Supplementary File 3. GRADE Evidence Profile

Question: Advanced versus 2D conventional techniques for whole lung irradiation (WLI) for Wilms Tumor with lung metastasis

Bibliography:

1. Morgan TM, Danish H, Nanda RH, Esiashvili N, Meacham LR. Whole lung irradiation in stage IV Wilms tumor patients: Thyroid dosimetry and outcomes. Pediatr Blood Cancer. 2018 Feb;65(2).
2. Demoor-Goldschmidt C, Chiavassa S, Josset S, Mahé MA, Supiot S. Respiratory-gated bilateral pulmonary radiotherapy for Ewing's sarcoma and nephroblastoma in children and young adults: Dosimetric and clinical feasibility studies. Cancer Radiother J Soc Francaise Radiother Oncol. 2017 Apr;21(2):124–9.
3. Kalapurakal JA, Lee B, Bautista J, Rigsby C, Helenowski I, Gopalakrishnan M. Cardiac-Sparing Whole Lung Intensity Modulated Radiation Therapy in Children With Wilms Tumor: Final Report on Technique and Abdominal Field Matching to Maximize Normal Tissue Protection. Pr Radiat Oncol. 2019 Jan;9(1):e62–73.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerati	Advanced RT	Conventional RT	Relative (95% CI)	Absolute (95% CI)		
Event-free survival (lung metastasis progression-free survival at 2 years)												
1	phase 1/2	serious [a]	not serious	not serious	serious [b]	none	3/3 (100%)	No comparator	All 14 patients (newly diagnosed with different primaries, of which, 3 WT) were alive and without lung metastasis progression at 2 years. For WT, this corresponds to an estimate of 29-100%.		⊕◯◯◯ VERY LOW	CRITICAL
Overall survival (at 2 years)												
1	1 phase 1/2	serious [a]	not serious	not serious	serious [b]	none	3/3 (100%)	No comparator	All 14 patients (newly diagnosed with different primaries, of which, 3 WT) were alive at 2 years.		⊕◯◯◯ VERY LOW	CRITICAL
Acute moderate to severe pneumonitis												
2	retrospective	serious [a]	not serious	not serious	serious [b]	none	2/10 (50%)	1/7 (14%)	**RR 1.40** (0.97 to 1.01)	**57 more per 1,000** (from 339 fewer to 388 more)	⊕◯◯◯ VERY LOW	CRITICAL
Acute moderate to severe hepatotoxicity												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerati	Advanced RT	Conventional RT	Relative (95% CI)	Absolute (95% CI)		
1	retrospective	serious [a]	not serious	not serious	serious [b]	none	0/10 (0%)	0/7 (0%)	**RR 0.73** (0.62 to 1.03)	**0 fewer per 1,000** (from 354 fewer to 276 more)	⊕◯◯◯ VERY LOW	CRITICAL
Any late hepatotoxicity												
1	retrospective	serious [a]	not serious	not serious	serious [b]	none	0/5 (0%)	0/6 (0%)	**RR 0.86** (0.02 to 37.00)	**0 fewer per 1,000** (from 435 fewer to 390 more)	⊕◯◯◯ VERY LOW	CRITICAL
Any late cardiac toxicity												
1	phase 1/2	serious [a]	not serious	not serious	serious [b]	none	0/5 (0%)	No comparator	Of the 20 patients (with different primaries, newly diagnosed or relapsed, of which, 5 WT), one with rhabdomyosarcoma who received cumulative doxorubicin dose of 375mg/m2, developed cardiac dysfunction at 5.5y. The rest did not develop clinical, electrocardiographic or echocardiographic evidence of cardiac dysfunction.		⊕◯◯◯ VERY LOW	CRITICAL
Any late pulmonary toxicity												
1	phase 1/2	serious [a]	not serious	not serious	serious [b]	none	0/5 (0%)	No comparator	Of the 20 patients (with different primaries, newly diagnosed or relapsed, of which, 5 WT), one with rhabdomyosarcoma who received cumulative doxorubicin dose of 375mg/m2, developed pulmonary restrictive disease at 5.5y. The rest did not develop clinical or radiologic pneumonitis.		⊕◯◯◯ VERY LOW	CRITICAL
Any primary hypothyroidism (cumulative lifetime incidence)												
1	retrospective	serious [c]	not serious	not serious	not serious	none	2/20 (10%)	No comparator	Of the 28 patients, 20 were followed up. Two developed primary hypothyroidism requiring levothyroxine.		⊕⊕◯◯ LOW	CRITICAL

Explanations

a. Issues on selection bias: patients with lung metastases from different pediatric solid tumors were included (Kalapurakal, 2019; Demoor-Goldschmidt, 2017); older experimental cohort which could relate to worse prognosis and better technique feasibility (Demoor-Goldschmidt, 2017).

b. Issues on sample size, leading to imprecise estimates (Kalapurakal, 2019; Demoor-Goldschmidt, 2017)

c. Issue on analysis bias: high attrition rate (29%)(Morgan, 2018)

Question: Advanced versus 2D conventional techniques for whole abdominal irradiation (WAI) or flank radiotherapy for Wilms Tumor

Bibliography:

1. Chen MJ, Leao CR, Simoes RCP, Belletti FS, Figueiredo MLS, Cypriano MS. Kidney-sparing whole abdominal irradiation in Wilms tumor: Potential advantages of VMAT technique. Pediatr Blood Cancer. 2020 May;67(5):e28223.
2. Mul J, Seravalli E, Bosman ME, van de Ven CP, Littooij AS, van Grotel M, et al. Estimated clinical benefit of combining highly conformal target volumes with Volumetric-Modulated Arc Therapy (VMAT) versus conventional flank irradiation in pediatric renal tumors. Clin Transl Radiat Oncol. 2021 Jul;29:20–6.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerati	Advanced RT	Conventional RT	Relative (95% CI)	Absolute (95% CI)		
Locoregional control rate (at 2 years)												
1	retrospective	not serious	not serious	not serious	not serious	none	34/36 (94%)	No comparator	An estimated 86-100% will have locoregional control at 2 years, comparable to conventional RT cohorts.		⊕⊕◯◯ LOW	CRITICAL
Disease-free survival (at 2 years)												
1	retrospective	not serious	not serious	not serious	not serious	none	33/36 (91%)	No comparator	An estimated 81-100% will be alive and without disease at 2 years, comparable to conventional RT cohorts.		⊕⊕◯◯ LOW	CRITICAL
Overall survival (at 2 years)												
1	retrospective	not serious	not serious	not serious	not serious	none	34/36 (94%)	No comparator	An estimated 86-100% will be alive at 2 years, comparable to conventional RT cohorts.		⊕⊕◯◯ LOW	CRITICAL
Acute moderate to severe enteritis												
1	retrospective	serious [a]	not serious	not serious	serious [b]	none	0/7 (0%)	0/7 [c] (0%)	**RR 1.00** (0.02 to 44.50)	**0 fewer per 1,000** (from 354 fewer to 354 more)	⊕⊕◯◯ LOW	CRITICAL
Acute moderate to severe nephrotoxicity												
1	retrospective	serious [a]	not serious	not serious	serious [b]	none	0/7 (0%)	0/7 [c] (0%)	**RR 1.00** (0.02 to 44.50)	**0 fewer per 1,000** (from 354 fewer to 354 more)	⊕⊕◯◯ LOW	CRITICAL
Any late nephrotoxicity												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerati	Advanced RT	Conventional RT	Relative (95% CI)	Absolute (95% CI)		
1	retrospective	serious [a]	not serious	not serious	serious [b]	none	1/7 (14%)	0/7 [c] (0%)	**RR 3.00** (0.14 to 63.15)	**143 more per 1,000** (from 230 fewer to 513 more)	⨁⨁◯◯ LOW	CRITICAL

Explanations

a. Issue on selection bias, however, *favoring the comparator* (Chen, 2020)

b. Issue on sample size, leading to imprecise estimates (Chen, 2020)

c. The comparator used was patients with no RT indicated and given.

Question: Delayed versus early flank or abdominal radiotherapy for Wilms Tumor

Bibliography:

1. Kalapurakal JA, Li SM, Breslow NE, Beckwith JB, Macklis R, Thomas PRM, et al. Influence of radiation therapy delay on abdominal tumor recurrence in patients with favorable histology Wilms' tumor treated on NWTS-3 and NWTS-4: a report from the National Wilms' Tumor Study Group. Int J Radiat Oncol [Internet]. 2003 Oct [cited 2023 Feb 17];57(2):495–9.
2. Stokes CL, Stokes WA, Kalapurakal JA, Paulino AC, Cost NG, Cost CR, et al. Timing of Radiation Therapy in Pediatric Wilms Tumor: A Report From the National Cancer Database. Int J Radiat Oncol Biol Phys [Internet]. 2018;101(2):453–61.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delayed RT	Early RT	Relative (95% CI)	Absolute (95% CI)		
Flank recurrence (cumulative incidence at 8 years)												
1	retrospective	not serious	not serious	not serious	not serious	patterns of care [a], compliance [b]	5/494 [c] (1.01 %)	13/732 [c] (1.78%)	**RR 0.57** (0.20 to 1.59)	**8 fewer per 1,000** (from 8 fewer to 21 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Abdominal recurrence (cumulative incidence at 8 years)												
1	retrospective	not serious	not serious	not serious	not serious	patterns of care [a], compliance [b]	25/494 [c] (3.45 %)	34/732 [c] (3.34%)	**RR 1.09** (0.66 to 1.80)	**4 more per 1,000** (from 20 fewer to 3 more)	⊕⊕⊕◯ MODERATE	CRITICAL
Overall survival at (8 years) for entire cohort												
1	retrospective	not serious	not serious	not serious	not serious	patterns of care [a], compliance [b]	398/463 [c] (85.9 %)	950/1025 [c] (92.7%)	**RR 0.93** (0.89 to 0.97)	**67 fewer per 1,000** (from 34 fewer to 105 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Overall survival at (8 years) in non-metastatic disease												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delayed RT	Early RT	Relative (95% CI)	Absolute (95% CI)		
1	retrospective	not serious	not serious	not serious	not serious	patterns of care [a], compliance [b]	271/312 [c] (86.9%)	670/699 [c] (95.9%)	**RR 0.91** (0.87 to 0.95)	**90 fewer per 1,000** (from 53 fewer to 134 fewer)	⊕⊕⊕◯ MODERATE	CRITICAL
Overall survival at (8 years) in metastatic disease												
1	retrospective	not serious	not serious	not serious	not serious	patterns of care [a], compliance [b]	127/151 [c] (84.3%)	278/326 [c] (85.3%)	**RR 0.99** (0.91 to 1.07)	**11 fewer per 1,000** (from 87 fewer to 54 more)	⊕⊕⊕◯ MODERATE	CRITICAL

Explanations

a. Patients perceived with high recurrence risk could have been pushed to get early RT more frequently than patients perceived to have lower recurrence risk. Stage 3 is heterogenous in this aspect, which could not have been accounted for even when accounting for stage on multi-variate analysis.

b. There is no information on toxicity associated with early RT and its effect on treatment compliance.

c. Unadjusted for other co-variates.