Evidence tables

Clinical question 1. Is there an increased risk for DTC after therapeutic ^{131}I-MIBG only in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Clement SC et al. Long-term efficacy of current thyroid prophylaxis and future perspectives on thyroid protection during ^{131}I-metaiodobenzylguanidine treatment in children with neuroblastoma. Eur J Nucl Med Nucl Imaging. 2015; 42:706-715				
Study design: Retrospective cohort study **Treatment era:** 1999-2012 **Years of follow-up:** Median: 9.0 (1.9-13.8) **Lost to follow-up:** N=0	**Study population:** N=24 **Gender:** Male: 11/24 (46%) Female:13/24(54%) **Age at primary cancer diagnosis (yrs):** NR **Age at first ^{131}I-MIBG (yrs):** Median: 1.3 (range 0.1-5.2) **Age at follow-up time (yrs):** Median: 10.2 (range 4.6-15.0) **EBRT on the field including the thyroid gland:** N=0 **Average ^{131}I-MIBG dose:** Median: 270 (range 50-400 mCi) **Average number of ^{131}I-MIBG treatments:** Median 2.0 (range 1.0-5.0)	**Primary outcome:** To investigate the long-term efficacy of current thyroid prophylaxis, to explore the relationship between thyroid dysfunction and thyroid volume after exposure to ^{131}I-MIBG and to evaluate the possible negative effects of ^{131}I − on the parathyroid glands. **Inclusion criteria:** Patients who (1) were treated for NBL with^{131}I-MIBG at Emma Children's Hospital, during the period August 1999 through October 2012; (2) were given DBR prophylaxis during ^{123}/ ^{131}I-MIBG administration; (3) had a follow-up of more than 1 year after the first administration of ^{131}I-MIBG; and (4) had stable disease or were in remission after completion of therapy at the time of follow-up **Exclusion criteria:** Patients who had been treated with external radiotherapy to a field involving the (para)thyroid gland(s). **Outcome assessment:** • Patients received thyroxine (T4), methimazole and potassium iodide as thyroid protection (DBR prophylaxis). • All MIBG images were evaluated for thyroid uptake of radio-iodine. • In all patients (para)thyroid function was evaluated and ultrasound investigation of the (para)thyroid gland(s) was performed.	**Incidence thyroid carcinoma:** • N = 1/24 (4.2%) ○ Papillary thyroid carcinoma N=1 **Latency time thyroid carcinoma:** • 5.6 years	
Conclusion: • In a study cohort of 24 neuroblastoma survivors (median follow-up time 9.0 years) treated with ^{131}I-MIBG 1 survivor developed DTC after primary cancer diagnosis.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; EBRT: external beam radiotherapy; NR: not reported; MIBG: metaiodobenzylguanidine; mCi:millicurie; DBR: dilute, block, replace

Clinical question 1. Is there an increased risk for DTC after therapeutic ^{131}I-MIBG only in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Clement SC et al. Long-Term Follow-Up of the Thyroid Gland After Treatment With 131I-Metaiodobenzylguanidine in Children With Neuroblastoma: Importance of Continuous Surveillance. Pediatr Blood Cancer. 2013;60:1833-1838				
Study design: Retrospective cohort study **Treatment era:** 1989-1999 **Years of follow-up:** Median: 15.5 (11.2-20.2) **Lost to follow-up:** N=3	**Study population:** N=16 **Gender:** Male: 7/16 (43.8%) Female: 9/16 (56.3%) **Age at primary cancer diagnosis (yrs):** Median: 1.1 (0.2-4.7) **Age at first ^{131}I-MIBG (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT on the field including the thyroid gland:** N=0 **Average ^{131}I-MIBG dose:** Median: 305 mCi (range 89-503) **Average number of ^{131}I-MIBG treatments:** Median 4.0 (range 1.0-9.0)	**Primary outcome:** To investigate if the incidence and severity of thyroid damage increases in time. **Inclusion criteria:** All children treated for high-risk NBL (stages II–IVs) with ^{131}I-MIBG in the period 1989-1999 in Emma Children's Hospital **Exclusion criteria:** Patients who had been treated with external radiotherapy to a field involving the thyroid gland. **Outcome assessment:** • During exposure to ^{131}I-MIBG, patients received 100 mg KI per day as thyroid protection. • All MIBG images were evaluated for thyroid uptake of radio-iodine. • In all patients thyroid function was evaluated and ultrasound investigation of the thyroid gland was performed.	**Incidence thyroid carcinoma:** • N = 2/16 (12.5%) ○ Papillary thyroid carcinoma N=2 **Latency time thyroid carcinoma:** • 12.6-13.5 years	
Conclusion: • In a study cohort of 16 neuroblastoma survivors (median follow-up time 15.5 years) treated with ^{131}I-MIBG 2 survivors developed DTC after primary cancer diagnosis.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiotherapy; mCi:millicurie; MIBG: meta-iodobenzylguanidine; KI: potassium-iodide

Clinical question 2. Is there an increased risk for DTC after chemotherapy only in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Veiga LHS et al. A pooled analysis of thyroid cancer incidence following radiotherapy for childhood cancer. Radiat Res. 2012; 178: 365-376				

Study design:
Pooled analysis
 	
Treatment era:
1936-2000
 	
Years of follow-up:
Range: 3.0-55.6
 	
Lost to follow-up:
NR
	Study population:
	N=16,757
	
	Gender:
	NR
	
	Age at primary cancer diagnosis (yrs):
	Range: 0.1-20.9
	
	Age at EBRT (yrs):
	NR
	
	Age thyroid cancer diagnosis (yrs):
	Range: 3.7-46.2
	
	EBRT:
	N=13,099
	
	Average cumulative dose:
	NR
	
	Average thyroid dose (Gy):
	Range: 0.0007-67.3
	
	Average number of EBRT:
	NR
		Primary outcome:
		To evaluate the shape of the radiation dose-reponse at high doses and to investigate the relationship between radiotherapy and chemotherapy on the risk of thyroid cancer.
		
		Inclusion criteria:
		Childhood cancer studies of radiation-related thyroid cancer, including at least 10 thyroid cancer cases or more that were diagnosed as a second primary malignancy and with individual estimates of thyroid radiation dose.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• Medline was searched, references were reviewed and colleagues were queried to identify all relevant evidence.
		• Four studies were included (2 cohort studies and 2 case-control, CCSS-US, CCSS-Fr/UK, LESG, CCSS-Nordic).
		• All thyroid cancer cases were microscopically confirmed.
		
		Statistical analysis:
		• Pooled analyses combining cohort and case control data
		• Poisson regression was used to model disease risk.
			Incidence thyroid carcinoma (total group):
			• N =187/16,757 (0.011%)
			
			Latency time thyroid carcinoma:
			• NR
			
			Relative risk (RR) of thyroid carcinoma and use of chemotherapy by categories of thyroid radiation dose (0 Gy = chemotherapy alone), adjusted for study, gender, attained age, type of first cancer and year of birth (multivariable logistic regression):
			• Chemotherapy
			  ○ No: reference
			  ○ Yes: RR 2.4 (95% CI 0.5-12.3)
			• Alkylating agents
			  ○ No: reference
			  ○ Yes: RR 3.2 (95% CI 0.8-12.8)
			• Anthracyclines
			  ○ No: reference
			  ○ Yes: RR 4.5 (95% CI 1.3-15.7)*
			• Bleomycin
			  ○ No: reference
			  ○ Yes: RR 3.1 (95% CI 0.9-10.9)	

Conclusion: • In CAYAC survivors treatment with anthracyclines was significantly associated with an increased risk for the development of DTC compared to survivors who did not receive anthracyclines, in multiple regression analysis (RR 4.5 (95% CI 1.3-15.7). • Chemotherapy only, alkylating agents and bleomycine were not significantly associated with the development of DTC in CAYAC survivors, in multiple regression analysis.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiation treatment; Gy: gray; RR: relative risk; CI: confidence interval
* Significant risk factor

Clinical question 2. Is there an increased risk for DTC after chemotherapy only in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Taylor AJ et al. Risk of thyroid cancer in survivors of childhood cancer: results from the British childhood cancer survivors study. Int J Cancer. 2009;125:2400-2405				
Study design: Retrospective cohort study **Treatment era:** 1940-1991 **Years of follow-up:** Median: 17.4 years per survivor from 5 year survival **Lost to follow-up:** N=2728 (21%)	**Study population:** N=10,483 **Gender:** NR **Age at primary cancer diagnosis (yrs):** NR **Age at transplantation (yrs):** NR **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** NR **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To determine the risk of thyroid second malignant neoplasms in the Britisch Childhood Cancer Survivor Study. **Inclusion criteria:** Patients with childhood cancer, at age less than 15 years, between 1940 and 1991, surviving 5 years or more from diagnosis. **Exclusion criteria:** NR **Outcome assessment:** • All survivors aged at least 16 years who are alive and contactable through their general practitioner have been sent a questionnaire. • Information from questionnaires was complemented by "flagging" at the National Health Service central registers. • SMNs of the thyroid were verified pathologically either by a histopathology reports or by clinical correspondence containing a histopathology summary. **Statistical analysis:** • Multivariate Poisson regression models with the log of the expected umber of thyroid cancers as offset were employed to derive relative risks (RR).	**Incidence thyroid carcinoma:** • N=50/10483 (0.0047%) o Papillary carcinoma (N=31) o Follicular carcinoma (N=15) o Other histology (N=4) **Latency time thyroid carcinoma:** • Median: 15.3 years (4.2-29.7 years) **Risk factors for the incidence of thyroid carcinoma (multivariable logistic regression):** • Sex: o Male: reference o Female: RR 0.6 (95% CI 0.3-1.2) • Age at diagnosis: o 0-4 yrs: reference o 5-9 yrs: RR 1.0 (95% CI 0.4-2.2) o 10-14 yrs: RR 0.5 (95% CI 0.2-1.3) • Treatment era: o < 1970: reference o 1970-1979: RR 0.9 (95% CI 0.4-2.4) o 1980-1991: RR 1.2 (95% CI 0.4-3.6) • Follow-up period: o 0-9 yrs: reference o 10-19 yrs: RR 0.8 (95% CI 0.4-1.7) o 20-29 yrs: RR 0.4 (95% CI 0.1-1.3) o ≥ 30 yrs: RR 0.6 (95% CI 0.2-2.2) • Radiotherapy: o No: reference o Yes: RR 4.6 (95% CI 1.4-15.1)* • Chemotherapy: o No: reference o Yes: RR 0.8 (95% CI 0.3-2.1) • Type of primary cancer diagnosis: o Leukemia: reference o Hodgkin's disease: RR 3.3 (95% CI 1.1-10.1)* o NHL: RR 3.4 (95% CI 1.1-10.7)* o CNS primary: RR 0.7 (95% CI 0.2-2.5) o Other: RR 0.5 995% CI 0.2-1.5	

Conclusion:

- In CAYAC survivors, radiotherapy was significantly associated with an increased risk for the development of DTC compared to survivors who did not receive radiotherapy treatment, in multiple regression analysis (RR 4.6 (95% CI 1.4-15.1).
- In CAYAC survivors, Hodgkin's disease was significantly associated with an increased risk for the development of DTC compared to survivors who were diagnosed with leukemia as primary cancer diagnosis, in multiple regression analysis (RR 3.3 (95% CI 1.1-10.1).
- In CAYAC survivors, non-Hodgkin lymphoma was significantly associated with an increased risk for the development of DTC compared to survivors who were diagnosed with leukemia as primary cancer diagnosis, in multiple regression analysis (RR 3.4 (95% CI 1.1-10.7).
- Sex, age at diagnosis, treatment era, follow-up period and chemotherapy treatment were not significantly associated with the development of DTC

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiation treatment; Gy: gray; RR: relative risk; CI: confidence interval; NHL: non-Hodgkin lymphoma; CNS: central nervous system

* Significant risk factor

<u>Clinical question 3</u>. What is the shape of the dose-response curve for cumulative radiation dose and what are the roles of dose rate and fraction size in determining risk for DTC in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Veiga LHS et al. A pooled analysis of thyroid cancer incidence following radiotherapy for childhood cancer. Radiat Res. 2012; 178: 365-376				
Study design: Pooled analysis **Treatment era:** 1936-2000 **Years of follow-up:** Range: 3.0-55.6 **Lost to follow-up:** NR	**Study population:** N=16,757 **Gender:** NR 144,796 PY male 130,476 PY female **Age at primary cancer diagnosis (yrs):** Range: 0.1-20.9 **Age at EBRT (yrs):** NR **Age thyroid cancer diagnosis (yrs):** Range: 3.7-46.2 **EBRT:** N=13,099 **Average cumulative dose:** NR **Average thyroid dose (Gy):** Range: 0.0007-67.3 **Number of fractions:** 88% one treatment in 6 months (crude definition)	**Primary outcome:** To evaluate the shape of the radiation dose-reponse at high doses and to investigate the relationship between radiotherapy and chemotherapy on the risk of thyroid cancer. **Inclusion criteria:** Childhood cancer studies of radiation-related thyroid cancer, including at least 10 thyroid cancer cases or more that were diagnosed as a second primary malignancy and with individual estimates of thyroid radiation dose. **Exclusion criteria:** NR **Outcome assessment:** • Medline was searched, references were reviewed and colleagues were queried to identify all relevant evidence. • Four studies were included (2 cohort studies and 2 case-control, CCSS-US, CCSS-Fr/UK, LESG, CCSS-Nordic). • All thyroid cancer cases were microscopically confirmed. **Statistical analysis:** • Pooled analyses combining cohort and case control data • Standard linear excess modelling in Poisson (Epicure) with formal evaluation of effect modification of linear (3 studies) or linear-quadratic dose response terms (US CCSS only)	**Incidence thyroid carcinoma (total group):** • N =187/16,757 (0.011%) **Latency time thyroid carcinoma:** • NR **Dose-response curve for cumulative radiation dose:** Non-linear, that is linear up to about 10 Gy, plateau 10-30 Gy, then decline. Fitted RR at 10 Gy was 13.7 (95% CI 8.0-24.0). **Relative risk of thyroid cancer by radiation dose categories for each study and for all data combined:** • Radiation dose (Gy): o 0 (N=14): reference o >0-1 (N=32): RR 1.9 (95% CI 1.0-3.7) o 2-4 (N=13): RR 7.4 (95% CI (3.3-16.4)* o 5-9 (N=18): RR 14.9 (95% CI 7.1-31.4)* o 10-19 (N=36): RR 14.8 (95% CI 7.1-31.4)* o 20-29 (N=38): RR 15.2 (95% CI 7.8-28.4)* o 30-39 (N=21): RR 9.3 (95% CI 4.3-20.3)* o > 40 (N=15): RR 5.1 (95% CI (2.2-11.9) * **Dose rate:** High dose rate for most patients **Fraction size:** No effect modification by a crude surrogate of fractionation (No. RT treatment within 6 months) which only seemed to modify ERR/Gy in the French study (p=0.05) but not in the pooled analysis, nor in the other 3 individual studies. **<u>Limitations</u>** • Single study effect modification hard to proof in single studies, except for US-CCSS, given small numbers • Dosimetry methods taken from original studies are likely slightly different • French study does not include ALL cases, which is a major contributor to the other cohorts.	

			Strength • Largest collection of data on this topic worldwide to date & state of the art analysis by very experienced group, including biostatistician (J. Lubin).	

Conclusion:

- In CAYAC survivors, the shape of the dose response curve was non-linear: That is linear up to about 10 Gy, plateau 10-30 Gy, then decline.
- In CAYAC survivors, radiotherapy > 1 Gy that includes the thyroid gland was significantly associated with an increased risk for the development of DTC compared to survivors who did not receive radiotherapy treatment (>0-1 Gy: RR 1.9 (95% CI 1.0-3.7), 2-4 Gy: RR 7.4 (95% CI (3.3-16.4), 5-9 Gy: RR 14.9 (95% CI 7.1-31.4), 10-19 Gy: RR 14.8 (95% CI 7.1-31.4), 20-29 Gy: RR 15.2 (95% CI 7.8-28.4), 30-39 Gy: RR 9.3 (95% CI 4.3-20.3), > 40 Gy: RR 5.1 (95% CI (2.2-11.9).

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiation treatment; Gy: gray RR: relative risk; CI: confidence interval; RT: radiotherapy; CT: chemotherapy; ALL: acute lymphoblastic leukemia

* Significant risk factor

Clinical question 4. Are there any etiologic risk factors that alter the radiation risk for DTC after radiation therapy that includes the thyroid gland in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Piccardo A et al. Role of low-cost thyroid follow-up in children treated for primary tumors at high risk of developing a second thyroid tumor. Q J Nuc Med Mol Imaging. 2012; 56:459-467				

Study design:
Prospective cohort study
 	
Treatment era:
1981-?
 	
Years of follow-up:
Median: 12.0 (3.1-29.1)
 	
Lost to follow-up:
N=48
	Study population:
	N=252
	
	Gender:
	Male: 146/112 (58%)
	Female:106/112(42%)
	
	Age at primary cancer diagnosis (yrs):
	Mean: 7.6 ± 4.7
	
	Age at EBRT (yrs):
	Median: 8.4 (1.1-19.3)
	
	Age at follow-up time (yrs):
	NR
	
	EBRT:
	N=252
	
	Average cumulative dose:
	NR
	
	Average thyroid dose (Gy):
	NR
	
	Average number of EBRT:
	NR
		Primary outcome:
		To evaluate the incidence of differentiated thyroid carcinoma in pediatric-oncologic patients treated with radiotherapy.
		
		Inclusion criteria:
		Children with a diagnosis of primary tumor outside the brain, who underwent radiotherapy including the thyroid gland and had the oncologic therapy withdrawn at least two years earlier.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• Thyroid follow-up evaluation involved: 1) neck US, which was performed on completion of RT and every year thereafter if nodules were not found 2) thyroid function (FT4/TSH) at the end of RT and once every two yearly thereafter.
		• If nodules detected by US had a maximum diameter > 1 cm and/or suspicious US features FNAC was performed.
		
		Statistical analysis:
		• Logistic regression modelling was used to estimate the relative risk, in terms of incidence rate ratio (IRR), of having thyroid carcinoma, on adjusting for all the baseline confounding factors considered.
		• In addition it was also used to estimate the risk of thyroid carcinoma, on considering age on RT and doe of RT.
			Incidence thyroid carcinoma (total group):
			• N = 17/252 (6.7%)
			
			Latency time thyroid carcinoma:
			• Median 12.9 (range 5.0-18.0 years)
			
			Risk factors for the incidence of thyroid carcinoma (multivariable logistic regression):
			• Sex: NS
			• Type of primary tumor: NS
			• RT dose (Gy):
			  ○ 10-15: reference
			  ○ 15-20: OR 0.57 (95% CI 0.17-1.92, *P*=0.4)
			  ○ > 20: OR 0.23 (95% CI 0.05-1.15, *P*=0.07)
			• Age at the time of RT (yrs):
			  ○ < 6: reference
			  ○ 6-12: OR 0.53 (95% CI 0.09-3.0, *P*=0.4)
			  ○ > 12: OR 0.13 (95% CI 0.04-3.9, *P*=0.2)	

Conclusion: • In CAYAC survivors, a *trend* towards a negative correlation between radiotherapy dose (>20 Gy) and the development of DTC was found (OR 0.23 (95% CI 0.05-1.15, *P*=0.07) in comparison to survivors who were treated with a radiotherapy dose of 10-15 Gy. • Sex, type of primary tumor, and age at the time of radiotherapy were not significantly associated with the development of DTC.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiation treatment; Gy: gray US: ultrasonography; FNAC: fine-needle aspiration cytology; RT: radiotherapy; NS: non-significant; OR: odds-ratio; CI: confidence interval

Clinical question 4. Are there any etiologic risk factors that alter the radiation risk for DTC after radiation therapy that includes the thyroid gland in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Veiga LHS et al. A pooled analysis of thyroid cancer incidence following radiotherapy for childhood cancer. Radiat Res. 2012; 178: 365-376				
Study design: Pooled analysis **Treatment era:** 1936-2000 **Years of follow-up:** Range: 3.0-55.6 **Lost to follow-up:** NR	**Study population:** N=16,757 **Gender:** NR **Age at primary cancer diagnosis (yrs):** Range: 0.1-20.9 **Age at EBRT (yrs):** NR **Age thyroid cancer diagnosis (yrs):** Range: 3.7-46.2 **EBRT:** N=13,099 **Average cumulative dose:** NR **Average thyroid dose (Gy):** Range: 0.0007-67.3 **Average number of EBRT:** NR	**Primary outcome:** To evaluate the shape of the radiation dose-reponse at high doses and to investigate the relationship between radiotherapy and chemotherapy on the risk of thyroid cancer. **Inclusion criteria:** Childhood cancer studies of radiation-related thyroid cancer, including at least 10 thyroid cancer cases or more that were diagnosed as a second primary malignancy and with individual estimates of thyroid radiation dose. **Exclusion criteria:** NR **Outcome assessment:** • Medline was searched, references were reviewed and colleagues were queried to identify all relevant evidence. • Four studies were included (2 cohort studies and 2 case-control, CCSS-US, CCSS-Fr/UK, LESG, CCSS-Nordic). • All thyroid cancer cases were microscopically confirmed. **Statistical analysis:** • Pooled analyses combining cohort and case control data • Poisson regression was used to model disease risk.	**Incidence thyroid carcinoma (total group):** • N =187/16,757 (0.011%) **Latency time thyroid carcinoma:** • NR **Risk factors for the incidence of thyroid carcinoma (multivariable logistic regression):** • Sex: o Male: reference o Female: RR 2.0 (95% CI 1.5-2.8)* • Age at first cancer (yrs): o <1: reference o 1-4: RR 0.7 (95% CI 0.3-1.3) o 5-9: RR 0.6 (95% CI 0.3-1.3) o 10-14: RR 0.7 (95% CI 0.3-1.4) o ≥ 15: RR 0.3 (95% CI 0.1-0.6)* • Years since first cancer (yrs): o <15: reference o 15-19: RR 2.4 (95% CI 1.4-4.0)* o 20-24: RR 1.9 (95% CI 1.0-3.5)* o ≥ 25: 2.3 (95% CI 1.1-4.9)* • Attained age (yrs): o <20: reference o 20-29: RR 3.5 (95% CI 2.3-5.5)* o 30-34: RR 8.9 (95% CI 5.2-15.2)* o ≥ 35: RR 9.0 (95% CI 4.7-17.2)* • Type of primary cancer: o Kidney (Wilm's): reference o Bone cancer: RR 1.6 (95% CI 0.7-3.7) o CNS: RR 0.7 (95% CI 0.3-1.6) o Hodgkin lymphoma: RR 1.3 (95% CI 0.6-2.6) o Leukemia: RR 1.0 (95% CI 0.5-2.0) o NHL: RR 1.0 (95% CI 0.5-2.2) o Neuroblastoma: RR 1.9 (95% CI 0.9-3.8) o Soft tissue sarcoma: RR 1.0 (95% CI 0.5-2.3) o Others: RR 1.0 (95% CI 0.4-3.1) • Radiotherapy: o No: reference	

			Yes: RR 5.5 (95% CI 3.1-9.7)* • Chemotherapy: ○ No: reference Yes: RR 1.4 (95% CI 0.9-2.0)	

Conclusion:

- In CAYAC survivors, female gender was significantly associated with an increased risk for the development of DTC compared to male gender survivors in multiple-variable regression analysis (RR 2.0 (95% CI 1.5-2.8).
- In CAYAC survivors, age at first cancer (≥ 15.0) was significantly associated with a decreased risk for the development of DTC compared to survivors aged < 1.0 years at first cancer in multi-variable regression analysis (RR 0.3 (95% CI 0.1-0.6).
- In CAYAC survivors, years since first cancer (≥ 15.0) was significantly associated with an increased risk for the development of DTC compared to survivors < 15.0 years since first cancer in multi-variable regression analysis (RR 2.4 (95% CI 1.4-4.0).
- In CAYAC survivors, attained age (≥ 20.0) was significantly associated with an increased risk for the development of DTC compared to survivors with an attained age of < 20.0 in multi-variable regression analysis (RR 3.5 (95% CI 2.3-5.5).
- In CAYAC survivors, radiotherapy treatment was significantly associated with an increased risk for the development of DTC compared to survivors who did not receive radiotherapy treatment in multi-variable regression analysis (RR 5.5 (95% CI 3.1-9.7).
- Type of primary cancer and chemotherapy treatment were not significantly associated with the development of DTC.

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years NR: not reported; EBRT: external beam radiation treatment; Gy: gray RR: relative risk; CI: confidence interval; CNS: central nervous system; NHL: non-Hodgkin lymphoma

* Significant risk factor

Clinical question 4. Are there any etiologic risk factors that alter the radiation risk for DTC after radiation therapy that includes the thyroid gland in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Veiga LHS et al. Chemotherapy and thyroid cancer risk: a report from the childhood cancer survivor study. Cancer Epidemiol Biomarkers Prev. 2012;21:92-101				

Study design:
Retrospective cohort study
 	
Treatment era:
1970-1986
 	
Years of follow-up:
Range: 19.0-35.0
 	
Lost to follow-up:
N=209 (of 12756 survivors)
	Study population:
	N=12,547
	
	Gender:
	NR
	
	Age at primary cancer diagnosis (yrs):
	NR
	
	Age at EBRT (yrs):
	NR
	
	Age at follow-up time (yrs):
	NR
	
	EBRT:
	N=12,547/12547 (100%)
	
	Average cumulative dose:
	NR
	
	Average thyroid dose (Gy):
	NR
	
	Average number of EBRT:
	NR
		Primary outcome:
		To evaluate the chemotherapy-related risk of thyroid cancer in childhood cancer survivors and the possible joint effects of chemotherapy and radiotherapy.
		
		Inclusion criteria:
		Subjects diagnosed before age 21 years with a childhood cancer during 1970-1986 at one of 26 institutions in the US or Canada and had survived for at least 5 years.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• A baseline self-administrated questionnaire sent in 1994 collected data on demographic characteristics, social-economic state and new malignancies and other health outcomes. Subsequent surveys were mailed to cohort members in 2000, 2003 and 2005.
		• Cases were defined as patients who developed a subsequent thyroid cancer at least 5 years after a first childhood malignancy.
		• Thyroid cancers were ascertained through self-report (including surrogate respondents) on questionnaires.
		• Pathology reports were obtained and thyroid cancers were verified by a pathologist.
		
		Statistical analysis:
		• Cumulative incidence and relative risks were calculated with life-tables methods and Poisson regression. Chemotherapy-related risks were evaluated separately by categories of radiation dose.
			Incidence thyroid carcinoma (total group):
			• N = 119/12547 (0.09%)
			
			Latency time thyroid carcinoma:
			• 5-14 yrs: N=33
			• 15-19 yrs: N=41
			• 20-24 yrs: N=27
			• ≥ 25 yrs: N=18
			
			Risk factors for the incidence of thyroid carcinoma by type of treatment (multivariable logistic regression):
			• Type of treatment:
			  ○ No RT, had CT: reference
			  ○ RT alone: RR 3.0 (95% CI 0.9-9.7)
			  ○ Concomitant CT&RT: RR 4.7 (95% CI 1.5-15.0)*
			  ○ Sequential CT and RT: RR 5.4 (95% CI 1.6-18.4)*
			  ○ RT, then CT: RR 8.0 (95% CI 2.2-28.5)*
			  ○ CT, then RT: RR 5.2 (95% CI (1.3-21.3)*
			Risk of thyroid carcinoma with respect to chemotherapy by thyroid radiation dose (multivariable logistic regression):
			• No radiation thyroid dose = 0 Gy (N=12)
			  ○ CT no: reference
			  ○ CT yes: RR 4.6 (95% CI 0.8-86.3)
			• Radiation thyroid dose = < 20 Gy (N=61)
			  ○ CT no: reference
			  ○ CT yes: RR 4.0 (95% CI 1.4-16.5)*
			• Radiation thyroid dose = > 20 Gy (N=54)
			  ○ CT no: reference
			  ○ CT yes: RR 1.1 (95% CI 0.6-2.1)
			• Overall (N=115)
			  ○ CT no: reference
			  ○ CT yes: RR 1.6 (95% CI 1.0-2.7)	

Conclusion: • In CAYAC survivors, radiotherapy combined with chemotherapy treatment was significantly associated with an increased risk for the development of DTC compared to survivors who were treated with chemotherapy alone in Poisson regression analysis (concomitant CT and RT: RR 4.7 (95% CI 1.5-15.0), sequential CT and RT: RR 5.4 (95% CI 1.6-18.4), RT, then CT: RR 8.0 (95% CI 2.2-28.5), CT then RT RR 5.2 (95% CI 1.3-21.3). • In CAYAC survivors, chemotherapy in addition to a radiation thyroid dose < 20 Gy was significantly associated with an increased risk for the development of DTC compared to survivors who received no chemotherapy in addition to radiotherapy with a thyroid dose < 20 Gy in regression analysis (RR 4.0 (95% CI 1.4-16.5).				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiation treatment; Gy: gray RR: relative risk; CI: confidence interval; RT: radiotherapy; CT: chemotherapy * Significant risk factor

Clinical question 4. Are there any etiologic risk factors that alter the radiation risk for DTC after radiation therapy that includes the thyroid gland in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Bhatti P et al. Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the childhood cancer survivor study. Radiat Res. 2010;174:741-752				

Study design:
Retrospective cohort study
 	
Treatment era:
1970-1986
 	
Years of follow-up:
Range: 19.0-35.0
 	
Lost to follow-up:
N=209 (of 12,756 survivors)
	Study population:
	N=12,547
	
	Gender:
	NR
	
	Age at primary cancer diagnosis (yrs):
	NR
	
	Age at EBRT (yrs):
	NR
	
	Age at follow-up time (yrs):
	NR
	
	EBRT:
	N=12,547/12547 (100%)
	
	Average cumulative dose:
	NR
	
	Average thyroid dose (Gy):
	NR
	
	Average number of EBRT:
	NR
		Primary outcome:
		To quantify the long-term risk of thyroid cancer associated with radiation treatment.
		
		Inclusion criteria:
		Subjects diagnosed before age 21 years with a childhood cancer during 1970-1986 at one of 26 institutions in the US or Canada and had survived for at least 5 years.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• A baseline self-administrated questionnaire sent in 1994 collected data on demographic characteristics, social-economic state and new malignancies and other health outcomes.
		• Subsequent surveys were mailed to cohort members in 2000, 2003 and 2005.
		• Cases were defined as patients who developed a subsequent thyroid cancer at least 5 years after a first childhood malignancy.
		• Thyroid cancers were ascertained through self-report (including surrogate respondents) on questionnaires.
		• Pathology reports were obtained and thyroid cancers were verified by a pathologist.
		
		Statistical analysis:
		• The adjusted relative risk of developing a second malignancy was estimated with the use of Poisson multiple regression.
		• A fixed set of explanatory variables was selected a priori and was used to assess their simultaneous impact on the rate of developing a SMN without any statistical variable selection.
			Incidence thyroid carcinoma (total group):
			• N = 119/12,547 (0.09%)
			
			Latency time thyroid carcinoma:
			• 5-14 yrs: N=33
			• 15-19 yrs: N=41
			• 20-24 yrs: N=27
			• ≥ 25 yrs: N=18
			
			Risk factors for the incidence of thyroid carcinoma (multivariable logistic regression):
			• Thyroid radiation dose (mean) (Gy):
			  ○ 0: reference
			  ○ >0-<5 (0.8): RR 1.2 (95% CI 0.6-2.5)
			  ○ 5-<10 (7.4): RR 8.5 (3.2-22.6)*
			  ○ 10-<15 (12.3): RR 10.6 (95% CI 4.5-24.9)*
			  ○ 15-<20 (17.4): RR 13.8 (95% CI 6.3-30.3)*
			  ○ 20-<25 (22.0): RR 14.6 (95% CI 6.8-31.5)*
			  ○ 25-<30 (27.3): RR 9.3 (95% CI 3.9-21.9)*
			  ○ 30-<35 (32.4): RR 8.9 (95% CI 3.6-21.7)*
			  ○ 35-<40 (37.5): RR 3.6 (95% CI 1.3-10.2)*
			  ○ > 40 (45.6): RR 2.8 (95% CI 1.1-7.1) *
			• Sex:
			  ○ Male: reference
			  ○ Female: RR 2.3 (95% CI 1.6-3.4)*
			• Type of first cancer:
			  ○ Leukemia: reference
			  ○ Hodgkin lymphoma: RR 1.1 (95% CI (0.5-2.1)
			  ○ CNS cancer: RR 1.0 (95% CI 0.5-2.0)
			  ○ Kidney cancer (Wilms): RR 0.9 (95%CI 1.3-3.1)
			  ○ Bone cancer: RR 2.1 (95% CI 1.0-4.4)*
			  ○ Neuroblastoma: RR 2.2 (95% CI 1.0-4.9)*
			  ○ Non-Hodgkin lymphoma: RR 0.6 (95%CI 0.2-1.5)
			• Age at first cancer (yrs):
			  ○ <5: reference
			  ○ 5-9: RR 0.7 (95% CI 0.4-1.2)
			  ○ 10-14: RR 0.6 (95% CI 0.4-1.2)
			  ○ > 15: RR 0.2 (95% CI 0.1-0.4)*	

			• Type of treatment:
			  ○ CT and RT: reference
			  ○ CT alone: RR 0.3 (95% CI 0.2-0.6)*
			  ○ RT alone: RR 0.6 (95% CI 0.3-1.0)*
			  ○ No CT and RT: RR 0.08 (95% CI 0.01-0.6)*
			• Chemotherapy:
			  ○ No: reference
			  ○ Yes: RR 1.6 (95% CI 1.0-2.7)*	

Conclusion:

- In CAYAC survivors, thyroid radiation dose > 5 Gy was significantly associated with an increased risk for the development of DTC compared to survivors who received a radiation dose of < 5 Gy in multiple-variable regression analysis (RR 8.5 (95% CI 3.2-22.6).
- In CAYAC survivors, female gender was significantly associated with an increased risk for the development of DTC compared to male gender survivors in multiple-variable regression analysis (RR 2.3 (95% CI 1.6-3.4).
- In CAYAC survivors, bone cancer was significantly associated with an increased risk for the development of DTC compared to survivors diagnosed with leukemia as first cancer in multi-variable regression analysis (RR 2.1 (95% CI 1.0-4.4).
- In CAYAC survivors, neuroblastoma was significantly associated with an increased risk for the development of DTC compared to survivors diagnosed with leukemia as first cancer in multi-variable regression analysis (RR 2.2 (95% CI 1.0-4.9).
- In CAYAC survivors, age at first cancer (≥ 15.0) was significantly associated with a decreased risk for the development of DTC compared to survivors aged < 5.0 years at first cancer in multi-variable regression analysis (RR 0.2 (95% CI 0.1-0.4).
- In CAYAC survivors, chemotherapy treatment alone was significantly associated with a decreased risk for the development of DTC compared to survivors who were treated with a combination of chemotherapy and radiotherapy treatment in multi-variable regression analysis (RR 0.3 (95% CI 0.2-0.6).
- In CAYAC survivors, radiotherapy treatment alone was significantly associated with a decreased risk for the development of DTC compared to survivors who were treated with a combination of chemotherapy and radiotherapy treatment in multi-variable regression analysis (RR 0.6 (95% CI 0.3-1.0).
- In CAYAC survivors, no treatment with either chemotherapy or radiotherapy was significantly associated with an decreased risk for the development of DTC compared to survivors who were treated with a combination of chemotherapy and radiotherapy treatment in multi-variable regression analysis (RR 0.08 (95% CI 0.01-0.6).
- In CAYAC survivors, chemotherapy treatment was significantly associated with an increased risk for the development of DTC compared to survivors who did not receive chemotherapy treatment in multi-variable regression analysis (RR 1.6 (95% CI 1.0-2.7).

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiation treatment; Gy: gray RR: relative risk; CI: confidence interval; RT: radiotherapy; CT: chemotherapy; CNS: central nervous system

* Significant risk factor

Clinical question 4. Are there any etiologic risk factors that alter the radiation risk for DTC after radiation therapy that includes the thyroid gland in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Taylor AJ et al. Risk of thyroid cancer in survivors of childhood cancer: results from the British childhood cancer survivors study. Int J Cancer. 2009;125:2400-2405				
Study design: Retrospective cohort study **Treatment era:** 1940-1991 **Years of follow-up:** Median: 17.4 years per survivor from 5 year survival **Lost to follow-up:** N=2728 (21%)	**Study population:** N=10483 **Gender:** NR **Age at primary cancer diagnosis (yrs):** NR **Age at transplantation (yrs):** NR **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** NR **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To determine the risk of thyroid SMNs in the Britisch Childhood Cancer Survivor Study. **Inclusion criteria:** Patients with childhood cancer, at age less than 15 years, between 1940 and 1991, surviving 5 years or more from diagnosis. **Exclusion criteria:** NR **Outcome assessment:** • All survivors aged at least 16 years who are alive and contactable through their general practitioner have been sent a questionnaire. • Information from questionnaires was complemented by "flagging" at the National Health Service central registers. • SMNs of the thyroid were verified pathologically either by a histopathology reports or by clinical correspondence containing a histopathology summary. **Statistical analysis:** • Multivariate Poisson regression models with the log of the expected umber of thyroid cancers as offset were employed to derive relative risks (RR).	**Incidence thyroid carcinoma:** • N=50/10483 (0.0047%) o Papillary carcinoma (N=31) o Follicular carcinoma (N=15) o Other histology (N=4) **Latency time thyroid carcinoma:** • Median: 15.3 years (4.2-29.7 years) **Risk factors for the incidence of thyroid carcinoma (multivariable logistic regression):** • Sex: o Male: reference o Female: RR 0.6 (95% CI 0.3-1.2) • Age at diagnosis: o 0-4 yrs: reference o 5-9 yrs: RR 1.0 (95% CI 0.4-2.2) o 10-14 yrs: RR 0.5 (95% CI 0.2-1.3) • Treatment era: o < 1970: reference o 1970-1979: RR 0.9 (95% CI 0.4-2.4) o 1980-1991: RR 1.2 (95% CI 0.4-3.6) • Follow-up period: o 0-9 yrs: reference o 10-19 yrs: RR 0.8 (95% CI 0.4-1.7) o 20-29 yrs: RR 0.4 (95% CI 0.1-1.3) o ≥ 30 yrs: RR 0.6 (95% CI 0.2-2.2) • Radiotherapy: o No: reference o Yes: RR 4.6 (95% CI 1.4-15.1)* • Chemotherapy: o No: reference o Yes: RR 0.8 (95% CI 0.3-2.1) • Type of primary cancer diagnosis: o Leukemia: reference o Hodgkin's disease: RR 3.3 (95% CI 1.1-10.1)* o NHL: RR 3.4 (95% CI 1.1-10.7)* o CNS primary: RR 0.7 (95% CI 0.2-2.5) o Other: RR 0.5 995% CI 0.2-1.5)	

Conclusion:

- In CAYAC survivors, radiotherapy was significantly associated with an increased risk for the development of DTC compared to survivors who did not receive radiotherapy treatment, in multiple regression analysis (RR 4.6 (95% CI 1.4-15.1).
- In CAYAC survivors, Hodgkin's disease was significantly associated with an increased risk for the development of DTC compared to survivors who were diagnosed with leukemia as primary cancer diagnosis, in multiple regression analysis (RR 3.3 (95% CI 1.1-10.1).
- In CAYAC survivors, non-Hodgkin lymphoma was significantly associated with an increased risk for the development of DTC compared to survivors who were diagnosed with leukemia as primary cancer diagnosis, in multiple regression analysis (RR 3.4 (95% CI 1.1-10.7).
- Sex, age at diagnosis, treatment era, follow-up period and chemotherapy treatment were not significantly associated with the development of DTC.

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiation treatment; Gy: gray; RR: relative risk; CI: confidence interval; NHL: non-Hodgkin lymphoma; CNS: central nervous system

* Significant risk factor

Clinical question 4. Are there any etiologic risk factors that alter the radiation risk for DTC after radiation therapy that includes the thyroid gland in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Bhatia S et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the late effects study group. J Clin Oncol. 2003;21:4386-4394				

Study design:
Retrospective cohort study
 	
Treatment era:
1955-1986
 	
Years of follow-up:
Median: 17.0
 	
Lost to follow-up:
NR
	Study population:
	N=1380
	
	Gender:
	Male:897/1380 (65%)
	Female:480/1380 (35%)
	
	Age at primary cancer diagnosis (yrs):
	Median: 11.7 (0.3-16.9)
	
	Age at EBRT (yrs):
	NR
	
	Age at follow-up time (yrs):
	Median: 27.8
	
	EBRT:
	N=1274/1380 (92%)
	
	Average cumulative dose:
	NR
	
	Average thyroid dose (Gy):
	Direct: median 20 (range 2-50)
	Scattered: range 0.1-0.5
	
	Average number of EBRT:
	NR
		Primary outcome:
		The pattern and incidence of second malignant neoplasms occuring with extended follow-up.
		
		Inclusion criteria:
		Children ages 16 years or younger at diagnosis of Hodgkin's disease, who received their primary treatment between 1955 and 1986.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• Baseline characteristics and treatment-related factors and presence of SMNs were abstracted from the clinical records.
		• Pathologic findings were confirmed at the treating institution.
		
		Statistical analysis:
		• The adjusted relative risk of developing a second malignancy was estimated with the use of Poisson multiple regression.
		• A fixed set of explanatory variables was selected a priori and was used to assess their simultaneous impact on the rate of developing a SMN without any statistical variable selection.
			Incidence thyroid carcinoma (total group):
			• N=19/1380 (13%)
			  ○ Papillary carcinoma (N=12)
			  ○ Follicular carcinoma (N=7)
			
			Latency time thyroid carcinoma:
			• Median: 15.3 years (4.2-29.7 years)
			
			Risk factors for the incidence of thyroid carcinoma (multivariable logistic regression):
			• Age at diagnosis (yrs):
			  ○ 0-5: RR 3.70 (95% CI 0.82-12.04)*
			  ○ 6-9: RR 1.58 (95% CI 0.43-4.67)
			  ○ 10-16: reference
			• Sex:
			  ○ Male: RR 1.70 (95% CI 0.65-4.29)
			  ○ Female: reference
			• Stage of disease:
			  ○ Early (1-11): reference
			  ○ Late (III-IV): RR1.74 (95% CI 0.61-4.79)
			• Recurrence:
			  ○ No: reference
			  ○ Yes: RR 0.85 (95% CI 0.22-2.54)
			• Treatment:
			  ○ CT alone: RR 0.79 (95% CI 0.04-5.44)
			  ○ RT alone: RR reference
			  ○ CT and RT: RR 1.28 (95% CI 0.43-4.29)
			• Alkylating agent score:
			  ○ < 3: reference
			  ○ 3-9: RR 0.63 (95% CI 0.09-2.55)	

Conclusion: • In survivors of Hodgkin's disease, younger age (0-5 years) was significantly associated with an increased risk for the development of DTC compared to survivors with an older age (6-16 years) in multiple regression analysis (RR 3.70 (95% CI 0.82-12.04). • Sex, stage of Hodgkin's disease, recurrence of Hodgkin's disease, treatment modality and alkylating agent score were not significantly associated with the development of DTC.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years NR: not reported; EBRT: external beam radiation treatment; Gy: gray; SMN: second malignant neoplasm; RR: relative risk; CI: confidence interval

* Significant risk factor

Clinical question 4. Are there any etiologic risk factors that alter the radiation risk for DTC after radiation therapy that includes the thyroid gland in CAYAC survivors?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Somerville et al. Thyroid neoplasia following irradiation in adolescent and young adult survivors of childhood cancer. Med J Aust. 2002;176:584-587				

Study design:
Retrospective case series
 	
Treatment era:
1970-onwards
 	
Years of follow-up:
Mean 14.0
 	
Lost to follow-up:
N=35/177 (20%)
These patients did not differ from the included patients in diagnostic category or cancer therapy
	Study population:
	N=142
	
	Gender:
	Male: 72/142 (51%)
	Female: 70/142 (49%)
	
	Age at primary cancer diagnosis (yrs):
	Mean 5.8
	
	Age at EBRT (yrs):
	NR
	
	Age at follow-up time (yrs):
	Mean 16.0
	
	EBRT:
	N=142/142 (100%)
	
	Average cumulative dose:
	NR
	
	Average thyroid dose (Gy):
	Direct: median 20 (range 2-50)
	Scattered: range 0.1-0.5
	
	Average number of EBRT:
	NR
		Primary outcome:
		To describe a cohort of survivors of childhood malignancy at risk of developing thyroid abnormality.
		
		Inclusion criteria:
		Patients who had received direct or scattered irradiation to the thyroid from the 1970's onwards who attended the late effects clinic from May 1989 to December 1998.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• The thyroid doses were estimated from a retrospective review of radiation treatment data.
		• All subjects were examined by one of three endocrinologists (thyroid palpation).
		• All patients underwent ultrasound examination and thyroid function tests.
		
		Statistical analysis:
		• A multivariate logistic regression was used to examine the relation between prognostic factors and the incidence of malignancy.
			Incidence thyroid carcinoma (total group):
			• N=18/142 (13%)
			  ○ Papillary microcarcinoma (N = 5)
			  ○ Unifocal papillary carcinoma (N = 5)
			  ○ Multifocal papillary carcinoma (N = 3)
			  ○ Mixed papillary/follicular carcinoma (N = 4)
			
			Latency time thyroid carcinoma:
			NR
			
			Risk factors for the incidence of thyroid carcinoma (multivariable logistic regression):
			• Age at original diagnosis: NS
			• Sex: NS
			• Thyroid palpability: OR 4.1 95% CI 1.2-14.0, *P*=0.01*
			• Time since irradiation: NS
			• Dose of the thyroid: NS
			• Nodal type: NS
			• Nodal involvement: NS
				• The selection of variables for the multiple regression analysis is unclear.
				
				• The multivariable model exceeds the maximum number of independent variables (~10 cases/events per covariate/covariable).

Conclusion: • In CAYAC survivors, thyroid palpability was significantly associated with an increased risk for the development of DTC compared to survivors without a palpable thyroid in multiple regression analysis (OR 4.1 95% CI 1.2-14.0, *P*=0.01). • Age at original diagnosis, sex, time since irradiation, radiotherapy dose received by the thyroid, nodal type and nodal involvement were not significantly associated with the development of DTC. • Note that the selection of variables for the multiple regression analysis is unclear.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; EBRT: external beam radiation treatment; Gy: gray OR: odds-ratio; CI: confidence interval; NS: non-significant
* Significant risk factor

Clinical question 5. What is the diagnostic value of neck palpation versus thyroid ultrasonography to predict the presence of a thyroid nodule in children/adults exposed to irradiation?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Brignardello E et al. Ultrasound Screening for Thyroid Carcinoma in Childhood Cancer Survivors: A Case Series. J Clin Endo Metab. 2008, 93: 4840-4843				
Study design: Retrospective case series **Treatment era:** NR **Years of follow-up:** Median:15.8 (6.1-34.8)	**Study population:** N=129 **Gender:** Male: 80/129 (62%) Female: 49/129 (38%) **Age at primary cancer diagnosis (yrs):** Median: 11.5 (0.5-19) **Age at follow-up time (yrs):** Median: 25.1 (17.5-43.8) **EBRT:** N=129	**Primary outcome:** Detection of non-palpable thyroid nodules by thyroid ultrasound. **Inclusion criteria:** CCS who had received radiotherapy to head/neck/upper thorax for a pediatric cancer. **Exclusion criteria:** NR **Outcome assessment:** • All patients who had received radiotherapy to head/neck/upper thorax began ultrasound screening 5 yrs post treatment and repeated every third year if negative. • If screening was positive interval decreased to every 6-12 months or fine-needle aspiration was performed. • Indications for biopsy were nodule size >1 cm or suspicious ultrasound features.	**Thyroid nodules found by ultrasound screening:** • Prevalence of nodules in population screened: 35/129=27.1% **Thyroid nodules found by neck palpation:** • Prevalence of nodules in population screened: 6/129=4.7% **Diagnostic value neck palpation for detection of nodule:** • Sensitivity: 17% • Specificity: 100% • PPV: 100% • NPV: 76% **Results fine-needle aspiration:** • FNA performed in 19/129 patients=14.7% • Prevalence of cancer in population screened: 5/129=3.9% • Prevalence of cancer in population with nodules: 5/35=14.2% • Prevalence of occult cancer in population: 3/129=2.3% **Other:** • Interval from irradiation of primary cancer to thyroid cancer diagnosis: median 13.2 yrs (8.9-27.9) • 2/5 malignant nodules were palpable • 8/14 patients with nodules > 1 cm were not palpable • 2/2 patients with non-palpable cancers had local (central) or regional (lateral neck) disease • There were no instances of distally metastatic disease	
Conclusion: • Using thyroid ultrasound as the gold standard determination of the presence of a thyroid nodule in CAYAC survivors, the sensitivity of neck palpation was 17%, the specificity of palpation was 100%, the PPV was 100% and the NPV 76%.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; yrs: years; EBRT: external beam radiotherapy; CCS: childhood cancer survivors; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 5. What is the diagnostic value of neck palpation versus thyroid ultrasonography to predict the presence of a thyroid nodule in children/adults exposed to irradiation?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Metzger ML et al. Natural history of thyroid nodules in survivors of pediatric Hodgkin lymphoma. Pediatr Blood Cancer. 2006; 46:314-319				
Study design: Retrospective cohort study **Treatment era:** 1962-2001 **Years of follow-up:** Median: 21.3 (4.2-35.6)	**Study population:** N=67 **Gender:** Male: 34/67(51%) Female: 33/64 (49%) **Age at primary cancer diagnosis (yrs):** Median: 12.6 yrs (3.7-21.3) **Age at follow-up time (yrs):** NR **EBRT:** N=67	**Primary outcome:** Nodule detected by thyroid ultrasound and/or neck palpation. **Inclusion criteria:** Children treated for Hodgkin lymphoma, with a history of head and neck irradiation, with one or more nodule detected during or after therapy (selected from a population of N=647 Hodgkin's lymphoma survivors). **Exclusion criteria:** Pre-existing thyroid nodule **Outcome assessment:** • Hodgkin lymphoma survivors with a history of head and neck irradiation underwent yearly physical examination of the thyroid gland by a pediatric oncologist. • A subpopulation underwent routine ultrasound screening at discretion of oncologist (indication?) or were enrolled in prospective ultrasound screening study. • Patients were referred to a pediatric endocrinologist if a thyroid mass was detected or other endocrinologic concerns existed.	**Thyroid nodules found by ultrasound screening:** • Prevalence of nodules in population: 67/647=10.4% **Thyroid nodules found by neck palpation:** • Prevalence of nodules in population screened: 24/647=3.7% **Diagnostic value neck palpation for detection of nodule:** • Sensitivity: 39% • Specificity: 100% • PPV: 100% • NPV: 93% **Results fine-needle aspiration:** • Prevalence of thyroid cancer in population: 7/647=1.1% • Prevalence of cancer in population with nodules: 7/67=10.4% • Prevalence of occult cancer in population: 1/647=0.15% **Other:** • Time to detection of nodule by palpation: 12.3 yrs (3-24.8) • Time to detection of nodule by ultrasound: 10.1 yrs (0.2-19.3) • Time to diagnosis of malignancy by palpation:1 9.2 yrs (8.4-23.7) • Time to diagnosis of malignancy by ultrasound: 13.6 yrs (n=1) • Only 1 thyroid cancer was missed by physical exam (out of 7 malignancies). • 10/41 nodules detected by ultrasonography disappeared on repeat ultrasound imaging. • The median thyroid nodule size as determined by ultrasonography was 1 cm (range 0.2-2.9 cm) (results of N = 53 patients).	• Decision to pursue imaging was at the discretion of treating clinician. • No ultrasound features were predictive of malignancy, but ultrasonography only available for 3 patients with malignancy. • Does not state the number of patients that were screened by ultrasound that were negative.
Conclusion: • Using thyroid ultrasound as the gold standard determination of the presence of a thyroid nodule in CAYAC survivors, the sensitivity of neck palpation was 39%, the specificity of palpation was 100%, the PPV was 100% and the NPV 93.4%.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; yrs: years; EBRT: external beam radiotherapy; CCS: childhood cancer survivors; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 5. What is the diagnostic value of neck palpation versus thyroid ultrasonography to predict the presence of a thyroid nodule in children/adults exposed to irradiation?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Somerville HM et al. Thyroid neoplasia following irradiation in adolescent and young adult survivors of childhood cancer. MJA 2002;176:584-587				
Study design: Retrospective case series **Treatment era:** 1989-1998 **Years of follow-up:** Mean 14.0	**Study population:** N = 142 **Gender:** Male: 72/142 (51%) Female: 70/142 (49%) **Age at primary cancer diagnosis (yrs):** Mean 5.8 **Age at follow-up time (yrs):** Mean 16.0	**Primary outcome:** Nodule detected by ultrasound and/or palpation **Inclusion criteria:** CCS who had received direct or scattered irradiation to the thyroid from the 1970's onwards who attended the late effects clinic from May 1989 to December 1998. **Exclusion criteria:** NR **Outcome assessment:** • All subjects were examined by one of three endocrinologists (thyroid palpation). • The thyroid was describes as palpable (diffusely enlarged or containing nodules) or non-palpable. • All patients underwent ultrasound examination using high-resolution linear transducers at frequencies of 7-10 MHz. • Abnormal ultrasound results were reported to show single or multiple nodules.	**Ultrasound abnormalities:** • **Direct irradiation group (5-50 Gy)(N = 65)** • Thyroid palpable N = 19/65 (29%) o Ultrasound abnormal N = 18/65 (28%) o Thyroid surgery N = 14/18 (78%) • Thyroid impalpable N = 46/65 (71%) o Ultrasound abnormal N = 24/46 (37%) o Thyroid surgery N = 11/24 (46%) • **Scattered irradiation group (0.1-0.5 Gy)(N = 78)** • Thyroid palpable N = 22/78 (28%) o Ultrasound normal N = 3/22 (14%) o Thyroid surgery N = 19/22 (86%) • Thyroid impalpable N = 56/78 (72%) o Ultrasound normal N = 18/56 (32%) o Thyroid surgery N = 38/56 (68%) **Diagnostic value neck palpation:** • **Direct irradiation group (5-50 Gy)(N = 65)** o Sensitivity: 43% o Specificity: 96% o PPV: 95% o NPV: 48% • **Scattered irradiation group (0.1-0.5 Gy)(N = 78)** o Sensitivity: 33% o Specificity: 86% o PPV: 86% o NPV: 32%	• Thyroid *palpable* is defined as diffusely enlarged or containing nodules. No separate description of the amount of palpable thyroid nodules available. • Size of the impalpable thyroid nodules detected by thyroid ultrasound investigation is not mentioned.
Conclusion: • Using thyroid ultrasound as the gold standard determination of the presence of a thyroid nodule in CAYAC survivors, the sensitivity of neck palpation was 43%, the specificity of palpation was 96%, the PPV was 95% and the NPV 48% in the direct irradiation group. The sensitivity of neck palpation was 33%, the specificity of palpation was 86%, the PPV was 86% and the NPV 32% in the scattered irradiation group. Note that Thyroid *palpable* is defined as diffusely enlarged or containing nodules. No separate description of the amount of palpable thyroid nodules available.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years. NR: not reported; yrs: years; CCS: childhood cancer survivors; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 5. What is the diagnostic value of neck palpation versus thyroid ultrasonography to predict the presence of a thyroid nodule in children/adults exposed to irradiation?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Schneider AB et al. Thyroid nodules in the follow-up of irradiated individuals: comparison of thyroid ultrasound with scanning and palpation. J Clin Endocrinol Metab. 1997; 82: 4020-4027				
Study design: Longitudinal prospective cohort study **Treatment era:** 1939-1969 **Years of follow-up:** Median:15.8 (6.1-34.8)	**Study population:** N=54 **Gender:** Male: 20/54 (37%) Female: 34/54 (63%) **Age at radiation exposure (yrs):** High Tg group: 3.8 ± 2.1 Normal Tg group: 5.1 ± 3.8 **Age at follow-up time (yrs):** High Tg group: 47.3 ± 3.6 Normal Tg group: 46.9 ± 3.9	**Primary outcome:** To define the role of ultrasound for diagnosing thyroid nodules in irradiated individuals, in comparison with palpation and thyroid scan. **Inclusion criteria:** • Radiotherapy for benign conditions in the head/neck between 1939-1962 • Normal physical examination and thyroid scan at screening performed between 1974 – 1976 • Accurate thyroid specific radiation dose • Selection using a table of random numbers **Exclusion criteria:** • Thyroid surgery since original screening • Last known address not in the Chicago area • Dead • Lost to follow-up • Refuse to partecipate **Outcome assessment:** • The thyroid of all included subjects was examined by palpation, ^{99m}Tc-pertechnectate scan and ultrasound. Serum thyreoglobulin measurements were also performed. • Ultrasound examination was performed using a 7.5-MHz transducer.	**Thyroid nodules found by ultrasound screening:** • Prevalence of nodules in population screened: 47/54=87% **Thyroid nodules found by neck palpation:** • Prevalence of nodules in population screened: 8/54=15% • Subjects with thyroid nodules ≤ 1.5 cm: 5/11 (45.5%) • Subjects with thyroid nodules > 1.5 cm: 3/36 (8.3%) **Diagnostic value neck palpation for detection of nodule:** • Sensitivity: 17% • Specificity: 100% • PPV: 100% • NPV: 15% **Results fine-needle aspiration cytology:** • FNA performed in 6/54 patients=11%	

Conclusion:

- Using thyroid ultrasound as the gold standard determination of the presence of a thyroid nodule in children exposed to irradiation for benign lesions, the sensitivity of neck palpation was 17%, the specificity of palpation was 100%, the PPV was 100% and the NPV 20%.

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; yrs: years; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 5. What is the diagnostic value of neck palpation versus thyroid ultrasonography to predict the presence of a thyroid nodule in children/adults exposed to irradiation?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Inskip PD et al. Thyroid nodularity and cancer among Chernobyl cleanup workers from Estonia. Radiat Res. 1997; 147: 225-235				

Study design:
Cross-sectional study
 	
Treatment era:
Exposed to ionizing radiation at Chernobyl 1986
 	
Years of follow-up:
NR
	Study population:
	N=1984
	
	Gender:
	Male: 1984/1984 (100%)
	Female: -
	
	Age at exposure to ionizing radiation (yrs):
	Mean: 32.0
	
	Age at follow-up time (yrs):
	Mean: 40.0
	
	Exposed to ionizing radiation:
	N=1984
		Primary outcome:
		Presence or absence of thyroid nodules as determined by ultrasound determination
		
		Inclusion criteria:
		Former Chernobyl clean-up workers from Estonia
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• Screening examinations included palpation by a thyroid specialist and high-resolution ultrasonography by a radiologist.
		• Thyroid specialists and radiologists did not discuss findings for a given individual until each type of examination had been performed.
		• Examiners were unaware of the individual's radiation dose and work history.
		• Fine-needle aspiration biopsy was recommended for all palpable nodules that were 1 cm or more in diameter as determined by ultrasound or if palpation findings were clearly positive or impalpable thyroid nodules < 1cm provided that the ultrasound examiner could mark the precise location on the skin to guide the needle biopsy.
		• Two workers refused the needle biopsy.
			Thyroid nodules found by ultrasound screening:
			• Prevalence of nodules in population screened: 201/1979=10.2%
			
			Thyroid nodules found by neck palpation:
			• Prevalence of nodules in population screened: 44/1945=2.3%
			
			Diagnostic value neck palpation for detection of nodule:
			• Sensitivity: 22%
			• Specificity: 100%
			• PPV: 100%
			• NPV: 92%
			
			Results fine-needle aspiration cytology:
			• FNA performed in N=77/201 (38%)
			  ○ Papillary carcinoma N=2 (2.6%)
			  ○ Follicular neoplasm N=3 (3.9%)
			  ○ Inconclusive, possible neoplasm N=10 (13.0%)
			  ○ Benign thyroid nodule N=44 (57.1%)
			  ○ Inadequate sample N=18 (23.4%)
			
			Other:
			• Nodule size as:
			  ○ < 0.5 cm: N=26 (12.9%)
			  ○ 0.5-0.99 cm: N=87 (43.3%)
			  ○ 1.0-1.49 cm: N=53 (26%)
			  ○ > 1.5 cm: N=35 (17.4%)	

Conclusion: • Using thyroid ultrasound as the gold standard determination of the presence of a thyroid nodule in individuals exposed to ionizing radiation, the sensitivity of neck palpation was 22%, the specificity of palpation was 100%, the PPV was 100% and the NPV 92%.				

NR: not reported; yrs: years; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 5. What is the diagnostic value of neck palpation versus thyroid ultrasonography to predict the presence of a thyroid nodule in children/adults exposed to irradiation?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Takahashi T et al. An investigation into the prevalence of thyroid disease on Kwajalein Atoll, Marshall Islands. Health Phys. 1997; 73: 199-213				
Study design: Cross-sectional study **Treatment era:** Exposed to ionizing radiation from atomic weapons testing Marshall Islands between 1946-1958 **Years of follow-up:** NR	**Study population:** N=1275 (1993 phase of the study) **Gender:** NR **Age at exposure to ionizing radiation (yrs):** NR **Age at follow-up time (yrs):** NR **Exposed to ionizing radiation:** Not clear	**Primary outcome:** The prevalence of thyroid nodules and thyroid cancer in the indigenous population residing on Ebey Island, Kwajalein Atoll, in the republic of the Marshall islands. **Inclusion criteria:** Marshallese born before 1965 **Exclusion criteria:** NR **Outcome assessment:** • The thyroid screening investigation was composed of two components: a personal interview and a clinical examination. • Each subject was examined sequentially by two endocrine surgeons highly trained in the use of ultrasound and palpation. • The definition of a nodule as imaged by ultrasound included all focal abnormalities of the echo pattern that were larger than 2 mm in diameter through the minimum nodule size that could be reliably detected was 4 mm. • Every participant who had a palpable nodule was recommended to determine its nature with FNA cytology.	**Thyroid nodules found by ultrasound screening:** • Prevalence of nodules in population screened:151/1275=11.8% **Thyroid nodules found by neck palpation:** • Prevalence of nodules in population screened: 68/1275=5.3% **Diagnostic value neck palpation for detection of nodule:** • Sensitivity: 40% • Specificity: 99% • PPV: 88% • NPV: 92% **Results fine-needle aspiration cytology:** • FNA cytology performed in N=121/123 (98%) • Results FNA cytology not clear	
Conclusion: • Using thyroid ultrasound as the gold standard determination of the presence of a thyroid nodule in individuals exposed to ionizing radiation, the sensitivity of neck palpation was 40%, the specificity of palpation was 99%, the PPV was 88% and the NPV 92%.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adulthood cancer; yrs: years; NR: not reported; yrs: years; FNA: fine-needle aspiration; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 5. What is the diagnostic value of neck palpation versus thyroid ultrasonography to predict the presence of a thyroid nodule in children/adults exposed to irradiation?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Mettler FA et al. Thyroid nodules in the population living around Chernobyl. JAMA. 1992; 268: 616-619				
Study design: Cross-sectional study **Treatment era:** Exposed to ionizing radiation at Chernobyl 1986 **Years of follow-up:** NR	**Study population:** N=1060 **Gender:** Male: 509/1060 (48%) Female: 551/1060 (52%) **Age at exposure to ionizing radiation (yrs):** NR **Age at follow-up time (yrs):** 5 yrs: N=286 10 yrs: N=290 40 yrs: N=251 60 yrs: N=233 **Exposed to ionizing radiation:** N=391	**Primary outcome:** The prevalence, size, type and distribution of thyroid nodules **Inclusion criteria:** Individuals that had been continuously residing around Chernobyl from 1985 to 1990 in seven highly contaminated villages. Subjects were chosen by birth date to be 5, 10, 40, 60 years old at the time of the study. Data were compared with six nearby control villages of the same size and type. **Exclusion criteria:** NR **Outcome assessment:** • Each subject underwent a physical examination of the thyroid by at least two physicians. • At least two of the examing physicians had to agree as to the presence of a palpable nodule. • All subjects underwent sonographic examinations performed by one of three sonographers. • A thyroid was defined as an abnormality in echogenicity measuring more than 5 mm in diameter.	**Thyroid nodules found by ultrasound screening:** • Prevalence of nodules in population screened: 75/1060 =7.1% **Thyroid nodules found by neck palpation:** • Prevalence of nodules in population screened: 18/1060=1.7% **Diagnostic value neck palpation for detection of nodule:** • Sensitivity: 20% • Specificity: 100% • PPV: 83% • NPV: 94% **Results fine-needle aspiration:** • NR **Other:** • Nodule size as (N=81 nodules): o 5-9 mm: 30% of the nodules o 10-20 mm: 58% of the nodules o > 20 mm: 12% of the nodules	
Conclusion: • Using thyroid ultrasound as the gold standard determination of the presence of a thyroid nodule in individuals exposed to ionizing radiation, the sensitivity of neck palpation was 20%, the specificity of palpation was 100%, the PPV was 83% and the NPV 94%.				

DTC: differentiated thyroid carcinoma; yrs: years; NR: not reported; yrs: years; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 6. What is the diagnostic value of thyroid ultrasonography (defined as individual radiographic ultrasound features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Al Nofal et al. Accuracy of thyroid nodule sonography for the detection of thyroid cancer in children: systematic review and meta-analysis. Clin Endocrinol. 2016; 84:423-430				
Study design: Systematic review including meta-analysis **Included studies:** 12 studies **Publishing era:** Between 1995-2010	**Study population:** NR **Number of nodules evaluated:** N=750 (169 with a history of thyroid cancer) **Gender:** NR **Age at diagnosis (yrs):** NR	**Primary outcome:** The assess the diagnostic accuracy of different thyroid US features in detecting thyroid cancer in children. **Eligibility criteria:** Randomized and non-randomized studies published in English performed in children and adolescents (age < 21 years). **Exclusion criteria:** NR **Study identification:** • Searched multiple databases from each databases' earliest inception to September 2014. • Abstracts and titles were reviewed independently and in duplicate. **Quality assessment:** Independently and in duplicate using the QUADAS2 tool **Data extraction:** Independently and in duplicate **Statistical analysis:** • Two stage model to pool the diagnostic value for each studies thyroid US feature. • A sensitivity analysis using a bivariate model to allow correlation between sensitivity and specificity was also used to see if the choice of model impacted the results. • I^2 statistic to assess heterogeneity across studies.	**Thyroid cancer incidence:** • Pooled frequency of thyroid cancer was 24% **Meta-analysis:** **Pool estimates of US features to predict malignancy:** **Internal calcifications (N= 397)** Sens: 50% (40– 61) Spec: 92% (86–95) DOR: 9.38 (3.46 –24.43) **Enlarged/suspicious lymph nodes (N=553)** Sens: 53% (44–62) Spec: 86% (85– 91) DOR: 12.08 (3.29– 44.34) **Hypo-echoic (N=227)** Sens: 51% (39– 63) Spec: 68% (60– 76) DOR: 2.13 (1.14 –3.99) **Increased nodular blood flow (N=164)** Sens: 52% (34– 70) Spec: 73% (64– 80) DOR: 2.82 (1.08–7.35) **Irregular margins (N=147)** Sens: 35% (21– 50) Spec: 93% (86– 97) DOR: 4.01 (1.06 –15.20) **Taller than wide (N=71)** Sens: 27% (13– 46) Spec: 76% (60–89) DOR: 5.06 (0.78–32.62) **Solid (N=375)** Sens: 77% (65– 86) Spec: 69% (63 - 74) DOR: 6.59 (2.84–15.3) **Pool estimates of US features to predict benign nodules:** **Cystic nodule (N=5559)** Sens: 29% (23– 35) Spec: 90% (78– 97) DOR: 2.65 (0.98 –7.16) **Isoechoic (N=7181)** Sens: 27% (20–35) Spec: 72% (59– 82) DOR: 1.22 (0.60–2.51) **Pool estimates of US features in children with a history of radiation exposure (Belarus) (2 studies, N=148 patients):** **Irregular margins** Sens: 75% (64– 85) Spec: 79% (70– 87) DOR: 9.58 (4.44 –20.67) **Internal calcifications** Sens: 43% (10– 12) Spec: 97% (72–99) DOR: 1.43 (0.29 –7.07) **Hypo-echoic (N=227)** Sens: 67% (54– 78) Spec: 65% (55– 74) DOR: 3.52 (1.06 –11.7) **Absence of halo (N=1646)** Sens: 84% (73– 92) Spec: 72% (59–82) DOR: 1.22 (0.60–2.51)	• Note that histopathologic results were not available for all patients in all included studies.
Conclusion: • Using cytology and histopathological results after surgery as the gold standard reference test to diagnose DTC in children, the diagnostic value of individual radiographic features are as follow: sensitivity/specificity of internal calcifications 50/92%, sensitivity/specificity of enlarged/suspicious lymph nodes 53/86%, sensitivity/specificity of hypoechoic nodules 51/68%, sensitivity/specificity of increased nodular blood flow 52/73%, sensitivity/specificity of irregular margins 35/86%, sensitivity/specificity of taller than wider 27/76%, sensitivity/specificity of a solid				

nodule 77/69%. The findings of the patients with a history of radiation exposure (2 studies, N=148) consistent with the results from the meta-analysis of the studies that included patients with no radiation exposure.

DTC: differentiated thyroid carcinoma; yrs: years; DOR: diagnostic odds ratio; CI: confidence interval; US: ultrasound; sens: sensitivity; spec: specificity

Clinical question 6. What is the diagnostic value of thyroid ultrasonography (defined as individual radiographic ultrasound features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Remonti LR et al. Thyroid ultrasound features and risk of carcinoma: A systematic review and meta-analysis of observational studies. Thyroid. 2015;25:538-550				
Study design: Systematic review including meta-analysis **Included studies:** 52 studies **Publishing era:** Between 1985 -2012	**Study population:** NR **Number of nodules evaluated:** N=12,786 **Gender:** NR **Age at diagnosis (yrs):** Mean age ranging from 33.0-55.2	**Primary outcome:** To evaluate the diagnostic performance of US features for thyroid malignancy in patients with unselected thyroid nodules and nodules with indeterminate FNA cytology. **Eligibility criteria:** Observational studies of patients with thyroid nodules evaluated by US and submitted to thyroidectomy regardless of the reason for surgery (only studies with histopathologic diagnosis of surgical specimens were considered). **Exclusion criteria:** NR **Study identification:** • Searched multiple databases from each databases' earliest inception to July 2012 • Abstracts and titles were reviewed in duplicate (independently?) **Quality assessment:** Independently and in duplicate using the QUADAS2 tool **Data extraction:** In duplicate (independently?) **Statistical analysis:** • The overall OR was calculated to assess the predictive value of each US feature for malignancy. Risk estimates were obtained with a random effects meta-analysis. • I^2 statistic and Cochrane's Q test to assess heterogeneity across studies. • Publication bias was assessed using a funnel plot. Funnel plot asymmetry was analyzed by the Begg and Egger tests.	**Thyroid cancer incidence:** • Pooled frequency of thyroid cancer was 20% **Meta-analysis:** **Pool estimates of US features to predict malignancy:** **Taller than wide** Sens: 26.7% Spec: 96.6% **Halo absent** Sens: 56.4% Spec: 72.0% **Absence of elasticity** Sens: 87.9% Spec: 86.2% **Heterogeneity** Sens: 47.5% Spec: 70.0% **Hypoechogenicity** Sens: 62.7% Spec: 62.3% **Solid** Sens: 72.7% Spec: 53.2% **Microcalcifications** Sens: 39.5% Spec: 87.8% **Solitary** Sens: 53.0% Spec: 60.2% **Central vascularization** Sens: 45.9% Spec: 78.0% **Irregular margins** Sens: 50.5% Spec: 83.1% **Pool estimates of US features to predict malignancy in thyroid nodules with indeterminate FNA cytology:** **Hypoechogenicity** Sens: 49.7% Spec: 56.0% **Microcalcifications** Sens: 45.6% Spec: 81.9% **Central vascularization** Sens: 8.4% Spec: 96.0%	• Included studies had in general a low risk of bias. • Study has overlap of included studies with Brito et al. • Study has no overlap of included studies with Woliński et al. • Note that histopathologic results were not available for all patients in all included studies.
Conclusion: • Using cytology and histopathological results after surgery as the gold standard reference test to diagnose DTC in adults, the diagnostic value of individual radiographic features are as follow: sensitivity/specificity of taller than wide 27/97%, sensitivity/specificity of halo absent 56/72%, sensitivity/specificity of absence of elasticity 88/86%, sensitivity/specificity heterogeneity 48/70%, sensitivity/specificity of hypoechogenicity 63/62%, sensitivity/specificity of a solid nodule 73/53%, sensitivity/specificity of microcalcifications 40/88%, sensitivity/specificity of solitary 53/60%,				

sensitivity/specificity central vascularization 46/78%, sensitivity/specificity of irregular margins 51/83%.

NR: not reported; yrs: years; FNA: fine-needle aspiration; DOR: diagnostic odds ratio; CI: confidence interval; US: ultrasound; sens: sensitivity; spec: specificity

Clinical question 6. What is the diagnostic value of thyroid ultrasonography (defined as individual radiographic ultrasound features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Brito JP et al. The accuracy of thyroid nodule ultrasound to predict thyroid cancer: systematic review and meta-analysis. J Clin Endocrinol Metab. 2014;99:1253-1263				
Study design: Systematic review including meta-analysis **Included studies:** 31 studies **Publishing era:** Between 1985 -2012	**Study population:** N=13,736 **Number of nodules evaluated:** N=18,288 **Gender:** Male: 18% Female: 82% **Age at diagnosis (yrs):** Mean 47.0	**Primary outcome:** The accuracy of thyroid nodule ultrasound to predict thyroid cancer **Eligibility criteria:** RCT's and cohort studies that enrolled adults with thyroid nodules with sonography results or reported diagnostic measures of sonography. Studies in English were included, regardless of their sample size or publication status. **Exclusion criteria:** Reports that had a study population with a prior history of thyroid cancer or were clearly exposed to known risk factors for thyroid cancer e.g. Chernobyl survivors. **Study identification:** • Searched multiple databases from each databases' earliest inception to December 2012 • Abstracts and titles were reviewed independently and in duplicate **Quality assessment:** Independently and in duplicate using the QUADAS2 tool **Data extraction:** Independently and in duplicate **Statistical analysis:** • Random effects model of DerSimonian and Laird to pool sensitivities, specificities, likelihood ratios, and DORs and estimate the 95% CI for each feature • I^2 statistic and Cochrane's Q test to assess heterogeneity across studies • Publication bias was assessed using a funnel plot	**Thyroid cancer incidence:** • Pooled frequency of thyroid cancer was 20% **Meta-analysis:** **Pool estimates of US features to predict malignancy:** **Internal calcifications (N= 17,151)** Sens: 54% (52– 56) Spec: 81% (80–82) DOR: 6.78 (4.48 –10.24) **Hypoechoic (N=17,014)** Sens: 73% (72– 75) Spec: 56% (50– 57) DOR: 4.5 (3.2– 6.4) **Increased blood flow (centrally) (N=7578)** Sens: 48% (43– 51) Spec: 53% (51– 54) DOR: 1.8 (1.48 –2.2) **Infiltrative margins (N=4390)** Sens: 56% (50– 50) Spec: 79% (77– 80) DOR: 6.89 (3.35–14.1) **Taller than wider (N=3137)** Sens: 53% (50– 56) Spec: 93% (91– 94) DOR: 11.14 (6.6 –18.9) **Absence of halo (N=1646)** Sens: 26% (20– 32) Spec: 69% (66–71) DOR: 0.54 (0.21–1.39) **Solid nodule (N=6303)** Sens: 87% (85– 89) Spec: 56% (54–58) DOR: 4.45 (2.63–7.5) **Size nodule > 1 cm (N=8897)** Sens: 57% (54–60) Spec: 40% (39–41DOR: 1.1 (0.48 –2.5) **Size nodule > 3 cm N=582)** Sens: 37% (29–44) Spec: 59% (54–64) DOR: 0.94 (0.57–1.23) **Size nodule > 4 cm (N=380)** Sens: 24% (17– 32) Spec: 77% (70 - 82) DOR: 1.3 (0.47–3.79) **Pool estimates of US features to predict benign nodules:** **Isoechoic (N=7181)** Sens: 47% (46–48) Spec: 84% (83– 86) DOR: 3.6 (2– 6.3) **Increased blood flow (peripherally)(N= 766)** Sens: 38% (34–41) Spec: 86% (79–91) DOR: 3 (0.56 –16.3) **Spongiform (N= 880)** Sens: 10% (8–14) Spec: 99% (99 –100) DOR: 12 (0.61–234.3) **Cystic nodule (N=5559)** Sens: 32% (31– 33) Spec: 98% (97– 99) DOR: 6.78 (2.26 –20.3)	• Taller than wider was a feature reported in only 12 of the included studies. • Study has no overlap of included studies with Woliński et al. • Note that histopathologic results were not available for all patients in all included studies.
Conclusion: • Using cytology and histopathological results after surgery as the gold standard reference test to diagnose DTC in adults, the diagnostic value of individual radiographic features are as follow: sens/spec of internal calcifications 54/81%, sens/spec of hypoechoic nodules 73/56%, sens/spec of increased central blood flow 48/53%, sens/spec of infiltrative margins 56/79%, sens/spec of taller than wider 53/93%, sens/spec of absence of halo 26/69%, sens/spec of solid nodule 87/56%, sens/spec of nodule size > 1 cm 57/40%, sens/spec nodule size > 3 cm 37/59%, sens/spec nodule size > 4 cm 24/77%.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; RCT: randomized controlled trial; DOR: diagnostic odds ratio; CI: confidence interval; US: ultrasound; sens: sensitivity; spec: specificity

Clinical question 6. What is the diagnostic value of thyroid ultrasonography (defined as individual radiographic ultrasound features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Woliński K et al. Usefulness of different ultrasound features of malignancy in predicting the type of thyroid lesions: a meta−analysis of prospective studies. Pol Arch Med Wewn. 2014;124:97-104				
Study design: Systematic review including meta-analysis **Included studies:** 14 studies **Publishing era:** Between 2007-2013	**Study population:** N=4479 **Number of nodules evaluated:** N=5439 **Gender:** NR **Age at diagnosis (yrs):** NR	**Primary outcome:** Evaluate and compare the diagnostic value of ultrasound features of malignancy in differentiating benign and malignant thyroid lesions. **Eligibility criteria:** Only prospective studies conducted not earlier than in 2002 and performed with the use of a transducer with the frequency of at least 7.5 MHz. Only studies in English were included. **Exclusion criteria:** Studies in which the diagnosis of malignant, or suspicious, nodules was based only on cytopathology, without subsequent histopathological examination. Studies focusing only on particular subgroups of patients. Studies focusing only on particular types of nodules. **Study identification:** • Searched multiple databases from each databases' earliest inception to December 2012 • Abstracts were screened by one reviewer for inclusion, and checked for discrepancies by a second reviewer **Quality assessment:** NR **Data extraction:** Independently by two reviewers **Statistical analysis:** • OR's and risk ratios (RRs) using a random-effects model using the Statistica v.10 software with medical package.	**Incidence thyroid cancer:** • Pooled frequency of thyroid cancer was 20% **Meta-analysis:** **Microcalcifications (N= 5308 - 718 malignant, 13.5%)** Sens: 44.1% (37.9–51.3) Spec: 75.9% (70.3–82.0) OR: 7.1 (4.3–11.9) **Hypoechogenicity (N= 5179 nodules - 682 malignant, 13.2%)** Sens: 68.7% (58.8%–82.6%) Spec: 60.3% (53.4%–68.2%): OR: 3.2 (2.3–4.5) **Irregular margins (N= 5296 - 707 malignant, 13.3%)** Sens: 45.5% (30.9%–66.9%) Spec: 79.6% (71.9%–88.2%) OR: 7.2 (4.5–11.5) **Taller-than-wide shape (N=665 nodules - 170 malignant, 25.6%)** Sens: 25.9% (12.1%–55.3%) Spec: 95.9% (48.3%–100.0%) OR: 13.7 (4.1–45.7) **Halo absence (N= 648 nodules - 112 malignant, 17.2%)** Sens: 63.8% (38.1–100.0) Spec: 47.5% (33.4–67.8) OR: 3.8 (1.7–8.5) **Color Doppler examination (N= 1048 nodules - 214 malignant, 20.4%)** Sens: 44.2% (33.6–58.2) Spec: 81.5% (67.8–98.0) OR: 4.3 (3.1–6.1)	• Study has no overlap of included studies with Brito JP et al. • Note that histopathologic results were not available for all patients in all included studies.
Conclusion: • Using cytology and histopathological results after surgery as the gold standard reference test to diagnose DTC in adults, the diagnostic value of individual radiographic features are as follow: sens/spec of microcalcifications 44.1/75.9%, sens/spec of hypoechoic nodules 68.7/60.3%, sens/spec of irregular margins 45.5/79.6%, sens/spec of taller than wider 25.9/95.9%, sens/spec of absence of halo 63.8/47.5%, sens/spec of color doppler examination 44.2%/81.5%.				

DTC: Differentiated thyroid carcinoma; NR: not reported; yrs: years; OR: odds ratio; RR: relative risk's; CI: confidence interval; sens: sensitivity; spec: specificity

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Kim et al. Ultrasound-based diagnostic classification for solid and partially cystic thyroid nodules. AJNR. 2012 ;33:1144-1149				
Study design: Prospective cohort study	**Study population:** N=1036 **Number of nodules evaluated:** N=1289 **Gender:** Male: 160/1036 (15%) Female: 876/1036 (85%) **Age at US assessment (yrs):** Mean 49.0 ± 12.0 **Patients with a history of radiation exposure:** NR	**Primary outcome:** To assess the diagnostic efficacy of thyroid US with 5 category system **Inclusion criteria:** Patients who underwent thyroid US between January 2008 and December 2009 were enrolled in the study. Each underwent US-FNA cytology for ≥ 1 thyroid nodule ≥ 5 mm in the largest diameter. **Exclusion criteria:** NR **Outcome assessment:** • Real-time US was performed by an experienced radiologist by using a high-resolution sonographic instrument with a 12-to-5 MHz linear probe • The following US characteristics were assessed: 1) solid/cyst 2) echogenicity 3) calcification 4) margins 5) vascular pattern 6) cervical nodes • US classified as solid >> benign, probably benign, borderline, possibly malignant, malignant. If cystic/solid>> benign, probably benign, possibly malignant, malignant	**Size of the nodules:** Mean 1.5 (range 0.5-9.8 cm) **Inadequate FNA cytology results:** N=96 (4%) **Histological diagnosis:** Available for N=50/1289 (39%) nodules **Overall diagnostic value ultrasonography to predict malignant pathology:** **Solid (include borderline in malignant category):** • Sensitivity: 87.5% • Specificity: 81.2% • PPV: 89.9% • NPV: 77.3% • Accuracy: 85.4% **Partially cystic:** • Sensitivity: 66.7% • Specificity: 88.9% • PPV: 75.0% • NPV: 84.2% • Accuracy: 81.5%	• Histopathologic results were available for N=50 nodules (39%)
Conclusion: Using cytology and histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (US classification system based on the following US characteristics: solid/cyst, echogenicity, calcification, margins, vascular pattern, cervical nodes) was 87.5%, the specificity was 81.2%, the PPV was 89.9% and the NPV was 77.3%. This US classification has high good sensitivity, specificity, accuracy for predicting malignancy, slightly more so for solid vs. partially cystic. Note that histopathology results were available for 39% of the nodules and that US characteristics were prospectively assessed with real-time US.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; TIRADS: thyroid imaging reporting and data system; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNAC: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Ozel A et al. The diagnostic efficiency of ultrasound characterization for thyroid nodules: how many criteria are required to predict malignancy? Med Ultrason. 2012;14:24-28				

Study design:
Retrospective cohort study
	Study population:
	N=439
	
	Number of nodules evaluated:
	N=439
	
	Gender:
	Male: 56/439 (13%)
	Female: 307/439 (87%)
	
	Age at US assessment (yrs):
	Mean 47.6
	
	Patients with a history of radiation exposure:
	NR
		Primary outcome:
		To define the criteria for use in differentiating benign and malignant nodules.
		
		Inclusion criteria:
		a) Patients with an initial benign cytology and US follow-up b) patient who underwent surgery after FNA cytology for malignant nodules c) patients who underwent surgery after indeterminate cytology with FNA cytology.
		
		Exclusion criteria:
		Patients with nodules with non-diagnostic cytology and patients without a final tissue diagnosis
		
		Outcome assessment:
		• Thyroid US were performed with an Aplio XV with a 7-14 MHz linear array transducer.
		• The following US features were assessed for each nodule: shape, margin, echogenicity, echostructure, presence of calcifications, and vascularity on color Doppler.
		• US-guided FNA biopsies were performed by two experienced radiologists'.
		• The US features were determined by two experienced radiologists in consensus.
		• The presence or absence of each US feature were scored 1 and 0 respectively.
		• For each nodule the total US score was obtained by the sum of each individual score of US features.
		• The nodules were categorized in two groups in respect to size (≤ 10 mm and > 10 mm).
			Size of the nodules:
			Mean 17.3 (range 4-49 mm)
			
			Inadequate FNA cytology results:
			Excluded from the analysis
			
			Histological diagnosis:
			Available for N=36/439 (8%)
			• Malignant: N=22/36 (61%)
			• Benign: N=14/36 (39%)
			
			Overall diagnostic value ultrasonography to predict malignant pathology:
			• **< 10 mm:**
			  • Sensitivity: 83.5%
			  • Specificity: 94.9%
			  • PPV: 62.5%
			  • NPV: 98.2%
			  • Accuracy: 93.8%
			
			• **> 10 mm:**
			  • Sensitivity: 62.5%
			  • Specificity: 83.5%
			  • PPV: 30.3%
			  • NPV: 97.7%
			  • Accuracy: 89.9%
				• Histopathologic results were available for only N=36 patients (8%)

Conclusion: Using cytology and histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (US classification system based on the following US characteristics: shape, margin, echogenicity, echostructure, presence of calcifications, and vascularity on color Doppler) for nodules < 10 mm was 83.5%, the specificity was 94.9%, the PPV was 62.5% and the NPV was 98.2%. The sensitivity for nodules > 10 mm was 62.5%, the specificity was 83.5%, the PPV was 30.3% and the NPV was 97.7%. Note that histopathology results were available for only 8% of the patients.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Hong YJ et al. Positive predictive values of sonographic features of solid thyroid nodule. Clin Imaging. 2010;34:127-133				
Study design: Retrospective cohort study	**Study population:** N=462 **Number of nodules evaluated:** N=530 solid lesions **Gender:** Male: 75/462 (16%) Female: 387/462 (84%) **Age at US assessment (yrs):** Mean 50.6 (range 15-87) **Patients with a history of radiation exposure:** N=0	**Primary outcome:** The PPV value of the suspicious sonographic features of solid thyroid nodules. **Inclusion criteria:** Sonographically detected nodules on which the US-guided FNA cytology had been performed (had ≥ 1 suspicious US feature) between January to December 2005. **Exclusion criteria:** Nodules that were purely cystic, inadequate pathology, suspicious US with no surgery. **Outcome assessment:** • Sonography was performed by two radiologists with an HDI 3500 or HDI 5000 scanner, linear array 7-12 MHz transducer. • Two experienced radiologists (3 and 7 year respectively) evaluated all sonographic images retrospectively without any information. • Each lesion was described in terms of calcifications, margin, echogenicity and shape. • FNA biopsy was performed with 23-gauge needle with US-guidance, free-hand technique.	**Size of the nodules:** Mean 8.2 mm (range 3-35 mm) **Inadequate FNA cytology results:** N=36 (not included in the analysis) **Histological diagnosis:** Available for 105/462 (23%) patients • Malignant: N=79/105 (75%) • Suspicious: N=14/105 (13%) • Follicular: N=5/105 (5%) • Benign: N=7/105 (7%) **Overall diagnostic value ultrasonography to predict malignant pathology of more than two sonographic suspicious findings (microcalcifications, irregular margin, hypoechogenicity, taller than wide shape) :** ○ Sensitivity: 47.5% ○ Specificity: NR ○ PPV: NR ○ NPV: NR	• Not possible to calculate specificity, PPV and NPV due to N=145 cases with suspicious cytology. • Histopathology results were only available for N=105 patients (23%).
Conclusion: Using cytology and histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (more than two sonographic features (microcalcifications, irregular margin, hypoechogenicity, taller than wide shape) was 47.5%. Note that histopathology results were only available for N=105 patients (23%).				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Cavaliere A et al. A useful ultrasound score to select thyroid nodules requiring fine needle aspiration in an iodine-deficient area. J Endocrinol Invest. 2009;32: 440-444				

Study design:
Retrospective cohort study
	Study population:
	N=2642
	
	Number of nodules evaluated:
	N=3645
	
	Gender:
	Male: 739/3645 (20%)
	Female: 2906/3645 (80%)
	
	Age at US assessment (yrs):
	Mean 55.2 (range 5-91)
	
	Patients with a history of radiation exposure:
	NR
		Primary outcome:
		Utility of ultrasound to predict malignancy in Th2 (benign), Thy4 (susp), and Thy5(malignant) cytology lesions.
		
		Inclusion criteria:
		Patients undergoing ultrasound guided-FNA cytology for nodules >5mm, at the outpatient section of Endocrinology, department of internal medicine.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• All nodules were evaluated by color-doppler US.
		• In all cases a double cytologic sample was taken and reviewed in blind by two senior pathologists (Thy 1: non-diagnostic, Thy2: non-neoplastic, Thy 3: follicular lesion, Thy 4: suspicious of malignancy, Thy 5: diagnostic of malignancy).
		• To differentiate between thyroid cancer and benign thyroid nodules, the results were considered true-negative or false-negative when the US excluded thyroid cancer or failed to detect malignancy.
		• Nondiagnostic aspirate and follicular neoplasm aspirate were excluded from the analysis.
		• A 10-point score was constructed using the following US parameters: single nodule, solid, hypochoic, absent or partial halo, microcalcifications, echostructure, AP/TR>1, weighted on basis of the logistic regression analysis.
			Size of the nodules:
			Mean 2.45 cm (range 0.5-16 cm)
			
			Inadequate FNA cytology results:
			26 follicular lesions, 14 suspicious, 45 positive for malignancy (together - 2.1% of total population)
			
			Histological diagnosis:
			Available for 230/2642 (8%) patients
			• Malignant: N=49/230 (21%)
			• Benign/suspicious: N=181/230 (79%)
			
			Overall diagnostic value ultrasonography:
			10-point ultrasound score:
			• <2.4 points: 0.4% risk of cancer
			• 2.5-5.5 points: 1.1% risk of cancer
			• >5.4 points: 5.6% risk of cancer
			  ○ Sensitivity for US score >5.4:66%
			  ○ Specificity for US score >5.4: 76%
			  ○ PPV: NR
			  ○ NPV: NR
				• Nodules evaluated when >5mm
				
				• British Thyroid Association cytology classification used
				
				• Note -VERY HIGH rate of microcalcification noted (2256 of 3645 - 62%)
				
				• Iodine deficient area and population
				
				• 10-point US score only calculated for Thy2, Thy4, and Thy5 categories:
				
				• Thy4 and Thy5 grouped together - unclear if all Thy4 were malignant**?**
				
				• Histopathology results were only available for N=230 patients (8%)

Conclusion: Using cytology and histopathology results after surgery as the gold standard reference test to diagnose thyroid carcinoma, the sensitivity for combinations of radiographic features (using the 10-point ultrasound score with a cut-off value of > 5.4 points) was 66% and the specificity 76%. Note that this study was performed in an iodine deficient area and population and that histopathology results were only available for 230 patients (8%).				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration; AP: antero-posterior; TR: transversal
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Horvath E et al. An ultrasonogram reporting system for thyroid nodules stratifying cancer risk for clinical management. J Clin Endocrinol Metab. 2009;94:1748-1751				
Study design: Prospective cohort study	**Study population:** NR **Number of nodules evaluated:** N=1097 **Gender:** NR **Age at US assessment (yrs):** NR **Patients with a history of radiation exposure:** NR	**Primary outcome:** Evaluate TIRADS (thyroid Imaging Reporting and Data system) classification **Inclusion criteria:** Thyroid nodules submitted for FNA cytology between 2003 and 2006 were analyzed **Exclusion criteria:** NR **Outcome assessment:** • FNA biopsy was performed by five specialized radiologists under US guidance using a 19 or 21-gauge needle. • Two experienced pathologists read all the samples. • The following US findings were considered: echostructure, echogenicity, shape, orientation, acoustic transmission, borders, surface, presence or absence of a capsule, calcifications, and vascularisation. • The FNA cytology results were correlated to the defined US patterns and a TIRADS classification system was generated. • TIRADS 1-6 classification used: 1 Normal thyroid 2 Benign condition (0% malignancy) 3 Probably benign (<5% chance) 4 Suspicious (5-80% malignancy rate) 4a (5-10%) 4b (10-80%) 5 Probably malignant (malignancy >80%) 6 Biopsy proven malignant nodules • Nodules with malignant FNA cytology went to surgery, benign are being followed – after a follow-up of 3.9 yrs, 31% of pts with indeterminate histology had surgery.	**Size of the nodules:** Range 4-60 mm **Inadequate FNA cytology results:** NR **Histological diagnosis:** NR **Overall diagnostic value ultrasonography to predict malignant pathology according to the TIRADS classification:** ○ Sensitivity: 88% ○ Specificity: 49% ○ PPV: 49% ○ NPV: 88% ○ Accuracy: 94%	• Correlation between TIRADS classification and FNA cytology results investigated and not related to the histological diagnosis. • Unclear for how many patients' histopathology results were available.
Conclusion: Using cytology results as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (using the TIRADS classification) was 88%, the specificity was 49%, the PPV was 49% and the NPV was 88%. Note that it was unclear for how many patients' histopathology results were available.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; TIRADS: thyroid imaging reporting and data system; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Lin JH et al. The role of neck ultrasonography in thyroid cancer. AM J Otolaryngol. 2009;30:324-326				
Study design: Retrospective cohort study	**Study population:** N=378 **Number of nodules evaluated:** N=378 **Gender:** Male: 97/378 (26%) Female: 281/378 (74%) **Age at US assessment (yrs):** Mean: 43.5 (14-77) **Patients with a history of radiation exposure:** N=0	**Primary outcome:** To assess the diagnosis accuracy rate of neck ultrasonography characteristics in thyroid cancer. **Inclusion criteria:** Patients with palpable nodules who underwent thyroid total lobectomy or total thyroidectomy. **Exclusion criteria:** Patients with locally advanced thyroid nodules or those with distant metastasis during initial clinic examination, patients with known thyroid disease history, and the patients who had any radiation therapy to the head or neck area'. **Outcome assessment:** • Preoperative evaluations included neck US, US guided FNA cytology, and Tc-99m scintigraphy. • Neck US was performed using a real-time ultrasonographic scanner. • Thyroid nodules were measured in 3 dimensions. The echo structure, echogenicity, calcification, and margin were recorded. • Solid echo structure, hypoechogenicity, fine calcification, and ill-defined margin were classified as malignant US characteristics. • If any one malignant characteristic was recorded, this nodule was classified to the malignant group. • Benign group was without any one of malignant characteristics.	**Size of the nodules:** NR **Inadequate FNA cytology results:** NR **Histological diagnosis:** Available for N=378/378 (100%) patients • Malignant: N=81/378 (21%) • Benign: N=297/378 (79%) **Overall diagnostic value ultrasonography to predict malignant pathology:** • Sensitivity: 51.9% • Specificity: 93.9% • PPV: 63.6% • NPV: 90.5% • Accuracy: 86.8%	• Histopathologic results were available for all patients.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (using the presence of ≥ 1 malignant features (solid echo structure, hypoechogenicity, fine calcification, and ill-defined margin)) was 51.9%, the specificity was 93.9%, the PPV was 63.6% and the NPV was 90.5%. Note that histopathology results were available for all patients.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; TIRADS: thyroid imaging reporting and data system; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Popowicz B et al. The usefulness of sonographic features in selection of thyroid nodules for biopsy in relation to the nodule's size. Eur J of Endocrinol. 2009;161:103-111				

Study design:
Retrospective cohort study
	Study population:
	N=672
	
	Number of nodules evaluated:
	N=1141
	
	Gender:
	NR
	
	Age at US assessment (yrs):
	Mean 49.5 ± 11.4
	
	Patients with a history of radiation exposure:
	N=0
		Primary outcome:
		To evaluate the efficacy of selected US features of thyroid focal lesions useful for establishing indications for FNA cytology with regard to the lesion's size.
		
		Inclusion criteria:
		Patients for which there were US features, data on palpability and postoperative histopathological outcomes available.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• All the US examinations were performed by the team of three physicians with at least five years experience.
		• The following features were analysed: shape, echogenicity, pattern of blood flow in power Doppler imaging, the presence of intranodular microcalcifications, the presence of other lesions in the thyroid.
		• The efficacy of the US features was evaluated separately for small nodules (<15 mm) and large nodules (> 15 mm).
		• The impact of various criteria based on a combination of the above mentioned features was evaluated.
			Size of the nodules:
			• Large nodules (>15 mm): Mean 32.9 (range 15-80 mm)
			• Small nodules (<15 mm): Mean 11.25 (range 4-15 mm)
			
			Inadequate FNA cytology results:
			Excluded from the analysis
			
			Histological diagnosis:
			Available for N=1141/1141 (100%)
			• Malignant: N=96/1141 (8%)
			• Benign: N=1045/1141 (92%)
			
			Overall diagnostic value ultrasonography to predict malignant pathology:
			Lesions with at least one of the following US features: hypoechogenicity, microcalcifications, solitary occurrence or height-to-wide ratio
			• **< 15 mm:**
			  • Sensitivity: 98%
			  • Specificity: 44%
			  • PPV: NR
			  • NPV: NR
			
			Lesions with at least one of the following US features: hypoechoic more tall than wide, contain microcalcifications
			• **>15 mm:**
			  • Sensitivity: 84%
			  • Specificity: 72%
			  • PPV: NR
			  • NPV: NR
				• Histopathology results were available for all patients.

Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (US classification system based on nodules containing at least one of the following US features: hypoechogenicity, microcalcifications, solitary occurrence or height-to-wide ratio) for nodules < 15 mm was 98%, the specificity was 44%. The sensitivity for nodules > 15 mm was (US classification system based on nodules containing at least one of the following US features: hypoechogenicity, more tall than wide, contain microcalcifications) 84%, the specificity was 72%. Note that histopathology results were available for all patients.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FN: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Moon HG et al. Role of ultrasonography in predicting malignancy in patients with thyroid nodules. World J Surg. 2007;31:1410-1416				
Study design: Retrospective cohort study	**Study population:** N = 507 (authors describe 857 initial subjects, but exclude 252 individuals with indeterminate US findings and the another 98 with indeterminate/nondiagnostic cytology prior to analysis). **Number of nodules evaluated:** Unclear - most of the text implies that this was a "per patient" rather than "per nodule" analysis (diagnosis of cancer applied to patient rather than to specific nodule(s) within patient). **Gender:** NR for total group. For the subset of 153 operated patients: Male: 41/153 (27%) Female: 112/153 (73%) **Age at US assessment (yrs):** NR for total group. For the subset of 153 operated patients: mean 44.5 ± 21.3 yrs **Patients with a history of radiation exposure:** NR	**Primary outcome:** To determine if an US classification system can predict malignancy risk (comparison to cytology, then separate comparison of subset to operative pathology). **Inclusion criteria:** Patients who underwent US and US-guided FNA for euthyroid thyroid nodules between January 2004 and April 2006. **Exclusion criteria:** 1)previous thyroid surgery; 2) previous FNA cytology; 3) "thyroid nodules already confirmed to be malignant"; 4) "clinical findings such as suspicious cervical lymph node metastases, which suggests thyroid malignancy" **Outcome assessment:** • All US performed by a two radiologists using a >7.5 MHz linear-array transducer • The following US features were assessed in nodules and considered "features of malignancy": 1) irregular shape; 2) speculated or ill-defined margin status; 3) marked hypoechogenicity; 4) presence of micro- or microcalcifications; and 5) shape (height > width). • Radiologists categorized nodules as 1) suspicious malignancy (solid and >2 features of malignancy); 2) indeterminate (solid and 1 feature of malignancy); or 3) probably benign (cystic or no feature of malignancy). • FNA biopsies were performed with US guidance and cytologic results categorized as: ''malignancy''; ''probably malignancy", ''benign''; ''probably benign'; ''indeterminate cytology including follicular neoplasm"; or ''nondiagnostic aspirate".	**Size of the nodules:** NR for total group. For the subset of 153 operated patients: 1.68 +/- 1.13 cm **Indeterminate FNA cytology results:** At least 11.4% (98/605) **Histological diagnosis:** Available for N=153/507 (30%) Malignant N = 84/153 (55%) Benign N = 69/153 (45%) **Overall diagnostic value ultrasonography:** **Predictive value of US compared to operative pathology (N=153 patients):** Sensitivity: 93.3% Specificity: 90.6% PPV: 91.8% NPV: 92.3% **Predictive value of US compared to cytology (N=507 patients):** Sensitivity: 84.9% Specificity: 95.5% PPV: 96.9% NPV: 79.3%	• There seems to be a typographic error in the authors' description of US categorization under "Patients and methods" (page 2). The reviewer infers that the "suspicious malignancy" category includes nodules that display a solid nature with 2 or more features of malignancy, rather than "solid nature with more than two features of malignancy". Otherwise, nodules with 2 features of malignancy cannot be categorized.
Conclusion: Using cytology and histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features was 93.3%, the specificity was 90.6%, the PPV was 91.8% and the NPV was 92.3%. Using cytology results as the gold standard reference test to diagnose DTC, the sensitivity of combined radiographic features was 84.9%, the specificity was 95.5%, the PPV was 96.9% and the NPV was 79.3%. Note that histopathology results were available for only N=153 patients (30%).				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Cappelli C et al. Thyroid nodule shape suggests malignancy. Eur J Endocrinol 2006;155: 27-31				
Study design: Retrospective cohort study	**Study population:** N=4495 (original cohort 5198, patients with indeterminate FNA cytology results were not included in the analysis) **Number of nodules evaluated:** N=7455 (6135 evaluable) **Gender:** Male: 1377/4495 (31%) Female: 3118/4495 (69%) **Age at US assessment (yrs):** NR **Patients with a history of radiation exposure:** N=0	**Primary outcome:** To evaluate sonographic characteristics that predict malignant or benign disease independent of size **Inclusion criteria:** Thyroid nodules investigated by US-FNA cytology investigated by US_FNA cytology in 5198 patients refereed to our hospital from January 1991 to September 2004. **Exclusion criteria:** NR **Outcome assessment:** • US investigation was performed using an ultrasonographic scanner (Siemens Elegra or ATL 5000) equipped with a 10-12 MHz linear transducer for morphological study and 4.7 MHz for colour-Doppler evaluation. • Examinations were conducted and recorded by two skilled sonographers according to a standard procedure (not blinded to each other). • The following US characteristics were assessed: 1) echographic dimension 2) echogenicity 3) calcification 4) margins 5) vascular pattern. • UG- FNA cytology was performed in all patients using a 25-gauge needle and capillarity action with a free-hand technique. • All patients with suspicious (follicular and Hurthle) or malignant cytology underwent surgery. • Neoplastic lesions outside the nodule were considered incidental and not included in the analysis.	**Size of the nodules:** Mean 15.5 ± 9.0 mm < 1 cm: N=2865/7455 (38%) nodules > 1 cm: N=4590/7455 (62%) nodules **Inadequate FNA cytology results:** N=1320/7455 (18%) nodules (in N=703 patients). These nodules were not included in the analysis. **Histological diagnosis:** Available for N=349/4495 (8%) patients • Malignant N=284/349 (81%) • Benign N=65/349 (19%) **Diagnostic value US features:** **Model 1: DERIVED criteria: echographic dimension + at least two of the following US features: size, hypo-echoic, blurred margins, calcifications** ○ Sensitivity: 99% ○ Specificity: 57% ○ PPV:6% ○ NPV: 99% ○ Performed FNA cytology: 72% ○ Missed carcinoma: 0.9% **Model 2: DERIVED criteria: hypo-echoic pattern + at least one US features: size, hypo-echoic, blurred margins, calcifications, vascularity type 2:** ○ Sensitivity: 79% ○ Specificity: 61% ○ PPV:9% ○ NPV: 98% ○ Performed FNA cytology: 39% ○ Missed carcinoma: 23%	• Histopathology results were available for only 349 patients (8%).
Conclusion: Using cytology and histopathological results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (echographic dimension + at least two of the following ultrasound features: size, hypo-echoic, blurred margins, calcifications) was 99%, the specificity was 57%, the PPV was 6% and NPV 6%. The number of missed carcinomas: 0.9%. Note that histopathology results were available for only 349 patients (8%).				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
***Tae HJ* et al.** Diagnostic value of ultrasonography to distinguish between benign and malignant lesions in the management of thyroid nodules. Thyroid. 2007; 17:461-466				
Study design: Retrospective cohort study	**Study population:** N=580 **Number of nodules evaluated:** N = 580 (authors describe presence of 1255 nodules, but only 580 nodules had both US and cytologic/histologic data for correlation) **Gender:** Male: 77/580 (13%) Female: 503/580 (86%) **Age at US assessment (yrs):** Mean: 47.8 ± 13.9 **Patients with a history of radiation exposure:** NR	**Primary outcome:** To determine if an US classification system previously proposed by Kim et al in AJR 2002 178:687-691 can predict malignancy risk (comparison to cytology or operative pathology). **Inclusion criteria:** Patients who underwent thyroid US at St. Mary's Hospital, Seoul, Korea between 2003 and 2005 **Exclusion criteria:** After the initial description of US features in 580 patients, 38 patients (6.6%) with non-diagnostic aspirates were excluded from the final analysis of cytology and cancer risk. **Outcome assessment:** • All US performed by a single radiologist using a 5-12 MHz linear-array transducer. • The following US features were considered suspicious for malignancy and assessed in nodules: 1) microcalcifications; 2) irregular or microlobulated margin; 3) marked hypoechogenicity (compared to strap muscle); shape taller than wide (AP measurement >transverse measurement). • Nodules were categorized on the basis of US features into one of 3 categories: Category 3 (malignant) defined as having ≥1 of the above suspicious US features; Category 2 (benign) defined as having none of the above suspicious US features; Category 1 (benign) defined as an anechogenic cystic nodule.	**Size of the nodules:** Mean 2.1 ±1.0 cm **Indeterminate FNA cytology results:** NR **Histological diagnosis:** Available for N=78/580 (13%) • Malignant: N=96/1141 (8%) • Benign: N=1045/1141 (92%) Results divided by US category: • Category 3 (N=124, after excluding 8 with non-diagnostic FNA): Malignant N=60/124 (48%) Benign N=64/124 (52%) Note: 49 patients underwent surgery • Category 2 (N = 409, after excluding 27 with non-diagnostic FNA cytology): Malignant N = 9/409 (2%) Benign N=400/409 (%) Note: 29 patients underwent surgery • Category 1 (N=9, after excluding 3 with non-diagnostic FNA): Malignant N=0/9 (0%) Benign N=9/0 (100%) Note: 0 patients underwent surgery **Overall diagnostic value ultrasonography:** • Sensitivity: 87.0% • Specificity: 86.5% • PPV: 46.4% • NPV: 97.8%	• Histopathology results were available for only N=78 patients (13%).
Conclusion: Using cytology and histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (US classification system based on 3 categories) was 87.0%, the specificity was 86.5%, the PPV was 46.6% and the NPV was 97.8%. Note that histopathology results were available for only 13% of the patients.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Goldfarb M et al. Surgeon-performed ultrasound can predict benignity in thyroid nodules. Surgery. 2011;150:436-441				
Study design: Retrospective cohort study	**Study population:** N=624 **Number of nodules evaluated:** N=624 solitary or dominant nodules **Gender:** NR **Age at US assessment (yrs):** NR **Patients with a history of radiation exposure:** NR	**Primary outcome:** Sonographic features that predict benign nodules. **Inclusion criteria:** Patients who underwent surgical resection of their nodule between 2002-and 2009. **Exclusion criteria:** NR **Outcome assessment:** • Patients were after thyroidectomy subdivided into 2 groups: patients with benign disease and those with thyroid malignancy. • Pre-operative surgeon performed ultrasound (SUS) was performed using high-frequency linear array transducers 7.5-13 MHz. • Prospectively collected SUS characteristics of thyroid nodules included size, echogeneity, borders, calcifications, cystic component, shape, number of nodules and location. • A specific model for statistical analysis was created to predict benignity (univariate analysis for predictors was performed followed by logistic regression for use in creation of the final model. **Histological analysis:** • All patients underwent thyroidectomy	**Size of the nodules:** NR **Inadequate FNA cytology results:** NR **Histological diagnosis:** Available for 624/624 patients (100%) • Malignant: N=217/624 (35%) • Benign: N=407/624 (65%) **Overall diagnostic value ultrasonography to predict benign pathology:** **Model 1 - 5 criteria: isoechogenicity, cystic components, lack of microcalcification, regular nodule borders, and size <1 cm:** ○ Sensitivity: 10.6% ○ Specificity: 97.6% ○ PPV: NR ○ NPV: NR **Analysis after excluding patients with lesions > 4 cm or a previous history of thyroid cancer:** ○ Sensitivity: 9.6% ○ Specificity: 98.5% ○ PPV: NR ○ NPV: NR	• Only 401 nodules had data available for multiple regression analysis. • Selection – all patients/nodules in this study were undergoing surgical removal. 624 selected from 1356 originally. Only 401 available for multivariable analysis. • Primary outcome is the predictive diagnostic value of morphologic features for benign thyroid nodules.
Conclusion: Using histopathological results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (isoechogenicity, cystic components, lack of microcalcification, regular nodule borders and size< 1 cm) was 10.6% and the specificity 97.6% in the identification of benign lesions. After excluding patients with lesions > 4 cm or a previous history of thyroid cancer the sensitivity was 9.6% and the specificity 98.5%. Note that there might be selection bias since all patients/nodules in this study were undergoing surgical removal (624 selected from the original cohort of 1356 patients) and only 401/624 nodules had data available for multiple regression analysis. Furthermore, the primary outcome is the predictive diagnostic value of morphologic features for benign thyroid nodules.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 7. What is the diagnostic value of thyroid ultrasonography (defined as combinations of radiographic ultrasonography features) versus histological confirmation to predict the presence of DTC in children/adults diagnosed with a thyroid nodule?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Bonavita JA et al. Pattern recognition of benign nodules at ultrasound of the thyroid: which nodules can be left alone? AJR Am J Roentgenol. 2009;193: 207-213				
Study design: Retrospective cohort study	**Study population:** N=650 **Number of nodules evaluated:** N=1232 **Gender:** Male: 64/650 (90%) Female: 436/650 (10%) **Age at US assessment (yrs):** Mean: 54.7 (17-88) **Patients with a history of radiation exposure:** NR	**Primary outcome:** Morphologic features predictive of benign thyroid nodules. **Inclusion criteria:** Patients in which both pathology reports and ultrasound images were available. From the alphabetized list generated, the first 500 nodules were reviewed. **Exclusion criteria:** NR **Outcome assessment:** • All diagnostic ultrasound examinations and FNA biopsies were performed with an Acuson x300 or Antares unit. • Ultrasound images were reviewed in consensus by two blinded radiologists. • Each nodule was evaluated for the presence or absence of individual sonographic features and was assigned one of 10 distinct recognizable morphologic patterns. • The final diagnosis was based on the cytologic result; final pathologic confirmation was limited to the 20 malignant tumors resected.	**Size of the nodules:** < 1 cm: N=7 1-2 cm: N=288 > 2 cm: N=206 **Inadequate FNA cytology results:** NR **Histological diagnosis:** Available for N=20/650 (3%) patients • Malignant: N=20/20 (100%) **Diagnostic value of the presence of sharp border, absence of calcification, absence of halo and presence of hyperechogenicity in identification of benign masses:** • Sensitivity: 100% • Specificity: 65.9% • PPV: 20.3% • NPV: 100% **Diagnostic value reproducible patterns of morphology in the identification of benign nodules:** • **Spongiform without hypervascularity:** 100% specificity • **Cyst with avascular colloid plug:** 100% specificity • **Giraffe pattern – with blocks of hyperechogenicity or white, separated by bands of hypoechogenicity, or black:** 100% specificity • **Uniform hyperechogenicity:** 100% specificity	• Histopathologic results were available for only 20 patients (3%) with malignant tumors. • Primary outcome is the predictive diagnostic value of morphologic features for benign thyroid nodules.
Conclusion: Using cytology and histopathological results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for combinations of radiographic features (presence of sharp border, absence of calcification, absence of halo and presence of hyperechogenicity) was 100%, the specificity 65.9%, PPV 20.3% and NPV 100% in the identification of benign masses. Note that histopathology results were available for only 20 patients (3%) with malignant tumors and that the primary outcome of this study is the predictive diagnostic value of morphologic features for benign thyroid nodules.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; FNA: fine-needle aspiration
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN)

Clinical question 8. Are there any clinical risk factors that contribute to an increased likelihood for DTC in children/adults diagnosed with a thyroid nodule?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Campanella P et al. Quantification of cancer risk of each clinical and ultrasonographic suspicious feature of thyroid nodules: a systematic review and meta-analysis. Eur J of Endocrinol 2014;170:203-211				
Study design: Systematic review including meta-analysis **Included studies:** 41 studies **Publishing era:** Between 1989 -2012	**Study population:** N=> 10,000 **Number of nodules evaluated:** N=26,678 **Gender:** NR **Age at diagnosis (yrs):** NR	**Primary outcome:** To quantify the risk of each clinical and US suspicious feature of thyroid nodules. **Eligibility criteria:** English language studies that investigated the association between clinical and/or US thyroid nodule feature and the risk of malignancy, no restriction criteria for the inclusion of detected nodules, had histologically confirmed diagnoses of malignancy, and reported univariable analysis. **Exclusion criteria:** NR **Study identification:** • Searched multiple databases from each databases' published between 1989 and December 2012. • Abstracts were screened by one reviewer for inclusion, and checked for discrepancies by a second reviewer. **Quality assessment:** NR **Data extraction:** Independently by two reviewers **Statistical analysis:** • Random effects model of DerSimonian and Laird to pool sensitivities, specificities, likelihood ratios, and DORs and estimate the 95% CI for each feature. • Heterogeneity across studies: I^2 statistic and Cochrane's Q test. • Publication bias: funnel plot and Egger's test.	**Incidence thyroid cancer:** NR **Histological results:** • All diagnosis of malignancy were histologically confirmed • In 23 studies where all patients underwent surgery, the diagnosis of benign nodules was all histologically confirmed • In 18 studies that included subjects who did not undergo surgery, the diagnosis of benign nodules was histologically confirmed in patients who underwent surgery and by clinical observation in patients who did not undergo surgery **Meta-analysis:** **Pool estimates clinical features to predict malignancy:** **Family history of thyroid carcinoma** OR 2.29 (95% CI 1.45-3.64), *P* <0.001 **Prior head and neck irradiation** OR 1.29 (95% CI 1.02-1.64), *P* =0.03 **Gender (male)** OR 1.22 (95% CI 1.01-1.47), *P* =0.04 **Age < 18 (years)** OR 1.33 (95% CI 0.70-2.50), *P* =0.37 **Age > 65 (years)** OR 1.15 (0.70-2.45), *P* =0.06 **TSH 2.5 mU/l** OR 1.05 (95% CI 0.45-2.45), *P* =0.90	• The funnel plot asymmetry and the Egger's test result (*P*=0.01) for intranodular vascularization suggest the presence of publication bias that may distort the meta-analysis. • No quality assessment performed. • Papillary and follicular thyroid carcinoma accounted for > 90% of the thyroid cancer cases.
Conclusion: Using cytology and histopathological results after surgery as the gold standard reference test to diagnose thyroid carcinoma, family history of thyroid carcinoma (OR 2.29 (95% CI 1.45-3.64), *P* <0.001), prior head and neck irradiation (OR 1.29 (95% CI 1.02-1.64), *P* =0.03) and male gender (OR 1.22 (95% CI 1.01-1.47), *P* =0.04) revealed to be significant risk factors for thyroid nodule malignancy in patients diagnosed with nodules. Age at diagnosis and TSH value were not significantly associated with thyroid nodule malignancy. Note that there was no quality assessment of the included studies performed in this systematic review and that <10% of the included thyroid cancer cases were diagnosed with medullary thyroid carcinoma, which might have influenced the results.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; RCT: randomized controlled trial; OR: odds ratio; CI: confidence interval; US: ultrasound

Clinical question 9. Do changes of the thyroid nodule over time contribute to an increased risk of the diagnosis of clinically relevant DTC in children and adults who received radiation therapy that includes the thyroid gland?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
No studies identified				

Clinical question 10a. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in children with a 'positive screen' (=suspicious nodule)?				
Study Design	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Izquierdo R et al. Ultrasound-guided fine-needle aspiration in the management of thyroid nodules in children and adolescents. Thyroid 2009;19:703-705.				
Study design: Retrospective cohort study **Treatment era:** 1999-2006	**Study population:** N=42 **Number of FNAC's evaluated:** N=52 **Gender:** Male: 13/42 (31%) Female: 29/69 (69%) **Age at FNAC (yrs):** Mean: 14.75 (8.67-19.75) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To assess the diagnostic accuracy of US-FNAC of thyroid nodules in children and adolescents. **Inclusion criteria:** Children and adolescents who underwent US-FNA biopsy of thyroid nodule >1 cm at SUNY Upstate Medical University, Syracuse between January 1999-October 2006. **Exclusion criteria:** NR **Outcome assessment:** • Thyroid nodules > 1cm were aspirated under US guidance using 25-gauge needle attached to 10-mL syringe. • Two to four asses were obtained per nodule. Two slides were made from each pass, and each slide was air-dried and stained with Diff-Quik or fixed immediately in 95% ethanol and stained using Papanicolaou method. • FNAC was considered to be adequate if at least five groups of 10 follicular cells were viewed. • One endocrinologist performed all thyroid exams, US imaging, and aspirations. • Histopathological and cytological diagnoses were compared for patients who underwent surgical treatment. • "Positive" cytology = malignant or indeterminate cytology (this latter category included lesions with cytological features that were atypical, suspicious for PTC, or follicular neoplasm). • Negative cytology = non-neoplastic cytological result.	**Results FNAC:** • Benign: N=43/52 (82.7%) • Malignant: N=6/52 (11.5%) • Indeterminate: N=2/52 (3.9%) • Inadequate: N=1/52 (1.9%) **Histological diagnosis:** • Available for N=16/52 (31%) nodules • Of the patients with benign FNAC results "several underwent surgery", none were malignant. Other patients with benign nodules were followed with US for at least 20 months, no change was seen. • Presumably all patients with malignant FNAC results underwent surgery, but this was not explicitly stated. • There was one false-positive case. **Diagnostic value FNAC:** • Sensitivity: 100% • Specificity: 88.9% • PPV: NR • NPV: NR • Accuracy: 93.7%	• Histopathologic results were available for N=16 nodules (31%). • Note that data comparing FNAC with surgical histology were not described in detail or provided in a table. • Note that the numbers (of nodules and patients) were small in this study and cytological categories were lumped together in non-standardized ways (e.g. the indeterminate group included atypical, suspicious for PTC, and follicular neoplasm).
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 100% and the specificity was 88.9%. Note that histopathology results were available for 31% of the nodules and that data comparing FNAC results with histopathology results were note described in detail or provided in a table.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PTC: papillary thyroid carcinoma; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10a. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in children with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Hosler GA et al. Cytopathologic analysis of thyroid lesions in the pediatric population. Diagn Cytopathol. 2006;34:101-105				
Study design: Retrospective cohort study **Treatment era:** 1989-2003	**Study population:** N=82 **Number of FNAC's evaluated:** N=101 **Gender:** Male: 19/82 (23%) Female: 63/82 (77%) **Age at FNAC (yrs):** Mean: 14.6 (8.0-18.0) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To ascertain the utility and limitations of FNAC in childhood thyroid lesions. **Inclusion criteria:** Children ≤18 yrs undergoing thyroid FNAC at Johns Hopkins or Memorial Sloan Kettering Cancer Center 1989-2003. **Exclusion criteria:** NR **Outcome assessment:** • The cytopathology archives were reviewed retrospectively. • The cytopathology results were correlated with the surgical pathology reports in patients who had subsequent surgical resections. • All cytopathology and surgical pathology specimens were obtained either by a cytopathologist in an outpatient setting (using 25-gauge needle attached to syringe) or by a radiologist under US- guidance (using 25-gauge needle). • Smears were air-dried and stained with Diff-Quik or wet- fixed in 95% ethanol and stained with Papanicolaou stain. • Available surgical pathology specimens were paraffin embedded and stained with H&E.	**Results FNAC:** • Benign: N=48/101 (47.5%) • Malignant: N=20/101 (19.8%) • other malignancy: N=2/101 (2.0%) • Neoplasm: N=5/101 (5.0%) • Atypical: N=13/101 (12.9%) • Unsatisfactory: N=13/101 (12.9%) **Histological diagnosis:** • Available for N=45/82 (54.9%) patients. • Of the 48 patients with benign FNAC results 15 underwent surgery (histology results: 11 benign, 4 malignant). • Of the 20 patients with malignant FNAC results 15 underwent surgery (4 lost to follow-up, 1 did not undergo surgery) (histology results: 3 benign, 12 malignant). • Of the 5 patients with neoplasm FNAC results 5 underwent surgery (histology results: 3 benign, 2 malignant). • Of the 13 patients with atypical FNAC results 8 underwent surgery (3 lost to follow-up, 1 did not undergo surgery) (histology results: 5 benign, 3 malignant). • Of the patients with unsatisfactory FNAC results 1 did undergo surgery (histology results: benign 1). **Diagnostic value FNAC:** • Sensitivity: 87% • Specificity: 92% • PPV: 87% • NPV: 92%	• Histopathologic results were available for N=45 patients (55%). • Note that 1 patient had 8 unsatisfactory procedures and the 9th FNAC showed sarcoma. • Note that of the patients with "atypical" cytology, 23% had PTC, which suggests such patient should be closely followed up and perhaps re-biopsied over time.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 87%, the specificity 92%, the PPV 87% and the NPV 92%. Note that histopathology results were available for 55% of the patients. There was a relatively high rate of unsatisfactory lesions, but this was biased by a single case of a sarcoma, which had extensive fibrosis and yielded multiple unsatisfactory biopsies.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PTC: papillary thyroid carcinoma; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10a. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in children with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Willgerodt H et al. Diagnostic value of fine-needle aspiration biopsy of thyroid nodules in children and adolescents. J Pediatr Endocrinol Metab. 19: 2006; 507-517				
Study design: Retrospective cohort study **Treatment era:** 1989-2003	**Study population:** N=169 **Number of FNAC's evaluated:** N=188 **Gender:** Male: 39/169 (23%) Female: 130/169 (77%) **Age at FNAC (yrs):** Mean: 14.9 (5.08-17.83) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To report on nearly 30 years experience, with collaboration of paediatricians, pediatric surgeons and pathologists/cytologists, of the use of FNAC in children and adolescents. **Inclusion criteria:** Children undergoing thyroid FNAC at the day clinic in Leipzig between 1989-2003. **Exclusion criteria:** NR **Outcome assessment:** • FNAC was performed preoperatively and the results were compared with the final postoperative histologic evaluation. FNAC was performed using a 22 gauge needle mounted on a syringe and constant suction provides adequate material for examination. • The needle was inserted into nodule 4-5 times in different directions and then withdrawn under slight suction. • It was prepared at least five smears. All smears were dried in air and May-Gruenwald (Giemsa) stained. • FNAC examination results were classified according to cell type—no thyroid cells, normal thyrocytes, degenerative or inflammatory changes, atypical thyroid cells of uncertain identity, oncocytes so called follicular proliferation, suspicious or malignant cells.	**Results FNAC:** • Benign: N=123/188 (65.4%) • Malignant: N=31/188 (16.5%) • Suspicious: N=2/188 (1.1%) • Inadequate: N=26/188 (13.8%) **Histological diagnosis:** • Available for N=118/169 (69.8%) nodules • Histopathological results: benign N=105/118 (89%), malignant N=13/118 (11%) **Diagnostic value FNAC:** • Sensitivity: 78.9% • Specificity: 63.3% • PPV: 26.9% • NPV: 94.7% • Accuracy: 77.2%	• Histopathologic results were available for N=118 patients (70%). • Note that data comparing FNAC with surgical histology were not described in detail or provided in a table.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 78.9%, the specificity 63.3%, the PPV 26.9% and the NPV 94.7%. Note that histopathology results were available for 70% of the patients.				

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Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10a. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in children with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Amrikachi M et al. Thyroid fine-needle aspiration biopsy in children and adolescents: Experience with 218 aspirates. Diagn Cytopathol. 2005;32:189-192				
Study design: Retrospective cohort study **Treatment era:** 1982-1998	**Study population:** N=185 **Number of FNAC's evaluated:** N=218 **Gender:** Male: 23/185 (12%) Female: 162/185 (88%) **Age at FNAC (yrs):** Mean: 17.0 (10.0-21.0) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To evaluate the role of FNAC of thyroid nodules in pediatric and adolescent patients. **Inclusion criteria:** Children (age ≤ 21 years) who underwent FNAC at 1 of 4 institutions between 1982 and 1998. **Exclusion criteria:** NR **Outcome assessment:** • 85% of procedures were done by endocrinologists without US guidance or assessment of specimen adequacy at the time. Slides were alcohol fixed and sent to lab for staining and evaluation. • Remaining 15% of procedures were done by cytopathologists or radiologists using 22- to 25- gauge needles connected to 10- or 20-ml syringes. • Adequacy of sample was assessed; other slides were immediately ethanol fixed and stained with Papanicolaou stain. • Cytological diagnoses were reviewed and categorized as "benign," "malignant," "suspicious for malignancy," and "unsatisfactory". • Records were reviewed for FNAC diagnosis and final histological diagnosis (when available). • FNAC results were compared for 10-15 years old and 15-21 years old age groups.	**Results FNAC:** • Benign: N=119/218 (54.6%) • Malignant: N=17/218 (7.8%) • Suspicious: N=20/218 (9.2%) • Inadequate: N=62/218 (28.4%) **Histological diagnosis:** • Available for N=32/185 (17.3%) nodules • Of the 119 patients with benign FNAC results 11 underwent surgery (histology results: 11 benign). • Of the 17 patients with malignant FNAC results 11 underwent surgery (histology results: 1 benign, 10 malignant). • Of the 20 patients with suspicious FNAC results 9 underwent surgery (histology results: 5 benign, 4 malignant). • Of the 62 patients with inadequate FNAC results 1 underwent surgery (histology results: 1 benign). **Diagnostic value FNAC:** • Sensitivity: 100% • Specificity: 65% • PPV: NR • NPV: NR **Other:** • The rates of benign, malignant, suspicious, and unsatisfactory lesions did not differ between the two age groupings.	• Histopathologic results were available for N=32 (17%) patients. • Note that there was a high rate of unsatisfactory specimens, likely due to most biopsies being done without US guidance and lack of assessment of specimen adequacy at the time of the procedure.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 100% and the specificity 65%. Note that histopathology results were available for only 17% of the patients. There was a high rate of unsatisfactory specimens, likely due to most biopsies being done without US guidance and lack of assessment of specimen adequacy at the time of the procedure.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10a. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in children with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Arda IS et a. Fine needle aspiration biopsy of thyroid nodules. Arch Dis Child. 2001;85:313-317				
Study design: Prospective cohort study **Treatment era:** 1995-2001	**Study population:** N=46 **Number of FNAC's evaluated:** N=46 **Gender:** Male: 9/37(24%) Female: 28/37 (76%) **Age at FNAC (yrs):** Mean: 9.0 (5.0-16.0) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To investigate the reliability of FNAC in the evaluation and management of thyroid nodules. **Inclusion criteria:** Children who presented with thyroid nodules in their thyroid glands during a six year period. **Exclusion criteria:** NR **Outcome assessment:** • The same surgeon performed aspirations in all cases. • In children with multiple nodules the largest nodule was biopsied. • The nodule was fixed in position manually, and a 23 gauge needle attached to a 20 ml disposable inserted perpendicular to the anterior surface of the neck. • If no sample was drawn into the syringe on the first attempt, the needle was inserted in a different direction to obtain adequate material without withholding it outside the skin. • All smears were dried in air and Giemsma stained. • One cytopathologist evaluated the smears. • The presence of more than seven groups of cells per stained smear was considered sufficient aspirate volume. • FNAC examination results were classified according to cell type – benign, malignant or follicular pattern. • Biopsy specimens were labelled suspicious when cell types could not be determined.	**Results FNAC:** • Benign: N=38/46 (82.6%) • Malignant: N=2/46 (4.3%) • Suspicious: N=3/46 (6.5%) • Inadequate: N=2/46 (4.3%) • Other malignancy: N=1/46 (2.2%) **Histological diagnosis:** • Available for N=31/46 (67.4%) nodules • Of the 38 patients with benign FNAC results 23 underwent surgery (histology results: 23 benign). • Of the 2 patients with malignant FNAC results 2 underwent surgery (histology results: 2 malignant). • Of the 3 patients with suspicious FNAC results 3 underwent surgery (histology results: 2 benign, 1 malignant). • Of the 2 patients with inadequate FNAC results 2 underwent surgery (histology results: 2 benign). **Diagnostic value FNAC:** • Sensitivity: 100% • Specificity: 95% • PPV: 67% • NPV: 100% • Accuracy: 95% **Other:** • Size of the nodules: six (13%) were less than 1 cm, 28 (61%) were between 1 and 2 cm, and 12 (26%) were larger than 2 cm.	• Histopathologic results were available for N=31 nodules (67%).
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 100%, the specificity 95%, the PPV 67% and the NPV 100%. Note that histopathology results were available for 67% of the nodules.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10a. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in children with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Lugo-Vicente H et al. Pediatric Thyroid Nodules: Management in the Era of Fine Needle Aspiration. J Pediatr Surg. 1998; 3:1302-1305				
Study design: Retrospective cohort study **Treatment era:** 1985-1995	**Study population:** N=24 **Number of FNAC's evaluated:** N=18 **Gender:** Male: 4/24(17%) Female: 20/24 (83%) **Age at FNAC (yrs):** Mean: 14.9 (9.0-18.0) **Patients with a history of radiation exposure:** N=0	**Primary outcome:** To determine whether management of pediatric thyroid nodules has changed in the era of FNAC. **Inclusion criteria:** Children with thyroid nodules managed at two major institutions in Puerto Rico from January 1985 to June 1995. **Exclusion criteria:** NR **Outcome assessment:** • Retrospective analysis of all medical charts was performed. • Most aspirates were done by a pathologist using a 22-gauge needle attached to a 10-mL syringe manually or using a mechanical aspiration device. Two-to five aspirates were done. • Smears are placed in 95% ethanol fixative in preparation for Papanicolaou stain or air dried to be stained with modified Wright stain. • More than seven groups of cells per stain smear were sufficient.	**Results FNAC:** • Benign: N=11/18 (61.1%) • Malignant: N=2/18 (11.1%) • Suspicious: N=2/18 (11.1%) • Inadequate: N=3/18 (16.7%) **Histological diagnosis:** • Available for N=24/24 (100%) nodules (FNAC results were not available for 6 patients). • Of the 11 patients with benign FNAC results 11 underwent surgery (histology results: 9 benign, 2 malignant). • Of the 2 patients with malignant FNAC results 2 underwent surgery (histology results: 2 malignant). • Of the 3 patients with suspicious FNAC results 2 underwent surgery (histology results: 1 benign, 1 malignant). • Of the 3 patients with inadequate FNAC results 3 underwent surgery (histology results: 3 benign). **Diagnostic value FNAC:** • Sensitivity: 60% • Specificity: 90% • PPV: 75% • NPV: 81% • Accuracy: 80%	• Histopathology results were available for N=24 (100%).
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 60%, the specificity 90%, the PPV 75% and the NPV 81%. Note that histopathology results were available for 100% of the patients (FNAC results were not available for N=6/24 patients).				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10b. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in adults with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Sinna E et al. Diagnostic accuracy of fine-needle aspiration cytology in thyroid lesions. J Egypt Nat Canc Inst. 2012; 24: 63-70				
Study design: Retrospective cohort study **Treatment era:** 2005-2010	**Study population:** N=296 **Number of FNAC's evaluated:** N=296 **Gender:** Male: 48/296 (16.2%) Female: 248/296 (83.8%) **Age at FNAC (yrs):** Mean: 44.0 (14.0-77.0) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To evaluate the accuracy of FNAC in the diagnosis of different thyroid lesions. **Inclusion criteria:** All patients diagnosed with thyroid nodules referred to the cytology unit, NCI, who underwent FNAC for diagnosis in the period between January 2005 and December 2010. **Exclusion criteria:** NR **Outcome assessment:** • Thyroid swellings were aspirated using (23/24) gauge disposable needles using standard procedures. • The aspirated contents of the needle were expelled onto glass slides. Four slide smears were made for each case and immediately fixed in 95% ethyl alcohol for about 30 min. All the slides (aspirated in our unit and received as US guided material) were stained with Papanicolaou stain. • Cytology was categorized according to Bethesda criteria 5 categories (insufficient for diagnosis, atypical follicular lesions of undetermined significance, follicular neoplasm, suspicious for malignancy, malignant sampling).	**Results FNAC:** • Benign: N=98/296 (33.1%) • Follicular lesion of US: N=40/296 (13.5%) • Follicular neoplasm: N=49/295 (16.5%) • Malignant: N=58/296 (19.5%) • Suspicious: N=30/296 (10.1%) • Inadequate: N=21/296 (7.1%) **Histological diagnosis:** • Available for N=235/296 (79.4%) nodules • Of the 98 patients with benign FNAC results 98 underwent surgery (histology results: 90 benign, 8 malignant). • Of the 88 patients with malignant or suspicious FNAC results 88 underwent surgery (histology results: 3 benign, 85 malignant). • Of the 49 patients with follicular neoplasm FNAC results 49 underwent surgery (histology results: 4 benign, 45 malignant). **Diagnostic value FNAC:** • Sensitivity: 92.8% • Specificity: 94.2% • PPV: 91.8% • NPV: 94.5% • Accuracy: 93.6%	• Histopathology results were available for N=235 (79%). • Size of the nodules NR. • Note that patients with "unsatisfactory" or "follicular" cytology results were excluded in calculation of the diagnostic efficacy.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 92.8%, the specificity 94.2%, the PPV 91.8% and the NPV 94.5%. Note that histopathology results were available for 79% of the patients and that that patients with "unsatisfactory" or "follicular" cytology results were excluded in calculation of the diagnostic efficacy.				

Differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

<u>Clinical question 10b</u>. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in <u>adults</u> with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Kim DW et al. Ultrasonography-guided fine-needle aspiration cytology for thyroid nodules. Diagn Cytopathol. 2012; 40:E48-E54				
Study design: Retrospective cohort study **Treatment era:** 2007-2009	**Study population:** N=977 **Number of FNAC's evaluated:** N=1456 **Gender:** Male: 139/977 (14.2%) Female: 838/977 (85.7%) **Age at FNAC (yrs):** Mean: 49.0 (13.0-81.0) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To assess the adequacy and efficacy of US-guided FNAC with one-sampling technique for the cytological diagnosis of thyroid nodules. **Inclusion criteria:** All patients diagnosed with a thyroid nodules with a likelihood of malignancy, as detected by US; a small solid thyroid nodule contralateral to the lobe with a known thyroid malignancy; and or small solid thyroid nodule in high-risk patients for malignancy. **Exclusion criteria:** NR **Outcome assessment:** • A single radiologist with an eight-year experience in thyroid US-FNAC performed the entire procedure using a 10-mL plastic syringe attached to a conventional 23-gauge needle. • Each sample was immediately mounted onto a glass slide. After two to three smearing duplications, four to six slide samples were obtained for each nodule. • Specimens were fixed in 95% ethanol and sent for pathological analysis. • The cytological diagnoses included ''benign'' (e.g., adenomatous hyperplasia, pseudonodule related to thyroiditis, and colloid nodule), ''suspicious for malignancy,'' ''malignant,'' ''indeterminate for malignancy,'' or ''insufficient for diagnosis.''	**Results FNAC:** • Benign: N=856/1456 (58.8%) • Malignant: N=222/1456 (15.3%) • Suspicious: N=109/1456 (7.5%) • Indeterminate for malignancy: N=102/1456 (7.0%) • Inadequate: N=167/1456 (11.5%) **Histological diagnosis:** • Available for N=568/1456 (39.0%) nodules • Of the 856 patients with benign FNAC results 154 underwent surgery (histology results: 136 benign, 18 malignant). • Of the 331 patients with malignant or suspicious FNAC results 312 underwent surgery (histology results: 12 benign, 300 malignant). • Of the 102 patients with indeterminate for malignancy FNAC results 52 underwent surgery (histology results: 26 benign, 26 malignant). • Of the 167 patients with inadequate FNAC results 50 underwent surgery (histology results 29 benign, 21 malignant). **Diagnostic value FNAC:** • Sensitivity: 94.3% • Specificity: 91.9% • PPV: 96.2% • NPV: 88.3% • Accuracy: 93.6% **Other:** • Size of the nodules: Mean 1.2 (range 0.1-8.5 cm	• Histopathology results were available for N=568 (39%). • Note that patients with "indeterminate for malignancy" and "insufficient for diagnosis" were excluded in calculation of the diagnostic efficacy.
<u>Conclusion:</u> Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 94.3%, the specificity 91.9%, the PPV 96.2% and the NPV 88.3%. Note that histopathology results were available for only 39% of the patients and that patients with "indeterminate for malignancy" and "insufficient for diagnosis" were excluded in calculation of the diagnostic efficacy.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10b. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in adults with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Ozluk Y et al. The use of the Bethesda terminology in thyroid fine-needle aspiration results in a lower rate of surgery for non-malignant nodules: a report from a reference center in Turkey. Intl J Surg Path. 2011;19:761-771				
Study design: Retrospective cohort study **Treatment era:** 2004-2007	**Study population:** N=515 **Number of FNAC's evaluated:** N=581 **Gender:** Male: 94/515 (18.3%) Female: 421/515 (81.7%) **Age at FNAC (yrs):** Mean: 50.4 ± 13.2 **Patients with a history of radiation exposure:** NR	**Primary outcome:** To assess whether the Bethesda classification system offer any advantages in reporting thyroid FNAC results and facilitating clinical management in routine practice. **Inclusion criteria:** All thyroid FNAC patients with histological follow-up that were diagnosed at the department of pathology, Istanbul Faculty of Medicine, between January 2004 and December 2007. **Exclusion criteria:** NR **Outcome assessment:** • FNAC was performed by an endocrinologist or radiologist under US guidance using a 25-gauge needle. • One to two slides for each nodule were stained with hematoxylin-eosin for the evaluation of specimen adequacy. • All other slides were subjected to Papanicolau staining after 95% (v/v) alcohol fixation and Romanowsky staining after air-drying. • All patients were classified by the Bethesda system (non-diagnostic, benign, suspicious follicular cells, follicular lesion or neoplasia, suspicious for malignancy, malignant).	**Results FNAC:** • Benign: N=223/442 (50.5%) • Suspicious follicular cells: N=25/442 (5.7%) • Suspicious for follicular neoplasm: N=35/442 (7.9%) • Suspicious for malignancy: N=42/442 (9.5%) • Malignant: N=81/442 (18.3%) • Inadequate: N=36/442 (8.1%) **Histological diagnosis:** • Available for N=442/581 (76.1%) nodules • Histology results of the 223 patients with benign FNAC: 10% benign, 90% malignant. • Histology results of the 25 patients with suspicious follicular cells FNAC: 36% benign, 64% malignant. • Histology results of the 35 patients with suspicious for follicular neoplasm FNAC: 33% benign, 66% malignant. • Histology results of the 42 patients with suspicious for malignancy FNAC: 19% benign, 81% malignant. • Histology results of the 36 patients with inadequate FNAC: 75% benign, 25% malignant. **Diagnostic value FNAC:** • Sensitivity: 85% • Specificity: 94% • PPV: 89% • NPV: 92% • Accuracy: 90%	• Histopathology results were available for N=442 (76.1%). • Note that patients with follicular thyroid tumor of uncertain malignant potential were considered to be histologically positive in calculation of the diagnostic efficacy.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 85%, the specificity 94%, the PPV 89% and the NPV 92%. Note that histopathology results were available for 76.1% of the patients. Note that patients with follicular thyroid tumor of uncertain malignant potential were considered to be histologically positive in calculation of the diagnostic efficacy.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10b. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in adults with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Lumachi F et al. Fine-needle aspiration cytology and ^{99m}Tc-pertechnetate scintigraphy together in patients with differentiated thyroid carcinoma. Anticancer Res. 2010; 30: 3083-3086				
Study design: Retrospective cohort study **Treatment era:** NR	**Study population:** N=357 **Number of FNAC's evaluated:** N=357 **Gender:** Male: 73/357(20.5%) Female: 284/357 (79.5%) **Age at FNAC (yrs):** Mean: 43.0 (19.0-73.0) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To evaluate the usefulness of FNAC and 99mTc-pertrechnate scintigraphy together in patients with DTC. **Inclusion criteria:** Patients with a solitary thyroid nodule of 10 mm or more and no signs or symptoms of thyroid hyperfunction, who had undergone both FNAC and 99mTc-pertrechnate scintigraphy before surgery. **Exclusion criteria:** NR **Outcome assessment:** • The equipment required for aspiration included a standard disposable 21 gauge needle, standard disposable plastic syringe (20 ml) and disposable extension lines (1.5 mm x 25 cm). • The needle was positioned into the target thyroid nodule under US guidance. • One slide was evaluated immediately in order to verify the adequacy of specimen with 'rapid' Giemsa stain. • The smear was fixed in 95% ethanol for 15 seconds, stained in Giemsa solution for 30 seconds, rinsed in tap water for 5 seconds and covered with a coverslip. • The procedure was normally repeated in the presence of a non-diagnostic sample. • FNAC distinguishes three different groups of thyroid nodules: benign, follicular neoplasm and thyroid cancer.	**Results FNAC:** • Benign: N=223/442 (50.5%) • Suspicious follicular cells: N=25/442 (5.7%) • Suspicious for follicular neoplasm : N=35/442 (7.9%) • Suspicious for malignancy: N=42/442 (9.5%) • Malignant: N=81/442 (18.3%) • Inadequate: N=36/442 (8.1%) **Histological diagnosis:** • Available for N=357/357 (100%) nodules • N=61/357 (17.1%) of the patients were diagnosed with thyroid carcinoma. **Diagnostic value FNAC:** • Sensitivity: 82.0% • Specificity: 99.3% • PPV: 96.1% • NPV: 96.4% • Accuracy: 96.0% **Other:** • Size of the nodules: Mean 21.1 (range 10-55 mm)	• Histopathology results were available for N=357 (100%). • Note that FNAC data were not described in detail or provided in a table. • Note that data comparing FNAC with surgical histology were not described in detail or provided in a table.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 82%, the specificity 99.3%, the PPV 96.1% and the NPV 96.4%. Note that histopathology results were available for 100% of the patients, but that FNAC results and data comparing FNAC with surgical histology were not described in detail or provided in a table.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; DTC: differentiated thyroid carcinoma; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10b. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in adults with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
***Sahin M et al*.** Ultrasound-guided fine-needle aspiration biopsy and ultrasound features of infracentimetric nodules in patients with nodular goiter: correlation with pathological. Endocr Path. 2006;17:67-74				
Study design: Retrospective cohort study **Treatment era:** 1999-2004	**Study population:** N=207 **Number of FNAC's evaluated:** N=472 **Gender:** Male: 37/207(17.9%) Female: 170/207 (82.1%) **Age at FNAC (yrs):** Mean: 51.5 ± 13.1 **Patients with a history of radiation exposure:** NR	**Primary outcome:** To evaluate the usefulness of US-guided FNAC for infracentrimetric nodules. **Inclusion criteria:** Patients with nodular goiter who underwent US-FNAC prior to surgery at Baskent University in Ankara between January 2002 and December 2005. **Exclusion criteria:** NR **Outcome assessment:** • After US examination the radiologist performed an US-FNAC on nodules that were 0.5 cm or larger. • US-FNAC was done using a 21-gauge needle and a 10 mL syringe. • Each aspirate was smeared on a slide, immediately fixed in 95% ethanol and stained using Papanicolauo method. • Cytologic diagnoses were made by an experienced pathologist who classified each specimen as being in one of five categories: benign, suspicious of follicular neoplasm, suspicious of cancer, consistent with carcinoma, and insufficient for cytologic diagnoses.	**Results FNAC:** • Benign: N=245/472 (51.9%) • Suspicious: N=132/472 (28.0%) • Follicular neoplasm: N=54/472 (11.4%) • Malignant: N=21/472 (4.4%) • Inadequate: N=27/472 (5.7%) **Histological diagnosis:** • Available for N=472/472 (100%) nodules • Histology results of the 245 patients with benign FNAC: 243 benign, 2 malignant. • Histology results of the 132 patients with suspicious FNAC: 76 benign, 13 malignant. • Histology results of the 54 patients with suspicious for follicular neoplasm FNAC: 47% benign, 7% malignant. • Histology results of the 27 patients with inadequate FNAC: 19 benign, 8 malignant. **Diagnostic value FNAC infracentimetric nodules (N=145):** • Sensitivity: 96.3% • Specificity: 71.2% • PPV: 44.8% • NPV: 98.8% • Accuracy: 76.1% **Diagnostic value FNAC supracentimetric nodules (N=327):** • Sensitivity: 98.2% • Specificity: 63.1% • PPV: 35.6% • NPV: 99.4% • Accuracy: 69.1%	• Histopathology results were available for N=472 (100%). • Average number of FNAC's per patient > 2. This suggests that this is a study of multinodular goiters. • Study patients were from an iodine-deficient area of Turkey.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC of infracentimetric nodules was 96.3%, the specificity 71.2%, the PPV 44.8% and the NPV 98.8%. Whereas the sensitivity for FNAC of supracentimetric nodules was 98.2%, the specificity 63.1%, the PPV 35.6% and the NPV 99.4. Note that primarily patients with a multi-nodular goiter were included in this study from an iodine-deficient area of Turkey (low malignancy rate).				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10b. What is the diagnostic value of fine-needle aspiration cytology compared to the gold standard (histological confirmation) to predict the presence of differentiated thyroid carcinoma in adults with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Martinek A et al. Importance of guided fine needle aspiration cytology (FNAC) for the diagnostics of thyroid nodules – own experience. Biomed papers. 2004; 148: 45-50				
Study design: Retrospective cohort study **Treatment era:** 1986-2002	**Study population:** N=245 **Number of FNAC's evaluated:** N=245 **Gender:** Male: 51/245(20.8%) Female: 194/245 (79.2%) **Age at FNAC (yrs):** Men: mean: 66.0 (46.0-82.0) Women: mean: 59.0 (13.0-87.0) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To assess the accuracy and limitations of US guided FNAC of thyroid nodules. **Inclusion criteria:** Patients with thyroid nodules who underwent an US-FNAC at the department of internal medicine, faculty hosp. Ostrava between 1986-2002. **Exclusion criteria:** Patients with malignant FNAC and without final histology confirmation (N=9). **Outcome assessment:** • US-FNAC was performed with the use of a 7.5 MHz probe, 22-gauge needles, 20 ml syringes and syringe pistols. • The obtained material was used for the preparation of smears. Particles of material were fixed by 10% solution of formalin. Liquid material was processed by the cytospin technique. • Definite benign diagnosis was confirmed during long-term observation in most cases. • The puncture had to be repeated on 92 persons (38%) of the group during their second visit. • Cytology: 4 categories (malignancy, suspicion of malignancy, benign, inconclusive). • Definition malignant diagnosis = FNAC malignancy+ suspicious of malignancy.	**Results FNAC:** • Benign: N=126/245 (51.4%) • Suspicious for malignancy: N=28/245 (11.4%) • Malignant: N=30/245 (12.2%) • Inconclusive: N=29/245 (11.8%) • Inadequate: N=32/245 (13.1%) **Histological diagnosis:** • Available for N=245/245 (100%) nodules • Histology results of the 126 patients with benign FNAC: 122 benign, 4 malignant. • Histology results of the 28 patients with suspicious FNAC: 18 benign, 10 malignant. • Histology results of the 30 patients with malignant FNAC: 4 benign, 26 malignant. • Histology results of the 29 patients with inconclusive FNAC: 21 benign, 8 malignant. • Histology results of the 32 patients with inadequate FNAC: 24 benign, 8 malignant. **Diagnostic value FNAC:** • Sensitivity: 90% • Specificity: 85% • PPV: NR • NPV: NR • Accuracy: 86%	• Histopathology results were available for N=245 (100%). • Note that the puncture had to be repeated on 92 persons (38%) of the group during their second visit.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 90% and the specificity 85%. Note that the puncture had to be repeated on 92 persons (38%) of the group during their second visit.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10b. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in adults with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Koike E et al. Effect of combining ultrasonography and ultrasound-guided fine-needle aspiration biopsy findings for the diagnosis of thyroid nodules. Eur J Surg. 2001; 167: 656-661				
Study design: Prospective cohort study **Treatment era:** 1999	**Study population:** N=309 **Number of FNAC's evaluated:** N=329 **Gender:** Male: 30/309 (9.7%) Female: 297/309 (96.1%) **Age at FNAC (yrs):** Mean: 53.0 (15.0-82.0) **Patients with a history of radiation exposure:** NR	**Primary outcome:** To assess the accuracy of ultrasonography and cytology in predicting malignancy in thyroid nodules. **Inclusion criteria:** Patients who underwent an US-FNAC and thyroid surgery. **Exclusion criteria:** NR **Outcome assessment:** • Specifics US: linear probe 6-13 MHz, spatial resolution 2 mm (performed by 8 investigators). • Specifics FNAC: 22 gauge needle, 2 ml syringe, free-hand technique with US guidance; slide smear fixed with 95% ethanol, stain Papanicalaou (performed by 8 investigators). • Cytology: single interpreter; 4 categories (malignant, suspicious of malignancy, benign, inadequate). • final preoperative diagnosis derived from combined US + cytology criteria.	**Results FNAC:** • Benign: N=145/329 (44.1%) • Malignant: N=168/329 (51.1%) • Inadequate: N=16/329 (4.9%) **Histological diagnosis:** • Available for N=329/329 (100%) nodules • Histology results of the 145 patients with benign FNAC: 148 benign, 20 malignant. • Histology results of the 168 patients with malignant FNAC: 12 benign, 133 malignant. • Histology results of the 16 patients with inadequate FNAC: 10 benign, 6 malignant. **Diagnostic value FNAC:** • Sensitivity: 84% • Specificity: 87% • PPV: NR • NPV: NR • Accuracy: 85% **Other:** • The mean (SD) number of US-FNAC was 1.33 (0.59)/nodule.	• Histopathology results were available for N=329 (100%).
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 84%, the specificity 87%.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 10b. What is the diagnostic value of FNA cytology compared to the gold standard (histological confirmation) to predict the presence of DTC in adults with a 'positive screen' (=suspicious nodule)?				
Study Design Treatment era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Mikosch et al. Value of ultrasound-guided fine-needle aspiration biopsy of thyroid nodules in an endemic goitre area. Eur J Nucl Med. 2000; 27:62-69				
Study design: Retrospective cohort study **Treatment era:** 1994-1996	**Study population:** N=718 **Number of FNAC's evaluated:** N=718 **Gender:** NR **Age at FNAC (yrs):** NR **Patients with a history of radiation exposure:** NR	**Primary outcome:** To determine the value, advantages and limitations of US-guided FNAC in an endemic goitre area. **Inclusion criteria:** Outpatient who underwent US-FNAC for hypoechoic nodules and/or hypofunctional nodules. **Exclusion criteria:** NR **Outcome assessment:** • Cytology: interpreted by 9 investigators, 6 categories (non-malignant, non-malignant follicular proliferation, malignancy cannot be ruled out, malignant, inadequate, sampling error). • Specifics US: transducers 5 + 7.5 MHz • Specifics US-FNAC: performed by 4 investigators, free handed, 21 gauge needle, 20ml syringe, smears stained with May-Grünwald-Giemsa and Papanicalaou. • Additional $TC99^{m}$ scintigraphy for functional assessment nodules. • 61 re-FNAC, no alteration cytology when adequate material was obtained.	**Results FNAC:** • Non-malignant: N=303/718 (42.2%) • Non-malignant follicular proliferation: N=177/718 (24.7%) • Suspicious for malignancy: N=133/718 (18.5%) • Malignant: N=61/718 (8.5%) • Inadequate: N=34/718 (4.7%) • Sampling error: N=10/718 (1.4%) **Histological diagnosis:** • Available for N=718/718 (100%) nodules • Histology results of the 303 patients with benign FNAC: 300 benign, 3 malignant. • Histology results of the 177 patients with non-malignant follicular proliferation FNAC: 171 benign, 6 malignant. • Histology results of the 133 patients with suspicious for malignant FNAC: 122 benign, 11 malignant. • Histology results of the 61 patients with malignant FNAC: 7 benign, 54 malignant. • Histology results of the 34 patients with inadequate FNAC: 31 benign, 3 malignant. **Diagnostic value FNAC:** • Sensitivity: 87.8% • Specificity: 78.5% • PPV: 33.5% • NPV: 98.1% • Accuracy: 79.5%	• Histopathology results were available for N=718 (100%). • Note that patients with inadequate or sampling error FNAC results were not considered in the comparison of cytology and histology results.
Conclusion: Using histopathology results after surgery as the gold standard reference test to diagnose DTC, the sensitivity for FNAC was 87.8%, the specificity 78.5%, the PPV 33.5% and the NPV 98.1%. Note that patients with inadequate or sampling error FNAC results were not considered in the comparison of cytology and histology results.				

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; FNAC: fine-needle aspiration cytology; US: ultrasound; PPV: positive predictive value; NPV: negative predictive value
Sensitivity: TP/(TP+FN); specificity: TN/(FP+TN); PPV: TP/(TP+FP); NPV:TN/(TN+FN); accuracy: (TP+TN)/(TP+TN+FP+FN)

Clinical question 11. What is the complication rate of FNA biopsy in children and adults diagnosed with a positive screen (= suspicious thyroid nodule)?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Polyzos Sa et al. Clinical complications following thyroid fine-needle biopsy: a systematic review. Clin Endocrinol. 2009;71:157-165				
Study design: Systematic review **Included studies:** 12 studies **Publishing era:** Between 1984-2008	**Study population:** N=17,730 **Cases:** N=191 **Gender:** NR **Age at FNA biopsy (yrs):** NR	**Primary outcome:** Clinical adverse events of FNA biopsies **Eligibility criteria:** Series of five or more cases of complications were included. The search was not limited by publication time and not restricted to English literature. **Exclusion criteria:** Articles reporting post-FNA biopsy histological or biochemical changes were excluded. **Study identification:** • Computerized advanced search for primary evidence was performed in the PubMed electronic database. • Unclear whether abstracts and titles were reviewed independently and in duplicate. **Quality assessment:** NR **Data extraction:** NR **Statistical analysis:** N/A	**Complications** • **Pain/discomfort** o Ramacciotti et al. (1984): N=13/221 (5.9%) o Silverman et al. (1986): N=1/309 (0.32%) o Gursoy et al. (2007): N=45/49 (92%) o Gursoy et al. 2007: N=46/52 (88%) • **Intranodular haemorrhage/haematomas** o Ramacciotti et al. (1984): N=5/221 (2.3%) o Silverman et al. (1986): N=1/309 (0.32%) o Newkirk et al. (2000): N=15/234 (6.4%) o Braga et al. (2001): N=11/42 (26%) o Khoo et al. (2008): N=3/311 (0.96%) • **Recurrent laryngeal nerve palsy** o Tomodo et al. (2006): N=4/10,974 (0.036%) o Silverman et al. (1986): N=2/309 (0.65%) o Ramacciotti et al. (1984): N=1/221 (0.45%) o Newkirk et al. (2000): N=2/234 (0.85%) o Khoo et al. (2008): N=2/311 (0.64%) • **Needle tract seeding of papillary carcinoma** o Block et al. (1980): N=1/54 (1.9%) o Ito et al. (2005): N=10/4912 (0.20%) • **Post-aspiration thyrotoxicosis** o Kobayashi et al. (1992): N=5/500 (1%) • **Very rare complications:** o Tracheal puncture (one case) o Dysphagia (one case) o Infection (3 cases)	
Conclusion: Post FNA biopsy pain and discomfort is the most common complication in patients who underwent FNA biopsy (incidence varied from 0.32-88%), followed by intranodular haemorrhage/hamatomos (incidence ranged between 0.32-26%), needle tract seeding of papillary carcinoma (0.2-1.9%), post-aspiration thyrotoxicosis (1%) and recurrent laryngeal nerve palsy (0.036-0.85%). Most complications following FNA biopsy have low morbidity and are self-limiting (pain/discomfort and intranodular haemorrhage/haematomas. Serious complications are very rare.				

NR: not reported; yrs: years; FNA: fine-needle aspiration

Clinical question 12. Does early identification of DTC contribute to a reduction in morbidity, recurrence and mortality rates, irrespective of treatment modality, in children and adults?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Clement SC et al. Is outcome of differentiated thyroid carcinoma influenced by tumor stage at diagnosis? *Cancer Treat Rev* 2015; 41: 9–16.				
Study design: Systematic review **Included studies:** 46 studies **Publishing era:** Between 1987-2013	**Study population:** NR **Cases:** N/A **Gender:** NR **Age at diagnosis (yrs):** NR	**Primary outcome:** Is outcome of DTC influenced by tumor stage at diagnosis? **Eligibility criteria:** I) articles were an original report, II) the study design was not a case report, editorial, letter to the editor or non-systematic review III), at least 97.5% of the study population was diagnosed with DTC IV) published in the English language V) and the study population should contain at least 20 patients. In case of multiple publications from the same study population, the largest or most complete study for the outcome of interest was included.. **Exclusion criteria:** Pre-selection of patients (*i.e.* only DTC patients with distant metastasis or only DTC patients with microcarcinoma), and lack of multivariate risk factor analysis on mortality or recurrence. **Study identification:** • PubMed was searched for relevant English-language articles through August 2013. • Additionally, reference lists of all eligible studies and reference lists from prior relevant reviews were hand searched to identify missed relevant articles. • Unclear whether abstracts and titles were reviewed independently and in duplicate. **Quality assessment:** • All available literature was systematically reviewed and conclusions were drawn based on the level of evidence (A: high level of evidence, B: moderate to low level of evidence, C: very-low level of evidence) **Data extraction:** NR **Statistical analysis:** N/A	**Overall conclusions for the benefits of detection of DTC at an early stage in <u>children</u>** • There is some suggestion that detection of DTC at an early stage is associated with a lower recurrence rate (level C evidence) • There is some suggestion that detection of DTC at an early stage is associated with a lower mortality rate (level C evidence) • There is no clear evidence to conclude that detection of DTC at an early stage influences the occurrence of surgical complications (conflicting evidence) • No studies reported on the dose dependency of second primary malignancies after radioactive iodine treatment in children (no evidence) **Overall conclusions for the benefits of detection of DTC at an early stage in <u>adults</u>** • There is some evidence that detection of DTC at an early stage is associated with a lower recurrence rate (level B evidence) • There is evidence that detection of DTC at an early stage is associated with a lower mortality rate (level A evidence) • There is evidence that detection of DTC at an early stage, conceivably resulting in less extensive surgery, decreases the risk to develop transient hypoparathyroidism (level A evidence) • There is no clear evidence that detection of DTC at an early stage, conceivably resulting in less extensive surgery, decreases the risk to develop permanent hypoparathyroidism or recurrent nerve injury (level A evidence) • There is some evidence that detection of DTC at an early stage, resulting in a reduction of the administrated number and dosage of radioactive iodine treatment, decreases the risk to develop second primary malignancies (level B evidence)	
<u>Conclusion:</u>				

Identification of DTC in an early stage is beneficial for both children (very-low level evidence) and adults (moderate to high level evidence), despite the excellent prognosis.

DTC: differentiated thyroid carcinoma; NR: not reported; yrs: years; N/A: not applicable

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Schmiegelow K et al. Second malignant neoplasms after treatment of childhood acute lymphoblastic leukemia. J Clin Oncol. 2013;31: 2469-2476				
Study design: Retrospective cohort study **Treatment era:** 1980-2007 **Years of follow-up:** Range: 3.0-30.0 **Lost to follow-up:** NR	**Study population:** N=54,068 **Gender:** NR **Age at primary cancer diagnosis (yrs):** NR **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** NR **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To analyze data on risk factors and outcomes of children with SMNs occuring after treatment for ALL. **Inclusion criteria:** Children who developed a SMN after treatment for ALL from 18 collaborative study groups between 1980 and 2007. **Exclusion criteria:** Children in which the clonal relationship between the SMN and original leukemia could not be confidentially verified. **Outcome assessment:** • Data on individuals with SMNs were collected from the groups' central ALL databases. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N=642 patients developed ≥ 1 SMN **Incidence thyroid carcinoma:** • N=32 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Mean: 10.1 (range 7.8–13.5 years) **Other:** • Not clear how many patients diagnosed with thyroid carcinoma did receive radiotherapy treatment.	• The screening strategy for thyroid carcinoma in this study cohort is not clear. • Note that it was not clear how many patients diagnosed with thyroid carcinoma did receive radiotherapy treatment.
Conclusion: In a study cohort of 544 childhood acute lymphoblastic leukemia survivors (follow-up time ranging between 3.0-30.0 years) 32 survivors DTC after a mean latency time of 10.1 years (range 17.1-26.3 years). Note that it was not clear how many patients diagnosed with DTC did receive radiotherapy treatment.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; ALL: acute lymphoblastic leukemia

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Piccardo A et al. Role of low-cost thyroid follow-up in children treated for primary tumors at high risk of developing a second thyroid tumor. Q J Nuc Med Mol Imaging. 2012; 56:459-467				
Study design: Prospective cohort study **Treatment era:** 1981-? **Years of follow-up:** Median: 12.0 (3.1-29.1) **Lost to follow-up:** N=48	**Study population:** N=252 **Gender:** Male: 146/112 (58%) Female:106/112(42%) **Age at primary cancer diagnosis (yrs):** Mean: 7.6 ± 4.7 **Age at EBRT (yrs):** Median: 8.4 (1.1-19.3) **Age at follow-up time (yrs):** NR **EBRT:** N=252 **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To evaluate the incidence of DTC in pediatric-oncologic patients treated with radiotherapy. **Inclusion criteria:** Children with a diagnosis of primary tumor outside the brain, who underwent radiotherapy including the thyroid gland and had the oncologic therapy withdrawn at least two years earlier. **Exclusion criteria:** NR **Outcome assessment:** • Thyroid follow-up evaluation involved: 1) neck US, which was performed on completion of RT and every year thereafter if nodules were not found 2) thyroid function (FT4/TSH) at the end of RT and once every two yearly thereafter. • If nodules detected by US had a maximum diameter > 1 cm and/or suspicious US features, fine-needle aspiration biopsy was performed. • Latency time was defined as time interval between RT treatment of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N/A **Incidence thyroid carcinoma:** • N=17 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • N=106 **Latency time thyroid carcinoma:** • Median 12.9 (range 5.0-18.0 years) **Other:** • N=17/17 patients diagnosed with thyroid carcinoma received radiotherapy treatment	
Conclusion: In a study cohort of 252 CAYAC survivors (median follow-up time 12.0 years) 17 survivors developed DTC after a mean latency time of 12.9 years (range 5.0-18.0 years).				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; RT: radiotherapy

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Berger C et al. Second malignant neoplasms following childhood cancer: A study of a recent cohort (1987-2004) from the childhood cancer registry of the Rhone-Alpes Region (ARCERRA) in France. 2011; 28:364-379				
Study design: Prospective population-based cohort study **Treatment era:** 1987-2004 **Years of follow-up:** Median: 9.7 (0.0-22.8) **Lost to follow-up:** 16.4%	**Study population:** N=2907 **Gender:** Male:1532/2907 (52%) Female:1375/2907 (47%) **Age at primary cancer diagnosis (yrs):** Median: 5.6 (0.0-14.9) **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** Median: 16.3 (0.13-35.9) **EBRT:** NR **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To determine the incidence of SMNs occurring any time after diagnosis of the first cancer in a recent cohort of patients, the types of SMNs, and the latency of the second cancer. **Inclusion criteria:** Patients reported to the Childhood Cancer Registry of the Rhone-Alpes region (ARCERRA) between 1987-2004, who were diagnosed with a first cancer before age 15 years and lived in the Rhone Alpes region of France. **Exclusion criteria:** Patients for whom no information had been recorded in the 5 years prior to the cutoff date of September 30, 2009, were considered lost to follow-up. **Outcome assessment:** • Solid tumors were considered unrelated to irradiation if there was no prerequisite irradiation in the site of the second cancer. • Person-years at risk were calculated starting with original diagnosis and continuing until occurrence of an SMN, loss to follow-up, or death as of September 30, 2009. • Latency time was defined as the time interval between first and second cancers.	**Overall incidence SMN's:** • N=54 SMNs were reported in N=52 patients **Incidence thyroid carcinoma:** • N=12 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Median: 8.5 years **Other:** • N=11/12 patients diagnosed with thyroid carcinoma received radiotherapy or TBI • All 12 patients were diagnosed with papillary thyroid carcinoma	• Median follow-up time short for the purpose of this paper. • The screening strategy for thyroid carcinoma in this study cohort was not clear. • Note that one patient who did not receive radiotherapy was diagnosed with thyroid carcinoma.
Conclusion: In a study cohort of 2907 CAYAC survivors (median follow-up time 9.7 years) 12 CAYAC survivors developed DTC after a median latency time of 8.5 years. Note that the median follow-up time of this cohort was relatively short for the purpose of this study and that one patient who did not receive radiotherapy treatment was diagnosed with DTC.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; TBI: total body irradiation

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Renard M et al. Second neoplasm in children treated in EORTC 58881 trial for acute lymphoblastic malignancies: low incidence of CNS tumors. Pediatr Blood Cancer. 2011; 57: 119-125				
Study design: Retrospective cohort study **Treatment era:** 1989-1998 **Years of follow-up:** Median: 7.5 (1.0-13.5) **Lost to follow-up:** NR	**Study population:** N=2216 **Gender:** Male: 1240/2216 (56%) Female:952/2216 (44%) **Age at primary cancer diagnosis (yrs):** NR **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** NR **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To report the incidence of SMNs which occured in patients recruited in EORTC 58881 trial for acute lymphoblastic malignancies. **Inclusion criteria:** Children who were treated in the EORTC trial 58881 fir newly diagnosed acute lymphoblastic malignancies. **Exclusion criteria:** NR **Outcome assessment:** • The long-term status of the patients has been monitored by sending of follow-up forms every 3 months during the first 2 years and thereafter at least once a year until 5 years after diagnosis. Subsequently, a form was sent to the EORTC Headquarters every 2-3 years or in case a new event occurred. • SMN was defined as any malignancy having occurred after the initial acute lymphoblastic malignancy and distinct from it, whatever the remission status of the patient was. • All cases were diagnosed by tissue biopsy or by cytological examination by the local pathologist. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N=22 patients developed ≥ 1 SMN **Incidence thyroid carcinoma:** • N=2 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Mean 5.4 years (range 4.8-6.03 years) **Other:** • One patient received radiotherapy as part of the conditioning protocol for high-dose chemotherapy. One patient did not receive radiotherapy.	• The screening strategy for thyroid carcinoma in this study cohort is not clear. • The mean follow-up time of this study cohort was short for the aim of the study.
Conclusion: In a study cohort of 2216 CAYAC survivors (median follow-up time 7.5 years) 17 survivors developed DTC after a mean latency time of 5.4 years (range 4.8-6.03 years). Note that one patient who developed DTC did not receive radiotherapy treatment.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; N/A: not applicable

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Bhatti P et al. Risk of second primary thyroid cancer after radiotherapy for a childhood cancer in a large cohort study: an update from the childhood cancer survivor study. 2010;174:741-752				
Study design: Retrospective cohort study **Treatment era:** 1970-1986 **Years of follow-up:** Range: 19.0-35.0 **Lost to follow-up:** N=209 (of 12,756 survivors)	**Study population:** N=12,547 **Gender:** NR **Age at primary cancer diagnosis (yrs):** NR **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** N=12,547 **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To quantify the long-term risk of thyroid cancer associated with radiation treatment. **Inclusion criteria:** Subjects diagnosed before age 21 years with a childhood cancer during 1970-1986 at one of 26 institutions in the US or Canada and had survived for at least 5 years. **Exclusion criteria:** NR **Outcome assessment:** • A baseline self-administrated questionnaire sent in 1994 collected data on demographic characteristics, social-economic state and new malignancies and other health outcomes. • Subsequent surveys were mailed to cohort members in 2000, 2003 and 2005. • Cases were defined as patients who developed a subsequent thyroid cancer at least 5 years after a first childhood malignancy. • Thyroid cancers were ascertained through self-report (including surrogate respondents) on questionnaires. • Pathology reports were obtained and thyroid cancers were verified by a pathologist. • Latency time was defined as time since first cancer to SMN diagnosis.	**Overall incidence SMN's:** • N/A **Incidence thyroid carcinoma:** • N=119 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • 5-14 yrs: N=33 • 15-19 yrs: N=41 • 20-24 yrs: N=27 • ≥ 25 yrs: N=18 **Other:** • N=119/119 patients diagnosed with thyroid carcinoma received radiotherapy treatment • N=111 cases were second primary cancers, N=8 were third primary cancers	• The screening strategy for thyroid carcinoma in this study cohort was not clear. • Thyroid cancers were ascertained through self-report (including surrogate respondents) on questionnaires. • Thyroid carcinomas who developed < 5 yrs from primary cancer diagnosis were excluded and not defined as cases. • Histology of thyroid cancer was unclear in N=9 patients. • Average follow-up time of CAYAC survivors is not mentioned.
Conclusion: In a study cohort of 12,547 CAYAC survivors (follow-up time 19.0-35.0 years) 119 survivors developed DTC with a peak incidence after a latency time of 15-19 years (N=41) years (latency time ranged between 5.0 and ≥ 25 years). Note that the DTC were ascertained through self-report on questionnaires and that DTC who developed < 5 yrs from primary cancer diagnosis were excluded.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; N/A: not applicable

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
O'Brien MM et al. Second malignant neoplasms in survivors of pediatric Hodgkin's lymphoma treated with low-dos radiation and chemotherapy. J Clin Oncol. 2010;28:1232-1239				
Study design: Retrospective cohort study **Treatment era:** 1970-1990 **Years of follow-up:** Median: 20.6 (2.0-32.9 **Lost to follow-up:** NR	**Study population:** N=112 **Gender:** Male: 75/112 (69%) Female:35/112(31%) **Age at primary cancer diagnosis (yrs):** Range :1.7-17.6 **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** Range: 7.4-44.9 **EBRT:** NR **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To report the long-term outcome of a cohort of pediatric survivors of Hodgkin's lymphoma treated with chemotherapy and low-dose radiation. **Inclusion criteria:** All pediatric patients treated for Hodgkin's Disease at Stanford from 1970-1990 using two consecutive regimens with "low dose" radiation therapy. **Exclusion criteria:** NR **Outcome assessment:** • Baseline characteristics and treatment-related information were abstracted from medical records. • Patients without documented death and with last known address in the United States (N=95) were sent a follow-up questionnaire regarding interval development of SMNs, N=46 (48%) returned the questionnaire. • All malignancies counted in the population incidence rates of the registry of the SEER program of the NCI were considered SMNs. • Nonmelanoma skin cancers, meningiomas and schwannomas were excluded. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N=18 patients developed ≥ 1 SMN **Incidence thyroid carcinoma:** • N=5 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Mean 15.5 (range 8.2-24.4 years) **Other:** • N=5/5 patients diagnosed with thyroid carcinoma received radiotherapy treatment	• The screening strategy for thyroid carcinoma in this study cohort is not clear.
Conclusion: In a study cohort of 112 childhood Hodgkin's lymphoma survivors (median follow-up time 20.6 years) 5 survivors developed DTC after a mean latency time of 15.5 years (range 8.2-24.4 years).				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; SEER: Surveillance, Epidemiology, and End Results (SEER); NCI: National cancer institute

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Taylor AJ et al. Risk of thyroid cancer in survivors of childhood cancer: Results from the British Childhood Cancer Survivor Study. Int J Cancer. 2009;125:2400-2405				
Study design: Retrospective cohort study **Treatment era:** 1940-1991 **Years of follow-up:** Median: 17.4 years per survivor from 5 year survival **Lost to follow-up:** N=2728 (21%)	**Study population:** N=10,483 **Gender:** NR **Age at primary cancer diagnosis (yrs):** NR **Age at transplantation (yrs):** NR **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** NR **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To determine the risk of thyroid SMNs in the Britisch Childhood Cancer Survivor Study. **Inclusion criteria:** Patients with childhood cancer, at age less than 15 years, between 1940 and 1991, surviving 5 years or more from diagnosis. **Exclusion criteria:** NR **Outcome assessment:** • All survivors aged at least 16 years who are alive and contactable through their general practitioner have been sent a questionnaire. • Information from questionnaires was complemented by "flagging" at the National Health Service central registers. • SMNs of the thyroid were verified pathologically either by a histopathology reports or by clinical correspondence containing a histopathology summary. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N/A **Incidence thyroid carcinoma:** • N=50 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Median: 20.7 (range 6.0-38.0 years) **Other:** • N=47/50 patients (94%) diagnosed with thyroid carcinoma received radiotherapy treatment.	• The screening strategy for thyroid carcinoma in this study cohort is not clear.
Conclusion: In a study cohort of 10,483 of CAYAC survivors (median follow-up time 17.4 years from 5 year survival) 50 survivors developed DTC after a mean latency time of 20.7 years (range 6.0-38.0 years). Note that 3 patients (6%) diagnosed with DTC did not receive radiotherapy treatment.				

NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; N/A: not applicable

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Borgmann A et al. Secondary malignant neoplasms after intensive treatment of relapsed acute lymphoblastic leukaemia in childhood. 2008;44:257-268				

Study design:
Retrospective cohort study
 	
Treatment era:
1989-2001
 	
Years of follow-up:
Mean: 13.1 (4.3-22.9)
 	
Lost to follow-up:
N=12
	Study population:
	N=1376
	
	Gender:
	Male:886/1376 (64%)
	Female:490/1376 (36%)
	
	Age at primary cancer diagnosis (yrs):
	NR
	
	Age at EBRT (yrs):
	NR
	
	Age at follow-up time (yrs):
	NR
	
	EBRT:
	N=1130
	
	Average cumulative dose:
	NR
	
	Average thyroid dose (Gy):
	NR
	
	Average number of EBRT:
	NR
		Primary outcome:
		The cumulative incidence of and the risk factors for developing SMN in children and adolescents following treatment for relapse of ALL.
		
		Inclusion criteria:
		Patients up to 18 years of age with first relapse of non-B-cell ALL were treated and achieved a 2nd complete remission. The treatment followed trial protocol in 5 multicenter trials of the ALL-REZ-BFM study group between March 1983 and December 2001.
		
		Exclusion criteria:
		NR
		
		Outcome assessment:
		• SMN was defined as malignant (or non-malignant for selected entities) which occurred after a 2nd or 3rd remission of ALL.
		• Follow-up was calculated from the time of diagnosis of ALL relapse until death, the occurrence of a SMN, or until the last report of survival.
		• Latency time was defined as time from initial diagnosis of ALL to diagnosis of SMN and as time from relapse diagnosis to diagnosis of SMN.
			Overall incidence SMN's:
			• N=21 SMNs were reported in N=21 patients
			
			Incidence thyroid carcinoma:
			• N=2 patients were diagnosed with thyroid carcinoma
			
			Incidence thyroid nodules:
			• NR
			
			Latency time thyroid carcinoma:
			• Time from initial diagnosis of ALL to diagnosis of SMN:
			  ○ Mean: 15.7 years (10.8-20.5 years)
			• Time from relapse diagnosis to diagnosis of SMN:
			  ○ Mean 13.4 years (8.1-18.7 years)
			
			Other:
			• N=2/2 patients diagnosed with thyroid carcinoma received radiotherapy treatment.
				• The screening strategy for thyroid carcinoma in this study cohort is not clear.

Conclusion: In a study cohort of 1376 ALL survivors (mean follow-up time 13.1 years) 2 survivors developed DTC after a mean latency time of 15.7 years (range 10.8-20.5 years).				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; ALL: acute lymphoblastic leukaemia

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Constine LS et al. Subsequent malignancies in children treated for Hodgkin's disease: associations with gender and radiation dose. 2008;72:24-33				
Study design: Retrospective cohort study **Treatment era:** 1960-1990 **Years of follow-up:** Mean: 16.8 (0.08-39.4) **Lost to follow-up:** NR	**Study population:** N=930 **Gender:** Male:532/930 (57%) Female:398/930 (43%) **Age at primary cancer diagnosis (yrs):** Mean 13.6 (range 0.3-18.9) **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** N=848 **Average cumulative dose:** • EBRT alone: mean: 37.1 (6-49.8 Gy) • EBRT+CT: mean: 32.9 (2-50 Gy) **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To evaluate select dempographic and therapeutic factors associated with SMNs. **Inclusion criteria:** Children and adolescents < 19 yrs of age at Hodgkin's disease diagnosis treated between 1960 and 1990 in one of the five participating institutions. **Exclusion criteria:** Patients with a history of cancer before Hodgkin's disease diagnosis. **Outcome assessment:** • Data abstraction was performed at each institution. • Subsequent malignancies included all invasive malignancies as well as ductal carcinoma in situ (basal and squamous cell carcinoma of the skin were the only malignancies not considered in the analysis). • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N=102 patients developed ≥ 1 SMN **Incidence thyroid carcinoma:** • N=14 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Median:14.4 years (8.5-23.0 years) **Other:** • N=14/14 patients diagnosed with thyroid carcinoma received radiotherapy treatment.	• The screening strategy for thyroid carcinoma in this study cohort is not clear. • Contact was documented in 89% of the patients in the previous 5 yrs and in 59% of the patients in the previous 2 yrs.
Conclusion: In a study cohort of 930 of Hodgkin's disease survivors (mean follow-up time 16.8 years) 14 survivors developed DTC after a median latency time of 14.4 years (range 8.5-23.0 years).				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Brignardello E et al. Ultrasound Screening for Thyroid Carcinoma in Childhood Cancer Survivors: A Case Series. J Clin Endo Metab 2008, 93: 4840-4843				
Study design: Retrospective case series **Treatment era:** NR **Years of follow-up:** Median:15.8 (6.1-34.8) **Lost to follow-up:** N=0	**Study population:** N=129 **Gender:** Male: 80/129 (62%) Female: 49/129 (38%) **Age at primary cancer diagnosis (yrs):** Median: 11.5 (0.5-19) **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** Median: 25.1 (17.5-43.8) **EBRT:** N=129/129 (100%) **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** Detection of non-palpable thyroid nodules by thyroid ultrasound. **Inclusion criteria:** Childhood cancer survivors who had received radiotherapy to head/neck/upper thorax for a pediatric cancer. **Exclusion criteria:** NR **Outcome assessment:** • All patients who had received radiotherapy to head/neck/upper thorax began ultrasound screening 5 yrs post treatment and repeated every third year if negative. • If screening was positive interval decreased to every 6-12 months or fine-needle aspiration was performed. • Indications for biopsy were nodule size >1 cm or suspicious ultrasound features. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N/A **Incidence thyroid carcinoma:** • N=5 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • N=35 **Latency time thyroid carcinoma:** • Mean: 15.8 (range 8.9-27.9 years) **Other:** • N=5/5 patients who developed thyroid carcinoma received radiotherapy.	• Note that thyroid ultrasound screening began 5.0 years post treatment.
Conclusion: In a study cohort of 129 of CAYAC survivors (median follow-up time 15.8 year2) 50 survivors developed DTC after a mean latency time of 15.8 (range 8.9-27.9 years). Note that thyroid ultrasound screening began 5.0 years post treatment.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm; N/A: not applicable

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Kowalczyk JR et al. Incidence and clinical characteristics of a second malignant neoplasm in children: a multicenter study of a polish pediatric leukemia/lymphoma group. Med Sci Monit. 2004;10:117-122				
Study design: Retrospective cohort study **Treatment era:** 1970-1997 **Years of follow-up:** NR **Lost to follow-up:** NR	**Study population:** N=4100 **Gender:** NR **Age at primary cancer diagnosis (yrs):** NR **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** N=4100 **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To examine various characteristics of children who developed SMNs following succefull therapy for primary leukemia or Hodgkin's disease. **Inclusion criteria:** Children with various forms of leukemia and children treated with Hodgkin's disease treated between 1970-1997 in 7 Polish pediatric hemotology/oncology centers. **Exclusion criteria:** NR **Outcome assessment:** • A follow-up of each patient was performed in one of the 7 Polish pediatric hemotology/oncology centers. • Details regarding the SMNs concerned the data of the second diagnosis, histologic examination, site, therapy and outcome. • The at-risk time for a SMN began at the start of the first treatment and ended on the date of diagnosis of the SMN, the date of death, or the date of the most recent follow-up examination, whichever came first'. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N=36 patients developed ≥ 1 SMN **Incidence thyroid carcinoma:** • N=5 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Mean 9.9 (range 7.1-12.8 years) **Other:** • N=5/5 patients diagnosed with thyroid carcinoma received radiotherapy treatment	• The screening strategy for thyroid carcinoma in this study cohort is not clear.
Conclusion: In a study cohort of 4100 childhood leukemia and Hodgkin's disease survivors (exact follow-up time not reported) 5 survivors developed DTC after a mean latency time of 9.9 years (range 7.1-12.8 years).				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Bhatia S et al. High risk of subsequent neoplasms continues with extended follow-up of childhood Hodgkin's disease: report from the late effects study group. J Clin Oncol. 2003;21:4386-4394				
Study design: Retrospective cohort study **Treatment era:** 1955-1986 **Years of follow-up:** Median: 17.0 **Lost to follow-up:** NR	**Study population:** N=1380 **Gender:** Male:897/1380 (65%) Female:480/1380 (35%) **Age at primary cancer diagnosis (yrs):** Median: 11.7 (0.3-16.9) **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** Median: 27.8 **EBRT:** N=1274/1380 (92%) **Average cumulative dose:** NR **Average thyroid dose (Gy):** Direct: median 20 (range 2-50) Scattered: range 0.1-0.5 **Average number of EBRT:** NR	**Primary outcome:** The pattern and incidence of SMN's occuring with extended follow-up . **Inclusion criteria:** Children ages 16 years or younger at diagnosis of Hodgkin's disease, who received their primary treatment between 1955 and 1986. **Exclusion criteria:** NR **Outcome assessment:** • Baseline characteristics and treatment-related factors were abstracted from the clinical records. • Presence or absence of SMN's and current activity of Hodgkin's disease were abstracted from the clinical records. • For patients in whom SMN's developed, the date of diagnosis, histology and site of tumor, and whether or not the tumor arose in the radiation therapy field was recorded. • Pathologic findings were confirmed at the treating institution. • The time at risk for SMN's was computed from the date of diagnosis of Hodgkin's disease to the date of SMN, date of death or the date of last contact, whichever came first. • Latency time was defined as the time interval between diagnoses of Hodgkin's disease to the date of SMN.	**Overall incidence SMN's:** • N=212 SMNs were reported in N=173 patients **Incidence thyroid carcinoma:** • N=19 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Median: 15.3 years (4.2-29.7 years) **Other:** • N=18/19 patients diagnosed with thyroid carcinoma received radiotherapy. • Patients were diagnosed with either papillary thyroid carcinoma (N=12) or follicular carcinomas (N=7). • The cumulative incidence of developing thyroid cancer approached 1.9% at 20 years from Hodgkin's disease diagnosis and 4.4% at 30 years from Hodgkin's disease diagnosis.	• The screening strategy for thyroid carcinoma in this study cohort is not clear. • Note that one patient who did not receive radiotherapy was diagnosed with thyroid carcinoma.
Conclusion: In a study cohort of 1380 Hodgkin's disease survivors (median follow-up time 17.0 years) 19 survivors developed DTC after a median latency time of 15.3 years (range 4.2-29.7). Note that one patient who did not receive radiotherapy treatment was diagnosed with DTC.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Gold DG et al. *S*econd neoplasms after megavoltage radiation for pediatric tumors. Cancer. 2003;97:2588-2596				
Study design: Retrospective cohort study **Treatment era:** 1954-1980 **Years of follow-up:** Median: 19.5 (4.8-40.0) **Lost to follow-up:** N=13	**Study population:** N=446 **Gender:** NR **Age at primary cancer diagnosis (yrs):** Mean 6.2 (range 0.04-17.0) **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** N=446 **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To evaluate the nature and risk of SMNs in pediatric patients treated with megavoltage radiotherapy as children. **Inclusion criteria:** Pediatric patients treated with megavoltage radiation, at age < 17 years, for malignant disease between January 1954 and December 1980 at the University of Minnesota Hospital. A minimum of 5 years following radiotherapy was required for inclusion. **Exclusion criteria:** Patients with bilateral retinoblastoma or neurofibromatosis were excluded from the study. **Outcome assessment:** • Follow-up information was acquired from medical records, physicians involved in patient care, patients and parents. • Information obtained from patients or parents were verified by contacting patient physicians. • Pathologic analysis of SPM specimens (when available) was performed at the University of Minnesota. • If the SMN was diagnosed at an outside institution, pathology reports were obtained from the institution. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N=37 patients developed $\geq$ 1 SMN **Incidence thyroid carcinoma:** • N=3 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Mean:9.3 years (4.0-16.0 years) **Other:** • N=3/3 patients diagnosed with thyroid carcinoma received radiotherapy treatment.	• The screening strategy for thyroid carcinoma in this study cohort is not clear.
Conclusion: In a study cohort of 446 CAYAC survivors (mean follow-up time 19.5 years) 3 survivors developed DTC after a median latency time of 9.3 years (range 4.0-16.0 years).				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Green DM et al. Second malignant neoplasms after treatment for Hodgkin's disease in childhood or adolescence. J Clin Oncol. 2000;18:1492-1499				
Study design: Retrospective cohort study **Treatment era:** 1960-1989 **Years of follow-up:** Mean: 17.3 (4.8-40.0) **Lost to follow-up:** N=0	**Study population:** N=182 **Gender:** Male: 100/182 (55%) Female: 82/182 (45%) **Age at primary cancer diagnosis (yrs):** Mean 15.3 ± 3.7 **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** NR **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To determine the frequency of and risk factors for SMNs after treatment for Hodgkin's disease diagnosed in children. **Inclusion criteria:** Previously untreated patients with Hodgkin's disease who were younger than 20 years of age at diagnosis. **Exclusion criteria:** NR **Outcome assessment:** • Annual contact with the patients who survived was maintained through clinic visits or by mail. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N=36 SMNs were reported in N=28 patients **Incidence thyroid carcinoma:** • N=6 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Range 7.79-23.5 years **Other:** • N=6/6 patients diagnosed with thyroid carcinoma received radiotherapy treatment. • The cumulative percentage of patients who developed thyroid cancer was 7.5% ± 3.2% at 30 years after diagnosis of Hodgkin's disease'.	• The screening strategy for thyroid carcinoma in this study cohort is not clear.
Conclusion: In a study cohort of 182 Hodgkin's disease survivors (mean follow-up time 17.3 years) 6 survivors developed DTC after latency time ranging from 7.70-23.5 years.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Socie G et al. New malignant diseases after allogeneic marrow transplantation for childhood acute leukemia. J Clin Oncol. 2000;18:348-357				
Study design: Retrospective cohort study **Treatment era:** 1964-1992 **Years of follow-up:** Median: 0.9 (0.08-20.7) **Lost to follow-up:** < 10%	**Study population:** N=3182 **Gender:** Male: 1945/3182 (61%) Female: 1237/3182 (39%) **Age at primary cancer diagnosis (yrs):** NR **Age at transplantation (yrs):** Median: 10.1 (0.1-16.9) **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** N=2766 **Average cumulative dose:** NR **Average thyroid dose (Gy):** NR **Average number of EBRT:** NR	**Primary outcome:** To determine the incidence of and risk factors for second malignancies after allogeneic bone marrow transplantation for childhood acute leukemia. **Inclusion criteria:** Patients younger than 17 years who received allogeneic or syngeneic bone marrow transplantation for acute leukemia were identified via two different registries. **Exclusion criteria:** NR **Outcome assessment:** • Pathology reports and selected slides were reviewed centrally for 95% of the patients with new solid tumors. • Latency time was defined as time interval between date of transplantation and diagnosis of the SMN.	**Overall incidence SMN's:** • N=26 patients developed ≥ 1 SMN **Incidence thyroid carcinoma:** • N=5 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Mean: 9.3 (range 4.5-14.3 years) **Other:** • N=5/5 patients diagnosed with thyroid carcinoma received radiotherapy treatment	• The screening strategy for thyroid carcinoma in this study cohort is not clear. • The median follow-up time is relatively short for the purpose of this study.
Conclusion: In a study cohort of 3182 childhood acute leukemia survivors (median follow-up time 0.9 years) 5 survivors developed DTC after a mean latency time of 9.3 years (range 4.5-14.3 years). Note that the median follow-up time was relatively short for the purpose of this study.				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm

Clinical question 13. What is the latency time to develop DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Treatment era Years of follow-up	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
Rubino C et al. Long-term risk of second malignant neoplasms after neuroblastoma in childhood: role of treatment. Int J Cancer. 2003;107: 791-796				
Study design: Retrospective cohort study **Treatment era:** 1948-1986 **Years of follow-up:** Mean: 15.0(5.0-38.0) **Lost to follow-up:** N=48	**Study population:** N=544 **Gender:** Male: 4372/7670 (57%) Female:3298/7670 (43%) **Age at primary cancer diagnosis (yrs):** Mean 8.3 **Age at EBRT (yrs):** NR **Age at follow-up time (yrs):** NR **EBRT:** N=299 **Average cumulative dose:** Mean: 6.7 Gy **Average thyroid dose (Gy):** Average ERR was 0.50 per Gy (95% CI 0–16) to the thyroid. **Average number of EBRT:** NR	**Primary outcome:** To quantify the risk of SMNs among long-term survivors of neuroblastoma and to study the influence of treatment on risk. **Inclusion criteria:** Children (before age 16) with a first primary neuroblastoma, surviving for at least 5 years, who received treatment in 8 treatment centers in France and Great Britain were included. **Exclusion criteria:** NR **Outcome assessment:** • Clinical and pathologic characteristics of the first and second cancers were recorded from the hospital charts. • Latency time was defined as time interval between diagnosis of the primary tumor and diagnosis of the SMN.	**Overall incidence SMN's:** • N=12 SMNs were reported in N=400 patients **Incidence thyroid carcinoma:** • N=5 patients were diagnosed with thyroid carcinoma **Incidence thyroid nodules:** • NR **Latency time thyroid carcinoma:** • Mean: 20.6 (range 17.1–26.3 years) **Other:** • N=5/5 patients diagnosed with thyroid carcinoma received radiotherapy treatment	• The screening strategy for thyroid carcinoma in this study cohort is not clear.
Conclusion: In a study cohort of 544 neuroblastoma survivors (mean follow-up time 15.0 years) 5 survivors developed DTC after a mean latency time of 20.6 years (range 17.1-26.3 years).				

DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescence and young adulthood cancer; NR: not reported; yrs: years; EBRT: external beam radiotherapy; Gy: gray; SMN: second malignant neoplasm

Clinical question 14. Are there any modifiers of risk factors of latency time for DTC in CAYAC survivors who received radiation therapy that includes the thyroid gland?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
No studies identified				

Clinical question 15. What is the average growth rate of a thyroid nodule possible indicating the presence of DTC in children/adults?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
No studies identified				

Clinical question 16. How long after childhood cancer treatment subsides the incidence of radiation-induced DTC in CAYAC survivors?				
Study Design Included studies Publishing era	**Participants**	**Study methods**	**Main outcomes**	**Additional remarks**
No studies identified				