2022 ETA Guidelines for the Management of Pediatric Thyroid Nodules and Differentiated Thyroid Carcinoma

Appendix C Summary tables

Summary table Clinical question 1. What is the sensitivity and specificity of thyroid ultrasound for distinction of thyroid cancer from a benign thyroid nodule of a child?						
Study (n=5)	**No. of participants**	**Age patients (mean±SD/ median (range)) (yrs)**	**Minimum size thyroid nodule**	**Ultrasound characteristics**	**Sensitivity of US**	**Specificity of US**
Richman (2018) 29714678	314 (404 nodules)	14.9	NS	Solitary Taller-than-wide shape Solid Hypoechogenicity Lack of smoot margin Any calcifications Speckled calcifications alone Abnormal lymph node *(percentage (95% CI))*	Solitary: 74.0% (63.6-83.1) Taller-than-wide shape: 26.4% (17.0-38.3) Solid: 75.3% (64.0-84.1) Hypoechogenicity: 63.0% (50.9-73.8) Lack of smooth margin: 59.7% (47.9-70.6) Any calcifications: 63.6% (51.8-74.2) Speckled calcifications alone: 58.4% (46.6-69.4) Abnormal lymph node: 36.5% (25.8-48.5)	Solitary: 58.1% (52.5-63.5) Taller-than-wide shape: 92.3 (88.7-94.9%) Solid: 75.2% (70.1-79.7) Hypoechogenicity: 50.2% (43.5-56.9) Lack of smooth margin: 94.1% (90.9-96.4) Any calcifications: 89.2% (85.3-92.3) Speckled calcifications alone: 93.3% (89.8-95.6) Abnormal lymph node: 96.7% (93.2-98.4)
Creo (2019) 30326152	99 (131 nodules)	15.4 ± 3.8	NS	Hypoechogenicity (+1), Increased vascularity (+1) Taller than wide (+1) Coarse (+1) or microcalcification (+2) Enlarging (>10% (+1), >30% (+2)) Abnormal lymph nodes (+2) Size (2-2.9 (+2), 3-3.9 (+3). 4+ (+4)	≥2 points 93.2% ≥3 points 77.3% ≥4 points 56.8%	≥2 points 41.4% ≥3 points 70.1% ≥4 points 87.4%
Gannon (2018) 29546281	152 (241 nodules)	14.2 ± 3.8	≥ 0.5 cm	Nodule size >1 cm ≤ 25% solid nodule composition Nonisoechoic echogenicity Taller-than-wide shape Increased Doppler flow Calcifications Infiltrative/microlobular margin Extrathryoidal extension All features combined *(percentage (95% CI))*	Nodule size >1 cm: 81% (71-89.1) ≤ 25% solid nodule composition: 85% (75.3-92) Nonisoechoic echogenicity: 83.5 (73.5-90.9) Taller-than-wide shape: 21.2% (12.9-31.8) Increased Doppler flow: 90.9% (82.2-96.3) Calcifications: 60.0% (48.4-70.8) Infiltrative/microlobular margin: 51.9% (40.4-63.3) Extrathryoidal extension: 16.2% (8.9-26.2) All features combined: 58.7% (46.7-69.9)	Nodule size >1 cm: 32.1% (24.8-40) ≤ 25% solid nodule composition:46.2% (38.2-54.3) Nonisoechoic echogenicity: 52.6% (44.4-60.8) Taller-than-wide shape: 89.7% (83.9-94.0) Increased Doppler flow: 25.9% (19-33.7) Calcifications: 85.8% (79.3-90.9) Infiltrative/microlobular margin: 89.1 (83.1-93.5) Extrathryoidal extension: 98.1 (94.5-99.6) All features combined: 91.6% (85.8-95.6)

Koltin (2016) 27089403	27	13.1±3.4	NS	Microcalcifications, size, ill-defined margin	Microcalcifications and size and ill-defined margin: 80.7% Microcalcifications and ill-defined margins and hypoechogenicity: 73.6% Hypoechogenicity and irregular outline or type 3 vascularity or microcalcifications: 28.1%	Microcalcifications and size and ill-defined margin: 79.2% Microcalcifications and ill-defined margins and hypoechogenicity: 75% Hypoechogenicity and irregular outline or type 3 vascularity or microcalcifications: 100%
Lyshchik (2005) 15770036	103 (Solid thyroid nodules found by screening of children and adolescents out of radiation contaminated areas of Belarus)	14.6±2.6 (DTC) 14.2±2.9 (benign)	≥ 0.5 cm	Hypoechogenicity, irregular outline, type 3 vascularity, microcalcifications, absence of halo, subcapsular location, heterogenicity	*All nodules* Hypoechogenicity: 55.3% Irregular outline: 71.1% Type 3 vascularity: 71.1% Microcalcifications: 5.3% Absence of halo: 78.9% Subcapsular location: 76.3% Heterogenicity: 73.7% *Nodule size ≤15mm:* Hypoechogenicity: 52.2% Irregular outline: 69.6% Type 3 vascularity: 69.6% Microcalcifications: 8.7% Absence of halo: 82.6% Subcapsular location: 65.2% Heterogenicity: 69.6% *Nodule size >15 mm:* Hypoechogenicity: 60.0% Irregular outline: 73.3% Type 3 vascularity: 73.3% Microcalcifications: NA Absence of halo: 73.3% Subcapsular location: 93.3% Heterogenicity: 80.0%	*All nodules* Hypoechogenicity: 64.8% Irregular outline: 80.2% Type 3 vascularity: 97.8% Microcalcifications: 96.7% Absence of halo: 38.5% Subcapsular location: 63.7% Heterogenicity: 39.6% *Nodule size ≤15mm:* Hypoechogenicity: 57.6% Irregular outline: 86.4% Type 3 vascularity: 87.9% Microcalcifications: 98.5% Absence of halo: 40.9% Subcapsular location: 86.4% Heterogenicity: 47.0% *Nodule size >15 mm:* Hypoechogenicity: 84.0% Irregular outline: 64.0% Type 3 vascularity: 52.0% Microcalcifications: NA Absence of halo: 32.0% Subcapsular location: 4.0% Heterogenicity: 20.0%

GRADE assessment:	
Study design:	*+4 Observational evidence for a diagnostic question*
Study limitations:	*0 Limitations; low of bias (blinded assessment in all studies)*
Consistency:	*-1 Inconsistency between studies*
Directness:	*-1 Indirectness; major variability in presented results*
Precision:	*0 No important imprecision*
Publication bias:	*0 Unlikely*
Effect size:	*+1 Strong evidence of association*
Dose-response:	*0 NA*
Plausible confounders	*0 NA*
Quality of evidence: ⊕⊕⊕⊖ **(Moderate)** Conclusion: The sensitivity of thyroid ultrasound for distinction of thyroid cancer from a benign thyroid nodule in children depends on multiple ultrasound characteristics. The sensitivity of the following ultrasound characteristics varies between: Hypo echogenicity: 52.2-63.0% *(2 studies)* Calcifications: 5.3-63.6% *(3 studies)* Taller-than-wide shape: 21.2-26.4% *(2 studies)* Irregular margin: 51.9-73.3% *(3 studies)* Increased vascularization: 69.9-90.9% *(2 studies)* *Features combined (depending on study): 28.1-93.2% (3 studies)* The specificity of thyroid ultrasound for distinction of thyroid cancer from a benign thyroid nodule in children depends on multiple ultrasound characteristics. The specificity of the following ultrasound characteristics varies between: Hypo echogenicity: 50.2-84.0% *(2 studies)* Calcifications: 89.2-98.5% *(3 studies)* Taller-than-wide shape: 89.7-92.3% *(2 studies)* Irregular margin: 80.2-94.4% *(3 studies)* Increased vascularization: 25.9-97.8% *(2 studies)* *Features combined (depending on study): 41.4-100% (3 studies)*	
Abbreviations: US, ultrasound; SD, standard deviation; IQR, interquartile range; yr, year; NS, not specified; CI, confidence interval; AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias	

Summary table Clinical question 9.
What is the prevalence of non-clinical relevant thyroid nodules in a child (non-childhood cancer survivors)?

Study (n=3)	No. of participants	Characteristics participants	Age at diagnosis thyroid nodule (mean/median, range)	Mode of detection	Prevalence non clinical relevant thyroid nodules
Baez (2015) 26295673	2525	Patients who had thoracic contrast enhanced CT	13.6 ± 6.2 yrs	Contrast enhanced CT	1.4% (95% CI 1-2%)
Calle-Toro (2019) 30811014	324	Healthy infants aged 0-8 months	Range 4-8 weeks	US	2%
Suzuki (2016) 27098220	300.476	Patients living in Fukushima Prefecture at time of the nuclear accident	10.7 ± 5.0 yrs	US	Nodule(s) >5 mm: n=2275 (0.8%) Nodule(s) ≤5 mm: n=1715 (0.6%)

GRADE assessment:	
Study design:	+4 Observational evidence for a diagnostic question
Study limitations:	0 Low risk of bias
Consistency:	0 No major inconsistency between studies
Directness:	-1 No general population
Precision:	0 No important imprecision
Publication bias:	0 Unlikely
Effect size:	0 NA
Dose-response:	0 NA
Plausible confounders	0 No adjustment

Quality of evidence: ⊕⊕⊕⊖ (Moderate quality)
Conclusion: The prevalence non clinical relevant thyroid nodules in a non childhood cancer survivor cohort of children seems to vary between 0.6-2%

Abbreviations: AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias; yrs, years; US, ultrasound

Summary table Clinical Question 10. What is the difference in outcome of DTC in children (with microcarcinoma) treated with a total thyroidectomy versus hemi or subtotal thyroidectomy?						
Study (n=12)	**No. of participants**	**Age participants (yrs)**	**Follow-up time (yrs)**	**Surgery**	**Main outcome**	**Our conclusion**
Sugino (2015) 25802237	227	mean 18 (7-20)	Median 12.9 (1.3-35.2)	TT: n=69 (30.4%) Less than TT: n=158 (69.6%) *(no definition of less TT mentioned)*	Prognostic factors DFS Univariate analysis TT: OR 2.29, 95%CI 1.150–4.330, p<0.05 Multivariate analysis TT: OR 1.40, 95%CI 0.678-2.760, not significant *Preoperative LNM OR 3.80,* 95%*CI 1.920–2.625 p<0.001* *Extrathyroidal invasion OR 1.75* 95%*CI 1.094–2.625 p<0.05* *(variable RAI not in uni/multivariate analysis)*	In a univariate analysis, TT might be superior to less than TT with respect to DFS. In a multivariate analyses no differences were found between treatment groups.
Sugino (2020) 31910105	153 LR: n=117 (*no risk factors)* IR: n=33 (*1 risk factor)* HR: n=3 (*2 risk factors)* *Risk levels based on preoperatively cN and gross ETE based on imaging/clinical features.* *Clinically apparent nodal disease diagnosed by preoperative physical examination, US, FNABC, and intraoperative inspection was defined as clinical N1 (cN1), whereas no clinically apparent nodal disease was defined as clinical N0 (cN0)*	Median 16 (7-18)	Median 14.8 (1.1-37.9)	TT: n=37 (24.2%) Less than TT: n=116 (75.8%) *(no definition of less TT mentioned)* *LND* *No dissection: n=26 (17%)* *CND (therapeutic/profylactic): n=33 (21.6%) (3/30)* *MND (therapeutic/profylactic): n=94 (61.4%) (27/67)*	RF associated with DFS: cN1 and ETE (multivariate) *(RAI not in multivariate analysis)* 10-yr DFS (LR, IR, HR): 82.4%, 55.7% and 0% 20-yr DFS (LR, IR, HR): 81.8%, 40.6%, and 0% DFS in the LR patients treated by lobectomy (n=102) was not significantly inferior to that in the patients treated by TT N=15). *(no numbers shown)* Prediction of recurrence according risk stratification: Low risk: ref Intermediate: 5.3 (2.51-11.03) High: 101.5 (18.8-498.8) *(excluding data of metastatic lymph nodes diagnosed after surgery)*	Disease free survival in low patients without clinically apparent nodal disease and without gross extra thyroidal extension treated by lobectomy does not seem to be inferior to that in patients treated by TT.

Qu (2016) 26695148 (meta-analysis)	146	Mean 16.2± 3.1	Mean 5.7 (0.5-24.3)	TT: n=67 (45.9%) Lobectomy+isthmectomy (L): n=79 (54.1%)	RF for recurrence: Extent of thyroidectomy HR 0.978 (95%CI 0.471-2.032) (p=0.952) (univariate) HR 0.417 (95%CI 0.044-3.959) (p=0.446) (multivariate) *(variable RAI in uni/multivariate analysis)*	Extent of thyroidectomy does not seem to be associated with the risk of recurrence.
Bal (2015) 25210762	53	Median 16 (6-21)	Median 6.0	TT: n=45 (85%) sTT: n=7 (13%) no surgery: n=1 (2%)	Prognostic factors remission Univariate TT vs sTT/no surgery: OR 5.83, 95%CI 1.18-28.74, p=0.03 Multivariate TT vs sTT/no surgery: OR 10.17, 95%CI 1.29-80.27, p=0.028 *(variable RAI not in uni/multivariate analysis; All patients received post-surgery RAI therapy)*	TT might be a prognostic factor for remission (found in as well in a univariate analysis as well in a multivariate analysis)
Spinelli (2019) 29935896	30 (FTC)	Mean 13.73 ± 3.83 (range 5-18)	6.1 ± 2.9 (0.5–10)	HT: n=21 Completion of thyroidectomy (CT): n=11 (11/21) TT: n= 9	Incidence of recurrence: no recurrence of disease or after-surgery relapse in all patients OS: 100%	No significant differences in incidence of recurrence and OS between treatment groups
Olmsted (2017) 28902626	81	<21	31.7 (inter-quartile range [IQR]=27.9–37.3)	TT: n= 64 Lesser than TT: n= 17	RFS: TT vs less than total p=0.2	No significant differences in recurrence free survival between treatment groups.
Nice (2015) 25819020	3861	Mean 17.6 ± 3.3 SD	Median follow-up was 6.9 with a maximum of 14.9	Total thyroidectomy (TT): n=3474 (90.0%) Partial thyroidectomy (PT): n=387 (10.0%)	Estimated 15-yr overall survival 96.10% after TT and 96.18% after PT (p=0.0855) Survival for patients undergoing TT was not statistically improved over those undergoing PT (HR 0.81, p=0.694)	No significant differences in OS between treatment groups.
Balachandar (2016) 26854950	62 (n=55 follow-up data available)	Median 13.8 (range 2.7-18.9)	4.0 (0.0–14.8)	TT: n=57 (91.9%) sTT: n=5 (8.1%)	Disease status last moment of follow-up: TT NED: n=39 (75.0%) PD: n=10 (19.2%) RPD: n=3 (5.8%)	No statistical analysis on differences in disease status at last moment of follow-up between treatment groups.

					sTT NED: n=3 (100%) Event-free survival was not associated with TT (p=0.35 [log rank test])	No association of TT with event-free survival
Palaniappan (2018) 30147104	67	Mean 16.8	Median 8.7 (2.1–19.6)	HT: n= 7 HT followed by completion thyroidectomy: n=11 TT with CCND: n=9 TT with CCND + unilateral LND: n=33 TT with CCND+bilateral LND: n=7	5-yr DFS: 100% (HT), 84.2% (TT) 10-yr DFS: 85.7% (HT), 81% (TT) Univariate analysis OS: HR 0.689 (HT), 1.000 (TT) (p=0.72) *No multivariate analysis has been performed.*	No statistical analysis on differences in disease free survival between treatment groups. Univariate analysis does not show a difference in OS between treatment groups
Zong (2018) 30282585	35 (n=13 unilateral TC)	Median 9.5 (range 4-14)	3.75 (1.2-4.3) (lobectomy) 3.8 (1.3–7) (TT)	Lobectomy: n=6 TT: n=7	Recurrence: lobectomy: n=2 (33.3%); TT: n=1 (14.3%) OS: lobectomy=100%; TT= 100% There was no statistically significant difference in recurrence and survival rate between two groups by Fisher's exact test	No significant difference in recurrence and survival rate between treatment groups.
Mihailovic (2014) 24722527	51	Mean 16.5	10 (1–30)	TT + RAI: n=46 TT only: n=2 sTT: n=3	Recurrence rate during FU TT + RAI: 6/46 (13%) TT only: 2/2 (100%) sTT: 3/3 (100%) Recurrence was significantly influenced by initial treatment (p=0.0001)	A significant difference in recurrence rate was found between treatment groups: patients treated with TT + RAI showed a lower recurrence rate compared to patient treated with TT only or sTT.
Markovina (2014) 24731094	112	<22 years	18.1 (5.0–42.8	TT: n=1002 (91.1%) sTT: n=3 (2.7%) lobectomy: n=7 (6.3%)	Progressive free survival (PFS): no detriment in PFS for patients who underwent subtotal thyroidectomy or lobectomy. *(no numbers shown)*	No significant difference in PFS between treatment groups.
GRADE assessment: Study design: Study limitations: Consistency: Directness: Precision: Publication bias: Effect size: Dose-response: Plausible confounders				+2 Observational evidence for intervention questions -1 Limitations; high risk of confounding 0 Most studies show similar results 0 Population of interest 0 No important imprecision. *4/15 show confidence intervals* 0 Unlikely +1 Strong evidence of association 0 NA 0 No adjustment		

Quality of evidence: ⊕⊕⊖⊖ (low quality)
Conclusion:
Based on the studies including risk factor analysis, total thyroidectomy might be superior subtotal thyroidectomy in children with DTC in view of disease/recurrence free survival *(univariate analysis, 1 study*). However, in a multivariate analyses no differences were found between TT and subTT *(2 studies*). Bal et al. (2015) found TT as significant prognostic factor for remission (as well in a univariate analysis as well in a multivariate analysis). *(1 study)*

Disease free survival in low patients without clinically apparent nodal disease (by preoperative physical examination, US, FNABC, and intraoperative inspection) and without gross extra thyroidal extension (based on imaging/clinical features) treated by lobectomy does not seem to be inferior to that in patients treated by TT (*1 study*).

Abbreviations: MI-FTC, minimally invasive follicular thyroid carcinoma; WI-FTC, widely invasive follicular thyroid carcinoma; yrs, year; PTC, papillary thyroid carcinoma; DTC, differentiated thyroid carcinoma; FTC, follicular thyroid carcinoma; OS, overall survival; DFS, disease-free survival; CI, confidence interval; TMC, thyroid microcarcinoma; TT, total thyroidectomy; STT, subtotal thyroidectomy; HT, hemi thyroidectomy; PT, partial thyroidectomy; DSS, disease specific survival; CND, central neck dissection; LND, lateral neck dissection; RFS, recurrence free survival; no evidence of disease (NED); persistent disease (PD); recurrent/progressive disease (RPD); AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias

Summary table Clinical Question 11. What is the difference in outcome of DTC in children with microcarcinoma (TMC) treated with a total thyroidectomy versus hemi or subtotal thyroidectomy?							
Study (n=2)	**No. of participants**	**Age participants (yrs)**	**Tumor size**	**Follow-up time**	**Surgery**	**Outcome**	**Our conclusion**
Lerner (2015) 25854844	154 TMC 1671 DTC>1cm	TMC ≤19 yrs (0-14, 18.2%; 81.8% (15-19) DTC>1cm ≤19 yrs (0-14, 24.3%; 75.7% (15-19)	TMC (≤ 1 cm) versus DTC >1 cm	7.1 years	TMC: PT in 29.2% DTC >1cm: PT in 10.8%	OR of being TMC PT: OR 3.01 (95%CI 1.68-5.38, p<0.001) No RAI: OR 1.89 (95%CI 1.13-3.17, p=0.016) Overall survival (OS) Mean OS TMC: 253.58 months, 95%CI 247.36–259.81 Mean OS DTC >1cm: 257.82 months, 95%CI 255.93–259.70 (p=0.360) DSS TMC: 256.38 months, 95%CI 251.39–261.36 DTC>1 cm: 260.60 months, 95%CI 259.56–261.64 (p=0.180) Number of deceased patients TMC deceased: N=4 (n=2 disease specific deaths, 1.3%) DTC >1cm deceased: n=20 (n=7 disease specific deaths, 0.4%)	Patients with thyroid microcarcinoma (<1 cm) were more often treated with partial thyroidectomy and without RAI compared to patients with DTC > 1cm. No significant differences in OS and DSS were found between patients with TMC and DTC >1cm. No analysis of OS and DSS in TMC treatment groups has been performed.
Golpanian (2016) 26717936	2504 (n=2077, surgical data available)	Mean 16 (range 0-19)	TMC (≤ 1 cm) versus DTC >1 cm	Not mentioned	Removal of less than lobe: n=22 (1.1%) Lobectomy: n=174 (8.4%) Subtotal thyroidectomy (sTT) or TT: n=1881 (90.6%)	Patients with **tumor sizes <1 cm** more likely received lobectomies/isthmusectomies versus ST/TT [OR = 3.03 (2.12, 4.32); P < 0.001]. Patients with **tumors ≥1 cm** and lymph node-positive statuses [OR = 99.0 (12.5, 783); P < 0.001] more likely underwent subtotal/total thyroidectomy compared to lobectomy/isthmusectomy. DSS not differ based on procedure type (p=0.84) Regardless of the type of surgery, disease specific 5-yrs, 10-yrs, 15-yrs, and 30-yrs DSS were maintained 100%	Patients with thyroidmicrocarcinoma were more likely to receive lobectomies/isthmusectomies versus ST/TT. No significant differences in DSS did not differ between treatment groups. No analysis DSS in TMC treatment groups has been performed.

GRADE assessment:	
Study design:	+2 Observational evidence for intervention questions
Study limitations:	-1 Important limitation, high risk of selection bias
Consistency:	0 Studies show similar results
Directness:	0 Population of interest
Precision:	0 No important imprecision.
Publication bias:	0 Unlikely
Effect size:	0 Strong evidence of association
Dose-response:	0 NA
Plausible confounders	0 No adjustment
Quality of evidence: ⊕⊖⊖⊖ (very low quality) Conclusion: No studies have looked into differences in outcome of patients with TMC treated with total thyroidectomy versus hemi or subtotal thyroidectomy. Two studies reported no differences in disease specific survival and overall survival between patients with TMC and patients with DTC >1cm, although patients with TMC were more often treated with partial thyroidectomy/ lobectomies/isthmusectomies (2 studies) and not followed by RAI (1 study)	
Abbreviations: DTC, differentiated thyroid carcinoma; OS, overall survival; DSS, disease specific survival; CI, confidence interval; TMC, thyroid microcarcinoma; TT, total thyroidectomy; STT, subtotal thyroidectomy; PT, partial thyroidectomy; AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias	

Summary table Clinical Question 12. **What is the difference in outcome of DTC in children treated with a (prophylactic) central neck dissection versus no central neck dissection?**					
Study (n=3)	**No. of participants**	**Age participants (yrs)**	**Surgery**	**Main outcome**	**Our conclusion**
Olmsted (2017) 28902626	81	<21 years	LND: n=31 Limited node excision: n=24 No LND: n=26 *TT: n= 64, lesser than TT: n= 17 81.5% (n=66) of the patient received RAI* *No definition of LND; unknown if prophylactic LND is mentioned.*	RFS: LND vs limited node excision or no LND: no difference (p=0.31)	No difference in recurrence free survival was found between patients treated with LND compared to limited node excision of no LND.
Rubinstein (2019) 30361076	48	17 (range 6–21)	Total thyroidectomy with prophylactic central neck dissection (TTpCND): n=32 Total thyroidectomy with unilateral modified radical neck dissection (TTMRND): n= 16 *Use of RAI not mentioned*	Recurrence as function of LNR (ratio metastatic LNs to number investigated LNs) Recurrence rates of patients treated with TTMRND vs TTpCND with an LNR ≤0.45: 30.8% and 4.2%, respectively Recurrence rates of patients treated with TTMRND vs TTpCND with an LNR >0.45: 100.0% and 25.0%, respectively *Conclusion authors:* *Incorporated as a predictive tool, the LNR may be of value in improving risk stratification for recurrence in pediatric PTC by providing a quantitative metric for "minimal" or "extensive" disease and may inform clinical conversations with patients, surveillance strategies, and practice paradigms.* *Suggestion to perform prophylactic CND to better stratify recurrence risk and to decide whether additional RAI is indicated.*	This observation suggests that an aggressive surgical approach may both simultaneously decrease the risk of recurrence and improve prognostication on patients with more advanced or aggressive disease.

GRADE assessment:	
Study design:	+2 Observational evidence for a intervention question
Study limitations:	-1 Limitations; high risk of selection bias
Consistency:	-1 Inconsistency between studies
Directness:	0 Population of interest
Precision:	0 No important imprecision
Publication bias:	0 Unlikely
Effect size:	0 No strong evidence of association
Dose-response:	0 NA
Plausible confounders	0 No adjustment
Quality of evidence: ⊕⊖⊖⊖ (Very low quality) Conclusion: Conflicting results were found. One study suggests that an aggressive surgical approach may both simultaneously decrease the risk of recurrence and improve prognostication on patients with more advanced or aggressive disease. Another study showed no difference in recurrence free survival between patients treated with lymph node dissection (LND) compared to limited node excision of no LND. However, location of LND was not specified in this study. It remains unclear if these patients underwent prophylactic central LND. (2 studies)	
Abbreviations: CCLN, central compartiment lymph nodes; yrs, year; TTpCND, total thyroidectomy with prophylactic central neck dissection; TTMRND, total thyroidectomy with unilateral modified radical neck dissection; TT, total thyroidectomy; LND, lateral neck dissection; LC, lateral compartiment; CC, central compartiment; AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias	

Summary table Clinical Question 15.
Is rhTSH effective and safe in children during treatment with I-131?

Study (n=3)	No. of participants	Age participants (yrs)	Indication rhTSH	Objectives/definitions	Dose rhTSH	Main outcome
Iorcansky (2005) 16174712	53 (19 patients received rhTSH injection) Numbers of patients per age group are not shown	rhTSH patients: mean 13.6 ± 3.4 (range 7-18) controls: mean 13.6 ± 3.7 (range 4.6-18)	Children with TC who underwent RAI WBS	TSH elevation (withdrawal levothyroxine therapy vs rhTSH) rhTSH dosing regimen: children vs adults rhTSH in different age groups Safety	0.9 mg (x2) i.m.	Withdrawal levothyroxine therapy vs rhTSH (188+/-118 mIU/l (range, 110 – 452 mIU/l) vs 134+/-75 mIU/l (range, 32–290 mIU/liter)), no significant difference (p=0.07) The mean TSH levels achieved in children after rhTSH injections are remarkably similar to values previously reported in adults despite marked differences in clinical characteristics between children and adults. No significant differences were seen in the mean serum TSH levels at the time of RAI administration after two consecutive rhTSH injections in children (<13 yrs) (187 ± 107 mIU/l), young teenagers (13-15 yrs) (88 ± 71 mIU/l), and older teenagers (15-18 yrs)(130 ± 76 mIU/l). No significant adverse side effects were reported
Rosario (2012) 22236503	12	Median 12.0	Children who underwent RAI treatment after TT for DTC	TSH levels after rhTSH Safety	0.9 mg (x2) i.m.	TSH levels >50 mIU/l were achieved in all patients No significant adverse side effects were reported
Hoe (2006) 16509525	7	Range 6-14	Children with TC who underwent RAI WBS	TSH levels after rhTSH	0.9 mg (x2) i.m.	Serum TSH levels 224 ± 93 mIU/l (mean, SD) No significant adverse side effects were reported in the patients undergoing rhTSH stimulation

GRADE assessment:	
Study design:	+2 Observational evidence for an intervention question
Study limitations:	0 Low risk of bias
Consistency:	0 No inconsistency between studies
Directness:	0 Population of interest
Precision:	0 No important imprecision *(However, two studies with relatively few number of patients)*
Publication bias:	0 Unlikely
Effect size:	0 NA
Dose-response:	0 NA
Plausible confounders	0 No adjustment

Quality of evidence: ⊕⊕⊖⊖ (low quality)
Conclusion All studies reported TSH levels after rhTSH stimulation of > 50mIU. No significant side effects were reported. No studies reported on iodine uptake after rhTSH injection.

Abbreviations: rhTSH, recombinant human TSH; yrs, years; i.m., intramuscular; RAI, radioactive iodine; TSH, thyroid stimulating hormone; TC, thyroid carcinoma; WBS, whole body scan; DTC, differentiated thyroid carcinoma; TT, total thyroidectomy; SD, standard deviation

Summary table Clinical Question 18.
What is the difference in outcome of DTC in children treated with alternative medication versus surgery and I-131?

Study (n=2)	No. of participants	Age participants (yrs)	Alternative medication	Indication alternative medication	Main outcome
Mahajan (2018) 30226445 (case series)	3	1.14 year-old-female, 2.15-year-old male, 3.5-year-old male	Lenvatinib (14mg/m2/day)	1.Extensive PTC not amenable to upfront surgery of RAI 2.Iodine non-avid diffuse pulmonary disease after initial TT and CLND 3.Pulmonary disease progression after TT and CLND and RAI treatment	*Complications*: respiratory distress requiring oxygen caused by extensive bilateral metastatic pulmonary disease (all) *Disease outcome:* first two patients remained clinically stable on Lenvatinib 23 and 11 months after initiation of therapy, respectively, and the third patient transitioned to a tumor-specific targeted therapy after one month.
Waguespack (2009) 19355831 (case report)	1	14-year-old female	Sorafenib (start 200mg, twice daily)	Progressive lung metastases	*Disease outcome:* After 67 days, dramatic improvement in the lung metastases. Minimal regrowth of the pulmonary metastases was observed, and a second treatment course of Sorafenib 200 mg every other day was equally successful in achieving a clinical response.

GRADE assessment:	
Study design:	+2 Observational evidence for a intervention question
Study limitations:	-1 Limitations: high risk of selection bias
Consistency:	0 NA
Directness:	0 Population of interest
Precision:	0 No important imprecision
Publication bias:	0 Unlikely
Effect size:	0 NA
Dose-response:	0 NA
Plausible confounders	0 No adjustment

Quality of evidence: ⊕⊖⊖⊖ (Very low quality)
Conclusion: Based on these case reports, Lenvatinib and Sorafenib may play an important role in the management of disease in these very rare cases of the pediatric patient with progressive RAI-refractory PTC, for which no good systemic therapy exists.

Abbreviations: yrs, year; TT, total thyroidectomy; CLND, Central lateral neck dissection; RAI, radioactive iodine; mg, milligram; AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias

Summary table
Clinical question 19. What is the sensitivity/specificity of neck ultrasound for recurrent DTC in follow-up of children who have been treated for DTC?

Study (n=1)	No. of participants	Age patients (mean±SD/ median (range)) (yrs)	Follow-up time	Recurrence rate	Suspicious findings for malignancy	Confirmation method	Sensitivity of US	Specificity of US
Vali (2014) 25524437	N=40 (original cohort 54), (US follow-up of 40 patients available, no differences between all patients and patients with US follow-up)	14.3±3.6	34 months	42.5% (17/40)	Suspicious defined as: hypoechoic appearance, hyperechoic foci, peripheral vascularization, and round-shape node without hyperechoic hilum	Histopathology was considered the gold standard to assess the results of US. In cases where histopathology was not available a combination of stimulated thyroglobulin levels >10 ng/ml and post-therapy whole-body iodine scan was used as the gold standard	85.7%	89.4%

GRADE assessment:	
Study design:	+4 Observational evidence for a diagnostic question
Study limitations:	0 No serious limitations: low risk of bias
Consistency:	0 NA
Directness:	0 Population of interest
Precision:	-1 Sparse data
Publication bias:	0 Unlikely
Effect size:	0 NA
Dose-response:	0 NA
Plausible confounders	0 NA

Quality of evidence: ⊕⊕⊕⊖ **(Moderate)**
Conclusion:
The sensitivity and specificity of thyroid ultrasound for recurrent DTC in follow-up of children who have been treated for DTC is 85.7% and 89.4% respectively. *(1 study)*

Abbreviations: US, ultrasound; AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias

Summary table Clinical Question 21. What are the late effects of treatment of childhood DTC?						
Study (n=8)	**No. of participants**	**Age at diagnosis (yrs)**	**Follow-up time (yrs)**	**Late effect(s)**	**Objectives/definitions**	**Main outcome**
Nies (2020) 32079487	56	Median 16.0 (range 13.7-17.5)	Median 15.4 (IQR 8.3-24.7)	Fertility	Reproductive characteristics (pregnancies, live births, AMH levels (µg/L) *(versus control group)*	45.5% (≥18 yrs) reported ≥1 pregnancies, total n=64 pregnancies reported (2.6 pregnancies per survivor who reported to ever having been pregnant), 45 live births, 10.9% visited a fertility doctor or clinic. No differences in AMH levels between DTC survivors and comparison group [2.0 (IQR 1.0-3.7) µg/L vs 1.6 (IQR 0.6-3.1) µg/L, respectively, p=0.244]. No major abnormalities in reproductive characteristics nor in predictors of ovarian failure in female survivors of DTC who received I-131 treatment during childhood.
Nies (2018) 29254931	39	Mean 15.6 (range 12.0-18.7)	Median 10.7 (5.0-23.3)	Quality of life	Achievement of psychosocial milestones (social, autonomy, and psychosexual development) measured with course of life questionnaire (CoLQ) *(versus control group)*	CoLQ did not significantly differ between survivors of childhood DTC and two non-affected groups (non-affected with cancer and other CCS) Survivors of childhood DTC scored significantly higher on social development than other CCS, but scores were similar on autonomy and psychosexual developmental scales.
Nies (2017) 28001468	67	Median 15.8 (range 7.9-18.8)	Median 17.8 (5.0-44.7)	Quality of life	Short-Form 36 (SF-36) Multidimensional Fatigue Inventory 20 (MFI-20) Hospital Anxiety and Depression Scale (HADS) Thyroid cancer-specific HRQoL (THYRCA-QoL) *(versus control group)*	On most QoL subscales, scores of survivors and controls did not differ significantly. SF-36: more physical problems (P = 0.031), more role limitations due to physical problems (P = 0.021) MFI-20: more mental fatigue (P = 0.016) HADS: no differences Treatment with a higher cumulative dose of 131-I was associated with more complaints of headache (P = 0.006).
Klein Hesselink (2017) 29132262	66	Median 15.9 (range 7.9-18.9)	Median 17 (5-43)	Cardiac dysfunction	Echocardiography 24-hour Holter electrocardiography Plasma biomarkers (N-terminal probrain natriuretic peptide, high-sensitive troponin-T, galectin-3)	Mean of septal and lateral early diastolic tissue velocity (mean 14.5 versus 15.8 cm/s, P= 0.006, survivors vs controls, respectively) Diastolic dysfunction in n=14 (21.2%) asymptomatic survivors All survivors showed sinus rhythm; AF was not observed. In survivors, biomarkers were not associated with diastolic dysfunction

					(versus control group)	
Monteiro de Barros (2016) 26056020	17	Mean 12.6 ± 2.2 *(age start TSH suppression therapy)*	14.2 ± 7.2 *(duration TSH suppression therapy)*	Bone mineral density	Dual-energy X-ray absorptiometry (DXA) HR-pQCT *(versus control group)*	No differences were found between patients and controls with respects to BMD and Z scores at any site evaluated by DXA. No differences were found in the bone microstructure parameters evaluated by HR-pQCT
Leonova (2014) 25374130	124 (females only)	Mean 14.04 ± 5.03	Mean 11.50 ± 4.14	Bone mineral density	Calcium-D3 supplementation and TSH suppressive therapy on bone mineral density (BMD)	No Calcium-D3 supplementation vs Calcium D3 supplementation (mean ± SD) TSH: 0.69 ±1.51 vs 0.62 ±1.67 (p=0.08) FT4: 21.88 ±6.57 vs 23.32 ±6.1 (p=0.16) Parathormone: 28.74 ±10.77 vs 11.66 ±9.93 (p=0.0001) Ca: 2.33 ±0.22 vs 2.03 ±0.28 (p=0.0001) Ca2+: 1.19 ±0.09 vs 1.06 ±0.16 (p=0.0001) 25(OH)-vitamin D: 37.57 ±9.65 vs 45.17 ±11.81 (p=0.050) Phosphate: 1.23 ±0.19 vs 1.64 ±0.32 (p=0.0001) Lumbar spine BMD (L1-L4) (g/cm2): 1.21 ±0.16 vs 1.34 ±0.18 (p=0.0001) Lumbar spine T-score: 0.06 ±1.13 vs 1.15 ±1.41 (p=0.0001) Lumbar spine Z-score: 0.27 ±1.0 vs 1.32 ±1.37 (p=0.0001) Total proximal femur BMD (g/cm2): 1.03 ±0.13 vs 1.14 ±0.32 (p=0.0001) Proximal femur T-score: 0.27 ±1.06 vs 1.32 ±1.14 (p=0.0001) Proximal femur Z-score: 0.39 ±0.96 vs 1.42 ±1.14 (p=0.0001) *Calcium-D3 medication has a beneficial effect on BMD* *TSH-suppressive therapy does not affect BMD in women treated for DTC at young age, at least after 10 years of follow-up.*
Selvakumar (2018) 30504138	65	15 (IQR 13-17)	Median 11 (IQR 6-22)	Salivary gland dysfunction Xerostomia	Unstimulated whole saliva flow ≤0.2mL/min and/or a stimulated whole saliva flow ≤0.7 mL/min Xerostomia related complaints were evaluated using the XI questionnaire	Salivary dysfunction: n=30 (47.6%) Xerostomia (moderate to severe): n=22 (35.5%) Stimulated salivary secretion was lower and the severity of xerostomia complaints higher in patients treated with higher cumulative ^{131}I activity
Albano (2017) 28436606	105		Late effects: at least a few weeks after hospital discharge	Salivary gland dysfunction BM suppression	BM suppression defined as significant reduction in the number of leukocytes, erythrocytes, and platelets (according CTCAE)	N=12 children ≥ 1 late complication (n=20 complications) Permanent salivary dysfunction: n=2 Permanent BM suppression: n=2 Pulmonary fibrosis: n=5

				Pulmonary fibrosis Second cancers Fertility	Fertility defined as all problems which determine the incapacity to fulfill pregnancy after a reasonable time of sexual intercourse with no contraceptive measures taken No definitions with regards to registered side effects as salivary gland dysfunction and pulmonary fibrosis	Second cancers: n=4 Fertility alterations: n=5 Late events, except fertility alterations, were correlated with the number of therapies and cumulative activities of I-131.

GRADE assessment:	
Study design:	+4 Observational evidence for a diagnostic question
Study limitations:	0 Low risk of bias
Consistency:	0 No important inconsistency between studies
Directness:	0 Population of interest
Precision:	-1 Relatively few patients and few events
Publication bias:	0 Unlikely
Effect size:	0 NA
Dose-response:	0 NA
Plausible confounders	0 No adjustment

Quality of evidence: ⊕⊕⊕⊖ (moderate quality)
Conclusion: In these studies, several potential late effects in survivors of DTC are investigated.
Cardiac dysfunction: In 21.2% of asymptomatic survivors diastolic dysfunction was found (1 study).
Salivary gland dysfunction: In 1.9-47.6% and 35.5% of the DTC survivors salivary dysfunction and xerostomia were found, respectively (2 studies)
Quality of life: No differences were found in the course of life questionnaire between DTC survivors and two non-affected groups (non-affected with cancer and other CCS). Also on most quality of life subscales, score of DTC survivors and controls did not differ significantly. However, more physical problems, more role limitations due to physical problems and more mental fatigue was described by DTC survivors (2 studies).
Bone mineral density: No differences were found with respects to BMD and Z scores at any site evaluated by DXA and in bone microstructure parameters between DTC survivors and controls. However, Calcium-D3 medication has a beneficial effect on BMD. TSH-suppressive therapy does not affect BMD in women treated for DTC at young age, at least after 10 years of follow-up (2 studies)
Female fertility: No major abnormalities in reproductive characteristics nor in predictors of ovarian failure in female survivors of DTC who received I-131 treatment during childhood were reported (1 study)

Abbreviations: AMH, anti-mullerian hormone; CTCAE, common terminology criteria for adverse events; IQR, interquartile range; yrs, year; HRQoL, health related quality of life; AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias

Summary table Clinical question 22.
Is presentation, outcome or disease course of DTC in children with genetic syndromes different than in children without genetic syndromes for which treatment or follow up should be adjusted?

Study (n=2)	No. of participants	Age patients at diagnosis DTC	Genetic syndrome	Cancer type and behavior	Genetic analysis	Conclusion papers	Suggestion therapy adjustment
Van der Tuin (2019) 30260442	10	Mean 14.7±6.2 years	DICER1	10/10 thyroid specimens showed diffuse nodular hyperplasia with multiple, discrete, well-circumscribed, and occasionally encapsulated nodules. No infiltrative growth, extra thyroidal extension, vascular invasion, or lymph node metastasis	9/10 DICER1-related DTCs lacked well-known oncogenic driver DNA variants and gene rearrangements.	On the basis of our clinical, histological, and molecular data, we consider that most DICER1-related DTCs form a low-risk subgroup.	Authors: Radioiodine treatment may be unnecessary given the patients' ages and the tumors' low propensity for metastases.
Jonker & Lebbink (2020) 33088791	27 (all cases of DTC identified in the literature in PHTS patients)	Median 12 (range 4-17)	PTHS	52% FTC 2/27 metastatic DTC 2/27 recurrence	*PTEN* mutation	No reports of more aggressive behavior of DTC, defined as increased risk for metastasized disease at diagnosis, recurrence, or increased morbidity or mortality when compared to children with sporadic DTC, could be found.	

GRADE assessment:	
Study design:	*+2 Observational evidence for a intervention question*
Study limitations:	*-1 Limitations (small number of patients)*
Consistency:	*0 NA*
Directness:	*0 No indirectness*
Precision:	*0 No important imprecision*
Publication bias:	*0 Unlikely*
Effect size:	*0 NA*
Dose-response:	*0 NA*
Plausible confounders	*0 NA*

Quality of evidence: ⊕⊖⊖⊖ (very low)
Conclusion:
DICER1: Histological characteristics and molecular data may show signs of less aggressive tumor behavior in these children. *(1 study)*
PHTS: DTC in pediatric PHTS patients does not seem to be more aggressive than sporadic DTC. *(1 study)*

Abbreviations: DTC, differentiated thyroid carcinoma; AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias

Summary table Clinical question 23. **Is presentation, outcome or disease course of DTC in children with a history of radiation exposure different than in children without a history of radiation exposure for which treatment or follow-up should be adjusted?**				
Study (n=4)	**No. of participants**	**Cohort**	**Aim**	**Outcome**
Clement & Lebbink (2020) 32449692	31 *(only 9/31 were ≤18 years of age at diagnosis of DTC)*	CCS (18/31 (58.1%) had received RT to a field including the thyroid gland)	To evaluate the mode of detection, presentation, treatment and outcome of subsequent DTC among CCS	CCS with subsequent DTC tended to have on average smaller tumors (1.9 vs 2.4 cm, respectively, (P = 0.051), and more often bilateral (5/25 (60.0%) vs 28/92 (30.4%), P = 0.024). There were no significant differences in the occurrence of surgical complications, recurrence rate or disease-related death.
Sassolas (2013) 23286372	24 *(only 16/24 were ≤20 years of age at diagnosis of DTC)*	CCS (All radiation exposed (RAD))	To evaluate clinical presentation of thyroid cancers in patients with previous external radiation exposure (RAD), and to compare the evolution of such patients to that of nonexposed patients (matched-controls).	The mean tumor size (largest diameter) was higher in controls (p<0.05). More microcarcinomas were found in the CCS (p=0.05). There was no difference in the proportions of multifocality, ETE, and LNM. No difference in the risk of cervical recurrence between the RAD group and controls (low and high risk)
Pacini (1997) 9360507	472	Chernobyl cohort *(compared to cohort Italy/France)*	To compare clinical and epidemiological features of children with thyroid carcinoma in the Chernobyl region (radiation exposed) to controls	Significant higher proportion of follicular carcinomas in cases compared to controls (p=0.0001) More ETE and LNM in cases (49.1%, p=0.0001; and 64.6%, p= 0.002, respectively) with respect to controls (24.9% and 53.9%, respectively).
Bogdanova (2019) 31569930	187 *4-14 yrs (n=121)* *15-18 yrs (n=66)*	Chernobyl cohort (4-18 yrs) 4-14 yrs: OCh (+): n=10 (8.3%) OCh (-): n=111 (91.7%) 15-18 yrs: OCh (+): n=4 OCh (-): n=62	Histopathological characteristics of potentially radiogenic PTC depending on oncocytic changes availability in tumor cells (oncocytic changes (OCh): defined as oncyphilic/Hurtle cell metaplasia in tumor cells)	4-14 yrs: significant more solid-trabecular characteristics in OCh (+) vs OCh (-) tumors (100% vs 55.0%, p<0.001) *Difference not found in age group 15-18 yrs* No significant differences in ETE, multifocality, lymphatic/vascular invasion, LNM, distant lung metastases between Och(+) and Och(-) tumors 4-14 yrs: Significant more chronic thyroiditis in patients with OCh (+) vs OCh (-) tumors (60% vs 8.1%, p<0.001)

				Difference not found in age group 15-18 yrs No significant differences in recurrence of regional metastases or additional non-thyroidal cancer.

GRADE assessment:	
Study design:	*+2 Observational evidence for a intervention question*
Study limitations:	*-1 Limitations (small number of patients)*
Consistency:	*-1 Inconsistency*
Directness:	*0 No important indirectness*
Precision:	*0 No important imprecision*
Publication bias:	*0 Unlikely*
Effect size:	*0 NA*
Dose-response:	*0 NA*
Plausible confounders	*0 NA*

Quality of evidence: ⊕⊖⊖⊖ (very low)
Conclusion:
Presentation:
CCS with subsequent DTC tended to have on average smaller tumors and might have more often bilateral disease (2 studies)
Disease course:
Inconsistent findings about difference in tumor characteristics (ETE and LNM) were reported. ETE and LMN might be more frequently found in radiation induced thyroid tumors in children diagnosed in the Chernobyl region *(2 studies)*
Outcome:
No significant differences were found between CCS with subsequent DTC and controls in the occurrence of surgical complications, recurrence rate or disease-related death. *(2 studies)*

Abbreviations: DTC, differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; CCS, childhood cancer survivors; OCh, oncocytic changes; ETE, extra thyroidal extension; LNM, lymph node metastases; RAD, external radiation exposure; RT, radiotherapy; AB, attrition bias; CI, confidence interval; CF, confounding; DB, detection bias; SB, selection bias