

Conclusions of evidence for DTC surveillance in CAYAC survivors

	Level of evidence
Does detection of DTC in an early phase by surveillance impact morbidity and mortality?	
Possible benefits of detection of DTC at an early stage	
Detection of DTC at an early stage is associated with a lower recurrence rate in <i>children</i>	Level C [20]
Detection of DTC at an early stage is associated with a lower recurrence rate in <i>adults</i>	Level B [20]
Detection of DTC at an early stage is associated with a lower mortality rate in <i>children</i>	Level C [20]
Detection of DTC at an early stage is associated with a lower mortality rate in <i>adults</i>	Level A [20]
If early identification of DTC results in less extensive surgery, does it contribute to a reduction of surgical complications?	
Decreased risk for surgical complications after detection of DTC at an early stage in <i>children</i>	Conflicting evidence
Decreased risk of temporary hypoparathyroidism after detection of DTC at an early stage in <i>adults</i>	Level A [20]
Does early identification DTC, possibly resulting in a reduction of the number and dosage of radioiodine treatment, contribute to a reduction of severe adverse effects (second primary malignancies (SPM) of radioiodine treatment)?	
Increased risk for SPM following radioiodine treatment after detection of DTC at an early stage in <i>children</i>	No studies
Increased risk for SPM following radioiodine treatment after detection of DTC at an early stage in <i>adults</i>	Level B [20]
	Level of evidence
Who should be counseled about the risk of DTC and informed about possible DTC surveillance?	
Risk following radiation therapy that includes the thyroid gland	
Increased risk after radiation therapy > 1 Gy	Level A [8, 10, 23–26]
Risk following therapeutic ¹³¹ I-MIBG	
Increased risk after therapeutic ¹³¹ I-MIBG	Level C [27, 28]
Risk following chemotherapy only	
No increased risk after chemotherapy only	Level B [10, 26]
Increased risk after anthracyclines	Level B [10]
Factors that alter the radiation risk	
Risk by radiation dose	
>0-1 Gy: RR 1.9 (95% CI 1.0-3.7)	Level A [10]
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)	
Increased risk after high fraction size	No studies
Increased risk after high dose-rate	No studies
Increased risk in survivors of CAYAC who were young at primary cancer diagnosis	Level B [10, 25]
Increased risk in female vs. male survivors of CAYAC	Conflicting evidence [23–26]

Increased risk after chemotherapy in addition to a radiation thyroid dose < 20 Gy vs. radiotherapy alone < 20 Gy	Conflicting evidence [9],[26]
Increased risk after persistent elevated thyrotrophin levels throughout follow-up	No studies
If the decision to commence surveillance is made, what surveillance modality should be used to detect a thyroid nodule that may represent a DTC?	
Diagnostic value of thyroid neck palpation vs. ultrasonography to detect a thyroid nodule possibly indicating the presence of DTC	
Poor diagnostic value of neck palpation	Level A [24, 29–34]
Sensitivity: 17-43%	
Specificity: 96-100%	
Diagnostic value of US vs neck palpation to detect a thyroid nodule	Level A [35–37]
Sensitivity: ~95-100%	
Specificity: ~95-100%	
Diagnostic value of sonographic features vs. cytological and histological confirmation to detect the presence of DTC	
Poor diagnostic value of <i>individual</i> sonographic features	Level A [38–41]
The diagnostic value of <i>combinations</i> of sonographic features is higher than <i>individual</i> sonographic features but varied considerably from study to study	Level A [42–51]
Sensitivity: 48-99%	
Specificity: 44-96%	
Which additional risk factors can be used to predict the presence of thyroid cancer in patients with a thyroid nodule?	
Risk factors that increase the risk of thyroid cancer in patients with a thyroid nodule	
Increased risk after prior head and neck irradiation	Level B [52]
Increased risk in male vs. female patients	Level B [52]
Increased risk in patients with a family history of thyroid cancer	Level B [52]
Which additional diagnostic tests can be used to predict the presence of DTC in patients with a thyroid nodule?	
Diagnostic value of fine needle aspiration cytology vs. histological confirmation to predict the presence of DTC	
Fair diagnostic value of fine needle aspiration cytology in <i>children</i>	Level A [53–59]
Sensitivity: 60-100%	
Specificity: 65-95%	
Inadequacy rate: 2-28%	
Good diagnostic value of ultrasound-guided fine needle aspiration cytology in <i>adults</i>	Level A [60–67]
Sensitivity: 82-96%	
Specificity: 71-99%	
Inadequacy rate: 5-12%	
Fine needle aspiration biopsy is in general a safe procedure	Level A [68]
If the decision to commence surveillance is made at what frequency should DTC surveillance be performed?	
There is a peak incidence of radiation induced thyroid cancer 10.0-20.0 years after primary cancer diagnosis (range 4.2-38.0 years)	Level B [8, 23, 26, 29, 69–79, 95, 96]
Risk factors that alter the latency time	No studies
Average growth rate of thyroid nodules	No studies
Course of DTC risk over time	No studies

Level A, high level of evidence (i.e. consistent evidence from well performed and high quality studies or systematic reviews with a low risk of bias, and direct, consistent and precise results); level B, moderate to low level of evidence (i.e. evidence from studies or systematic reviews with few important limitations); and level C, very low level of evidence (i.e. evidence from studies with serious flaws, only expert opinion or standards of care).

Abbreviations: DTC: differentiated thyroid carcinoma; CAYAC: childhood, adolescent and young adult cancer; MIBG: meta-iodobenzylguanidine; Gy: gray; RR: relative risk; CI: confidence interval; SPM: second primary malignancy