusion:** This CPG provides evidence-based surgical management recommendations for RMS that can be adapted to diverse resource settings.

INTRODUCTION

Surgery is an integral part of the multimodal therapy for rhabdomyosarcoma (RMS), aiming to remove the tumor and enhance the likelihood of a cure. The approach to surgery varies and is highly individualized depending on the tumor's size, location, and stage, as well as the patient's overall health and functional needs.

Biopsies are performed to confirm the diagnosis and assess the tumor's histological type, which influences the surgical approach. The primary goal of surgery for RMS is to achieve complete resection of the tumor with a margin of normal tissue. This helps minimize the risk of residual cancer cells and reduces the likelihood of recurrence. Preservation of function and appearance is also a key consideration, especially in pediatric patients. This can involve intricate planning to balance tumor removal with the need to maintain limb function or other critical anatomical features.

The surgical management of rhabdomyosarcoma is complex and nuanced and requires a multidisciplinary approach. Given the variation in surgical practices for the treatment of RMS, the aim of this work is to provide guidance for key questions by developing an evidence-based clinical practice guideline (CPG).

METHODS

The CPG development was accomplished in several steps beginning with the formation of CPG steering and development groups, followed by evidence generation and voting on recommendations. The target users of these guidelines are surgeons providing care to children with RMS, particularly in settings with limited resources. Recommendations are also intended to inform the development of national and institutional policies. The CPG was developed following the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.

Step 1. Formation of guideline steering and development groups

A Guideline Steering Group (GSG) was formed, consisting of two methodologists, two clinicians, two coordinators, and a research associate. A Guideline Development Group (GDG) was constituted to include multidisciplinary content expertise, geographic, and gender representation. Participants were identified through St. Jude Global, the International Society of Pediatric Surgical Oncology, and the Global Initiative for Children's Surgery.

Disclosure and management of potential conflicts of interest

All members of the GSG and GDG provided conflict-of-interest disclosures prior to the voting process.

Step 2. Question selection

GSG and GDG, representing its constituent societies, identified the initial list of topic areas and questions to be addressed in the CPG related to surgical management of RMS. The scoping exercise concluded with a selection of 10 questions related to various aspects of the surgical management of RMS for inclusion in the CPG.

Step 3. Search, selection, data abstraction and synthesis

All questions selected by the GSG and GDG were converted into a specific question format using the PICO (patient, intervention, comparison and outcome) model. Selection criteria for each question were determined *a priori* based on the patient population and exposures in each question. Only comparative studies (systematic reviews of comparative studies, randomized controlled trials, cohort studies, case-control studies, and cross-sectional studies) were eligible for inclusion. A systematic search of PubMed through February 1, 2024, was performed to find studies addressing the questions included in the CPG. Additionally, we manually reviewed the reference lists of all relevant systematic reviews and included studies to find additional eligible studies. The titles and abstracts of all identified references were reviewed by a clinician and a methodologist from the GSG. Studies identified for full-text review were then reviewed by all members of the GSG, and any reasons for exclusion were noted.

Data from the included studies were extracted by two members of the GSG. The risk of bias in the included studies was assessed using the appropriate tool for each study design. The Cochrane RCT tool was used for randomized controlled trials. The Newcastle-Ottawa tool was used for cohort and case-control studies. Data on outcomes from similar studies were extracted and pooled when appropriate by using the random-effects model. The main outcomes of interest were overall survival, mortality, completeness of resection, local recurrence, complications, and intensity of therapy, as important outcomes to inform recommendations. All comparative analyses were performed using the RevMan software package. Pooled estimated for each outcome and certainty of evidence were summarized using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Summary of Findings tables.

Step 4. Training of GDG members

All GDG members participated in four one-hour virtual sessions focusing on the GRADE evidence to decision framework, fundamentals of study design, and interpretation of summary measures associated with diagnostic, prognostic, and intervention studies. The final session focused on interpretation of the summary of findings table and a mock session on the deliberation and voting process associated with CPG development.

Step 5. Development of recommendations

The development of recommendations was accomplished over 2 virtual sessions. Each question was presented to the GDG members by the methodologist, who was not a voting member, along with GRADE summary of findings table focusing on benefits and risks associated with the intervention. Summary of finding presentation was followed with deliberations among GDG members focusing on a variety of issues including patient values and preferences, resource use associated with the use of intervention and feasibility.

Step 6. Grading recommendations

All questions were transformed into recommendations prior to anonymous voting. Post deliberation, the recommendation associated with the intervention was presented to the GDG members followed by a discussion focusing on the framing of the recommendation. For consistency, all recommendations were initially framed as "recommend" and based on voting results by the GDG members were changed to "recommend" or "suggest" and in favor or against the intervention. The GDG members initially voted for or against each recommendation, followed by a vote on the strength of the recommendation (strong or weak). A simple majority of >50% was used as the threshold to determine the direction and strength of the recommendations.

Update plan

Guidelines are to be updated every 4 years.

Source of funding

This guideline development effort was supported by funds from the American Lebanese Syrian Associated Charities (ALSAC).

RESULTS

Overall, there were 14 GDG members, of whom, 36% were females (n=5). Most of the GDG members were surgeons (86%; n=12), with one radiation oncologist and one pathologist. The majority of members practiced in the public sector (57%; n=8) and worked in a tertiary setting (93%; n=13). The priority questions guiding the evidence review and synthesis for these guidelines are listed in Supplemental Table S1. The glossary of terms and phrases and their meanings for the purposes of this guideline are summarized in Supplemental Table S2.

RECOMMENDATIONS

The panel recommends surgical evaluation of regional lymph nodes for the management of paratesticular RMS who are more than 10 years old and extremity RMS *(Strong recommendation, Certainty of evidence: Very Low, Supplemental Table S3).*

We identified eight comparative studies assessing lymph node evaluation versus no evaluation. However, after removing studies with patient overlap, we included five retrospective cohort studies enrolling 2081 patients in the analysis. Pooled results did not show any difference in mortality, event-free survival, or relapses for paratesticular RMS who are more than 10 years old. However, overall mortality was lower in those receiving lymph node evaluation compared to no evaluation (OR 0.46, 95% CI 0.22 to 0.96). In patients with RMS of extremities, mortality was lower for those receiving lymph node evaluation (OR 0.32, 95% CI 0.17 to 0.60).

Panel deliberation.

The incidence of regional lymph node involvement in rhabdomyosarcoma varies between 10-40% and depends on the fusion status and location of the tumor. Lymph node involvement in rhabdomyosarcoma is associated with worse outcome.[1-13]

Accurate staging and assessment of lymph node involvement play a crucial role in determining the appropriate treatment and prognosis for patients with rhabdomyosarcoma[1-11]. The purpose of surgical evaluation of regional lymph nodes is primarily diagnostic.

For primaries in all sites, clinically enlarged lymph nodes should be evaluated pathologically as approximately 75% of enlarged lymph nodes will be confirmed positive for tumor cells.

Clinically uninvolved regional lymph node evaluation is particularly essential for patients with fusion positive disease, those with paratesticular RMS who are more than 10 years old by means of nodal basin sampling and those with extremity or trunk primary by means of sentinel lymph node biopsy[1-11]. However, prophylactic radical node dissection is of no therapeutic value and is not recommended.

Radiation therapy (RT) is the therapeutic modality of choice for regional lymph node metastases.

The panel is uncertain about timing of resection (upfront versus delayed) in patients with RMS. *(No recommendation, Certainty of evidence: Very Low, Supplemental Table S4).*

We identified seven comparative retrospective cohort studies assessing delayed primary excision (DPE) versus upfront resection. Of the seven, only 6 had extractable data enrolling 279 patients. The overall certainty of evidence was very low. Pooled results showed no significant difference in overall mortality, relapse, or need for additional intensive therapy. Incomplete resection was significantly lower in those with delayed primary excision compared to upfront resection (OR 0.27, 95% CI 0.15 to 0.51) including patients with RMS of the liver-bile duct (OR 0.05, 95% CI 0.00 to 0.52), extremity (OR 0.37, 95% CI 0.17 to 0.79), and mixed population (OR 0.09, 95% CI 0.02 to 0.48).

Panel deliberation.

Most (61-75%) localized RMS are unresectable at presentation and resection with negative margins is achievable in only 12 to 18% of patients[14-16]. Opting for upfront versus delayed primary excision of RMS depends on feasibility of a resulting microscopic negative margins and function preservation[14,17]. While upfront resection for paratesticular RMS is almost always possible; this is not necessarily the case for other locations. There is no role for upfront resection when achieving negative margins is not feasible or when upfront resection is mutilating. Determinants of resectability include tumor site, size, and relationship to critical structures. RT can be safely omitted if upfront R0 resection can be achieved, and the tumor is negative for translocation. However, there is a paucity of well-defined clinical criteria to guide selection for upfront resection versus delayed primary excision.

Neoadjuvant chemotherapy decreases the size, often alters the anatomic relationship of tumors to critical structures and improves feasibility of function-preserving resection[18-23]. Delayed primary excision after neoadjuvant chemotherapy potentially qualifies patients for radiation dose reduction[24,25] and improves overall survival for extremity and non-bladder-prostate genitourinary RMS[14,17,26].

Debulking surgery offers no local control or survival advantages; therefore, debulking has no role in curative RMS resection. Biopsy sites should be planned to facilitate en bloc resection of the biopsy tract at the time

of surgical local control.

The panel suggests pretreatment re-excision in patients with incompletely resected RMS *(Weak recommendation, Certainty of evidence: Very Low, Supplemental Table S5).*

We identified three retrospective cohort studies enrolling 284 patients assessing pretreatment re-excision versus no pretreatment re-excision. The overall certainty of evidence is very low. Pooled results did not show any difference in overall mortality or relapse. In patients with RMS of the extremity or trunk, mortality was significantly lower in those with pretreatment excision versus no pretreatment excision (OR 0.31, 95% CI 0.11 to 0.92).

Panel deliberation.

Pretreatment re-excision is indicated when initial excisional biopsy or resection leaves behind gross residual tumor, has microscopically involved margins, or when the margin status is uncertain[28-30]. In such situations, pretreatment re-excision is considered only when a wide re-excision can be achieved with the aim of resecting all residual tumor with negative margins, without causing significant surgical complications and undue delay in starting chemotherapy. Pretreatment re-excision in RMS, particularly for trunk and extremities[30], plays a critical role in ensuring margin-negative resection, downgrading risk stratification, and de-intensification of therapy. Patients who achieve a negative resection margin before starting chemotherapy with pretreatment re-excision are classified as group 1, have improved survival, and potentially qualify for reduced radiation dose[31]. All outcome analyses are improved for group 1 in comparison to group 2 and group 3. Group 1 achieved by either upfront resection or pretreatment re-excision have equally good outcomes[28-30]. In patients with group 1 disease, FOXO fusion-negative status may avoid the need for radiation therapy[32].

The panel suggests early preoperative radiation therapy for patients with unresectable RMS. *(Weak recommendation, Certainty of evidence: Very Low, Supplemental Table S6)*

We identified one retrospective cohort study enrolling 88 patients assessing preoperative radiation therapy for unresectable tumors versus no preoperative radiation therapy. The certainty of evidence is very low. Pooled results did not indicate any significant difference in overall mortality, mortality/event, or relapse. Incomplete resection was significantly lower in patients undergoing preoperative RT versus no preoperative RT (OR 0.02, 95% CI 0.00 to 0.08).

Panel deliberation.

Complete resection with negative margin is associated with improved local control and survival. However, negative margin resection is not the goal for orbital RMS or for large tumors where morbidity would be significant[38,39]. Although the choice of a 0.5 cm margin is somewhat arbitrary, such a narrow margin may be more feasible and simultaneously enable pathological confirmation of R0 resection. At the time of surgical local control, the fundamental principle of complete excision with a surrounding "cuff" of normal tissue should be followed to ascertain pathological negative margins, provided there is no loss of function or cosmetic appearance. The surgical team should ensure that the specimen is handed to pathology intact and abstain from any "on-table" dissection of the specimen that may violate the surrounding cuff of normal tissue. To ensure accurate margin evaluation, the specimen should be oriented, and margins labeled. It is inevitable to have narrow margins in some cases with complex tumor anatomy. In such cases, the surgeon ought to obtain biopsies of the resection bed especially adjacent to areas with questionable margins. These biopsies ought to be accurately labeled and sent for pathologic examination. To guarantee the accuracy of the margin inspection, communication with the local pathologist is required. A narrow margin of <1 mm is acceptable for sites with anatomic restrictions like non-parameningeal head and neck RMS to preserve form and function. Similarly, very aggressive resection is not warranted for RMS of the perineum or anus because of the proximity to urethra and anus that limits the feasibility of complete resection without compromising function preservation[40]. Neurovascular and other critical structures should not be resected to achieve arbitrary margin widths.

The panel suggests intraoperative tumor-bed marking with surgical clips for patients with RMS. *(Weak recommendation, Certainty of evidence: Very Low)*

We identified no comparative studies that assessed marking of tumor bed with surgical clips versus no marking.

Panel deliberation.

Titanium clips should be used in the tumor bed to identify the site of any probable microscopic or gross residual tumor. Radiation oncologists use these clips to precisely target the area where the tumor was located, minimizing radiation exposure to surrounding healthy tissues. Overall, the use of titanium clips for marking the resection bed in RMS surgery is a standard practice that enhances precision in further local control planning. Techniques to mitigate postoperative clip migration include ensuring the clip is placed exactly at the area of the tissue of interest, placing clips in a series or at multiple points along corners of the resection bed, and applying clips between two knots of a securely placed Prolene suture.

The panel does not suggest late resection after completion of therapy in patients with RMS. *(Weak recommendation; Certainty of evidence: Very Low, Supplemental Table S7)*

We identified eight comparative studies (seven retrospective cohort studies and one prospective nested cohort study) enrolling 939 patients assessing late resection after completion of therapy versus no resection. The overall certainty of evidence is very low. Pooled results showed no significant difference in overall mortality, relapse, need for additional intensive therapy, or non-relapse mortality.

Panel deliberation.

End of chemo-radiation therapy evaluation shows residual mass in one third of patients. End of therapy residual mass is often non-viable; resection of such mass is not associated with improved local control or overall survival. Moreover, such resection often fails to achieve complete resection and is associated with increased complications[25,27,41-48]. However, DPE, a pre-planned part of the initial treatment strategy, should be considered when feasible[24,25,26].

The panel suggests local treatment of residual metastatic disease after completion of chemotherapy. *(Weak recommendation; Certainty of evidence: Very Low)*

No comparative studies assessed resection of residual metastatic disease after completion of chemotherapy compared to no resection of residual metastatic disease.

Panel deliberation.

Twenty percent of RMS are metastatic at presentation and outcomes are dismal except for younger patients with embryonal RMS. Local treatment of all metastatic deposits improves event free survival and overall survival[49]. Evidence supports aggressive local treatment to both primary tumor and metastatic sites[50]. However, upfront resection of metastatic deposits at the time of diagnosis is generally not indicated and should be avoided.

The panel suggests resection of relapsed disease for the management of relapsed RMS. (Weak recommendation; Certainty of evidence: Very Low*, Supplemental Table S8*)

We identified seven retrospective studies assessing resection versus no resection of relapsed disease. However, of the seven, only six retrospective cohort studies had extractable data and enrolled 446 patients. The overall certainty of evidence is very low. The pooled overall mortality was significantly lower in those with resection of relapsed disease compared to no resection (OR 0.15, 95% CI 0.06 to 0.39).

Panel deliberation.

Approximately one third of RMS patients will develop progression or relapse with a dismal but variable outcome depending on tumor biology and stage[51]. Predictors of the outcome of RMS relapse include unfavorable site and size, FOXO fusion status, presence and number of metastases, lymph node metastases,

prior multimodal therapy, and interval to relapse. Lower risk patients may benefit from aggressive local and systemic multimodal therapy[52-59]. Relapse patients with initially small tumors, favorable site, Group I, Stage 1, and FOXO fusion negative have favorable outcome[51,56,57,60-63]. Resection of relapsed disease is suggested as part of the armamentarium for potentially salvageable patients to improve survival[53-59].

The panel suggests biopsy and diversion when indicated for patients with RMS presenting emergently with obstruction *(Weak recommendation; Certainty of evidence: Very Low, Supplemental Table S9)*

We identified two retrospective cohort studies enrolling 488 patients assessing upfront debulking surgery versus initial biopsy for locally advanced RMS. The overall certainty of evidence is very low. Pooled results did not indicate a significant difference in mortality or failure-free mortality.

DISCUSSION

This study convened a diverse international panel to develop evidence-based recommendations for the surgical management of rhabdomyosarcoma (RMS). Our effort underscores the importance of standardizing surgical practices in a condition where treatment approaches can significantly vary across different regions and healthcare systems. The panel formulated ten recommendations aimed at addressing critical questions identified by experts in the field, reflecting both clinical significance and the practical needs of diverse healthcare settings.

A notable limitation highlighted was the scarcity of robust evidence addressing the prioritized questions. Many existing studies were of low certainty, primarily retrospective cohort designs, which inherently have suboptimal rigor. This gap indicates a pressing need for well-designed and comprehensive international prospective studies to elucidate the true impact of various surgical interventions on outcomes in RMS. Future research should focus on generating higher-quality evidence that can more definitively guide surgical practices.

Despite the limitations in the evidence base, the recommendations provided by the panel are grounded in practical considerations. Most suggested interventions are consistent with standard care practices across various resource settings and do not impose additional risks to patients. For instance, the recommendation for regional lymph node evaluation is crucial, as our analysis indicates a potential survival benefit in patients with extremity and paratesticular RMS who are more than 10 years old. This is particularly relevant given the varied surgical approaches currently employed worldwide.

Moreover, the emphasis on pre-treatment re-excision for incompletely resected RMS reflects a growing understanding of the importance of achieving negative margins to minimize recurrence risk. Similarly, the suggestion for early preoperative radiation therapy in cases of unresectable RMS acknowledges the need for alternative strategies to enhance resectability and highlight the utility of radiation therapy as the primary local control modality when surgery is not feasible.

The global nature of this guideline development effort highlights its potential applicability across different healthcare settings. The recommendations aim to provide a framework for improving surgical outcomes in RMS, which can be adapted to local resources and practices. By promoting standardization, we hope to reduce disparities in care and outcomes for children with RMS worldwide.

As we look to the future, we encourage ongoing dialogue and collaboration among pediatric cancer care providers to refine these guidelines further. Regular updates, planned every four years, will ensure that our recommendations evolve alongside advancements in surgical management and evidence.

In conclusion, our panel's recommendations for the surgical management of RMS are designed to bridge existing gaps in care and provide a foundation for enhancing surgical outcomes across diverse healthcare environments. By fostering a shared understanding and application of these guidelines, we aim to improve the prognosis for children affected by this challenging disease.

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Table S1: The priority questions guiding the evidence review and synthesis for the guidelines.

Topic	Research (PIC
Loco-regional evaluation	1- In patients v
Timing of resection	2- In patients v
Pretreatment re-excision	3- In patients v
Neoadjuvant radiation therapy	4- In patients v
Margin	5- In patients v
Tumor bed marking	6- In patients v
Resection at the end of therapy	7- In patients v
Resection of metastatic disease	8- In patients v
Resection of relapsed disease	9- In patients v
Resection of locally advanced disease presenting with obstruction versus biopsy and diversion if indicated.	10- In patients

not-yet-known not-yet-known not-yet-known unknown

Term/Phrase	Meaning
Regional Lymph Node Evaluation	The assessment of nearby lymph nodes to determine if cancer has spread from its origi
Upfront Resection	The surgical removal of a tumor as the first step in treatment, before any other therapi
Pre-treatment Re-excision	A surgical procedure performed to remove any remaining cancerous tissue that was not
Neoadjuvant Radiation Therapy	Radiation therapy given before surgery to shrink tumors and improve the chances of su
Margin	The edge or boundary of the tissue removed during surgery, indicating whether any can
Tumor Bed	The area of tissue where a tumor was located prior to its removal; often marked or mon
Residual Metastatic Disease	Cancer that remains in the body after initial treatment, having spread to other locatio
Relapsed Disease	The return of cancer after a period of improvement or remission, indicating that cancer
Locally Advanced Disease	A stage of cancer in which the tumor has grown into and invaded nearby tissues or org

Table S3: Lymph node evaluation compared to no lymph node evaluation in patients with rhabdomyosarcon

Patient or population: Rhabdomyosarcoma **Intervention:** Lymph node evaluation **Comparison:** No lymph node evalu
Outcomes
(studies)
Follow-up
(GRADE)
(95% CI)

Mortality
Mortality - Extremities
Mortality - Paratesticular
Relapse
The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison gr
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to

not-yet-known not-yet-known

not-yet-known

unknown

Explanations a. There were differences between patients who underwent node sampling and those who did not on basis of age in Routh 2020 and Weiner 2001. c. Moderate heterogeneity between studies. b. The confidence intervals are wide.

Table S4: Delayed primary excision compared to upfront excision for Rhabdomyosarcoma
Patient or population: Rhabdomyosarcoma **Intervention:** Delayed primary excision **Comparison:** Upfront excision
Outcomes
(studies)
Follow-up
(GRADE)
(95% CI)

Mortality
Mortality - Head and neck
Mortality - Liver-bile duct
Mortality - Chest wall
Relapse
Relapse - Head and neck
Relapse - Liver-bile duct
Relapse - Mixed population
Incomplete resection
Incomplete resection - Head and neck
Incomplete resection - Liver-bile duct
Incomplete resection - Chest wall
Incomplete resection - Perianal/perineal
Incomplete resection - Extremity
Incomplete resection - Mixed population
Need for additional intensive therapy
Need for additional intensive therapy - Liver-bile duct
The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison gr
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to

Explanations

a. Baseline differences between patients selected for upfront resection versus delayed resection exist.

b. The confidence intervals are wide.

Table S5: Pretreatment excision compared to No pretreatment excision for Rhabdomyosarcoma
Patient or population: Rhabdomyosarcoma **Intervention:** Pretreatment excision **Comparison:** No pretreatment excisi
Outcomes
(studies)
Follow-up
(GRADE)
(95% CI)

Mortality
Mortality - Paratesticular
Mortality - Extremity or trunk
Relapse
Relapse - Mixed
The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison gr
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to

Explanations

a. The control group was selected from patients in whom primary re-excision was not feasible

b. The confidence intervals are wide.

Table S6: Preoperative radiation therapy compared to No preoperative radiation therapy for Rhabdomyosa
Patient or population: Rhabdomyosarcoma with unresectabe tumor **Intervention:** Preoperative radiation therapy **Con**
Outcomes
(studies)
Follow-up
(GRADE)
(95% CI)

Mortality
Mortality or event
Relapse
Incomplete resection
The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison gr
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to

Explanations

a. There are baseline differences between patients who received preoperative therapy versus those who did not. The two groups were treated 5 years apart.

b. There is a risk of misclassification bias. It is not clear if all patients received radiotherapy.

c. The confidence intervals are wide.

Table S7: Late resection compared to No late resection for Rhabdomyosarcoma

Patient or population: Rhabdomyosarcoma **Intervention:** Late resection **Comparison:** No late resection
Outcomes
(studies)
Follow-up
(GRADE)
(95% CI)

Mortality
Mortality – Bladder

Mortality - Vagina, vulva
Mortality - Mixed population
Relapse
Relapse - Bladder

Relapse - Mixed population
Need additional intensive therapy
Non-relapse mortality
The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison gr
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to

Explanations

a. There are baseline differences between the late resection group and the control group.

b. The heterogeneity between studies is moderate.

c. The confidence interval is wide.

d. The heterogeneity between studies is high.

not-yet-known not-yet-known not-yet-known unknown

Table S8: Resection of relapsed disease compared to No resection for Rhabdomyosarcoma
Patient or population: RhabdomyosarcomaIntervention: Resection of relapsed diseaseComparison: No resection
Outcomes
(studies)
Follow-up
(GRADE)
(95% CI)

Mortality
The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group a
GRADE Working Group grades of evidenceHigh certainty: we are very confident that the true effect lies close to that of the

Explanations

a. Baseline differences between patients selected for resection versus no resection exist.

b. Heterogeneity between studies was high (I^2=69%)

Table S9: Resection at time of emergency presentation compared to biopsy or diversion for rhabdomyosarc
Patient or population: Rhabdomyosarcoma **Intervention:** Resection at time of emergency presentation **Comparison:**
Outcomes
(studies)
Follow-up
(GRADE)
(95% CI)

Mortality
Failure free mortality
Failure free mortality - Retroperitoneum/pelvis
Failure free mortality - Mixed population
The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison gr
GRADE Working Group grades of evidence High certainty: we are very confident that the true effect lies close to

Explanations

a. Confidence intervals are wide.

b. High heterogeneity between studies (I^2=77%).