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National Institute for Health and Care Excellence

Draft

Thyroid cancer

[G] Evidence review for imaging for further staging

NICE guideline <number>

Evidence reviews underpinning recommendations 1.2.17 to 1.2.19 and the research recommendation in the NICE guideline

June 2022

Draft for Consultation

These evidence reviews were developed by NGC

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1 Imaging

1.1 Review question

In people with differentiated thyroid cancer at different initial disease stages (based on prior investigations), what is the clinical and cost-effectiveness of further refinement of staging by CT (with or without contrast), MRI, PET or bone scan?

1.1.1 Introduction

Imaging of tumours following their diagnosis can help determine the extent of thyroid cancer. Should the tumor have invaded local structures, spread to the trachea or voice box or metastasised to the lungs then it can lead to a worse prognosis for the person and could mean a different pathway or more treatment. This review seeks to determine the clinical and cost effectiveness of different imaging modalities (in terms of improving subsequent health outcomes) when they are used as a further staging tool. Very importantly, because it is believed that the efficacy of different imaging modalities depends on patient characteristics, this review will determine the relative efficacy of the different imaging modalities in each of several different patient groups defined by their initial diagnostic findings. This will help to inform clinicians which modalities are most suited to each of these patient groups; in this way, the indications (in terms of patient's initial diagnostic characteristics) for the modalities will become apparent.

1.1.2 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 with a diagnosis of thyroid cancer Exclusion: Children under 16
Intervention	• CT • MRI • PET • Bone scans These may be in head or neck or cover a larger region or whole body (see sub-grouping strategy)
Comparison	To each other, alone and in combination No imaging / US alone / usual care
Outcomes	• mortality • quality of life • progression of disease (not including imaging findings) • adverse effects Time of follow up: longest available in papers
Study design	RCTs, or SRs of RCTs

1.1.3 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.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

We searched for RCTs, comparing the different imaging modalities in people with differentiated thyroid cancer after thyroidectomy and RAI treatment, but no RCTs were found. Therefore, no studies have been included for this review.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.7 Economic evidence

1.1.7.1 Included studies

No health economic studies were included.

1.1.7.2 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.

1.1.8 Summary of included economic evidence

None.

1.1.9 Economic model

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

1.1.10 Unit costs

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

Resource	Unit costs	Source
Outpatient Computerised Tomography Scan of One Area		
Without Contrast	£91	NHS Reference Costs 2019-2020[12]
With Post-Contrast Only	£138	NHS Reference Costs 2019-2020[12]
With Pre- and Post-Contrast	£185	NHS Reference Costs 2019-2020[12]
Outpatient Magnetic Resonance Imagining Scan of One Area		
Without Contrast	£146	NHS Reference Costs 2019-2020[12]
With Post-Contrast Only	£180	NHS Reference Costs 2019-2020[12]
With Pre- and Post-Contrast	£307	NHS Reference Costs 2019-2020[12]
Positive Emission Tomography		
Outpatient	£568	NHS Reference Costs 2019-2020[12]

1.1.11 Economic evidence statements

No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

The outcomes that matter most

The outcomes considered for this review were mortality, health related quality of life, progression of disease and adverse effects. For purposes of decision-making all outcomes were equally regarded as being of critical importance. No evidence was identified for any of these outcomes as no relevant articles were included in the review.

The quality of the evidence

No evidence was included in the review.

Benefits and harms

In the absence of evidence, the committee used consensus to form recommendations. The committee were mindful that the key aim of this review question was not merely to decide on the optimal imaging modality for later staging overall, but to evaluate how the performance of the modalities varied across different categories of patients, as defined by their different initial disease stages. In this way, the indications for the different modalities would become apparent.

The committee agreed that for patients with T1 disease and no other indications (this would include people without signs of metastases or suspicious symptoms such as a cough), that the initial ultrasound should be the main form of imaging used to inform further staging and no further investigations were required. This decision was based upon the agreement that

ultrasound would be sufficiently sensitive to pick up the relatively superficial structural lesions that might occur in the vast majority of this stratum. For this group, there were harms of deeper imaging modalities that might not be offset by any advantages. For example, CT carries radiation risks, particularly to younger patients, and MRI can be traumatic for some patients.

However, for people at stage T2 with high risk features, the committee agreed that imaging capable of surveying at greater depth should be considered because spread may be more extensive. Therefore, the benefits for these patients would overcome the harms. Hence cross-sectional imaging modalities such as CT or MRI should be considered as it will help with surgical planning. Thyroid cancer most commonly spreads to the neck and chest and therefore imaging was restricted to these areas. The committee agreed that age and sex should be included in the decision-making process, as greater age and male sex have been shown to increase the risk of spread and recurrence. For patients at even higher levels of risk, such as those at stage T3/4 or those with any local spread to nodes or distant metastases, then cross-sectional imaging modalities should also be considered.

CT and MRI were the chosen as they are more commonly used for staging in the UK than other techniques. Additionally, PET scanning is more expensive and not widely available in the UK.

The committee were careful to stress that imaging could be used either before or after any surgery. The need to stage and thus inform treatment decisions was important at all points along the pathway, both to inform surgical decisions, but also to inform decisions post-surgery. However the committee stressed that clinicians should be mindful of the impact of intravenous CT contrast on any subsequent RAI treatments. This was believed to be particularly pertinent in relation to the relatively marginal imaging gains for the patient in terms of additional staging versus the impact of potential RAI delays.

Cost effectiveness and resource use

No heath economic study was included in this question review.

In the absence of published evidence, the committee were presented with the unit cost of CT MRI and PET scan. As the committee were expecting, PET is the most expensive scan followed by MRI and CT. The committee made a recommendation reflecting current practice recommending no further imaging testing to people with low-risk cancer T1, while recommending cross sectional imaging tests for people with concerning characteristics. This is in line with current practice and should not require any additional resource.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.2.17 to 1.2.19 and the research recommendation on further imaging.

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Appendices

Appendix A – Review protocols

Review protocol for oesophagectomy vs endoscopy

Field	Content
PROSPERO registration number	CRD42021283303
Review title	Indications for imaging using CT scans (with or without contrast), MRI, PET or bone scans for further staging in people diagnosed with differentiated thyroid cancer.
Review question	In people with differentiated thyroid cancer at different initial disease stages (based on prior investigations), what is the clinical and cost-effectiveness of further refinement of staging by CT (with or without contrast), MRI, PET or bone scan?
Objective	To determine the best imaging strategy for patients in different levels of initial staging.
Searches	The following databases 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 submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Thyroid cancer
Population	Inclusion: People aged 16 or over with a diagnosis of thyroid cancer Exclusion: Children under 16

Intervention/Exposure/Test	• CT • MRI • PET • Bone scans These may be in head or neck or cover a larger region or whole body (see sub-grouping strategy)
Comparator/Reference standard/Confounding factors	To each other, alone and in combination No imaging / US alone / usual care
Types of study to be included	• Systematic reviews • RCTs Non-randomised studies will be excluded.
Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	N/A
Primary outcomes (critical outcomes)	• Mortality • Quality of life

	• Progression of disease (not including imaging findings) • Adverse effects Time of follow up: longest available in papers
Secondary outcomes (important outcomes)	N/A
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).

Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
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	<u>Stratification</u> The strata will reflect the main classes of indications. 1. Known staging at the time of investigation (based on US and FNA diagnostic procedures) <u>Sub-grouping</u> If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: • Location of imaging: head and neck vs everywhere else
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?RecordID=283303
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

1 Health economic review protocol

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 for all years 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 2006, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Studies published in 2006 or later, that were included in the previous guidelines, will be reassessed for inclusion and may be included or selectively excluded based on their relevance to the questions covered in this update and whether more applicable evidence is also identified. 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).[11] **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 2006 or later (including any such studies included in the previous guidelines) but that depend on unit costs and resource data entirely or predominantly from before 2006 will be rated as ‘Not applicable’.
- Studies published before 2006 (including any such studies included in the previous guidelines) 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.

1 **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).[10] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included.

Where there is discretion

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

The health economist will be guided by the following hierarchies.

Setting:

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

Health economic study type:

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

Year of analysis:

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

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

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

Appendix B – Literature search strategies

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

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

Clinical literature search strategy

This literature search strategy was used for the following review:

- What are the indications for using CT (with or without contrast), MRI, PET or bone scans for further staging?

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 2: 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	Exclusions (clinical trials, conference abstracts)

Database	Dates searched	Search filters and limits applied
	Issue 12 of 12, December 2021 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.	Tomography/
29.	exp Tomography, Emission-Computed/
30.	exp Tomography, X-Ray/
31.	tomograph*.ti,ab,kf.

32.	tomodensitometry.ti,ab,kf.
33.	Magnetic Resonance Imaging/
34.	(MRI or NMRI).ti,ab,kf.
35.	((magnet* or MR or MTC or MT or NMR or spin or chemical shift or diffus* or perfusion) adj3 (imag* or scan* or resonance* or spectroscop*)).ti,ab,kf.
36.	Radionuclide Imaging/
37.	radionuclide imag*.ti,ab,kf.
38.	radiometry.ti,ab,kf.
39.	(scintigraph* or scintiphotograph* or scintiscan*).ti,ab,kf.
40.	exp Positron-Emission Tomography/
41.	exp Diffusion Magnetic Resonance Imaging/
42.	(Diffusion weighted or DWI).ti,ab,kf.
43.	(CT or MDCT or CAT or PET or PETCT or SPECT).ti,ab,kf.
44.	((bone* or radioisotop* or isotop* or gamma camera) adj3 (scan* or imag*)).ti,ab,kf.
45.	or/28-44
46.	27 and 45
47.	randomized controlled trial.pt.
48.	controlled clinical trial.pt.
49.	randomi#ed.ab.
50.	placebo.ab.
51.	randomly.ab.
52.	clinical trials as topic.sh.
53.	trial.ti.
54.	or/47-53
55.	Meta-Analysis/
56.	Meta-Analysis as Topic/
57.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
58.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
59.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
60.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
61.	(search* adj4 literature).ab.
62.	(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.
63.	cochrane.jw.
64.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
65.	or/55-64
66.	46 and (54 or 65)

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.	*tomography/
28.	exp *computer assisted tomography/ or exp *emission tomography/
29.	exp *whole body tomography/ or exp *x-ray tomography/
30.	tomograph*.ti,ab,kf.
31.	tomodensitometry.ti,ab,kf.
32.	*nuclear magnetic resonance imaging/ or *nuclear magnetic resonance/ or *functional magnetic resonance imaging/ or *interventional magnetic resonance imaging/ or *multiparametric magnetic resonance imaging/ or *perfusion weighted imaging/ or *whole body mri/
33.	(MRI or NMRI).ti,ab,kf.
34.	((magnet* or MR or MTC or MT or NMR or spin or chemical shift or diffus* or perfusion) adj3 (imag* or scan* or resonance* or spectroscop*)).ti,ab,kf.
35.	*radionuclide Imaging/
36.	radionuclide imag*.ti,ab,kf.
37.	radiometry.ti,ab,kf.
38.	*scintiscanning/ or exp *bone scintiscanning/ or exp *scintigraphy/ or *thyroid scintiscanning/ or *tumor scintiscanning/ or *whole body scintiscanning/
39.	(scintigraph* or scintiphotograph* or scintiscan*).ti,ab,kf.
40.	*positron emission tomography/ or *computer assisted emission tomography/ or *positron emission tomography-computed tomography/ or *whole body pet/
41.	*diffusion weighted imaging/
42.	(Diffusion weighted or DWI).ti,ab,kf.
43.	(CT or MDCT or CAT or PET or PETCT or SPECT).ti,ab,kf.
44.	((bone* or radioisotop* or isotop* or gamma camera) adj3 (scan* or imag*)).ti,ab,kf.
45.	or/27-44

46.	26 and 45
47.	random*.ti,ab.
48.	factorial*.ti,ab.
49.	(crossover* or cross over*).ti,ab.
50.	((doubl* or singl*) adj blind*).ti,ab.
51.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
52.	crossover procedure/
53.	single blind procedure/
54.	randomized controlled trial/
55.	double blind procedure/
56.	or/47-55
57.	systematic review/
58.	Meta-Analysis/
59.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
60.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
61.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
62.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
63.	(search* adj4 literature).ab.
64.	(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.
65.	cochrane.jw.
66.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
67.	or/57-66
68.	46 and (56 or 67)

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: [Tomography] this term only
#9.	MeSH descriptor: [Tomography, Emission-Computed] explode all trees
#10.	MeSH descriptor: [Tomography, X-Ray] explode all trees
#11.	tomograph*:ti,ab
#12.	tomodensitometry:ti,ab
#13.	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees
#14.	(MRI or NMRI):ti,ab
#15.	((magnet* or MR or MTC or MT or NMR or spin or chemical shift or diffus* or perfusion) near/3 (imag* or scan* or resonance* or spectroscop*)):ti,ab
#16.	MeSH descriptor: [Radionuclide Imaging] explode all trees

#17.	radionuclide imag*:ti,ab
#18.	radiometry:ti,ab
#19.	(scintigraph* or scintiphotograph* or scintiscan*):ti,ab
#20.	MeSH descriptor: [Positron-Emission Tomography] explode all trees
#21.	MeSH descriptor: [Diffusion Magnetic Resonance Imaging] explode all trees
#22.	(diffusion weighted or DWI):ti,ab
#23.	(CT or MDCT or CAT or PET or PETCT or SPECT):ti,ab
#24.	((bone* or radioisotop* or isotop* or gamma camera) near/3 (scan* or imag*)):ti,ab
#25.	(or #8-#24)
#26.	#7 and #25

Epistemonikos search terms

1.	(title:((title:(thyroid) OR abstract:(thyroid)) AND (title:(cancer* OR neoplasm* OR nodule* OR carcinoma*) OR abstract:(cancer* OR neoplasm* OR nodule* OR carcinoma*)) AND (title:(tomograph* OR tomodensitometry OR resonance imag* OR MRI OR NMRI OR Radionuclide Imag* OR radiometry OR scintigraph* OR scintiphotograph* OR scintiscan* OR DWI OR PET OR bone* scan*) OR abstract:(tomograph* OR tomodensitometry OR resonance imag* OR MRI OR NMRI OR Radionuclide Imag* OR radiometry OR scintigraph* OR scintiphotograph* OR scintiscan* OR DWI OR PET OR bone* scan*))) OR abstract:((title:(thyroid) OR abstract:(thyroid)) AND (title:(cancer* OR neoplasm* OR nodule* OR carcinoma*) OR abstract:(cancer* OR neoplasm* OR nodule* OR carcinoma*)) AND (title:(tomograph* OR tomodensitometry OR resonance imag* OR MRI OR NMRI OR Radionuclide Imag* OR radiometry OR scintigraph* OR scintiphotograph* OR scintiscan* OR DWI OR PET OR bone* scan*) OR abstract:(tomograph* OR tomodensitometry OR resonance imag* OR MRI OR NMRI OR Radionuclide Imag* OR radiometry OR scintigraph* OR scintiphotograph* OR scintiscan* OR DWI OR PET OR bone* scan*))))

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

Database	Dates searched	Search filters and limits applied
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
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

2 **INHATA search terms**

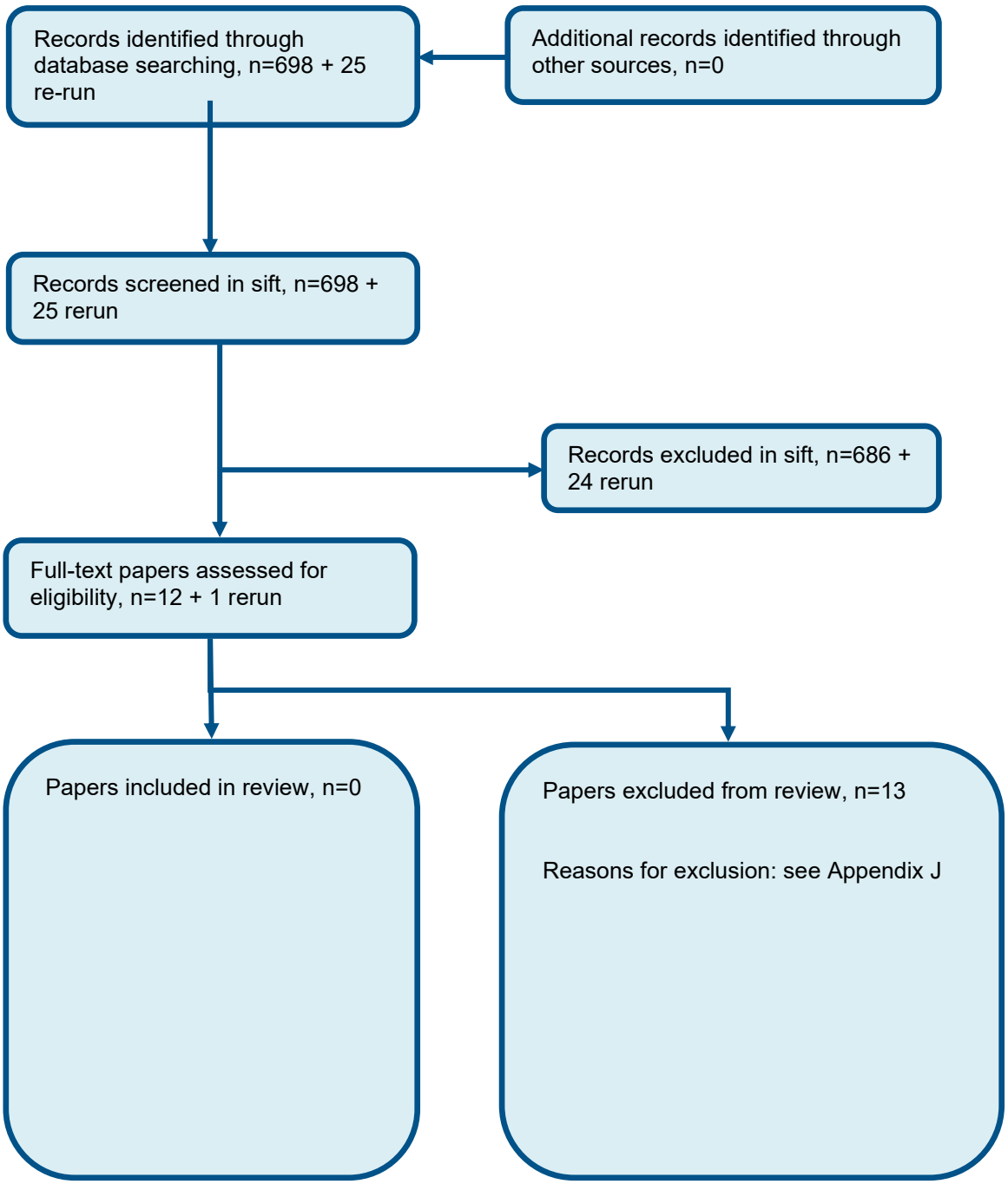
1.	(Thyroid Neoplasms)[mh] OR (thyroid neoplasms) AND (thyroid cancers)

3

4

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of surveillance versus no surveillance



Appendix D – Effectiveness evidence

No evidence found

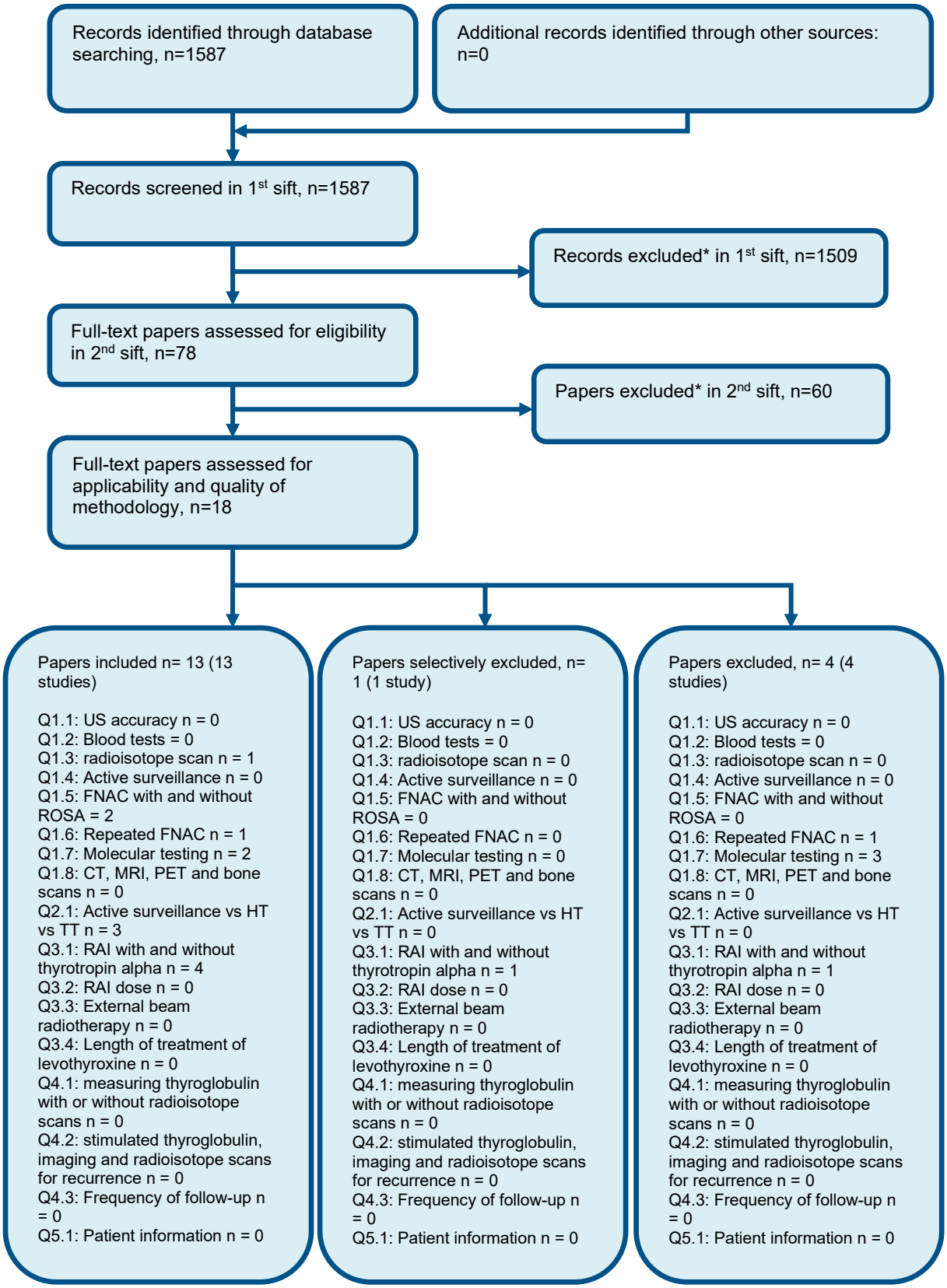
Appendix E – Forest plots

No evidence found

Appendix F – GRADE tables

No evidence found

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

Clinical studies

Table 3: Studies excluded from the clinical review

Study	Reason for exclusion
A, 2004[1]	Review - non systematic. No references found by cross-referencing
Avram, 2013[2]	non randomised; no relevant outcomes
Binse, 2016[3]	non randomised; no relevant outcomes
Bulzacka, 2020[4]	non randomised; no relevant outcomes; wrong population
Capoccetti, 2009[5]	non-randomised study
De Koster, 2022[6]	Population were not diagnosed with thyroid cancer – the purpose of the imaging was diagnosis, not further staging.
Freesmeyer, 2019[7]	non randomised; incorrect interventions
Gabriel, 2004[8]	non randomised; no relevant outcomes
Iwata, 2004[9]	non randomised; no relevant outcomes
Sakurai, 2013[13]	non randomised; no relevant outcomes
Wei, 2018[14]	non randomised; no relevant outcomes
Yeom, 2019[15]	Randomised study but wrong comparators: compared CT with reduced contrast material to standard CT; no relevant outcomes
Zampella, 2021[16]	Review - non systematic. No references found by cross-referencing

Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2006 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.

Appendix J Research recommendations – full details

J.1.1 Research recommendation

For people diagnosed with differentiated thyroid cancer who have initial ultrasound evidence of extensive local spread (T2N1), what is the clinical and cost effectiveness of CT, MRI or PET scanning, with or without US, as part of a further staging strategy?

J.1.2 Why this is important

After a patient has been diagnosed with differentiated thyroid cancer, there is a need to evaluate how best to treat the patient. The treatment will depend on the staging of the disease, and this may be best evaluated by further imaging strategies. However, there may not be a further imaging strategy that works best for all. It is thought that the optimal imaging strategy may depend on the characteristics manifested early on, during initial US evaluation. For example, for people who show superficial spread on initial US, the optimal imaging may be further ultrasound, as this will avoid the harms associated with CT, and the expense associated with MRI. However, for patients where initial US shows more extensive spread, the optimal imaging will probably need to be one that evaluates tissue deeper than US, though it may also benefit from having US as part of the strategy. Importantly, the benefits of evaluating deeper tissues in such patients will exceed the potential harms. Importantly, there are currently no randomised controlled trials comparing clinical outcomes when different imaging strategies are used in people with more extensive local spread, and there is therefore a clear need for this.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	This research question may allow the development of imaging strategies that can be targeted to specific groups of patients, helping to ensure that staging is performed as effectively as possible, and that therefore patient outcomes are optimised.
Relevance to NICE guidance	The efficacy of imaging tests has been considered in this guideline, but we did not find any RCTs evaluating them. The development of such RCTs is therefore required.
Relevance to the NHS	This research question may allow the development of imaging strategies that can be targeted to specific groups of patients, helping to ensure that staging is performed as effectively as possible, and that therefore patient outcomes are optimised.
National priorities	None known
Current evidence base	There is currently no RCT evidence.
Equality considerations	None known

J.1.4 Modified PICO table

Population	People diagnosed with differentiated thyroid cancer who have initial ultrasound evidence of extensive local spread
Intervention	CT vs MRI vs PET, with or without US
Comparator	To each other (see above)
Outcome	Quality of life, mortality, recurrence, progression
Study design	RCT
Timeframe	Long term
Additional information	This will be a randomised 'diagnostic' trial, where accuracy of staging will not be directly evaluated. Instead, the indirect effects of accurate determination of staging on downstream patient reported health outcomes will be evaluated.