

Online Resource 3: Presented are detailed data about included papers (first author, year of publication), extracted data (country of the included cohort, relative effect endpoint and results, crude incidence of SPMs, follow-up period, number of participants, rate of patients treated with RAI) and the evaluated risk of bias of each study. Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; OR, odds ratio; RAI, radioactive iodine; ROB, risk of bias; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results Program; SHM, secondary hematologic malignancy; SIR, standardized incidence ratio; SPM, second primary malignancy.

Occurrence of SPMs in patients treated with RAI versus without RAI							
Study/ Citation	Cohort/Country	Risk of bias	Relative effect endpoint	Results	Crude Incidence of SPM	Follow-up period	Participants (rate of RAI treatment)
Silva-Vieira, 2017 [15]	Portugal	Moderate	RR of “treatment with radioiodine – yes versus no“	1.84 (95% CI: 1.02–3.31)	Total: 6.4% RAI(+): 6.9% RAI(-): 4.8%	Median: 8.8y Range: 5.0-17.0y	2,031 (77%)
Hirsch, 2016 [19]	Israel	Critical	HR “for SPM in patients after first RAI treatment compared to patients with no RAI treatment, adjusted for age and sex”	1.27 (95% CI: 0.88–1.82)	Total: 9.3%	Mean ± SD: 9.3 ± 9.6y	1,792 (81.9%)
Khang, 2015 [20]	Korea	Critical	OR [RAI(+) vs. RAI(-)]	1.14 (95% CI: 0.672–1.915)	Total: 2.5%	Median: 7.0y Range: 1.0-33.0y	2,468 (56.6%)
Rubino, 2003 [16]	Sweden/Italy/ France	Serious	RR, stratified by study group and adjusted for external radiotherapy: I-131 vs. no I-131	1.2 (95% CI: 1.0-1.4)	Total: 8.4%	Mean: 13y Range: 2-55y	6,841 (62%)
Teng, 2016 [21]	Taiwan	Serious	aHR of the cumulative RAI activity per 30 mCi [1.11 GBq] increase; patients receiving external beam radiation or chemotherapy were excluded	1.01 (95% CI: 1.00-1.02)	Total: 3.4%	Median: 5.9y IQR: 3.1-9.9y	20,235 (58.3%)
Hakala, 2016 [22]	Finland	Critical	Two numerical results were analyzed to compare the two rate ratios (RR) for no RAI vs. controls and RAI vs. controls	No RAI vs controls: 1.49 (95% CI: 0.96–2.30) RAI vs. controls: 1.04 (95% CI: 0.83–1.32)	Total: 12%	Mean ± SD: 16.2 ± 6.9y	910 (81%)
Lang, 2012 [39]	Hong Kong	Moderate	SIR	RAI(+) group: 1.51 (95% CI: 1.14–1.96) RAI(-) group: 0.84 (95% CI: 0.36–1.66)	Total: 7.2%	Median: 7.8y Range: 2.0-47.6y	895 (71.8%)
Brown, 2008 [18]	SEER, U.S.	Serious	SIR , <36-month latency exclusion, 1988-2002 exclusion, all sites of SPM	No radiotherapy: 1.04 (95% CI: 0.9–1.2) “Radioisotopes”: 1.23 (95% CI: 1.04–1.45)	Total: 7.1%	Median: 8.6y Range: 0.2-29.9y	30,278 (44.0%)

Dose-response relationship – Occurrence of SPM according to cumulative RAI activity							
Study	Cohort/Country	Overall RoB	Relative effect endpoint(s)	Results	Crude Incidence of SPM	Follow-up period	Participants (rate of RAI treatment)
Silva-Vieira, 2017 [15]	Portugal	Moderate	HR – Cox regression model (no competitive risk) – Cumulative activity each activity subgroup vs. 0 mCi [0 GBq]	<100 mCi [<3.7 GBq]: 1.16 (95% CI: 0.44–3.06) 100–199 mCi [3.7–7.363 GBq]: 1.76 (95% CI: 0.95–3.28) 200–299 mCi [7.4–11.063 GBq]: 2.53 (95% CI: 1.21–5.30) ≥300 mCi [≥11.1 GBq]: 2.45 (95% CI: 1.12–5.36)	Total: 6.4% RAI(+): 6.9% RAI(-): 4.8%	Median: 8.8y Range: 5.0-17.0y	2,031 (77%)
Teng, 2016 [21]	Taiwan	Serious	aHR according to the cumulative radioactive activity category; patients receiving external beam radiation or chemotherapy were excluded	1-30 mCi [0.037–1.11GBq] : 1.05 (95% CI: 0.81–1.35) >30–100 mCi [>1.11–3.7 GBq] : 1.07 (95% CI: 0.85–1.34) >100–150 mCi [>3.7–5.55 GBq] : 1.13 (95% CI: 0.85–1.50) >150 mCi [>5.55 GBq] : 1.52 (95% CI: 1.19 - 1.95)	Total: 3.4%	Median: 5.9y IQR: 3.1-9.9y	20,235 (58.3%)
Hirsch, 2016 [19]	Israel	Critical	HR depending on cumulative activity category [in mCi]	1–100 [0.037–3.7 GBq]: 1.5 (95% CI: 0.99–2.3) 101–150 [3.737–5.55GBq]: 1.3 (95% CI: 0.8–2.1) 151–299 [5.587–11.063 GBq]: 0.7 (95% CI: 0.3–1.5) ≥300 [≥11.1 GBq]: 13 (95% CI: 0.8–2.4)	Total: 9.3%	Mean ± SD: 9.3 ± 9.6y	1,792 (81.9%)
Hakala, 2016 [22]	Finland	Critical	(Patients vs. controls) as Rate ratio (RR) for subgroups according to their cumulative RAI activity	≤3.7 GBq: 0.94 (95% CI: 0.70–1.25) >3.7 GBq: 1.37 (95% CI: 0.90–2.09)	Total: 12%	Mean ± SD: 16.2 ± 6.9y	910 (81%)
Khang, 2015 [20]	Korea	Critical	OR [RAI(+)] according to cumulative activity group vs. RAI(-)]	1.1–5.55 GBq: 0.87 (95% CI: 0.469–1.620) 5.56–22.2 GBq: 0.67 (95% CI: 0.272–1,659) 22.3–36.9 GBq: 2.04 (95% CI: 0.477–8.696) ≥37.0 GBq: 5.54 (95% CI: 2.635-11.634)	Total: 2.5%	Median: 7.0y Range: 1.0-33.0y	2,468 (56.6%)

Lang, 2012 [39]	Hong Kong	Moderate	RR , Cox proportional hazards analysis, cumulative RAI activity [GBq]	None: Reference 3.0–8.9 GBq: 2.777 (95% CI: 1.089–7.145) >9.0 GBq: 3.149 (95% CI: 0.645–12.816)	Total: 7.2%	Median: 7.8y Range: 2.0–47.6y	895 (71.8%)
Fallahi, 2011 [38]	Iran	Serious	OR of SPM with increasing cumulative activity of RAI	<10 GBq: 1.00 (reference) 10–20 GBq: 3.11 (95% CI: 0,24-39,83) 20–30 GBq: 9.29 (95% CI: 0,69-125,01) 30–40 GBq: No SPM cases 40–50 GBq: 113.42 (95% CI: 8,60-1495,64) ≥50 GBq: 122.90 (95% CI: 5.56-2716.93)	Total: 1.1%	Median: 6y Mean: 7.5y Range: 3-26y	973 (100%)
Rubino, 2003 [16]	Sweden/ Italy/ France	Serious	RR : The occurrence of second primary solid cancers depending on the cumulative RAI activity administered, patients treated with external radiotherapy excluded.	≤0.2 GBq: 1.0 (reference) 0.2–3.6 GBq: 1.2 (95% CI: 0.9–1.5) 3.7–7.3 GBq: 0.9 (95% CI: 0.7–1.2) 7.4–14.7 GBq: 1.4 (95% CI: 1.0–2.1) ≥14.8 GBq: 1.5 (95% CI: 0.8–2.6)	Total: 8.4%	Mean: 13y Range: 2-55y	6,841 (62%)

Occurrence of SHM in patients treated with RAI versus without RAI

Study	Cohort/Country	Risk of Bias	Measure	Data	Crude Incidence	Follow-up period	Participants (RAI rate)
Molenaar, 2018 [41]	SEER, U.S.	Moderate	SIR for all SHMs combined, additional risk from RAI	1.30 (95% CI: 1.12–1.51)	Total: 0.53%	Median: 6.6y IQR: 3.3-11.2y	148,215 (47%)
Rubino, 2003 [16]	Sweden/Italy/France	Serious	RR , stratified by study group and adjusted for external radiotherapy: I-131 vs. no I-131 for the outcome leukemia	2.5 (95% CI: 1.0–7.4)	Total: 18/6,841 (0.26%)	Mean: 13y Range: 2-55y	6,841 (62%)
Teng, 2016 [21]	Taiwan	Serious	aHR of cumulative RAI activity per 30 mCi [1.1 GBq] increase; patients receiving external beam radiation or chemotherapy were excluded	Leukemia: 1.03 (95% CI: 1.02–1.04) Non-Hodgkin Lymphoma: 0.86 (95% CI: 0,73-1,00)	Leukemia: 19/20,235 (0.09%) Non-Hodgkin Lymphoma: 26/20,235 (0.13%)	Median: 5.9y IQR: 3.1-9.9y	20,235 (58.3%)