PHILIPPINE GUIDELINES ON THE MANAGEMENT OF WILMS TUMOR

Disclaimer and Contact Information

This clinical practice guideline (CPG) is intended to be used by healthcare professionals who have received specialized training in pediatric oncology, pediatric surgery, pediatric urology, radiology, radiation oncology, and pathology. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the clinicians in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and their responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG, but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

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This CPG on Wilms tumor (WT) was developed through the technical assistance of the Philippine Children's Medical Center (PCMC). This project would not have been possible without the initiative and financial support from the DOH. The DOH neither imposed any condition nor exerted any influence on the operations and the final output formulation.

The Task Force members undertook extensive technical work in (1) searching and synthesizing the evidence while ensuring objectivity in each stage of the process, (2) presenting the evidence in the panel discussion, and documenting and writing the final report. They were also indispensable in carrying out the legwork, coordinating among various individuals, groups, and committees, and facilitating the *en banc* meeting. The CPG Central Steering Committee and the Task Force Steering Committee were responsible for overall organization and management and were accountable for the quality of the CPG.

Lastly, this guideline was completed through the invaluable contribution and participation of panelists from different sectors of healthcare who committed their time and effort. Their knowledge, experience, and expertise in analyzing the scientific evidence and their values and preferences were crucial in formulating the recommendations.

We thank all in contributing to this endeavor.

How to cite:

Participating Societies, Organizations, Agencies and/or Institutions

List of Abbreviations

3DCRT	Three-dimensional conformal radiation therapy
AE	Adverse event
AGREE	Appraisal of Guidelines Research & Evaluation
AUC	Area under the curve
CI	Confidence interval
COG	Children's Oncology Group
COI	Conflict of interest
CP	Consensus Panel
CPG	Clinical practice guideline
CPN	Central parenteral nutrition
CR	Complete response
CT	Computed tomography
CXR	Chest radiography
DCOI	Declaration of conflict of interest
DD4A	Vincristine/dactinomycin/doxorubicin regimen
DN	Delayed nephrectomy
DOH	Department of Health
EFS	Event-free survival
EN	Enteral nutrition
ERE	Evidence review expert
EtD	Evidence-to-Decision
FHWT	Favorable histology Wilms tumor
FISH	Fluorescence in situ hybridization
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HR	Hazard ratio
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
IQR	Interquartile range
IR	Incomplete response
LC-MS	Liquid chromatography–mass spectrometry
LMIC	Low and middle-income countries
LN	Lymph node
LN+	Lymph node positive
LND	Lymph node density
LOH	Loss of heterozygosity
MD	Mean difference
MVA	Multivariate analysis
NACT	Neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Database
NWTSG	National Wilms Tumor Study Group
OC	Oversight Committee
OR	Odds ratio
OS	Overall survival
PCMC	Philippine Children's Medical Center
PCR	Polymerase chain reaction
PE	Physical examination
PICO	Population, intervention, comparator, outcome

PN	Parenteral nutrition
PPN	Peripheral parenteral nutrition
QoL	Quality of life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	Randomized controlled trial
RFS	Relapse-free survival
ROBINS-I	Risk of Bias in Non-randomized Studies – of Interventions
RR	Risk ratio
RT	Radiation therapy
RTSG	Renal Tumor Study Group
SBRT	Stereotactic body radiotherapy
SC	Steering Committee
SEER	Surveillance, Epidemiology, and End Result
SIOP	International Society of Paediatric Oncology
SRI	Surgery-to-RT interval
TF	Task Force
TWG	Technical Working Group
UKCCSG	United Kingdom Children's Cancer Study Group
UN	Upfront nephrectomy
VMAT	Volumetric modulated arc therapy
WAI	Whole abdominal irradiation
WHO	World Health Organization
WLI	Whole lung irradiation
WT	Wilms tumor

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Executive Summary

Wilms tumor or nephroblastoma is the most common malignant renal tumor in children accounting for about 6-7% of pediatric cancers. Majority of cases are diagnosed before 5 years old with a median age diagnosis of 3.5 years, but patients with a positive family history may have an earlier onset of presentation. The global incidence rate of Wilms tumor is about 7 to 10 per million children (0-14 years of age). Survival rates reach 90% in high-income countries with current treatment protocols. LMICs report higher incidence rates with poorer outcomes attributed to challenges in detection and treatment of Wilms tumor.

At the Philippine Children's Medical Center (PCMC), a clinical care pathway for the diagnosis and management of Wilms tumor was developed in 2013 due to the dismal outcome reported for this tumor since 2009. Similar efforts to standardize the diagnosis and treatment for Wilms tumor have been initiated by various institutions that cater to a significant number of childhood cancer patients. However, a multidisciplinary, concerted approach in formulating locally applicable guidelines for Wilms tumor can ensure cost-efficiency and better survival outcomes.

The development of the Wilms tumor Clinical Practice Guidelines aimed to formulate up-to-date, evidence-based recommendations on the diagnosis, treatment, and surveillance of Wilms tumor.

Following the standard CPG development process outlined in the DOH Manual for CPG Development and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology, 11 evidence summaries and 15 recommendations were generated by 13 Consensus Panelists (CP) representing their specific health organizations and institutions.

Table 1. Summary of recommendations for Wilms Tumor

Recommendation	Strength of recommendation	Certainty of Evidence
Question 1: Among patients with WT, would chest Xray alone vs CT scan alone vs CXR + CT scan in detecting lung metastasis result in improved EFS and OS, and other outcomes (cost effectiveness, AE)?		
Among patients with WT, we recommend the use of non-enhanced CT scan alone to detect lung metastasis as part of the baseline staging workup.	Strong	Low
Among patients with WT, we suggest the use of chest X-ray alone as an alternative to non-enhanced CT scan to detect lung metastasis as part of the baseline staging workup.	Weak	Low

Question 2: Among patients with non-metastatic and operable WT, would delayed nephrectomy (DN) with neoadjuvant chemotherapy result in improved treatment goals (survival and toxicity), when compared to upfront nephrectomy (UN)?		
Among patients with unilateral, non-metastatic, operable WT, we recommend either delayed nephrectomy with neoadjuvant chemotherapy or upfront nephrectomy.	Strong	Moderate
Question 3: Among patients with metastatic, operable WT, would upfront nephrectomy (UN) vs neoadjuvant chemotherapy with delayed nephrectomy (DN) improve treatment outcomes?		
Among patients with metastatic, operable, unilateral WT, we suggest either upfront nephrectomy or neoadjuvant chemotherapy to improve treatment outcomes.	Weak	Very Low
Question 4: Among patients with WT undergoing surgery, would lymph node sampling result in improved EFS and OS and reduction of harm?		
Among patients with WT undergoing surgery, we recommend lymph node sampling as it results in improved overall survival.	Strong	Low
Question 5: Among malnourished patients with WT, would chemotherapy dose modification improve treatment outcomes?		
Among malnourished patients with WT, we recommend dose adjustment in initiating chemotherapy and reduction of vincristine to 2/3 of usual dose.	Strong	Very Low
Question 6: Among patients diagnosed with Stage III WT, what is the optimal timing for radiotherapy (RT)?		
Among patients with Stage III WT, we recommend starting radiotherapy between days 9-14 after operation.	Strong	Very Low
Question 7: Among patients with WT, would RT technique (conventional vs advanced) and timing (early versus delayed) result in improved treatment goals (survival and toxicity)?		
Among patients with WT for whom RT is indicated, we recommend the use of 3D conformal RT.	Strong	Low
Among patients with WT without metastasis and for whom flank RT or whole abdominal irradiation (WAI) is indicated, we recommend to keep the surgery-RT	Strong	Moderate

interval to 9 to 14 days, unless medically contraindicated.		
Question 8A: Among patients with WT, would obtaining molecular analysis for LOH 1p/16q compared to no molecular analysis improve treatment outcomes?		
Among patients with WT Stage I/II, we suggest testing LOH 1p/16q for augmentation of therapy.	Weak	Low
Among patients with WT Stage III/IV, we suggest testing LOH 1p/16q for augmentation of therapy.	Weak	Very Low
Question 8B: Among patients with WT, would obtaining molecular analysis (1q gain) compared to no molecular analysis improve treatment outcomes?		
Among patients with favorable histology WT with isolated lung metastasis, we suggest 1q gain analysis for augmentation of therapy.	Weak	Very Low
Question 9: Among patients with WT with complete response to treatment, would interval history and physical examination (PE) alone vs routine evaluation using chest x-ray (CXR) and whole abdominal ultrasound (US) vs chest computed tomography (CT) and whole abdominal CT scan improve event-free and disease-free survival, and aid early detection of recurrence?		
Among patients with WT who have completed therapy, we recommend the use of surveillance imaging in addition to history and physical examination in the detection of relapse.	Strong	Very Low
Among patients with WT who have completed therapy, we suggest the use of chest x-ray and abdominal ultrasound versus chest and abdominopelvic CT scan in the detection of relapse.	Weak	Very Low
Question 10: Among patients with WT, what is the appropriate nutritional intervention based on nutritional status that will result in improved treatment outcomes?		
Among malnourished children with WT upon diagnosis, we suggest the use of central parenteral nutrition (CPN) as means of nutritional support for weight gain.	Weak	Very Low
In patients with WT at high nutrition risk, multidisciplinary and individualized comprehensive assessment should be done to determine appropriate nutrition management and support.	Good Practice Statement	

1. Introduction

Wilms tumor (WT) or nephroblastoma is an embryonal malignant renal tumor that accounts for up to 7% of all childhood cancers and 95% of juvenile renal tumors, making it the most common pediatric renal tumor [1, 2]. In the Philippines, it is estimated to account for 3.4% of all childhood cancers [3]. The additional treatment options and improvement in the treatment protocols in the past century have greatly improved the overall survival for Wilms tumor from 30% in the 1930s to up to 85% and above [4,5]. However, this improvement seems to be isolated to upper-middle- and high-income countries [4,6]. In low-middle income countries (LMICs) such as the Philippines, 5-year overall survival reports still range from 24% to 85%. Barriers to improvement of survival within the LMICs have been attributed to late presentations, malnutrition, drug toxicity, lack of resources, and lack of education, specifically, low health literacy in families and lack of cancer treatment education among providers. Given the following challenges faced by LMICs, the need for a national guideline with resource-sensitive recommendations is paramount.

This guideline will support the objectives stated in the Universal Health Care Act [7] that all Filipinos are given access to quality and affordable medical services, including primary care benefits. The development of this guideline is one of the strategies put forth by the PCMC to support the WHO's Global Initiative for Childhood Cancer. This guideline provides recommendations on ten (11) prioritized clinical questions in staging, management, and surveillance of patients with Wilms tumor.

In the guideline development, evidence-based recommendations for the prioritized clinical questions were formulated using the GRADE Evidence-to-Decision (EtD) framework [8, 9]. The EtD framework aims to facilitate the adaptation of recommendations and decisions of experts and stakeholders based on specific contexts, essential health outcomes, benefits, and harms while looking through the equity, applicability, and feasibility lenses.

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2. Objective, Scope, Target Population and Target Users

This CPG is a systematic synthesis of evidence to address the staging, management, and surveillance of Wilms tumor. Recommendations were made on eleven (11) clinical questions on imaging modality for detecting lung metastasis, upfront vs delayed nephrectomy, utility of lymph node sampling, chemotherapy dose modification for malnourished patients, timing and technique of RT, utility of molecular analysis, surveillance, and nutritional intervention.

Table 2. Scope of the CPG described using PIPOH

Population	Pediatric patients with unilateral, non-syndromic Wilms tumor
Intervention	Staging, management, and surveillance
Professionals	Pediatric oncologists, pediatric surgeons, pediatric urologists, pediatric nephrologists, radiologists, radiation oncologists, and pathologists
Outcomes	Diagnostic accuracy, event-free survival, overall survival, cost-effectiveness, adverse events
Healthcare setting	Tertiary level of care

3. CPG Development Methodology

3.1 Organization of the Process

Following the international standards, the DOH Manual for CPG Development outlined the guideline development process into four phases: 1) preparation and prioritization, 2) CPG generation, 3) CPG appraisal, and 4) implementation [1].

In the preparation and prioritization phase, the Steering Committee set the CPG objectives, scope, target audience, and clinical questions. They consulted different stakeholders in prioritizing and developing the guideline questions. They identified and formed the working groups involved in creating the evidence base and finalizing the recommendations for each clinical question included.

The Evidence Review Experts (ERE) or the Technical Working Group (TWG) were tasked to review existing CPGs, appraise and summarize the evidence, and draft the initial recommendations. The evidence summaries were then presented to the CP members to finalize the recommendations.

The CP consisted of multisectoral representatives tasked to review the evidence summaries and develop recommendations during the *en banc* meeting. In the meeting, they prioritized critical and important outcomes, discussed necessary considerations revolving around the recommendations, and voted on each recommendation and its strength. They participated in a modified Delphi activity to decide on recommendations that were not resolved during the *en banc* meeting.

- Convening the Steering Committee, Technical Working Group, Consensus Panel and Oversight Committee

The SC convened the CP, considering possible conflicts of interests of each panel member. To ensure fairness and transparency, the composition was guided by the DOH manual [1]. Content experts and other key stakeholders were invited to join the CP. The key stakeholders included policymakers, patient advocates, and physicians from different settings (e.g., public primary care settings, private practice, occupational health settings). In the choice of CP, the Task Force (TF) ensured that all stakeholders were part of the target population for the CPG.

- Managing Conflicts of Interest (COI)

The Central Executive Committee convened an Oversight Committee (OC) whose task was to thoroughly review the declaration of conflict of interest (DCOI) of each of the TF members, particularly CP and make recommendations on how to manage the COI. For TF members with potential significant COIs, the members of OC conducted additional investigations with due diligence to ensure the integrity of the CPG process and submitted the final recommendations.

All TF members submitted a DCOI and their *curriculum vitae* (CV) prior to the initiation of the guideline development process. The disclosure included a 4-year period of personal potential intellectual and/or financial COI.

Declared COIs of the TF were deliberated and managed by the OC using the pre-agreed criteria. A full description of the methods can be found in the Final Technical report.

Those with significant potential COI were not allowed to join the roster of TF members. See Conflict of Interest Declaration at the end of the document.

- Prioritizing the Clinical Questions

Currently, there are two major research groups that developed treatment approaches for patients with WT - the Children's Oncology Group (COG) and the International Society of Paediatric Oncology (SIOP). The COG approach is based on upfront surgical resection for children with unilateral WT followed by adjuvant chemotherapy while SIOP employs preoperative or neoadjuvant chemotherapy. In the Philippine setting, adaptation of a singular approach might not be outright beneficial hence guidelines that are responsive to the local and even institutional context need to be crafted. Review of existing literature, other clinical practice guidelines and expert opinions formed the basis for prioritizing the clinical questions. The SC rigorously discussed and proposed relevant clinical questions that can be addressed with available evidence, and actionable for healthcare providers. After exhaustive consultative meetings, a total of 11 priority topics were identified.

3.2 Evidence Summaries

- Search Methods and Strategies

A systematic search for relevant literature of at least 3 electronic databases, such as MEDLINE via PubMed, Embase, Google Scholar, and UpToDate was performed. The search strategies used were based on the PICO (population, intervention/exposure, comparison, and outcomes), MeSH and free text, set for each question. *De novo* systematic reviews and meta-analysis were done for each clinical question.

- Inclusion and Exclusion Criteria

The inclusion criteria were based on the PICO of each clinical question. Only those published or translated in English were included. Articles published beyond 10 years from the date of search were excluded. For some clinical questions with very limited published articles, no restriction with regards to publication year was applied.

- Study Quality Assessment and Certainty of Evidence

Appraisal tools for clinical studies using the Cochrane Risk of Bias (RoB), Painless EBM, and Newcastle Ottawa Scale or Quality Assessment of Diagnostic Accuracy Studies (QUADAS), were utilized by the EREs. Systematic reviews and meta-analysis

using the Cochrane approach were used. Clinical practice guidelines were assessed using the AGREE 2 tool.

- Data Synthesis

The clinical questions were developed using the PICO (population, intervention, comparator and outcome) format. The ERE searched and appraised international practice guidelines related to the diagnosis and management of Wilms tumor, including but not limited to those of the National Wilms Tumor Study Group (NWTSG)/Children's Oncology Group (COG) and the International Society of Paediatric Oncology (SIOP).

The results of the appraisal of existing CPGs and their evidence summaries determined the need for a systematic search in electronic databases (MEDLINE via PubMed, CENTRAL, Google Scholar, Web of Science, Scopus, EBSCOHost, EuropePMC, Cochrane, Embase, Elsevier through ScienceDirect) for *de novo* systematic reviews and meta-analysis for each question. All searches were done from January to April 2023. Details on the time periods were discussed under the specific questions (please see evidence summaries in Appendices). Relevant local databases and websites of medical societies were also utilized in the search (HERDIN, Acta Medica Philippina). Keywords were based on PICO (MeSH and free text) set for each question. The ERE also contacted authors of related articles to verify details and identify other research studies for appraisal, if needed.

At least two reviewers worked on each PICO question. The search strategy and inclusion criteria were based on the PICO question and are included in their respective evidence summaries. Evidence reviewers appraised the directness, methodological validity, results, and applicability of each relevant article included. RevMan, STATA, and GRADEPro were used for the quantitative synthesis of important clinical outcomes for each question. The ERE generated evidence summaries for each of the eleven (11) questions. Each evidence summary included evidence on the burden of the problem, benefits, harm, and social and economic impact of the intervention. Evidence/information that will facilitate the decision (i.e. cost of treatment, cost-effectiveness studies, qualitative studies) were also included in the evidence summaries. The Quality of Evidence was assessed using the GRADE approach (See Table 3).

Table 3. Basis for Assessing the Quality of the Evidence using GRADE Approach [2]

Certainty of Evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect

Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Factors that lower quality of the evidence are:

- Risk of bias
- Important inconsistency of results
- Some uncertainty about directness
- High probability of reporting bias
- Sparse data/Imprecision
- Publication bias

Additional factors that may increase quality are:

- All plausible residual confounding, if present, would reduce the observed effect
- Evidence of a dose-response gradient
- Large effect

3.3 Formulation of the Recommendations

- Evidence to Decision Framework

Draft recommendations were formulated based on the quality of evidence, trade-offs between benefit and harm, cost-effectiveness, applicability, feasibility, equity, resources and uncertainty due to research gaps. Prior to the series of online consensus panel meetings, the CP received the draft recommendations together with evidence summaries based on the EtD framework shown in Table 4. These recommendations, together with the evidence summaries, were presented during the *en banc* meeting.

Table 4. Detailed considerations based on the EtD framework [3]

1. Is the problem a priority? 2. How substantial are the desirable anticipated effects? 3. How substantial are the undesirable anticipated effects? 4. What is the certainty of the evidence? 5. Is there important uncertainty about or variability in how much people value the main outcomes?

6. Does the balance between desirable and undesirable effects favor the intervention or the comparison?
7. How large are the resource requirements (costs)?
8. What is the certainty of the evidence of resource requirements (costs)?
9. Does the cost-effectiveness of the intervention favor the intervention or the comparison?
10. What would be the impact on health equity?
11. Is the intervention acceptable to key stakeholders?
12. Is the intervention feasible to implement?

The strength of each recommendation (i.e., strong or weak) was determined by the CP considering all the factors mentioned above. Strong recommendation means that the panel is "confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects" while weak recommendation means that the "desirable effects of adherence to a recommendation probably outweigh the undesirable effect but is not confident" [4].

- Consensus Process

The recommendation for each question and its strength was determined through voting. A consensus decision was reached if 75% of all CP members agreed [2]. If consensus was not reached in the first voting, questions and discussions were encouraged. Two further rounds of voting on an issue were conducted. Evidence-based draft recommendations were also revised based on inputs arrived at by consensus during the *en banc* discussions.

3.4 Plan for Dissemination and Implementation

The SC discussed with relevant stakeholders such as DOH and PhilHealth to prepare a dissemination plan that will actively promote the adoption of this CPG with strategies for copyrights. Suggestions ranged from making the CPG available on websites, press conferences, social media sites, professional society conventions, and journal publications.

3.5 External Review

The CPGs were reviewed by independent stakeholders, who were not members of the TF. They were also presented in conferences and to relevant societies for their comments and suggestions.

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4. Recommendation and Evidence Summaries

General Principles of Management

Children with a probable Wilms tumor should be managed in a pediatric cancer center. [1] Optimal management of these children relies on a comprehensive and multidisciplinary approach that involves the collaboration of various health professionals. [2] A multidisciplinary team, including pediatric oncologists, pediatric surgeons, radiation oncologists, radiologists, pathologists, and specialized nurses, should collaborate in the treatment planning process. Regular tumor board meetings should be conducted to discuss complex cases and ensure consensus on treatment plans. [3]

Treatment of Wilms tumor involves multimodal therapy (surgery, chemotherapy, and radiation) hence expertise in the respective fields is mandatory. Surgical resection should be performed by experienced pediatric surgeons following established guidelines for tumor excision and lymph node sampling. Chemotherapy should be coordinated and monitored by pediatric oncologists, with appropriate supportive care measures to minimize treatment-related toxicities. Radiation planning and delivery should be performed by radiation oncologists specialized in pediatric malignancies, utilizing modern techniques to minimize radiation-related toxicities. Long-term follow-up care should likewise be provided by a multidisciplinary team to monitor for disease recurrence, manage treatment-related late effects, and support the overall well-being of survivors. [4]

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4.1 Imaging modality for baseline staging work up of patients with Wilms tumor

Question 1: Among patients with WT, would chest Xray alone vs CT scan alone vs CXR + CT scan in detecting lung metastasis result in improved EFS and OS, and other outcomes (cost effectiveness, AE)?

RECOMMENDATIONS

1. **Among patients with WT, we recommend the use of non-enhanced CT scan alone to detect lung metastasis as part of the baseline staging workup.** ***(Strong recommendation, low certainty of evidence)***
2. **Among patients with WT, we suggest the use of chest X-ray alone as an alternative to non-enhanced CT scan to detect lung metastasis as part of the baseline staging workup.** ***(Weak recommendation, low certainty of evidence)***

Considerations

The consensus panel considered the following when formulating these recommendations:

- The panel highlighted that the use of non-enhanced chest CT scan is more beneficial in early-stage Wilms tumor because it can affect management.
- Despite the low certainty of evidence, the panelists were unanimous in recommending the use of non-enhanced CT scan in detecting lung metastasis at baseline due to its high sensitivity and cost-effectiveness.

Key Findings

- No studies were found regarding event-free survival, overall survival, cost, adverse events, and quality of life in relation to the use of chest X-ray versus CT scan versus chest X-ray plus CT scan in detecting lung metastasis among patients with WT.
- There was one retrospective study that compared the performance of chest X-ray and CT scan in detecting lung metastasis in patients with WT.
    - Overall, the chest X-ray and chest CT findings were consistent in 79/81 (98%) in detecting lung metastasis.
    - The authors of the study concluded that chest X-ray alone is accurate in the diagnosis or exclusion of lung metastasis in patients with WT, and CT scan will not provide additional information that may alter the treatment or outcome of the patient.
    - When computed, the chest X-ray's sensitivity and specificity in detecting lung metastases when compared to CT scan are 0.8 and 1.0, respectively.

- The paper included in the review is downgraded to low because of the small sample size from a single hospital.
- If it will be based on sensitivity and specificity only, chest X-ray is a good alternative to CT scan in detecting lung metastases among patients with WT.

Background

In the management of Wilms tumor, it is important to look for lung metastasis because the lungs are a common site of metastasis for this type of cancer. Studies show that about 10-14% of patients with WT present with lung metastasis at diagnosis [1,2]. Detecting lung metastasis is important because it affects the staging and treatment plan for Wilms tumor. Patients with lung metastasis are generally considered to have a higher stage of disease, which may affect the type and intensity of treatment they receive. Surgery, chemotherapy, and radiation therapy are all used to treat lung metastasis in Wilms tumor, and early detection of these metastases can improve treatment outcomes and overall survival rates [3].

Imaging studies are needed to presumptively diagnose WT, stage the disease, and measure tumor volume after neoadjuvant chemotherapy for postoperative treatment stratification. Various guidelines recommended the use of CT scan and chest X-ray to determine the presence of lung metastasis among patients with WT. The National Comprehensive Cancer Network (NCCN) recommends the use of chest CT scan to check for lung metastasis and for post-treatment surveillance, while SIOP recommends chest CT scan as a mandatory test to assess for lung metastasis [4,5]. SIOP also recommends the use of chest X-ray in two planes as an alternate approach to undertake the initial evaluation for lung metastasis [5]. As opposed to chest X-rays, chest CT scan is considered as a more sensitive modality for detecting lung nodules. However, one drawback of using CT scan in this setting is that it cannot differentiate between small benign lesions and actual lung metastases which may lead to overtreatment [6]. In a resource-limited setting, chest X-ray is mainly used to examine lung metastasis in patients with WT, followed by a chest CT scan for those patients who have lung metastasis findings [7].

Review Methods

A systematic search was done from January 24 to 30, 2023 using PubMed, the Cochrane library, Web of Science, SCOPUS, EBSCOHost, Google Scholar, ClinicalKey (Elsevier), Elicit, and HERDIN with a combined MeSH and free-text search using terms related to Wilms tumor, CT scan, chest X-ray, and lung metastasis. Initial search resulted in only 1 study, which looked at the clinical significance of lung nodules detected by CT scan and not chest X-ray for favorable histology WT. Upon review of the paper, it does not answer the key question, so it was decided to drop the paper. Afterwards, the search strategy was shifted to a broader approach. Bibliography of recent WT guidelines made by the NCCN, SIOP and COG were checked as well. Official websites of relevant scientific societies such as the NCCN, SIOP and COG were accessed for ongoing or previously completed clinical trial protocols. Bibliographies of relevant guidelines and protocols were searched for other pertinent

titles. Preprints in MedRxiv and BioRxiv were also searched for any study related to the research question. We searched for systematic reviews, randomized controlled trials, and observational studies from 2000 to 2023.

Results

Characteristics of Included Studies

Upon literature search, we were not able to find any meta-analysis, systematic review, or RCTs that directly answered the clinical question. Specifically, no studies about the diagnostic sensitivity and specificity, event-free survival, overall survival, cost-effectiveness, adverse events, and effects on quality of life of using chest x-ray, CT scan, or both, for detecting lung metastasis in patients with WT were found.

A retrospective study compared the efficacy of chest X-ray and chest CT scan in evaluating lung metastasis in patients with WT. The study included 83 WT pediatric patients treated in the author's institution from 1980 to 1993. Two were eventually excluded from the study due to absence of any imaging results from their records. Ten patients with WT (4 males and 6 females, average age = 6.8 years) who had pulmonary nodules and available imaging results were included in the study, while a random group of 14 patients with WT without pulmonary nodules were designated as controls (i.e., negative from lung metastasis based on CT and chest X-ray re-review). Separate, blinded interpretation of the chest X-rays and chest CTs were done by three pediatric radiologists. Chest X-ray detected lung metastasis in eight out of ten patients, while all ten patients had positive CT results. Two patients had pulmonary nodules detected by CT scan only, and six patients had more metastases detected from CT when compared with their X-ray results. The remaining 57 patients included in the study were negative from lung metastasis based on both the chest X-ray and CT scan readings. Overall, the chest X-ray and chest CT findings agreed in 79/81 (98%) patients with WT in the study in detecting lung metastases. The authors of the study concluded that chest X-ray alone is accurate in the diagnosis or exclusion of lung metastasis in patients with WT, and CT scan will not provide additional information that may alter the treatment or outcome of the patient [8].

Using the data derived from the same retrospective study, it is possible to compute for the sensitivity and specificity of chest X-ray in detecting lung metastases secondary to WT, when compared to a chest CT scan which is considered by some authors as the gold standard for detecting lung metastases [9,10].

Table 5. Two by two (2 x 2) table of the data from the retrospective study by Wootton-Gorges *et al*.

Chest X-ray	**CT Scan**		
	With lung metastasis	***Without lung metastasis***	***Total***
Positive	8	0	8
Negative	2	71	73
Total	10	71	81

GRADE Summary of Findings

Table 6. Sensitivity and specificity of chest X-ray vs chest CT scan in detecting lung metastasis, based on the data from the retrospective study by Wootton-Gorges *et al*.

Pooled analysis	Basis	Pooled estimate	95% Confidence Interval	Certainty of Evidence
Sensitivity *(Refers to the proportion of persons with disease who correctly have a positive test)*	# of studies: 1 n = 10 of 81	0.80	0.44-0.97	LOW
Specificity *(Refers to the proportion of persons with no disease who correctly have a negative test)*	# of studies: 1 n = 71 of 81	1.00	0.95-1.00	LOW

When compared to chest CT scan, chest X-ray has a sensitivity of 0.80. This means that for all the WT cases with lung metastasis scanned with both CT scan and chest X-ray, 20% of such cases were not detected by chest X-ray, but positive in the CT scan results.

Efficacy Outcomes

No studies were found regarding the event-free survival, overall survival, cost-effectiveness, adverse events, and effects on quality of life in relation to the use of chest X-ray vs CT scan in detecting lung metastasis among patients with WT.

Safety Outcomes

No studies were found detailing the safety outcomes of using chest X-ray and CT scan in detecting lung metastasis among patients with WT.

Recommendations from Other Groups

Group or Agency	Date CPG was released	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
UpToDate	09 June 2022	Routinely perform CT of the chest. Alternative: perform the initial evaluation for pulmonary metastases with chest radiography in two planes CT is performed in cases of suspicious or positive chest radiography	Not available

National Cancer Institute – Wilms Tumor and Other Childhood Kidney Tumors Treatment (PDQ®)	23 December 2022	Recommends the use of CT scan for lung metastasis detection. Chest x-ray is unnecessary if chest CT is performed initially.	Not available
National Cancer Comprehensive Network (NCCN)	11 October 2022	CT of the chest is recommended to assess for lung metastases. If concerned with mediastinal/thoracic hilar involvement, contrast may be helpful.	Not available
SIOP – Collaborative Wilms Tumour Africa Treatment Guidelines	07 April 2022	Chest X-rays, postero-anterior (and if available lateral) are made to detect lung metastases that present as white round lesions often in the periphery of the lungs.	Not available
Indian Council of Medical Research	31 January 2017	CT scan (ideal) or chest X-ray can be used to detect lung metastasis	Not available
SIOP – 2016 UMBRELLA Protocol	October 2016	An unenhanced chest CT scan is a mandatory diagnostic procedure to assess lung metastasis. Chest X-ray with AP (or PA) will be performed at diagnosis as a mandatory baseline procedure.	Not available

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4.2 Delayed vs Upfront Nephrectomy for non-metastatic, operable Wilms tumor

Question 2: Among patients with non-metastatic and operable WT, would delayed nephrectomy (DN) with neoadjuvant chemotherapy result in improved treatment goals (survival and toxicity), when compared to upfront nephrectomy (UN)?

RECOMMENDATION

Among patients with unilateral, non-metastatic, operable WT, we recommend either delayed nephrectomy with neoadjuvant chemotherapy or upfront nephrectomy. ***(Strong recommendation, moderate certainty of evidence)***

Considerations

The consensus panel considered the following when formulating this recommendation:

- The panel suggested the option of doing upfront nephrectomy because the population is patients with operable WT and the lack of evidence on the superiority of delayed nephrectomy vs upfront nephrectomy.
- The panelists were divided in voting for the strength of recommendation due to lack of evidence. Consensus was not reached after three rounds of voting. Eventually, consensus was reached after one round of modified Delphi, making it a strong recommendation. Two panelists voted for weak because based on evidence, delayed nephrectomy has a slight advantage over upfront nephrectomy due to tumor rupture and the stage should also be considered.
- Based on the evidence review, there are 2 philosophies for this matter, which are outright opposite (COG vs SIOP). The decision most likely depends on the school of thought and the confidence of the surgeon to use whether upfront or delayed nephrectomy.

Key Findings

- Three studies report on a multi-national randomized controlled trial (RCT) that investigated survival, relapse, and surgical complications.
- The findings indicate lower risk for intraoperative tumor rupture with delayed nephrectomy (DN) but were inconclusive in regards to survival benefit.
- The study was at high risk for bias due to imprecise risk estimates for critical outcomes, warranting downgrading of level of certainty to moderate.

Background

There are two philosophies in regards to surgery timing in WT. The North American National Wilms Tumor Study Group (NWTSG) (now the Children's Oncology Group – Renal Tumors Committee, COG – RTC) has favored and continue to advocate upfront

surgery followed by adjuvant chemo- and radiotherapy based on histopathologic and surgical staging [1,2], while reserving neoadjuvant chemotherapy for unresectable disease.

Due to historically high intraoperative tumor rupture rates with upfront surgery, the SIOP explored and continues to advocate for neoadjuvant therapy, delayed surgery, and risk- and function-adapted adjuvant therapy [3,4]. In the SIOP 1 and 2 trials, neoadjuvant radiotherapy allowed for downstaging and lower intraoperative tumor rupture rates but with long-term sequelae risks. SIOP 5 showed that neoadjuvant chemotherapy (NACT) is as effective as neoadjuvant radiotherapy with less late toxicity risks.

Contemporary NWTS and SIOP studies (e.g., NWTS4 and SIOP 9) showed similar event-free and overall survival rates [5,6]. However, the potential for downstaging, reduction of intraoperative tumor rupture rates, and treatment reduction through a risk-adapted strategy after neoadjuvant treatment prompted the United Kingdom Children's Cancer Study Group (UKCCSG) to conduct a randomized clinical trial (RCT), the UKW3, comparing the two approaches in patients with resectable, non-metastatic disease [7].

After the publication of the UKW3 findings in 2006, several institutions published their experiences comparing upfront nephrectomy (UN) and delayed nephrectomy (DN). Some report on outcomes with sequential shifts from UN to DN [8–10], or from DN to UN [11]; with selective DN and UN [12]; or with mixed prevailing local practices [13,14]. The findings are conflicting, partly due to the proportion of included unresectable or metastatic disease, and differences in resectability criteria.

This evidence review was conducted to determine the survival and toxicity benefits of DN + NACT, compared to UN in pediatric patients with unilateral, resectable and non-metastatic WT.

Review Methods

A systematic search was done from March 13 to April 9, 2023 using PubMed, EuropePMC, EBSCOHost and HERDIN with a combined MeSH and free-text search using terms related to Wilms tumor, delayed nephrectomy, neoadjuvant chemotherapy, upfront nephrectomy, survival, cost and toxicity. We searched for ongoing or recently completed systematic reviews in the PROSPERO and COCHRANE registries, and for ongoing or recently completed clinical trials in the NIH clinicaltrials.gov and the International Clinical Trials Registry Platform. Official websites of relevant scientific societies such as the National Comprehensive Cancer Network (NCCN), SIOP and Children's Oncology Group (COG) were accessed for guidelines, and ongoing or recently completed clinical trial protocols. Bibliographies of relevant guidelines, guidelines and protocols were searched for other pertinent titles.

Eligibility Criteria

RCTs comparing DN + NACT and UN were included. If no RCTs were available, lower-level comparative study designs such as non-randomized clinical trials, prospective cohorts, and retrospective cohorts, were included, in that order. Outcomes of interest

included survival (event-free survival, overall survival), toxicity (acute and late toxicity), cost, and cost-effectiveness.

Studies that report on pediatric (aged <18 years) WT with unilateral, resectable and non-metastatic disease in the primary (non-recurrent) setting were included. Unresectable disease (presence of gross carcinomatosis, intravascular thrombus above hepatic veins, perinephric spread, or adjacent organ infiltration) was excluded. Borderline resectable disease (massive bulk of primary, adenopathy, or tumor crossing midline) was included. Histology must be nephroblastoma; clear cell sarcoma or rhabdoid tumor was excluded. Bilateral WT was excluded. No restriction with regards to publication year was applied. Eligible studies must have at least three months of median follow-up, to ensure adequate capture of at least the early surgical complications. Only articles reported in the English language were included.

Screening and Risk of Bias Assessment

All primary research identified from the systematic search were imported to a citation manager software. Duplicates were identified and removed. Eligibility assessment was performed independently by two reviewers. In case of two or multiple publications from the same group and on a largely similar cohort, the outcomes data from the most recent publication that best satisfies the above criteria were included. Any disagreement between the reviewers in the study selection and data abstraction processes were resolved first by discussion and, if necessary, by adjudication by a third reviewer. SC members were contacted to resolve any uncertainties.

The risk of bias for non-randomized studies was assessed using the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) assessment tool and the Painless EBM criteria. The risk of bias assessment was made by two reviewers and disagreements were resolved by discussion and, if necessary, by adjudication by a third reviewer.

Data Synthesis

Only one randomized clinical trial was identified. The findings were summarized in the text and tables.

Results

Characteristics of Included Studies

We identified and screened 127 unique studies and included five eligible studies in this review: three studies that report on a multi-national RCT (UKW3) that was conducted in the UK, Norway and Australia from 1991-2001 (UKW3)[7,15,16].

In this RCT (n=205), initial investigation included at least an abdominal ultrasound (US) and a chest x-ray (CXR). Patients had to have non-metastatic, unilateral, and intrarenal tumors that were considered potentially resectable. Tumor extension into the inferior vena cava was an absolute contraindication; very large tumors obscuring hilar access was a relative contraindication. Wholly cystic tumors were excluded and managed with UN.

In contrast to SIOP trials, percutaneous biopsy for the DN arm was required to ensure that no child with a benign tumor gets chemotherapy and that children with other tumor types get the appropriate chemotherapy.

Outcomes investigated included relapse [7,17,18] event-free survival (EFS) [7], overall survival (OS) [7], preoperative tumor rupture [15], and any surgical complication including intraoperative tumor rupture rates [15].

Efficacy Outcomes

The relapse and survival rates are summarized in Table 7.

The RCT (UKW3) showed that DN is associated with equivalent or worse relapse rates (RR 1.37, 95% CI 0.78-2.40), while the relative risks for EFS and OS are inconclusive [7].

Safety Outcomes

The adverse event outcomes are summarized in Table 8.

The median preoperative tumor size was not significantly different in the DN and UN groups (10.0cm and 11.0cm, p=0.522, respectively). In the DN arm, in which pre-treatment percutaneous needle biopsy was mandatory, no relapses occurred in the biopsy needle track. Preoperative tumor rupture was rare in both the DN and UN arms (2% and 1% respectively, p=1.00). DN was associated with lower surgical complication rates (RR 0.03, 95% CI 0.002-0.54), particularly intraoperative tumor rupture (RR 0.05, 95% CI 0.007-0.35) which occurred in none in the DN arm and in 15% in the UN arm. Other surgical complications were rare: adhesion obstruction (3% in DN, 1% in UN), excessive bleeding (2%, 0%) and pneumonia (1%, 0%).

GRADE Summary of Findings

Table 7. Efficacy outcomes with delayed nephrectomy versus upfront nephrectomy

Critical Outcomes	Basis	Relative Risk	95% CI	Interpretation	Certainty of Evidence
Relapse					
Any relapse	One randomized controlled trial (n=205)	1.37, p=0.25	0.78-2.40	Inconclusive	Moderate
Survival					
5y event-free survival	One randomized controlled trial (n=205)	0.80, p=0.52	0.43-1.47	Inconclusive	Moderate
5y overall survival	One randomized controlled trial (n=205)	1.19, p=0.18	0.53-2.63	Inconclusive	Moderate

Table 8. Adverse event outcomes with delayed nephrectomy versus upfront nephrectomy

Critical Outcomes	Basis	Relative Risk	95% CI	Interpretation	Certainty of Evidence
Pre-op tumor rupture	One randomized controlled trial (n=205)	2.02, p=0.56	0.19-21.93	Inconclusive	Moderate
Intra-op tumor rupture	One randomized controlled trial (n=205)	0.05, p=0.003	0.007-0.35	Benefit	High
Any surgical complication	One randomized controlled trial (n=205)	0.03, p=0.02	0.002-0.54	Benefit	High

Certainty of Evidence

The RCT had no serious risk for bias: selection and confounding bias addressed by block randomization; measurement bias, by objective outcomes criteria, including analyses according to local and central pathology review; and analysis bias, by adequate follow-up and low attrition rate (2%), which warranted maintaining the level of certainty at high.

Recommendations from Other Groups

Table 9. Summary of recommendations from other groups on delayed vs upfront nephrectomy for non-metastatic, resectable WT

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/ Quality of Evidence
National Comprehensive Cancer Network [19]	• UN, in the absence of contraindications • Contraindications: unacceptable anesthesia risk due to tumor bulk causing pulmonary compromise; high risk for morbidity, mortality, tumor spill or residual tumor per surgeon judgement; inferior vena cava thrombus above the level of the hepatic veins; retro-hepatic cava involvement (relative)	Uniform consensus based on lower-level evidence (category 2A)
St. Jude Global – International Society of Pediatric Oncology – Global Initiative for Children's Surgery [20]	• NACT + delayed resection in patients with typical clinical features of WT	Weak recommendation; Moderate certainty
	• Biopsy or upfront resection in patients with renal tumor with an atypical clinical feature	Strong recommendation; Very low certainty

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/ Quality of Evidence
International Society of Pediatric Oncology – Collaborative Wilms Tumor Africa Protocol [21]	• NACT + delayed resection	Not indicated.
Indian Council of Medical Research [22]	• NACT + delayed resection	Not indicated.
International Society of Pediatric Oncology – Renal Tumor Study Group [23]	• NACT + delayed resection	Not indicated.

Ongoing Studies and Research Gaps

Selective DN and UN according to surgical judgement on borderline resectability

The UKW3 trial included borderline resectable disease due to bulk or obscured hilar access. The trial reported on a non-randomized cohort (n=292) consisting of enrolled cases that declined the randomized allocation and opted for DN (n=103) and UN (n=189) due to surgical and/or parental decision [15], reflecting outcomes with real-world decision-making.

In this cohort, the median preoperative tumor size was higher in the DN compared to the UN arm (13.0cm and 10.0cm, $p<0.001$, respectively). The relative risks for intraoperative tumor rupture and surgical complications were wide and therefore inconclusive. This could reflect no clear advantage of DN over UN when a selective approach is used.

Patient selection criteria

A mono-institutional retrospective cohort from India reports on their outcomes using a high-risk radiologic criteria on CT to select patients for DN [12]: (1) suspicion of perinephric spread or adjacent organ infiltration (lobulations on tumor surface or indistinct margins with retroperitoneal organs or a bare area of liver or spleen), (2) tumor extension across midline, (3) presence of intravascular thrombus (even if only

in the renal vein), (4) presence of ureteral extension, and (5) extensive retroperitoneal adenopathy. DN was recommended in the presence of any of these features.
The interobserver analysis showed 100% agreement (Cohen's kappa 1) in ruling out all the five features. There was 100% agreement in identifying midline extensions. There was variability in identifying the other four features: agreement was poorest for retroperitoneal adenopathy. Nevertheless, the variability did not result in change of decision-making for or against DN.

Applicability in limited resource settings

Two studies report on a mono-institutional prospective comparative cohort that were conducted in Egypt from 2004-2015 [17,18]. Abdominal US or computed tomography (CT) and CXR or chest CT were used as initial imaging modalities. Unilateral stage II to III disease was included; no resectability criteria were described. Outcomes investigated were any relapse.
DN was associated with 8-fold higher relapse rates (RR 8.00, 95% CI 1.08-59.33)[17]. The prospective study had unclear risk for selection bias due to lacking details on patient selection (inclusion of unresectable disease, criteria for resectability), and serious risk for analysis bias due to short follow-up duration (mean follow-up 20 months), which warranted downgrading the level of certainty from low to very low.

Additional Considerations

Cost

The potential tumor downstaging and reduction in intraoperative tumor spillage with DN and NACT may translate to treatment reduction in terms of radiotherapy and doxorubicin indications, making it a logical strategy in resource-limited settings in the Philippines.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

In patients with renal tumors with features atypical for WT, UN, or percutaneous biopsy may be preferable to avoid giving chemotherapy for a benign disease, or a regimen not suitable for a non-WT histology.

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4.3 Upfront nephrectomy vs neoadjuvant chemotherapy with delayed nephrectomy in metastatic, operable Wilms tumor

Question 3: Among patients with metastatic, operable WT, would upfront nephrectomy (UN) vs neoadjuvant chemotherapy with delayed nephrectomy (DN) improve treatment outcomes?

RECOMMENDATION

Among patients with metastatic, operable, unilateral WT, we suggest either upfront nephrectomy or neoadjuvant chemotherapy to improve treatment outcomes. ***(Weak recommendation, very low certainty of evidence)***

Considerations

The consensus panel considered the following when formulating this recommendation:

- One of the panelists disagreed with using either UN or DN for metastatic, operable Wilms tumor, pointing out that if it is operable, UN is the more appropriate approach.
- The panel voted for weak due to the lack of evidence that one is advantageous over the other and so that the specialists can decide which is more beneficial for their patient considering harm, costs, and other factors.

Key Findings

- There were 4 cohort studies included in this review.
- There was no difference in the 3-year, 10-year, 15-year OS, 10-year and 15-year EFS, and post-operative complications between UN versus DN with neoadjuvant chemotherapy in children with metastatic, resectable Wilms tumor. Over-all certainty of evidence was very low due to serious risks of bias, imprecision, and indirectness.

Background

One of the main controversies in the management of children with unilateral WT is whether to do UN or administer neoadjuvant chemotherapy. The SIOP recommends preoperative chemotherapy in all patients over six months of age to reduce the tumor size and prevent intraoperative spillage due to tumor rupture and increase the proportion of children with a lower tumor stage that require less overall treatment [1-5], while the COG recommends UN to define the accurate stage of the tumor and histology, on which further treatment stratification is decided. Both treatment approaches yield almost equivalent clinical outcomes in several studies though debate remains about the merits of each approach.[6]

Review Methods

A systematic search was conducted by two evidence reviewers from January 25 to February 10, 2023 using PubMed, Cochrane Library and Europe PMC with a combined MeSH and free text search using the terms Wilms tumor, neoadjuvant chemotherapy, and nephrectomy. Ongoing studies were searched in the NIH *clinicaltrials.gov* and ICTRP. Preprints were also searched using medRxiv and bioRxiv. Relevant articles were further cross-referenced. (Appendix 1 and 2)

Eligibility Criteria

RCTs, cohort, cross-sectional analytic studies, and case-control studies were included. If such studies were not available, descriptive cross-sectional and case series studies were included. Case reports, letters, and reports were excluded. Participants were children and adolescents with metastatic Wilms tumor, of any type of histology. There was no restriction on language for the inclusion of studies. The outcomes considered in the review were OS, EFS, acute, late, or long-term toxicities/complications, harm reduction, quality of life (QoL), and cost-effectiveness. Studies involving patients with recurrent Wilms tumor and case series involving less than five patients were excluded.

Risk of bias of efficacy studies was assessed using the revised Painless-EBM and Cochrane risk-of-bias tool for randomized trials (RoB 2) and ROBINS-I for non-randomized studies.

Certainty of evidence was rated using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.

Descriptive statistics was used for characteristics of included studies. Pooling of effect estimates with 95% CI was done using a fixed effects model, or random effect model, if found to be heterogeneous. Heterogeneity was assessed using I^2 statistic with a value of > 50% interpreted as significant. Subgroup analysis was planned in the presence of heterogeneity based on age (<2 or older) and stage (IV vs I to III) of disease, and localized vs metastatic if participants were not homogenous.

Results

Characteristics of Included Studies

We found four (4) cohort studies that included a total of 434 children with non-metastatic (n=318, 72%) and metastatic (n= 116, 28%), operable WT [7-10]. There were eight (8) articles in Chinese that were not retrieved. One study was non-English and translated. Patients' age ranged from one year to 12 years old, with an equal proportion of males and females. Two studies included patients with metastatic WT (n= 40), while two studies had patients with localized (n= 318), metastatic, operable (n=83) or inoperable (n=17) WT. Data for subgroup analysis of metastatic cases were not available in these two studies. One study reported that preoperative radiotherapy was done in some patients. It also had, as comparator, either neoadjuvant chemotherapy or radiotherapy. Follow-ups of patients were up to 15 years. In one

study, 18/40 (45%) in the neoadjuvant group, and 29/40 (72.5%) in the UN group did not complete treatment and were not followed up. Outcomes evaluated were OS and EFS at varying intervals, and post-operative complications. Event was defined as relapse, progression of tumor, or no response to either intervention.

Efficacy Outcomes

Based on one cohort study, UN did not show any significant difference compared to neoadjuvant chemotherapy in 15-year OS (RR 0.67, 95% CI 0.03-14) and 15-year EFS (RR 1.29, 95% CI 0.84, 2.00) (n= 16, very low certainty).

In another cohort study, UN showed no significant difference in 10-year OS (RR 0.96, 95% CI 0.88-1.04) and 10-year event-free rate (RR 0.998, 95% CI 0.90-1.10) compared to neoadjuvant chemotherapy (n=328, very low certainty).

There was no significant difference in three-year OS between the two interventions, as reported in another cohort study (RR 1.7, 95% CI 0.31, 9.27) (n=24, very low certainty).

In another cohort study, OS, with unknown duration, was not significantly different between UN and neoadjuvant chemotherapy (RR 1.075, 95% CI 0.89, 1.29) (n= 33, very low certainty).

Safety Outcomes

Two cohort studies showed no difference in the incidence of post-operative complications among patients who had UN compared to those who had neoadjuvant chemotherapy (RR 3.59, 95% 0.71-18.28 I^2=0) (n=40, very low certainty).

Certainty of Evidence

Of the 4 studies, 3 studies had high risk of bias due to varying tumor stage, concomitant preoperative radiotherapy in some patients, inclusion of patients in cardiac failure at the time of surgery, and lost to follow-up leading to selection, confounding, and measurement biases. [7,9-10] The risk of bias summary is shown in Appendix 3. Over-all certainty of evidence was then downgraded to very low because of these serious risks of bias across the different critical outcomes, and due to imprecision and indirectness.

GRADE Summary of Findings

Table 10. Safety of upfront nephrectomy vs neoadjuvant chemotherapy + delayed nephrectomy

Critical Outcomes	Basis (No and Type of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
15-year OS	1 cohort n= 16	RR 0.67	0.03, 14.00	Inconclusive	Very low
15-year EFR	1 cohort n=16	RR 1.29	0.84, 2.00	Inconclusive	Very low
10-year OS	1 cohort n=328	RR 0.96	0.88, 1.04	Inconclusive	Very Low
10-year EFR	1 cohort n= 328	RR 0.998	0.90, 1.10	Inconclusive	Very low
3-year OS	1 cohort n=24	RR 1.7	0.31, 9.27	Inconclusive	Very low
OS, unknown duration	1 cohort n= 33	RR 1.075	0.89,1.29	Inconclusive	Very low
Adverse events: postoperative complications	2 cohort studies n=40	RR 3.59	0.71, 18.28	Inconclusive	Very low

Recommendations from Other Groups

Table 11. Recommendations from other groups on upfront nephrectomy vs delayed nephrectomy with neoadjuvant chemotherapy in unilateral, metastatic, resectable WT

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Children's Oncology Group (COG) - National Wilms Tumor Study Group (NWTSG) -Children's Cancer Study Group (CCG) -Pediatric Oncology Group (POG)	Recommend upfront nephrectomy before any adjuvant treatments or radiotherapy.	Strong Recommendation

-Intergroup Rhabdomyosarcoma Study Group (IRS) (updated July 2011) American Cancer Society		
The International Society of Paediatric Oncology (SIOP) United Kingdom Children's Cancer Study Group (UKCCSG) Pediatric Oncology in Developing Countries (updated Sept 26, 2012)	Recommend pre-nephrectomy chemotherapy / neoadjuvant chemotherapy to all patients with Wilms tumor over six months of age. Recommend upfront nephrectomy for children under the age of 6 months.	Strong Recommendation
National Comprehensive Cancer Network (NCCN)	Neoadjuvant therapy is recommended for children with metastatic bilateral Wilms or metastatic unilateral Wilms with a predisposing condition (congenital or genetic condition)	Category 2A (based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate)

Ongoing studies and research gaps

No ongoing studies were found.

Additional Considerations

Cost

No studies were found.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found.

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4.4 Lymph node sampling for patients with Wilms tumor undergoing surgery

Question 4: Among patients with WT undergoing surgery, would lymph node sampling result in improved EFS and OS and reduction of harm?

RECOMMENDATION

Among patients with WT undergoing surgery, we recommend lymph node sampling as it results in improved overall survival. ***(Strong recommendation, low certainty of evidence)***

Considerations

The consensus panel considered the following when formulating this recommendation:

- Despite the low certainty of evidence, the panel unanimously agreed to recommend lymph node sampling due to its impact in the management of patients with WT.

Key Findings

- There were two observational studies that documented lymph node sampling and its utility in improving overall survival by predicting mortality among patients with WT undergoing surgery.
- Lymph node sampling showed that it may be effective in improving OS, as it predicts mortality among patients with WT who exhibited lymph node-positive (LN+) disease, and had a high lymph node density (LND). However, no studies were found demonstrating effects on EFS, and adverse outcomes were also not reported in the studies retrieved.
- All studies had risk of bias issues due to the lack of a reference standard in lymph node sampling procedures. This risk of bias, along with a risk of imprecision due to wide confidence intervals in the pooled measures, downgraded the evidence to moderate certainty for OS.

Background

Previous evidence has shown that lymph node sampling for patients with WT lead to better staging [1, 2], adequate adjuvant therapy, and leads to a good survival prognosis [3]. However, lymph node sampling is oftentimes omitted in WT surgery [2, 4], which leads to significant deviation and variation of practices among surgeons. Should lymph node sampling be done, the lack of standardization of lymph node sampling patterns may lead to errors in diagnosis especially in this population [5].

Review Methods

A systematic search was conducted from January 24, 2023 to February 28, 2023 using Medline, Google Scholar, clinicaltrials.gov, and the Cochrane CENTRAL using a combination of MeSH and free text using the terms Wilms tumor, lymph node, and

lymph node sampling. Primarily, clinical trials were aimed to be gathered for evidence appraisal and review, but the lack of available randomized controlled trials in all the search domains warranted the reviewers to look at well-designed prospective and/or retrospective cohort studies for inclusion to this review. Critical outcomes of interest included EFS, OS, and the occurrence of adverse events while important outcomes included harm reduction, quality of life evaluation, and cost effectiveness. No limits were placed on age as WT-related studies primarily included pediatric populations.

Results

Characteristics of Included Studies

Two retrospective cohort studies and two CPGs were retrieved from the literature search. The two retrospective cohorts reviewed data from national databases, including the National Cancer Database (NCDB) [6] and the Surveillance, Epidemiology, and End Result (SEER) database [5], both of which are based in the US. Data on all patients diagnosed with WT from 2004 to 2015 were obtained from the two databases according to their specifications and case definitions for WT. Outcomes measured included five-year OS and cancer-specific survival. Other adverse outcomes were noted, if present.

Efficacy Outcomes

Based on two retrospective cohort studies, LN sampling may be effective in improving five-year OS based on the pooled hazard ratio of the two studies (HR 1.04, 95%CI 0.95-1.14, I^2=0%). Pooled data are also available on LND, and determining this index may also help in improving five-year OS (HR 2.95, 95%CI 0.14-62.57, I^2=0%).

Safety Outcomes

The two studies did not report any serious adverse events, as the studies collected data only on the demographic and clinical characteristics of their sample populations and followed up only on survival as an outcome.

Certainty of Evidence

From the two studies, the main risk of bias was the lack of a reference standard, as both studies commented that there is no threshold or standard reference value that can be used to determine LN+ disease in the susceptible population. Overall certainty of evidence was graded as low due to the studies having an observational design, unclear risk of bias, and imprecision issues in the pooled estimates.

GRADE Summary of Findings

Table 12. Safety outcomes of LN sampling for patients with WT undergoing surgery

Critical Outcomes	Basis (No and Type of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Five-year OS based on presence of LN+ disease	2 observational studies (n=3,829)	HR 1.04	0.95,1.14	Trend toward harm	Low
Five-year OS based on LN density	2 observational studies (n=3,829)	HR 2.95	0.14,62.57	Trend toward harm	Low

Recommendations from Other Groups

Table 13. Recommendations from other groups on LN sampling for patients with WT

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
St. Jude Global, International Society of Paediatric Surgical Oncology, and Global Initiative for Children's Surgery guidelines (accessed February 15, 2023) [8]	Recommends adequate and documented surgical staging (through lymph node sampling) for the management of WT	Strong recommendation, Certainty of evidence: Very low

Ongoing Studies and Research Gaps

The studies included in the summary expounded on the lack of a reference standard for LN sampling and its impact in staging disease among those with WT. Both studies specifically mentioned that the lack of a mandated number of LNs [8] to be sampled leads to a significant variation in the LN yield and therefore LN density. Though it is understood that LN yield depends on other factors aside from the aforementioned reason, factors such as pathologist degree of scrutiny for LN specimen and surgeon experience may not also be entirely accounted for in the databases they utilized for review. They acknowledged that the results presented in their studies have not controlled for such factors. The studies, as well as the guideline included, also did not

report on EFS and adverse outcomes; hence, recommendations for these items could not be formulated.

Additional Considerations

Cost

No studies were found regarding the additional cost of LN staging as part of the diagnostics done for patients with WT, as well as any cost-utility, cost-benefit, or cost-effectiveness analyses aligned with the topic.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

For WT, pathologic and surgical staging is very important for postsurgical therapy. The guidelines appraised with this evidence summary have cited that there is a possibility of surgery being the only source of tumor spillage [7]. In this case, LN sampling and documentation of local invasion must be done, including seeding, tumor spillage, or vascular extension. Failure to do this procedure may result in inadequate tumor staging.

References

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4.5 Chemotherapy dose modification for malnourished patients with Wilms tumor

Question 5: Among malnourished patients with WT, would chemotherapy dose modification improve treatment outcomes?

RECOMMENDATION

Among malnourished patients with WT, we recommend dose adjustment in initiating chemotherapy and reduction of vincristine to 2/3 of usual dose. ***(Strong recommendation, very low certainty of evidence)***

Considerations

The consensus panel considered the following when formulating this recommendation:

- Despite the low certainty of evidence, the panel recommends chemotherapy dose modification as it reduces the risk of myelosuppression.

Key Findings

- There were three studies related to malnourished patients with WT though none had direct comparison between standard versus modified chemotherapy. All studies recognized the impact of malnutrition on adverse outcomes such as death and relapse.
- One cohort study reported malnutrition defined as low weight-for-age z-score at diagnosis had significant association with patient death and relapse. Another cohort study reported that malnourished patients defined as low z-score for corrected weight-for-height significantly contributed to decreased vincristine clearance rate which could lead to increased incidence and severity of drug toxicity. The findings were adapted by one (1) CPG recommending dose adjustment for vincristine as modification for malnourished patients.
- There is paucity in literature regarding chemotherapy among malnourished patients with WT. There is no literature directly comparing standard versus modified chemotherapy on event-free survival, overall survival, harm reduction, cost-effectiveness, and quality of life. However, malnutrition is an independent risk factor for death and relapse.

Background

Nutritional status defined either as undernutrition or overnutrition among pediatric oncology patients. [1,2] There are limited studies regarding nutritional status and clinical outcomes. A systematic review by Joffe, *et al*., reviewed related literature with one study on WT concluding no significant difference in clinical outcome between nutritional status and survival but could not be generalized. Studies on patients with solid tumors where nutritional status was objectively measured are lacking. [3] Despite this limitation, nutritional status remains a poor prognostic factor. [2] This key question

aims to review if chemotherapy dose modification among malnourished patients with WT will improve clinical outcomes.

Review Methods

A systematic search was done for studies published from 2012 until January 31, 2023 using PubMed, Medline, Cochrane Library, Google Scholar, Scopus, EuropePMC, HERDIN, Acta Medica Philippina, and PCHRD with a combined MeSH and free text search using the terms (("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh]. RCTs that compared standard from modified chemotherapy among malnourished patients with WT were ideally included in this review. CPGs, systematic reviews, meta-analysis, and cohort studies were also included if RCTs were not available. Outcomes of interest included the following: weight gain, EFS, OS, harm reduction, adverse events, cost-effectiveness, and quality of life. In appraising risk of bias, AGREE was used for the CPG, while Painless EBM was used for cohort studies.

In the study by Israels *et al*., linear regression was used to assess the correlation between log AUC of vincristine clearance and nutritional status. In the study by Rahiman *et al*., logistic cox regression was used to establish association of malnutrition to adverse outcomes (death and relapse). The clinical guideline gave a summary table of recommendations but did not give GRADE recommendation or level of evidence.

Results

Characteristics of Included Studies

In the study by Israels, *et al*., patients less than 18 years old with localized WT were included after consenting to participate. Vincristine concentration was analyzed either via high-performance liquid chromatography coupled to tandem mass spectrometry (LC–MS/MS) method or used a validated liquid chromatography–mass spectrometry (LC–MS) assay. Cross-validation of the assays was carried out.

For the quantification of the protein-unbound vincristine fraction, ultrafiltrate was prepared from plasma. Vincristine pharmacokinetic parameters were calculated for all patients by non-compartmental analysis using the Stata (Release 10) software package. The area under the plasma concentration-time curve (AUC) was calculated from 0 to 24-hours using the trapezoidal rule.

In the study by Rahiman, the population included 210 patients with WT either via fine needle aspiration cytology or clinical-radiologic findings confirmed by histopathology post nephrectomy. On diagnosis, 68 of 190 (36%) of patients were underweight and 29 (15%) were severely underweight.

Efficacy Outcomes

In the study by Israels, *et al*., nutritional status reported as z-score for corrected weight-for-height significantly affected the difference in vincristine clearance measured as log AUC via linear regression analysis. A decrease in z-score by -1 is associated with an

increase of log AUC by 0.061 (p=0.043). Higher AUC values were seen in malnourished patients.

On the other hand, the study by Rahiman, *et al*., used the weight-for-age z-score to measure nutritional status. Undernutrition was defined using WHO growth standards as moderate (z-score -2 to -3) and severe (z-score <-3). Z-score was measured 4 times: diagnosis, first postoperative visit, end of treatment, and last follow up. Weight-for-age z-score at diagnosis was significantly associated with adverse outcome (death and relapse) (p=0.011). On multivariate analysis via logistic cox regression on patient age, histology risk classification, stage, tumor volume at diagnosis, and weight-for-age z-score at diagnosis, factors with high significance were tumor volume at diagnosis and weight-for-age z-score at diagnosis (p = 0.002; OR: 1.68; 95% CI: 1.21–2.33). Weight-for-age z-score at diagnosis is a significant risk factor for relapse alone (p=0.003; OR: 0.69;95%CI: 0.54–0.88).

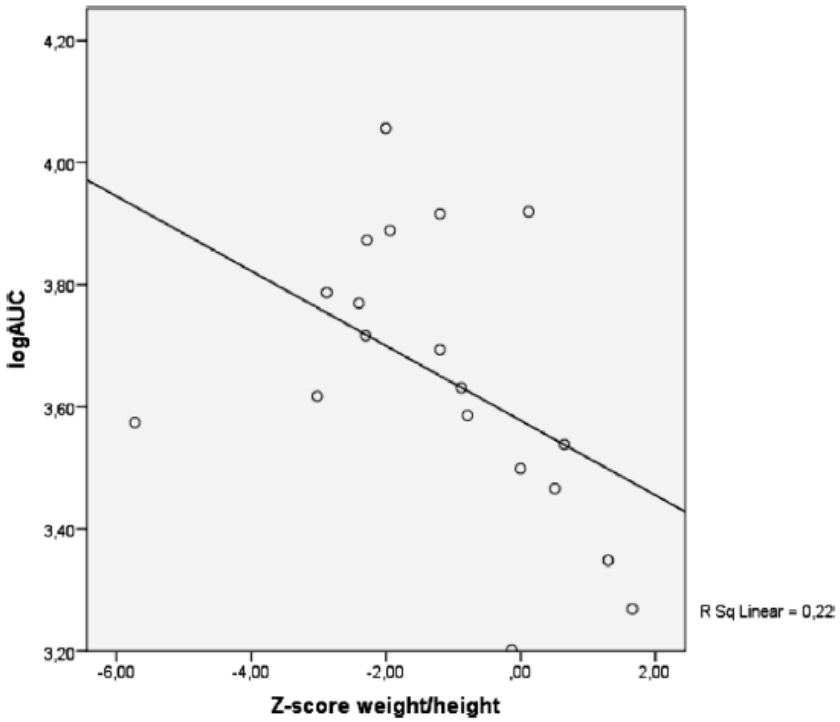

Figure 1. Relationship between patient nutritional status as determined by z-score for corrected weight-for-height and log AUC of vincristine in patients with WT

Safety Outcomes

No studies were found.

Certainty of Evidence

The certainty of evidence was maintained at low as both studies were cohorts.

GRADE Summary of Findings

Table 14. Association of undernutrition with adverse outcomes

Critical Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Adverse Outcome (Death and Relapse)	1 Cohort study (n= 210)	OR: 1.68	1.21-2.33	Significant association	Very low
Primary Outcome (Decreased vincristine clearance)	1 Cohort (n= 19)	-	-	Malnutrition = decreased vincristine clearance (p=0.043)	Very low

Recommendations from Other Groups

Table 15. Recommendations from other groups for chemotherapy dose modification for malnourished patients with WT

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
SIOP PODC: Clinical Guidelines for the Management of Children with WT in a low-income setting (Published online 9/26/2012)	Specific recommendations for WT diagnosis and treatment: Start with lower dosage of drugs (2/3) in severely malnourished children	none

Ongoing Studies and Research Gaps

No ongoing studies were found.

Additional Considerations

Cost

No studies were found.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found.

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4.6 Optimal timing of RT for Stage III Wilms tumor

Question 6: Among patients diagnosed with Stage III WT, what is the optimal timing for radiotherapy (RT)?

RECOMMENDATION

Among patients with Stage III WT, we recommend starting radiotherapy between days 9-14 after operation. ***(Strong recommendation, very low certainty of evidence)***

Considerations

The consensus panel considered the following when formulating this recommendation:

- Despite the low certainty of evidence, the panel recommends starting radiotherapy between days 9-14 after operation because it correlates with improved overall survival and the risk of relapse increases if RT is given after 14 days.

Key Findings

- There were 9 articles included in the literature review. No RCTs were found during this review; however, there were 2 subject review papers and 4 guidelines (2 consensus documents and 2 guidelines) that state recommendations on RT timing for WT. The three (3) cohort studies supported the recommendations stated in the review and guideline papers.
- The recommended RT timing in all reviews and guidelines is between 9 to 14 days post-operation, regardless of stage. An RT timing of δ10 days was found to increase the 5-year incidence of intestinal obstruction in a small number of patients. In a big cohort study, however, RT timing of < 14 days was shown to increase 5-year OS for tumors without metastasis. All 3 cohort studies included Stage III participants but did not perform per stage analysis of the stated outcomes. The 2 biggest cohorts are the study on flank/abdominal recurrence, which included patients from the NWTS-3 and NWTS-4 studies, and the study on OS, which followed up patients from a cancer database in the USA

Background

Additional treatment options like RT and improvement in the treatment protocols in the past century has greatly improved the OS for WT from 30% in the 1930s to up to 85% and above [1,3]. However, this improvement seems to be isolated to upper-middle- and high-income countries [1,4]. In low-middle income countries (LMICs) such as the Philippines, 5-year OS reports still range from 24% to 85%. Barriers to improvement of survival within the LMICs have been attributed to late presentations, malnutrition, drug toxicity, lack of resources such as radiotherapy facilities, low health literacy in families and inadequate information on early cancer management among primary

health providers. Given the following challenges faced by LMICs the need for a guideline with resource-sensitive recommendations is paramount.

Review Methods

A systematic search was done from February 13, 2023, until February 28, 2023 using PubMed, Web of Science, EuropePMC, EBSCOHost, PROSPERO, and Cochrane Library. The search terms strategy used was kept broad to maximize yield and search strategy was drafted in PubMed search builder as follows: (1) Wilms tumor [MeSH Major Topic], (2) Wilms tumor stage III [All Fields], (3) radiotherapy [MeSH Terms], (4) surviv* [Title/Abstract], (5) cost [Title/Abstract], (6) toxicit* [Title/Abstract], (7) quality of life [Title/Abstract], (8) 1 OR 2, (9) 8 AND 3, (10) 4 OR 5 OR 6 OR 7, (11) 9 AND 10.

This strategy was repeated and adapted according to the indexing system of the other databases. Search filters used for all databases limited the results to studies on human subjects, publications from year 2000 onwards, and available in English.

Due to the paucity of literature on the topic, the search included all types of studies that used RT as part of their treatment for WT. Analysis should include timing of RT relative to surgery. Preferably, the studies should focus on patients with Stage III WT, but inclusion of patients other than Stage III was also considered. All studies must include patients that were treated from 1990 onwards or those treated earlier given that the different doses and methods of administered radiotherapy are detailed. Studies that report on re-irradiation were excluded. All studies must have at least 3-months of follow up to ensure adequate capture of at least acute adverse events. Outcomes should include the following endpoints: (1) EFS, (2) OS, (3) harm reduction (a) toxicity (b) adverse events (acute and long-term complications), (4) quality of life, and (5) cost/cost-effectiveness. Studies with only dosimetric or physics outcomes are excluded.

All 3 cohort studies have risk of bias issues which included lack of consideration for confounding bias, selection bias, nondifferential misclassification bias of intervention and outcome. Additionally considering that the cohort study results report aggregate stage outcomes, it also suffers from precision issues. This risk of bias and imprecision issue ranks the evidence as very low certainty of evidence for the outcome on 5-year incidence of intestinal obstruction, 8-year incidence of flank/abdominal recurrence and 5-year OS following receipt of RT 9 to 14 days post-operation.

Results

Characteristics of Included Studies

There were no RCTs that investigated the optimal timing of radiotherapy in Stage III WT. Instead, we found three (3) cohort studies done in the USA that included 2,756 patients with WT. One (1) included 1,488 patients from the National Cancer Database (NCDB), a hospital-based registry that captures about 70% of incident cases in the USA and draws data from > 1,500 accredited cancer programs [5]. Included participants were aged 25 or less with a first oncologic histologic diagnosis of

nephroblastoma, diagnosed between 2004-2014. Participants' surgery-to-RT interval must be within two standard deviations from the mean (60 days) to be included to avoid immortal time bias. The second cohort used 1,226 patients with Stage II, III or IV favorable histology tumors treated on the NWTS-3 and NWTS-4 [6]. And the third cohort used records of children who received RT for WT at the Children's Hospital of Iowa from 1968 to 1994 [7]. The RT timing for all 3 studies followed the NWTS group recommendation of ≤ 9 days; whereas, one (1) study used the COG recommendation of ≤ 14 days [5].

Efficacy Outcomes

Outcomes relating to RT timing were measured during the follow-up period ranging from 60 to 306 months. These included incidence of intestinal obstruction [7], flank/ abdominal recurrence [6], and OS [5]. Survival outcome from the reviewed study can only be interpreted as an aggregate for all non-metastatic tumors and not for Stage III Wilms tumor alone. The 5-year OS using the COG recommendation was worse for > 14 days post-operation compared to ≤ 14 days, both for the entire cohort (85.9% vs 92.7% at 8 years, p=0.033) and for the non-metastatic patients (86.9% vs 95.9%, p=0.005) in the unadjusted analysis of incidence. This remained statistically significant even after adjusting for covariates (HR for mortality if RT started after 14 days: 2.13, CI 1.17-3.87, p=0.013). However, when using the 9-day cutoff in NWTS studies, OS was not different in either the non-metastatic or metastatic group.

Safety Outcomes

Two (2) cohorts investigated adverse effects and tumor recurrence among all patients with WT. Again, in all these studies, there is no subgroup analysis involving only patients with Stage III WT. In a study using a small cohort, small bowel obstruction was more likely to develop in patients who received RT ≤ 10 days compared to those who received it > 10 days post-operation (5/23 vs 1/19). In the bigger cohort study, this same cut-off did not demonstrate any benefit in decreasing the risk for flank/ abdominal recurrence using the whole cohort.

Certainty of Evidence

All three studies had serious and critical risk of bias in different ways. The study by Paulino *et al*., had a critical risk of reporting bias as not all analyzed outcomes and all analysis results were reported in their paper. The small sample size and the limitation of study patients to only one institution adds to a serious risk of selection bias and confounding for this study. The study by Kalapurakal *et al.*, had serious risk for misclassification of outcome. Lastly, the study by Stokes *et al.,* had serious risk for misclassification bias of disease stage and misclassification of outcome. The risk of bias summary is shown in Appendix 3. Overall certainty of evidence is deemed to be very low because of the serious risks of bias across the three (3) studies.

GRADE Summary of Findings

Table 16. Different timing of RT administration

Critical Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Overall survival	1 Cohort study (n=1488)	Adjusted analysis reporting 5-year HR for mortality in nonmetastatic tumors: RT started after 14 days: **2.13*** RT started after 10 days: **1.63**	 (1.17, 3.87) (0.72, 3.70)	Benefit if RT is started within 14 days are followed.	Very low
Flank recurrence	1 Cohort study (n=1226)	8-year RR if RT started after 10 days NWTS 3 cohort only: 2.30 NWTS 4 cohort only: 0.50 combined NWTS 3 & 4: 0.57	(0.21, 25.33) (0.14, 1.76) (0.20, 1.59)	Inconclusive	Very low
Abdominal recurrence	1 Cohort study (n=1226)	8-year RR if RT started after 10 days NWTS 3 cohort only: 1.85 NWTS 4 cohort only: 0.75 combined NWTS 3 & 4: 1.09	(0.85, 4.01) (0.35, 1.59) (0.66, 1.80)	Inconclusive	Very low
Small bowel obstruction	1 Cohort study (n = 42)	RR if RT started after 10 days: 0.24	(0.03, 1.90)	Decreased risk for small bowel obstruction if RT started after 10 days from surgery.	Very low

Recommendations from Other Groups

Table 17. Recommendations from other groups on RT timing for patients with WT

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
Evidence based surgical guidelines for treating children with WT in low-resource settings [4]	The panel suggests postoperative abdominal radiation therapy within 14 days of surgery for patients with WT who require adjuvant radiation therapy.	Weak recommendation; Certainty of evidence: Very low
NCCN v2.2021 (Updated August 2021)	Recommends that RT should be started by day 10 after surgery but no later than day 14 if surgery is designated day 0.	Category 2A: Low-level evidence but panel consensus

		that intervention is appropriate.
ICMR Consensus document (2017)	Radiotherapy is to be started within 9–14 d of surgery unless medically contraindicated.	None provided
Harmonica consensus [8]	RT timing for WT is generally commended to start 10–14 days after surgery.	None provided.

Ongoing Studies and Research Gaps

No ongoing studies were found that evaluated the effect of RT timing on survival and adverse events involving Stage III WT patients alone.

Additional Considerations

Cost

No studies were found that assessed the cost-effectiveness of varying RT timing.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

Although there were no studies that give the above-mentioned outcomes, McAleer *et al*., [8] noted that in LMICs, timing recommendations may not be achievable due to limited resources, late referrals, long RT waiting lists, and or long travelling distances to access RT centers.

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4.7 Optimal RT technique and timing for patients with Wilms tumor

Question 7: Among patients with WT, would RT technique (conventional vs advanced) and timing (early versus delayed) result in improved treatment goals (survival and toxicity)?

RECOMMENDATIONS

1. **Among patients with WT for whom RT is indicated, we recommend the use of 3D conformal RT.** ***(Strong recommendation, low certainty of evidence)***

2. **Among patients with WT without metastasis and for whom flank RT or whole abdominal irradiation (WAI) is indicated, we recommend to keep the surgery-RT interval to 9 to 14 days, unless medically contraindicated.** ***(Strong recommendation, moderate certainty of evidence)***

Considerations

The consensus panel considered the following when formulating the first recommendation:

- Despite the low certainty of evidence, the panel recommends the use of 3DCRT due to its availability and low cost.

Key Findings

Radiotherapy Technique

- There were three studies that investigated survival and/or toxicity with the use of advanced RT techniques for whole lung irradiation (WLI). A one-arm phase 1/2 clinical trial included three WT cases who were alive, without lung-metastasis progression and without toxicity at 2-year follow-up after cardiac-sparing intensity-modulated radiotherapy (IMRT) for WLI (Demoor-Goldschidmt, 2018) . A two-arm retrospective study showed no acute severe lung or liver toxicity or late liver toxicity in both the respiratory-gated and conventional (free-breathing) WLI (Kalapurakal *et al*., 2018) A one-arm retrospective study showed low lifetime incidence (10%) of primary hypothyroidism with three-dimensional conformal RT (3DCRT) (Morgan, 2017).
- One small retrospective study investigated toxicity with advanced RT for whole abdominal irradiation (WAI). This is a two-arm retrospective study that reported one late non-severe (14%) renal toxicity in the volumetric modulated arc therapy (VMAT) group, compared to none in the group for which RT was not given (Chen, 2020).
- Another retrospective study investigated survival with advanced RT for flank RT. This one-arm retrospective study showed high 2-year disease-free survival (91%) and OS (94%) with VMAT for flank RT (Mul *et al*., 2021)

- Data could not be pooled due to heterogeneity in interventions and outcomes. Three studies had no or one serious risk for bias due to selection bias (population), analysis bias (attrition), or imprecise estimate (small sample size), which warranted maintaining evidence certainty as low. The other two had multiple serious risks due to selection bias, confounding bias and imprecise estimate (small sample size), warranting downgrading evidence certainty from low *to* very low.

Radiotherapy Timing

- There were two large retrospective studies that compared disease recurrence or mortality rates with early versus delayed WAI or flank RT after nephrectomy for WT (Kalapurakal *et al*., 2003; Stokes *et al*., 2018).
- One pooled data from two (2) NWTSG trials found that delayed RT (ε9 days post-operatively) was not associated with higher flank or abdominal recurrence at 8 years when compared to early RT (<9 days). The other, a NCDB analysis, found a 2x higher mortality risk with delayed RT (at >14 days post-operatively) when compared to early RT (at <14 days), among patients with non-metastatic WT (Stokes *et al*., 2018). The increased risk was not seen when the delay cut-off was 9 days, among patients with metastatic WT.
- Data could not be pooled because the studied outcomes were different.
- While both are retrospective studies, the large sample size allows for reliable estimates. Important confounders have been accounted for through restriction, stratification, and multivariate analysis (MVA). Finally, the MVA findings when RT timing is taken as a dichotomous variable are supported by the findings when it is taken as a continuous variable. These warranted upgrading evidence certainty from low to moderate.

Background

Radiotherapy Technique

Even with the relatively low RT doses used in the management of WT, long-term follow-up of survivors treated with two-dimensional (2D) CRT reveal prevalent musculoskeletal growth deficits [1], clinically significant endocrine [2], reproductive [3,3–5], hepatic [6], renal [7–12], cardiovascular [13,14], pulmonary [1], and hematologic [15] toxicities, and higher risk for secondary malignancies [16–18].

Dosimetric studies on more modern RT techniques show better organ sparing [24,25], better dose homogeneity [26], smaller target margins [27,28] and safer target dose-escalation [29]. Current American and European guidelines recommend the use of 3DCRT, intensity modulated RT (IMRT), or image-guided RT (IGRT) in the delivery of flank, WAI, or WLI, especially when boost doses are needed [20,22,23].

Locally, 3DCRT and IMRT are currently available in most RT facilities but entail additional costs, and possibly longer RT sessions due to more complex delivery and thus, longer sedation if required for a pediatric patient. 3DCRT is affordable for the average Filipino, but IMRT remains costly. More advanced techniques such as

volumetric modulated arc therapy (VMAT) and IGRT (including gated RT) are less available and even more costly.

Radiotherapy Timing

The delay of adjuvant RT from surgery has been associated with higher mortality rates [30]. This has been shown true for non-metastatic, but not for metastatic disease. In the adjuvant setting, the optimal surgery-to-RT interval (SRI) has been recommended to be ≤9 and ≤14 days according to the NWTS5 and COG trials. Current guidelines recommend the SRI to be 9-14, unless medically contraindicated [23,31,32].

Risk-adapted WLI is an emerging approach [20,33]. It entails omission in favorable histology (FH) WT with complete response (CR) to chemotherapy, or resected post-chemotherapy, therefore delaying possible WLI until after evaluation post-chemotherapy.

Locally, there are high rates of prolonged delays to RT, partly due to prolonged recovery from surgery or its complications, to limited radiotherapy services, or to logistics or financial constraints.

Review Methods

A systematic search was done from January 24 to 30, 2023 using PubMed, EuropePMC, EBSCOHost and HERDIN with a combined MeSH and free-text search using terms related to Wilms tumor, radiotherapy, survival, cost and toxicity (*See Appendix 1*). The search strategy was kept broad to maximize yield given paucity of literature based on a preliminary or scoping search. We searched for ongoing or recently completed systematic reviews in the PROSPERO and COCHRANE registries, and for ongoing or recently completed clinical trials in the NIH clinicaltrials.gov and the International Clinical Trials Registry Platform. Official websites of relevant scientific societies such as the NCCN, SIOP and Oncology COG were accessed for ongoing or previously completed clinical trial protocols. Bibliographies of relevant guidelines, guidelines and protocols were searched for other pertinent titles.

Eligibility Criteria

Due to lack of randomized clinical trials pertinent to the question, non-randomized clinical trials, prospective/retrospective cohorts, cross-sectional, and case-control studies were included in this review. Relevant comparisons were included: advanced RT technique versus no RT, conventional RT, or another advanced RT technique, or early versus delayed adjuvant RT. Non-comparative studies that report on outcomes with advanced RT techniques were included. Outcomes of interest included EFS/OS, toxicity (acute and late toxicity), cost, and cost-effectiveness. Subgrouping by stage (non-metastatic vs metastatic) was planned.

Studies that report on RT in the primary setting with curative intent, whether in non-metastatic or metastatic disease, were included; studies that report on reirradiation were excluded. Studies were limited to megavoltage photon RT; studies on orthovoltage RT, particle RT, or brachytherapy were excluded. Studies with only dosimetric or technical outcomes were excluded. Studies that were published from 2000 onwards and that report on patients treated from 1990 onwards were included. Restricting the publication year to 2000 onwards and for treatment period from 1990

onwards limited the inclusion of studies reporting on outcomes of outdated radiotherapy techniques, while allowing us to capture late toxicity outcomes such as secondary malignancies, from patients treated from 1990 onwards. Eligible studies must have at least three months of median follow-up, to ensure adequate capture of at least the acute adverse events. Only articles reported in the English language were included.

Screening and Risk of Bias Assessment

All primary research identified from the systematic search were imported to a citation manager software. Duplicates were identified and removed. Eligibility assessment was performed independently by two reviewers. In case of two or multiple reports from the same group and on a largely similar cohort, the most recent report that best satisfies the above criteria were included. Any disagreement between the reviewers in the study selection and data abstraction processes were resolved first by discussion and, if necessary, by adjudication by a third reviewer. Study authors were contacted to resolve any uncertainties.

The risk of bias for non-randomized studies was assessed using the ROBINS-I assessment tool [34] and the Painless EBM criteria [35]. The risk of bias assessment was made by two reviewers and disagreements were resolved by discussion and, if necessary, by adjudication by a third reviewer.

Data Synthesis

For the studies on RT techniques, data could not be pooled due to heterogeneity of population and intervention. For the studies on RT timing, data could not be pooled because the two studies investigated different outcomes.

Therefore, systematic narrative synthesis was performed with information summarized in the text and tables to highlight the characteristics and findings of the studies.

Results

Characteristics of Included studies

We identified and screened 314 unique studies and included seven eligible studies in this review: one phase 1/2 one-arm trial, four retrospective two-arm studies, and two retrospective one-arm studies; one published in 2003, and the rest, from 2017 to 2021. All were conducted in first-world countries (US, France, Netherlands), except one, which was conducted in a newly industrialized country (Brazil) like the Philippines.

- Radiotherapy Techniques

  The phase 1/2 trial and two retrospective studies investigated advanced RT techniques for WLI: 3DCRT [36], IGRT (compared against 2D conventional technique) [37], and cardiac-sparing IMRT [24]; one retrospective study, on kidney-sparing VMAT for WAI (compared to non-irradiated patients with WT) [38], and one retrospective study, on highly conformal flank RT [25].

  Outcomes investigated included disease control: lung-metastasis progression free survival [24], locoregional control [25]; survival: disease-free survival [25] and OS [25]; and toxicity: primary hypothyroidism [36], lung [24,37], cardiac [24], liver [37], intestinal [38], and renal [38] toxicities.

The studies are heterogenous in terms of the specific interventions and outcomes studied. Therefore, data pooling could not be done.

- Radiotherapy Timing
  Two retrospective studies compared early versus delayed adjuvant flank RT or WAI [30,39]. Two cutoffs were investigated: 9 [30,39] and 14 [30] days after surgery. The two studies investigated different outcomes: flank and abdominal recurrence [39] and mortality [30]. Therefore, data pooling could not be done.

Efficacy Outcomes

The disease control and survival outcomes for the individual studies are summarized in Table 18 (WLI), Table 21 (flank RT) and Table 22 (early versus delayed RT).

All three newly diagnosed patients with WT treated with cardiac-sparing IMRT for WLI were alive and without lung-metastasis progression at 2 years follow-up. High locoregional control, disease-free and OS rates were achieved with highly conformal VMAT for flank RT; outcomes are comparable to those reported in the COG and SIOP protocols [40–43].

On multivariate analysis, an SRI >9 days was not associated with higher recurrence risk, for the NWTS-3, the NWTS-4, and the entire cohort [1]. However, an SRI of >14 days was associated with a 2x higher risk for mortality in patients with non-metastatic disease, but not in those with metastatic disease [2]. Multivariate analysis using SRI as a continuous variable resulted in a mortality HR of 1.04 (95%CI 1.01-1.07, p 0.006) in non-metastatic disease, and 1.00 (95%CI 0.97-1.02, p=0.842) in metastatic disease.

Safety Outcomes

The toxicity outcomes for the individual studies are summarized in Table 19 (WLI) and Table 20 (WAI). The toxicity rates are generally low; however, the studies are small and the data are inconclusive.

Certainty of Evidence

- Radiotherapy Technique
  Three studies had no or one serious risk for bias due to selection bias (population), analysis bias (attrition) [36], or imprecise estimate (small sample size) [38], which warranted *maintaining* evidence certainty as *low*.

  Two studies [3,4], both on WLI, had multiple serious risks due to selection bias and imprecise estimate (small sample size), warranting *downgrading* evidence certainty from *low to very low*. Both included patients with lung metastases from different pediatric solid tumors, although outcomes for the WT cases could be derived in Kalapurakal *et al*. (2019). In Demoor-Goldschmidt *et al*., the intervention group was older than the control group, which could lead to worse prognosis but better technique feasibility.

- Radiotherapy Timing

While both are retrospective studies, the large sample size allows for reliable estimates. Kalapurakal *et al*., (2003) [39] pooled data that were derived from prospective clinical trials. In both studies, important confounders have been accounted for through restriction, stratification and multivariate analysis. Finally, the findings on multivariate analysis are congruent when RT timing is taken as a dichotomous variable or continuous variable (consistency). These warranted upgrading evidence certainty from low to moderate.

GRADE Summary of Findings

Table 18. Efficacy outcomes with intensity modulated radiotherapy (IMRT) for whole lung irradiation (WLI)

Critical Outcomes	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Event-free survival					
2y lung-metastasis progression-free survival	One 1-arm Ph 1/2 (n=3)[a]	100%	29-100%	Inconclusive	Very low
Overall survival					
2y overall survival	One 1-arm Ph 1/2 (n=3)[a]	100%	29-100%	Inconclusive	Very low
[a] *Mixed population. Three are primary WT.*					

Table 19. Toxicity outcomes with advanced RT techniques for whole lung irradiation (WLI)

Critical Outcomes	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Acute toxicity					
G≥3 pneumonitis (Gating)	One 2-arm retrospective cohort (n=17)[b]	RR 1.40 p=0.76	0.16-12.60	Inconclusive	Very low
G≥3 hepatotoxicity (Gating)	One 2-arm retrospective cohort (n=17)[b]	RR 0.73[c] p=0.87	0.16-32.93	Inconclusive	Very low
Any pneumonitis (IMRT)	One 1-arm Ph 1/2 (n=5)[a]	0%	0-52%	Inconclusive	Very low
Late toxicity					
Primary hypothyroidism (3D)	One 1-arm retrospective cohort (n=20)	10%	1-32%	Inconclusive	Low
Any hepatotoxicity (Gating)	One 2-arm retrospective cohort (n=11)[b]	RR 0.86[c] p=0.94	0.02-37.00	Inconclusive	Very low

Any cardiopulmonary (IMRT)	One 1-arm Ph 1/2 (n=5)[a]	0%	0-52%	Inconclusive	Very low

[a] Mixed population. Three are primary, and 2, relapsed WT. Toxicity developed in 1 with RMS, post doxorubicin +RT
[b] Mixed population. Separate data for the WT cases (2 gated RT; 3 conventional RT) not derivable.
[c] No event was reported.

Table 20. Toxicity outcomes with volumetric modulated arc therapy (VMAT) for whole abdominal irradiation (WAI)

Critical Outcomes	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Acute toxicity					
Any enteritis	One 2-arm retrospective cohort (n=14)[a]	RR 1.00[b] p=1.00	0.02-44.50	Inconclusive	Low
G≥3 renal toxicity	One 2-arm retrospective cohort (n=14)[a]	RR 1.00[c] p=1.00	0.02-44.50	Inconclusive	Low
Late toxicity					
Any renal toxicity	One 2-arm retrospective cohort (n=14)[a]	RR 3.00[d] p=0.71	0.14-63.15	Inconclusive	Low

[a] Comparator is patients for which no RT was indicated and given.
[b] No event reported.
[c] One event reported, in the VMAT group, but due to vascular injury during surgery.
[d] One event reported, in the VMAT group.

Table 21. Efficacy outcomes with volumetric modulated arc therapy (VMAT) for flank radiotherapy

Critical Outcomes	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Event-free survival					
2y locoregional control rate	One 1-arm retrospective cohort (n=36)	94%	86-100%	Inconclusive	Low
2y disease-free survival	One 1-arm retrospective cohort (n=36)	91%	81-100%	Inconclusive	Low
Overall survival					
2y overall survival	One 1-arm retrospective cohort (n=36)	94%	86-100%	Inconclusive	Low

Table 22. Efficacy outcomes with delayed versus early adjuvant flank or abdominal RT

Critical Outcomes	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Event-free survival					
8y flank recurrence (SRI > vs ≤9d)	One 2-arm retrospective cohort (n=1226)	RR 0.57 (p=0.28)	0.20-1.59	No difference	Moderate
8y abdominal recurrence (SRI > v ≤9d)	One 2-arm retrospective cohort (n=1226)	RR 1.09 (p=0.74)	0.66-1.80	No difference	Moderate
Overall survival in non-metastatic disease					
Adjusted mortality (SRI > v ≤14d)	One 2-arm retrospective cohort (n=1011)	HR 2.13 (p=0.013)	1.17-3.87	Harm	Moderate
Adjusted mortality (SRI > v ≤9d)	One 2-arm retrospective cohort (n=1011)	HR 1.63 (p=0.242)	0.72-3.70	No difference	Moderate
Overall survival in metastatic disease					
Adjusted mortality (SRI > v ≤14d)	One 2-arm retrospective cohort (n=477)	HR 0.77 (p=0.411)	0.40-1.45	No difference	Moderate
Adjusted mortality (SRI > v ≤9d)	One 2-arm retrospective cohort (n=477)	HR 1.08 (p=0.835)	0.51-2.32	No difference	Moderate

Recommendations from Other Groups

Table 23. Summary of recommendations from published guidelines on RT technique and timing for patients with WT

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/ Quality of Evidence
[a] National Comprehensive Cancer Network, 2022	**Radiotherapy Techniques**	
	• For flank RT, use 2D (opposed anteroposterior and posteroanterior fields, AP/PA)[a,b].	Not available

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/ Quality of Evidence
[b] French Society for Radiation Oncology, 2022 [c] St. Jude Global – International Society of Pediatric Oncology – Global Children's Surgery Initiative, 2022 [d] International Society of Pediatric Oncology – Collaborative Wilms Tumor Africa Protocol, 2020 [e] Indian Council of Medical Research, 2017 [f] International Society of Pediatric Oncology – Renal Tumor Study Group	• Consider IMRT, in case of large pelvic or midline WT[b]	Not available
	• For WAI, use four-dimensional computed tomography (4DCT) to guide RT fields [a].	Not available
	• Consider kidney-sparing IMRT [b].	Not available
	• For WLI, use 2D (AP/PA) or IMRT [a].	Not available
	• For WLI + flank RT/WAI, use one large field to avoid match lines and increased organ (e.g., heart) doses [a,e].	Not available
	• Consider cardiac-sparing IMRT [b].	Not available
	• For boost doses, use more conformal modalities such as 3DCRT [a], IMRT [a],(including simultaneous integrated boost, SIB [f]), protons [a]., or stereotactic body radiotherapy (SBRT)[f].	Not available
	• Consider 4DCT to guide fields [a].	Not available
	Radiotherapy Timing	
	• RT should be started within 9-14 days from surgery, unless medical contraindicated [e].	Not available
	• RT should start preferably by day 10 after surgery (day 0) [a,d].	Not available
	• RT should start no later than day 14 [a,c].	Weak recommendation [c]. Certainty of evidence: very low [c].

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/ Quality of Evidence
	• Flank RT or WAI should start within 2-4 weeks after abdominal surgery [f].	Not available
	• Timing is less important for favorable histology (FH) WT than for unfavorable histology (UFH) WT [c].	Not available
	• Flank RT or WAI should start within 2-4 weeks after abdominal surgery [f].	Not available
	• If WLI is possible, flank RT/WAI could be postponed after (chemotherapy and) lung surgery, to give both using a single field [f].	Not available
	• If there is high risk for local recurrence (mainly, in diffuse anaplasia), flank RT/WAI should not be delayed and could be delivered separately from WLI [f].	Not available
	• WLI can be delayed until week 6 of chemotherapy in select patients with FH WT who only have metastases in the lung [a].	Not available

Ongoing Studies and Research Gaps

Radiotherapy Technique

Of the three clinical trials identified from the ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP), two were on proton beams and are currently recruiting [NCT04968990, NCT03810651] [44,45]. One is on stereotactic body radiotherapy (SBRT) for lung metastasis in pediatric solid tumors including WT. This has been terminated in April 2021 due to slow accrual and study design limitations [NCT02581384] [46].

The COG is currently studying the feasibility of cardiac-sparing IMRT for WLI [47]. An international project is being planned to investigate the role of magnetic resonance (MR)-guided RT for better visualization of the pancreatic tail and spleen [48].

Most importantly, long-term local control and toxicity will be evaluated in the SIOP-RTSG 2016 UMBRELLA trial, where 2D conventional RT volumes were translated to conformal volumes, and advanced RT techniques (3DCRT, IMRT, stereotactic RT and IGRT) were employed [20,47].

Radiotherapy Timing

In the upcoming COG protocols, flank RT or WAI will be deferred until week 6 for patients with lung metastases so that it could be given simultaneously with WLI without overlapping fields [47,49].

Additional Considerations

Cost

3DCRT and IMRT are already widely available in the Philippines, even in government centers. 3DCRT is affordable for most but IMRT remains costly for the average Filipino. IMRT could take longer to deliver, which may or may not require a dedicated linear accelerator and anesthesia team.

Image-guided RT including gating and VMAT are not yet widely available locally and are not affordable for the average Filipino. Gated RT would take longer to deliver and would require a dedicated linear accelerator and anesthesia team. VMAT could be quicker to deliver. These advanced techniques would require training (physics team, pediatric anesthesia) and organizational costs.

Patient's Values and Preference, Equity, Acceptability, and Feasibility

No studies were found.

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4.8A Molecular analysis for LOH 1p/16q for patients with Wilms tumor

Question 8A: Among patients with WT, would obtaining molecular analysis for LOH 1p/16q compared to no molecular analysis improve treatment outcomes?

RECOMMENDATIONS

1. **Among patients with WT Stage I/II, we suggest testing LOH 1p/16q for augmentation of therapy.** ***(Weak recommendation, low certainty of evidence)***

2. **Among patients with WT Stage III/IV, we suggest testing LOH 1p/16q for augmentation of therapy.** ***(Weak recommendation, very low certainty of evidence)***

Considerations

The consensus panel considered the following when formulating these recommendations:

- Despite the very low certainty of evidence, the panel still suggests testing LOH 1p/16q because it can affect the management of WT.
- The molecular analysis for LOH 1p/16q is not yet available locally and is costly.

Key Findings

- Three non-randomized experimental studies and two retrospective observational studies were included, with primary research on unilateral, pediatric Wilms tumor assessing loss of heterozygosity of 1p, 16q, or both that result in either clinical utility with change in therapeutic regimen or lack of clinical utility with no difference in prognosis compared to a negative LOH.
- Although studies reveal changes in therapeutic outcomes based on LOH 1p/16q, there are no directly observed comparisons through randomized clinical trials for those who tested or did not test for 1p/16q, leading to a low certainty of evidence.
- The non-randomized experimental studies demonstrated improvement in event-free survival among those who tested 1p/16q leading to a change in the therapeutic regimen. However, these had issues in randomization, allocation concealment, and blinding. The observational studies demonstrated a lack of difference in 1p/16q were poorly powered, and were unable to create multivariate comparisons that control for confounding.
- The authors recommended, with low certainty and strength, to test LOH 1p/16q among patients with unilateral Wilms tumors who do not fall into the category of very low risk. Further, among those with very low-risk Wilms tumor, age <2

years, Stage I favorable histology, and tumor weighing <550 g, there is little clinical utility of LOH 1p/16q testing.

Background

While there are several different emerging molecular markers for the prognosis of WT, the LOH 1p/16q has been the most well-established prognostic molecular marker, initially validated by the NWTS Group in 2005.[1] In the Philippines, this work-up requires additional expenses through FISH or PCR followed by capillary electrophoresis of molecular markers [2]. But despite this, the clinical utility of this molecular test to improve treatment outcomes needs to be explored.

Review Methods

A literature review followed by a systematic search was conducted from January 30, 2023 to March 10, 2023 through PubMed, EuropePMC, Scopus, Embase, ScienceDirect, Web of Science, EBSCOHost, and COCHRANE through an initially free text search of molecular markers that have been used in WT treatment decisions.

Although at least 17 molecular markers have shown promise in prognosticating WT, the only molecular marker used to change treatment decisions is 1p/16q. [3] The TF decided to focus on whether testing patients with an established prognostic marker, specifically 1p/16q, will improve treatment outcomes among children with unilateral, non-syndromic WT.

The key question focused on the clinical utility of an established prognostic marker, hence the best evidence to answer this would be RCTs. Such studies are almost non-existent for ethical and financial reasons. [4] Therefore, a surrogate outcome such as augmentation of treatment was used in this review. Studies that indicated lack of prognostic value of 1p/16q in certain populations were also included. The search strategy accounted for outcomes that involved survival, risk, cost-benefit, harm reduction, complications, and quality of life.

The studies were summarized without being pooled due to their heterogeneity. Painless EBM criteria [5] were used and ROBINS-I [6] to assess the risk of bias.

Results

Characteristics of Included Studies

Two non-randomized experimental studies from the USA were found, one for Stage I to IV Wilms tumors with unspecified metastatic location [7] and another for Stage IV with lung metastasis [8]. These two studies that compared changes in treatment regimen based on LOH 1p/16q status had a total of 441 patients.

Studies with very small sample sizes were also included to give a broader view, because of the paucity of large clinical trials. A non-randomized experimental study from the USA focused on relapse after nephrectomy in patients with very low-risk tumors (Stage I FHWT weighing < 550 g in patients < 2 years of age at diagnosis).

However, the sample size of only 4 patients with 1p and 8 patients with 16q seemed inadequate to make a generalizable conclusion [9]. Another Singapore-based observational study among 49 Asian children assessed differences in EFS and OS with five (5) having LOH 1p and and five (5) having LOH 16q [10]. A Korean-based retrospective cohort study was also included, with a sample size of 14 patients with LOH 1p and 14 patients with LOH 16q [11].

Outcome measures included 4-year EFS and OS of Stage I-IV WT [7] and Stage IV WT with lung metastasis [8], three-year EFS [11], differences in relapse rates over a median follow-up of 80 months with Fisher's exact test [9], and univariate odds ratios of stages, metastasis at diagnosis, nephrogenic rests, lymph node metastasis related to LOH 1p/16q [10].

Efficacy Outcomes

The studies in NWTS show that among those with 1p mutations and Stage II WT, there is a 74.9% 4-year relapse-free survival (RFS), while for those who do not have 1p mutations, there is an 86.2% 4-year RFS [11]. On the other hand, among those with 16q mutations and Stage II WT there is a 74.6% 4-year EFS, while for those without 16q mutations, there is an 86.8% 4-year EFS [11].

A non-randomized experimental trial in the USA, the 4-year EFS in patients with Stage I/II WT of 87.3% is statistically higher in those who augmented the treatment regimen vs 68% among those who did not change the regimen based on LOH 1p/16q. There was also an increase in OS from 91.6% to 100%, though not statistically significant, among patients in the same cohort. Among patients with Stage III/IV WT, there was a statistically significant improvement in 4-year EFS, from 61.3% to 90.1% and not statistically significant increase in OS [7].

In another USA non-randomized experimental trial on patients with Stage IV WT and lung metastasis with incomplete remission, changing therapy based on LOH 1p/16q status improved EFS from 88.5% to 100% and OS from 95.4% to 100%. Changes in treatment regimen based on LOH 1p/16q did not benefit those with complete remission of lung metastasis. This study, however, had a small sample size - 8 patients with positive LOH with complete lung nodule response and 10 patients with positive LOH and incomplete lung nodule response [8].

From a COG study of patients with very low-risk WT, there was no significant difference of LOH 1p or 16q on relapse rates, and LOH 1p/16q was uncommon among this population [9]. There was also no significant difference in the OR for survival based on LOH 1p or LOH 16q status among Asian children in Singapore [10]. Finally, the retrospective cohort study among Korean children found no significant difference in 3-year EFS among those with LOH 1p. However, there was a significant reduction in 3-year EFS among those with LOH 16q [12].

Safety Outcomes

In the study on WT Stages I to IV, using Regimen M (vincristine, dactinomycin, and doxorubicin alternating with cyclophosphamide and etoposide, with radiation therapy) resulted in the expected adverse events that were classified as Grade 3 and higher, including febrile neutropenia (39.2%) and infections (21.6%). One patient on Regimen M developed non-fatal sinusoidal obstruction syndrome while Regimen DD4A did not have any events that required reporting (Grade 4 and higher) [7].

In a study with lung metastasis, 14 events were reported in those receiving Regimen M and eight receiving DD4A. One patient died from surgical complications, while another on Regimen M died from unknown causes. One (1) patient on DD4A and two (2) on Regimen M had sinusoidal obstruction syndrome [8].

Other studies could not compare any adverse events related to changes in therapy based on LOH 1p/16q.

Certainty of Evidence

Among five studies, only one had a grade of moderate to high certainty because of a higher sample size, although the study remained an indirect measure of the intervention. Rather than being able to compare between testing and not testing for LOH 1p/16q, the study measured treatment outcomes from a change in treatment plan best on testing for LOH 1p/16q.[7] Another study did not report the confidence intervals of the treatment group [8], while other studies did not have an adequate sample size to compare LOH 1p/16q statuses.[9,10,12] The overall certainty of evidence for Stage I/II is low while the overall certainty of evidence for Stage III/IV is very low.

GRADE Summary of Findings

Table 24. Testing for LOH 1p/16q with changes in treatment plan vs no changes in treatment plan for management of Wilms tumor

Critical Outcomes	Basis (No and Type of Studies, Total Participants)	Effect Size (Augmentation of therapy vs. no augmentation of therapy)	95% CI	Interpretation	Certainty of Evidence
4-year EFS for Stage I/II[7]	1 study, 80 participants	Survival Percentage: 87.3 with vs 68.8	75.1-99.5 vs 55.2-82.3	Benefit	Moderate
4-year OS for Stage I/II[7]	1 study, 80 participants	Survival Percentage: 100 vs 91.6	100 (CI not reported) vs 83.6-99.6	No Benefit	Low
4-year EFS for Stage III/IV[7]	1 study, 88 participants	Survival Percentage:	81.7-98.6 vs. 44.9-	Benefit	High

		90.2 vs 61.3	77.6		
4-year OS for Stage III/IV[7]	1 study, 88 participants	Survival Percentage: 96.1 vs 86.0	90.5-100 vs. 74.5-97.5	No benefit	Low
4-year EFS for Stage IV, lung nodule response: complete[8]	1 study, 132 participants	Survival Percentage: 100 vs 79	100 (CI not reported) vs 71.2-87.8	No benefit	Very Low
4-year OS for Stage IV, lung nodule response: complete[8]	1 study, 132 participants	Survival Percentage: 100 vs 96.1	100 (CI not reported) vs 92.1-100	No Benefit	Very Low
4-year EFS for Stage IV, lung nodule response: incomplete[8]	1 study, 141 participants	Survival Percentage: 100 vs 88.5	100 (CI not reported) vs. 81.8-95.3	Benefit	Very Low
4-year OS for Stage IV, lung nodule response: incomplete[8]	1 study, 141 participants	Survival Percentage: 100 vs. 95.4	100 (CI not reported) vs. 90.9-99.8	Benefit	Very Low

Recommendations from Other Groups

Table 25. Recommendations from Other Groups on LOH 1p/16q testing for patients with WT

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
COG	Uses LOH 1p/16q to guide chemotherapy after surgery. Those classified as very low risk do not require chemotherapy. COG uses upstaging from low to standard risk regimen (DD4A to EE4A) [3]	Strong Recommendation
SIOP	The European (SIOP) protocols does not currently use LOH 1p/16q to stratify risk, but recommends the immediate use of preoperative chemotherapy prior to surgery using vincristine and dactinomycin [13]	Strong recommendation
UMBRELLA	The UMBRELLA SIOP-RTSG protocol is currently investigating other molecular	Strong recommendation

	markers, especially gain of function at chromosome 1q, however, no changes in treatment direction have yet been proposed [3]	
NCCN Guidelines Version 1. 2023 Wilms tumor (Nephroblastoma)	Changes in chemotherapy are based on 1p/16q, however, it is recommended to use whole lung irradiation for gain of 1q. Cytogenetic and molecular testing for LOH 1p and 16q and 1q gain is recommended for all children with newly diagnosed favorable histology Wilms tumor [14]	Strong recommendation

Additional Considerations

Cost

Currently PCR testing for LOH 1p/16q is not yet available in the Philippines.

Patient's Values and Preferences, Equity, Acceptability, and Feasibility

No studies were found.

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4.8B Molecular analysis for 1q gain for patients with Wilms tumor

Question 8B: Among patients with WT, would obtaining molecular analysis (1q gain) compared to no molecular analysis improve treatment outcomes?

RECOMMENDATION

Among patients with favorable histology WT with isolated lung metastasis, we suggest 1q gain analysis for augmentation of therapy. ***(Weak recommendation, very low certainty of evidence)***

Considerations

The consensus panel considered the following when formulating this recommendation:

- The main issues considered by the panel are accessibility and availability of the test locally.

Key Findings

- There were three (3) studies related to recognition of 1q gain as a poor prognostic factor for patients with WT, though none had direct comparison between molecular analysis (1q gain) vs no molecular analysis that shows improved treatment outcomes. One study showed a potential treatment approach modification for patients with favorable histology WT with isolated lung nodules and 1q gain.
- Two (2) cohort studies determined the association of 1q gain as a poor prognostic factor measured by EFS and OS representing WT patients' treatment through both SIOP and COG approach. Both studies were able to establish poor EFS and OS for patients with 1q gain.
- One cohort study performed a *post hoc* analysis on treatment modification and 1q gain of patients with favorable histology WT with isolated lung nodules. Results showed that for incomplete nodule response, Regimen M + lung RT could overcome the negative prognostic value of 1q gain and for complete nodule response, 1q gain could be an indication for lung RT as part of treatment.
- There is paucity in literature regarding 1q gain analysis as a marker for improved treatment outcomes. There is no literature directly comparing 1q gain with EFS, OS, harm reduction, cost-effectiveness, and quality of life. However, 1q gain is a recognized poor prognostic marker with the potential of being an indication for treatment modification.

Background

Certain subsets of patients have low survival estimates including those with favorable histology who relapse, those with anaplastic histology, and those with bilateral

disease. Improvement in clinical outcomes can be achieved by identifying novel biologic prognostic factors that would improve our ability to better tailor therapy. [1]

The combined LOH of 1p and 16q is the only molecular prognostic factor used in clinical studies for risk stratification [2] yet 1q gain is one of the most common genetic abnormalities in WT [3].

Review Methods

A systematic search was done from April 3-4, 2023. Studies published from January 2012 to March 2023 were included. The databases utilized were PubMed, Medline, Cochrane Library, Google Scholar, Scopus, Europe PMC, HERDIN, Acta Medica Philippina, and PCHRD with free text search using the terms “Wilms tumor” AND “1q gain” OR “1q+” AND/OR “outcomes”. CPGs, systematic reviews, meta-analysis, and cohort studies were included. Outcomes of interest included the following: EFS, OS, harm reduction, adverse events, cost-effectiveness, and quality of life. In appraising risk of bias, Painless EBM was used for cohort studies.

Results

Characteristics of Included Studies

In the study by Changtai *et al*., patients registered prospectively in the SIOP WT 2001 clinical trial and treated with preoperative chemotherapy according to standardized risk-stratified regimens based on tumor stage, histology, and metastatic response to preoperative chemotherapy with stage I to IV WT and available frozen tumor were eligible for this study. The principal aim of this study was to assess the feasibility of using 1q gain as a prognostic biomarker by determining its association with EFS and OS in a cohort drawn entirely from the SIOP WT 2001 clinical trial [4].

In the study by Gratias *et al*., unilateral FHWTs from 1,114 patients enrolled in NWTS-5 that were informative for 1p and 16q microsatellite markers (previously determined) and informative for 1q gain, 1p loss, and 16q loss using multiplex ligation-dependent probe amplification were analyzed [1].

In the study by Dix *et al*., patients with FHWTs and isolated lung metastasis showing complete lung nodule response (CR) after 6 weeks of DD4A continued receiving chemotherapy without lung RT. Patients with incomplete response (IR) and LOH 1p/16q received lung RT and four cycles of cyclophosphamide/etoposide (Regimen M) in addition to DD4A drugs [5].

Efficacy Outcomes

In the study by Changtai *et al*., 5-year EFS in the 1q-gain group was 75.0% and 88.2% in the no-gain group. The corresponding OS values were 88.4% and 94.4%, respectively. At the alpha significance level of 0.05, univariable analyses using the Cox proportional hazards regression model showed that 1q gain was associated with poorer EFS (HR: 2.33; log-rank P=0.001) and OS (HR: 2.16; P =0.01) [4].

In the study by Gratias *et al*., the 8-year EFS and OS estimates for all 1,114 patients were 86% and 94%, respectively. A gain of 1q was present in 317 of 1,114 tumors (28%). Patients with 1q gain were older (median age, 51.5 months) than were those without 1q gain (median age, 36.5 months; p=0.001 [Wilcoxon test]). The 8-year EFS estimate was 77% for those with 1q gain and 90% for those without 1q gain (p=0.001). The 8-year OS estimate was 88% for those with 1q gain and 96% for those without 1q gain (p= 0.001) Patients with 1q gain were more likely to have Stage IV than Stage I disease. The frequency of 1q gain for the entire cohort was 28% (Stage I - 20%; Stage II - 26%; Stage III - 32%; and Stage IV - 44%). Gain of 1q was associated with significant inferior EFS in patients with Stages I, III, and IV disease and with clearly inferior OS in patients with stages I and IV disease [1].

In the study by Dix *et al,* they conducted a *post hoc* analysis of the prognostic significance of tumor 1q gain in 212 patients enrolled in AREN0533 with isolated pulmonary metastasis and available tumor DNA (Table 27). For patients with lung nodules and had CR, 4-year EFS was significantly worse for patients with 1q gain, with a trend toward inferior OS. For patients with incomplete lung nodule response, there was no significant difference in EFS or OS based on 1q gain status. A *post hoc* analysis of the prognostic value of 1q gain using the AREN0533 treatment paradigm showed that among patients with incomplete lung nodule response, there was no significant difference in EFS or OS according to 1q gain status, suggesting that Regimen M overcame the negative prognostic effect of 1q gain. In contrast, among patients with complete lung nodule response, EFS was markedly inferior in patients with 1q gain. This important observation indicates that the presence of 1q gain provides a valuable method to identify patients with complete lung nodule response who are not good candidates for omission of lung RT [5].

Table 26. Prognostic Significance of 1q Gain in Wilms Tumor Based on Eight-Year EFS and OS by Disease Stage and 1q Status (Gratias *et al*, 2016)

Disease Stage	No. (% of stage group)	8-Year EFS (95% CI)	*P* (EFS)	8-Year OS (95% CI)	*P* (OS)
Stage I (n=241, 21.6%)					
1q gain	46 (20)	85 (72 to 98)		90 (80 to 100)	
No 1q gain	195 (80)	95 (91 to 99)	0.0052	98 (96 to 100)	0.0015
Stage II (n=382, 34.3%)					
1q gain	98 (26)	81 (71 to 91)		94 (87 to 100)	
No 1q gain	284 (74)	87 (83 to 92)	0.0075	97 (94 to 99)	0.1917
Stage III (n=358, 32.1%)					
1q gain	115 (32)	79 (70 to 87)		91 (85 to 97)	
No 1q gain	243 (68)	89 (84 to 94)	0.0100	95 (91 to 98)	0.3335
Stage IV (n=133, 11.9%)					
1q gain	58 (44)	64 (48 to 79)		74 (60 to 88)	
No 1q gain	75 (56)	91 (83 to 99)	0.0004	92 (84 to 99)	0.0110

Table 27. Prognostic Significance of 1q Gain in Wilms Tumor Based on Outcomes According to 1q Gain Status (Dix *et al,* 2018)

Group	No. (%)	4-Year EFS, % (95% CI)	*P*	4-Year OS, % (95% CI)	*P*
Incomplete lung nodule response					
1q gain+	42 (36.2)	86 (72.2 to 99.3)		93 (83.1 to 100)	
1q gain-	74 (63.8)	92 (84.4 to 99.8)	0.150	96 (90.4 to 100)	0.450
Complete lung nodule response					
1q gain+	21 (21.9)	57 (73.4 to 100)		89 (73.4 to 100)	
1q gain-	75 (78.1)	86 (73.4 to 100)	0.001	97 (73.4 to 100)	0.160

Safety Outcomes

No studies were found.

Certainty of Evidence

Certainty of evidence was initially set to low since all were cohort studies. While all the studies reported outcomes were EFS and OS, results could not be pooled due to varying years (i.e., 4-, 5-, and 8-years EFS and OS). Overall certainty of evidence was downgraded to very low due to limitation in generalizing interpretation of study outcomes.

GRADE Summary of Findings

Table 27. Association of 1q gain vs no gain with critical outcomes

Critical Outcomes		Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
IR	4-year EFS	1 Cohort study (n = 212)	1q gain: 86	72.2 to 99.3	1q gain vs no gain (p=0.15)	Very Low
			no gain: 92	84.4 to 99.8		
	4-year OS	1 Cohort study (n = 212)	1q gain: 93	83.1 to 100	1q gain vs no gain (p=0.45)	Very Low
			no gain: 96	90.4 to 100		
CR	4-year EFS	1 Cohort study (n = 212)	1q gain: 57	73.4 to 100	1q gain vs no gain (p=0.001)	Very Low
			no gain: 86	73.4 to 100		

	4-year OS	1 Cohort study (n = 212)	1q gain: 89	73.4 to 100	1q gain vs no gain (p=0.16)	Very Low
			no gain: 97	73.4 to 100		

Recommendations from Other Groups

Table 28. Recommendations from other groups on molecular testing for 1q gain for patients with WT

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
SIOP	International Society of Pediatric Oncology-Renal Tumor Study Group (SIOP-RTSG) UMBRELLA 2016 protocol aims to validate new prognostic factors particularly genomic 1q gain as a prognostic marker in Wilms tumor with the goal of improving treatment stratification and to delineate novel therapeutic targets.	None

Ongoing Studies and Research Gaps

No studies were found.

Additional Considerations

Cost

No studies were found.

Patient's Values and Preferences, Equity, Acceptability, and Feasibility

No studies were found.

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4.9 Surveillance workup for patients with Wilms tumor with complete response to treatment

Question 9: Among patients with WT with complete response to treatment, would interval history and physical examination (PE) alone vs routine evaluation using chest x-ray (CXR) and whole abdominal ultrasound (US) vs chest computed tomography (CT) and whole abdominal CT scan improve event-free and disease-free survival, and aid early detection of recurrence?

RECOMMENDATIONS

1. **Among patients with WT who have completed therapy, we recommend the use of surveillance imaging in addition to history and physical examination to detect relapse.** ***(Strong recommendation, very low certainty of evidence)***

2. **Among patients with WT who have completed therapy, we suggest the use of chest x-ray and abdominal ultrasound versus chest and abdominopelvic CT scan to detect relapse.** ***(Weak recommendation, very low certainty of evidence)***

Considerations

The consensus panel considered the following when formulating these recommendations:

- The panel unanimously recommends the use of surveillance imaging in addition to history and PE in detection of relapse despite the low certainty of evidence due to its efficacy.
- One of the panelists voted against the use of CXR and US because some lesions are better detected by CT scan.

Key Findings

- Three (3) retrospective analyses of WT databases were included in this review. Two (2) of which are international, multicenter studies, which serve as a basis of guidelines in the management of WT and one study from a research hospital in the United States. There is a scarcity of relevant literature that directly answers the clinical question hence this review utilized available studies that could provide supporting evidence to address the key question.
- Based on the results obtained, 5-year OS and detection rates were significantly higher among those whose relapse was detected by surveillance imaging than those detected by PE. However, a conclusion on which of the two modalities can detect the relapse earlier cannot be derived.

- There is no significant difference observed in the 5-year OS between patients whose relapses were detected by CXR/ultrasound and CT-scan even if they are sub grouped according to stage on initial diagnosis. A significant 5-year OS

benefit was observed among patients who had relapses at sites other than the lungs detected by CXR/US vs those detected by CT-scan.

- The certainty of evidence was graded very low due to risk of bias and indirectness in the included studies. The population in two (2) of the three (3) studies included patients older than 15 years old. The timing of relapse detection cannot be directly compared for both CXR/US and CT scan since only one imaging technique is being conducted during the patient's follow-up in the two larger studies.

Background

WT generally recurs mostly within the first two years after the treatment ends. [1] Although only less than 15% of treated cases recur, the 5-year OS for all patients who had relapse was 56% and 67% from the SIOP and NWTSG/COG databases, respectively.[3,6] Surveillance after completion of therapy is a standard practice with the goal of detecting relapse before signs and symptoms develop to improve post-relapse survival.[3] Surveillance imaging through CXR, US, and CT scan are being employed, however, there is a scarcity of evidence that would support which methodology can be recommended in terms of prompt detection and improved survival rates.

Review Methods

A systematic search for articles from the last 10 years was done from February 11 to March 10, 2023 using Pubmed (MEDLINE), Cochrane Library, EBSCoHost, and ProQuest using combination of keywords "Wilms tumor," "relapse," "recurrent," "guideline," "surveillance," and "imaging". The search strategy was kept broad due to limited yield. Bibliographies of relevant literature were also scanned for additional literature.

Results

Characteristics of Included Studies

There were three (3) retrospective studies included in the review. Two of which are retrospective analyses of the studies conducted by NWTSG/COG and SIOP. These studies were also referred to by NCCN Guidelines for WT in their recommendation for post-treatment surveillance [4]. The third study was a review of the database in a research hospital in the United States.

The studies included children with WT recurrence post-treatment. Patients registered under the NWTSG/COG study included both children and adults until 21 years old (n=336) [5] while the SIOP group registered patients aged between six (6) months and 18 years (n=538) [6]. Patients less than 15 years old, which is the population defined in this review, was not delineated in both studies mentioned. The third study included patients between three (3) months and 8.7 years [7]. The methodologies used to detect the recurrence of WT in the above studies were PE or signs/symptoms [3,7,8]; CXR/ultrasound [3,8], ultrasound [7]; and CT scan [3]. Outcome measures were 5-year OS, timing of relapse, and detection rate. [3,6,7]

- Signs and Symptoms vs. Surveillance Imaging
  Only the NWTSG/COG was able to provide the 5-year OS post-treatment. Of the 336 patients included in the study, only the 281 patients with FH were included in the analysis since the 55 patients with anaplastic histology had low survival rate that prevented identification of imaging features associated with the outcome. Among patients with recurrence post-treatment, a significant difference was observed in the 5-year OS between those detected using signs/symptoms and by surveillance imaging using either CXR/US or CT-scan (55% vs 76%, p = 0.02). [3]

- CXR/US vs. CT scan
  No significant difference was observed in the 5-year OS between relapses detected using CXR/US vs CT scan (73% vs 65%, p = 0.20). A subgroup analysis was done according to WT stage on initial diagnosis. There was no significant difference between CXR/ultrasound and CT scan among Stage I or II FHWT (79% vs 85%; p = 0.53); Stages III and IV FHWT (66% vs 52%; p = 0.11); and Stage IV FHWT (64% vs 48%; p = 0.17). Likewise, a subgroup analysis of the 5-yr OS between CXR/US and CT-scan was conducted based on the sites of relapse. No significant difference was observed with lung only relapse (73% vs 73%; p = 0.91). However, a significant survival benefit was observed among patients with recurrence at other sites favoring the use of CXR/US (72% v. 48%; p = 0.02). [3]

Detection Rate

- Physical Examination vs. Surveillance Imaging

  A total of 538 patients from the SIOP study were included in the retrospective analysis of relapsed WT. Of these, only 410 patients have documented methods for relapse detection. Thirty-one (31%) of the relapses were detected by PE with or without imaging while 68% were detected by imaging only.[6]

Timing of Detection of Relapse

- Physical Examination vs. US
  The timing of detection of relapse from completion of therapy was determined in a unicentric study in eight (8) patients. PE detected the recurrence within 18 to 22 months while routine ultrasound detected it within 4 to 27 months.[7]

Safety Outcomes

Post-treatment surveillance using either CXR/US and CT scan is conducted among patients of WT as frequent as every three (3) months for the first two (2) years. Both CXR and CT scan would emit ionizing radiation, which can potentially cause cancer. According to the National Research Council (NRC), statistical limitations made it difficult to evaluate cancer risk in humans at doses below 100 millisieverts (mSv)/year,

however, they concluded that the risk of cancer would ‘‘continue in a linear fashion at lower doses without a threshold and that the smallest dose has the potential to cause a small increase in risk to humans.’’ They also cited that: (1) a dose as low as 100 mSv is associated with the development of 1 cancer in 100 individuals; the overall lifetime risk of the development of cancer is 42 cases per 100 individuals (2) even lower doses, such as that received from one CT scan (approximately 10 mSv), can be associated with an increased risk of cancer, on the order of 1 case per 1000 individuals. For a 1-year-old child, the lifetime cancer mortality risk from the radiation exposure from a single abdominal CT scan was estimated to be 1 in 550 (see Table 29 for estimated dose of radiation).[9]

In addition, pediatric patients who undergo CT scans would require the use of sedation or general anesthesia to facilitate the procedure which could add substantial risk to the patient. An observational cohort study revealed that sedation prior to the procedure is associated with a 2.9% incidence of hypoxemia and a failure rate of 7%.[10]

Table 29. Estimated dose (mSv) of surveillance imaging used in detection of WT relapse

Imaging Study	Estimated Dose (mSv)
CT chest	6
CT abdomen	7
CT pelvis	6
CXR	0.08

Certainty of Evidence

The certainty of evidence was graded very low due to risk of bias and indirectness. The population in one of the three studies included patients until 21 years old. The timing of relapse detection cannot be directly compared for both CXR/US and CT scan since only one imaging technique is being conducted during the patient’s follow-up in the two larger studies.

GRADE Summary of Findings

Table 30. Findings on physical examination vs surveillance imaging to detect relapse

Outcomes	Basis	Effect Estimate	95% Confidence Interval	Interpretation	Certainty of Evidence
5-yr OS	1 cohort; n = 281	SS = 55% SI = 76%	SS = 41 – 69% SI = 69 to 84% (p = 0.02)	Favors SI	Very low

Timing of Detection	1 cohort; n = 8	PE = 18 to 22 months US = 4 to 27 months		Inconclusive	Very low
Detection Rate	1 cohort; n = 410	PE = 31% SI = 58% Diff = 27%		Favors SI	Very low

Table 31. Five-year OS between chest X-ray/ultrasound vs CT scan to detect relapse

Outcomes	**Basis**	**Effect Estimate**	**p-value**	**Interpretation**	**Certainty of Evidence**
All patients with relapse	1 cohort; n = 281	CXR/US 73% CT Scan 65%	p = 0.2	No significant difference	Very low
WT stage on diagnosis					
Stage I or 2 FHWT	1 cohort; n = 281	CXR/US 79% CT Scan 85%	p = 0.53	No significant difference	Very low
Stage 3 and 4 FHWT	1 cohort; n = 281	CXR/US 66% CT Scan 52%	p = 0.11	No significant difference	Very low
Stage 4 FHWT	1 cohort; n = 281	CXR/US 64% CT Scan 48%	p = 0.17	No significant difference	Very low
Site of relapse					
Lung only	1 cohort; n = 281	CXR/US 73% CT Scan 73%	p=0.91	No significant difference	Very low
Other sites	1 cohort; n = 281	CXR/US 72% CT Scan 48%	P=0.05	No significant difference; favors CXR/US	Very low

Recommendations from Other Groups

Table 32. Recommendations from other groups on surveillance work-ups for patients with WT

Group	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
COG	Chest CT for the first 2-3 yrs, depending on the stage and histology, before switching to chest radiographs; abdominal evaluation with CT or MRI during the first 2 yrs after treatment.	Not mentioned
SIOP 2016	Investigations in patients during follow-up after after end-of- treatment include physical examination + blood pressure and abdominal ultrasound and chest x-ray AP or PA and lateral view as scheduled	Not mentioned
NCCN 2022	- Chest and abdominal imaging every 3 months for 2 years, then every 6 months for 2 years - Chest x-ray and abdominal US may be used in place of cross-sectional imaging with chest CT and abdominal CT or MRI	Low level of evidence

Ongoing Studies and Research Gaps

There remains a very limited number of studies on the different methods of detection of relapse and how these can affect the prognosis of patients with WT.

Additional Considerations

Cost

According to Medical Pinas [13], a website which provides information on topics related to medical and health care services in the Philippines, the cost of the diagnostic tests that are used in the detection of WT relapse are as follows: CXR PhP360, abdominal ultrasound PhP 950 to 1,600 (combined cost PhP 1,210 to 1,960); chest CT scan PhP 5,000, abdominal CT-scan PhP 5,200 (combined cost PhP 10,200).

Patients' Values and Preferences, Equity, Acceptability, and Feasibility

No studies were found.

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4.10 Appropriate nutritional intervention for patients with Wilms tumor

Question 10: Among patients with WT, what is the appropriate nutritional intervention based on nutritional status that will result in improved treatment outcomes?

RECOMMENDATION

Among malnourished patients with WT upon diagnosis, we suggest the use of central parenteral nutrition as means of nutritional support for weight gain. ***(Weak recommendation, very low certainty of evidence)***

Good Practice Statement

In patients with WT at high nutrition risk, multidisciplinary and individualized comprehensive assessment should be done to determine appropriate nutrition management and support.

Considerations

The consensus panel considered the following when formulating this recommendation:

- The panel highlighted that this recommendation is more applicable to patients who have better prognosis than those at the end-of-life care.
- A panelist suggested including the timing of the intervention ("upon diagnosis") in the recommendation because the majority of patients in low-income countries are malnourished on admission.
- Two panelists voted against the use of central parenteral nutrition among malnourished WT patients upon diagnosis due to the low certainty of evidence and the risk of sepsis.
- The SC considered the following questions in recommending inclusion of the Good Practice Statement: [1]
    - Is the statement clear and actionable?
    - Is the message really necessary in regard to actual health care practice?
    - After consideration of all relevant outcomes, will implementing the good practice statement result in large net positive consequences?
    - Is collecting and summarizing the evidence a poor use of a guideline panel's limited time and energy?
    - Is there a well-documented clear and explicit rationale connecting the indirect evidence? [2]
- The SC members voted yes to the questions above, necessitating the addition of the Good Practice Statement to the recommendations. A survey was then

sent to the CP and they unanimously concurred with the inclusion of the Good Practice Statement without further revisions.

Key Findings

- Two trials were identified which compared different means of delivery for nutritional support in patients with WT. No other studies were found which assessed the effectiveness or efficacy of other types of nutritional support.
- One randomized trial by Rickard *et al*., determined the effectiveness of central parenteral nutrition (CPN, n=9) versus peripheral parenteral nutrition (PPN, n=10) plus enteral nutrition in reversing protein-energy malnutrition among children with advanced neuroblastoma or WT. Both CPN and PPN had similar mean energy and protein intakes while a significant increase in weight, subscapular skinfold thickness, and albumin were observed from baseline to the first 28 days of treatment [3]. The level of improvement, however, did not differ significantly between the two groups. Infiltration and need to change lines occurred in all PPN patients and none in CPN. Anemia and rates of fever were comparable in both groups.
- Another trial by Rickard *et al*., compared PPN and enteral nutrition (EN) to CPN alone in patients with WT. Among thirteen (13) children with WT who are at high nutritional risk, they observed that CPN is associated with better weight gain than those who received PPN [4]. In terms of adverse events, sepsis, infiltration and catheter changes, and mortality did not differ significantly between PPN and CPN. The certainty of evidence is very low given the imprecision of results and risk of bias.
- There remains a lack of available evidence on the effect of different nutritional interventions on the EFS, OS, harm reduction, cost-effectiveness, and quality of life among children with WT.

Background

Frequent manifestations of progressive nutritional depletion in cancer patients include anorexia, weight loss, fatigue, muscle atrophy, fat mass loss, and decreased immunity. The initial nutritional issues caused by the tumor are quickly exacerbated by iatrogenic nutritional abnormalities, which are the result of the treatment and accompanying complications [5]. Malnutrition has severe implications, with children who are underweight upon diagnosis fare worse than those who are well nourished at diagnosis. Malnutrition contributes to decreased therapy tolerance, and protein calorie intake may influence chemosensitivity [6]. Given these, the need for nutritional support in children with WT is warranted to be explored.

Nutritional support is the provision of nutrients in place of or in addition to those provided by oral intake, and includes interventions relative to the means of delivery (e.g., parenteral or enteral) and/or nutritional composition (e.g., glutamine supplementation, high energy density). Enteral nutrition (EN) is any means of delivering nutrients through the gastrointestinal tract. It includes the consumption of oral food and fluids, but typically refers to enteral tube feeding via nasogastric,

nasojejunal, gastrostomy, or jejunostomy. Parenteral nutrition (PN) is the intravenous injection of nutrients that bypasses the digestive tract. It is possible to administer PN using a peripheral or central line. Central lines permit the infusion of more concentrated solutions and can therefore maximize nutritional intake in fluid-restricted patients or those with higher nutrient needs; they are also useful for long-term parenteral nutritional assistance. Parenteral or enteral nutrition typically consists of amino acids, glucose, fat, electrolytes, vitamins, and trace elements at a minimum [7].

Review Methods

A systematic search was done for studies published until January 31, 2023 using Embase, MEDLINE, Cochrane Library, and Google Scholar with a combined MeSH and free text search using the search strategy: (((wilms tumor) or "bilateral wilms" or "nephroblastoma" or "nephroblastomas" or "wilms' tumor" or "wilm tumor")) AND ("nutritional intervention" OR "nutritional treatment" OR ("nutrition therapy" or "medical nutrition therapy") OR "diet" OR "enteral nutrition" OR ("parenteral nutrition" or "intravenous feeding" or "parenteral feeding") OR supplementation). Only RCTs that compared different types of nutritional support or intervention were included in this review. Outcomes of interest included the following: weight gain, EFS, OS, harm reduction, adverse events, cost-effectiveness, and quality of life.

The Cochrane risk of bias assessment was used to determine the methodological quality of the study. In both the studies of Rickard [3,4], selection bias is possible despite the randomized trial design because the method of randomization and allocation concealment were not described. Detection bias is also a concern since no blinding was employed during measurement of outcome. Finally, attrition bias was also likely given the low sample size and high attrition rate in the study (>20% did not complete the study). Weight measurements from individual patients were reported in the two studies. Hence, the mean difference was computed along with 95% CI and p-value as seen in the paper of Ward [7]. Two-by-two tables were created for adverse events to compute for RR and 95% CI. Results from the two studies were pooled using random effects meta-analysis using mean difference and risk ratio as effect measures.

Results

Characteristics of Included Studies

One randomized trial by Rickard *et al*., determined the effectiveness of CPN (n=9) vs PPN (n=10) plus EN in reversing protein-energy malnutrition among children with advanced neuroblastoma or WT. Weekly dietary, anthropometric, and biochemical assessment were compared for 15 patients (CPN=8, PPN=7) who completed more than 25 days of nutritional support.

Another trial compared PPN and EN to CPN alone in patients with WT. Rickard *et al.,* included 19 malnourished children with high nutritional risk who were newly diagnosed with WT (10 CPN and 9 PPN). Four (4) weeks of initial intense treatment was given followed thereafter by EN and 13 children with high nutritional risk completed the study (7 CPN and 6 PPN).

Efficacy Outcomes

In the study of Rickard *et al*., the CPN group showed a weight gain average of 73 ±18 g/day while the PPN group had an average weight gain of 70 ±10 g/day (p=0.654). For energy intake, the average was 85 ±7 kcal/kg for the CPN group while the PPN group had 95 ±6 kcal/kg. For protein intake, the average was 2.5 ±0.3 protein/kg for the CPN group while the PPN group had 2.9 ±0.3 protein/kg. The two groups had no significant difference in the weekly changes of each variable over the 28-day period (p=>0.05) [3].

In another study by Rickard *et al*., the CPN group showed an average weight gain of 62 ±8 g/day while the PPN group had an average weight gain of 35 ±19 g/day. The CPN group had greater weight increases by week 4 (p=0.001). The average energy intake of the CPN group for the first 4 weeks was significantly higher (p=<0.05) than those of the PPN group. The average protein intake of both groups was similar. Energy and protein intakes for the CPN group averaged 97 ±19 kcal/kg of healthy children and 2.5 ±0.2 g protein/kg, respectively. PPN provided 76 ±12 kcal/kg of healthy children and 2.4 ±0.1 g protein/kg. Patients in both groups saw significant weight gains during the initial four (4) weeks of PN support, followed by weight loss after PN was removed and more cytotoxic treatment was administered.

Safety Outcomes

In the study of Rickard *et al*., (1983), 4 CPN patients and 2 PPN patients had sepsis (RR 3.2, 95%CI 0.41 to 24.41). All PPN patients and no CPN patients experienced peripheral subcutaneous infiltrations.

In the study of Rickard *et al*., (1989), sepsis was documented in 2 patients with CPN and 1 patient with PPN (RR 1.8, 95%CI 0.19 to 16.67). Infiltration and catheter changes occurred in 4 patients with CPN and 7 patients with PPN (RR 0.5, 95%CI 0.22 to 1.19). One death was documented in the CPN group.

Certainty of Evidence

The overall certainty of evidence was downgraded to very low due to imprecision of results and risk of bias.

GRADE Summary of Findings

Table 33. PPN versus CPN for nutritional intervention among patients with Wilms Tumor

Critical Outcomes	Basis (No and Type of Studies, Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Weight gain	2 studies (n=28)	MD 14.7	-8.8 to 38.2	Inconclusive	Very Low

Energy intake	2 studies (n=28)	MD 4.46	-25.9 to 34.8	Inconclusive	Very Low
Protein intake	2 studies (n=28)	MD -0.13	-0.62 to 0.36	Inconclusive	Very Low
Adverse events*	2 studies (n=28)	Sepsis RR 2.1 Infiltration and catheter change RR 0.2 Mortality 1 in CPN	0.6 to 7.0 0.01 to 3.5	Inconclusive	Very Low

Recommendations from Other Groups

None identified from the search.

Ongoing Studies and Research Gaps

There remains a lack of available evidence on the effect of different nutritional interventions on the EFS, OS, harm reduction, cost-effectiveness, and quality of life among children with WT.

Additional Considerations

Cost

No studies were found.

Patient's Values and Preferences, Equity, Acceptability, and Feasibility

No studies were found.

References

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treatment protocols for high and low nutritional risk children with Wilms' tumor. A prospective randomized study. Cancer. 1989 Jul 15;64(2):491-509.

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5. Research Implications/Gaps

Majority of the identified clinical questions in this CPG were unanswered in terms of cost-effectiveness, patient's values and preferences, equity, acceptability, and feasibility. There is also a lack of direct evidence to answer most of the identified clinical questions. Many of the studies about WT included in the evidence review were conducted in high-income countries, had small sample sizes, and were published more than 10 years ago.

No local studies on the cost-effectiveness of the interventions tackled in this CPG were found. Conducting studies about these topics is important so that resources can be properly allocated, especially in LMICs like the Philippines. Considering the social stratification in our country, conducting studies on equity is essential to allow targeting those who are most vulnerable in the society. Acceptability studies about the interventions tackled in this CPG were also not available. Acceptability among patients with WT and their family and among healthcare providers should be investigated as these factors will affect the implementation of the CPG recommendations.

Addressing these identified research gaps may provide a clearer picture of the impact of the various diagnostic modalities and treatment options for WT and may influence the recommendations for updating this guideline.

6. Dissemination and Implementation

The dissemination of the guideline will be done after clearance from the National Practice Guidelines Clearinghouse of the Department of Health. Dissemination platforms include the regular national forum of professional societies and the DOH-organized research forum.

The Steering Committee recommends the following dissemination indicators:

1. Number of guideline presentation
2. Number of attendees
3. Feedback of the participants on the presented guidelines

7. Applicability Issues

The WT Task Force accentuates some caveats of this CPG using equity, feasibility, and availability of some diagnostics and interventions included in this guideline that may influence the recommendations at a national level. This CPG does not necessarily supersede the consumers' (i.e., health professionals, hospital administrators, employers, payors, patients) values, settings, and circumstances.

Results of the follow-up rate in the clinical trials included in the review used in this guideline may not reflect the follow-up rate in real-world settings, particularly in areas

with limited resources. Active efforts must be done to address the issues of cost, accessibility, feasibility and equity to facilitate the implementation of the guideline.

8. Updating of the Guidelines

The recommendations herein shall hold until such time that new evidence on the diagnosis, management, and surveillance of WT dictate updating this guideline. This CPG will be updated every 3-5 years or earlier if new significant evidence becomes available. Interim updates shall be developed if important new evidence becomes available.

9. Appendices

Members of the CPG Task Force

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Name	Affiliation	Summary of Declared Conflicts of Interest	Management
Steering Committee			
Maria Cecilia Leongson-Cruz, MD	Philippine Children's Medical Center	Financial: Principal investigator- CALYPSO CT on a new deferasirox granule preparation (Novartis); received honoraria for speakership from Globo Asiatico Non-Financial: Member of PSPO; PSPO received a grant from St. Jude Children's Hospital to lead projects promoting WHO Global Initiative for Childhood Cancer, including Wilms Tumor	B
Michelle F. Rodriguez, MD	Asian Hospital and Medical Center	Non-Financial: helped develop consensus guidelines at PCMC for renal tumors in children, delivered a lecture on Wilms Tumor	B
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Joanna Choa-Go, MD	Philippine Society for Pediatric Radiology		
Maria Imelda Belen Vitug-Sales, MD	Pediatric Gastroenterologist	Financial Interests, Educational Activities: speakers bureau for pharmaceutical companies on probiotics and nutritional companies on optimizing a child's diet	B
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Search Strategy

1. Imaging modality for baseline staging work up of patients with Wilms tumor

Database	Search Strategy/Search Terms	Date and Time of Search	Results	
			Yield	Eligible
PubMed		08 Feb 2023		
	#13 AND #14		1	1
	#13 AND #14		1	1
	#13 AND #14		1	1
	#13 AND #14		1	1
	#13 AND #14		1	1
	#13 AND #14		4	
	#13 AND #16		1	
	#14 AND #15		47,860	
	#10 OR #11		5,508,413	
	#7 OR #8		232,789	
	#5 AND (#2 AND (#12 OR #6))		14	
	#3 OR #4		120,146	
	specificity		4,390,865	
	sensitivity		2,159,679	
	"overall survival"sensitivity		17,791	
	"overall survival"		225,133	
	"event-free survival"		13,437	
	"ct scan"			

	"lung metastas*" chest radiogra* chest x-ray "wilms tumor" WT		66,034 17,687 53,258 104,599 13,145 215,419	
Web of Science	((“wilms tumor” AND (“CT scan” OR “chest x-ray”)) AND “lung metas*”)	08 Feb 2023	29	0
Scopus	"wilms tumor" AND "CT scan" OR "chest x-ray" AND "lung metastas*"	09 Feb 2023	20	0
EBSCOhost	"wilms tumor" AND "CT scan" OR "chest x-ray" AND "lung metastas*"	09 Feb 2023	22	0
Medrxiv.org	"wilms tumor" AND "CT scan" OR "chest x-ray" AND "lung metastas*"	10 Feb 2023	149	0

2. Delayed vs Upfront nephrectomy for non-metastatic, resectable Wilms tumor

Source	Search Strategy / Search Terms	Date/Time of Search	Results	
			Yield	Eligible
Publication database				
PubMed	1. Wilms tumor [MeSH Major Topic] 2. Chemotherapy [MeSH Terms] 3. Neoadjuvant [MeSH Terms] 4. Pre-operative [Title/Abstract] 5. Nephrectomy [Title/Abstract] 6. Resection [MeSH Terms] 7. Delayed [Title/Abstract] 8. surviv* [Title/Abstract] 9. cost [Title/Abstract] 10. toxicit* [Title/Abstract] 11. 3 OR 4 12. 2 AND 11	April 9, 2023 12:00PM	55	

	13. 5 OR 6 14. 7 AND 13 15. 12 OR 14 16. 8 OR 9 OR 10 17. 1 AND 15 AND 16 Filters: Humans			
EuropePMC	1. Wilms tumor [Keyword including MeSH] 2. Chemotherapy [Keyword including MeSH] 3. Neoadjuvant [Keyword including MeSH] 4. Pre-operative [Abstract] 5. Nephrectomy [Abstract] 6. Resection [Abstract] 7. Delayed [Abstract] 8. survival [Abstract] 9. cost [Abstract] 10. toxicity [Abstract] 11. 3 OR 4 12. 2 AND 11 13. 5 OR 6 14. 7 AND 13 15. 12 OR 14 16. 8 OR 9 OR 10 17. 1 AND 15 AND 16 Filters: None	April 9, 2023 12:00PM	58	
HERDIN	1. Wilms tumor [Abstract] 2. Chemotherapy [Abstract] 3. Neoadjuvant [Abstract] 4. Pre-operative[Abstract] 5. Nephrectomy [Abstract] 6. Resection [Abstract] 7. Delayed [Abstract] 8. survival [Abstract] 9. cost [Abstract] 10. toxicity [Abstract] 11. 3 OR 4 12. 2 AND 11 13. 5 OR 6 14. 7 AND 13 15. 12 OR 14 16. 8 OR 9 OR 10 17. 1 AND 15 AND 16 Filters: None	April 9, 2023 12:00PM	0	
EBSCOHost	1. Wilms tumor [Subject Terms] 2. Chemotherapy [Abstract] 3. Neoadjuvant [Abstract] 4. Pre-operative[Abstract] 5. Nephrectomy [Abstract] 6. Resection [Abstract] 7. Delayed [Abstract] 8. survival [Abstract] 9. cost [Abstract] 10. toxicity [Abstract] 11. 3 OR 4 12. 2 AND 11 13. 5 OR 6 14. 7 AND 13 15. 12 OR 14	April 9, 2023 12:00PM	81	

	16. 8 OR 9 OR 10 17. 1 AND 15 AND 16 Filters: Medical databases			
Bibliography scan		April 9, 2023 12:00PM	12	
		Exact duplicates	92	
		Unique studies	114	51
Systematic Reviews Registry				
PROSPERO	MeSH DESCRIPTOR Wilms Tumor EXPLODE ALL TREES	April 9, 2023 12:00PM	3	
COCHRANE	Wilms in Title Abstract Keyword OR Nephroblastoma in Title Abstract Keyword - (Word variations have been searched)	April 9, 2023 12:00PM	1	
		Exact duplicates	0	
		Unique studies	4	0
Clinical Trials Registry				
clinicaltrials.gov	CONDITION Wilms Tumor, nephroblastoma INTERVENTION radiotherapy	April 9, 2023 12:00PM	9	
ICTRP	(wilms tumor OR nephroblastoma) AND (delayed nephrectomy OR neoadjuvant chemotherapy OR preoperative chemotherapy)	April 9, 2023 12:00PM	1	
		Exact duplicates	1	
		Unique studies	9	3

3. Upfront nephrectomy vs Neoadjuvant chemotherapy with Delayed nephrectomy in metastatic, operable Wilms tumor

Database	Search Strategy/Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Medline	((Wilms tumor[MeSH Major Topic]) AND ((neoadjuvant[MeSH Terms]) OR (neoadjuvant[Title/Abstract]))) AND (nephrectomy[Title/Abstract])	Jan 25, 2023 5:28	61	4
Cochrane	"Wilms tumor" in Title Abstract Keyword AND nephrectomy in Title Abstract	Jan 25, 2023 6:24	78	0

	Keyword - (Word variations have been searched)			
Europe PMC	Wilms AND neoadjuvant AND (((SRC:MED OR SRC:PMC OR SRC:AGR OR SRC:CBA) NOT (PUB_TYPE:"Review")))	Jan 25, 2023 8:05	773	0
Medrxiv.org and Biorxiv.org		Jan 25, 2023 14:05	50	0
ClinicalTrials.gov	nephrectomy | Wilms Tumor, Stage IV	Jan 25, 20203 16:10	3	0
Cross-referencing of Relevant articles		Jan 29, 2023 11:30	24	1 (duplicate)
Final		Feb 10, 2023		4

4. Lymph node sampling for patients with Wilms tumor undergoing surgery

Database	Search Strategy/Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Medline	(("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("lymph nodes"[MeSH Terms] OR ("lymph"[All Fields] AND "nodes"[All Fields]) OR "lymph nodes"[All Fields] OR ("lymph"[All Fields] AND "node"[All Fields]) OR "lymph node"[All Fields]) AND ("sample"[All Fields] OR "samples"[All Fields] OR "sampled"[All Fields] OR "samples"[All Fields] OR "sampling"[All Fields] OR "samplings"[All Fields])) AND (y_10[Filter]) Filters: March 26, 2021 to August 28, 2021	February 28, 2023 (latest), 9:00PM	46	3
Google Scholar	Wilms tumor AND lymph node sampling	February 28, 2023 (latest), 9:00PM	14,800	1
ClinicalTrials.gov	Wilms tumor AND lymph node sampling	February 28, 2023 (latest), 9:00PM	0	0

Cochrane CENTRAL	Wilms tumor AND lymph node sampling	February 28, 2023 (latest), 9:00PM	0	0

5. Chemotherapy dose modification for malnourished patients with Wilms tumor

Source	Search Strategy/Terms	Date/Time of Search	Results	
			Yield	Eligible
Publication Database				
PubMed	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh] Filter: From January 2012 to January 2023	Feb 19, 2023 9:00pm	6	
Scopus	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh] Filter: none	Feb 19, 2023 9:30pm	22	
EuropePMC	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh] Filter: From January 2012 to January 2023	Feb 19, 2023 10:00pm	194	
Cochrane	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh]	Feb 19, 2023 10:00pm	0	
Google Scholar	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh]	Feb 19, 2023 10:00pm	0	
Web of Science	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh]	Feb 19, 2023 10:00pm	0	
HERDIN	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh]	Feb 19, 2023 10:00pm	0	

Acta Medica Philippina	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh]	Feb 19, 2023 10:00pm	0	
PCHRD	(("Wilms Tumor"[Mesh]) AND "Malnutrition"[Mesh]) AND "Drug Therapy"[Mesh]	Feb 19, 2023 10:00pm	0	

6. Optimal timing of RT for Stage III Wilms tumor

Source	Search Strategy / Search Terms	Date/Time of Search	Results	
			Yield	Eligible
Publication database				
PubMed	1. (("wilms tumor"[MeSH Major Topic] OR (("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All Fields])) AND "radiotherapy"[MeSH Major Topic] AND ("surviv*"[Title/Abstract] OR "cost"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "quality of life"[Title/Abstract])) AND ((humans[Filter]) AND (2000:2023[pdat]) AND (english[Filter]))	February 13, 2023 21:05:07	11	
	2. (("wilms tumor"[MeSH Major Topic] OR (("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All Fields])) AND "radiotherapy"[MeSH Major Topic] AND ("surviv*"[Title/Abstract] OR "cost"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "quality of life"[Title/Abstract])) AND (english[Filter])		24	
	3. (("wilms tumor"[MeSH Major Topic] OR (("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All		24	

	Fields])) AND "radiotherapy"[MeSH Major Topic] AND ("surviv*"[Title/Abstract] OR "cost"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "quality of life"[Title/Abstract])) AND ((humans[Filter]) AND (english[Filter]))			
	4. ("wilms tumor"[MeSH Major Topic] OR (("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All Fields])) AND "radiotherapy"[MeSH Major Topic] AND ("surviv*"[Title/Abstract] OR "cost"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "quality of life"[Title/Abstract])		24	
	5. "surviv*"[Title/Abstract] OR "cost"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "quality of life"[Title/Abstract]		2,591,167	
	6. "surviv*"[Title/Abstract] OR "cost"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "quality of life"[Title/Abstract]		2,591,167	
	7. "radiotherapy"[MeSH Major Topic] OR "cost"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "quality of life"[Title/Abstract]		1,440,259	
	8. "quality of life"[Title/Abstract]			
	9. "surviv*"[Title/Abstract] OR "cost"[Title/Abstract] OR "toxicit*"[Title/Abstract] OR "stage iii"[Title/Abstract]		353,857	
	10. ("wilms tumor"[MeSH Major Topic] OR (("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All Fields])) AND "radiotherapy"[MeSH Major Topic]		2,325,812 103	
	11. "wilms tumor"[MeSH Major Topic] AND (("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All Fields]) AND "radiotherapy"[MeSH Major Topic]		3	
	12. ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR			

	"staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All Fields]		108,856	
	13. "wilms tumor"[MeSH Major Topic] AND "stage iii"[Title/Abstract] AND "radiotherapy"[MeSH Major Topic]			
	14. "stage iii"[Title/Abstract]		3	
	15. "toxicit*"[Title/Abstract]			
	16. "cost"[Title/Abstract]			
	17. "radiotherapy"[MeSH Major Topic]		39,066	
	18. "wilms tumor"[MeSH Major Topic] OR (("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All Fields])		491,007 541,855 112,856 7,291	
	19. ("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("stage"[All Fields] OR "staged"[All Fields] OR "stages"[All Fields] OR "staging"[All Fields] OR "stagings"[All Fields]) AND "III"[All Fields]		428	
	20. Wilms Tumor Stage III[MeSH Major Topic]			
	21. Wilms Tumor Stage III[MeSH Major Topic]			
	22. (wilms tumor[MeSH Major Topic]) AND (Stage III[MeSH Subheading])		0	
	23. (wilms tumor[MeSH Major Topic]) AND (Stage III[MeSH Subheading])		0	
	24. Stage III[MeSH Subheading]		0	
	25. Stage III[MeSH Subheading]			
	26. "wilms tumor"[MeSH Major Topic]		0	
	27. ("wilms tumour"[All Fields] OR "wilms tumor"[MeSH Terms] OR ("wilms"[All Fields] AND "tumor"[All Fields]) OR "wilms tumor"[All Fields]) AND ("radiotherapy"[MeSH Terms] OR "radiotherapy"[All Fields] OR "radiotherapies"[All Fields] OR "radiotherapy"[MeSH Subheading] OR "radiotherapy s"[All Fields]) AND ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) AND ("progression free survival"[MeSH Terms] OR ("progression free"[All Fields] AND "survival"[All Fields]) OR "progression free survival"[All Fields] OR ("event"[All Fields] AND "free"[All Fields] AND "survival"[All Fields]) OR "event free survival"[All Fields]) AND ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms]		0 0 7,187 47	

	OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields])			
EBSCO	S1 SU wilms tumor; Expanders - apply equivalent subjects; Search modes- Boolean/Phrase S2 TX wilms tumor, stage III; Expanders - apply equivalent subjects; Search modes- Boolean/Phrase S3 SU radiotherapy; Expanders - apply equivalent subjects; Search modes- Boolean/Phrase S4 surviv*; Expanders - apply equivalent subjects; Search modes- Boolean/Phrase S5 toxicit*; Expanders - apply equivalent subjects; Search modes- Boolean/Phrase S6 quality of life; Expanders - apply equivalent subjects; Search modes- Boolean/Phrase S7 ((S1 OR S2) AND S3) AND SU(S4 OR S5 OR S6); Expanders - apply equivalent subjects; Search modes- Boolean/Phrase S8 ((S1 OR S2) AND S3) AND SU(S4 OR S5 OR S6); Limiters - Published Date: 20000101-20221231; Expanders - apply equivalent subjects; Search modes- Boolean/Phrase S9 ((S1 OR S2) AND S3) AND SU(S4 OR S5 OR S6); Limiters - Published Date: 20000101-20221231; Expanders - apply equivalent subjects; Narrow by Language: - English; Search modes- Boolean/Phrase S10 ((S1 OR S2) AND S3) AND SU(S4 OR S5 OR S6); Limiters - Scholarly (Peer Reviewed) Journals; Published Date: 20000101-20221231; Expanders - apply equivalent subjects; Narrow by Language: - English; Search modes- Boolean/Phrase S11 ((S1 OR S2) AND S3) AND SU(S4 OR S5 OR S6); Limiters - Scholarly (Peer Reviewed) Journals; Published Date: 20000101-20221231; Expanders - apply equivalent subjects; Narrow by SubjectAge: - all infant; Narrow by SubjectAge: - infant, newborn: birth-1month; Narrow by SubjectAge: - all child; Narrow by SubjectAge: - all infant: birth-23 months; Narrow by SubjectAge: - infant: 1-23 months; Narrow by		Display Display 344584 Display Display 713807 128 95 91 90 75	

	SubjectAge: - adolescent: 13-18 years; Narrow by SubjectAge: - all child: 0-18 years; Narrow by SubjectAge: - child: 6-12 years; Narrow by Language: - English; Search modes- Boolean/Phrase			
Europe PMC	((KW:"wilms tumor" OR Title:"stage III") AND (KW:"radiotherapy")) AND ("surviv*" OR "cost" OR "toxicit*" OR KW:"quality of life") AND (FIRST_PDATE:[2000 TO 2023]) AND (((SRC:MED OR SRC:PMC OR SRC:AGR OR SRC:CBA) NOT (PUB_TYPE:"Review")) OR PUB_TYPE:REVIEW)	Februrary 14, 2023 1:05:00 AM	37	
WebOfScience	1. TS=(wilms tumor) 2. TI=(wilms tumor, stage III) 3. TS=(radiotherapy) 4. ALL=(surviv*) 5. ALL=(toxicit*) 6. ALL=(quality of life) 7. ((#1 OR #2) AND #3) AND (#4 OR #5 OR #6) Timespan: 2000-01-01 to 2023-12-31 8. ((#1 OR #2) AND #3) AND (#4 OR #5 OR #6) and Article (Document Types) and English (Languages) and English (Languages) and Oncology or Pediatrics or Radiology Nuclear Medicine Medical Imaging or Surgery (Web of Science Categories) and Proceeding Paper or Book Chapters or Early Access (Exclude – Document Types) and 1.118.300 Rhabdomyosarcoma (Exclude – Citation Topics Micro) Timespan: 2000-01-01 to 2023-12-31	February 13, 2023 23:15:02	9293 27 250271 1672751 590521 776366 298 180	

7. Optimal RT technique and timing for patients with Wilms tumor

Source	Search Strategy / Search Terms	Date/Time of Search	Results	
			Yield	Eligible
Publication database				
PubMed	1. Wilms tumor [MeSH Major Topic] 2. radiotherapy [MeSH Terms] 3. surviv* [Title/Abstract] 4. cost [Title/Abstract] 5. toxicit* [Title/Abstract] 6. 1 AND 2 7. 3 OR 4 OR 5 8. 6 AND 7 Filters: Humans, from 2000	January 24, 2023 9:00PM	57	
EuropePMC	1. Wilms tumor [Keyword including MeSH] 2. radiotherapy [Keyword including MeSH]	January 27, 2023 9:00PM	139	

	3. surviv [Abstract] 4. cost [Abstract] 5. toxicit [Abstract] 6. 1 AND 2 7. 3 OR 4 OR 5 8. 6 AND 7 Filters: From 2000			
HERDIN	1. Wilms tumor [MeSH] 2. radiotherapy [MeSH] 3. 1 AND 2 Filters: None applied	January 27, 2023 9:30PM	0	
EBSCOHost	1. Wilms tumor OR nephroblastoma [Abstract] 2. radiotherapy OR radiation therapy [Abstract] 3. surviv* [Abstract] 4. cost [Abstract] 5. toxicit* [Abstract] 6. 1 AND 2 7. 3 OR 4 OR 5 8. 6 AND 7 Filters: Medical databases, from 2000	January 30, 2023 8:00AM	129	
Bibliography scan		February 15, 2023 9:00PM	26	
		Exact duplicates	79	
		Unique studies	272	7
Systematic Reviews Registry				
PROSPERO	MeSH DESCRIPTOR Wilms Tumor EXPLODE ALL TREES	January 20, 2023 9:00PM	3	
COCHRANE	Wilms in Title Abstract Keyword OR Nephroblastoma in Title Abstract Keyword - (Word variations have been searched)	January 20, 2023 9:30PM	1	
		Exact duplicates	0	
		Unique studies	4	0
Clinical Trials Registry				
clinicaltrials.gov	CONDITION Wilms Tumor, nephroblastoma INTERVENTION radiotherapy	January 20, 2023 10:00PM	36	
ICTRP	(wilms tumor OR nephroblastoma) AND radiotherapy	January 20, 2023 10:30PM	4	
		Exact duplicates	2	
		Unique studies	38	3

8A. Molecular analysis for LOH 1p/16q for patients with Wilms tumor

Database	Search Strategy/Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Pubmed	"Wilms tumor"[MeSH Major Topic] AND ("loss of heterozygosity"[Title/Abstract] OR "LOH"[Title/Abstract] OR "1p"[Title/Abstract] OR "16q"[Title/Abstract] OR "1p/16q"[Title/Abstract]) AND ("risk"[Title/Abstract] OR "survival"[Title/Abstract] OR "benefit"[Title/Abstract] OR "cost-benefit"[Title/Abstract] OR "harm reduction"[Title/Abstract] OR "complications"[Title/Abstract] OR "quality of life"[Title/Abstract]) NOT ("syndrome"[Title/Abstract])	March 10, 2022, 5:11 pm	34	4
EuropePMC	((KW:"Wilms tumor" OR KW: "Wilms' Tumor" OR KW: "Wilms' Tumour" OR KW:"nephroblastoma") AND (ABSTRACT:"LOH" OR ABSTRACT:"loss of heterozygosity" OR ABSTRACT:"1p" OR ABSTRACT:"16q" OR ABSTRACT:"1p/16q") AND (ABSTRACT:"risk stratification" OR ABSTRACT:"survival" OR ABSTRACT:"benefit" OR ABSTRACT:"cost-benefit" OR ABSTRACT:"harm reduction" OR ABSTRACT:"complications" OR ABSTRACT:"quality of life")) AND (FIRST_PDATE:[2010 TO 2023]) NOT (syndrome) AND (((SRC:MED OR SRC:PMC OR SRC:AGR OR SRC:CBA) NOT (PUB_TYPE:"Review")) OR PUB_TYPE:REVIEW)	March 10, 2022, 6:02 pm	21	2 (1 duplicate)
WebOfScience	Results for "Wilms tumor" OR "Wilms' Tumor" OR "Wilms' Tumour" OR "nephroblastoma" (Keyword Plus ®) AND "loss of heterozygosity" OR "LOH" OR "1p" OR "6q" OR "1q" OR "11p15" OR "11q" OR "MYCN" (Abstract) AND "risk" OR "survival" OR "benefit" OR "cost-benefit" OR "harm reduction" OR "complications" OR "quality of life" (Abstract) NOT "syndrome" (Abstract)	March 10, 2022, 7:10 pm	5	0
ScienceDirect	Find articles with these terms	March 10, 2022, 7:35 pm	19	0

	("risk" OR "survival" OR "benefit" OR "cost-benefit" OR "harm reduction" OR "complications" OR "quality of life") Year 2010-2023 Title, abstract or author-specified keywords ("Wilms tumor") AND ("loss of heterozygosity" OR "LOH" OR "1p" OR "16q" OR "1p/16q") Title: NOT ("syndrome")			
Embase	('nephroblastoma':ti OR 'Wilms tumor':ti OR 'wilms*':ti OR 'wilms tumour':ti) NOT 'syndrome':ti AND ('loss of heterozygosity':ab OR 'loh':ab OR '1p/16q':ab OR '1p':ab OR '16q':ab) AND ('risk':ab OR 'survival':ab OR 'cost benefit':ab OR 'harm reduction':ab OR 'complications':ab OR 'quality of life':ab) AND [2010-2023]/py AND ('article'/it OR 'review'/it)	March 11, 2022, 7:54 pm	25	5 (5 duplicates)
Cochrane	7 Trials matching "Wilms tumor" OR "Wilms' Tumor" OR "Wilms' Tumour" OR "Wilms*" OR "nephroblastoma" in Title Abstract Keyword AND "loss of heterozygosity" OR "LOH" OR "1p" OR "16q" OR "1p/16q" in Title Abstract Keyword AND "survival" OR "benefit" OR "cost-benefit" OR "harm reduction" OR "complications" OR "quality of life" in Title Abstract Keyword NOT "syndrome" in Title Abstract Keyword - with Cochrane Library publication date Between Jan 2010 and Mar 2023, in Cochrane Reviews, Cochrane Protocols, Trials, Clinical Answers, Editorials, Special Collections (Word variations have been searched)	March 11, 2022, 8 pm	3	0
HERDIN	mesh:"Wilms tumor" OR "nephroblastoma" OR "Wilms* AND abstract:"loss of heterozygosity" OR "LOH" OR "1p" OR "16q" OR "1p/16q" NOT mesh:"syndrome" AND abstract:"survival" OR "benefit" OR "cost-benefit" OR "harm reduction" OR "complications" OR "quality of life"	March 11, 2022, 9:12 pm	0	0
Scopus	(TITLE ("Wilms tumor" OR "Wilms' Tumor" OR "Wilms' Tumour" OR "Wilms*" OR "nephroblastoma") AND TITLE-ABS-KEY ("loss of heterozygosity" OR "LOH" OR "1p" OR "16q" OR "1q" OR "11p15" OR "11q" OR "MYCN") AND TITLE-ABS-KEY ("survival" OR "benefit" OR "cost-benefit" OR "harm reduction" OR "complications"	March 11, 2022, 10:20 pm	33	4 (4 duplicates)

	OR "quality of life") AND NOT TITLE ("syndrome")) AND PUBYEAR > 2009 AND PUBYEAR > 2009			
Google Scholar	allintitle:("loss of heterozygosity" OR "LOH" OR "1p" OR "16q" OR "1p/16q) AND ("risk" OR "survival" OR "benefit" OR "cost-benefit" OR "harm reduction" OR "complications" OR "quality of life") AND "Wilms tumor"	March 11, 2022, 11:01 pm	0	0
EBSCOHost	TI ("Wilms tumor" OR "Wilms' Tumor" OR "Wilms' Tumour" OR "Wilms*" OR "nephroblastoma") AND AB ("loss of heterozygosity" OR "LOH" OR "1p" OR "16q" OR "1p/16q") AND AB ("risk" OR "survival" OR "benefit" OR "cost-benefit" OR "harm reduction" OR "complications" OR "quality of life") NOT TI "syndrome" Limiters - Peer Reviewed; Published Date: 20100101-20231231 Expanders - Apply related words; Apply equivalent subjects Age Xchild: 6-12 years Xall child: 0-18 years Xchild, preschool: 2-5 years. Xinfant: 1-23 months Xall child Xall infant: birth-23 months Xall infant Xinfant, newborn: birth-1 Search modes - Boolean/Phrase	March 11, 2022, 11:30 pm	18	4 (4 duplicates)
Total			175	5

8B. Molecular analysis for 1q gain for patients with Wilms tumor

Database	Search Strategy/Search Terms	Date and Time of Search	Results	
			Yield	Eligible
PubMed	“Wilms tumor” AND “1q gain” OR “1q+” AND/OR “outcomes” ("Wilms tumor" AND ("1q gain" OR "1q+")) AND ("event free survival" OR	April 2023	145715 12	 3

	"overall survival" OR "harm reduction" OR "adverse events" OR "cost effectiveness" OR "quality of life")			
Google Scholar	("Wilms tumor" AND ("1q gain" OR "1q+")) AND ("event free survival" OR "overall survival" OR "harm reduction" OR "adverse events" OR "cost effectiveness" OR "quality of life")	April 2023	293	3
Scopus	("Wilms tumor" AND ("1q gain" OR "1q+")) AND ("event free survival" OR "overall survival" OR "harm reduction" OR "adverse events" OR "cost effectiveness" OR "quality of life")	April 2023	19	3
Europe PMC	("Wilms tumor" AND ("1q gain" OR "1q+")) AND ("event free survival" OR "overall survival" OR "harm reduction" OR "adverse events" OR "cost effectiveness" OR "quality of life") ("Wilms tumor" AND ("1q gain" OR "1q+")) AND "treatment outcome"	April 2023	0 356	0 3
HERDIN	“Wilms tumor” AND “1q gain” OR “1q+”	April 2023	0	0
Acta Medica Philippina	“Wilms tumor” AND “1q gain” OR “1q+”	April 2023	0	0

9. Surveillance workup for patients with Wilms tumor with complete response to treatment

Database	Search Terms	Date/Time of Search	Results	
			Yield	Eligible
PubMEd	1.“Wilms tumor” [MeSH Major Topic] 2. Surveillance Filter: in the last 10 years	February 11, 2023/ 9:47 PM	310	1

Cochrane Library	1. Wilms tumor 2. Surveillance	February 18, 2023/ 7:16 PM	3	0
EBSCo Host	1. Wilms tumor 2. Surveillance	February 18, 2023/ 7:39 PM	68	0
PubMED	1.“Wilms tumor” [MeSH Major Topic] 2. Relapse 3. Recurrent Filter: in the last 10 years	February 26, 2023/ 8:04 PM	95	0
PubMED	1.“Wilms tumor” [MeSH Major Topic] 2. Guideline Filter: in the last 10 years	February 26, 2023/ 8:05 PM	8	0
Biblio Scan		February 26, 2023/ 8:06 PM	2	1
ProQuest	1. Wilms tumor 2. Surveillance 3. Relapse 4. Imaging	March 10, 2023/ 8:01 PM	232	0
Biblio Scan		March 10, 2023/ 8:02 PM	1	1

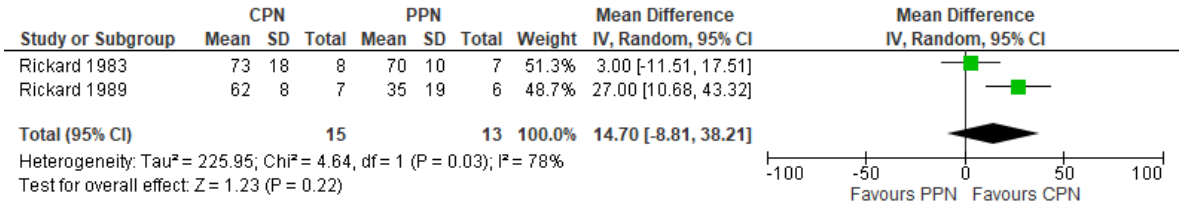
10. Appropriate nutritional intervention for patients with Wilms tumor

Database	Search Strategy/Search Terms	Date and Time of Search	Results	
			Yield	Eligible
Embase, MEDLINE	(((wilms tumor) or "bilateral wilms" or "nephroblastoma" or "nephroblastomas" or "wilm s tumor" or "wilm tumor")) AND ("nutritional intervention" OR "nutritional treatment" OR ("nutrition therapy" or "medical nutrition therapy") OR "diet" OR "enteral nutrition" OR ("parenteral nutrition" or "intravenous feeding" or "parenteral feeding") OR supplementation) AND (children OR child OR pedia*)	January 31, 2023 11:00AM	744	1
Cochrane Library	Nutrition and Wilms Tumor	January 31, 2023 11:10AM	7	1
Google Scholar	Nutrition and Wilms Tumor	January 31, 2023 11:30AM	20	0

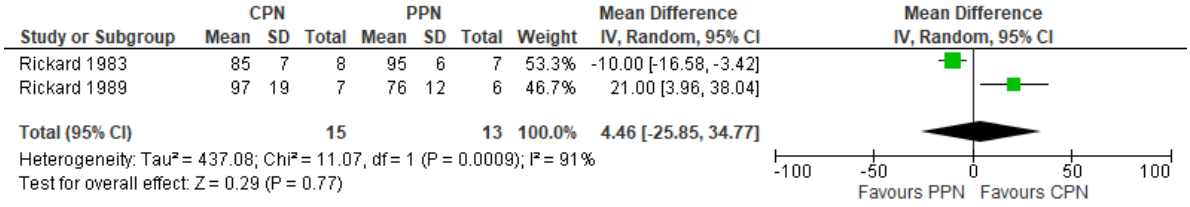
Forest Plots

Q10. Appropriate nutritional intervention for patients with Wilms tumor

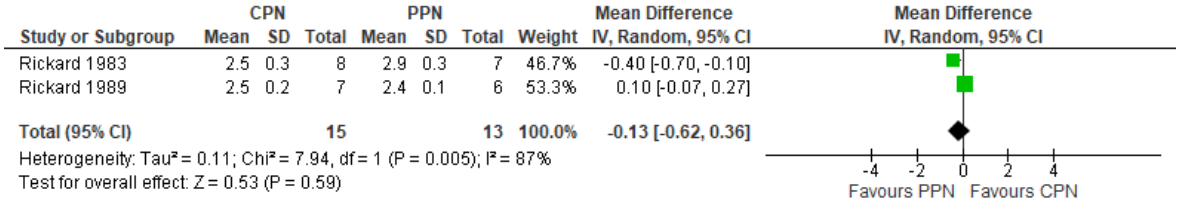
Weight gain



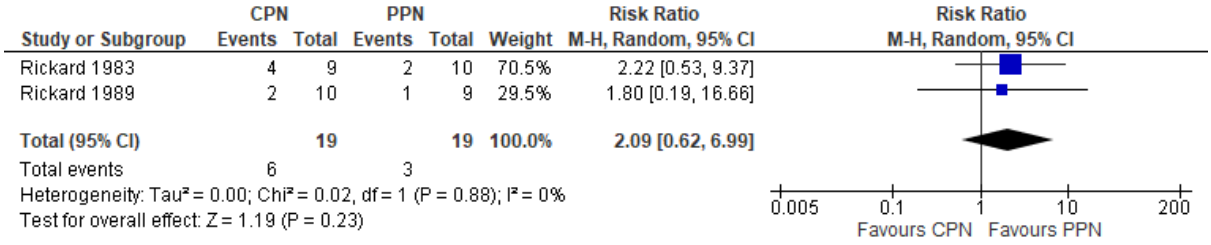
Energy intake



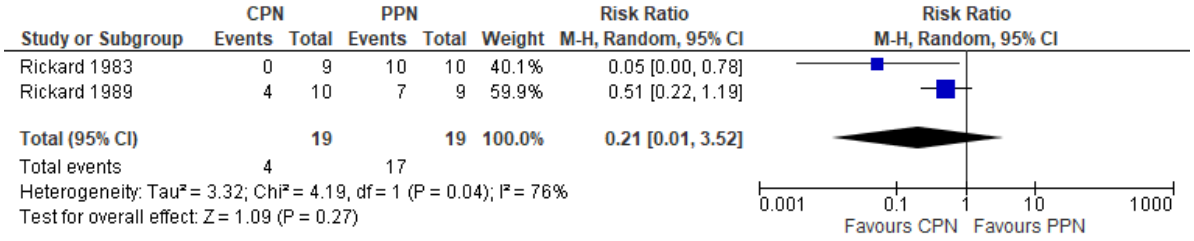
Protein intake



Risk of Sepsis



Risk of Infiltration



AGREE Reporting Checklist (Self Evaluation)

Fillable forms may be downloaded here: http://www.agreetrust.org/resource-centre/agree-reporting-checklist/

This checklist is intended to guide the reporting of clinical practice guidelines.

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	Page #
DOMAIN 1: SCOPE AND PURPOSE		
1. OBJECTIVES *Report the overall objective(s) of the guideline. The expected health benefits from the guideline are to be specific to the clinical problem or health topic.*	☒ Health intent(s) (i.e., prevention, screening, diagnosis, treatment, etc.) ☐ Expected benefit(s) or outcome(s) ☒ Target(s) (e.g., patient population, society)	17
2. QUESTIONS *Report the health question(s) covered by the guideline, particularly for the key recommendations.*	☒ Target population ☒ Intervention(s) or exposure(s) ☒ Comparisons (if appropriate) ☒ Outcome(s) ☒ Health care setting or context	Sections 4.1-4.10
3. POPULATION *Describe the population (i.e., patients, public, etc.) to whom the guideline is meant to apply.*	☒ Target population, sex and age ☒ Clinical condition (if relevant) ☒ Severity/stage of disease (if relevant) ☒ Comorbidities (if relevant) ☐ Excluded populations (if relevant)	17
DOMAIN 2: STAKEHOLDER INVOLVEMENT		
4. GROUP MEMBERSHIP *Report all individuals who were involved in the development process. This may include members of the steering group, the research team involved in selecting and reviewing/rating the evidence and individuals involved in formulating the final recommendations.*	☒ Name of participant ☐ Discipline/content expertise (e.g., neurosurgeon, methodologist) ☒ Institution (e.g., St. Peter's hospital) ☐ Geographical location (e.g., Seattle, WA) ☒ A description of the member's role in the guideline development group	103-108
5. TARGET POPULATION PREFERENCES AND VIEWS *Report how the views and preferences of the target population were sought/considered and what the resulting outcomes were.*	☒ Statement of type of strategy used to capture patients'/publics' views and preferences (e.g., participation in the guideline development group, literature review of values and preferences)	18

	☒ Methods by which preferences and views were sought (e.g., evidence from literature, surveys, focus groups) ☐ Outcomes/information gathered on patient/public information ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
6. TARGET USERS *Report the target (or intended) users of the guideline.*	☒ The intended guideline audience (e.g. specialists, family physicians, patients, clinical or institutional leaders/administrators) ☒ How the guideline may be used by its target audience (e.g., to inform clinical decisions, to inform policy, to inform standards of care)	17
DOMAIN 3: RIGOUR OF DEVELOPMENT		
7. SEARCH METHODS *Report details of the strategy used to search for evidence.*	☒ Named electronic database(s) or evidence source(s) where the search was performed (e.g., MEDLINE, EMBASE, PsychINFO, CINAHL) ☒ Time periods searched (e.g., January 1, 2004 to March 31, 2008) ☒ Search terms used (e.g., text words, indexing terms, subheadings) ☒ Full search strategy included (e.g., possibly located in appendix)	112-128
8. EVIDENCE SELECTION CRITERIA *Report the criteria used to select (i.e., include and exclude) the evidence. Provide rationale, where appropriate.*	☒ Target population (patient, public, etc.) characteristics ☒ Study design ☒ Comparisons (if relevant) ☒ Outcomes ☒ Language (if relevant) ☐ Context (if relevant)	Sections 4.1-4.10
9. STRENGTHS & LIMITATIONS OF THE EVIDENCE *Describe the strengths and limitations of the evidence. Consider from the perspective of the individual studies and the body of evidence aggregated across all the*	☒ Study design(s) included in body of evidence ☒ Study methodology limitations (sampling, blinding, allocation concealment, analytical methods) ☒ Appropriateness/relevance of primary and secondary outcomes considered	Sections 4.1-4.10

studies. Tools exist that can facilitate the reporting of this concept.	☒ Consistency of results across studies ☒ Direction of results across studies ☒ Magnitude of benefit versus magnitude of harm ☒ Applicability to practice context	
10. FORMULATION OF RECOMMENDATIONS *Describe the methods used to formulate the recommendations and how final decisions were reached. Specify any areas of disagreement and the methods used to resolve them.*	☒ Recommendation development process (e.g., steps used in modified Delphi technique, voting procedures that were considered) ☒ Outcomes of the recommendation development process (e.g., extent to which consensus was reached using modified Delphi technique, outcome of voting procedures) ☒ How the process influenced the recommendations (e.g., results of Delphi technique influence final recommendation, alignment with recommendations and the final vote)	21-22
11. CONSIDERATION OF BENEFITS AND HARMS *Report the health benefits, side effects, and risks that were considered when formulating the recommendations.*	☒ Supporting data and report of benefits ☒ Supporting data and report of harms/side effects/risks ☒ Reporting of the balance/trade-off between benefits and harms/side effects/risks ☒ Recommendations reflect considerations of both benefits and harms/side effects/risks	Sections 4.1-4.10
12. LINK BETWEEN RECOMMENDATIONS AND EVIDENCE *Describe the explicit link between the recommendations and the evidence on which they are based.*	☒ How the guideline development group linked and used the evidence to inform recommendations ☒ Link between each recommendation and key evidence (text description and/or reference list) ☒ Link between recommendations and evidence summaries and/or evidence tables in the results section of the guideline	Sections 4.1-4.10
13. EXTERNAL REVIEW *Report the methodology used to conduct the external review.*	☒ Purpose and intent of the external review (e.g., to improve quality, gather feedback on draft recommendations, assess applicability and feasibility, disseminate evidence)	22

	☒ Methods taken to undertake the external review (e.g., rating scale, open-ended questions) ☒ Description of the external reviewers (e.g., number, type of reviewers, affiliations) ☒ Outcomes/information gathered from the external review (e.g., summary of key findings) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations (e.g., guideline panel considered results of review in forming final recommendations)	
14. UPDATING PROCEDURE *Describe the procedure for updating the guideline.*	☒ A statement that the guideline will be updated ☒ Explicit time interval or explicit criteria to guide decisions about when an update will occur ☒ Methodology for the updating procedure	102
DOMAIN 4: CLARITY OF PRESENTATION		
15. SPECIFIC AND UNAMBIGUOUS RECOMMENDATIONS *Describe which options are appropriate in which situations and in which population groups, as informed by the body of evidence.*	☒ A statement of the recommended action ☒ Intent or purpose of the recommended action (e.g., to improve quality of life, to decrease side effects) ☒ Relevant population (e.g., patients, public) ☒ Caveats or qualifying statements, if relevant (e.g., patients or conditions for whom the recommendations would not apply) ☒ If there is uncertainty about the best care option(s), the uncertainty should be stated in the guideline	Sections 4.1-4.10
16. MANAGEMENT OPTIONS *Describe the different options for managing the condition or health issue.*	☒ Description of management options ☒ Population or clinical situation most appropriate to each option	Sections 4.1-4.10
17. IDENTIFIABLE KEY RECOMMENDATIONS *Present the key recommendations so that they are easy to identify.*	☒ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms ☒ Specific recommendations grouped together in one section	12-14

DOMAIN 5: APPLICABILITY		
18. FACILITATORS AND BARRIERS TO APPLICATION *Describe the facilitators and barriers to the guideline's application.*	☒ Types of facilitators and barriers that were considered ☒ Methods by which information regarding the facilitators and barriers to implementing recommendations were sought (e.g., feedback from key stakeholders, pilot testing of guidelines before widespread implementation) ☒ Information/description of the types of facilitators and barriers that emerged from the inquiry (e.g., practitioners have the skills to deliver the recommended care, sufficient equipment is not available to ensure all eligible members of the population receive mammography) ☒ How the information influenced the guideline development process and/or formation of the recommendations	101-102
19. IMPLEMENTATION ADVICE/TOOLS *Provide advice and/or tools on how the recommendations can be applied in practice.*	☒ Additional materials to support the implementation of the guideline in practice. For example: o Guideline summary documents o Links to check lists, algorithms o Links to how-to manuals o Solutions linked to barrier analysis (see Item 18) o Tools to capitalize on guideline facilitators (see Item 18) o Outcome of pilot test and lessons learned	101
20. RESOURCE IMPLICATIONS *Describe any potential resource implications of applying the recommendations.*	☒ Types of cost information that were considered (e.g., economic evaluations, drug acquisition costs) ☒ Methods by which the cost information was sought (e.g., a health economist was part of the guideline development panel, use of health technology assessments for specific drugs, etc.) ☒ Information/description of the cost information that emerged from the inquiry	Sections 4.1-4.10

	(e.g., specific drug acquisition costs per treatment course) ☒ How the information gathered was used to inform the guideline development process and/or formation of the recommendations	
21. MONITORING/ AUDITING CRITERIA *Provide monitoring and/or auditing criteria to measure the application of guideline recommendations.*	☒ Criteria to assess guideline implementation or adherence to recommendations ☒ Criteria for assessing impact of implementing the recommendations ☒ Advice on the frequency and interval of measurement ☒ Operational definitions of how the criteria should be measured	101
DOMAIN 6: EDITORIAL INDEPENDENCE		
22. FUNDING BODY *Report the funding body's influence on the content of the guideline.*	☒ The name of the funding body or source of funding (or explicit statement of no funding) ☒ A statement that the funding body did not influence the content of the guideline	3
23. COMPETING INTERESTS *Provide an explicit statement that all group members have declared whether they have any competing interests.*	☒ Types of competing interests considered ☒ Methods by which potential competing interests were sought ☒ A description of the competing interests ☒ How the competing interests influenced the guideline process and development of recommendations	18-19