

Online Resource 4: Summary of findings table presenting the results of the GRADE synthesis and rating process. Table created with the GRADEpro Guideline Development Tool: GRADEpro GDT: GRADEpro Guideline Development Tool [Software]. McMaster University, 2020 (developed by Evidence Prime, Inc.). Available from grade.org. Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RAI, radioactive iodine; ROB, risk of bias; RR, relative risk; SHM, secondary hematologic malignancy; SPM, second primary malignancy.

Question: Occurrence of second primary malignancies and hematologic malignancies after radioactive iodine therapy for differentiated thyroid carcinoma

Certainty assessment							Impact	Certainty
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		
Second Primary Malignancies								
8	observational studies	serious ^a	not serious	not serious	serious ^b	dose-response gradient	Relative effect range: (RR, OR, HR) 1.14–1.84 Vote counting: 7/8 studies showed an increased risk for SPM after RAI therapy compared to patients not exposed to RAI. 1/8 study showed an increased risk for SPM in patients without RAI therapy compared to patients who received RAI therapy. ^c	⊕○○○ VERY LOW
Secondary Hematologic Malignancies								
3	observational studies	not serious ^d	not serious	not serious	serious ^e	dose-response gradient	Relative effect range: (RR) 1.30-2.5 Vote counting: 3/3 studies showed an increased risk for SHM after RAI therapy compared to patients not exposed to RAI.	⊕⊕○○ LOW
Dose Response Gradient								
8	observational studies	serious ^f	not serious	not serious	serious ^g	dose-response gradient	The data indicate a dose-response gradient. Vote counting: Comparing the groups with the least and the greatest cumulative activity of RAI, 7/8 studies found an increased relative effect.	⊕○○○ VERY LOW

Explanations:

- a. We judged the risk of bias using the ROBINS-I Tool. We judged the overall ROB as serious because only 2/8 studies have a moderate ROB, while 3/8 have a serious ROB, and 3/8 have a critical ROB.
- b. The confidence intervals of most studies show a wide range and often include the relative effect under and above 1.0.
- c. Data of 4 studies were included in this analysis. Statistical significance was demonstrated in 1/4 studies. [Silva-Vieira et al.[15]]
- d. We judged the ROB using the ROBINS-I Tool. We judged the overall ROB not as serious because 2 studies were judged as having a serious ROB, but the largest and most up-to-date study was judged as having a moderate ROB.
- e. Teng et al. presented the data as HR per 30 mCi (1.11 GBq). These results are not directly comparable with those of the other two studies. Rubino et al.[16] presented results with wide confidence intervals. All in all, the data is based on rather few cases.
- f. We judged the ROB using the ROBINS-I Tool. We judged the overall ROB as serious because 2/8 studies have a moderate ROB, 3/8 studies have a serious ROB and 3/8 have a critical ROB. Whereas studies with a moderate or critical ROB analyzed rather small cohorts, two of the studies with a serious ROB analyzed larger cohorts ($N=6841$, $N=20235$).
- g. The confidence intervals of most studies showed a wide range and many studies analyzed rather few participants.

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