National Institute for Health and Care Excellence

Draft

Thyroid Cancer

[C] Evidence review for radioisotope scan

NICE guideline <number>

Evidence reviews underpinning recommendation 1.2.16 in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by National Guideline Centre

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Radioisotope scans

Review question

What is the clinical and cost effectiveness of radioisotope scans for people with suspected thyroid cancer?

Introduction

Some centres perform radioisotope scans to help determine if a lump felt by a Health Care Professional or an abnormal area in the thyroid seen on other imaging such as ultrasound, is likely to be a differentiated thyroid cancer. It is unclear that there is a benefit to this, nor whether there is evidence to show that radioisotope scans are accurate enough to replace other techniques such as repeat ultrasound and fine needle aspiration cytology (FNAC). Without this evidence it is unlikely that such an approach involving ionising radiation would be justified under the 2017 Ionising Radiation (Medical Exposures) Regulations (IRMER) (https://www.legislation.gov.uk/uksi/2017/1322/contents/made). This review seeks to establish the clinical and cost effectiveness of radioisotope scans in the diagnosis of thyroid cancer.

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 who are suspected of having thyroid cancer
Interventions	Radioisotope scans (except PET scans). We will combine all scans into a single intervention and not compare between sub-types. Sub-types will include: • Iodine 131 (by far the most common). And also possibly: • Radioiodine, I-123 Iodine 123 • I-124 Iodine-124 • Thallium-201, Tl201 • Tc-99m MIBI, MIBI, sestaMIBI • Tc-99m Tetrafosmin • In-111 octreotide, octreotide indium octreotide • Tc-99m octreotate, Tc-99m HYNICtate • Ga-68 DOTATATE • Tc-99m depreotide • Tc-99m DMSA(V) pentavalent DMSA
Comparisons	Usual care (not performing radioisotope scans but performing all other tests and imaging (i.e. ultrasound) as normal)
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: mortality • quality of life (any validated scores) • local cancer progression • incidence of distant metastases • cancer recurrence • delayed management • unnecessary further investigations

	• radiation-related adverse events (combined) • change in patient management
Study design	• Systematic reviews • RCTs

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.

Effectiveness evidence

Included studies

No relevant studies comparing various radioisotope scans with usual care in people suspected of having thyroid cancer were identified.

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.

Excluded studies

Thirteen studies were identified for full text eligibility assessment. Of these, 3 were narrative reviews and 4 were systematic reviews. References were checked for potential inclusion however none were RCTs. The remaining 6 were excluded due to incorrect study design as 5 were non-randomised studies, and one was an expert opinion review.

See the excluded studies list in Appendix I.

Summary of studies included in the effectiveness evidence

No evidence was identified.

Summary of the effectiveness evidence

No evidence was identified.

Economic evidence

Included studies

One health economic study with the relevant comparison was included in this review.[14] This is summarised in the health economic evidence profile below (see section 0) and the health economic evidence table in Appendix H.

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.

Summary of included economic evidence

Table 2: Health economic evidence profile: Radioisotope scans

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
Wale 2014 [14] ([UK])	Partially applicable [(a)]	Potentially serious limitations [(b)]	• Decision tree based on a chart review • Cost-effectiveness analysis (Life expectancy) • Population: Adults with palpable nodules and inadequate or benign FNAC (Thy1 and Thy2) • Comparators: 1. Repeat FNA as per BTA guidelines 2. MIBI thyroid scintigraphy combined with FNA • Follow-up: Lifetime	-£590 [(c)]	Life expectancy: 0.1 years	Repeat FNA + MIBI thyroid scintigraphy is dominant	Probability MIBI thyroid scintigraphy cost effective (£20/30k threshold): NA Uncertainty: The model was most sensitive to the prevalence of malignancy; at a prevalence of ≥16% FNA/MIBI was not cost-effective.

Abbreviations: BTA = British Thyroid Association; ICER = incremental cost-effectiveness ratio; NA = not applicable; NR = not reported; QALYs= quality-adjusted life years.

(a) Discounting was not reported for a model with a lifetime horizon. The model refers to the old BTA guidelines where Thy2 were required to re-do a FNAC in 3-6 months; The most recent guidelines and current practice require a re-do test only if there are clinical concerns (EU TIRADS>4).

(b) Model did not account for clinical experience and preparatory investigations influence selection of thyroid nodules for FNA. Meta-analysing diagnostic accuracy requires an assumption that the diagnostic threshold is the same in each study, which is rarely the case due to variation in patient selection and changing technology over time. Assuming similar sensitivity and specificity of repeated FNA likely overestimates the performance of FNA. Details regarding resource use values and sources were not reported. Unit costs for comparators was obtained from hospital pricing structures rather than national reference costs. Cost year was not reported and was assumed to be the year prior to publication for purpose of inflating cost to present day. Incremental analysis can be calculated from the results.

(c) 2013 UK pounds. Cost components incorporated: FNA, MIBI scan, thyroidectomy of suspicious nodules.

Economic model

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

Unit costs

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

Resource	Unit costs	Source
(Sestamibi) Parathyroid Scan	£189	NHS Reference Costs 2016/2017[10]

Economic evidence statements

One cost-effectiveness analysis found that FNAC combined with MIBI dominates repeat FNAC in people with inadequate (Thy1) or benign (Thy2) cytology. The study was assessed partially applicable with potentially serious limitations.

The committee's discussion and interpretation of the evidence

The outcomes that matter most

Protocol-specified outcomes of mortality, quality of life, local cancer progression, incidence of distant metastases, cancer recurrence, delayed management, unnecessary further investigations, radiation-related adverse events and change in patient management were all deemed critical and were therefore of equal importance in decision-making.

The quality of the evidence

No evidence was found for this question, and so recommendations were made on the basis of consensus.

Benefits and harms

In the absence of evidence from the review, the committee agreed to form a recommendation by consensus. The committee initially described current practice, stating that radioisotope (Tc-99m pertenetate with or without TC-99m MIBI) scans are not widely used in the UK for the diagnosis of thyroid cancer, although some centres do still use them. Individual committee members described how they had made very little use of this modality, with one estimate being as low as two occasions over the previous ten years. Based on their knowledge of the literature on the risks of radiation exposure, the committee agreed that the potential harms of radioisotope scans to patients exceeded any benefits. Drawing on their clinical experience, the committee also agreed that radioisotope scans were no more accurate than FNAC, and that therefore the benefits would normally be unable to exceed the harms. This led to the recommendation that radioisotope scans should not normally be considered.

The committee were clear that they did not have enough hard evidence to make a clear statement that people should *never* use radioisotope scans. Therefore, they recommended that they should not routinely be used. It was agreed that there might be certain very rare and specific situations where it might be beneficial to use radioisotope scanning, although the committee did not elaborate on examples. This was because any such examples would be extremely context-dependent and there was an awareness that because descriptions of these examples could never encompass the full complexity of such decision-making, such examples might be misconstrued as a 'green light' to use radioisotope scanning in conditions merely approximate to the actual conditions in which it might properly be used. The committee were also aware of the Ionising Radiation (Medical Exposure) Regulations 2017 that require radiation exposure to be kept to a minimum. Without evidence of benefit the

committee agreed that the potential for harm justified not routinely recommending radioisotope scans.

Cost effectiveness and resource use

One health economics study was included for question 1.3. This was a cost effectiveness analysis comparing Tc-99m MIBI scintigraphy with repeat FNAC for people with inadequate (Thy1) or benign (Thy2) cytology on a fine-needle aspiration (FNA) test.

The study was assessed to be partially applicable as it compared a mixed MIBI/FNAC strategy with repeat FNAC after 3-6 months for people with benign cytology (Thy2) as recommended by the old BTA guidelines, which does not reflect NHS current practice anymore as further investigation with FNAC after benign or inadequate cytology is usually only done for people with suspected thyroid cancer where there is clinical concern. The study had potentially serious methodological limitations as it did not account for costs and consequences of surgery complications, RAI and monitoring, did not report a discounting rate, used a meta-analysis with different diagnostic thresholds, assumed similar sensitivity and specificity of repeat FNAC which likely overestimates the performance of FNAC, did not report resource use and took unit costs from a single hospital not reflecting national reference costs. The analysis found MIBI scintigraphy to dominate BTA guidelines as it was associated with a lower cost and a longer life expectancy. The sensitivity analysis found the results to be very sensitive to the cancer prevalence assumed as when the prevalence increases above 16%, MIBI/FNA was not cost effective anymore. This suggest that this strategy may potentially be cost effective only for people with a FNAC Thy1 or Thy2. The cost of a radioisotope scan is taken as similar to the HRG for “Parathyroid Scan” of the NHS Reference Costs which ranges between £189 and £369 depending on the version. The committee stated that the cost of a MIBI scintigraphy has recently reduced due to technological improvements suggesting that the real cost should be around or below the lower estimation provided. Moreover, the committee were aware that the use of a MIBI scintigraphy has sharply reduced following the publications of more precise guidelines regarding the management of people receiving FNAC.

The clinical and economic evidence provided was considered insufficient to support the recommendation of radioisotope scans which are currently seen as an old practice by most of the committee. Moreover, there is concern that exposing people to radiation for a test not clinically or superior to FNAC could actually represent a health hazard in the long term. Therefore, the committee decided to make a recommendation stating that there is no evidence to justify the routine use of radioisotope scan. This represents current practice where radioisotope scans are rarely used only when there are additional concerns and therefore should not lead to an increase of the use of NHS resources.

Other factors the committee took into account

A research recommendation was not carried out because the committee felt that to do so would suggest the committee thought the issue of radioisotope scanning was still viable, and the committee were strongly of the opinion that it wasn’t.

The committee agreed that while radioisotope scans should not routinely be used for the diagnosis of thyroid cancer, there may be value in their when assessing recurrent thyroid cancer. Diagnosis for recurrent thyroid cancer was not part of this review question.

Recommendations supported by this evidence review

This evidence review supports recommendation 1.2.16.

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Appendices

Appendix A – Review protocols

A.1 Review protocol for Radioisotope scans

Field	Content
PROSPERO registration number	CRD42021264298
Review title	The clinical and cost effectiveness of radioisotope scans for people with suspected thyroid cancer?
Review question	What is the clinical and cost effectiveness of radioisotope scans for people with suspected thyroid cancer?
Objective	To establish the efficacy and cost-effectiveness of radioisotope scans in the diagnosis of 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 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 are suspected of having thyroid cancer Exclusion: Children under 16
Intervention/Exposure/Test	Radioisotope scans (except PET scans). We will combine all scans into a single intervention and not compare between sub-types.

	Sub-types will include: Iodine 131 (by far the most common). And also possibly: • Radioiodine, I-123 Iodine 123 • I-124 Iodine-124 • Thallium-201, Tl201 • Tc-99m MIBI, MIBI, sestaMIBI • Tc-99m Tetrafosmin • In-111 octreotide, octreotide indium octreotide • Tc-99m octreotate, Tc-99m HYNICtate • Ga-68 DOTATATE • Tc-99m depreotide • Tc-99m DMSA(V) pentavalent DMSA
Comparator/Reference standard/Confounding factors	Usual care (not performing radioisotope scans but performing all other tests and imaging (i.e. ultrasound) as normal)
Types of study to be included	• Systematic reviews • RCTs Non-randomised studies will be excluded. In such 'test and treat' studies randomisation is essential because the scope for confounding when non-randomised will be exaggerated by the fact that the treatments subsequent to the different diagnostic strategies being tested could differ. The differences in treatment may be non-overlapping (for example in a historical cohort study where completely different treatment approaches may have been used across groups) that statistical adjustment for such confounding will not be possible.

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	Radioisotope scans aim to detect remaining thyroid cancer cells, usually after surgery and radio ablation. The scan is usually done as an outpatient procedure. Radioactive iodine is introduced into the body, and makes its way to any thyroid cancer cells. The scan, which detects the radioactive iodine that has migrated to any cancerous cells, is undertaken one hour later (if iodine injected) or several hours or days later (if iodine taken by mouth). There is some controversy about the use of such scans, with the possibility that they may cause more harm than good for patients. This question is designed to identify the benefits and harms so that an appropriate recommendation can be made.
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 (any validated scores) • local cancer progression • incidence of distant metastases • cancer recurrence • delayed management • unnecessary further investigations

	• radiation-related adverse events (combined) • change in patient management Time of follow up: longest available
Secondary outcomes (important outcomes)	Not applicable
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. 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). 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)
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. 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: none Subgroups that will be investigated if heterogeneity is present: If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: • Presence of multinodular goitre (Y/N)
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 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?ID=CRD42021264298
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	Atrial Fibrillation, statins
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).[9] **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.

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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 clinical and cost effectiveness of radioisotope scans for people with suspected thyroid cancer?

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 3: 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 Exclusions (animal studies, letters, comments, editorials, case studies/reports, children) English language
Embase (OVID)	1974 – 13 January 2022	Randomised controlled trials Systematic review 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 Cochrane Central Register of Controlled Trials to Issue 12 of 12, December 2021	Exclusions (clinical trials, conference abstracts)

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.	Radionuclide Imaging/
29.	Lymphoscintigraphy/
30.	Perfusion imaging/
31.	Radioimmunodetection/
32.	((radionuclide* or radio nuclide* or gamma or radioisotope* or radioiodi?e* or radio iodi?e* or isotope* or perfusion) adj3 (scan* or scinti* or imag* or tracer* or tracing)).ti,ab.
33.	(lymphoscinti* or radioimmunodetect* or radioimmunoimag* or radioimmunoscinti* or radiolabel* immunoscinti*).ti,ab.
34.	exp Iodine Isotopes/
35.	Radioisotopes/
36.	Iodine Radioisotopes/
37.	(iodi?e adj2 (radioisotope* or isotope*)).ti,ab.
38.	(iodi?e 131 or 131-I or I-131).ti,ab.
39.	or/28-38
40.	27 and 39
41.	randomized controlled trial.pt.
42.	controlled clinical trial.pt.
43.	randomi#ed.ab.

44.	placebo.ab.
45.	randomly.ab.
46.	clinical trials as topic.sh.
47.	trial.ti.
48.	or/41-47
49.	Meta-Analysis/
50.	Meta-Analysis as Topic/
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.	40 and (48 or 59)

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.	*scintiscanning/ or *scintigraphy/ or *gamma scintigraphy/ or *scintiangiography/ or scintiscanning/ or *thyroid scintiscanning/
28.	*lymphoscintigraphy/
29.	((radionuclide* or radio nuclide* or gamma or radioisotope* or radioiodi?e* or radio iodi?e* or isotope* or perfusion) adj3 (scan* or scinti* or imag* or tracer* or tracing)).ti,ab.
30.	(lymphoscinti* or radioimmunodetect* or radioimmunoimag* or radioimmunoscinti* or radiolabel* immunoscinti*).ti,ab.
31.	*radioisotope/
32.	*iodine 123/ or *iodine 124/ or *iodine 125/ or *iodine 129/ or *iodine 131/
33.	(iodi?e adj2 (radioisotope* or isotope*)).ti,ab.
34.	(iodi?e 131 or 131-I or I-131).ti,ab.
35.	or/27-34
36.	26 and 35
37.	random*.ti,ab.
38.	factorial*.ti,ab.
39.	(crossover* or cross over*).ti,ab.
40.	((doubl* or singl*) adj blind*).ti,ab.
41.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
42.	crossover procedure/
43.	single blind procedure/
44.	randomized controlled trial/
45.	double blind procedure/
46.	or/37-45
47.	systematic review/
48.	Meta-Analysis/
49.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
50.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
51.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
52.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
53.	(search* adj4 literature).ab.
54.	(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.
55.	cochrane.jw.
56.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
57.	or/47-56
58.	36 and (46 or 57)

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: [Radionuclide Imaging] this term only
#9.	MeSH descriptor: [Lymphoscintigraphy] this term only
#10.	MeSH descriptor: [Perfusion Imaging] this term only
#11.	MeSH descriptor: [Radioimmunodetection] this term only
#12.	((radionuclide* or radio nuclide* or gamma or radioisotope* or radioiodi?e* or radio iodi?e* or isotope* or perfusion) near/3 (scan* or scinti* or imag* or tracer* or tracing)):ti,ab
#13.	(lymphoscinti* or radioimmunodetect* or radioimmunoimag* or radioimmunoscinti* or radiolabel* immunoscinti*):ti,ab
#14.	MeSH descriptor: [Iodine Isotopes] explode all trees
#15.	MeSH descriptor: [Radioisotopes] this term only
#16.	MeSH descriptor: [Iodine Radioisotopes] this term only
#17.	(iodi?e near/2 (radioisotope* or isotope*)):ti,ab
#18.	(or #8-#17)
#19.	#7 and #18

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

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

NHS EED and HTA (CRD) search terms

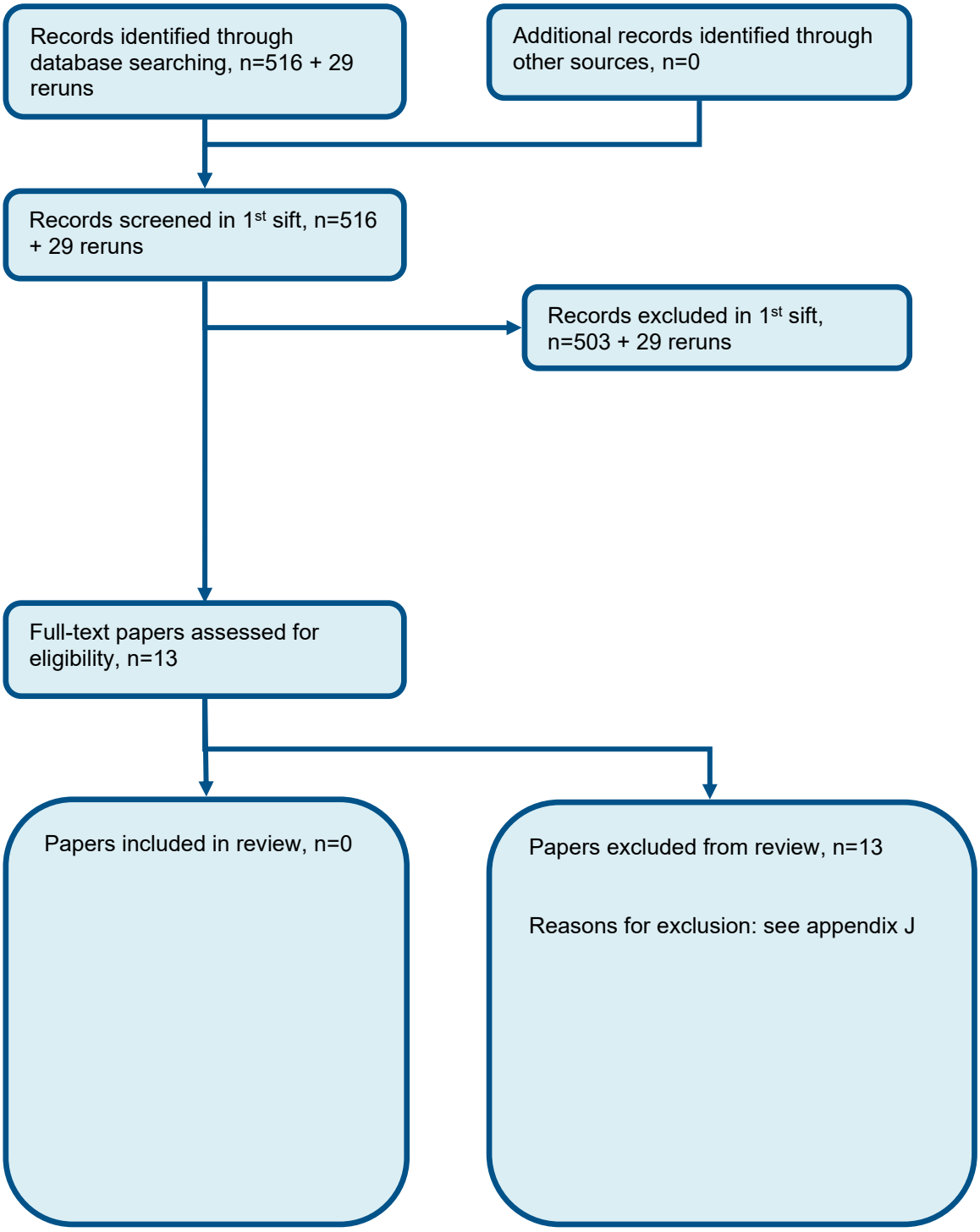
#1.	MeSH DESCRIPTOR Thyroid Neoplasms EXPLODE ALL TREES
#2.	((thyroid NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)))
#3.	(((papillar* or follicul* or medullary or anaplastic)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



Appendix D –Effectiveness evidence

No evidence was identified.

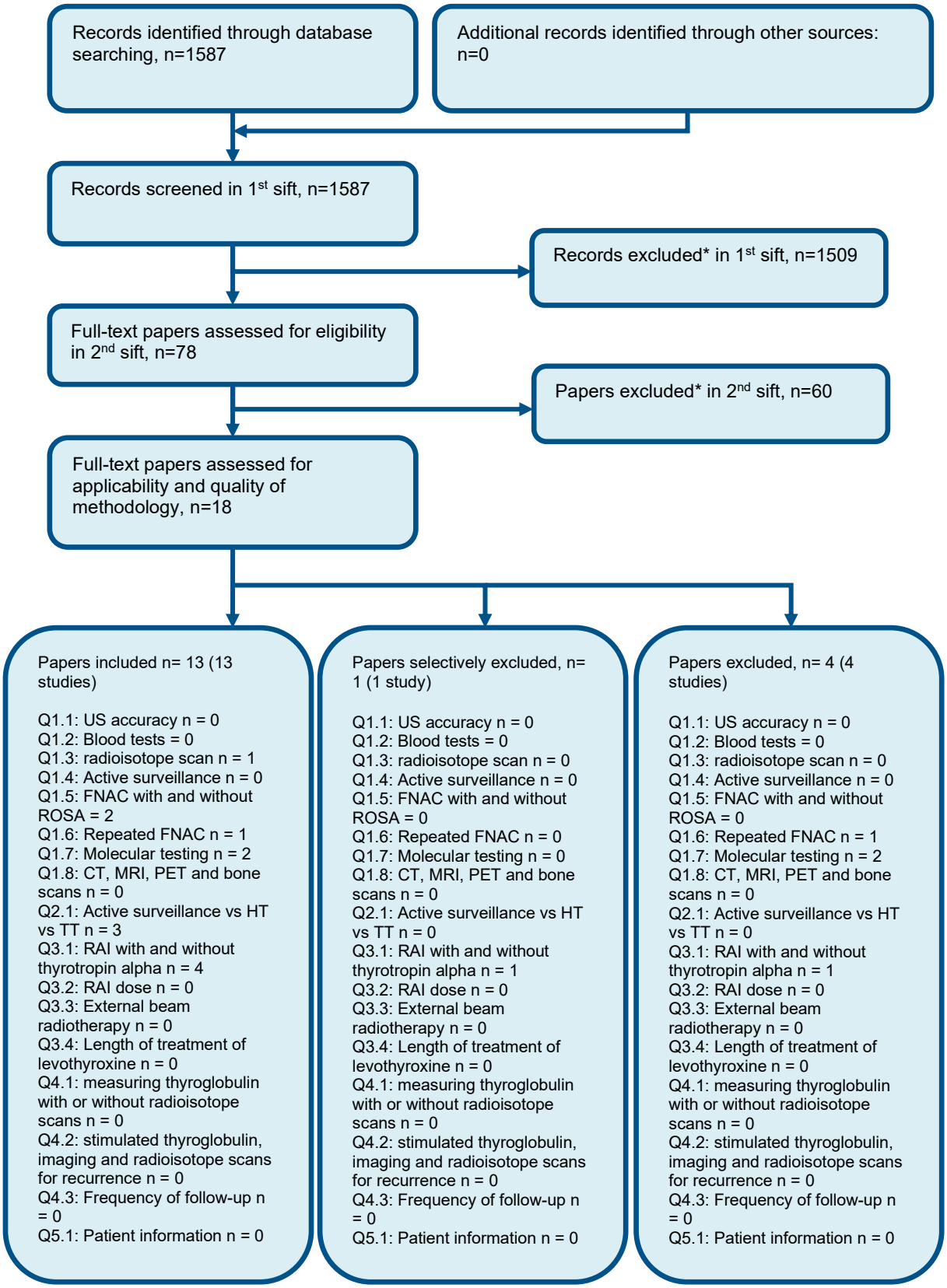
Appendix E – Forest plots

No evidence was identified.

Appendix F – GRADE tables

No evidence was identified.

Appendix G – Economic evidence study selection



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

Appendix H – Economic evidence tables

Study	Wale 2014 [14]			
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome: Life years) **Study design:** Decision tree based on retrospective chart review **Approach to analysis:** Each test resulted in a diagnosis of likely or definitely neoplastic followed by thyroidectomy, nonneoplastic followed by discharge, or nondiagnostic followed by consideration of thyroidectomy. **Perspective:** UK NHS **Time horizon:** Lifetime **Discounting:** Costs: NR Outcomes: NR	**Population:** Adults with palpable nodules and inadequate or benign FNAC (Thy1 and Thy2) **Cohort settings:** Median age: NR Male: NR **Intervention 1:** Repeat FNA (BTA guidelines) **Intervention 2:** FNA/MIBI scintigraphy	**Total costs (mean per patient):** Intervention 1: £2,445 Intervention 2: £1,855 Incremental (2−1): -£590 (95% CI: NR; p=NR) **Currency & cost year:** 2013 UK pounds **Cost components incorporated:** FNA, MIBI scan, thyroidectomy of suspicious nodules	**Life expectancy (mean per patient):** Intervention 1: 34.45 years Intervention 2: 34.46 years Incremental (2−1): 0.01 years (95% CI: NR; p=NR) **Proportion of nodules accurately diagnosed:** Intervention 1: 37.8% Intervention 2: 62.9% **Proportion of cancers detected:** Intervention 1: 99.0% Intervention 2: 97.5%	**ICER (Intervention 2 versus Intervention 1):** Dominant 95% CI: NR Probability that MIBI thyroid scintigraphy was cost effective (£20k/30k threshold): NR The FNA/MIBI strategy was less costly and more accurate but detected fewer cancers. **Analysis of uncertainty:** The model was most sensitive to the prevalence of malignancy; at a prevalence of ≥16% FNA/MIBI was not cost-effective.
Data sources				

Health outcomes: The diagnostic accuracy of MIBI and baseline prevalence of malignancy was obtained from a literature review and meta-analysis conducted for this study. Diagnostic accuracy of FNA was obtained from an audit of records from patients attending the multidisciplinary thyroid clinic. Histological data were used as the gold standard assessment. Sensitivity and specificity of FNA was assumed to be the same when used as the first-line investigation, after MIBI scintigraphy, and when used on Thy1 samples. Inadequate fraction was estimated as double the baseline for repeat FNA based on a study by Nguyen 2005. Mortality from hemithyroidectomy was modelled based on postoperative haematomas based on Shrime 2007. Baseline life expectancy was based on people with diagnosed thyroid cancer, benign thyroid lesions and undiagnosed thyroid cancer obtained from Links 2005. **Quality-of-life weights:** NA **Cost sources:** Unit costs of MIBI scintigraphy and FNA cytology were estimated from pricing structures at the hospital. The cost of thyroidectomy was obtained from the Healthcare Resource Groups version 3.5 National Health Service Casemix service.
Comments
Source of funding: This study was partially sponsored by Bristol-Myers Squibb. Other partial funders were not reported. **Limitations:** Discounting was not reported for a model with a lifetime horizon. The model refers to the old BTA guidelines where Thy2 were required to re-do a FNAC in 3-6 months; The most recent guidelines and current practice require a re-do test only if there are clinical concerns (EU TIRADS>4). Model did not account for clinical experience and preparatory investigations influence selection of thyroid nodules for FNA. Meta-analysing diagnostic accuracy requires an assumption that the diagnostic threshold is the same in each study, which is rarely the case due to variation in patient selection and changing technology over time. Assuming similar sensitivity and specificity of repeated FNA likely overestimates the performance of FNA. Details regarding resource use values and sources were not reported. Unit costs for comparators was obtained from hospital pricing structures rather than national reference costs. Cost year was not reported and was assumed to be the year prior to publication for purpose of inflating cost to present day. **Other:** None
Overall applicability:[a] Partially applicable **Overall quality:**[b] Potentially serious limitations

Abbreviations: 95% CI= 95% confidence interval; BTA = British Thyroid Association; da= deterministic analysis; FNA = fine needle aspiration; ICER= incremental cost-effectiveness ratio; MIBI = ^{99m}Tc-methoxyisobutylisonitrile; NA = not applicable; NPV: negative predictive value; NR= not reported; pa= probabilistic analysis; PPV: positive predictive value; QALYs= quality-adjusted life years.

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Appendix I – Excluded studies

I.1 Clinical studies

Table 4: Studies excluded from the clinical review

Study	Exclusion reason
Cox 1991[1]	Incorrect study design (non-randomised study)
Freesmeyer 2019[2]	Incorrect study design (non-randomised study)
Fu 2021[3]	Incorrect study design (narrative review, references have been checked)
Giovanella 2014[4]	Incorrect study design (narrative review, references have been checked)
Hurtado-lopez 2004[5]	Incorrect study design (non-randomised study)
Iwata 2004[6]	Incorrect study design (non-randomised study)
Kalinyak 2004[7]	Incorrect study design (narrative review, references have been checked)
Kim 2018[8]	Systematic review: study designs inappropriate
Torizuka 1993[11]	Incorrect study design (non-randomised study)
Treglia 2013[12]	Systematic review: study designs inappropriate
Urhan 2009[13]	Incorrect study design (expert opinion, references have been checked)
Wong 2016[15]	Systematic review: study designs inappropriate
Wu 2019[16]	Systematic review: study designs inappropriate

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.

None.