Survival and Toxicity Outcomes with Radiotherapy Technique and Timing in the Management of Wilms Tumor: a Systematic Review to Inform a National Clinical Practice Guideline Development

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ABSTRACT

Purpose Wilms tumor (WT) management has evolved into a multimodality paradigm that includes radiotherapy (RT), usually as an adjuvant or consolidative modality. Protocols are refined to maximize cure and compliance while minimizing acute toxicity and long-term effects. RT technique and timing are two factors that could improve these outcomes. We reviewed the evidence on survival and toxicity outcomes among WT patients with conventional versus advanced RT techniques and early versus delayed RT to inform a Department of Health (DOH) commissioned guideline.

Materials and Methods We systematically searched PubMed, EuropePMC, EBSCOHost, HERDIN, systematic review and clinical trial registries and official websites of scientific societies for relevant publications and grey literature. Eligibility screening, risk-of-bias assessment and data extraction were performed using a single-reviewer approach. Given the study and data heterogeneity, only a qualitative synthesis was performed. Certainty of evidence assessment was done using the GRADE approach.

Results We screened 314 studies and included seven in the review, including a phase 1/2 trial and six retrospective studies, all from first-world countries (US, France, Netherlands), except one from a newly industrialized country (Brazil). The certainty of evidence on the survival and toxicity outcomes with advanced RT techniques was very low.

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Moderate-certainty evidence supports that giving RT >14 days after surgery leads to increased mortality. **Conclusion** Current evidence does not support the routine use of advanced RT techniques; proper contextualization is necessary. Tertiary centers managing WT should strive to administer RT within 14 days after surgery whenever possible.

Keywords Wilms tumor, nephroblastoma, radiotherapy, intensity-modulated radiotherapy, survival, toxicity

Study Registration PROSPERO CRD42023393387

INTRODUCTION

Current multimodality management of Wilms tumor (WT) includes radiotherapy (RT) as an adjuvant or consolidative modality. Protocols continue to be refined to maximize cure and compliance and to minimize acute toxicity and long-term effects. Long-term effects are increasingly crucial since WT is predominantly a pediatric disease, and current management is associated with long-term survival. RT technique and timing are two factors that could improve these outcomes.

Technique: Despite the relatively low RT doses used in WT protocols, long-term follow-ups of survivors treated with two-dimensional (2D) conventional RT reveal prevalent musculoskeletal growth deficits,[1], clinically significant endocrine,[2] reproductive,[3–5] hepatic,[6] renal,[7–12] cardiovascular,[13,14] pulmonary[1] and hematologic[15] toxicities, and higher risk for secondary malignancies.[16–18] Conversely, the addition of boost doses to areas of gross residual disease is prescribed in ongoing clinical trials[19–21] and recommended in recent guidelines.[22,23]

Dosimetric studies on 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 three-dimensional conformal RT (3DCRT), intensity-modulated RT (IMRT), or image-guided RT (IGRT) in the delivery of flank, whole abdominal irradiation (WAI), or whole lung irradiation (WLI), especially when boost doses are needed.[20,22,23]

Timing: The delay of adjuvant RT from surgery has been associated with higher mortality rates.[30] This has been shown to be 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 per the National Wilms Tumor Study (NWTS) 5 and Clinical Oncology Group (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, delaying possible WLI until after evaluation post-chemotherapy.

We conducted a systematic review to evaluate the survival and toxicity outcomes with conventional versus advanced RT techniques and early versus delayed RT to inform a Department of Health (DOH) commissioned clinical practice guideline.

Materials and Methods

The protocol was registered to PROSPERO (CRD42023393387) before implementation. The protocol development and reporting are per PRISMA guidelines.[34]

Information Sources

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 Supplementary File 1). Given the lack of literature based on a preliminary or scoping search, the search strategy was kept broad to maximize yield.

We searched for ongoing or recently completed systematic reviews in the PROSPERO and COCHRANE registries and 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), International Society for Pediatric Oncology (SIOP) and Children's Oncology Group (COG) were accessed for ongoing or previously completed clinical trial protocols. Bibliographies of relevant guidelines and protocols were searched for other pertinent titles.

The searches were last run on September 5, 2023.

Eligibility Criteria

Due to the lack of randomized clinical trials, non-randomized clinical trials, prospective/retrospective cohorts, and cross-sectional and case-control studies were included. Relevant comparisons included advanced RT technique versus no RT, conventional RT or another advanced RT technique, or early versus delayed adjuvant RT. Non-comparative studies that reported outcomes with advanced RT techniques were included. Outcomes of interest included survival (event-free survival, overall survival), toxicity (acute and late toxicity), cost and cost-effectiveness. Subgrouping by stage (non-metastatic versus metastatic) was planned.

Studies that reported on RT in the primary setting with curative intent, whether in non-metastatic or metastatic disease, were included; studies that reported on re-irradiation 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 reported on patients treated from 1990 onwards were included. Restricting the publication year to 2000 onwards and treatment period from 1990 onwards limited the inclusion of studies reporting on outcomes of outdated RT techniques while allowing us to capture late toxicity outcomes, such as secondary malignancies. 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 studies identified from the systematic search were imported into a citation manager software. Duplicates were identified and removed. Eligibility assessment was performed independently by any two reviewers using the single-reviewer approach. A second reviewer reviewed all studies excluded by the first to ensure that all relevant titles were included. In the case of two or multiple reports from the same group and on a broadly similar cohort, the most recent report that best satisfied the above criteria was included.

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[35] and the Painless Evidence-Based Medicine (EBM) criteria.[36] Two reviewers made the risk of bias assessment using the single-reviewer approach; a second reviewer reviewed the evaluation made by the first to ensure integrity.

Data Items and Data Extraction

Standardized forms were used to extract the following data:

Setting: period of treatment, country

Study design and size: eg, clinical trial, prospective cohort, retrospective cohort; number of patients

Patient characteristics: median/mean age, gender

Disease characteristics: histology, disease stage

Intervention characteristics: (a) timing relative to surgery or chemotherapy; and (b) technique.

Outcomes: (a) event-free survival, (b) overall survival, (c) cost/cost-effectiveness and (d) adverse events (acute and long-term complications).

Duration of follow-up: median, range

Type and source of financial support (for clinical trial reports)

Publication status (for clinical trial reports)

When needed, means and measures of dispersion were derived from reported data or estimated from figures (such as Kaplan-Meier curves) in the reports. Whenever possible, results from an intention-to-treat analysis were reported.

Data extraction was done using the single-reviewer approach. For each study, a primary reviewer extracted the data; a second reviewer then verified their accuracy and completeness.

Any disagreement between the reviewers in the study selection, data abstraction and risk-of-bias assessment was resolved by discussion and, if necessary, by adjudication by a third reviewer.

Outcomes and Prioritization

The primary outcomes were (1) event-free survival, (2) overall survival and (3) cost/cost-effectiveness. The secondary outcomes were adverse events (acute and long-term complications).

Primary outcomes: Event-free survival pertains to the interval after RT completion when patients remained free of complications or events that the RT was intended to prevent or delay. Overall survival pertains to the interval from the start of cancer treatment to when patients remained alive. Cost

pertains to direct and indirect treatment financial costs.

Secondary outcomes: Acute toxicity pertains to toxicity that developed during treatment and up to three months after treatment completion; late toxicity pertains to toxicity that developed after or persisted beyond three months after treatment completion.

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 different outcomes were investigated. Therefore, a qualitative synthesis was performed, and information was summarized in the text and tables to highlight the characteristics and findings of the studies.

Certainty of Evidence

The GRADE approach was used to evaluate the certainty of evidence. This is a systematic approach to assess the quality of the best available evidence towards developing healthcare recommendations and entails considering the number of studies of the highest study design and evaluation of the risk of bias within studies, inconsistency of findings among studies, indirectness of outcome measures and imprecision of outcome estimates.[37] Presence of multiple counts of high risk for bias, inconsistency, indirectness, imprecision, or publication bias warranted downgrading of evidence certainty; absence of the foregoing and presence of a large effect, evidence for dose response, and opposing bias and confounders that support certainty warranted upgrading of evidence certainty.[38–40]

RESULTS

Characteristics of Included Studies

We screened 314 unique studies and included seven as summarized in the PRISMA Flow Diagram (Figure 1): 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).

On radiotherapy techniques: The phase 1/2 trial and two retrospective studies investigated advanced RT techniques for WLI: 3DCRT,[41] IGRT (compared against 2D conventional technique),[42] and cardiac-sparing IMRT;[24] one retrospective study on kidney-sparing volumetric modulated arc therapy (VMAT) for WAI (compared to non-irradiated WT patients),[43] 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 overall survival;[25] and toxicity: primary hypothyroidism,[41] lung,[24,42] cardiac,[24] liver,[42] intestinal,[43] and renal[43] toxicities.

The studies were heterogeneous in terms of interventions and outcomes. Therefore, data pooling could not be done.

On radiotherapy timing: Two retrospective studies compared early versus delayed adjuvant flank RT or WAI.[30,44] Two cutoffs were investigated: 9[30,44] and 14[30] days after surgery. The two studies investigated different outcomes: flank and abdominal recurrence[44] and mortality.[30] Therefore, data pooling could not be done.

The study characteristics are detailed in Table 1.

Efficacy Outcomes

The disease control and survival outcomes for individual studies are summarized in Table 2 (WLI, flank RT and early versus delayed RT).

All three newly diagnosed WT patients treated with cardiac-sparing IMRT for WLI were alive and without lung metastasis progression at two-year follow-up. High locoregional control, disease-free and overall survival rates were achieved with highly conformal VMAT for flank RT; outcomes are comparable to those reported in the Children's Oncology Group (COG) and International Society of Pediatric Oncology (SIOP) protocols.[45–48]

On multivariate analysis, an SRI >9 days was not associated with a higher recurrence risk for the NWTS-3, the NWTS-4 and the entire cohort.[44] 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.[30] Multivariate analysis using SRI as a continuous variable resulted in a mortality hazard

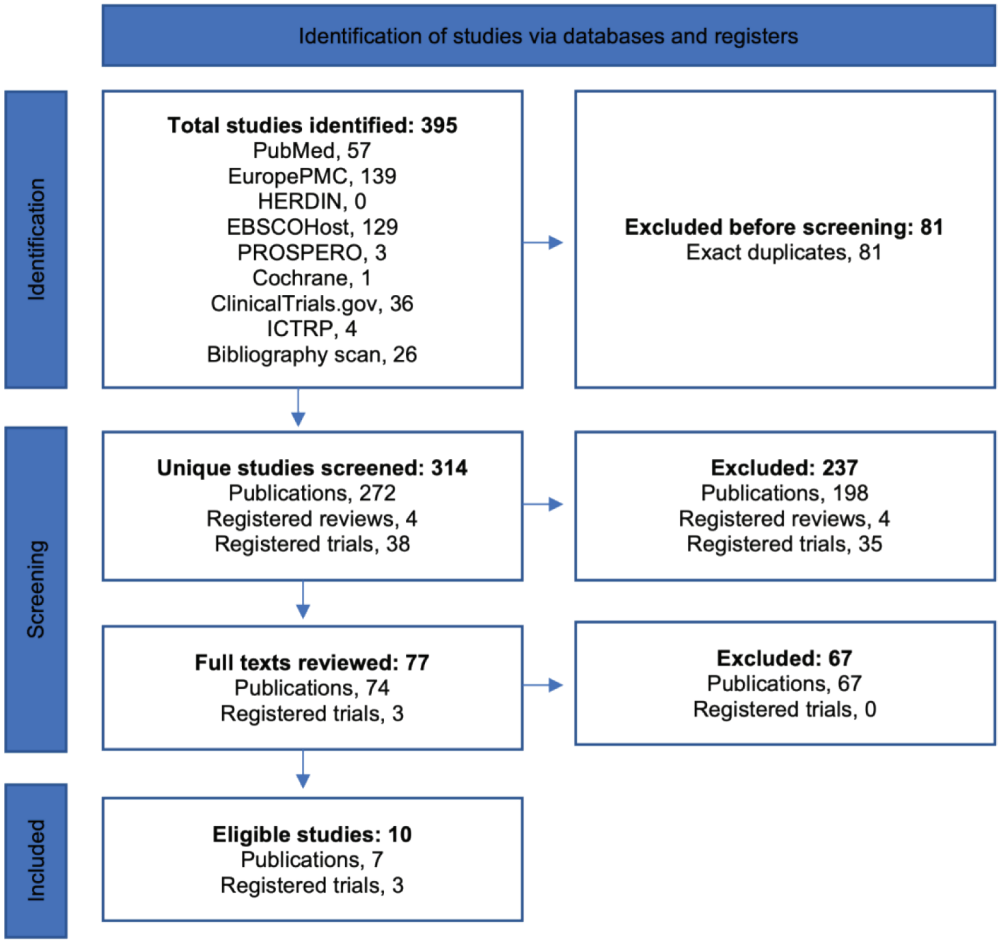

Figure 1 PRISMA Flow Diagram

ratio (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 individual studies are summarized in Table 3 (WLI, WAI). The toxicity rates are generally low; however, the studies are small and data inconclusive.

Risk of Bias Assessment and Certainty of Evidence

The detailed risk of bias assessment is provided as Supplementary File 2.

On radiotherapy technique: Three studies had no or one serious risk for bias due to selection bias (population), analysis bias (attrition),[Morgan, 2018][41] or imprecise estimate (small sample size),[Chen, 2020][43] which warranted maintaining evidence certainty as low (see Supplementary File 3).

Two studies, [Demoor-Goldschmidt, 2017; Kalapurakal, 2019][24,42] both on WLI, had multiple severe risks due to selection bias and imprecise estimate (small sample size), warranting downgrading evidence certainty from low to very low (see Supplementary File 3). Both included patients with lung metastases from different pediatric solid tumors, although outcomes for the WT cases could be derived from Kalapurakal, 2019. In Demoor-Goldschmidt, 2017, the intervention group was older than the control group, which could lead to a worse prognosis, but better technique feasibility.

On radiotherapy timing: While both are retrospective studies, the large sample sizes allowed reliable estimates. Kalapurakal, 2003[44] pooled data from prospective clinical trials. Both studies accounted for important confounders through restriction, stratification and multivariate analysis (MVA). Finally, the findings on MVA were congruent when RT timing was taken as a dichotomous or continuous variable (consistency). These warranted upgrading evidence certainty from low to moderate (see Supplementary File 3).

Table 1 Study Characteristics

Title/Author	Study Design	Country	No. of patients	Population	Intervention Group(s)	Control	Outcomes
Radiotherapy Technique							
Morgan, 2017	Retrospective	United States	28	Median age 5y (1-9) WT with lung metastases M:F 1:1.8	3D WLI (no intentional thyroid-sparing)	None	Primary hypothyroidism
Demoor-Goldschmidt, 2018	Phase 1/2 trial	France	17 (WT,5)	Solid tumors with lung mets	Deep-inspiration breath-hold WLI, 10: WT, 2 Mean age 15.6y (8.6-19.7) Mean FU 3.9y (1.1-7.6)	Free-breathing WLI, 7: WT, 3 Mean age 11.9y (4.9-21.1) Mean FU 9.48y (1.6-19.0)	Acute G≥3 lung or liver toxicity Any late lung or liver toxicity
Kalapurakal, 2018	Retrospective	United States	20 (WT,5)	Median age 10y (2-25) Solid tumors with lung mets 14, at diagnosis: WT, 3 6, at relapse: WT, 2	Cardiac-sparing IMRT WLI	None	2y LM-PFS, OS Acute lung toxicity Late lung or cardiac toxicity
Chen, 2020	Retrospective	Brazil	14	WT treated per SIOP 2001	Kidney-sparing VMAT WAI Median age 4.8y (2.4-14.0)	No RT indicated and given Median 1.7y (0.8-2.9)	Acute intestinal or renal toxicity Late renal toxicity
Mul, 2021	Retrospective	Nether-lands	36	WT treated with flank RT ± WLI per SIOP-RTSG	Highly conformal VMAT flank RT Median age 3.1y (0.3-14.0)	None	Locoregional control rate Disease-free survival Overall survival
Radiotherapy Timing							
Kalapurakal, 2003	Retrospective	United States	1226	Pedia (<16) WT FH in NWTS-3 (657), or -4 (569)	Surgery-RT interval (SRI) >9d	SRI ≤9d	Flank or abdominal recurrence
Stokes, 2018	Retrospective	United States	1488	Mean age 4.3y WT UH/FH who had surgery + RT M0, 68%; M1, 32%	Surgery-RT interval (SRI) >14d; >9d	SRI ≤14d; ≤9d	Mortality

3D, three-dimensional. d, days. FH, favorable histology. FU, follow-up. IMRT, intensity-modulated radiotherapy. LM-PFS, lung-metastases progression-free survival. M:F, male-to-female ratio. NWTS, National Wilms Tumor Study. OS, Overall survival. RT, radiotherapy. RTSG, Renal Tumor Study Group. SIOP, Société Internationale d'Oncologie Pédiatrique. UFH, unfavorable histology. VMAT, volumetric arc therapy. WAI, whole abdominal irradiation. WLI, whole lung irradiation. WT, Wilms tumor.

Table 2 Survival Outcomes

Critical Outcomes	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Intensity-modulated radiotherapy (IMRT) for whole lung irradiation (WLI)					
Event-free survival					
2y lung-metastasis progression-free survival	One 1-arm Phase 1/2 (n=3)[a]	100%	29-100%	Inconclusive	Very low
Overall survival					
2y overall survival	One 1-arm Phase 1/2 (n=3)[a]	100%	29-100%	Inconclusive	Very low
Volumetric modulated arc therapy (VMAT) for flank radiotherapy					
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
Delayed versus early adjuvant flank or abdominal RT					
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

HR, hazard ratio. RR, relative risk. SRI, surgery-to-radiotherapy interval.
[a] *Mixed population. Three are WT primaries.*

Ongoing Studies and Research Gaps

On radiotherapy technique: Of the three clinical trials identified from the ClinicalTrials.gov and International Clinical Trials Registry Platform (ICTRP), two are on proton beams and are currently recruiting [NCT04968990, NCT03810651]. [49,50] One is on stereotactic body radiotherapy (SBRT) for lung metastases in pediatric solid tumors, including WT, which was terminated in April 2021 due to slow accrual and study design limitations. [NCT02581384][51]

The COG is currently studying the feasibility of cardiac-sparing IMRT for WLI.[52] 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.[53] Long-term local control and toxicity will be evaluated in the SOIP-RTSG 2016 UMBRELLA trial, where 2D conventional RT volumes are translated to conformal volumes, and advanced RT techniques (3DCRT, IMRT, stereotactic RT and IGRT) are employed.[20,52]

On radiotherapy timing: In upcoming COG protocols, flank RT or WAI will be deferred until week 6 for patients with lung metastases so that it can be given simultaneously with WLI without overlapping fields.[52,54]

Table 3 Toxicity Outcomes

Critical Outcomes	Basis	Effect Estimate	95% CI	Interpretation	Certainty of Evidence
Advanced RT techniques for whole lung irradiation (WLI)					
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 0.73c 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 0.86c 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
Volumetric modulated arc therapy (VMAT) for whole abdominal irradiation (WAI)					
Acute toxicity					
Any enteritis	One 2-arm retrospective cohort (n=14)[d]	RR 1.00e p=1.00	0.02-44.50	Inconclusive	Low
G≥3 renal toxicity	One 2-arm retrospective cohort (n=14)[d]	RR 1.00f p = 1.00	0.02-44.50	Inconclusive	Low
Late toxicity					
Any renal toxicity	One 2-arm retrospective cohort (n=14)[d]	RR 3.00g p = 0.71	0.14-63.15	Inconclusive	Low

3D, three-dimensional. IMRT, intensity-modulated radiotherapy. RR, relative risk.
[a] *Mixed population. Three are primary and two 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.*
[d] *Comparator is patients for which no RT was indicated and given.*
[e] *No event reported.*
[f] *One event reported, in the VMAT group, but due to vascular injury during surgery.*
[g] *One event reported, in the VMAT group.*

DISCUSSION

While emerging evidence supports the safety and benefit of advanced RT, the evidence certainty ranges from very low (for WLI) to low (for WAI and flank RT). The certainty of evidence for early flank or abdominal RT after surgery is modest. The generalizability of these findings requires judicious evaluation of a particular case when personalizing treatment and contextualization according to local settings when formulating healthcare recommendations or guidelines.

In developed countries, health financing systems allow the use of advanced RT techniques without significant additional out-of-pocket costs, and the availability of ancillary health technologies and expertise allows for manageable or minimal additional workforce and infrastructure requirements and workflow restructuring. These could support the earlier adoption of advanced RT techniques. Several international guidelines recommend their use for certain situations.(Tables 4, 5)

3DCRT and IMRT are widely available in the Philippines, even in government centers. However, while 3DCRT is affordable for most, 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 require a dedicated linear accelerator and anesthesia team, unlike VMAT. These advanced techniques require training (physics team, pediatric anesthesia) and organizational costs.

Table 4 Published Guidelines

Guideline	Year	Discipline	Context
National Comprehensive Cancer Network	2022	Multidisciplinary	North American guidelines, mainly COG-based, on the diagnosis, staging, management and follow-up of WT
French Society for Radiation Oncology	2022	Radiation Oncology	French guidelines on pediatric RT procedures, including WT
St. Jude Global – International Society of Pediatric Oncology – Global Initiative for Children's Surgery	2022	Surgical Oncology	International surgical guidelines adapted to low-resource settings
International Society of Pediatric Oncology – Collaborative Wilms Tumor Africa Protocol	2020	Multidisciplinary	SIOP protocol adapted to African context, where RT services are limited. Allows for omission of RT where unavailable.
Indian Council of Medical Research	2017	Multidisciplinary	Indian guidelines adapting COG and SIOP approached to limited-resource setting, with preference for preoperative chemotherapy approach
International Society of Pediatric Oncology – Renal Tumor Study Group	2016	Multidisciplinary	SIOP protocol and guidelines updating preceding SIOP RT protocols by defining 3D volumes for advanced (non-conventional) RT techniques

Ongoing trials incorporating advanced RT technologies could provide more evidence to inform the adoption and guide the implementation of advanced RT modalities and coverage by national health insurance in the Philippines.

Current evidence supports that giving RT for >14 days after surgery is associated with increased mortality among patients with non-metastatic disease. However, the early administration of abdominal or flank RT after surgery (within 9-14 days) could probably not be imposed individually; the intervention could not be given in the presence of a surgical or medical contraindication. Nevertheless, it could be a useful performance indicator and guide to improving surgical and medical systems in oncology. Earlier administration could be achieved with enhanced preoperative patient optimization, judicious use of neoadjuvant chemotherapy, improved surgical teams and infrastructure, and post-anesthesia and intensive care.[55–58]

Local studies on the epidemiology, outcomes and factors in managing WT are scarce[59] and necessary to contextualize the above studies and international guidelines.

CONCLUSION

Current evidence does not support the routine use of advanced RT techniques; proper contextualization and case-to-case evaluation are necessary. Tertiary centers managing WT should strive to administer RT within 14 days after surgery whenever possible.

Author Contribution

WB initiated the study, conceptualized the study design, participated in the data collection and analysis and drafted the manuscript. JB participated in the data collection and analysis and revision of the manuscript. MR participated in the data analysis and revision of the manuscript. MC initiated the study, participated in the study design, data analysis and revision of the manuscript. All authors read and approved the final manuscript.

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Statement of Ethics

Study approval statement: Not applicable. Ethical clearance not required for systematic reviews.

Consent to participate statement: Not applicable. No human participants involved.

Table 5 Guideline Recommendations

Group or Agency	Recommendation	Strength of Recommendation/ Certainty/Quality of Evidence
	Radiotherapy Techniques	
[a] National Comprehensive Cancer Network, 2022 (*Accessed 12 February 2023*)	• For flank RT, use 2D (opposed anteroposterior and posteroanterior fields, AP/PA)a,b	Not available
[b] French Society for Radiation Oncology, 2022 (*Accessed 12 February 2023*)	• Consider IMRT, in case of large pelvic or midline WTb	Not available
[c] St. Jude Global – International Society of Pediatric Oncology – Global Children's Surgery Initiative, 2022 (*Accessed 15 February 2023*)	• For WAI, use four-dimensional computed tomography (4DCT) to guide RT fieldsa	Not available
[d] International Society of Pediatric Oncology – Collaborative Wilms Tumor Africa Protocol, 2020 (*Accessed 12 February 2023*)	• Consider kidney-sparing IMRTb	Not available
	• For WLI, use 2D (AP/PA) or IMRTa	Not available
[e] Indian Council of Medical Research, 2017 (*Accessed 12 February 2023*)	• For WLI + flank RT/WAI, use one large field to avoid match lines and increased organ (eg, heart) dosesa,e	Not available
[f] International Society of Pediatric Oncology – Renal Tumor Study Group (*Accessed 12 February 2023*)	• Consider cardiac-sparing IMRTb	Not available
	• For boost doses, use more conformal modalities such as 3DCRTa, IMRTa,(including simultaneous integrated boost, SIBf), protonsa, or stereotactic body radiotherapy (SBRT)f	Not available
	• Consider 4DCT to guide fieldsa	Not available
	Radiotherapy Timing	
	• RT should be started within 9-14 days from surgery, unless medically contraindicatede	Not available
	• RT should start preferably by day 10 after surgery (day 0)a,d	Not available
	• RT should start no later than day 14a,c	Weak recommendation[c]. Certainty of evidence: very low[c]
	• Flank RT or WAI should start within 2-4 weeks after abdominal surgeryf	Not available
	• Timing is less important for favorable histology (FH) WT than for unfavorable histology (UFH) WTc	Not available
	• Flank RT or WAI should start within 2-4 weeks after abdominal surgeryf	Not available
	• If WLI is possible, flank RT/WAI could be postponed after (chemotherapy and) lung surgery, to give both using a single fieldf	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 WLIf	Not available
	• WLI can be delayed until week 6 of chemotherapy in select patients with FH WT who only have metastases in the lunga	Not available

2D, two-dimensional. IMRT, intensity-modulated radiotherapy. RT, radiotherapy. WAI, whole abdominal irradiation. WLI, whole lung irradiation. WT, Wilms tumor.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

No new data were generated in this study. The detailed risk of bias assessment is included as a supplementary file.

List of Supplementary Files

Search strategy and yield per database
Risk of Bias Assessment
GRADE Evidence Profile

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