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

Appendix A. Clinical questions

Diagnostics/staging

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?	
P (Population):	Children diagnosed with a thyroid nodule
I (etiologic/risk factor):	Thyroid ultrasound characteristics of thyroid cancer; i.e. solid composition,
C (comparison):	Thyroid ultrasound characteristics of a benign nodule
O (outcome):	Ultrasound characteristics compared to histopathological result
T (type of question):	Etiology
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N=20
Type of search:	Extensive systematic search (PubMed)

Clinical question 2. What is the sensitivity/specificity of different suspicious US findings for presence of DTC metastasis to a lymph node?	
P (Population):	Children or young adolescents diagnosed with a thyroid nodule
I (etiologic/risk factor):	Suspicious thyroid ultrasound findings in a child or young adolescent with lymph node metastases
C (comparison):	Thyroid ultrasound findings in a child or young adolescent without lymph node metastases
O (outcome):	Study describing sensitivity/ specificity for US findings of a suspicious lymph node to be DTC
T (type of question):	Diagnostic
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N=20
Type of search:	Extensive systematic search (PubMed)

Clinical question 3. Will molecular testing in a FNB specimen of a thyroid nodule in a child help you to distinguish from a benign nodule?	
P (Population):	Children diagnosed with a thyroid nodule(s) by ultrasound with an indeterminate FNA result (AUS, SFN, SFM)
I (etiologic/risk factor):	Genetic testing of FNA sample for specific mutation (e.g. BRAF 600E, NRAS, RET/PTC and cancer predisposition syndromes such as PTEN, DICER-1)
C (comparison):	Benign thyroid nodule
O (outcome):	Genetic analyses in FNA specimen related to histopathology
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N=20
Type of search:	Extensive systematic search (PubMed)

Clinical question 4. Does genetic testing in thyroid carcinoma tissue in a child or young adolescent alter its management?	
P (Population):	Histopathological tissue of children with thyroid carcinoma
I (etiologic/risk factor):	Genetic testing for specific mutations (e.g. BRAF 600E,NRAS, RET/PTC, and/or cancer predisposition syndromes such as PTEN , DICER-1)
C (comparison):	No genetic testing
O (outcome):	Genetic analyses in thyroid tissue related to outcome of disease
T (type of question):	Genetics
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N=20
Type of search:	Extensive systematic search (PubMed)

Clinical question 5. What is sensitivity of the different imaging modalities for presence of pre-operative metastasis?	
P (Population):	Children or young adolescents with DTC, pre-operatively
I (etiologic/risk factor):	Ultrasound/radio iodine scan/MRI/other
C (comparison):	-
O (outcome):	Study describing sensitivity/ specificity for an imaging modality to determine the presence of metastasis (pre operatively)
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 6. Are histopathological criteria related to distant/any metastases?	
P (Population):	Post thyroidectomy thyroid cancer children or young adolescents
I (etiologic/risk factor):	Histopathological criteria: size, capsular invasiveness, vascular ingrowth, surrounding tissue
C (comparison):	-
O (outcome):	Histopathological features related to postoperative staging
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 7. Which imaging modality is most sensitive for the presence of DTC, post-operatively?	
P (Population):	Post thyroidectomy thyroid cancer children or young adolescents
I (etiologic/risk factor):	Ultrasound/ radio iodine / CT scan / FDG-PET/other
C (comparison):	-
O (outcome):	Study describing sensitivity/ specificity for an imaging modality to determine the presence of metastasis (post operatively)
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N=20
Type of search:	Extensive systematic search (PubMed)

Clinical question 8. What is the diagnostic value of serum calcitonin in a child with a thyroid nodule?	
P (Population):	Children or young adolescents diagnosed with a thyroid nodule
I (etiologic/risk factor):	Calcitonin
C (comparison):	-
O (outcome):	Sensitivity / specificity of calcitonin to for presence of medullary thyroid carcinoma
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 9. What is the prevalence of clinical non-clinical relevant thyroid nodules in a child?	
P (Population):	Children or young adolescents diagnosed with a thyroid nodule, incidental finding, no suspicious features
I (etiologic/risk factor):	Wait-and-see
C (comparison):	Surgical removal
O (outcome):	Study describing prevalence non clinical relevant thyroid nodules in a child/prevalence study incidentaloma child and outcome /follow-up study
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N=20
Type of search:	Extensive systematic search (PubMed)

Treatment

Clinical question 10.1 What is the difference in outcome of DTC in children treated with a total thyroidectomy versus hemi thyroidectomy?	
P (Population):	Children or young adolescents diagnosed with thyroid carcinoma, irrespective of stage
I (intervention):	Total thyroidectomy
C (comparison):	Hemi thyroidectomy
O (outcome):	Rates of complete remission (comparing total vs hemithyroidectomy) OR Complications/complication rates
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 10.2 What is the difference in outcome of DTC in children treated with a total thyroidectomy versus subtotal thyroidectomy?	
P (Population):	Children or young adolescents diagnosed with thyroid carcinoma, irrespective of stage
I (intervention):	Subtotal thyroidectomy
C (comparison):	Total thyroidectomy
O (outcome):	Rates of complete remission (comparing subtotal vs total thyroidectomy) OR Complications/complication rates
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 11.1 What is the difference in outcome of DTC in children with microcarcinoma (<1 cm) treated with nodule excision/resection versus subtotal resection?	
P (Population):	Children or young adolescents diagnosed with micro carcinoma
I (intervention):	Nodule excision/resection/subtotal resection
C (comparison):	Hemithyroidectomy
O (outcome):	Rates of complete remission (comparing nodule excision vs subtotal resection) OR Complications/complication rates
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 11.2 What is the difference in outcome of DTC in children with microcarcinoma (<1 cm) treated with total thyroidectomy versus hemi thyroidectomy?	
P (Population):	Children or young adolescents diagnosed with micro carcinoma
I (intervention):	Total thyroidectomy
C (comparison):	Hemithyroidectomy
O (outcome):	Rates of complete remission (comparing total vs hemithyroidectomy) OR Complications/complication rates
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

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?	
P (Population):	Children or young adolescents diagnosed with DTC
I (intervention):	Central neck dissection
C (comparison):	No central neck dissection
O (outcome):	Rates of complete remission (comparing lateral and/or central neck dissection vs no dissection) OR Complications/complication rates
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 13. Is outcome of micro carcinoma worse in children not treated with I-131 versus not treated with I-131?	
P (Population):	Post thyroidectomy thyroid micro carcinoma children
I (intervention):	I-131 therapy
C (comparison):	No I-131 therapy
O (outcome):	Thyroid cancer recurrence/thyroid cancer related mortality or morbidity (after treatment with I-131)
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 14. Is the most optimal dose effect curve of radio iodine with least side effects calculated by body weight/fixed dose or dosimetry?	
P (Population):	Post thyroidectomy thyroid cancer children
I (intervention):	Fixed/body-weight adapted I-131 activity
C (comparison):	I-131 activity based on dosimetry
O (outcome):	Uptake of I-131 in thyroid bed
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children or young adolescents <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 15. Is rhTSH effective and safe in children during treatment with I-131?	
P (Population):	Post thyroidectomy thyroid cancer children or young adolescents
I (intervention):	rhTSH
C (comparison):	Withdrawal of LT4
O (outcome):	Complaints, adverse effects, sensitivity of Tg measurement with rhTSH versus withdrawal TSH, efficacy after treatment (outcome: % complete remission after I-131, uptake of I-131)
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children or young adolescents <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 16. What is the difference in outcome in children with measurable but not rising Tg after treatment for DTC (incomplete biochemical response with I-131 versus a wait-and-see approach?	
P (Population):	Persistent thyroid cancer in children
I (intervention):	RAI
C (comparison):	Wait-and-see
O (outcome):	Thyroid cancer recurrence / thyroid cancer related morbidity or mortality
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children or young adolescents <21 years of age Study population of at least N=
Type of search:	Extensive systematic search (PubMed)

Clinical question 17. What is the difference in outcome in children or young adolescents with recurrent disease/progressive thyroid cancer treated with additional RAI/surgery/other versus a wait-and-see approach?	
P (Population):	Recurrent disease/progressive thyroid cancer or young adolescents in children
I (intervention):	Additional RAI/surgery/ other
C (comparison):	Wait-and-see
O (outcome):	Thyroid cancer related morbidity or mortality
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 18. What is the difference in outcome of DTC in children treated with different treatment than surgery and I-131?	
P (Population):	Children or young adolescents with differentiated thyroid cancer
I (intervention):	TKI, BRAF inhibitors, external beam radiation, (all other treatments but surgery or I-131)
C (comparison):	-
O (outcome):	Thyroid cancer related morbidity or mortality
T (type of question):	Treatment
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age
Type of search:	Extensive systematic search (PubMed)

Follow up

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?	
P (Population):	Children or young adolescents after treatment for DTC
I (intervention):	Neck ultrasound and Tg measurement
C (comparison):	Neck palpation for lymphadenopathy and Tg measurement
O (outcome):	Study describing sensitivity/ specificity for US findings for recurrent DTC (compared to neck palpation for lymphadenopathy and Tg measurement) OR Outcome of disease/% recurrences in patients with follow up using ultrasound and Tg measurement
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N=20
Type of search:	Extensive systematic search (PubMed)

Clinical question 20. What is the sensitivity of I-124 or I-123 for DTC/thyroid rest or recurrent disease in follow up of children who have been treated for DTC?	
P (Population):	Children or young adolescents who have been treated for DTC and need follow up
I (etiologic/risk factor)	I-124 or I-123 and Tg measurement
C (comparison):	Ultrasound neck and Tg measurement
O (outcome):	Sensitivity of I-124/I-123 for DTC/thyroid rest / recurrent disease
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)

Clinical question 21. What are the late effects of treatment of DTC? (Cardiac late effects, salivary glands, psychosocial, bone, female fertility)	
P (Population):	Children or young adolescents treated for DTC
I (etiologic/risk factor)	-
C (comparison):	-
O (outcome):	Thyroid cancer related cardiac, salivary gland, female fertility, bone or psychosocial morbidity/mortality
T (type of question):	Diagnosis
S (study design):	Cohort study
Inclusion/exclusion criteria studies:	English language Children or young adolescents <21 years of age Study population of at least N=20
Type of search:	Extensive systematic search (PubMed)

Clinical question 22. Is presentation, outcome and/or disease course of DTC in children or young adolescents with genetic syndromes different than in children without genetic syndromes for which treatment and/or follow up should be adjusted?	
P (Population):	Children or young adolescents treated for DTC
I (etiologic/risk factor)	Genetic syndromes (Cowden, DICER, Li Fraumeni, Lynch syndrome, FAP, Carney complex).
C (comparison):	Patients without genetic syndromes
O (outcome):	Thyroid cancer recurrence / thyroid cancer related mortality
T (type of question):	Etiology
S (study design):	Cohort study (multi-variate analysis)
Inclusion/exclusion criteria studies:	English language Children <21 years of age
Type of search:	Extensive systematic search (PubMed)

Clinical question 23. Is presentation, outcome and/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 and/or follow up should be adjusted?	
P (Population):	Children or young adolescents treated for DTC
I (etiologic/risk factor)	History of radiation exposure
C (comparison):	Patients with no history of radiation exposure
O (outcome):	Thyroid cancer recurrence/thyroid cancer related mortality
T (type of question):	Etiology
S (study design):	Cohort study (multi-variate analysis)
Inclusion/exclusion criteria studies:	English language Children <21 years of age Study population of at least N= 20
Type of search:	Extensive systematic search (PubMed)