National Institute for Health and Care Excellence

Final

Thyroid cancer: assessment and management

[K] Evidence review for activity of radioactive iodine after thyroidectomy

NICE guideline NG230

Evidence reviews underpinning recommendations 1.3.17 to 1.3.18 in the NICE guideline

December 2022

Final

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ISBN: 978-1-4731-4870-3

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1 Activity of Radioactive iodine after thyroidectomy

1.1 Review question

1.1.1 What is the most clinically and cost-effective administered activity for people receiving radioactive iodine after thyroidectomy?

1.1.2 Introduction

If radioactive iodine (RAI) ablation is indicated, it has been customary to give a standard amount of radioactivity which was based on the original practice in the USA from the 1940s and 1950s. Therefore, until recently almost every patient received a similar amount of radioactivity (3-3.7GBq). In the early 2000s work coming from India suggested that successful thyroid ablation could be achieved using much less radioactivity especially in those patients with smaller cancers at diagnosis and those with low-risk pathology. In the UK there is a legal imperative to reduce the radiation dose that patients receive to a minimum (Ionising Radiation (Medical Exposure) Regulations-IRMER,2017). It has been suggested that these low-risk patients can be successfully ablated using a single administration of a much lower level of radiation normally 1-1.5GBq. This review examines the evidence for the activity of administered RAI strategy after surgery for differentiated thyroid cancer.

1.1.3 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	People aged 16 or over receiving radioactive iodine after thyroidectomy
Interventions	• radioactive iodine ablation at higher activity (>3 GBq) • radioactive iodine ablation at intermediate activity (2-3 GBq). • radioactive iodine ablation at lower activity (<2 GBq).
Comparisons	Each other
Outcomes	• Successful ablation (thyroglobulin levels / USS / diagnostic RAI) • mortality • quality of life • local cancer progression • incidence of distant metastases • cancer recurrence • second primary malignancy
Analysis of sub-groups	Stratification (unconditional splitting) Different levels of disease severity (low risk / high risk / patients with known metastatic disease) Sub-grouping (conditional splitting) of the above strata or whole body of evidence If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: • Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement

	• Prior dietary restriction of iodine vs no prior iodine restriction. • Ablation vs treatment • Longest follow up in study: <1 yr, 1-5 yrs, >5 yrs
Study design	Systematic review RCT

1.1.4 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

1.1.5 Effectiveness evidence

1.1.5.1 Included studies

Fifteen RCTs from 18 papers were included in the review.[2-4, 9, 12, 14, 15, 17, 19, 23, 26, 28, 29, 34, 36, 41, 48, 49] These are summarised in Table 2 below. Fifteen studies compared high activity to low activity RAI, one study compared high activity to intermediate activity RAI, and two studies compared intermediate activity to low activity RAI. Three studies were of a low risk population, one study was of a high risk population, and ten studies included a mixed or unclear population.

Evidence from these studies is summarised in the clinical evidence summary below (Table 3). In some meta-analyses serious heterogeneity (manifested by an I^2 of >50%) was observed. This was investigated using the 4 pre-hoc sub-grouping strategies outlined in the protocol, but these failed to explain the inconsistencies. Therefore, for all such analyses with serious heterogeneity a Random Effects model was used.

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.5.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.6 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Bal 1996[4]	RAI at higher activity: Radioactive iodine ablation – with prior withdrawal of thyroid hormone replacement. Thirty patients were treated with a single dose of 120-200 mCi (4.44-7.4 GBq) RAI at a lower activity: Radioactive iodine ablation – with prior withdrawal of thyroid hormone replacement. Twenty-seven patients were treated with a single dose of 25-34 mCi (0.9-1.3 GBq)	Patients had residual functioning tissue in thyroid region and no evidence of extrathyroidal or distant metastases Age – Mean (range): Higher activity: 39 (27-68) Lower activity: 38 (25-59) RCT India	• Successful ablation	Unclear strata – stage not reported
Bal 2012[3]	RAI at higher activity: Radioactive iodine ablation – with prior withdrawal of thyroid hormone replacement. Seventy--nine patients were treated with a single dose of 3.7 GBq RAI at a lower activity: Radioactive iodine ablation – with prior withdrawal of thyroid hormone replacement. One hundred and seventy-two patients were treated with a single dose of 0.925 GBq and 171 patients were treated with a single dose of 1.85 GBq	Patients with differentiated thyroid cancer limited to the thyroid bed and no extra thyroidal or distant metastases size T1-T3 Age – Mean (SD): 37.02 (13.01) RCT India	• Successful ablation	Mixed/unclear risk strata - Differentiated thyroid cancer, 70% stage 1, 11.3% stage 2, 18.6% stage 3. Nodes absent in 72.2%.

Study	Intervention and comparison	Population	Outcomes	Comments
Caglar 2012[9]	RAI at higher activity: Radioactive iodine ablation. Fifty-five patients were treated with a single dose of 3.7 GBq RAI at a lower activity: Radioactive iodine ablation. Fifty-three patients were treated with a single dose of 0.8 GBq)	Patients with nonmetastatic, unifocal T1 or T2 and multifocal T1, well differentiated thyroid cancer (DTC) limited to the thyroid Age – Mean (range): Higher activity: 44 (22-74) Lower activity: 47 (20-75) RCT Turkey	• Successful ablation	Mixed/unclear strata - Unifocal T1 or T2 and multifocal T1 well differentiated cancer, 97% papillary or follicular, 43.5% multifocal
Fallahi 2012[17]	RAI at higher activity: Radioactive iodine ablation – with prior withdrawal of thyroid hormone replacement. One hundred and seventy patients were treated with a single dose of 3.7 GBq RAI at a lower activity: Radioactive iodine ablation – with prior withdrawal of thyroid hormone replacement. One hundred and seventy-one patients were treated with a single dose of 0.8 GBq	Patients with confirmed differentiated thyroid carcinoma Age – Mean (SD): Higher activity: 40.52 (13.01) Lower activity: 38.30 (11.07) RCT Iran	• Successful ablation • Recurrence	Mixed/unclear strata – stage not mentioned (95.6% papillary)
Giovanella 2013[19]	RAI at higher activity: Radioactive iodine ablation – with prior withdrawal of thyroid hormone replacement. Sixty-nine patients were treated with a single dose of 3.7 GBq	Patients with histologically proven low-risk differentiated thyroid carcinoma primarily treated by lobectomy Age – Mean (SD): Higher activity: 45 (22)	• Successful ablation	Low risk strata (likely stage 1 or 2) Presence of T1b-T2 unifocal DTC

Study	Intervention and comparison	Population	Outcomes	Comments
	RAI at a lower activity: Radioactive iodine ablation – with prior withdrawal of thyroid hormone replacement. One hundred and seventy-one patients were treated with a single dose of 1.1 GBq	Lower activity: 42 (19) RCT Switzerland		
Kukulska 2010[23]	RAI at higher activity: Radioactive iodine ablation. Ninety-five patients were treated with a single dose of 3.7 GBq RAI at an intermediate activity: Radioactive iodine ablation. One hundred and twenty-eight patients were treated with a single dose of 2.2 GBq RAI at a lower activity: Radioactive iodine ablation. Eighty-six patients were treated with a single dose of 1.1 GBq	Two cohorts of patients were recruited: patients with low risk differentiated thyroid cancer were randomised to lower or intermediate activity; patents with staged pT1b-T4 N0-1 DTC were randomised to intermediate or higher activity groups. Age: Not reported RCT Poland	• Successful ablation • Recurrence • Incidence of distant recurrence	Mixed/unclear strata – described by authors as low risk. T1b 23.3%, T2 48.9%, T3 8.1%, T4 4.5%, Tx 15.2%; N0 55.9%, N1 5.8%, Nx 38.2%
Ma 2017[26]	RAI at higher activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. One-hundred and twenty-three patients were treated with a single dose of 3.7 GBq RAI at a lower activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. One-hundred and	Patients with papillary thyroid cancer and follicular thyroid cancer Age – Mean (SD): 44 (13) RCT China	• Successful ablation • Recurrence	Mixed/unclear risk strata - Papillary (96.4%) or follicular thyroid cancer, tumour stage 1, 2 or 3 with or without lymph node movement. T1 (61.5%), T2 (11%), T3 (17.6%), Tx (9.7%). N0 (30%), N1a (47%), N1b (26.6%)

Study	Intervention and comparison	Population	Outcomes	Comments
	fifty-five patients were treated with a single dose of 1.85 GBq			
Maenpaa 2008[28] (Ahtiainen, 2020[2])	RAI at higher activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. Seventy-nine patients were treated with a single dose of 3.7 GBq RAI at a lower activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. Eighty-one patients were treated with a single dose of 1.11 GBq	Patients with histologically confirmed thyroid carcinoma Age – Median (range): Higher activity: 45 (18-90) Lower activity: 49 (23-79) RCT USA	• Successful ablation • Incidence of distant metastases • All-cause mortality	Mixed/unclear strata - Papillary (91%) or follicular thyroid cancer, 33.75% multifocal
Mallick 2012[29] (Dehbi 2019[11])	RAI at higher activity: Radioactive iodine ablation. Half of the patients received thyrotropin alfa on each of the two days before ablation (0.9mg), and the other half underwent thyroid hormone withdrawal. Two-hundred and eighteen patients were treated with a single dose of 3.7 GBq RAI at a lower activity: Radioactive iodine ablation. Half of the patients received thyrotropin alfa on each of the two days before ablation (0.9mg), and the other half underwent thyroid hormone withdrawal. Two-hundred and twenty patients were treated with a single dose of 1.1 GBq	Patients had tumour stage T1 to T3, with possible spread to nearby lymph nodes but without metastasis Age – median (range): Thyrotropin alfa subgroup: low-dose 44 (20-83) years; high dose 44 (21-76) years. Thyroid hormone withdrawal: low dose 45 (17-73) years; high dose 43 (18-77) years. RCT UK	• Quality of life • Successful ablation • Recurrence	Low risk strata - Differentiated thyroid cancer stage – tumour stage T1 (29%), T2 (47.75%), T3 (23%), nodal stage N0 (58.75%), N1 (15.75%), Nx (26%)

Study	Intervention and comparison	Population	Outcomes	Comments
Pilli 2008[34]	RAI at higher activity: Radioactive iodine ablation. Thirty-six patients were treated with a single dose of 3.7 GBq RAI at a lower activity: Radioactive iodine ablation. Thirty-six patients were treated with a single dose of 1.85 GBq	Patients with newly diagnosed differentiated thyroid cancer recently treated with near total thyroidectomy Age – Mean (SD): Higher activity: 50.5 (15.6) Lower activity: 47.9 (13.9) RCT Finland	• Successful ablation	Mixed/unclear risk strata - Differentiated thyroid cancer, papillary (92%), T1-T3 NX (72%), T1-T3 N0 (9.7%), T1-T3 N1 (18%)
Qu 2017[36]	RAI at higher activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. Sixty-nine patients were treated with a single dose of 3.7 GBq RAI at a lower activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. Sixty-eight patients were treated with a single dose of 1.1 GBq	Low/intermediate risk differentiated thyroid cancer patients Age – Mean (SD): 41.61 (10.34) RCT China	• Successful ablation	Low risk strata - Described by authors as low/intermediate risk, including papillary and follicular, T1 N0-1 and T2 N0
Shinto 2013[41]	RAI at intermediate activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. Twenty-five patients were treated with 2.78 GBq RAI at a lower activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. Forty-six patients	Patients with differentiated thyroid cancer limited to the thyroid bed Age – Mean (SD): 39 (12.7) RCT India	• Successful ablation	Mixed/unclear strata – 84% papillary, no information on stage (does report mean tumour size as 3.8 cm)

Study	Intervention and comparison	Population	Outcomes	Comments
	were treated with 1.1 GBq and thirty-four were treated with 1.85 GBq			
Zaman 2006[48]	RAI at high activity: Radioactive iodine ablation. Twenty patients were treated with 3.7 GBq RAI at a lower activity: Radioactive iodine ablation. Twenty patients were treated with 1.85 GBq	Patients with differentiated thyroid carcinoma who had undergone total or near total thyroidectomy Age – Mean (SD): 38.3 (11.7)	• Successful ablation	Mixed/unclear – differentiated papillary/follicular, no further information regarding stage
Zhang 2015[49]	RAI at higher activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. Fifty-three patients were treated with 3.7 GBq RAI at a lower activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. Fifty-three patients were treated with 1.11 GBq	Patients who had undergone total thyroidectomy and had differentiated thyroid cancer Age: Higher activity: <45 years n=34, ≥45 years n=17 Lower activity: <45 years n=30, ≥45 years n=21 RCT China	• Successful ablation	High risk strata - Differentiated cancer, pT4 stage and any N stage (N0 26.5%, N1 73.5%), 98% papillary
Dong, 2021[15] (Dong, 2021[14])	RAI at higher activity: Radioactive iodine ablation – with prior thyroid hormone withdrawal. 261 patients were treated with 3.7 GBq RAI at a lower activity: Radioactive iodine ablation – with prior thyroid hormone	Age at diagnosis 18 years or older; patients undergoing total or near total thyroidectomy and those with lymph node involvement undergoing lymph node dissection; primary RAI therapy after surgery; low- / intermediate risk DTC; TNM stage confirmed on	• Successful ablation	low- / intermediate risk DTC; TNM stage confirmed on pathological examination of the surgical specimen; T1 (<2cm) N0-1 and T2 (>2 cm but <4cm) N0;

Study	Intervention and comparison	Population	Outcomes	Comments
	withdrawal. 255 patients were treated with 1.11 GBq	pathological examination of the surgical specimen; T1 (<2cm) N0-1 and T2 (>2 cm but <4cm) N0; absence of distant metastasis Age - Median (range): Low activity group 43 (21-70); high activity group 41 (19-75). Gender (M:F): 140:352.		

See Appendix D for full evidence tables.

1.1.7 Summary of the effectiveness evidence

1.1.7.1 Low risk stratum

Table 3: Clinical evidence summary: Low risk stratum: Higher versus lower activity RAI for thyroid cancer

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with lower activity	Risk difference with higher activity (95% CI)
Successful ablation	1195 (4 studies) 6 months to 7 years	VERY LOW[1 2] due to inconsistency	Random effects RR 1.06 (0.93 to 1.20)	Moderate	
				870 per 1000	50 more per 1000 (from 58 fewer to 165 more)
Recurrence	434 (1 study) 78.4 months	LOW[3] due to imprecision	RR 0.91 (0.39 to 2.1)	Moderate	
				51 per 1000	5 fewer per 1000 (from 31 fewer to 56 more)
Quality of life - physical domains Scale from: 0 to 100.	438 (1 study) 3 months	HIGH		The mean quality of life - physical domains in the control groups was 20	The mean quality of life - physical domains in the intervention groups was 7 lower (27.2 lower to 13.2 higher)
Quality of life - psychological domains Scale from: 0 to 100.	438 (1 study) 3 months	HIGH		The mean quality of life - psychological domains in the control groups was 19.4	The mean quality of life - psychological domains in the intervention groups was 4.4 higher (16.2 lower to 25 higher)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

2 Downgraded because the heterogeneity was very serious (I^2>75%) and unexplained by subgroup analysis

3 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. For binary variables the MIDs were set at RR of 0.8 and 1.25. For the continuous outcomes the MIDs were set at ±0.5 x median standard deviation of the control group. For quality of life (physical domains) the sd was 107.84, so the MID was ±53.92, and for quality of life (psychological domains) the sd was 109.98, so the MID was ±54.99

Table 4: Clinical evidence summary: Low risk stratum: Higher versus intermediate activity RAI for thyroid cancer

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with intermediate activity	Risk difference with higher activity (95% CI)
Successful ablation	223 (1 study) 6-12 months	⨁⨁⨁⨀ MODERATE1 due to risk of bias	RR 1.03 (0.94 to 1.14)	Moderate	
				867 per 1000	26 more per 1000 (from 52 fewer to 121 more)
Recurrence	223 (1 study) 10 years	⨁⨀⨀⨀ VERY LOW1,2 due to risk of bias, imprecision	RR 1.01 (0.23 to 4.41)	Moderate	
				31 per 1000	0 more per 1000 (from 24 fewer to 106 more)
Incidence of distal metastases	223 (1 study) 10 years	⨁⨁⨁⨀ LOW1,2 due to risk of bias, imprecision	Risk difference 0 (-0.02 to 0.02)	Moderate	
				0 per 1000	0 more per 1000 (from 18 fewer to 18 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 For risk ratios, downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (0.8 or 1.25). For the risk differences, the imprecision was based on optimal information size, with sample sizes of 70-350 indicating serious imprecision.

Table 5: Clinical evidence summary: Low risk stratum: Intermediate versus lower RAI activity for thyroid cancer

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with lower activity	Risk difference with intermediate activity (95% CI)
Successful ablation	214 (1 study) 6-12 months	⨁⨁⨀⨀ LOW1,2 due to risk of bias, imprecision	RR 1.11 (0.98 to 1.27)	Moderate	
				779 per 1000	86 more per 1000 (from 16 fewer to 210 more)
Recurrence	214 (1 study) 10 years	⨁⨀⨀⨀ VERY LOW1,2	RR 1.34 (0.25 to 7.18)	Moderate	
				23 per 1000	8 more per 1000 (from 17 fewer to 142 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with lower activity	Risk difference with intermediate activity (95% CI)
		due to risk of bias, imprecision			
Incidence of distal metastases	214 (1 study) 10 years	⨁⨁⨁⊖ LOW1,2 due to risk of bias, imprecision	Risk difference 0 (-0.02 to 0.02)	Moderate	
				0 per 1000	0 more per 1000 (from 19 fewer to 19 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 For risk ratios, downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (0.8 or 1.25). For the risk differences, the imprecision was based on optimal information size, with sample sizes of 70-350 indicating serious imprecision.

1.1.7.2 High risk stratum

Table 6: Clinical evidence summary: High risk stratum: Higher versus lower RAI activity for thyroid cancer

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with lower activity	Risk difference higher activity (95% CI)
Successful ablation	102 (1 study) 6 months	⨁⨁⨁⨁ HIGH	RR 1.02 (0.87 to 1.2)	Moderate	
				843 per 1000	17 more per 1000 (from 110 fewer to 169 more)

1.1.7.3 Mixed/unclear risk stratum

Table 7: Clinical evidence summary: Mixed/unclear risk stratum: Higher versus lower RAI activity for thyroid cancer

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with lower activity	Risk difference higher activity (95% CI)
Successful ablation	1634 (9 studies) 6 months - 3.8 years	⨁⨀⨀⨀ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	Random effects RR 1.15 (1.03 to 1.28)	Moderate	
				630 per 1000	94 more per 1000 (from 19 more to 176 more)
Recurrence	800 (3 studies) 1-10 years	⨁⨁⨁⨀ MODERATE1 due to risk of bias	Risk difference 0 (-0.01 to 0.02)	Moderate	
				12 per 1000	12 fewer per 1000 (from 12 fewer to 12 more)
Incidence of distal metastases	370 (2 studies) 6-13 years	⨁⨁⨀⨀ LOW1,2 due to risk of bias, inconsistency	Risk difference 0.01 (-0.04 to 0.07)	Moderate	
				6 per 1000	15 more per 1000 (from 40 fewer to 70 more)
All-cause mortality	160 (1 study) 13 years	⨁⨁⨀⨀ LOW3 due to imprecision	RR 0.73 (0.24 to 2.21)	Moderate	
				86 per 1000	23 fewer per 1000 (from 65 fewer to 104 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded due to significant heterogeneity unexplained by subgroup analysis
3 For risk ratios, downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (0.8 or 1.25). For the risk differences, the imprecision was based on optimal information size, with sample sizes of >350 indicating no serious imprecision.

Table 8: Clinical evidence summary: Mixed/unclear risk stratum: Intermediate versus lower RAI activity for thyroid cancer

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with lower activity	Risk difference with intermediate activity (95% CI)
Successful ablation	105 (1 study)	⨁⨁⨁⊖ MODERATE1 due to risk of bias	RR 1.01 (0.85 to 1.19)	Moderate	
				875 per 1000	9 more per 1000 (from 131 fewer to 166 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

See Appendix F for full GRADE

1.1.8 Economic evidence

1.1.8.1 Included studies

No health economic studies were included.

1.1.8.2 Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.9 Summary of included economic evidence

None.

1.1.10 Economic model

1.1.11 This area was not prioritised for new cost-effectiveness analysis.

1.1.12 Unit costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Resource	Unit costs	Source
Low activity RAI (day care)	£406	NHS Reference Costs 2018-2019[32], Committee's expert opinion
Low activity RAI	£628	NHS Reference Costs 2018-2019[32], Committee's expert opinion
High activity RAI	£961	NHS Reference Costs 2018-2019[32], Committee's expert opinion

1.1.13 Economic evidence statements

No relevant economic evaluations were identified.

1.1.14 The committee's discussion and interpretation of the evidence

1.1.14.1 The outcomes that matter most

The outcomes of successful ablation, mortality, quality of life (any validated scores), local cancer progression, incidence of distal metastases, cancer recurrence and second primary malignancy were all deemed critical outcomes, and were therefore of equal importance in decision-making. The longest follow-up time point was reported for all the outcomes.

There was no evidence for local cancer progression or second primary malignancy.

1.1.14.2 The quality of the evidence

The quality of evidence ranged from very low to high, with most of the downgrading resulting from risk of bias and imprecision. Risk of bias was generally low across studies, although some were downgraded for selection bias. There were a few outcomes downgraded for serious risk of inconsistency that were not resolved by pre-hoc testing strategies.

1.1.14.3 Benefits and harms

The evidence showed that the RAI activity level did not influence mortality, quality of life, incidence of distal metastases, or cancer recurrence, and this applied across all population strata that were reviewed. However, for the outcome of successful ablation, there was a benefit for higher (3.7 GBq) over lower activity (1.1 GBq) in the low risk stratum and the mixed/unclear stratum. In both cases this benefit was accompanied by 95% confidence intervals that did not cross the null line, indicating that the direction of effects in the population were probably being accurately estimated by the direction of the sample effects. The committee discussed how this result reflected the established belief that complete ablation is more likely with higher activities. However, the risk differences of the point estimates were relatively small (6%), suggesting numbers needed to treat of around 16 for the low risk stratum and 10 for the mixed/unclear stratum. The committee agreed that these risk differences and numbers needing to treat were probably not clinically significant, and that higher activities would only benefit a small proportion (6%) of patients in the lower risk and mixed/unclear strata.

The committee stressed the legal requirement to keep radiation exposure to the absolute minimum necessary to achieve clinical benefit (IRMER 2017). Harms of radiation exposure are not trivial, and include increased initial complication rates, such as nausea and salivary gland dysfunction, as well as longer term effects such as increased risk of a second primary cancer. Therefore, it was agreed that giving most patients a high activity solely to accommodate the needs of a very small proportion of who might not initially respond to a lower activity was not appropriate, given the harms of radiation exposure. There is also a small probability of patients coming to harm if they need to wait 4-6 months for a second treatment. Therefore, the committee agreed that the evidence did not suggest that the majority of patients should be treated with higher activities, and recommended that most patients should be treated with a low (1.1GBq) activity. The committee also discussed that while the usual activity is 1.1GBq in practice this may vary by plus or minus 10%.

Nevertheless, the committee agreed that there would be a specific group of patients for whom a higher activity (3.7GBq) should be considered. These would include people such as those with T4 disease, N1B disease, M1 disease or aggressive subtypes. In more aggressive cancers timely treatment is very important. Therefore, it becomes essential to ensure all normal thyroid tissue is ablated as quickly as possible so that thyroglobulin can be used to monitor for recurrent or metastatic disease. A higher activity would be better to reduce the likelihood of the cancer recurring. The committee also agreed a higher activity would be appropriate for people in whom multiple ablations should be avoided. This included people with significant co-morbidities such as cardiovascular disease, mobility issues, or complex social concerns. For these people, the potential harms of a higher activity would probably be overcome by the potential benefits resulting from more complete ablation after a single exposure. In particular, the committee noted that for people with cardiovascular disease, every time you change the thyroid function, as is needed before RAI treatment, you put them at risk of their cardiac disease becoming worse.

1.1.14.4 Cost effectiveness and resource use

There was no cost-effectiveness evidence for this question.

The committee recommended low activity RAI to people unless they belong to a high-risk group or there is a health concern to avoid multiple ablations. High activity RAI implies a higher cost as patients would need to be admitted to the hospital for longer, be absent from work due to radiation restriction and have possibly higher individual cost due to increased morbidity (e.g. second malignancy). Finally, higher RAI activity has a higher global impact on the society in terms of higher radiation exposure.

The unit cost for RAI was estimated to be around £400 (NHS Reference Costs 2018-2019) and hardly changing between low and high activity as most of the cost is expected to be administrative according to the committee. The highest cost differential is due to bed cost: low activity RAI requires an inpatient stay of one night only whereas with high activity RAI people would need to be admitted for an average of 2.5 nights according to the committee. Assuming an average cost per bed day of £222 as reported by NICE, lower activity RAI would save, on average, £333 compared to high activity RAI. This figure would probably be lower if we take into account that there is a higher probability with low activity RAI to require an additional RAI if the first treatment was not effective.

The recommendations reflect current practice in the UK as low activity RAI is already preferred to high activity RAI due to the imperative of keeping radiation exposure to society low. It is possible, though, that following the recommendations low activity RAI will be offered instead of high activity RAI more often, which should reduce the cost for the NHS with positive impacts for patients who would have a lower risk of developing second malignancy due to radiation exposure. Thus, we expect the efficiency of the NHS to improve.

1.1.14.5 Other factors the committee took into account

The committee discussed equality issues regarding gender and disabilities.

Exposure to radioiodine during pregnancy is harmful to the developing fetus with consequent fetal hypothyroidism and potential cognitive disorders. Pregnancy should therefore be avoided after radioiodine for at least six months to avoid exposure to radioactivity, and to ensure the mother is in remission and with adequate levothyroxine replacement. If radioiodine is required after delivery, breast feeding should be stopped for at least six weeks. Mothers receiving radioiodine should avoid breast feeding. Therefore, careful consideration is required for these women as to the timing of RAI treatment.

There is some evidence suggesting that radioiodine may adversely affect fertility men. Some centres offer sperm banking for men if multiple doses of radioiodine are planned, particularly if the cumulative planned dose is >13GBq or they are attempting conception within 18 months of treatment. However, this is not offered by all centres.

Overall, the committee agreed there is standard and accepted advice around what to do and recommended that written and verbal information is provided on how treatment may affect pregnancy and fertility. The committee also recommended surgery is deferred until after pregnancy where possible. As radioactive iodine is only given postoperatively then by default it would also be deferred.

In addition, in people who have significant physical and mental co-morbidities and disabilities which may impact on the safe administration of RAI the committee agreed that usual practice is for them to have a patient specific risk assessment and care plan arranged before RAI is administered.

1.1.15 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.17 to 1.3.19.

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Appendices

Appendix A – Review protocols

A.1 Review protocol for dose of RAI after thyroidectomy

Field	Content
PROSPERO registration number	CRD42021241541
Review title	Clinically and cost-effective administered activity of radioactive iodine after thyroidectomy for differentiated thyroid cancer.
Review question	What is the most clinically and cost-effective administered activity for people receiving radioactive iodine after thyroidectomy?
Objective	To determine the best radiation activity strategy for radioactive iodine (RAI) ablation after surgery for differentiated thyroid cancer
Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by:

	• English language • Human studies • Letters and comments are excluded. Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before the final submission committee meeting of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Thyroid cancer
Population	Inclusion: People aged 16 or over receiving radioactive iodine after thyroidectomy Exclusion: Children and young people under 16
Intervention/Exposure/Test	• radioactive iodine ablation at higher activity (>3 GBq)

	• radioactive iodine ablation at intermediate activity (2-3 GBq). • radioactive iodine ablation at lower activity (<2 GBq).
Comparator/Reference standard/Confounding factors	Each other
Types of study to be included	• Systematic reviews • RCTs
Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	Dosage of RAI is an important area of uncertainty in this area.
Primary outcomes (critical outcomes)	• Successful ablation (thyroglobulin levels / USS / diagnostic RAI) • mortality • quality of life • cost effectiveness • local cancer progression • incidence of distant metastases • cancer recurrence

	• second primary malignancy Longest follow up available in each study
Secondary outcomes (important outcomes)	None
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary). The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).

	10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately

	a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent.

	Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
Analysis of sub-groups	<u>Stratification (unconditional splitting)</u> Different levels of disease severity (low risk / high risk / patients with known metastatic disease) <u>Sub-grouping (conditional splitting) of the above strata or whole body of evidence</u> If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: • Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement • Prior dietary restriction of iodine vs no prior iodine restriction. • Ablation vs treatment • Longest follow up in study: <1 yr, 1-5 yrs, >5 yrs
Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)

Language	English
Country	England
Named contact	**Named contact** National Guideline Centre **Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
Review team members	From the National Guideline Centre: Carlos Sharpin, Guideline lead Mark Perry, Senior systematic reviewer Vimal Bedia, Systematic reviewer Giulia Zuodar, Project manager Alfredo Mariani, Health economist Lina Gulhane, Head of Information specialists
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.

Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10150/documents
Other registration details	N/A
Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=241541
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	None
Details of existing review of same topic by same authors	N/A
Additional information	N/A
Details of final publication	www.nice.org.uk

A.2 Review protocol health economic evidence

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see Appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[31] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion**

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as 'Not applicable'.
- Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual, 2014 (updated 2020) https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission.

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

Clinical literature search strategy

This literature search strategy was used for the following review:

- What is the most clinically and cost-effective administered activity for people receiving radioactive iodine after thyroidectomy?

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 9: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1946 – 13 January 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, children) English language
Embase (OVID)	1974 – 13 January 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts, children) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 12 of 12, December 2021	Exclusions (clinical trials, conference abstracts)

Database	Dates searched	Search filters and limits applied
	Cochrane Central Register of Controlled Trials to Issue 12 of 12, December 2021	
Epistemonikos (The Epistemonikos Foundation)	Inception – 13 January 2022	Systematic review Exclusions (Cochrane reviews) English language

Medline (Ovid) search terms

1.	exp Thyroid Neoplasms/
2.	(thyroid and (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or follicul* or lymphoma* or anaplastic or sarcoma* or medullar* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or follicul* or medullar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump* or lymphoma*)).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to english language
26.	exp radiotherapy/
27.	radiotherapy dosage/
28.	Iodine Radioisotopes/
29.	radioiodine.ti,ab.
30.	(iodi?e adj2 (radio* or isotope*)).ti,ab.
31.	(iodi?e 131 or 131-I or I-131).ti,ab.
32.	remnant ablation.ti,ab.

33.	(iodi?e adj2 (ablation or treatment* or therap* or medic* or procedure* or intervention*)).ti,ab.
34.	(RAA or RRA or RAI).ti,ab.
35.	or/26-34
36.	25 and 35
37.	randomized controlled trial.pt.
38.	controlled clinical trial.pt.
39.	randomi#ed.ab.
40.	placebo.ab.
41.	randomly.ab.
42.	clinical trials as topic.sh.
43.	trial.ti.
44.	or/37-43
45.	Meta-Analysis/
46.	Meta-Analysis as Topic/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
48.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/45-54
56.	Epidemiologic studies/
57.	Observational study/
58.	exp Cohort studies/
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	Controlled Before-After Studies/
63.	Historically Controlled Study/
64.	Interrupted Time Series Analysis/
65.	(before adj2 after adj2 (study or studies or data)).ti,ab.
66.	exp case control study/
67.	case control*.ti,ab.
68.	Cross-sectional studies/
69.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
70.	or/57-70
71.	36 and (44 or 55 or 70)

Embase (Ovid) search terms

1.	exp Thyroid Cancer/

2.	(thyroid adj3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)).ti,ab.
5.	or/1-4
6.	letter.pt. or letter/
7.	note.pt.
8.	editorial.pt.
9.	case report/ or case study/
10.	(letter or comment*).ti.
11.	(conference abstract or conference paper).pt.
12.	or/6-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	5 not 22
24.	limit 23 to english language
25.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
26.	24 not 25
27.	exp radiotherapy/
28.	radiotherapy dosage/
29.	radioactive iodine/
30.	radioiodine.ti,ab.
31.	(iodi?e adj2 (radio* or isotope*)).ti,ab.
32.	iodine 131/
33.	(iodi?e 131 or 131-I or I-131).ti,ab.
34.	remnant ablation.ti,ab.
35.	(iodi?e adj2 (ablation or treatment* or therap* or medic* or procedure* or intervention*)).ti,ab.
36.	(RAA or RRA or RAI).ti,ab.
37.	or/27-36
38.	26 and 37
39.	random*.ti,ab.
40.	factorial*.ti,ab.
41.	(crossover* or cross over*).ti,ab.
42.	((doubl* or singl*) adj blind*).ti,ab.
43.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
44.	crossover procedure/
45.	single blind procedure/

46.	randomized controlled trial/
47.	double blind procedure/
48.	or/39-47
49.	systematic review/
50.	Meta-Analysis/
51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.
56.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-58
60.	Clinical study/
61.	Observational study/
62.	family study/
63.	longitudinal study/
64.	retrospective study/
65.	prospective study/
66.	cohort analysis/
67.	follow-up/
68.	cohort*.ti,ab.
69.	67 and 68
70.	(cohort adj (study or studies or analys* or data)).ti,ab.
71.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
72.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
73.	(before adj2 after adj2 (study or studies or data)).ti,ab.
74.	exp case control study/
75.	case control*.ti,ab.
76.	cross-sectional study/
77.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
78.	or/60-66,69-77
79.	38 and (48 or 59 or 78)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2.	(thyroid near/3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)):ti,ab
#3.	DTC:ti,ab
#4.	((papillar* or anaplastic) near/2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)):ti,ab
#5.	#1 or #2 or #3 or #4

#6.	conference:pt or (clinicaltrials or trialsearch):so
#7.	#5 not #6
#8.	MeSH descriptor: [Iodine Radioisotopes] explode all trees
#9.	MeSH descriptor: [Radiotherapy] explode all trees
#10.	MeSH descriptor: [Radiotherapy Dosage] this term only
#11.	radioiodine:ti,ab
#12.	((iodi?e) near/2 (radio* or isotope*)):ti,ab
#13.	(iodi?e-131 or I-131):ti,ab
#14.	remnant ablation:ti,ab
#15.	((iodi?e) near/2 (ablation or treatment* or therap* or medic* or procedure* or intervention*)):ti,ab
#16.	(RAA or RRA or RAI):ti,ab
#17.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18.	#7 and #17

Epistemonikos search terms

1.	(title:(remnant ablation OR RAI OR RRA OR RAA) OR abstract:(remnant ablation OR RAI OR RRA OR RAA)) OR (title:(thyroid AND (iodine OR iodide)) OR abstract:(thyroid AND (iodine OR iodide)))

Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Thyroid Cancer population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies
	Quality of Life 1946 – 16 December 2021	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
Embase (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies
	Quality of Life 1974 – 16 December 2021	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language

Database	Dates searched	Search filters and limits applied
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 16 December 2021	English language

Medline (Ovid) search terms

1.	exp Thyroid Neoplasms/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to english language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, medical/
30.	Economics, nursing/

31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/52-70
63.	24 and 62

Embase (Ovid) search terms

1.	exp Thyroid Cancer/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.

10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to english language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36
38.	quality-adjusted life years/
39.	"quality of life index"/
40.	short form 12/ or short form 20/ or short form 36/ or short form 8/
41.	sickness impact profile/
42.	(quality adj2 (wellbeing or well being)).ti,ab.
43.	sickness impact profile.ti,ab.
44.	disability adjusted life.ti,ab.
45.	(qal* or qtime* or qwb* or daly*).ti,ab.
46.	(euroqol* or eq5d* or eq 5*).ti,ab.
47.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
48.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
49.	(hui or hui1 or hui2 or hui3).ti,ab.
50.	(health* year* equivalent* or hye or hyes).ti,ab.
51.	discrete choice*.ti,ab.
52.	rosser.ti,ab.
53.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
54.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
55.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
56.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.

57.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
58.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
59.	or/37-58
60.	22 and 59

NHS EED and HTA (CRD) search terms

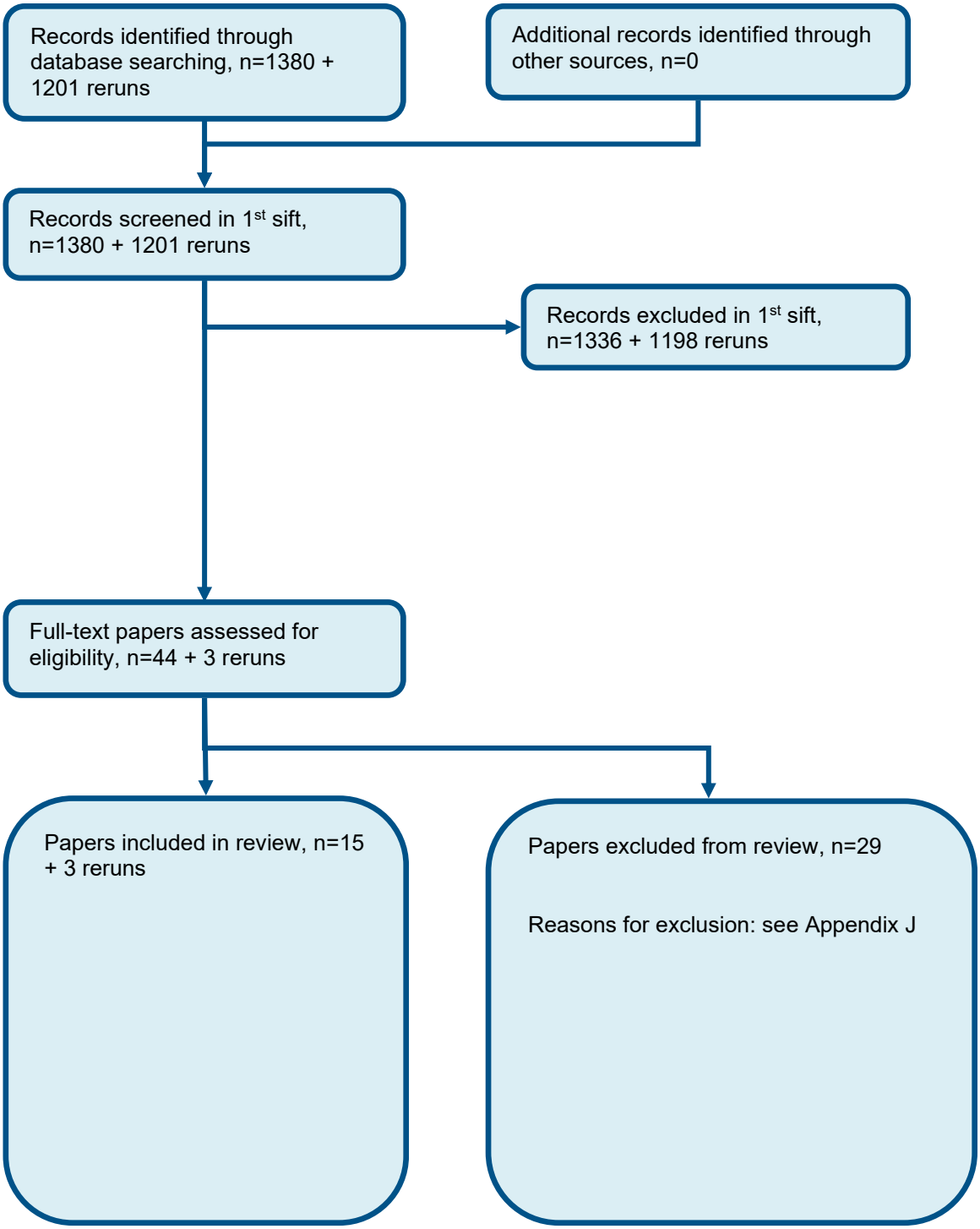
#1.	MeSH DESCRIPTOR Thyroid Neoplasms EXPLODE ALL TREES
#2.	((thyroid NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)))
#3.	(((papillar* or follicul* or medullary or anaplastic) NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)))
#4.	#1 OR #2 OR #3

INHATA search terms

1.	(Thyroid Neoplasms)[mh] OR (thyroid neoplasms) AND (thyroid cancers)

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of RAI activity



Appendix D – Effectiveness evidence

Study	Bal 1996[4]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=149)
Countries and setting	Conducted in India; Setting: A Nuclear Medicine Clinic of the All India Institute of Medical Science
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 1.5-6 years (mean 3.8 years)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Participants were assessed with scintigraphy
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with scintigraphic evidence of residual functioning tissue in thyroid region and no evidence of extrathyroidal or distant metastases at the time of presentation
Exclusion criteria	Participants who had demonstrable nodal and pulmonary metastases were excluded
Recruitment/selection of patients	Newly registered thyroid cancer patients from a single institute
Age, gender and ethnicity	Age - Mean (range): 39 (24-68). Gender (M:F): 45/104. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=27) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). A single dose ranging from 24 to 35 mCi. Duration N/A. Concurrent medication/care: Between 48 hours and 1 week post therapy a scan was done to rule out any occult metastasis which was missed on the first 5 mCi scan. Patients were then out on suppressive doses of L-thyroxine of 0.2 to 0.3 mg daily for 6 months to 1 year, when a 5 mCi whole body scan and uptake at 48 hours were done after stopping L-thyroxine for 4-6 weeks. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: >5 years (Follow up period ranged from 1.5-6 years with a mean of 3.8 years). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Participants were advised not to take food or drugs known to contain high amounts of iodine). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear

	(n=30) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Participant were given 120 to 200mCI. Duration N/A. Concurrent medication/care: Between 48 hours and 1 week post therapy a scan was done to rule out any occult metastasis which was missed on the first 5 mCi scan. Patients were then out on suppressive doses of L-thyroxine of 0.2 to 0.3 mg daily for 6 months to 1 year, when a 5 mCi whole body scan and uptake at 48 hours were done after stopping L-thyroxine for 4-6 weeks. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: >5 years (Follow up period ranged from 1.5-6 years with a mean of 3.8 years). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Participants were advised not to take food or drugs known to contain high amounts of iodine). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ) versus RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) Protocol outcome 1: successful ablation at Define - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful ablation at Mean 3.8 years; Group 1: 17/27, Group 2: 23/30 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in the proportion of men/women in each group (35% men vs 58%); Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Define; cancer recurrence at Define; Incidence of distant metastases at Define; local cancer progression at Define; mortality at Define; second primary malignancy at Define; Do not use at Define

Study	Bal 2012[3]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=360)
Countries and setting	Conducted in India; Setting: Tertiary care teaching hospital
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with disease confirmed to be limited only to the thyroid bed by clinical, radiological, preoperative and postsurgical I-131 scintigraphic examination and having no evidence of extra thyroidal or distant metastases at the time of I-131 treatment and patients with tumour size of only T1-T3
Exclusion criteria	Patients who had undergone less than total/near-total thyroidectomy and those with T4 tumour size, aggressive histology such as tall cell and columnar cell papillary carcinoma, Hurthle cell carcinoma and poorly differentiated carcinoma; patients in whom extra thyroidal disease in the form of either nodal or distant metastases was detected before the first-dose outcome at any time; pregnant and breast-feeding patients; and patients who did not give consent
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 37.02 (13.01). Gender (M:F): 94/266. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients were treated with 3.7 GBq iodine-131. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (No special low-iodine diet was prescribed but patients were advised not to take known iodine rich food and drugs). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone

	replacement: prior withdrawal of thyroid hormone replacement (Patients were kept off L-thyroxin for 4-6 weeks if it was started after surgery). (n=343) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients received either 0.925 GBq (n=172) or 1.85 GBq (n=171). Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients were kept off L-thyroxin for 4-6 weeks if it was started after surgery).
Funding	Academic or government funding (Senior Research Fellowship from India Council of Medical Research, Government of India)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation at Define
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful ablation at 6 months; Group 1: 69/78, Group 2: 278/334
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Loss to follow up; Group 2 Number missing: 9, Reason: Loss to follow up

Protocol outcomes not reported by the study	Quality of life at Define; cancer recurrence at Define; Incidence of distant metastases at Define; local cancer progression at Define; mortality at Define; second primary malignancy at Define; Do not use at Define

Study	Caglar 2012[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=108)
Countries and setting	Conducted in Turkey; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 5-7 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Classification and staging were performed according to the TNM system
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with nonmetastatic, unifocal T1 or T2 and multifocal T1, well-differentiated thyroid cancer (DTC) limited to the thyroid
Exclusion criteria	Patients who had undergone subtotal thyroidectomy, those with lymph node or distant metastases, an unfavourable histology (tall-cell, columnar-cell, diffuse sclerosing for papillary carcinoma, and widely invasive or poorly differentiated for follicular carcinoma) and T3 and T4 tumours were excluded
Recruitment/selection of patients	Not reported
Age, gender and ethnicity Further population details	Age - Mean (range): Low activity group 47 (20-75); high activity group 44 (22-74). Gender (M:F): 16/92. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=53) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients were given a therapeutic ablation does of 800 MBq (0.8 GBq). Duration N/A. Concurrent medication/care: Endogenous thyroid-stimulating hormone stimulation (TSH >30 mIU/ml) was achieved before radioiodine administration. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (Mean time between ablation and follow up was 6.5 months (6-12 months)). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (A strict low-iodine diet was recommended for four weeks). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone

	replacement: Not stated / Unclear (n=55) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients were given a therapeutic ablation does of 3700 MBq (3.7 GBq). Duration N/A. Concurrent medication/care: Endogenous thyroid-stimulating hormone stimulation (TSH >30 mIU/ml) was achieved before radioiodine administration. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 1-5 years (The mean time between ablation and follow up was 12 months (range 6-75 months)). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (A strict low-iodine diet was recommended for four weeks). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ) versus RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ)

Protocol outcome 1: successful ablation at Define
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Thyroglobulin + ultrasonography (strict criteria) at Mean 12 months (6-7); Group 1: 28/47, Group 2: 32/48; Comments: Strict criteria = thyroglobulin <0.2
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in tumour size (0.83 vs 1.14); difference in presence of multi focal cancer (28% vs 58%); Group 1 Number missing: 6, Reason: Presence of anti-Tg antibodies ; Group 2 Number missing: 7, Reason: Presence of anti-Tg antibodies
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Thyroglobulin + ultrasonography (lax criteria) at Mean 12 months (6-7); Group 1: 42/47, Group 2: 41/48; Comments: Lax criteria = thyroglobulin = <2
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in tumour size (0.83 vs 1.14); difference in presence of multi focal cancer (28% vs 58%); Group 1 Number missing: 6, Reason: Presence of anti-Tg antibodies ; Group 2 Number missing: 7, Reason: Presence of anti-Tg antibodies
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Ultrasonography (presence of remnant) at Mean 12 months (6-7); Group 1: 3/47, Group 2: 4/44
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: Difference in tumour size (0.83 vs 1.14); difference in presence of multi focal cancer (28% vs 58%); Group 1 Number missing: 6, Reason: Presence of anti-Tg antibodies ; Group 2 Number missing: 7, Reason: Presence of anti-Tg antibodies

Protocol outcomes not reported by the study	Quality of life at Define; cancer recurrence at Define; Incidence of distant metastases at Define; local cancer progression at Define; mortality at Define; second primary malignancy at Define; Do not use at Define

Study	**Dong 2021[14, 15]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=516)
Countries and setting	Conducted in China; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6-8 months[15], and 4.5 years[14]
Method of assessment of guideline condition	Adequate method of assessment/diagnosis:
Stratum	Disease severity - low- / intermediate risk DTC; TNM stage confirmed on pathological examination of the surgical specimen; T1 (≤2cm) N0-1 and T2 (>2 cm but ≤4cm) N0;
Subgroup analysis within study	Not applicable
Inclusion criteria	Age at diagnosis 18 years or older; patients undergoing total or near total thyroidectomy and those with lymph node involvement undergoing lymph node dissection; primary RAI therapy after surgery; low- / intermediate risk DTC; TNM stage confirmed on pathological examination of the surgical specimen; T1 (≤2cm) N0-1 and T2 (>2 cm but ≤4cm) N0; absence of distant metastasis
Exclusion criteria	Presence of aggressive histologic subtypes, including tall cell, insular, poorly differentiated, and diffuse sclerosing thyroid cancer; anaplastic or medullary thyroid cancer; history of other cancers; pregnancy; presence of unstable diseases or other conditions that might prevent participation.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): Low activity group 43 (21-70); high activity group 41 (19-75). Gender (M:F): 140:352. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=255) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients were given a therapeutic ablation does of 1.1 GBq. Concurrent medication/care: Thyroid hormone therapy for mean (sd) 100 (61) days, followed by thyroid hormone withdrawal for 21 days. Iodine uptake also

	stimulated by prior restriction of dietary iodine. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 6-8 months. 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (21 days). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Thyroid hormone withdrawal for 21 days prior to RAI. (n=261) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients were given a therapeutic ablation does of 3.7 GBq. Concurrent medication/care: Thyroid hormone therapy for mean (sd) 95 (57) days, followed by thyroid hormone withdrawal for 21 days. Iodine uptake also stimulated by prior restriction of dietary iodine. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 6-8 months. 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (21 days). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Thyroid hormone withdrawal for 21 days prior to RAI.
Funding	National Natural Science Foundation of China; Post-doctoral Research project grant award

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ) versus RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ)

Protocol outcome 1: successful ablation at 6-8 months
- Actual outcome for successful ablation – no detectable TbAb and with stimulated Tg <1.0 ng/ml and negative cervical ultrasonography in those with THW; Group 1: 206/236, Group 2: 206/238; Comments:
Risk of bias: All domain – Very high, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: TSH level on day of ablation Group 1 median 89, group 2 median 91; Group 1 number missing 19, group 2 number missing 43; Reason: unclear

Protocol outcome 2: successful ablation at 4.5 years
- Actual outcome for successful ablation – incomplete structural/biochemical response at 4.5 years; Group 1: 2/251, Group 2: 5/255; Comments:
Risk of bias: All domain – High, Selection - High, Blinding - Low, Incomplete outcome data - low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: TSH level on day of ablation Group 1 median 89, group 2 median 91; Group 1 number missing 4, group 2 number missing 6; Reason: unclear

Protocol outcomes not reported by the study	Quality of life at Define; cancer recurrence at Define; Incidence of distant metastases at Define; local cancer progression at Define; mortality at Define; second primary malignancy at Define; Do not use at Define

Study	Fallahi 2012[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=341)
Countries and setting	Conducted in Iran; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who fulfilled the inclusion criteria after TT or NTT.
Exclusion criteria	Cases with a history of radioiodine ablation therapy, a postsurgical palpable mass in the thyroid bed, inoperable cervical lymph nodes in the neck, histopathological evidence of high risk and invasive tumours such as Hurthle cell or tall cell subtypes, capsular or vascular invasion of lymph node involvement, scintigraphic evidence of functioning metastasis, and pregnant or breastfeeding women were not included. Patients in whom a distant functioning metastasis was found on post radioiodine therapy WBS or those who refused to comply with the regular care after ablation
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Lower activity: 38.3 (11.07); higher activity 40.52 (13.02). Gender (M:F): 55/186. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=170) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients received 3700 MBq I-131 for post-thyroidectomy ablation therapy. The interval between thyroid surgery and ablation therapy was 4-6 weeks. . Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 1-5 years (12 months after radioiodine ablation). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone

	replacement: prior withdrawal of thyroid hormone replacement (Participants were instructed to discontinue liothyonine consumption for two weeks). (n=171) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients received 1110 MBq I-131 for post-thyroidectomy ablation therapy. The interval between thyroid surgery and ablation therapy was 4-6 weeks. . Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 1-5 years 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement
Funding	Academic or government funding (The Tehran University of Medical Sciences)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation at Define
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Success rate after first does at 12 months; Group 1: 117/170, Group 2: 71/171
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcome 2: cancer recurrence at Define
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Recurrence rate at 12 months; Group 1: 4/170, Group 2: 2/171
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Quality of life at Define; Incidence of distant metastases at Define; local cancer progression at Define; mortality at Define; second primary malignancy at Define; Do not use at Define

Study	Giovanella 2013[19]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=136)
Countries and setting	Conducted in Switzerland; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Disease severity - low risk
Subgroup analysis within study	Not applicable
Inclusion criteria	Age at least 18 years; presence of T1b-T2 unifocal DTC, histologically proven after thyroid lobectomy; and normal sized residual lobe with no nodules seen on ultrasound examination
Exclusion criteria	Patients with aggressive tumour histotypes (e.g. tall cell, diffuse sclerosing and poorly differentiated papillary thyroid carcinoma, extensively invasive follicular thyroid carcinoma and Hurtle cell carcinomas), multifocal cancers and patients with signs of nodes and/or distant metastases, as well as pregnant or breast-feeding women
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Lower activity: 42 (19); higher activity 45 (22). Gender (M:F): 28/108. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients received 3.7 GBq of I-131. Radioiodine therapy was administered 28 days after lobectomy (range 22-37 days). . Duration N/A. Concurrent medication/care: Adjuvant medication with a mild laxative was introduced in patients with constipation to decrease radiation exposure to the gastrointestinal tract. If needed, treatment with non steroidal anti-inflammatory drugs or prednisone was introduced. . Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 1-5 years (12 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Patients were placed on a low iodine diet for 2 weeks

	before ablation). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients did not receive thyroid hormone substitution therapy between surgery and remnant ablation). (n=67) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients received 3.7 GBq of I-131. Radioiodine therapy was administered 28 days after lobectomy (range 22-37 days). . Duration N/A. Concurrent medication/care: Adjuvant medication with a mild laxative was introduced in patients with constipation to decrease radiation exposure to the gastrointestinal tract. If needed, treatment with non steroidal anti-inflammatory drugs or prednisone was introduced. . Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 1-5 years (12 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Patients were placed on a low iodine diet for 2 weeks before ablation). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients did not receive thyroid hormone substitution therapy between surgery and remnant ablation).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Ablation success at 12 months; Group 1: 48/69, Group 2: 36/67
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life; cancer recurrence; Incidence of distant metastases; local cancer progression; mortality at Define; second primary malignancy

Study	Kukulska 2010[23]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=210)
Countries and setting	Conducted in Poland; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): Median follow up was 10 years for those in the lower and intermediate group and 6 years for the higher activity group
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with differentiated thyroid cancer with no clinical signs of persistent disease were included in this follow up. Only patients with low risk DTC were randomised to lower or intermediate activity, and only patients with pT1b-T4 N0-1 were randomised to intermediate or higher activity.
Exclusion criteria	For the lower/intermediate group, only patients without lymph node metastases staged pT1b-T3 or Tx and N0 or Nx were included. For the intermediate/higher activity group, only those who were disease free following total thyroidectomy and central/lateral lymph node dissection were included
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Not reported. Gender (M:F): 24/285. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=86) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients received 1.1 GBq of I-131. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 1-5 years (12 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: Not stated / Unclear 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement

	(n=128) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at intermediate activity (2-3 GBq).. Patients received 60mCi (2.2 GBq) I-131 iodine. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 1-5 years (12 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: Not stated / Unclear 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear (n=95) Intervention 3: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients received 100 mCi (3.7 GBq) of I-131. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: 1-5 years (12 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: Not stated / Unclear 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear
Funding	Academic or government funding (The Ministry of Science and Higher Education of Poland - the grant of the Polish Thyroid Association)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ) versus RADIOACTIVE IODINE ABLATION AT INTERMEDIATE ACTIVITY (2-3 GBQ).

Protocol outcome 1: successful ablation
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Complete thyroid remnant ablation at Median 10 years; Group 1: 67/86, Group 2: 111/128
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Incidence of distant metastases
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Distant recurrence at Median 10 years for intermediate activity; Group 1: 0/86, Group 2: 0/128
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: cancer recurrence
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Relapse at Median 10 years; Group 1: 2/86, Group 2: 4/128
Risk of bias: All domain - --, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ) versus RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ)

Protocol outcome 1: successful ablation
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Complete thyroid remnant ablation at Median 10 years for lower activity and 6 years for higher activity; Group 1: 67/86, Group 2: 85/95
Risk of bias: All domain - --, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Incidence of distant metastases
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Distant recurrence at Median 10 years for intermediate activity and 6 years for higher activity; Group 1: 0/86, Group 2: 0/95
Risk of bias: All domain - --, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: cancer recurrence
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Relapse at Median 10 years for lower activity and 6 years for higher activity; Group 1: 2/86, Group 2: 3/95
Risk of bias: All domain - --, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT INTERMEDIATE ACTIVITY (2-3 GBQ). versus RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ)

Protocol outcome 1: successful ablation
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Complete thyroid remnant ablation at Median 10 years for intermediate activity and 6 years for higher activity; Group 1: 111/128, Group 2: 85/95
Risk of bias: All domain - --, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Incidence of distant metastases
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Distant recurrence at Median 10 years for intermediate activity and 6 years for higher activity; Group 1: 0/128, Group 2: 0/95
Risk of bias: All domain - --, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: cancer recurrence - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Relapse at Median 10 years for intermediate activity and 6 years for higher activity; Group 1: 4/128, Group 2: 3/95 Risk of bias: All domain - --, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; local cancer progression; mortality; second primary malignancy

Study	Ma 2017[26]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=327)
Countries and setting	Conducted in China; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6-9 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: WHO criteria
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	16-18 years of age; histological confirmation of papillary thyroid cancer (PTC) and follicular thyroid cancer according to the World Health Organisation, tumour stage T1-T3 with or without lymph node involvement but no distant metastasis (i.e. N0, NX, N1 or M0 in the tumour-node-metastasis staging system), post total thyroidectomy (TT) or near-total thyroidectomy (NTT), with or without cervical lymph node dissection
Exclusion criteria	The presence of aggressive malignant variants, including follicular variant PTC, tall-cell, columnar-cell, poorly differentiated, and diffuse sclerosing thyroid cancer, pregnant or breastfeeding women ; severe co-existing conditions; serious abnormality in hepatic function or renal function; and white blood cell count <3.0 x 10^9/L. Patients in whom a distant functioning metastasis was found on post-radioiodine therapy whole body scanning or those who refused to comply with the regular care after ablation were also excluded
Recruitment/selection of patients	Patients presenting for radioiodine ablation
Age, gender and ethnicity	Age - Mean (SD): Lower activity: 44 (13); higher activity: 45 (13). Gender (M:F): 128/199. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=123) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients received high dose radioiodine (3.7GBq). The interval between thyroid surgery and ablation therapy was 1-6 months. . Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year

	(6-9 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Patients were instructed to follow a low-iodine diet for four weeks before ablation). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients were instructed to discontinue levothyroxine for four weeks before ablation). (n=155) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients received low dose radioiodine (1.85GBq). The interval between thyroid surgery and ablation therapy was 1-6 months. . Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6-9 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Patients were instructed to follow a low-iodine diet for four weeks before ablation). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients were instructed to discontinue levothyroxine for four weeks before ablation).
Funding	Academic or government funding (The National Natural Science Fund, Shanghai Puijang Program and Shanghai Health Bureau Fund)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful ablation at 6-9 months; Group 1: 106/123, Group 2: 128/155
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 18, Reason: 6 were revised as T4/FVP, 6 had metastasis, 16 were lost to follow up; Group 2 Number missing: 21, Reason: 2 were revised as T4/FVP, 3 had metastasis, 16 were lost to follow up

Protocol outcome 2: cancer recurrence
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Recurrence at 2-3 years; Group 1: 0/123, Group 2: 0/155
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 18, Reason: 6 were revised as T4/FVP, 6 had metastasis, 16 were lost to follow up; Group 2 Number missing: 21, Reason: 2 were revised as T4/FVP, 3 had metastasis, 16 were lost to follow up

Protocol outcomes not reported by the study	Quality of life; Incidence of distant metastases; local cancer progression; mortality; second primary malignancy

Study	Maenpaa 2008[28] (Ahtiainen, 2020[2])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=160)
Countries and setting	Conducted in Finland; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 4-8 months and 13 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Histologically confirmed
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with histologically confirmed thyroid carcinoma. Patients were required to have undergone either total or near total thyroidectomy, have either papillary or follicular thyroid carcinoma diagnosed according to the World Health Organization criteria, and were expected to tolerate radioiodine administration
Exclusion criteria	Patients who presented with macroscopic inoperable locoregional disease or with distant metastases and pregnant women
Recruitment/selection of patients	Consecutive participants
Age, gender and ethnicity	Age - Median (range): Lower activity: 49 (23-79); higher activity: 45 (18-90). Gender (M:F): 32/128. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients received 3.7 GBq of I-131 radioiodine 5-6 weeks after thyroidectomy. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (4-8 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (A low iodine content diet was recommended prior to ablation). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Abstaining from levothyroxine administration for a minimum of 4 weeks prior to radioiodine administration).

	(n=81) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients received 1.1 GBq of I-131 radioiodine 5-6 weeks after thyroidectomy. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (4-8 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (A low iodine content diet was recommended prior to ablation). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Abstaining from levothyroxine administration for a minimum of 4 weeks prior to radioiodine administration).
Funding	Academic or government funding (The Helsinki University Central Hospital Research Funds)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation at 4-8 months
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful ablation at 4-8 months; Group 1: 43/77, Group 2: 42/81
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: High radioiodine uptake in the thyroid bed after administration of 7.4 MbQ test dose; Group 2 Number missing: 0

Protocol outcome 2: mortality at 51 months
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: All-cause mortality at Median 51 months; Group 1: 1/79, Group 2: 2/81
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 3: Incidence of distant metastases at 51 months
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Distant metastases at Median 51 months; Group 1: 3/79, Group 2: 0/81
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 4: mortality at 13 years - Actual outcome for Disease severity - mixed (no group >75%) or unclear: All-cause mortality at 13 years; Group 1: 5/79, Group 2: 7/81 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 5: Incidence of distant metastases at 13 years - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Distant metastases at 13 years; Group 1: 4/79, Group 2: 1/81 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; cancer recurrence; local cancer progression; second primary malignancy

Study (subsidiary papers)	Mallick 2012[29] (Dehbi 2019[12])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=438)
Countries and setting	Conducted in United Kingdom; Setting: 29 Centres across the UK
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 7 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Histological confirmation of differentiated thyroid cancer
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Median (range): Thyrotropin alfa subgroup: low-dose 44 (20-83); high dose 44 (21-76). Thyroid hormone withdrawal: low dose 45 (17-73); high dose 43 (18-77). Gender (M:F): NR. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=220) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Radioiodine ablation was recommended 1 to 6 months after surgery. Radioactive iodine-131 was administered at a dose of 1.1 GBq. Duration N/A. Concurrent medication/care: 110 patients received thyrotropin alfa, which was administered on each of the 2 days before ablation by intramuscular injection (0.9 mg). 110 patients received thyroid hormone withdrawal. Among these patients thyroxine (average dose, 200 µg per day) was discontinued 4 weeks before ablation in 11 patients, and triiodothyronine (average dose, 60 µg per day) was discontinued for 2 weeks in 204 patients; data were missing for 4 patients. Thyrotropin levels were similar in the thyroxine and triiodothyronine groups (median, 80.5 mU and 61.5 mU per liter, respectively; P = 0.56). Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: >5 years (7 years). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior

	dietary restriction of iodine (Patients were instructed to start a low-iodine diet 3 weeks before the diagnostic scan). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Systematic review: mixed (Half of patients had thyrotrophin alfa and half had thyroid hormone withdrawal). (n=218) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Radioiodine ablation was recommended 1 to 6 months after surgery. Radioactive iodine-131 was administered at a dose of 3.7 GBq. Duration N/A. Concurrent medication/care: 109 patients received thyrotropin alfa, which was administered on each of the 2 days before ablation by intramuscular injection (0.9 mg). 109 patients received thyroid hormone withdrawal. Among these patients thyroxine (average dose, 200 µg per day) was discontinued 4 weeks before ablation in 11 patients, and triiodothyronine (average dose, 60 µg per day) was discontinued for 2 weeks in 204 patients; data were missing for 4 patients. Thyrotropin levels were similar in the thyroxine and triiodothyronine groups (median, 80.5 mU and 61.5 mU per liter, respectively; P = 0.56). Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: >5 years (7 years). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (a low-iodine diet 3 weeks before the diagnostic scan). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Systematic review: mixed (Half of patients had thyrotrophin alfa and half had thyroid hormone withdrawal).
Funding	Academic or government funding (Cancer Research UK and University College London and the University College London Hospital Comprehensive Biomedical Research Centre)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ) versus RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ)

Protocol outcome 1: Quality of life
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: SF36 - physical domains (change score) at 3 months; MD; 7.0 (95%CI -13.3 to 27.2) (p value: 0.37) SF36 0-100 Top=High is good outcome, Comments: Change score. Mean change in low frequency group 20.0; mean change in high frequency group 13.0;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

- Actual outcome for Disease severity - mixed (no group >75%) or unclear: SF36 - psychological domains (change score) at 3 months; MD; -4.4 (95%CI -25 to 16.2) (p value: 0.58) 0-100 Top=High is good outcome, Comments: Change score. Mean change in low frequency group 19.4; mean change in high frequency group 23.8; Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: successful ablation - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Ablation success based on both diagnostic scan and thyro-globulin at 6-9 months; Group 1: 182/214, Group 2: 184/207 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: Did not undergo assessment at 6-9 months; Group 2 Number missing: 11, Reason: Did not undergo assessment at 6-9 months Protocol outcome 3: cancer recurrence - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Recurrence (detected by ultrasonography and/or fine-needle aspiration and/or CT) at Median 13 months; Group 1: 3/214, Group 2: 3/207 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 6, Reason: Did not undergo assessment at 6-9 months; Group 2 Number missing: 11, Reason: Did not undergo assessment at 6-9 months - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Long term recurrence at Median 78.4 months (range 0.3-127.3); Group 1: 11/217, Group 2: 10/217; Comments: One recurrence in the low activity group was thought to be a possible secondary malignancy Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: No follow up data post ablation; Group 2 Number missing: 1, Reason: No follow up data post ablation Protocol outcome 4: second primary malignancy - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Second malignancy at 6 months - 7 years; Group 1: 3/217, Group 2: 4/217 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness, Comments: Does not state that the malignancy was primary; Group 1 Number missing: 3, Reason: No follow up data post ablation; Group 2 Number missing: 1, Reason: No follow up data post ablation	
Protocol outcomes not reported by the study	Incidence of distant metastases; local cancer progression; mortality

Study	Pilli 2007[34]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=72)
Countries and setting	Conducted in Italy; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6-8 months
Method of assessment of guideline condition	--
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Newly diagnosed DTC patients, more than 18 yr old, recently treated by near total thyroidectomy
Exclusion criteria	Evidence of distant metastases and/or significant extrathyroidal invasion [T4 of the latest Tumor-Node-Metastasis (TNM) classification]
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Lower activity: 47.9 (13.9); lower activity: 50.5 (15.6). Gender (M:F): 12/60. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=36) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Participants received 3700 MBq I-131 radioiodine. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6-8 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: Not stated / Unclear 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear (n=36) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Participants received 1100 MBq I-131 radioiodine. Duration N/A.

	Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6-8 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: Not stated / Unclear 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear
Funding	Academic or government funding (Ministero dell'Instruzione Universita e Ricerca Italy, and Associazione Italiana per la Ricerca sul Cancro)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation at Define
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful ablation at 6-8 months; Group 1: 32/36, Group 2: 32/36
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life; cancer recurrence; Incidence of distant metastases; local cancer progression; mortality; second primary malignancy

Study	Qu 2017[36]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=140)
Countries and setting	Conducted in China; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6-24 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	1. Age at diagnosis C18 years; 2. Patients undergoing total thyroidectomy and those with lymph node involvement undergoing lymph node dissection; 3. Low-/intermediate-risk DTC confirmed by post-operative pathological examination, including PTC and FTC, T1 (tumour diameter B2 cm) N0–1 and T2 (tumour diameter[2 cm but B4 cm) N0 (defined according to the 7th edition of the American Joint Committee on Cancer Staging Manual/Union for International Cancer Control TNM Classification); 4. Absence of distant metastases; and 5. Primary 131I therapy after surgery.
Exclusion criteria	1. Invasive pathological subtype, including tall cell, insular, poorly differentiated, and diffuse sclerosing variants of anaplastic or medullary thyroid carcinoma; 2. a history of other malignancies; and 3. the presence of unstable diseases or other conditions of clinical significance that might prevent patient enrolment in and completion of the study
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): 41.86 (10.46). Gender (M:F): 33/99. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=69) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients received high dose I-131 radioiodine ablation (3.7

	GBq). Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Low iodine diet for 3 weeks until TSH >30 mU/L). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients were withdrawn from or never received levo-thyroxine). (n=68) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients received high dose I-131 radioiodine ablation (1.1 GBq). Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients were withdrawn from or never received levo-thyroxine).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ) Protocol outcome 1: successful ablation - Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful ablation at 6 months; Group 1: 56/66, Group 2: 53/66 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 25, Reason: Excluded participants not withdrawn from L-T4 (i.e. those who had never had it) (n=22), lost to follow up (n=3); Group 2 Number missing: 13, Reason: Excluded participants not withdrawn from L-T4 (i.e. those who had never had it) (n=11), lost to follow up (n=2)	
Protocol outcomes not reported by the study	Quality of life; cancer recurrence; Incidence of distant metastases ; local cancer progression; mortality; second primary malignancy

Study	Shinto 2013[41]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=108)
Countries and setting	Conducted in India; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 18 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients having disease confirmed to be limited to the thyroid bed only by clinical, radiological, preoperative and postsurgical I-131 scintigraphic examination and having no evidence of extrathyroid or distant metastases at the time of presentation
Exclusion criteria	Patients with inadequate surgery, qualitatively defined as significant bilateral thyroid uptake on the first I-131 scan or >5cm initial tumour size on histology. Patients with extrathyroid disease in the form of either nodal or distant metastases or with adverse histopathology such as Hurthle cell carcinoma, poorly differentiated carcinoma, insular carcinoma, medullary thyroid carcinoma and aggressive variant of papillary carcinoma. If the first postoperative thyroid scan of patients who had had a TT showed substantial uptake in the thyroid bed, they were re-classified as having a subtotal thyroidectomy and excluded
Recruitment/selection of patients	Not reported
Age, gender and ethnicity Further population details	Age - Mean (SD): 39 (12.7). Gender (M:F): 2.6 female to male ratio. Ethnicity: Not reported
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at intermediate activity (2-3 GBq).. The interval between surgery and referral for remnant ablation ranged from 2 days to 2 months (median 1 month). Patients received 2.775 GBq.. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year

	(6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (No special low-iodine diet was prescribed, but they were advised not to take known rich iodine containing food or drugs or undergo contrast CT scans). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients were kept off L-thyroxin for 4-6 weeks). (n=80) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). The interval between surgery and referral for remnant ablation ranged from 2 days to 2 months (median 1 month). Patients received 1.11 GBq (n=46) or 1.85 GBq (n=34).. Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (No special low-iodine diet was prescribed, but they were advised not to take known rich iodine containing food or drugs or undergo contrast CT scans). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Patients were kept off L-thyroxin for 4-6 weeks).
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT INTERMEDIATE ACTIVITY (2-3 GBQ). versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful ablation at 6 months; Group 1: 22/25, Group 2: 70/80
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life; cancer recurrence; Incidence of distant metastases; local cancer progression; mortality; second primary malignancy

Study	Zaman 2006[48]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Pakistan; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Unclear method of assessment/diagnosis
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with differentiated thyroid carcinoma who had undergone total or near-total thyroidectomy without any evidence of local or distant metastasis and serum thyroid simulating hormone above 30iu/mL
Exclusion criteria	Pregnant or lactating females with inadequate surgery
Recruitment/selection of patients	Patients referred to the thyroid OPDs of Karachi Institute of Radiotherapy and Nuclear Medicine and Atomic Energy Medical Centre
Age, gender and ethnicity	Age - Mean (SD): 38.3 (11.7). Gender (M:F): 9/31. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients were randomised to high activity I-131 radioiodine ablation therapy (3.7 GBq). Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: Not stated / Unclear 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear (n=20) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients were randomised to low activity I-131 radioiodine ablation therapy (1.85 GBq). Duration N/A. Concurrent medication/care: Not reported. Indirectness: No indirectness

	Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: Not stated / Unclear 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: Not stated / Unclear
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful IAT at 6 months; Group 1: 12/20, Group 2: 8/20
Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Quality of life; cancer recurrence; Incidence of distant metastases ; local cancer progression; mortality; second primary malignancy; Do not use

Study	Zhang 2015[49]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=106)
Countries and setting	Conducted in China; Setting: Not reported
Line of therapy	2nd line
Duration of study	Follow up (post intervention): 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Histologically confirmed
Stratum	Disease severity - mixed (no group >75%) or unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Age 18 years or older; had undergone total thyroidectomy; had histologically confirmed DTC; were of pT4 stage (with extrathyroidal extension according to both operation record and pathological report) and any N stage, with no evidence of DM; had ps-Tg 5ng/ml or less and thyroglobulin antibodies level 46 IU/ml or less; and had no iodine contamination
Exclusion criteria	Pregnancy and other tumour or serious conditions
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Other: Low activity: <45 years n=30, ≥45 n=21; high activity <45 years n=34, ≥45 n=17. Gender (M:F): Define. Ethnicity: Not reported
Further population details	
Indirectness of population	No indirectness
Interventions	(n=53) Intervention 1: Radioactive iodine ablation - radioactive iodine ablation at higher activity (>3 GBq). Patients received high dose RAI (3.7GBq). Duration N/A. Concurrent medication/care: Patients were advised to take levothyroxine (2-2.2ug/kg body weight) daily on an empty stomach from the third day after ablation to suppress TSH at a level lower than 0.1uIU/ml. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year (6 months). 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Patients were instructed to follow a low-iodine diet from the beginning of thyroid hormone withdrawal to 3 weeks after ablation). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Before

	ablation TSH stimulation (TSH≥30mU/l) was achieved by thyroid hormone withdrawal). (n=53) Intervention 2: Radioactive iodine ablation - radioactive iodine ablation at lower activity (<2 GBq). Patients received low activity RAI (1.1 GBq). Duration N/A. Concurrent medication/care: Patients were advised to take levothyroxine (2-2.2ug/kg body weight) daily on an empty stomach from the third day after ablation to suppress TSH at a level lower than 0.1uIU/ml. Indirectness: No indirectness Further details: 1. ablation vs treatment: ablation 2. longest follow up in study: <1 year 3. Prior dietary restriction of iodine vs no prior iodine restriction.: prior dietary restriction of iodine (Patients were instructed to follow a low-iodine diet from the beginning of thyroid hormone withdrawal to 3 weeks after ablation). 4. Use of methods to increase iodine uptake: prior thyrotropin alfa vs prior withdrawal of thyroid hormone replacement: prior withdrawal of thyroid hormone replacement (Before ablation TSH stimulation (TSH≥30mU/l) was achieved by thyroid hormone withdrawal).
Funding	Academic or government funding (Ministry of Health Industry Special Scientific Research Projects of China)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: RADIOACTIVE IODINE ABLATION AT HIGHER ACTIVITY (>3 GBQ) versus RADIOACTIVE IODINE ABLATION AT LOWER ACTIVITY (<2 GBQ)

Protocol outcome 1: successful ablation at 6 months
- Actual outcome for Disease severity - mixed (no group >75%) or unclear: Successful ablation at 6 months; Group 1: 44/51, Group 2: 43/51
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 2, Reason: Incomplete data, reasons not specified; Group 2 Number missing: 2, Reason: Incomplete data, reasons not specified

Protocol outcomes not reported by the study	Quality of life; cancer recurrence; Incidence of distant metastases ; local cancer progression; mortality; second primary malignancy;

Appendix E – Forest plots

E.1 Low risk strata

E.1.1 Higher versus lower activity RAI

Figure 2: Successful ablation (at 6 months – 7 years)

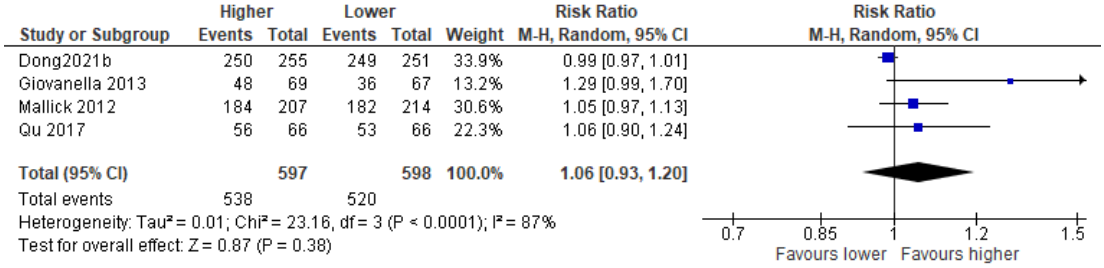


Figure 3: Recurrence (at 78.4 months)

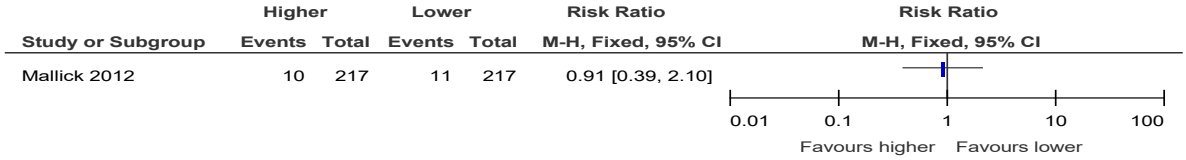


Figure 4: Quality of life – physical domains (at 3 months, SF36, 0-100, change, score, higher score is better outcome)

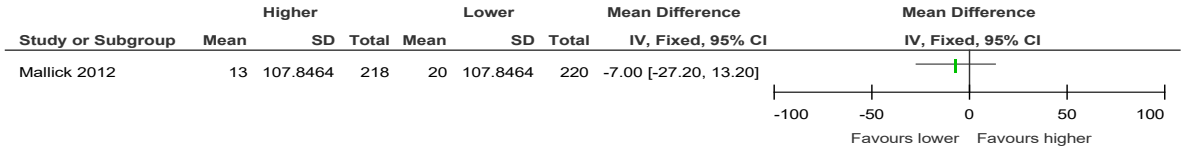
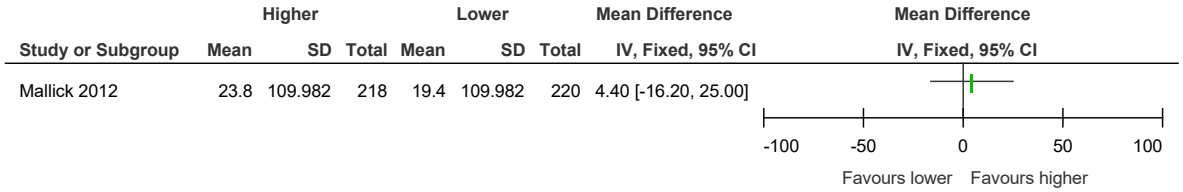


Figure 5: Quality of life – psychological domains (at 3 months, SF36, 0-100, change, score, higher score is better outcome)



E.1.2 Higher versus intermediate activity RAI

Figure 6: Successful ablation (at 6-12 months)

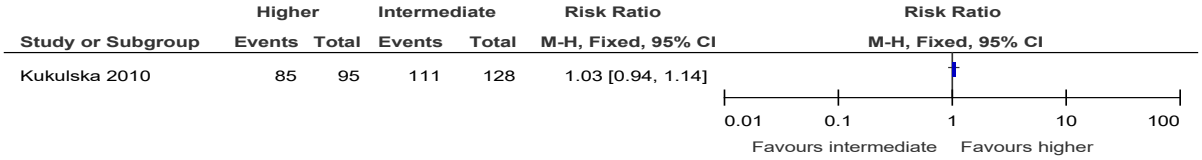


Figure 7: Recurrence (at median 10 years)

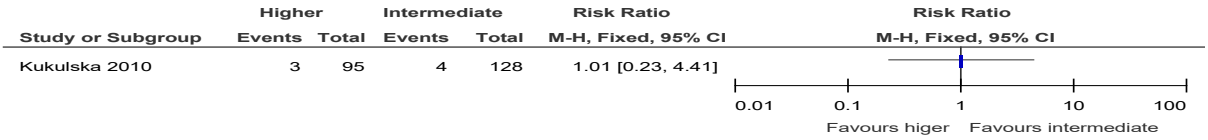
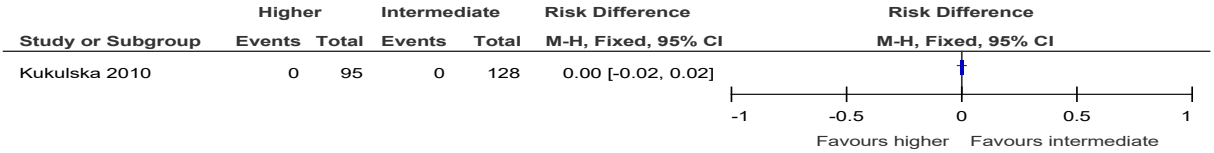


Figure 8: Incidence of distal metastases (at median 10 years)



E.1.3 Intermediate versus lower activity RAI

Figure 9: Successful ablation (at 6-12 months)

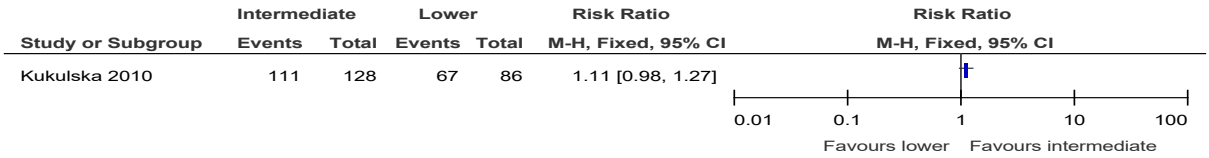


Figure 10: Recurrence (at median 10 years)

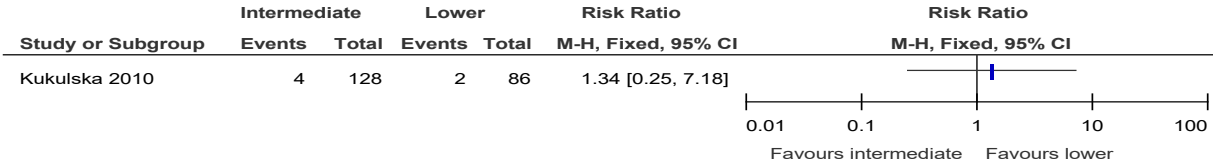
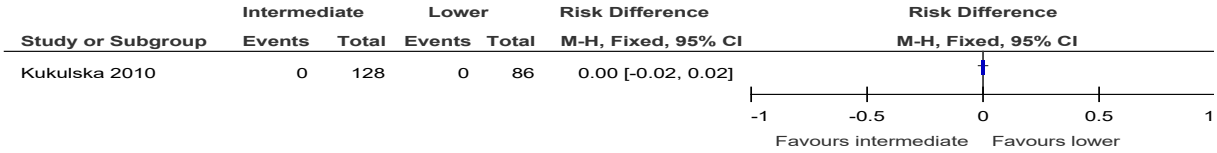


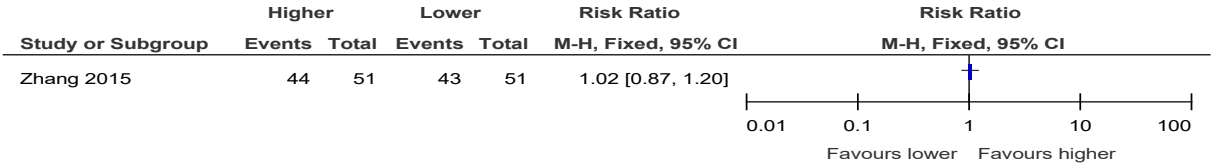
Figure 11: Incidence of distal metastases (at median 10 years)



E.2 High risk strata

E.2.1 Higher versus lower activity RAI

Figure 12: Successful ablation (at 6 months)



E.3 Mixed/unclear risk strata

E.3.1 Higher versus lower activity RAI

Figure 13: Successful ablation (at 6 months - 3.8 years)

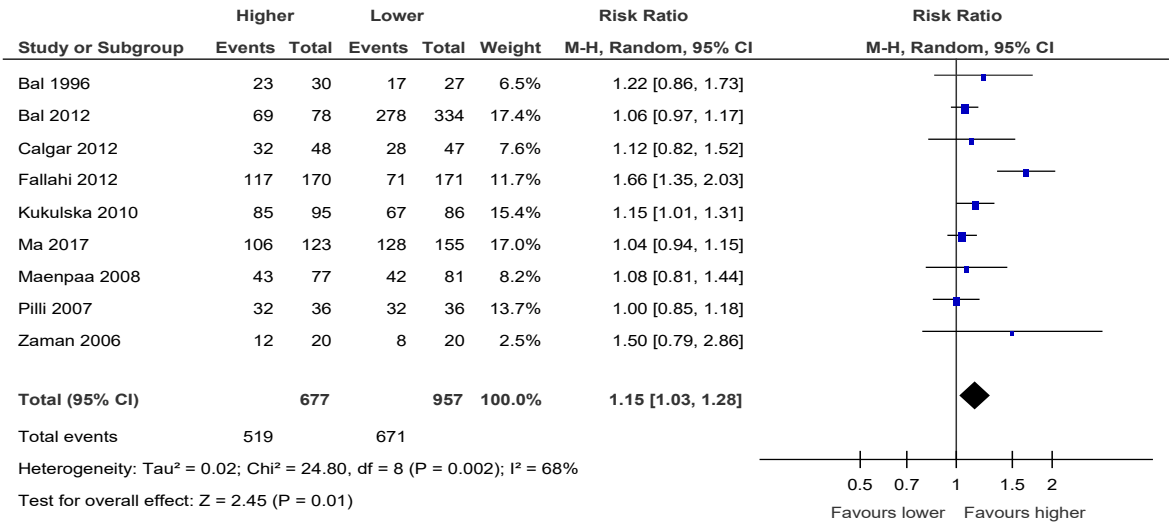


Figure 14: Recurrence (at 1-10 years)

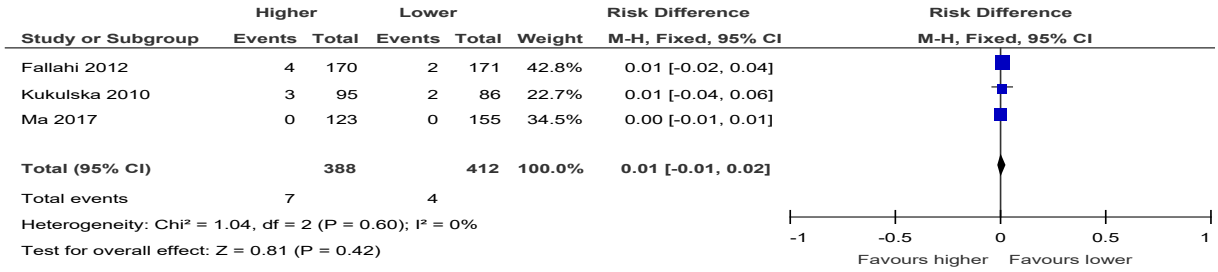


Figure 15: Incidence of distal metastases (at 6-13 years)

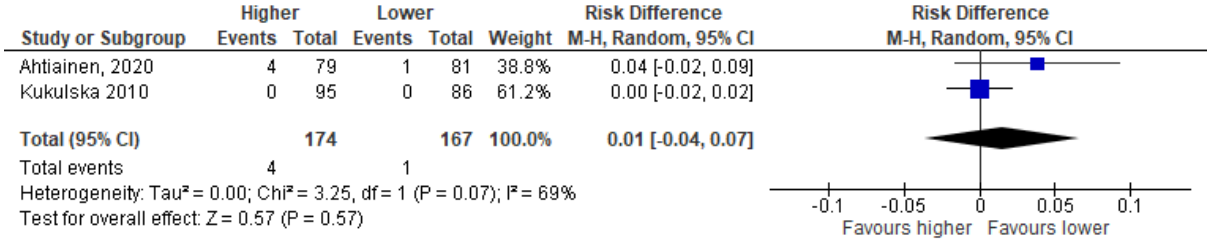
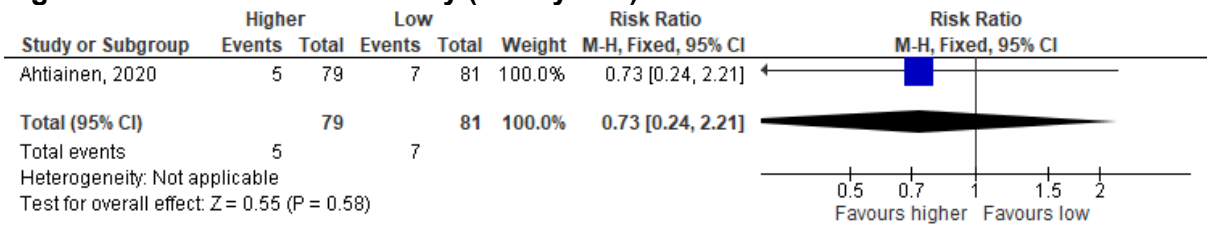
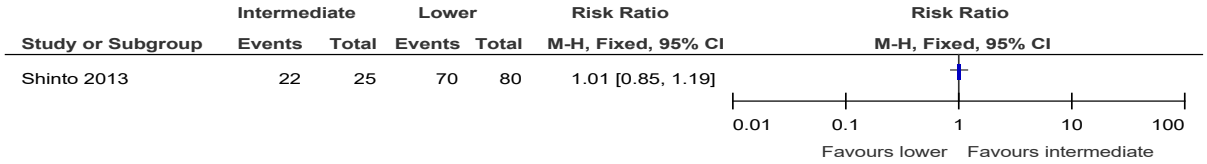


Figure 16: All-cause mortality (at 13 years)



E.3.2 Intermediate versus lower activity RAI

Figure 17: Successful ablation (at 6 months)



Appendix F – GRADE and/or GRADE-CERQual tables

F.1 Low risk strata

Table 10: Clinical evidence profile: Low risk strata: Higher versus lower activity RAI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher activity	Lower activity	Relative (95% CI)	Absolute		
Successful ablation (follow-up 6months-7years)												
4	randomised trials	serious[1]	Very serious inconsistency[3]	no serious indirectness	no serious imprecision	none	538/597 (90.1%)	87.0%	RR 1.06 (0.93 to 1.20)	50 more per 1000 (from 58 fewer to 165 more)	VERY LOW	CRITICAL
Recurrence (follow-up 78.4 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	10/217 (4.6%)	5.1%	RR 0.91 (0.39 to 2.1)	5 fewer per 1000 (from 31 fewer to 56 more)	LOW	CRITICAL
Quality of life - physical domains (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	218	220	-	MD 7 lower (27.2 lower to 13.2 higher)	HIGH	CRITICAL
Quality of life - psychological domains (follow-up 3 months; range of scores: 0-100; Better indicated by higher values)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	218	220	-	MD 4.4 higher (16.2 lower to 25 higher)	HIGH	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs. For binary variables the MIDs were set at RR of 0.8 and 1.25. For the continuous outcomes the MIDs were set at $\pm$0.5 x median standard deviation of the control group. For quality of life (physical domains) the sd was 107.84, so the MID was $\pm$53.92, and for quality of life (psychological domains) the sd was 109.98, so the MID was $\pm$54.99

[3]Downgraded for very serious inconsistency was I^2 > 75% and not resolved by pre-hoc sub-grouping strategies

Table 11: Clinical evidence profile: Low risk strata: Higher versus intermediate activity RAI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher activity	Intermediate activity	Relative (95% CI)	Absolute		
Successful ablation (follow-up 6-12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	85/95 (89.5%)	86.7%	RR 1.03 (0.94 to 1.14)	26 more per 1000 (from 52 fewer to 121 more)	MODERATE	CRITICAL
Recurrence (follow-up median 10 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/95 (3.2%)	3.1%	RR 1.01 (0.23 to 4.41)	0 more per 1000 (from 24 fewer to 106 more)	VERY LOW	CRITICAL
Incidence of distal metastases (follow-up median 10 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious imprecision	none	0/95 (0%)	0%	Risk difference 0 (-0.02 to 0.02)	-	LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] For risk ratios, downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (0.8 or 1.25). For the risk differences, the imprecision was based on optimal information size, with sample sizes of 70-350 indicating serious imprecision.

Table 12: Clinical evidence profile: Low risk strata: Intermediate versus lower activity RAI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intermediate activity	Lower activity	Relative (95% CI)	Absolute		
Successful ablation (follow-up 6-12 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	111/128 (86.7%)	77.9%	RR 1.11 (0.98 to 1.27)	86 more per 1000 (from 16 fewer to 210 more)	LOW	CRITICAL

Recurrence (follow-up median 10 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/128 (3.1%)	2.3%	RR 1.34 (0.25 to 7.18)	8 more per 1000 (from 17 fewer to 142 more)	VERY LOW	CRITICAL
Incidence of distal metastases (follow-up median 10 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	Serious imprecision	none	0/128 (0%)	0%	Risk difference 0 (-0.02 to 0.02)	-	LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] For risk ratios, downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (0.8 or 1.25). For the risk differences, the imprecision was based on optimal information size, with sample sizes of 70-350 indicating serious imprecision.

F.2 High risk strata

Table 13: Clinical evidence profile: High risk strata: Higher versus lower activity RAI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Higher activity**	**Lower activity**	**Relative (95% CI)**	**Absolute**		
Successful ablation (follow-up 6 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	44/51 (86.3%)	84.3%	RR 1.02 (0.87 to 1.2)	17 more per 1000 (from 110 fewer to 169 more)	HIGH	CRITICAL

F.3 Mixed/unclear risk strata

Table 14: Clinical evidence profile: Mixed/unclear risk strata: Higher versus lower activity RAI

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher activity	Lower activity	Relative (95% CI)	Absolute		
Successful ablation (follow-up 6 months - 3.8 years)												
9	randomised trials	serious[1]	serious[2]	no serious indirectness	serious[3]	none	519/677 (76.7%)	63%	RR 1.15 (1.03 to 1.28)	94 more per 1000 (from 19 more to 176 more)	VERY LOW	CRITICAL
Recurrence (follow-up 1-10 years)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	7/388 (1.8%)	1.2%	Risk difference 0 (-0.01 to 0.02)	12 fewer per 1000 (from 12 fewer to 12 fewer)	MODERATE	CRITICAL
Incidence of distal metastases (follow-up 6-13 years)												
2	randomised trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	4/174 (1.7%)	0.6%	Risk difference 0.01 (-0.04 to 0.07)	15 more per 1000 (from 40 fewer to 70 more)	LOW	CRITICAL
All-cause mortality (follow-up 51 months)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	5/79 (6.3%)	8.6%	RR 0.73 (0.24 to 2.21)	23 fewer per 1000 (from 65 fewer to 104 more)	LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

[2] Downgraded due to significant heterogeneity unexplained by subgroup analysis

[3] For risk ratios, downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs (0.8 or 1.25). For the risk differences, the imprecision was based on optimal information size, with sample sizes of >350 indicating no serious imprecision.

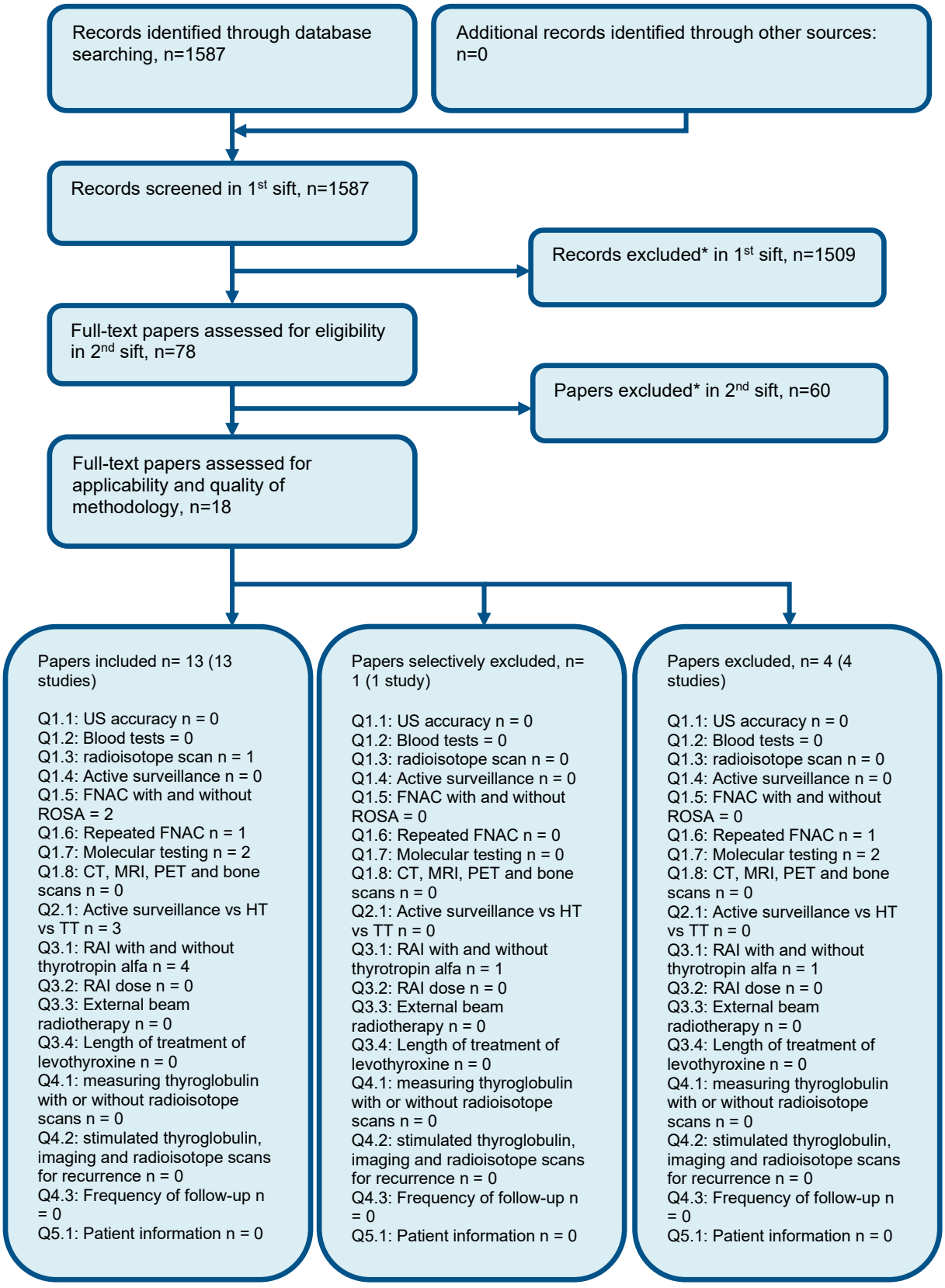
Table 15: Clinical evidence profile: Mixed/unclear risk strata: Intermediate versus lower activity RAI

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Intermediate activity**	**Lower activity**	**Relative (95% CI)**	**Absolute**		
Successful ablation												

1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/25 (88%)	87.5%	RR 1.01 (0.85 to 1.19)	9 more per 1000 (from 131 fewer to 166 more)	MODERATE	

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

None.

Appendix I – Excluded studies

I.1 Clinical studies

Table 16: Studies excluded from the clinical review

Study	Exclusion reason
Abdulrezzak 2017[1]	No relevant outcomes
Bal 2002[5]	Inappropriate comparison
Bal 2004[6]	Incorrect interventions
Barbaro 2010[7]	Incorrect study design
Baskin 1994[8]	Incorrect study design
Cheng 2013[10]	Review - references checked
Creutzig 1987[11]	No relevant outcomes
Doi 2007[13]	Systematic review: references checked
Du 2015[16]	Systematic review: checked for references
Fang 2013[18]	Systematic review: references checked
Hackshaw 2007[20]	Systematic review: references checked
Jin 2019[21]	Incorrect interventions
Johansen 1991[22]	Excluded participants having more than one dose from the success after first dose outcome
Leger 1998[24]	No relevant outcomes
Luster 2003[25]	Inappropriate comparison
Ma 2005[27]	Systematic review: references checked
Maxon 1992[30]	Incorrect study design
Nixon 2020[33]	Systematic review: references checked
Piruzan 2016[35]	Incorrect interventions
Roos 1999[37]	Systematic review: references checked
Rosario 2004[38]	Incorrect study design
Samuel 1994[39]	Incorrect study design
Shengguang 2016[40]	Systematic review: references checked
Sisson 2002[42]	Incorrect study design
Song 2015[43]	Systematic review: references checked
Valachis 2013[44]	Systematic review: references checked
Wei 2019[45]	Incorrect study design
Welsh 2013[46]	Incorrect study design
Yang 2019[47]	Incorrect study design

I.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.