National Institute for Health and Care Excellence

1

Draft

Thyroid Cancer

[Q] Evidence review for frequency and duration of follow up

NICE guideline <number>

Evidence reviews underpinning recommendations 1.6.1 to 1.6.4 and the research recommendations in the NICE guideline

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These evidence reviews were developed by National Guideline Centre

1

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ISBN:

Contents

1

1 Follow up

1.1 Review question

1.1.1 For people who have had treatment for differentiated thyroid cancer, what is the optimum frequency of follow-up according to the severity, spread of the disease and treatment given?

1.1.2 Introduction

Following treatment for differentiated thyroid cancer, initial follow-up aims to assess the completeness of remission. Subsequent follow-up seeks to detect early signs of recurrence to allow prompt treatment.

Follow-up protocols vary widely between different centres reflecting the uncertainty of rates of recurrence after long term remission. For patients who have had an excellent response to initial treatment, an infrequent follow-up schedule may be sufficient whilst other patients with a high risk of recurrence may benefit from more frequent assessments.

This review seeks to determine the effectiveness of different frequencies and lengths of follow up for different strata of severity and spread of disease.

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	Inclusion: People aged 16 or over who have had treatment for differentiated thyroid cancer Exclusion: Children and young people under 16 years
Intervention(s)	<u>Frequency question</u> Use whatever frequency parameters are compared in the papers <u>Length of follow up question</u> Use whatever length of FU parameters are compared in the papers
Comparison(s)	For each question, use whatever comparators are in the papers (see above)
Outcomes	• Mortality • Quality of life • Structural or biochemical cancer progression of residual or known recurrent malignancy • Structural or biochemical* cancer recurrence (distant/local)
Study design	• Systematic reviews • RCTs We will drop down to non-RCTs if we don't find any RCTs (do separately for each sub-question). This will include any study design that has used a suitable comparator group and adequate adjustment for confounding
Strata	This is based on age, severity and spread of the disease. • People with residual disease after initial treatment • people treated with curative intent stratified at 12 months into excellent response

- people treated with curative intent stratified at 12 months into indeterminate response
- people treated with curative intent stratified at 12 months into incomplete response.

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

No randomised trials were found, so the search was extended to observational studies. In the absence of any observational studies directly comparing groups of patients with different durations or frequencies of follow up, a large number of prognostic studies were selected for full-text review because of the possibility that the independent variables of follow up frequency and duration might be factors included in their multivariable analyses. If so, the independent effects of these variables upon the outcomes relevant to this review might be extracted. The 166 studies were scrutinised in detail, but only three of them were eligible for the review.[14, 93, 118] These are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summaries below (Table 3 and Table 4).

These studies aimed to evaluate the independent effects of all plausible factors associated with the outcome of tumour recurrence/persistence using a multivariable logistic regression. Consequently, the duration and frequency of follow up were evaluated in terms of adjusted odds ratios, these odds ratios being based upon a reference category which was 'one increment below' in terms of the units of duration or frequency. It is unclear from the studies what these units are, but it appears most likely to be 'number of follow ups' for frequency and 'months' for duration in the Lee[93] and Park[118] studies (although in the Bosset[14] study the unit may be 'years'). For example, for duration, the odds ratio of 0.5 for recurrence indicates that any extra month duration of follow up confers a halving of the odds of recurrence. Similarly, for frequency, the odds ratio of 0.5 for recurrence indicates that any extra follow up session per unit time confers a halving of the odds of recurrence.

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	Stratum
Bosset, 2021[14]	Again, this study was not a conventional trial set up to compare two or more specific durations or frequencies of follow up. Instead, it was an observational study that aimed to measure each participant's duration of follow up and relate to outcome in a multivariable logistic regression analysis, with multivariable adjustment for other variables (age, sex, histological subtype, cancer focality and predicted risk of recurrence categorised using the 2015 ATA guidelines).	Consecutive patients who underwent a thyroid lobectomy for differentiated thyroid cancer, between 1970 and 2010 in a tertiary endocrinology center. Age at surgery – mean (sd): 39.8 (12) years; Gender (M:F): 61/234. Ethnicity: not reported Pre-op staging: T1 145, T2 110, T3 40.	Tumour recurrence	Low recurrence rate reported so the stratum was *people treated with curative intent stratified at 12 months into excellent response*
Lee, 2018[93] N=253 10 years	This study did not directly compare specific durations of follow up or frequencies of follow up with each other. Instead, this study aimed to evaluate the independent effects of all plausible factors associated with the outcome of tumour recurrence/persistence using a multivariable logistic regression. These were adjusted for each other and for all the other factors in the model: age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multifocality. Consequently, the	South Korea Inclusion: Patients who underwent total thyroidectomy for papillary thyroid carcinoma, followed by post-operative neck US.	Tumour recurrence/persistence	Based on the information given in the paper the stratum was *people treated with curative intent stratified at 12 months into excellent response*, as only 4.3% developed recurrence

Study	Intervention and comparison	Population	Outcomes	Stratum
	duration and frequency of follow up have been evaluated in terms of adjusted odds ratios.	Exclusion: Patients not undergoing postoperative US Age – mean (sd): 53.9 (12.1) years; Gender (M:F): Female/male ratio: 252/20. Ethnicity: not reported Pre-op staging: T1a n=107, T1b n=107, T2 n=31, T3a n=3, T3b n=5, T4a n=0, T4b; N0 n=158, N1a n=72, N1b n=23		
Park, 2018[118] N=525 2 years	This study appears to have been carried out by the same team as Lee, 2018, and the intervention and comparison details are exactly as above. The population, however, appear to be different, thus permitting the inclusion of both studies.	South Korea Inclusion: Patients undergoing total thyroidectomy for the treatment of papillary thyroid carcinoma, followed by routine neck US. Exclusion: Patients not undergoing postoperative follow up US Age – mean (sd): 47.6 (11.3) years; Gender (M:F): Female/male ratio: 460/65. Ethnicity: not reported	Tumour recurrence/persistence	As above - based on the information given in the paper the stratum was *people treated with curative intent stratified at 12 months into excellent response*, as only 5.9% developed recurrence

Study	Intervention and comparison	Population	Outcomes	Stratum
		Pre-op staging: T1a n=278, T1b n=167, T2 n=71, T3a n=7, T3b n=2, T4a n=0, T4b; N0 n=253, N1a n=226, N1b n=46		

See Appendix D for full evidence tables.

1.1.7 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Effect of duration of follow up (with an increment of 1 month) on tumour recurrence/persistence

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with follow up duration of 1 month increment less	Absolute risk difference (risk difference accrued by a follow up duration that it is 1 month greater than comparator) (95% CI)
Tumour recurrence/persistence	1073 (3 studies) 2-19 years	VERY LOW[1,2]	Adjusted* OR 1.00 (0.97, 1.03)	-	-

*Adjusted for age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multifocality
[1] Downgraded by one increment due to serious risk of bias or two increments due to very serious risk of bias
[2] Downgraded for heterogeneity

Table 4: Clinical evidence summary: Effect of follow up frequency (number of US follow up sessions) on tumour recurrence/persistence

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with endoscopy	Absolute risk difference (surveillance minus no surveillance) (95% CI)
Tumour recurrence/persistence	778 (2 studies) 2-10 years	VERY LOW[1,2,3]	Adjusted* OR 1.47 (1.07, 2.01)	-	-

[1] Downgraded by one increment due to serious risk of bias
[2] Downgraded for indirectness because number of follow up sessions does not necessarily denote frequency. If the number of follow up sessions were all fitted within the same time period then the number of sessions can be taken as equivalent to a frequency measure. However, it is possible that some patients will have had longer follow ups, and so a greater number of follow up sessions may not imply a greater frequency at all – and in fact could be consistent (if the follow up time were sufficiently long) with a reduced frequency in certain cases.
[3] Downgraded by one increment as the 95% CIs crossed one of the default MIDs (0.8 or 1.25).

*adjusted for age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multifocality

These results show that there is a relationship between a greater frequency of US follow up and a greater detected recurrence. That is, for every additional increment of frequency [given by an additional one session] the odds of tumour recurrence would be multiplied by 1.47 (and therefore would increase by 47%). Initially this might seem counterintuitive, because greater frequency of follow up would tend to be seen as a 'good thing to do', whilst more recurrence is a negative outcome. We certainly wouldn't expect more follow up to actually *cause* recurrences. Counterintuitive findings often suggest spurious findings relating to selection bias. For example, we might expect those with a higher T staging to be followed up more frequently and to also have more recurrence, thus creating such a pattern of results, but the multivariable adjustment for T staging should hopefully ameliorate this spurious effect on results to at least some degree. Indeed, the association has been adjusted for multiple factors, suggesting that selection bias cannot be the sole explanation for the finding. A more likely explanation is that those people given greater frequency of follow up are simply having their recurrences detected to a greater degree than those who are being followed up less frequently. So, these results probably just show that frequent follow ups are a good way of uncovering recurrences that are already there. In other words, frequent follow ups don't *cause* recurrences, but they cause them to be detected. Although in itself spurious, this effect wasn't eliminated by multivariable adjustment because the spuriousness was not due to selection bias – it was independent from the other variables being considered.

Meanwhile, there does not appear to be a significant relationship between duration of follow up and recurrence. For every additional increment of duration [probably one month] the odds of tumour recurrence would be multiplied by 1.0034 (and therefore would increase by a very small percentage of 0.34% per month). However, the confidence intervals show the result is very much in agreement with the null hypothesis (that in the population duration does not affect recurrence).

See Appendix F for full GRADE and/or GRADE-CERQual tables

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

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

1.1.11 Economic evidence statements

No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1 The outcomes that matter most

The outcomes considered for this review were mortality, health related quality of life, structural or biochemical cancer progression of residual or known recurrent malignancy, and structural or biochemical cancer recurrence. For purposes of decision-making all outcomes were equally regarded as being of critical importance. No evidence was identified for mortality, health related quality of life, or structural or biochemical cancer progression of residual or known recurrent malignancy.

1.1.12.2 The quality of the evidence

For the effect of duration (time from diagnosis to last follow up visit) on tumour recurrence/persistence, the quality of evidence was rated as very low. The downgrade was due to very serious risk of bias and inconsistency. The risk of bias was from attrition bias and selection bias from a non-randomised design, but this was only a single downgrade because a rigorous logistic regression had been used to adjust for biologically plausible confounders, such as age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multifocality. The downgrade for inconsistency was due to serious heterogeneity and a random effects analysis was used.

For the effect of frequency, the quality of evidence was rated as very low. The downgrade was due to selection bias from a non-randomised design (ameliorated as before because a rigorous logistic regression had been used to adjust for biologically plausible confounders, such as age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multifocality), imprecision and indirectness. The downgrade for indirectness was due to the lack of clarity about the definition of the outcome as 'frequency', when in fact it was quantified as the number of follow up visits. The number of follow up visits will only equate to frequency if there is a constant duration of time, but the duration varied between individuals. Therefore, the validity of the outcome as a measure of frequency was in doubt.

1.1.12.3 Benefits and harms

The committee commented on the lack of evidence and how the available evidence from the three studies was biased by very early disease and was therefore not representative of much of the relevant patient population.

The committee discussed the implications of the evidence. The point estimate suggested no association between duration of follow up and recurrence, but the committee were uncomfortable about accepting this at face value, partly because it conflicted with their clinical intuition and experience, but also because the estimate of the association between duration of follow up and recurrence was too uncertain to allow any meaningful conclusions about the effect in the population. Therefore, for the variable of 'duration of follow up', the committee relied on consensus to form recommendations.

For the variable of 'frequency of follow up', indirect evidence showed a greater number of follow up sessions showed a clear association with *greater* recurrence. Greater frequency of follow up would be expected to lead to a better, not worse, outcome, and yet was associated with greater recurrence. The committee accepted that this could not be wholly due to selection bias because of the logistic regression analysis having adjusted for highly relevant confounders such as T stage or N stage. It was agreed that the unexpected relationship was probably a reflection of the fact that greater frequency of follow up allowed a greater *detection* of recurrence that might perhaps not be detected otherwise. Overall, however, the committee were unconvinced of the evidence and again preferred to make the recommendations from consensus, because the evidence had not told them anything they did not know already – that if you look harder you see more.

The committee first discussed what should occur for people at stage pT1a, with no local (cN0) or distant (cM0) spread, who had been treated. For this group the committee agreed that the risks of further spread or recurrence were so low that the harms of further follow up to detect recurrence would outweigh any benefits. Such harms would include the anxiety around the investigations involved in follow up, and the radiation risks of some forms of detection.

For people with stage T1b or greater who have had a hemithyroidectmy or total thyroidectomy without RAI, then an US at 6-12 months followed by an annual follow up for 5 years was recommended. This group was regarded as having a small but real risk of recurrence and spread, and therefore the benefits of follow up, such as better prognosis resulting from early detection and treatment, would start to outweigh the harms outlined above. The timing of the initial follow up was based on current practice and the frequency of every year for a duration of 5 years was based on the committee's understanding of how quickly recurrences and spread may occur, and at what point it tends to be safe to assume that, provided no recurrence or spread has occurred up to that point, further problems are unlikely.

For people who had had both a total thyroidectomy and RAI, then the duration and frequency of follow up was based on the assumed level of risk or recurrence of the cancer. The criteria were based on the response to treatment. For people at low risk with no evidence of disease on imaging and a thyroglobulin level of <0.2microgram/L, or a stimulated thyroglobulin level of <1 microgram/L, then annual follow up was recommended for 2-5 years. For people at a medium risk, with thyroglobulin between 0.2 and 1.0 microgram/litre, or stimulated thyroglobulin of between 1 and 10 microgram/litre, it was recommended that follow up should occur annually for 5-10 years. For people deemed to be at high risk, with thyroglobulin of greater than 1.0 microgram/litre, or stimulated thyroglobulin of greater than 10 microgram/litre, it was recommended that follow up should occur annually for 10 years. The annual frequencies were again based on the committee's understanding of how quickly recurrences and spread may occur. The committee acknowledged while annual follow up is recommended there may be case in which a more frequent follow up period is required therefore recommended that follow up is 'at least' annually., The steadily increasing duration of total follow up duration with the level of presumed risk was based on the committee's experience that as risk increases the tendency for late recurrence and spread increases. Therefore, more prolonged vigilance is necessary, and outweighs any potential harms from follow up, such as anxiety of radiation.

For anyone at the highest levels of risk, with current biochemical or structural disease, the committee recommended that follow up should occur annually for an indefinite period unless, during follow up such patients transition to lower risk categories.

Finally, the committee agreed that if any person has had a total or completion thyroidectomy and RAI and has evidence of structural persistent disease then this should be discussed with a surgeon.

Although the committee agreed that the current evidence base was poor for both frequency and duration of follow up, they were relatively confident that an annual follow up was adequate and appropriate for most patients. They therefore did not seek further research on that topic area. However the committee thought that further research on the optimal duration of follow up would be of use, and so wrote a research recommendation. The research recommendation is entitled: What is the clinical and cost-effectiveness for different durations of follow up?

481.12.4 Cost effectiveness and resource use

No health economics study was included in this review.

The committee acknowledged that the clinical evidence was not sufficiently strong and reliable to make recommendations, so they decided to rely on consensus instead and to make a research recommendation on the clinical and cost effectiveness of different durations of follow up.

For very low-risk cancer, monitoring was not recommended as the risk of recurrence is very low. For patients with greater risk, different durations were recommended according to their risk whereas, for people with structural persistent disease, lifelong monitoring was recommended. These recommendations are in line with current practice and represent a rational and cost-effective use of NHS resources as monitoring frequency and mode are tailored to patients' risk and cancer characteristics.

11.12.5 Other factors the committee took into account

One inequality issue considered by the committee concerned people with mental health comorbidities. For this group of people follow up frequency may be an important parameter to consider. The

11.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.6.1 to 1.6.4 and the research recommendation on the clinical and cost effectiveness for different durations of follow up for people with differentiated thyroid cancer who have been treated.

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Appendices

Appendix A – Review protocols

A.1 Review protocol for length and frequency of follow-up

Field	Content
PROSPERO registration number	CRD42021287528
Review title	1. The optimum frequency of follow-up for people who have had treatment for differentiated thyroid cancer, given the severity and spread of the disease and treatment given. 2. The optimum length of follow-up for people who have had treatment for differentiated thyroid cancer, given the severity and spread of the disease and treatment given.
Review question	1. For people who have had treatment for differentiated thyroid cancer, what is the optimum frequency of follow-up according to the severity, spread of the disease and treatment given? 2. For people who have had treatment for differentiated thyroid cancer, what is the optimum length of follow-up according to the severity, spread of the disease and treatment given?
Objective	To determine the effectiveness of different frequencies and lengths of follow up for different strata of severity and spread of disease
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.

Field	Content
	Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies 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 who have had treatment for differentiated thyroid cancer Exclusion: Children and young people under 16 years
Intervention/Exposure/ Test	Frequency question Use whatever frequency parameters are compared in the papers Length of follow up question Use whatever length of FU parameters are compared in the papers
Comparator/Reference standard/Confounding factors	For each question, use whatever comparators are in the papers (see above)
Types of study to be included	• Systematic reviews • RCTs We will drop down to non-RCTs if we don't find any RCTs (do separately for each sub-question). This will include any study design that has used a suitable comparator group and adequate adjustment for confounding (see below)

Field	Content
	• Non RCTs have to have adjusted/accounted for any potential covariates. The committee have not specified any particular covariates that MUST be considered, but at the very minimum there needs to be a rigorous method to adjust for confounding, such as regression, ANCOVA, or stratification analysis, if potential covariates are found to differ between groups
Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	The ideal frequency and length of follow up is currently unknown, and this review aims to evaluate the ideal approach.
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • mortality • quality of life • structural or biochemical* cancer progression of residual or known recurrent malignancy • structural or biochemical* cancer recurrence (distant/local) duration of follow up: longest available
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. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. 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 all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately

Field	Content
	• 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. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
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) ROBINS will be used for appraisal on non-RCTs if no RCTs are available
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. Publication bias is tested for when there are more than 5 studies for an outcome.

Field	Content
	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	Stratification Strata based on age, severity and spread of the disease: People with residual disease after initial treatment / people treated with curative intent stratified at 12 months into excellent response /people treated with curative intent stratified at 12 months into indeterminate response / people treated with curative intent stratified at 12 months into incomplete response. Sub-grouping • Not applicable, as no pooling will be used.
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**

Field	Content
	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 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=287528

Field	Content
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	Thyroid cancer
Details of existing review of same topic by same authors	N/A
Additional information	N/A
Details of final publication	www.nice.org.uk

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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).{National Institute for Health and Care Excellence, 2014 #23} **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:

- For people who have had treatment for differentiated thyroid cancer, what is the optimum frequency of follow-up according to the severity, spread of the disease and treatment given?

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 5: 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

1 **Medline (Ovid) search terms**

1.	exp Thyroid Neoplasms/
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/
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 child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
27.	25 not 26
28.	((followup* or follow* up* or assess* or evaluat* or test* or retest* or screen* or surveillance or monitor* or check-up* or checkup* or measur* or examin* or recall* or visit* or revisit*) adj4 (interval* or frequen* or day* or week* or month* or year* or annual* or annum or time* or timing* or regular* or periodic* or ongoing or on-going or continu* or recurr* or repeat* or length or long-term or short-term or duration* or optimal or optimum or survivors or survivorship)).ti,ab.
29.	27 and 28

30.	randomized controlled trial.pt.
31.	controlled clinical trial.pt.
32.	randomi#ed.ab.
33.	placebo.ab.
34.	randomly.ab.
35.	clinical trials as topic.sh.
36.	trial.ti.
37.	or/30-36
38.	Meta-Analysis/
39.	Meta-Analysis as Topic/
40.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
41.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
42.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
43.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
44.	(search* adj4 literature).ab.
45.	(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.
46.	cochrane.jw.
47.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
48.	or/38-47
49.	Epidemiologic studies/
50.	Observational study/
51.	exp Cohort studies/
52.	(cohort adj (study or studies or analys* or data)).ti,ab.
53.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
54.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
55.	Controlled Before-After Studies/
56.	Historically Controlled Study/
57.	Interrupted Time Series Analysis/
58.	(before adj2 after adj2 (study or studies or data)).ti,ab.
59.	exp case control study/
60.	case control*.ti,ab.
61.	Cross-sectional studies/
62.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
63.	or/50-63
64.	29 and (37 or 48 or 63)

1 **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.	((followup* or follow* up* or assess* or evaluat* or test* or retest* or screen* or surveillance or monitor* or check-up* or checkup* or measur* or examin* or recall* or visit* or revisit*) adj4 (interval* or frequen* or day* or week* or month* or year* or annual* or annum or time* or timing* or regular* or periodic* or ongoing or on-going or continu* or recurr* or repeat* or length or long-term or short-term or duration* or optimal or optimum or survivors or survivorship)).ti,ab.
28.	26 and 27
29.	random*.ti,ab.
30.	factorial*.ti,ab.
31.	(crossover* or cross over*).ti,ab.
32.	((doubl* or singl*) adj blind*).ti,ab.
33.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
34.	crossover procedure/
35.	single blind procedure/
36.	randomized controlled trial/
37.	double blind procedure/
38.	or/29-37
39.	systematic review/
40.	Meta-Analysis/
41.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
42.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
43.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
44.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
45.	(search* adj4 literature).ab.

46.	(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.
47.	cochrane.jw.
48.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
49.	or/39-48
50.	Clinical study/
51.	Observational study/
52.	family study/
53.	longitudinal study/
54.	retrospective study/
55.	prospective study/
56.	cohort analysis/
57.	follow-up/
58.	cohort*.ti,ab.
59.	58 and 59
60.	(cohort adj (study or studies or analys* or data)).ti,ab.
61.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
62.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
63.	(before adj2 after adj2 (study or studies or data)).ti,ab.
64.	exp case control study/
65.	case control*.ti,ab.
66.	cross-sectional study/
67.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	or/51-57,60-68
69.	28 and (38 or 49 or 68)

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.	((followup* or follow* up* or assess* or evaluat* or test* or retest* or screen* or surveillance or monitor* or check-up* or checkup* or measur* or examin* or recall* or visit* or revisit*) NEAR/4 (interval* or frequen* or day* or week* or month* or year* or annual* or annum or time* or timing* or regular* or periodic* or ongoing or on-going or continu* or recurr* or repeat* or length or long-term or short-term or duration* or optimal or optimum or survivors or survivorship)):ti,ab
#7.	#5 and #6
#8.	conference:pt or (clinicaltrials or trialsearch):so
#9.	#7 NOT #8

Epistemonikos search terms

1.	(advanced_title_en:((thyroid AND (cancer* OR neoplasm* OR nodule* OR carcinoma*))) OR advanced_abstract_en:((thyroid AND (cancer* OR neoplasm* OR nodule* OR carcinoma*)))) AND (advanced_title_en:(((followup* OR follow* up* OR assess* OR evaluat* OR test* OR retest* OR screen* OR surveillance OR monitor* OR

	check-up* OR checkup* OR measur* OR examin* OR recall* OR visit* OR revisit*) AND (interval* OR frequen* OR day* OR week* OR month* OR year* OR annual* OR annum OR time* OR timing* OR regular* OR periodic* OR ongoing OR on-going OR continu* OR recurr* OR repeat* OR length OR long-term OR short-term OR duration* OR optimal OR optimum OR survivors OR survivorship))) OR advanced_abstract_en:(((followup* OR follow* up* OR assess* OR evaluat* OR test* OR retest* OR screen* OR surveillance OR monitor* OR check-up* OR checkup* OR measur* OR examin* OR recall* OR visit* OR revisit*) AND (interval* OR frequen* OR day* OR week* OR month* OR year* OR annual* OR annum OR time* OR timing* OR regular* OR periodic* OR ongoing OR on-going OR continu* OR recurr* OR repeat* OR length OR long-term OR short-term OR duration* OR optimal OR optimum OR survivors OR survivorship))))

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 Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1946 – 16 December 2021	
Embase (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 16 December 2021	
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

1 **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

1 **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

1 **NHS EED and HTA (CRD) search terms**

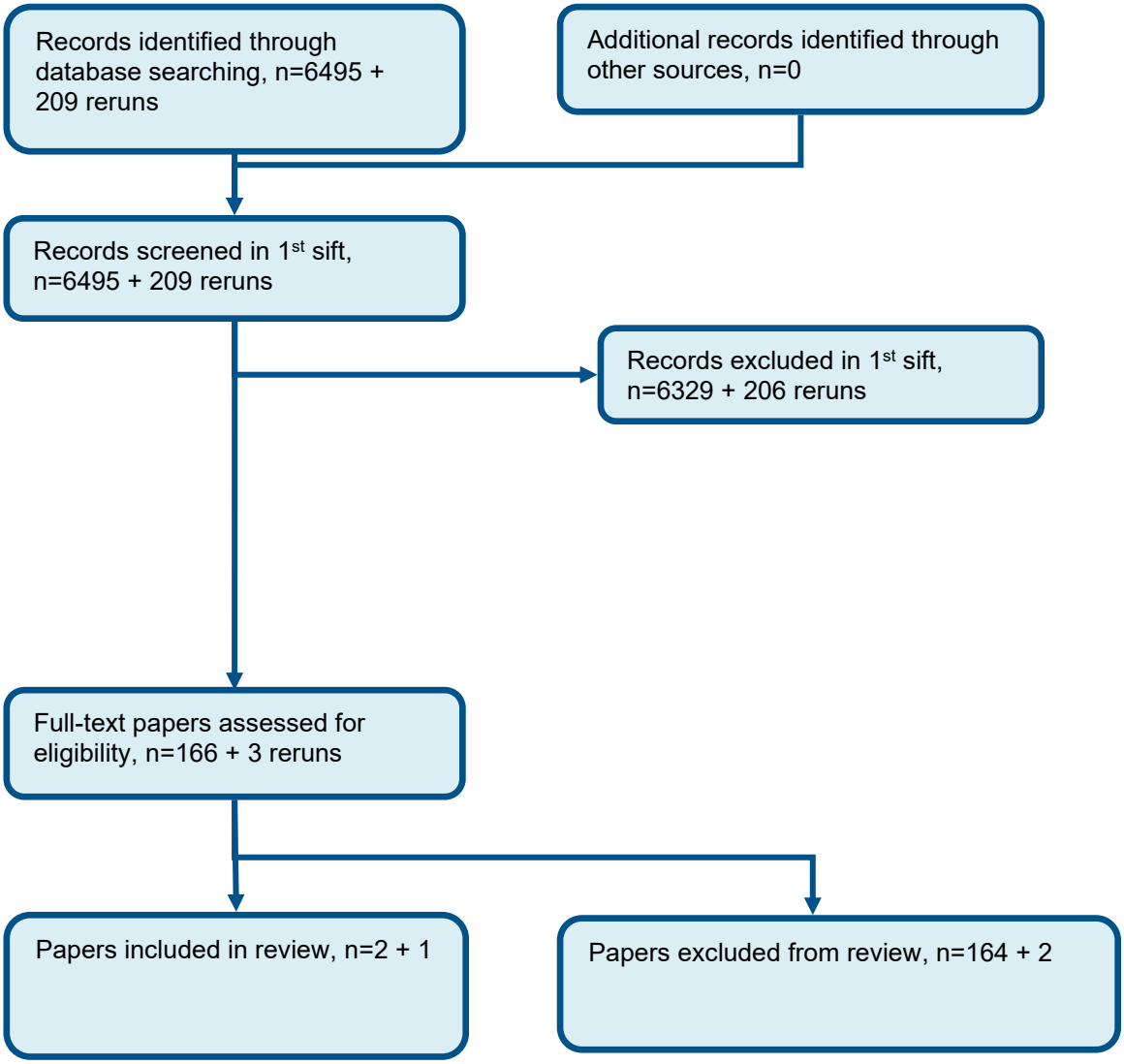
#1.	MeSH DESCRIPTOR Thyroid Neoplasms EXPLODE ALL TREES
#2.	((thyroid NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)))
#3.	(((papillar* or follicul* or medullary or anaplastic)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



Appendix D – Effectiveness evidence

Study	Bosset, 2021[14]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=295)
Countries and setting	France; data from a hospital database were used for this study.
Line of therapy	Not applicable
Duration of study	Mean 19.1 years
Method of assessment of guideline condition	Not described
Stratum	Unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion criteria were a documented histology, at least one cervical ultra- sound performed during the follow-up and a follow-up of >5 years for those without recurrence.
Exclusion criteria	Patients with postoperative thyroid completion, anaplastic thyroid cancer, or medullary thyroid cancer were excluded.
Recruitment/selection of patients	Consecutive patients who underwent a thyroid lobectomy for differentiated thyroid cancer, between 1970 and 2010 in a tertiary endocrinology center.

Age, gender and ethnicity	Age at surgery – mean (sd): 39.8 (12) years; Gender (M:F): 61/234. Ethnicity: not reported
Further population details	Pre-op staging: T1 145, T2 110, T3 40.
Indirectness of population	No indirectness
Interventions	This study was not a conventional trial set up to compare two or more specific durations or frequencies of follow up. Instead, it was an observational study that aimed to measure each participant's duration of follow up and relate to outcome in a multivariable logistic regression analysis, with multivariable adjustment for other variables (age, sex, histological subtype, cancer focality and predicted risk of recurrence categorised using the 2015 ATA guidelines).
Funding	No funding reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Duration of follow up

Protocol outcome 1: Structural or biochemical cancer recurrence
- Actual outcome: True recurrence

Adjusted OR for effect of the interval from surgery to the last follow up session on true recurrence: 1.042 (0.988-1.098). (CIs calculated by reviewer from the beta and SE of beta provided in paper, where OR is exponential function (*e*) raised to the power of beta and CIs are *e* raised to the power +/- 1.96 x SE of beta). This is based on an increment of one year. To adjust to an increment of 1 month, in order to tally with the other studies, the adjusted OR (95CI) is 1.0034(0.999 to 1.0078). This was calculated by dividing the beta and SE of beta by 12 and then repeating the conversion from natural logs to ORs.
Risk of bias: All domain – Very high, Selection - High, Blinding - NA, Incomplete outcome data - high, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments; Indirectness of outcome: No indirectness ; Baseline details: NA; Comments: multivariable adjustment for other variables (age, sex, histological subtype, cancer focality and predicted risk of recurrence categorised using the 2015 ATA guidelines)

Protocol outcomes not reported by the study	Mortality, quality of life, structural or biochemical cancer progression of residual or known recurrent malignancy

Study	Lee, 2018[93]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=253)
Countries and setting	South Korea
Line of therapy	Not applicable
Duration of study	10 years
Method of assessment of guideline condition	Not described
Stratum	Unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who underwent total thyroidectomy for papillary thyroid carcinoma, followed by post-operative neck US.
Exclusion criteria	Patients not undergoing postoperative US
Recruitment/selection of patients	Enrolled from January 2006 to December 2007. No other recruitment details provided.
Age, gender and ethnicity	Age – mean (sd): 53.9 (12.1) years; Gender (M:F): Female/male ratio: 252/20. Ethnicity: not reported

Further population details	Pre-op staging: T1a n=107, T1b n=107, T2 n=31, T3a n=3, T3b n=5, T4a n=0, T4b; N0 n=158, N1a n=72, N1b n=23
Indirectness of population	No indirectness
Interventions	This study was not a conventional trial set up to compare two or more specific durations or frequencies of follow up. Instead, it was an observational study that aimed to measure each participant's 1) duration of follow up and 2) number of follow up sessions and separately relate each to outcome in a logistic regression analysis, with multivariable adjustment for other variables (age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multifocality).
Funding	No funding reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Duration of follow up

Protocol outcome 1: Structural or biochemical cancer recurrence
- Actual outcome: tumour recurrence/persistence

Adjusted OR for effect of the interval from surgery to the last follow up session on tumour recurrence/persistence: 1.03 (0.97 to 1.08)
Risk of bias: All domain - high, Selection - high, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments; Indirectness of outcome: No indirectness ; Baseline details: NA; Comments: multivariable adjustment for other variables (age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multiplicity

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Frequency of follow up

Protocol outcome 1: Structural or biochemical cancer recurrence
- Actual outcome: tumour recurrence/persistence

Adjusted OR for effect of the 'number of follow up US sessions' on tumour recurrence/persistence: 1.45 (0.96 to 3.28) [Therefore this is an incremental OR, with the odds ratio for every increment increase in follow up sessions; for example it would be the odds for 6 sessions versus the odds for 5, or equally the odds for 17 sessions versus the odds for 16].
Risk of bias: All domain - high, Selection - high, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low,

Crossover - Low, Comments; Indirectness of outcome: No indirectness ; Baseline details: NA; Comments: multivariable adjustment for other variables (age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multiplicity	
Protocol outcomes not reported by the study	Mortality, quality of life, structural or biochemical cancer progression of residual or known recurrent malignancy

1

Study	**Park, 2018[118]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=525)
Countries and setting	South Korea
Line of therapy	Not applicable
Duration of study	2 years
Method of assessment of guideline condition	Not described
Stratum	Unclear
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing total thyroidectomy for the treatment of papillary thyroid carcinoma, followed by routine neck US.

Exclusion criteria	Patients not undergoing postoperative follow up US
Recruitment/selection of patients	Enrolled from January 2008 to December 2009. No other recruitment details provided.
Age, gender and ethnicity	Age – mean (sd): 47.6 (11.3) years; Gender (M:F): Female/male ratio: 460/65. Ethnicity: not reported
Further population details	Pre-op staging: T1a n=278, T1b n=167, T2 n=71, T3a n=7, T3b n=2, T4a n=0, T4b; N0 n=253, N1a n=226, N1b n=46
Indirectness of population	No indirectness
Interventions	This study was not a conventional trial set up to compare two or more specific durations or frequencies of follow up. Instead, it was an observational study that aimed to measure each participant's 1) duration of US follow up and 2) number of US follow up sessions and separately relate each to outcome in a logistic regression analysis, with multivariable adjustment for other variables (age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multiplicity).
Funding	No funding reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Duration of follow up

Protocol outcome 1: Structural or biochemical cancer recurrence
- Actual outcome: tumour recurrence/persistence

Adjusted OR for effect of the interval from surgery to the last follow up session on tumour recurrence/persistence: 0.96 (0.92 to 1.01) [unclear if this is an incremental OR but probably is. Very unclear what units are used – probably months. If so, this indicates that for every month increase in the duration of follow up the recurrence rate dropped by a factor of 0.96]
Risk of bias: All domain - high, Selection - high, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments; Indirectness of outcome: No indirectness ; Baseline details: NA; Comments: multivariable adjustment for other variables (age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multiplicity

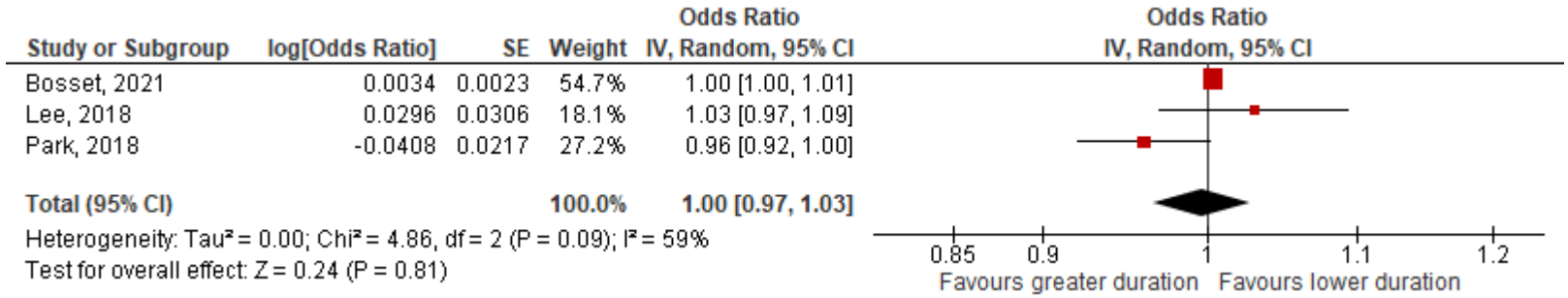
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: Frequency of follow up Protocol outcome 1: Structural or biochemical cancer recurrence - Actual outcome: tumour recurrence/persistence Adjusted OR for effect of the 'number of follow up US sessions' on tumour recurrence/persistence: 1.49 (0.91 to 2.46) [Therefore this is an incremental OR, with the odds ratio for every increment increase in follow up sessions; for example it would be the odds for 6 sessions versus the odds for 5, or equally the odds for 17 sessions versus the odds for 16]. Risk of bias: All domain - high, Selection - high, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Comments; Indirectness of outcome: No indirectness ; Baseline details: NA; Comments: multivariable adjustment for other variables (age, sex, size of primary PTC, location of primary PTC, T stage, N stage, and multiplicity

Protocol outcomes not reported by the study	Mortality, quality of life, structural or biochemical cancer progression of residual or known recurrent malignancy

Appendix E – Forest plots

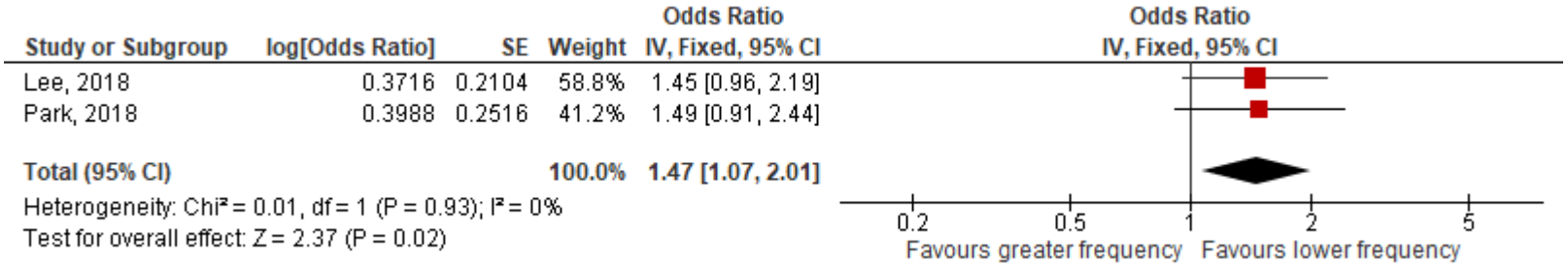
E.1 Duration of follow up

Figure 2: Effect of duration of follow up on odds of tumour recurrence/persistence



E.2 Frequency of follow up

Figure 3: Effect of frequency of follow up [number of follow up sessions] on odds of tumour recurrence/persistence



Appendix F – GRADE and/or GRADE-CERQual tables

Table 6: Clinical evidence profile: Effect of duration of follow up on tumour recurrence/persistence

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute		
Tumour recurrence/persistence at 2-19 years											
3	Observational studies	Very serious risk of bias[1]	Serious inconsistency[2]	no serious indirectness	no serious imprecision	none	1073	OR 1.00 (0.97 to 1.03)	--	VERY LOW	CRITICAL

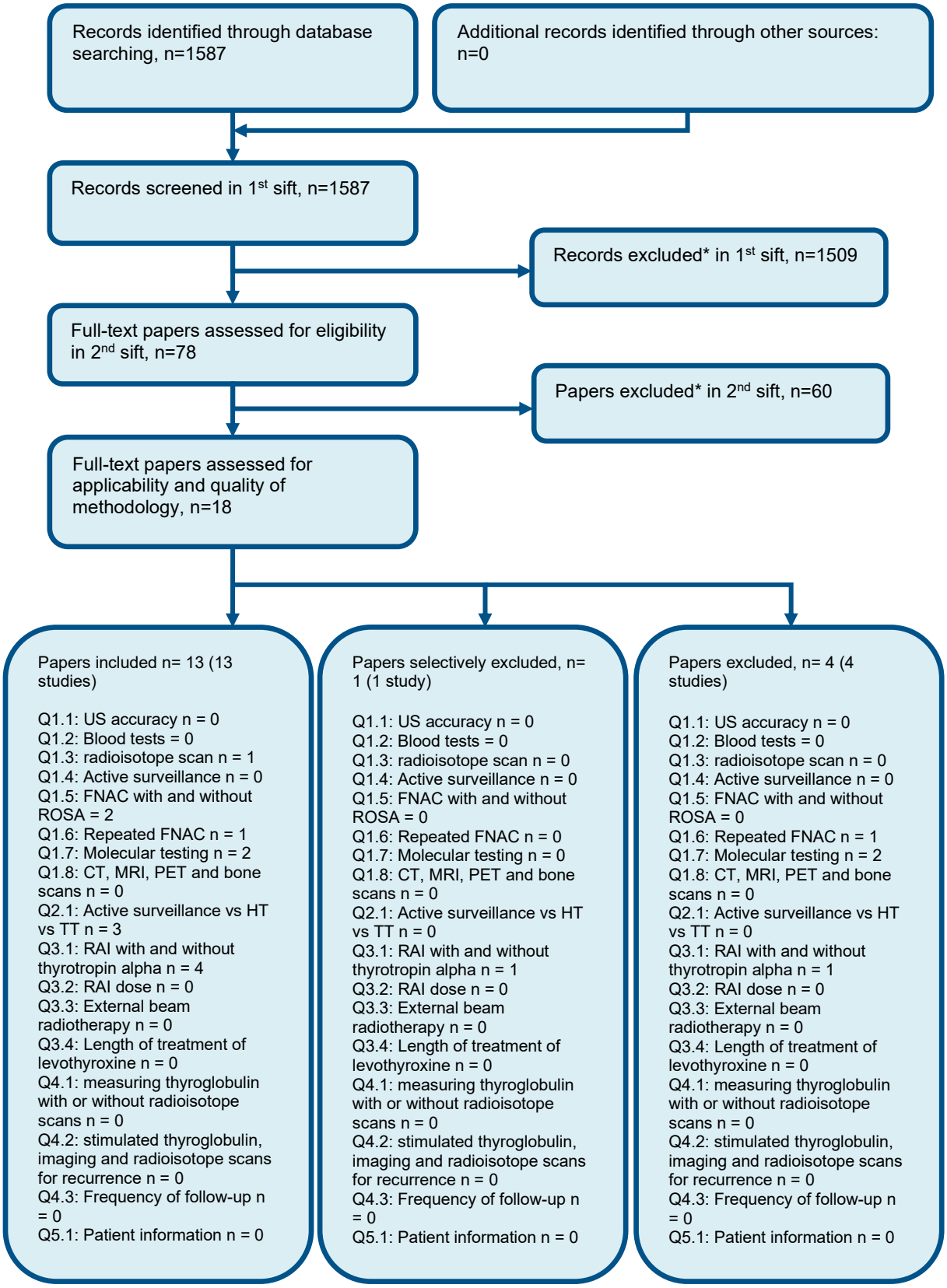
[1] Downgraded by two increments due to selection and attrition bias
[2] Downgraded for heterogeneity

Table 7: Clinical evidence profile: Effect of follow up frequency on tumour recurrence/persistence

Quality assessment							No of patients	Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute		
Tumour recurrence/persistence at 2-10 years											
2	Observational studies	Serious risk of bias[1]	no serious inconsistency	Serious indirectness[2]	Serious imprecision[3]	none	778	OR 1.47 (1.07 to 2.01)	-	VERY LOW	CRITICAL

[1] Downgraded by one increment due to serious risk of bias
[2] Downgraded for indirectness because number of follow up sessions does not necessarily denote frequency. If the number of follow up sessions were all fitted within the same time period then the number of sessions can be taken as equivalent to a frequency measure. However, it is possible that some patients will have had longer follow ups, and so a greater number of follow up sessions may not imply a greater frequency at all – and in fact could be consistent (if the follow up time were sufficiently long) with a reduced frequency in certain cases.
[3] Downgraded by one increment as the 95% CIs crossed one of the default MIDs (0.8 or 1.25).

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 8: Studies excluded from the clinical review

Reference	Reason for exclusion
Akkas, 2014[1]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Almeida, 2009[2]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Alzahrani, 2021[3]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Amin, 2020[4]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis. 'Time of follow up' was included as a univariate variable but this is distinct from the review independent variables and would not constitute being adjusted for other variables in any case.
Amit, 2014[5]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Ardito, 2013[6]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Bachmann, 2007[7]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Back, 2019[8]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Balachandar, 2016[9]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Banerjee, 2016[10]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Bernier, 2005[11]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Besic, 2008[12]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Bhattacharyya, 2006[13]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Boutzios, 2019[15]	Wrong population - benign thyroid disease
Bouvet, 2019[16]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Brierley, 2005[17]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Cao, 2021[18]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Cappelli, 2006[19]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Carhill, 2015[20]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis

Reference	Reason for exclusion
Casara, 1991[21]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Chan, 2021[22]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Chereau, 2016[23]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Choi, 2019[24]	Unadjusted analysis
Chow, 2002[25]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Chowdhury, 2016[26]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Cistaro, 2022[27]	Wrong population - children and adolescents
Clark, 2005[28]	Frequency or duration of follow up were not included as variables in the analysis
Cunningham, 1990[29]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Cushing, 2004[30]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
D'Avanzo, 2004[31]	Frequency or duration of follow up were not included as variables in the analysis
de Castro, 2016[32]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
de Melo, 2014[33]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Dinneen, 1995[34]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Dominguez, 2018[35]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Duntas, 2006[36]	Review - no eligible studies included
Eichhorn, 2003[37]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Ernaga-Lorea, 2018[38]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Feng, 2020[39]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Garas, 2013[40]	Review - none of the included studies were compatible with the protocol
Garg, 2015[41]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Gasior-Perczak, 2018[42]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Geron, 2019[43]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Giani, 2020[44]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Giordano, 2010[45]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis

Reference	Reason for exclusion
Gkatzia, 2021[46]	Frequency or duration of follow up were not included as variables; no multivariable regression analysis
Gonzalez, 2014[47]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Gray, 2018[48]	Review - no eligible studies included
Grogan, 2013[49]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Gulcelik, 2012[50]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Hamilton, 2015[51]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
He, 2016[52]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Heemstra, 2007[53]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Heng, 2020[54]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Henke, 2018[55]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Hoftijzer, 2008[56]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Hollenbeak, 2013[57]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Hovens, 2007[58]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Huang, 2017[59]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Ito, 2018[60]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Izkhakov, 2020[61]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Jeon, 2017[64]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Jeon, 2018[62]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Jeon, 2018[63]	No comparison of durations or frequencies
Jiang, 2017[67]	
Jiang, 2018[65]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Jiang, 2020[66]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Jo, 2017[68]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Joo, 2015[69]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kamel Hasan, 2020[70]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis

Reference	Reason for exclusion
Kim, 2008[80]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2012[72]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2014[79]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2016[73]	No comparison of durations or frequencies
Kim, 2016[77]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2016[78]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2017[71]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2017[74]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2017[75]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2017[81]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kim, 2021[76]	Medullary thyroid cancer
Kjellman, 2006[82]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Konturek, 2012[83]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Kuijpens, 1998[84]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lamartina, 2016[88]	Frequency or duration of follow up were not included as variables. No multivariable regression analysis
Lamartina, 2017[85]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lamartina, 2018[86]	Review - no eligible studies included
Lamartina, 2020[87]	Review - included papers not compatible with review protocol
Lang, 2012[89]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis. 'Time since treatment' was included as a (non-significant) univariate variable but this is distinct from the review independent variables and would not constitute being adjusted for other variables in any case.
Lang, 2014[90]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Ledwon, 2021[91]	Did not evaluate frequency or duration as prognostic factor
Lee, 2019[92]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lerch, 1997[94]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Leung, 2011[95]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis

Reference	Reason for exclusion
Li, 2016[97]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Li, 2019[96]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Liang, 2014[98]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lim, 2016[99]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lin, 2015[100]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Llamas-Olier, 2018[101]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lo, 2005[102]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lo, 2015[103]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lopez-Bru, 2015[104]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Lu, 2021[105]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Marques, 2014[106]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Matsuzu, 2014[107]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Mazzaferri, 1994[108]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Medas, 2019[109]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Moreno-Egea, 1995[110]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Morris, 1998[111]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Nilubol, 2013[112]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Noguchi, 1996[113]	Did not address review question
Oltmann, 2014[114]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Ortiz, 2001[115]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Palme, 2004[116]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Parikh, 2001[117]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Patel, 2019[119]	Did not compare different timings of durations or frequencies - this was a study of the toptimal time to check postoperative TG which did not answer the review question
Pedrazzini, 2013[120]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis

Reference	Reason for exclusion
Peiling Yang, 2015[121]	No comparison of durations or frequencies
Pelizzo, 2007[122]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Pelttari, 2010[123]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Perez, 2016[124]	Frequency or duration of follow up were not included as variables. No multivariable regression analysis
Phitayakorn, 2008[125]	Review of benign nodular disease
Powell, 1994[126]	Did not address review question
Pradhan, 2021[127]	Did not address review question
Raef, 2008[128]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Ratki, 2016[129]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis. There were univariate data for the effects of different follow up durations but these are outside the scope of the protocol that requires adjustment for confounding.
Ringel, 2004[130]	Review - no eligible studies included
Rodriguez-Cuevas, 2002[131]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Rosario, 2019[132]	No comparison of durations or frequencies
Ruiz Pardo, 2020[133]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Ruiz Pardo, 2021[134]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Ryoo, 2018[135]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis. There were univariate data for the effects of different follow up durations but these are outside the scope of the protocol that requires adjustment for confounding.
Saadi, 2001[136]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Sampson, 2007[137]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis. There were univariate data for the effects of different follow up durations but these are outside the scope of the protocol that requires adjustment for confounding.
Sapuppo, 2021[138]	Wrong population - children and adolescents; frequency or duration of follow up were not included as variables in the multivariable regression analysis.
Scheffel, 2015[139]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Schlumberger, 2004[140]	Review - no eligible studies included
Seejore, 2019[141]	Did not compare different timings of durations or frequencies - this was a follow up study to evaluate in which duration most people with recurrence would have a recurrence.
Seejore, 2022[142]	Did not compare different timings of durations or frequencies - this was a study of the time to discharge that would

Reference	Reason for exclusion
	minimise the number of cases missed, which did not answer the review question
Sek, 2021[143]	Did not address review question
Shaha, 1994[144]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Shaha, 1997[145]	No multivariable analysis
Shen, 2020[146]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Showalter, 2008[147]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Siddiqui, 2016[148]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Siraj, 2020[149]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Slook, 2019[150]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Soyluk, 2008[151]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Staunton, 1994	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Stojadinovic, 2002[152]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Suh, 2015[153]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis. There were univariate data for the effects of different follow up durations but these are outside the scope of the protocol that requires adjustment for confounding.
Tennvall, 1985[155]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Tennvall, 1986[154]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Usluogullari, 2015[156]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Vahedian Ardakani, 2017[157]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Velsen, 2021[158]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Wang, 2016[159]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Weng, 2021[160]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Xu, 2021[161]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Yan, 2018[162]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Yanir, 2008[163]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis

Reference	Reason for exclusion
Yin, 2021[164]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Zettinig, 2002[165]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Zhang, 2012	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Zhang, 2012[166]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis
Zheng, 2019[167]	Frequency or duration of follow up were not included as variables in the multivariable regression analysis

I.2 Health economics

None.

Appendix J Research recommendations

J.1.1 Research recommendation

What is the clinical and cost effectiveness for different durations of follow up for people with differentiated thyroid cancer who have been treated?

J.1.2 Why this is important

J.1.3 Although some non-randomised evidence was available, this was unable to give a conclusive answer to the question of the optimal duration of follow up. The result suggested no association between the duration of follow up and recurrence, but the committee agreed that this might be a spurious finding because they believed that duration of follow up would be an important influence on patient outcomes. The committee agreed that a trial where people were randomised to different durations of follow up, with a variety of patient-reported outcome measures, would provide more rigorous evidence and a more conclusive answer. Knowledge of the most optimal duration of follow up is important because this may improve patient outcomes and reduce costs.

J.1.4 Rationale for research recommendation

Importance to 'patients' or the population	Knowledge of the most optimal duration of follow up is important because this may improve patient outcomes and reduce costs.
Relevance to NICE guidance	The efficacy of different follow up durations has been considered in this guideline, but we did not find any RCTs. The development of such RCTs is therefore required.
Relevance to the NHS	Knowledge of the most optimal duration of follow up is important because this may improve patient outcomes and reduce costs.
National priorities	None known
Current evidence base	Observational evidence from 3 studies suggests no effect of follow up duration on the probability of recurrence.
Equality considerations	None known

J.1.5 Modified PICO table

Population	People with differentiated thyroid cancer who have been treated
Intervention	<5 years, 5-10 years, >10 years
Comparator	To each other (see above)
Outcome	Quality of life, mortality, recurrence
Study design	RCT
Timeframe	Long term
Additional information	None