National Institute for Health and Care Excellence

Final

Thyroid cancer: assessment and management

[L] Evidence review for external beam radiotherapy versus no external beam radiotherapy

NICE guideline NG230

Evidence reviews underpinning recommendations 1.3.19 and 1.3.20 and the research recommendation in the NICE guideline

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Final

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1.1 Review question

1.1.1 For people with residual, metastatic or recurrent thyroid cancer, what is the clinical and cost effectiveness of external beam radiotherapy?

1.1.2 Introduction

External Beam Radiation Therapy (EBRT) in differentiated thyroid cancer has a very limited role. It is used in a minority of patients. The usual indications will be as an adjuvant therapy to surgery in very high-risk cases with heavy nodal infiltrate and residual disease particularly that threatens the trachea or oesophagus, and very occasionally as primary treatment when surgery cannot be offered. Cases would normally be discussed at the MDT/Tumour board where multi-disciplinary advice can be given about alternative treatments. EBRT also has a role in the palliation of metastases in bones, brain, lung and local recurrences in the neck for symptom control.

This review seeks to determine the efficacy of EBRT in the management of differentiated thyroid cancer.

1.1.3 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: Adults with with residual, metastatic or recurrent thyroid cancer Exclusion: Children under 16
Intervention(s)	External beam radiotherapy Post-op radiotherapy
Comparison(s)	Usual care (any treatments other than external beam radiotherapy, including no treatment)
Outcomes	Primary outcome • Mortality • Progression free survival • Quality of life (any validated scores) • Local/regional cancer recurrence • Cancer recurrence • Postoperative dysphagia • Longest available follow up
Study design	• RCTs • Systematic reviews of RCTs

- If insufficient RCT evidence is available, prospective observational comparative studies will be considered only if they adjust for key confounders

1.1.4 Methods and process

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

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

1.1.5 Effectiveness evidence

1.1.5.1 Included studies

Eight non-randomized studies were included in the review.[19, 28, 29, 31, 43, 60, 72, 75] All these studies were adjusted for biologically plausible confounding. These studies are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

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

1.1.5.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.6 Summary of studies included in the effectiveness evidence

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Farahati, 1996[19]	External-beam radiation therapy (n=99) versus No External Beam Radiation therapy (n=70)	Patients with differentiated thyroid cancer (DTC) PTC and FTC with Stage pT4 (NO-1 MO) were treated and followed in their clinic between 1979 and 1992. Distributions of age, sex, and follow-up time were comparable in both irradiated and nonirradiated groups The standard treatment comprised of total thyroidectomy, ablative radioiodine therapy, and thyroid-stimulating hormone-suppressive therapy.	Locoregional and distant failure (LDF), and the time to locoregional recurrence (LR), was accomplished using Cox's proportional hazard model. Follow-up time of at least 2 years	Adjusted for age, sex, histology (FTC/PTC), lymph node invasion (N0/N1)
Keum,2006[31]	External-beam radiation therapy (n=25) versus No External Beam Radiation therapy (n=43)	Patient with a well differentiated thyroid cancers with tracheal invasion. Patients included received either: bilateral total thyroidectomy (28 patients) bilateral subtotal thyroidectomies (28 patients with unilateral total lobectomy (10 patients and debulking operation (2 patients)	10 Year Mortality 10 Year Progression of Disease	Adjusted for post-op residuum, age >45, male sex, thyroglobulin elevation, tracheal invasion, oesophageal invasion, recurrent laryngeal nerve involvement, lymph node involvement, Iodine treatment.
Vernat, 2019[72]	External-beam radiation therapy (n=216) versus No External Beam Radiation therapy (n=38)	Patients with locally advanced high-risk non-anaplastic thyroid carcinoma (naTC) at primary event or relapse. pT3-4, pN+, gross or microscopic residual disease. Patients underwent primary or salvage surgery of their thyroid with or without cervical neck dissection between November 1995 and 2015. 171 (68.1%) papillary, 22 (8.9%) follicular, 31	10-year progression of disease Local/regional recurrence.	Inverse probability of treatment weighting (IPTW) after multiple imputation was used to reduce selection biases.

Study	Intervention and comparison	Population	Outcomes	Comments
		(12.5%) PDTC and 38 (15.3%) medullary carcinomas patients		
Yang, 2017[75]	External-beam radiation therapy (n=816) versus No External Beam Radiation therapy (n=8038)	Patients with stage IV DTC who underwent primary surgical treatment between 2002 and 2012 All patients received surgical treatment with thyroidectomy, Patients subsequently received one of the three adjuvant radiation therapy's RAI, EBRT or no radiation therapy	10 years Mortality: Follicular 10 years IV-A: 10 years Mortality: Follicular 10 years IV-B 10 years Mortality: Follicular 10 years IV-C 10 years Mortality: Papillary 10 years IV-A 10 years Mortality: Papillary 10 years IV-B 10 years Mortality: Papillary 10 years IV-C	Adjusted for sex, ethnicity, surgery length of stay, treatment with neck dissection and socioeconomic factors
Hwang, 2021[28]	Adjuvant RT (n=24) versus usual care (n=33)	PTC confirmed by pathological diagnosis, rpT4/N1b, absence of distant metastasis (DM), and absence of history of other malignant diseases.	Locoregional cancer recurrence at 10 years	Adjusted for gender only in multivariable Cox regression analysis. Other potential confounders not significant on univariate testing.
Jin, 2021[29]	EBRT (n=152) versus usual care (n=152)	Patients newly diagnosed with medullary thyroid cancer (ICD-O-3 morphologic code 8345/3 or 8510/3, ICD-O-3 topographic code C73.9) between 1973 and 2015 were identified. Only patients without distant metastatic disease at diagnosis receiving a total or near-total thyroidectomy were included.	Disease specific mortality Overall mortality 10 years	After propensity score matching the groups were well-matched for biologically plausible confounders
Megwalu, 2019 [43]	EBRT (n=145) versus usual care	Adult patients diagnosed with T4 PTC who either received EBRT or did not; treatment with total/near	Disease specific mortality Overall mortality	A propensity matching approach was used, where

Study	Intervention and comparison	Population	Outcomes	Comments
	(n=725)	total thyroidectomy (with or without neck dissection) and RAI.	25 years	propensity scoring was based on age, gender, race, ethnicity, marital status, N classification, neck dissection, distant metastases, major invasion status.
Sit, 2021[60]	EBRT (n=211) versus usual care (n=194)	Patients treated for non-metastatic pT4 thyroid cancer with any nodal stage.	Locoregional recurrence Progression Disease specific mortality Overall mortality 14 years	Adjusted for N stage and age. Other plausible confounders were considered but not in final model as not significant in univariate testing.

See Appendix D for full evidence tables.

1.1.7 Summary of the effectiveness evidence

Table 3: Clinical evidence summary External-beam radiotherapy vs No External-beam Radiotherapy

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

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with EBRT (95% CI)
Mortality: Follicular 10 years IV-A	11,832 (1 study) 10 years	VERY LOW[1,2]	Adjusted HR: 1.14 [0.53, 2.46]	Not assessable	Not assessable
Mortality: Follicular 10 years IV-B	11,832 (1 study) 10 years	VERY LOW[1,2]	Adjusted HR: 0.28 [0.05, 1.51]	Not assessable	Not assessable
Mortality: Follicular 10 years IV-C	11,832 (1 study) 10 years	VERY LOW[1,2]	Adjusted HR: 0.90 [0.58, 1.38]	Not assessable	Not assessable
Mortality: Papillary 10 years IV-A	11,832 (1 study) 10 years	VERY LOW[1,2]	Adjusted HR: 1.29 [0.93, 1.79]	Not assessable	Not assessable
Mortality: Papillary 10 years IV-B	11,832 (1 study) 10 years	VERY LOW[1,2]	Adjusted HR: 1.74 [1.12, 2.70]	Not assessable	Not assessable
Mortality: Papillary 10 years IV-C	11,832 (1 study) 10 years	VERY LOW[1,2]	Adjusted HR: 1.25 [0.76, 2.08]	Not assessable	Not assessable
All-cause Mortality (RR)	1098 (1 study)	VERY LOW[1,2]	Adjusted RR: 1.20 [0.40, 4.2]	Not assessable	Not assessable

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with usual care	Risk difference with EBRT (95% CI)
	10 years				
All-cause mortality (HR)	1529 (3 studies) 10-25 years	VERY LOW[1,2]	Adjusted HR: 1.36 [1.08, 1.71]	Not assessable	Not assessable
Disease-specific mortality (HR)	1579 (3 studies) 10-25 years	VERY LOW[1,2]	Adjusted HR: 1.57 [1.19, 2.07]	Not assessable	Not assessable
Progression of disease (RR)	1098 (1 study) 10 years	LOW[1]	Adjusted RR: 0.05 [0.01, 0.25]	Not assessable	Not assessable
Progression of disease (HR)	405 (1 study) 14 years	VERY LOW[1,2]	Adjusted HR: 0.68 [0.49, 0.94]	Not assessable	Not assessable
Local/regional recurrence (HR)	954 (4 studies) 2 to 14 years	LOW[1]	Adjusted HR: 0.23 [0.17, 0.32]	Not assessable	Not assessable

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

1.1.8 Economic evidence

1.1.8.1 Included studies

No health economic studies were included.

1.1.8.2 Excluded studies

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

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

1.1.9 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
EBR single fraction	£111 – £133	NHS Reference Costs 2018-2019
Complete EBR treatment[(a)]	£3,420 - £4,080	NHS Reference Costs 2018-2019

(a) Assuming a CT without contrast to determine treatment plan, daily 2-Gy doses per fraction and a cumulative dosage needed of 60 Gy

1.1.11 Economic evidence statements

No relevant economic evaluations were identified.

1.1.12 The committee's discussion and interpretation of the evidence

1.1.12.1 The outcomes that matter most

The outcomes of mortality, progression free survival, quality of life (any validated scores), local/regional cancer recurrence and dysphagia were all deemed critical outcomes and were therefore of equal importance in decision-making. The longest follow-up time point was reported and ranged from 2 to 25 years. There was no evidence for quality of life, cancer recurrence or postoperative dysphagia.

1.1.12.2 The quality of the evidence

The quality of evidence was low to very low, with most of the downgrading from risk of bias. Risk of bias was very serious in all eight studies due to the observational nature of the evidence. Five of the studies had adjusted for plausible confounders, and the other three studies used propensity score matching, but it is highly likely that residual confounding would have remained. Most of the outcomes also had serious or very serious imprecision.

1.1.12.3 Benefits and harms

Compared to people given no external beam radiation, people with predominantly non-anaplastic and non-medullary thyroid cancer who were given external beam radiation (EBR) showed a clear benefit when measured in terms of long term local progression, and long term local-regional recurrence. However, studies showed a different direction of effect when mortality was measured. One study showed that in people with type IV-B papillary thyroid cancer (papillary thyroid cancer with no distant metastases, but with metastases to the spine or around the great vessels) there was an increased risk of mortality from EBR, compared to no EBR. In addition, there was a trend for a similar effect in people with type IV-A papillary thyroid cancer (papillary thyroid cancer with only local spread). The study showing harm from EBR had used a large data-set that used national-level data. The committee commented that coding in such studies was notorious for clinical coding error and were sceptical about the validity of findings. However, these findings were supported by several other studies showing a clear increase in the hazard of both all-cause mortality and disease-specific mortality when EBR was used. Taking all the evidence into consideration the committee concluded that EBR may have local benefits in the regions where it is directed, but that it may not be able to influence more distant spread and therefore may not reduce mortality. The committee explained the apparent *increase* in mortality from EBR by suggesting that the therapy may increase radiation-related harms. The committee were aware that the interplay of benefits and harms was not simple, and that if well-controlled local disease could improve quality of life this might represent a better outcome for some people than poorly controlled local disease accompanied by longer survival. The committee emphasised the extremely distressing local symptoms of advanced thyroid cancer such as difficulty swallowing, talking and breathing, and the great value in control of these local symptoms in improving quality of life. The committee therefore agreed that there was some evidence that EBR had a benefit for some people. Nevertheless, the committee were fully aware of the risks of EBR, which informed the careful tone of the recommendation, emphasising a person-centric decision-making approach.

The key view of the committee was that given its inherent radiation-related risks, EBR was not to be used indiscriminately, and that it should only be used in people where the potential benefits would outweigh the increased risks. The committee agreed that this decision should be made with the person, alongside a full multidisciplinary discussion, and it was stressed that it would always need to be made on a person-specific basis. The committee agreed that people who might be suitable for EBR based on the likelihood of local recurrence and the potential adverse effects of radiotherapy are those:

- with macroscopic disease which may include disease seen on additional diagnostic imaging;
- with histological appearances which may indicate more aggressive disease;
- who are receiving palliative care where cancer metastases or local residual disease can cause symptoms such as ulceration due to skin invasion, pressure symptoms or pain.

To further minimise risks in the people for which EBR was deemed suitable, the committee agreed that EBR should only be given to affected areas, where there was macroscopic disease after surgery, or disease unlikely to be controlled by RAI. This included EBR for people in a palliative care setting where deposits of disease cause symptoms, or are likely to cause symptoms, such as ulceration due to skin invasion, pressure symptoms or pain. To help achieve this, intensity modulated radiotherapy (IMRT) and stereotactic approaches were the committee's preferred types of EBR. These may reduce morbidity by allowing a far better control of intensity and treatment

location, allowing higher doses to the specific at-risk areas whilst reducing risk to other areas. Older methods of EBR were agreed to compromise on effective dose to maintain risk levels within reasonable limits. However, a specific recommendation was not made for the specific type of EBR because the review question had not set out to determine the optimal type of EBR, merely to evaluate whether EBR was effective and whether it should be utilised.

The committee also discussed the use of EBR in the younger age group. In this group external beam radiation is more problematic due to radiation risks which include local damage to tissues, including fibrosis and the potential for damage to the carotid artery, and the development of further malignancy later in life related to radiation. Moreover, disease in younger people is more likely to be radioiodine-sensitive and the committee agreed that the cancer is likely to be controlled by RAI. However, the committee also agreed that thyroid cancer is very rare in young people and their cancer is likely to be controlled by radioactive iodine.

The committee discussed the optimal treatment order for EBR and RAI. Again, the committee agreed that such a decision should be made on a person-by-person basis, and that there were no firm rules. However, the advantages of performing EBR first were explained for cases where a large tumour size would make it unlikely that initial RAI would have any impact on the tumour, whilst any potential adverse effects of RAI would continue undiminished. There is an opposing argument in clinical circles that prior EBR may reduce subsequent RAI uptake, but the committee agreed that this is rarely noted in practice. The only group where there was agreement that RAI might be better given first was in young people with well-differentiated papillary tumours, as these were people where RAI was usually very effective. Therefore, giving RAI to such people first might mean that subsequent EBR, with all its risks, might be unnecessary. No recommendation was made on the optimal treatment order because a review question had not been formulated to evaluate this question.

The committee discussed the common concern that EBR was harmful to the parathyroid glands but agreed that the evidence of which they were aware did not support this view, and that hypoparathyroidism was not a significant concern related to EBR.

A research recommendation for a randomised trial comparing EBR and no EBR was considered to be important because of the conflicting information about the efficacy of EBR. Such a trial was not thought to present ethical problems because there is genuine uncertainty in the effects of EBR and therefore being randomised to one group or another would not be considered to be ‘good’ or ‘bad’ based on current data. It was accepted that there would be difficulties in pursuing an RCT in this area, due to the need for a large number of consenting people to enable adequate random mixing of the complex array of possible presentations that will occur by the time that EBR treatment would be used in the clinical pathway. A small RCT, even if carried out with impeccable methodology, might not achieve good random mixing of characteristics and therefore might yield a study with selection bias. The case of a previous attempt at an RCT in Europe 15 years was discussed, where the study was discontinued because of the difficulty in recruiting enough people who would consent to randomisation. However, the committee did not feel that this meant that there were any fundamental reasons why an RCT would not be possible and given that it was an important issue the benefits of attempting to carry it out might be worth the logistic hurdles. The research recommendation is entitled: What is the clinical and cost effectiveness of external beam radiotherapy, for people with residual, metastatic or recurrent thyroid cancer?

1.1.12.4 Cost effectiveness and resource use

No health economics study on external beam radiation was identified. The cost of an external beam radiotherapy (EBR) fraction was estimated to range between £111 and £133 (SC22Z and SC23Z of the NHS Reference Cost 2018-2019). Assuming a CT without contrast beforehand to determine treatment plan and daily 2-Gy doses per fraction, to achieve the cumulative dosage of 60 Gy reported by the trials, a total of 30 fractions are needed for a total cost ranging between £3,420 and £4,080. The number of people currently receiving EBR in the UK is expected to be very low: less than 5% of people with differentiated thyroid cancer corresponding to about 190 people per year. EBR is currently offered to people with thyroid cancer and the recommendation is only likely to lead to a very small increase in the number of people receiving EBR. Therefore, it is unlikely that this will have a significant resource impact in England, as the number of EBRs performed each year would need to more than double to reach a cost of £1 million per year. It is more likely, instead, that the recommendation will lead to a more appropriate selection of people receiving EBR, so potentially reducing costs and increasing the efficiency of the NHS.

1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.20 and 1.3.21 and the research recommendation on external beam radiation therapy for people with residual or recurrent thyroid cancer.

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Appendices

Appendix A – Review protocols

1.1.13.1 Review protocol for external beam radiotherapy for people with residual, metastatic or recurrent cancer

Field	Content
PROSPERO registration number	CRD42020211072
Review title	Clinical and cost effectiveness of external beam radiotherapy, for people with residual, metastatic or recurrent thyroid cancer.
Review question	For people with residual, metastatic or recurrent thyroid cancer, what is the clinical and cost effectiveness of external beam radiotherapy?
Objective	To determine the efficacy of external beam radiotherapy in people with residual, metastatic or recurrent 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.
Condition or domain being studied	Thyroid cancer
Population	Inclusion: People aged 16 or over with residual, metastatic or recurrent thyroid cancer. This includes those with poorly differentiated cancers. Exclusion: Children under 16
Intervention/Exposure/Test	External beam radiotherapy
Comparator/Reference	Usual care (any treatments other than external beam radiotherapy, including

standard/Confounding factors	no treatment)
Types of study to be included	• Systematic reviews • RCTs Non-randomised studies (any controlled studies such as prospective or retrospective cohorts, or case control studies, with appropriate adjustment for plausible confounders) will be included if no RCTs are found.
Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	The role of external beam radiotherapy is currently uncertain, necessitating a systematic review to inform a useful recommendation.
Primary outcomes (critical outcomes)	• Mortality • Progression free survival • quality of life (any validated scores) • local/regional cancer recurrence • cancer recurrence • postoperative dysphagia Longest available follow up
Secondary outcomes (important outcomes)	None

Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study

	design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I (if a lack of any RCTs necessitate dropping down to non-randomised studies) 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: papers were included /excluded appropriately a sample of the data extractions correct methods are used to synthesise data a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome.

	Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. 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> • None <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: • Age 16-45 vs >45 • Gender • residual vs metastatic vs recurrent thyroid cancer • High dose of radiotherapy (adjuvant, post-operative or radical) versus low dose (palliative)
Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
Language	English
Country	England
Named contact	**Named contact** National Guideline Centre **Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre

Review team members	From the National Guideline Centre: Carlos Sharpin, Guideline lead Mark Perry, Senior systematic reviewer Vimal Bedia, Systematic reviewer Giulia Zuodar, Project manager Alfredo Mariani, Health economist Lina Gulhane, Head of Information specialists
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE

	website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10150/documents
Other registration details	N/A
Reference/URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=211072
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	None
Details of existing review of same topic by same authors	N/A
Additional information	N/A
Details of final publication	www.nice.org.uk

1.1.13.2 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).[44] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion**

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

The health economist will be guided by the following hierarchies.

Setting:

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

Health economic study type:

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

Year of analysis:

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

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

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

Appendix B – Literature search strategies

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

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

Clinical literature search strategy

This literature search strategy was used for the following review:

- For people with residual, metastatic or recurrent thyroid cancer, what is the clinical and cost effectiveness of external beam radiotherapy?

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 4: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1946 – 13 January 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, children) English language
Embase (OVID)	1974 – 12 January 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts, children) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 12 of 12, December 2021 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 and (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or follicul* or lymphoma* or anaplastic or sarcoma* or medullar* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or follicul* or medullar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump* or lymphoma*)).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to english language
26.	(exp 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.	exp Radiotherapy/
29.	Radiotherap*.ti,ab.
30.	(radiation adj2 (therap* or treatment* or beam*)).ti,ab.
31.	((post-op* or postop* or intraop* or intra-op*) adj3 (radiation or irradiat* or reirradiat* or re-irradiat* or radiosurger*)).ti,ab.
32.	((external* or electron*) adj3 (radiation or therap* or irradiation* or beam*)).ti,ab.
33.	((radical or conformal or intensity modulated or volumetric modulated arc or stereotactic or four-dimensional or 4d or 4-d or three-dimensional or 3-d or 3d or image guided or neutron or proton*) adj3 (radiation or therap* or irradiat* or reirradiat* or re-irradiat* or treatment* or radiosurger*)).ti,ab.
34.	(EBRT or XRT or IMRT).ti,ab.
35.	or/28-34
36.	27 and 35
37.	randomized controlled trial.pt.
38.	controlled clinical trial.pt.
39.	randomi#ed.ab.

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

Embase (Ovid) search terms

1.	exp Thyroid Cancer/
2.	(thyroid and (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or follicul* or lymphoma* or anaplastic or sarcoma* or medullar* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or follicul* or medullar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump* or lymphoma*)).ti,ab.
5.	or/1-4
6.	letter.pt. or letter/

7.	note.pt.
8.	editorial.pt.
9.	case report/ or case study/
10.	(letter or comment*).ti.
11.	or/6-10
12.	randomized controlled trial/ or random*.ti,ab.
13.	11 not 12
14.	animal/ not human/
15.	nonhuman/
16.	exp Animal Experiment/
17.	exp Experimental Animal/
18.	animal model/
19.	exp Rodent/
20.	(rat or rats or mouse or mice or rodent*).ti.
21.	or/13-20
22.	5 not 21
23.	limit 22 to english language
24.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
25.	23 not 24
26.	exp radiotherapy/
27.	Radiotherap*.ti,ab.
28.	(radiation adj2 (therap* or treatment* or beam*)).ti,ab.
29.	((post-op* or postop* or intraop* or intra-op*) adj3 (radiation or irradiat* or reirradiat* or re-irradiat* or radiosurger*)).ti,ab.
30.	((external* or electron*) adj3 (radiation or therap* or irradiation* or beam*)).ti,ab.
31.	((radical or conformal or intensity modulated or volumetric modulated arc or stereotactic or four-dimensional or 4d or 4-d or three-dimensional or 3-d or 3d or image guided or neutron or proton*) adj3 (radiation or therap* or irradiat* or reirradiat* or re-irradiat* or treatment* or radiosurger*)).ti,ab.
32.	(EBRT or XRT or IMRT).ti,ab.
33.	exp external beam radiotherapy/
34.	or/26-33
35.	25 and 34
36.	limit 35 to (conference abstract or conference paper or conference review or conference proceeding)
37.	35 not 36
38.	random*.ti,ab.
39.	factorial*.ti,ab.
40.	(crossover* or cross over*).ti,ab.
41.	((doubl* or singl*) adj blind*).ti,ab.
42.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
43.	crossover procedure/
44.	single blind procedure/
45.	randomized controlled trial/
46.	double blind procedure/
47.	or/38-46
48.	systematic review/
49.	Meta-Analysis/

50.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
51.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
52.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
53.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
54.	(search* adj4 literature).ab.
55.	(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.
56.	cochrane.jw.
57.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
58.	or/48-57
59.	Clinical study/
60.	Observational study/
61.	family study/
62.	longitudinal study/
63.	retrospective study/
64.	prospective study/
65.	cohort analysis/
66.	follow-up/
67.	cohort*.ti,ab.
68.	67 and 68
69.	(cohort adj (study or studies or analys* or data)).ti,ab.
70.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
71.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
72.	(before adj2 after adj2 (study or studies or data)).ti,ab.
73.	exp case control study/
74.	case control*.ti,ab.
75.	cross-sectional study/
76.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
77.	or/60-66,69-77
78.	37 and (47 or 58 or 77)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2.	thyroid and (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or follicul* or lymphoma* or anaplastic or sarcoma* or medullar* or cyst* or malignan*):ti,ab
#3.	DTC:ti,ab
#4.	((papillar* or follicul* or medullar* or anaplastic) near/2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump* or lymphoma*)):ti,ab
#5.	#1 or #2 or #3 or #4
#6.	MeSH descriptor: [Radiotherapy] explode all trees
#7.	Radiotherap*:ti,ab
#8.	(radiation NEAR/2 (therap* or treatment* or beam*)):ti,ab
#9.	((post-op* or postop* or intraop* or intra-op*) NEAR/3 (radiation or irradiat* or reirradiat* or re-irradiat* or radiosurger*)):ti,ab

#10.	((external* or electron*) NEAR/3 (radiation or therap* or irradiation* or beam*)):ti,ab
#11.	((radical or conformal or intensity modulated or volumetric modulated arc or stereotactic or four-dimensional or 4d or three-dimensional or 3d or image guided or neutron or proton*) NEAR/3 (radiation or therap* or irradiat* or reirradiat* or re-irradiat* or treatment* or radiosurger*)):ti,ab
#12.	(EBRT or XRT or IMRT):ti,ab
#13.	#6 or #7 or #8 or #9 or #10 or #11 or #12
#14.	#5 and #13
#15.	conference:pt or (clinicaltrials or trialsearch):so
#16.	#14 not #15

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
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	Inception - 16 December 2021	English language

Database	Dates searched	Search filters and limits applied
Technology Assessment (INAHTA)		

Medline (Ovid) search terms

1.	exp Thyroid Neoplasms/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to english language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.

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

Embase (Ovid) search terms

1.	exp Thyroid Cancer/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/

18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to english language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36
38.	quality-adjusted life years/
39.	"quality of life index"/
40.	short form 12/ or short form 20/ or short form 36/ or short form 8/
41.	sickness impact profile/
42.	(quality adj2 (wellbeing or well being)).ti,ab.
43.	sickness impact profile.ti,ab.
44.	disability adjusted life.ti,ab.
45.	(qal* or qtime* or qwb* or daly*).ti,ab.
46.	(euroqol* or eq5d* or eq 5*).ti,ab.
47.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
48.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
49.	(hui or hui1 or hui2 or hui3).ti,ab.
50.	(health* year* equivalent* or hye or hyes).ti,ab.
51.	discrete choice*.ti,ab.
52.	rosser.ti,ab.
53.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
54.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
55.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
56.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
57.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
58.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
59.	or/37-58
60.	22 and 59

NHS EED and HTA (CRD) search terms

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

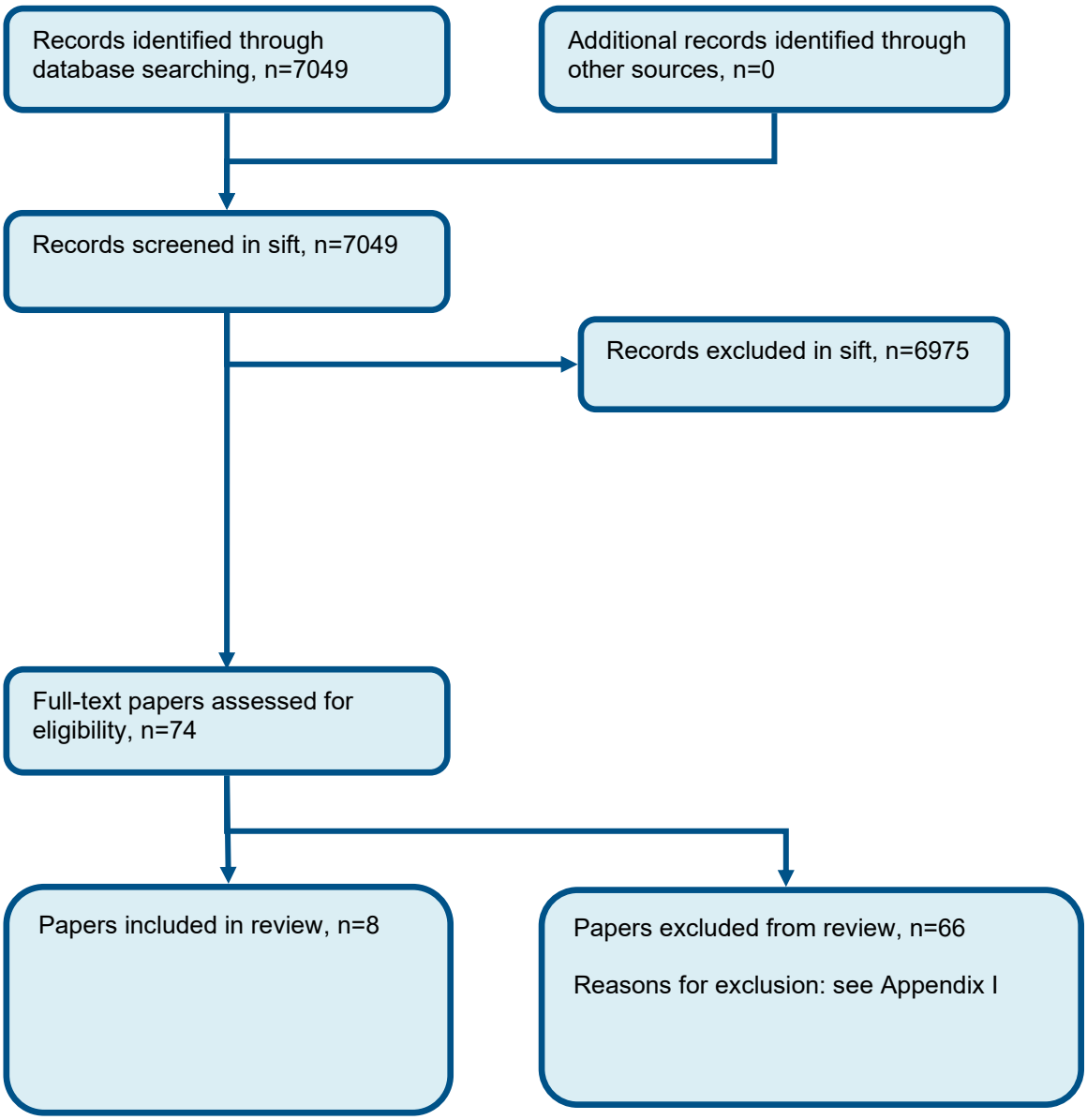
	or anaplastic)))
#3.	(((papillar* or follicul* or medullary or anaplastic) NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)))
#4.	#1 OR #2 OR #3

INHATA search terms

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

Appendix C – Effectiveness evidence study selection

Figure 1:Flow chart of clinical study selection for the review of Clinical and cost effectiveness of external beam radiotherapy, for people with residual, metastatic or recurrent thyroid cancer.



Appendix D – Effectiveness Evidence

Study	Farahati 1996[17]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=238)
Countries and setting	Conducted in Germany; Setting: Patients treated in the university hospital in Essen, Germany
Line of therapy	Adjunctive to current care
Duration of study	Not clear: not stated
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: PTC - Papillary thyroid cancer, FTC - Follicular thyroid cancer, DTC - Differentiated thyroid cancer
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients with well documented histologic, surgical, biochemical, and radiotherapeutic records, with a follow-up time of at least 2 years, were included in this study. Mixed papillary-follicular thyroid cancers were considered as PTC (according to the WHO classification). All tumour stages were reclassified according to UICC 1987
Exclusion criteria	All patients seen before 1979 were excluded - due to insufficient documentation. Patients with undifferentiated thyroid cancer, medullary thyroid cancer, or oxyphilic (both papillary and follicular types) thyroid cancer was excluded from this study. Among the 238 cases 69 were excluded due to initial metastases (T4 N0-1 M1)
Recruitment/selection of patients	
Age, gender and ethnicity	Age - Range of means: DTC (54+-15) PTC with EBT (55+-13) PTC Without EBT (51+-17) FTC with EBT (53+-12) FTC without EBT (48+-14). Gender (M: F): 173 females 65 males. Ethnicity: not identified
Further population details	1. Age: Not applicable 2. Cancer: Not applicable 3. Gender: Not applicable 4. High dose radiotherapy: Not applicable 5. Low dose radiotherapy: Not applicable
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=99) Intervention 1: External beam radiotherapy. Patients were treated with external radiation between the first and second courses of radioiodine treatment with a dose of 50-60 Gy.

	Duration 2 years. Concurrent medication/care: The standard treatment protocol in patients with DTC includes (1) total thyroidectomy before any subsequent therapy and modified neck dissection ("berry picking") in patients with lymph node involvement; (2) two courses of radioiodine treatment with a total activity of 7-12 GBq 1-131 with an interval of 3-4 months; (3) lymph node metastases without sufficient iodine uptake removed by surgery: (4) TSH-suppressive thyroid hormone treatment with a dose of -2.5 p, levothyroxine/kg body weight (basal TSH <0.1mUI1); Indirectness: No indirectness (n=70) Intervention 2: Usual care - any treatments other than external beam radiotherapy. usual treatment without External Beam radiation. Duration 2 years. Concurrent medication/care: The standard treatment protocol in patients with DTC includes (1) total thyroidectomy before any subsequent therapy and modified neck dissection ("berry picking") in patients with lymph node involvement; (2) two courses of radioiodine treatment with a total activity of 7-12 GBq 1-131 with an interval of 3-4 months; (3) lymph node metastases without sufficient iodine uptake removed by surgery: (4) TSH-suppressive thyroid hormone treatment with a dose of -2.5 p, levothyroxine/kg body weight (basal TSH <0.1mUI1); Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL BEAM RADIOTHERAPY versus ANY TREATMENTS OTHER THAN EXTERNAL BEAM RADIOTHERAPY ERT vs no ERT Protocol outcome 1: local/regional cancer recurrence Actual outcome: locoregional recurrence (LR) locoregional and/or distant failure (LDF) at 2-10 year. Locoregional and distant failure: adjusted RR* 0.3 (p=0.003). Adjusted for age, sex, histology (FTC/PTC), lymph node invasion (N0/N1) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - High, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality; Progression free survival; Quality of life; Cancer recurrence; Postoperative dysphagia

Study	**Hwang 2021[28]**
Study type	Non-randomised retrospective comparative study
Number of studies (number of participants)	1 (n=57)
Countries and setting	South Korea
Line of therapy	Adjunctive to current care
Duration of study	10 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: PTC - Papillary thyroid cancer (rT4/N1b PTC)
Subgroup analysis within study	Not applicable:
Inclusion criteria	PTC confirmed by pathological diagnosis, rpT4/N1b, absence of distant metastasis (DM), and absence of history of other malignant diseases.
Exclusion criteria	Tall cell variants of PTC; macroscopic residual disease
Recruitment/selection of patients	
Age, gender and ethnicity	Age – Median (range): 52 (20-82); Gender (M: F): 12:45. Ethnicity: not identified
Further population details	
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Adjuvant radiation therapy. Patients were treated with external radiation with a median dose of 61.6 Gy (range 57.6-70.4Gy) in daily fractions of 1.8 to 2.0. Duration unclear. Concurrent medication/care: unclear; Indirectness: indirectness as this was adjuvant treatment (n=33) Intervention 2: Usual care – not described; Indirectness: No indirectness
Funding	Korean University Grant
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL BEAM RADIOTHERAPY versus ANY TREATMENTS OTHER THAN EXTERNAL BEAM RADIOTHERAPY	

ERT vs no ERT *Locoregional cancer recurrence*: adjusted HR* for EBR vs no EBR 0.121 (0.039 – 0.367). Adjusted for gender only in multivariable Cox regression analysis. Other potential confounders not significant on univariate testing. * In paper HR given for No RT vs RT; therefore results here, for RT vs no RT, have been given as reciprocal of published results, which were HR: 8.292(2.722-25.254). Risk of bias: All domain - Very high, Selection – Very high, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Mortality; Progression free survival; Quality of life; Cancer recurrence; Postoperative dysphagia

Study	**Jin 2021[29]**
Study type	Non-randomised comparative study with propensity matching
Number of studies (number of participants)	1 (n=2046 before propensity matching, and 304 after propensity matching)
Countries and setting	USA
Line of therapy	Adjunctive to current care
Duration of study	10 years (retrospective)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Locoregional Medullary cancer
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients newly diagnosed with medullary thyroid cancer (ICD-O-3 morphologic code 8345/3 or 8510/3, ICD-O-3 topographic code C73.9) between 1973 and 2015 were identified. Only patients without distant metastatic disease at diagnosis receiving a total or near-total thyroidectomy were included.
Exclusion criteria	Patients without histologic confirmation of disease and those with invalid survival data (either 0 days of follow-up or incomplete survival data) were excluded.
Recruitment/selection of patients	Retrospective perusal of databases
Age, gender and ethnicity	Age – Mean (sd): EBR 55.32(15.63); no EBR 54.47(16.01) (20-82); Gender (M: F): 169: 135. Ethnicity: EBR 69.7% Caucasian, 3.3 Asian/Pacific Islander, 8.6% Black, 18.4% Hispanic; No EBR 71.1% Caucasian, 3.3 Asian/Pacific Islander, 6.6% Black, 19.1% Hispanic;

Further population details	After propensity score matching the groups were well-matched for biologically plausible confounders.
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=152) Intervention 1: EBRT. No details; Duration unclear. Concurrent medication/care: unclear; Indirectness: none (n=152) Intervention 2: Usual care – not described; Indirectness: No indirectness
Funding	No sponsorship or grants
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL BEAM RADIOTHERAPY versus ANY TREATMENTS OTHER THAN EXTERNAL BEAM RADIOTHERAPY ERT vs no ERT *Disease-specific survival* % (95% CIs) at 10 years: EBRT 70.2(61.1-80.7); No EBRT 80(71.5-89.5); HR: 1.660 (0.934-2.949) [this refers to the HR of disease-specific mortality for EBR vs no EBR] Risk of bias: All domain - High, Selection – High, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 *Overall survival* % (95% CIs) at 10 years: EBRT 52.3(43.3-63.2); No EBRT 58.3(48.2-70.5); HR: 1.115 (0.755-1.645) [this refers to the HR of overall mortality for EBR vs no EBR] Risk of bias: All domain - High, Selection – High, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Progression free survival; Quality of life; Cancer recurrence; Postoperative dysphagia

Study	Keum 2006[31]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=1098)
Countries and setting	Conducted in South Korea; Setting: Yonsei cancer centre, Yonsei university, college of medicine (Seoul, Korea)
Line of therapy	Adjunctive to current care
Duration of study	
Method of assessment of guideline condition	Method of assessment /diagnosis not stated
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Any patients between 1986 and 1997 that were diagnosed with a well differentiated thyroid cancer and were treated surgically at the Yonsei cancer centre. T stage was assigned retrospectively by the 6th American joint committee on cancer stage classification all cases except 1 had stage t4a tumour extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, oesophagus, or recurrent laryngeal nerve. Most patients with tracheal invasion showed types I or type II
Exclusion criteria	Patients with follicular and medullary carcinomas were excluded. Patients with metastasis to the mediastinal lymph nodes or distant metastasis at point of diagnosis were excluded from analysis
Age, gender and ethnicity	Age - Median (range): range of 21 to 80 with a median age of 57. Gender (M: F): 23 males and 45 females. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. Cancer: Not applicable 3. Gender: Not applicable 4. High dose radiotherapy: Not applicable 5. Low dose radiotherapy: Not applicable
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: External beam radiotherapy. external beam radiotherapy was administered with a dose of 1.8 Gy per fraction, 5 times a week total of 50-63 Gy to the tumour beds and neck. Duration N/A. Concurrent medication/care: patients who underwent surgical resection followed by external beam radiotherapy, the types of operations performed on patients included bilateral total thyroidectomy (28 patients) bilateral subtotal thyroidectomy (28 patients unilateral total lobectomy (10 patients and debulking operation (2

	patients) (n=43) Intervention 2: Usual care - any treatments other than external beam radiotherapy. Patients had no additional treatment to surgery, postoperative radioactive iodine treatment was administered to 14 patients in whom radioiodine was well concentrated by the tumour, 12 patients received 100-200 mCI and 2 patients received ablative doses of 30mCi. Duration N/A. Concurrent medication/care: patients in this arm included bilateral total thyroidectomy, bilateral subtotal thyroidectomy, unilateral total thyroidectomy. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL BEAM RADIOTHERAPY versus ANY TREATMENTS OTHER THAN EXTERNAL BEAM RADIOTHERAPY

ERT vs no ERT

Adjusted for post-op residuum, age >45, male sex, thyroglobin elevation, tracheal invasion, oesophageal invasion, recurrent laryngeal nerve involvement, lymph node involvement, Iodine treatment.

Protocol outcome 1: Mortality; Actual outcome: 10-year mortality: adjusted RR 1.2(0.4-4.2)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcome 2: Progression free survival; Actual outcome: 10-year progression of disease: adjusted RR 0.05 (0.01-0.25)
Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low, Other 1 - Low, Other 2 - Low, Other 3 - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Mortality ; Quality of life ; local/regional cancer recurrence ; Cancer recurrence ; Postoperative dysphagia

Study	Megwalu 2019[43]
Study type	Non-randomised retrospective comparative study
Number of studies (number of participants)	1 (n=870)
Countries and setting	USA
Line of therapy	Adjunctive to current care
Duration of study	Up to 25 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: PTC - Papillary thyroid cancer (T4)
Subgroup analysis within study	Not applicable:
Inclusion criteria	Adult patients diagnosed with T4 PTC who either received EBRT or did not; treatment with total/near total thyroidectomy (with or without neck dissection) and RAI.
Exclusion criteria	Multiple primary tumours, and cases where the mode of therapy was unknown
Recruitment/selection of patients	Retrospective review of patient data
Age, gender and ethnicity	Age – Mean (sd): EBRT 52.13 (15.76), no EBRT 51.74 (17.29); Gender (M: F): 352:518. Ethnicity: Black 4.1%, Hispanic 14.8%, White 82.9%;
Further population details	
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=145) Intervention 1: EBRT. No details given. Duration unclear. Concurrent medication/care: unclear; Indirectness: none (n=725) Intervention 2: No EBRT; Indirectness: No indirectness
Funding	No reports of funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL BEAM RADIOTHERAPY versus ANY TREATMENTS OTHER THAN EXTERNAL BEAM RADIOTHERAPY	

EBRT vs no EBRT *A propensity matching approach was used, where propensity scoring was based on age, gender, race, ethnicity, marital status, N classification, neck dissection, distant metastases, major invasion status.* *Overall survival: Propensity adjusted HR (EBRT vs no EBRT): HR 1.6 (1.18-2.16)* Risk of bias: All domain - high, Selection –high, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0 *Disease-specific survival: Propensity adjusted HR (EBRT vs no EBRT): HR 1.58 (1.09-2.30)* Risk of bias: All domain - high, Selection –high, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Recurrence; Progression free survival; Quality of life ; Cancer recurrence ; Postoperative dysphagia

Study	**Sit 2021[60]**
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=405)
Countries and setting	USA
Line of therapy	Adjunctive to current care
Duration of study	14.3 years (retrospective)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Well-differentiated thyroid cancer
Subgroup analysis within study	Not applicable:
Inclusion criteria	Patients treated for non-metastatic pT4 thyroid cancer with any nodal stage.
Exclusion criteria	Metastatic disease; poorly differentiated histology; age <18 years
Recruitment/selection of patients	Retrospective perusal of databases
Age, gender and ethnicity	Age – Mean: 53.3; Gender (M: F): 148: 257. Ethnicity: Not reported

Further population details	
Extra comments	
Indirectness of population	No indirectness
Interventions	(n=211) Intervention 1: EBRT. No details; Duration unclear. Concurrent medication/care: unclear; Indirectness: none (n=194) Intervention 2: Usual care – not described; Indirectness: No indirectness
Funding	No sponsorship or grants

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL BEAM RADIOTHERAPY versus ANY TREATMENTS OTHER THAN EXTERNAL BEAM RADIOTHERAPY

ERT vs no ERT

Locoregional recurrence % (95% CIs) at 15 years: HR: 0.334(0.192-0.579) [this refers to the HR of locoregional recurrence for EBR vs no EBR]. Adjusted for N stage and age. Other plausible confounders were considered but not in final model as not significant in univariate testing.
Risk of bias: All domain - High, Selection – High, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Progression free survival % (95% CIs) at 15 years: HR: 0.677(0.489-0.938) [this refers to the HR of progression for EBR vs no EBR]. Adjusted for major organ invasion, tumour size, N stage and age. Other plausible confounders were considered but not in final model as not significant in univariate testing.
Risk of bias: All domain - High, Selection – High, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Cause specific survival % (95% CIs) at 15 years: HR: 1.469(0.823-2.622) [this refers to the HR of cancer-specific death for EBR vs no EBR]. Adjusted for lymphovascular invasion, tumour size, and age. Other plausible confounders were considered but not in final model as not significant in univariate testing.
Risk of bias: All domain - High, Selection – High, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Overall survival % (95% CIs) at 15 years: HR: 1.216(0.817-1.810) [this refers to the HR of death for EBR vs no EBR]. Adjusted for major organ invasion, tumour size, histology, N stage and age. Other plausible confounders were considered but not in final model as not significant in univariate testing.
Risk of bias: All domain - High, Selection – High, Blinding - NA, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: 0; Group 2 Number missing: 0

Protocol outcomes not reported by the study	Progression free survival; Quality of life; Cancer recurrence ; Postoperative dysphagia

Study	Vernat 2019[72]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=254)
Countries and setting	Conducted in Multiple countries; Setting: 18 radiation therapy departments. multicentre
Line of therapy	Adjunctive to current care
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Between 1995 and 2015, postoperative naTC patients with a theoretical indication for EBRT were included based on criteria that were common to American-British-French current guidelines, i.e., pT3-4, pN+, gross or microscopic residual disease. Patients with papillary, follicular, poorly differentiated thyroid carcinoma (PDTC), medullary and anaplastic thyroid carcinomas were included. T classification: Tx + T0, T1 + T2 and T3 + T4 171 (68.1%) papillary, 22 (8.9%) follicular, 31 (12.5%) PDTC and 38 (15.3%) medullary carcinomas patients
Exclusion criteria	Not stated
Recruitment/selection of patients	216 patients underwent pEBRT (85.0%) and 38 had surgery without EBRT (15.0%; control group). Thirty-eight (16.9%), 15 (6.8%) and 6 (2.7%) patients had tracheal, oesophageal and laryngeal invasion,
Age, gender and ethnicity	Age - Median (range): 61 (51–69). Gender (M: F): 117/137. Ethnicity: Not stated
Further population details	1. Age: Age > 45 (Age >45 vs <45). 2. Cancer: 3. Gender: 4. High dose radiotherapy: 5. Low dose radiotherapy:
Extra comments	Between 1995 and 2015, postoperative non-anaplastic thyroid carcinoma patients with a theoretical indication for EBRT were included based on criteria that were common to American-British-French current guidelines, i.e., pT3-4, engross or microscopic residual disease. Inverse probability of treatment weighting (IPTW) after multiple imputation was used to reduce selection biases.
Indirectness of population	Serious indirectness: included medullary thyroid cancer in study <15%
Interventions	(n=216) Intervention 1: External beam radiotherapy. pEBRT patients, 106 were irradiated at primary event and 110 at relapse. A limited field technique (with irradiation of high-risk volume only) was used in 30 (14.1%) and

	an extensive field technique (including operative bed, thyroid area and lymph node areas prophylactically) in 183 (85.9%).IMRT or 2D/3D radiotherapy was used in 74 (36.8%) and 127 (63.2%) patients, respectively. Median dose to the high-risk volume (macroscopic disease) and intermediate low-risk volumes (microscopic disease and prophylactic volume) was 60 Gray (Gy) (interquartile range (IQR), 56 to 66) and 50 Gy (IQR, 45 to 54).Thirty patients (13.9%) had >66 Gy. Daily 2-Gy fractions were used in 103 (89.4%) patients. Duration n/a. Concurrent medication/care: Total thyroidectomy was performed in 217 (86.5%) patients, partial thyroidectomy or debulking surgery was used in the others, and 209 had a neck dissection (86.4%). Sixty-seven (30.5%) and 40 (18.2%) patients had microscopic or gross residual disease. Indirectness: Serious indirectness; Indirectness comment: included patients with medullary thyroid cancer (n=38) Intervention 2: Usual care - any treatments other than external beam radiotherapy. underwent surgery only. Duration n/a. Concurrent medication/care: Total thyroidectomy was performed in 217 (86.5%) patients, partial thyroidectomy or debulking surgery was used in the others, and 209 had a neck dissection (86.4%). Sixty-seven (30.5%) and 40 (18.2%) patients had microscopic or gross residual disease. Indirectness: Serious indirectness; Indirectness comment: included medullary thyroid cancer patients
Funding	Other (This research received no external funding.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL BEAM RADIOTHERAPY versus ANY TREATMENTS OTHER THAN EXTERNAL BEAM RADIOTHERAPY ERT vs no ERT Protocol outcome 1: Mortality - Actual outcome: Mortality: HR 0.82(0.41-1.64)Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: local/regional cancer recurrence - Actual outcome: Locoregional Failure at 10 Years; Local/regional recurrence: HR 0.17 (0.10-0.29) Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: Serious indirectness, Comments: includes medullary thyroid cancer ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Mortality ; Quality of life ; Cancer recurrence ; Postoperative dysphagia

Study	Yang 2017[75]
Study type	Non-randomised comparative study
Number of studies (number of participants)	1 (n=11832)
Countries and setting	Conducted in USA
Line of therapy	Adjunctive to current care
Duration of study	Not clear: not stated
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with stage IV papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) who received radioactive iodine (RAI), external beam radiation therapy (EBRT), or neither following surgery between 2002 and 2012
Exclusion criteria	not stated
Recruitment/selection of patients	The national cancer database collects mortality data for a random sample of all inpatient cancer discharges, data was collected from the NCDB from 200 -2012 which yielded a cohort of 11,832 patients with stage IV DTC who underwent primary surgical treatment
Age, gender and ethnicity	Age - Mean (SD): 61.6 (11.6). Gender (M: F): 5034/6798. Ethnicity: not stated
Further population details	1. Age: Not applicable 2. Cancer: Not applicable 3. Gender: Not applicable 4. High dose radiotherapy: Not applicable 5. Low dose radiotherapy: Not applicable
Extra comments	patients were stratified by cancer histology specifically follicular thyroid cancer carcinoma Vs papillary thyroid carcinoma, within the cohort of 11,832, 1036 had FTC and 10,796 had PTC.
Indirectness of population	No indirectness
Interventions	(n=816) Intervention 1: External beam radiotherapy. external beam radiation therapy was administered to patients postoperatively. Duration n/a. Concurrent medication/care: All patients received surgical treatment with thyroidectomy, Patients subsequently received one of the three adjuvant radiation therapies: RAI, Ebro no radiation therapy (n=8038) Intervention 2: Usual care - any treatments other than external beam radiotherapy.

	Radioactive Iodine therapy. Duration n/a. Concurrent medication/care: All patients received surgical treatment with thyroidectomy, Patients subsequently received one of the three adjuvant radiation therapy's RAI, Ebro no radiation therapy (n=2978) Intervention 3: Usual care - No treatment. no radiation therapies. Duration n/a. Concurrent medication/care: All patients received surgical treatment with thyroidectomy, Patients subsequently received one of the three adjuvant radiation therapies: RAI, EBRT or no radiation therapy
Funding	Funding not stated (The author discloses no competing financial interest)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: EXTERNAL BEAM RADIOTHERAPY versus RAI

ERT vs no ERT
Adjusted for sex, ethnicity, surgery length of stay, treatment with neck dissection and socioeconomic factors

Protocol outcome 1: Mortality
Actual outcome: 10 year Mortality at 10 years;
10 years Mortality:
Follicular 10 years IV-A: adjusted HR 1.14(0.53-2.46)
Follicular 10 years IV-B: adjusted HR 0.28(0.05-1.51)
Follicular 10 years IV-C: adjusted HR 0.9(0.58-1.38)
Papillary 10 years IV-A: adjusted HR 1.29(0.93-1.79)
Papillary 10 years IV-B: adjusted HR 1.74(1.16-2.70)
papillary 10 years IV-C: adjusted HR 1.25(0.76-2.08)

Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low, Subgroups - Low; Indirectness of outcome: No indirectness; Group 1 Number missing: ; Group 2 Number missing:

Protocol outcomes not reported by the study	Progression free survival; Quality of life; local/regional cancer recurrence; Cancer recurrence; Postoperative dysphagia

Appendix E Appendix E– Forest plots

E.1 Forest plot of comparison: EBRT vs no EBRT

Figure 1: Mortality at 10 years (Follicular, IV-A),

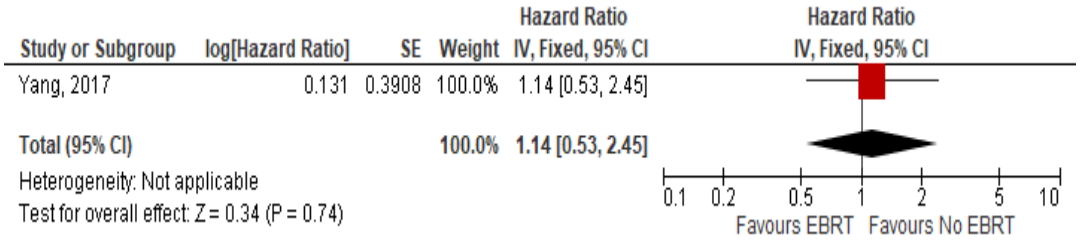


Figure 2: Mortality at 10 years (Follicular, IV-B),

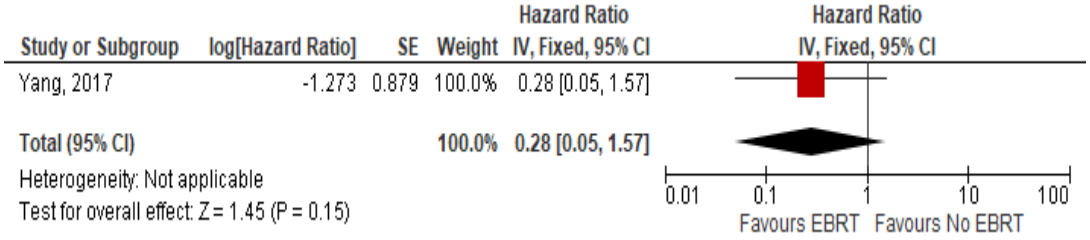


Figure 3: Mortality at 10 years (Follicular, IV-C),

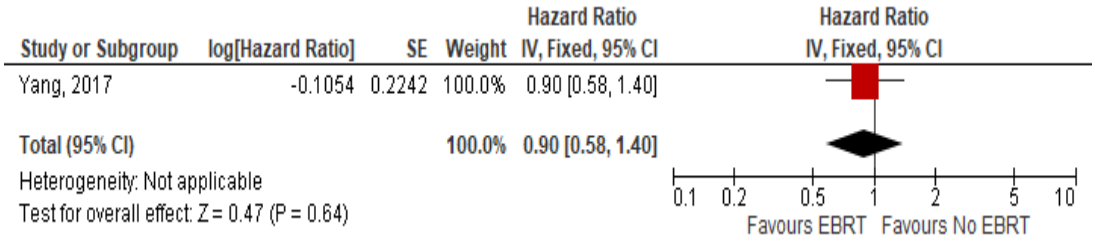


Figure 4: Mortality at 10 years (Papillary, IV-A),

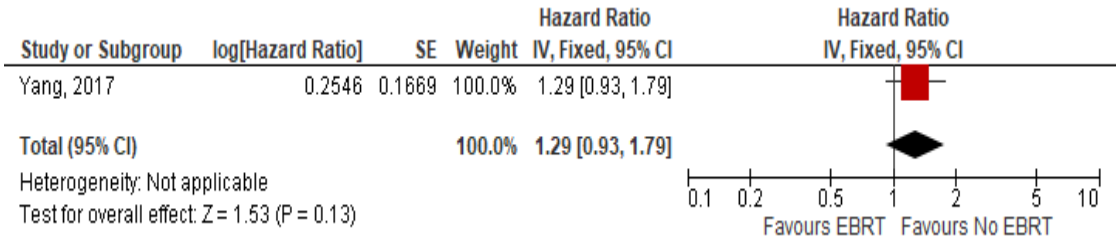


Figure 5: Mortality at 10 years (Papillary, IV-B),

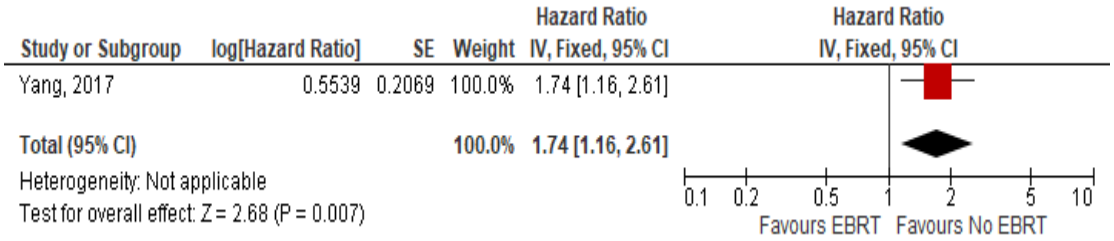


Figure 6: Mortality at 10 years (Papillary, IV-C),

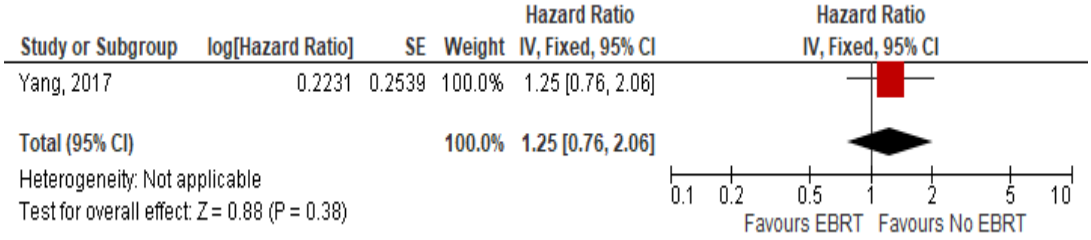


Figure 7: All-cause mortality (RR)

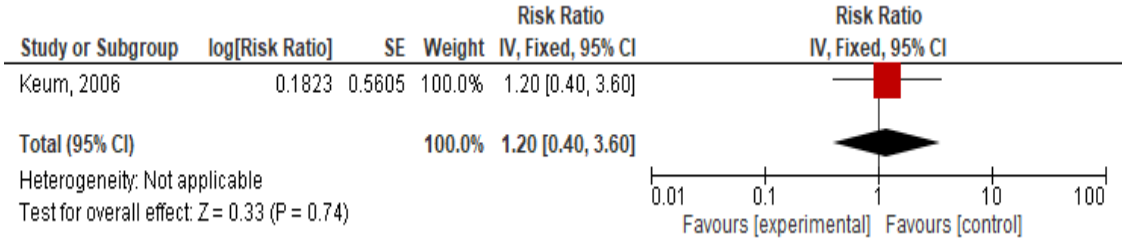


Figure 8: All-cause mortality (HR)

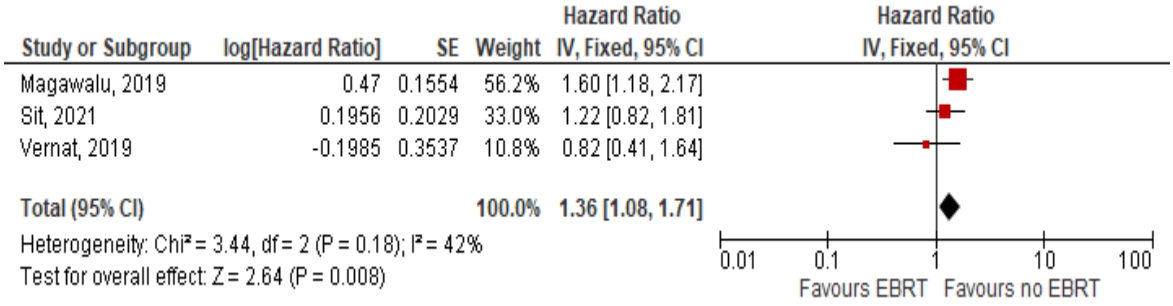


Figure 9: Disease-specific mortality (HR)

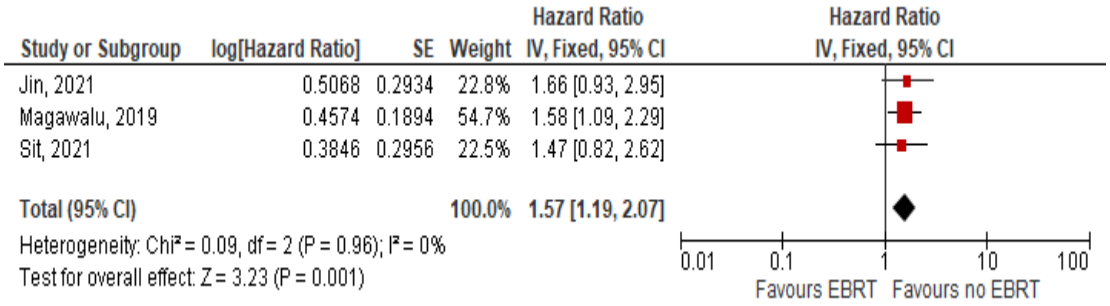


Figure 10: Progression of disease (RR)

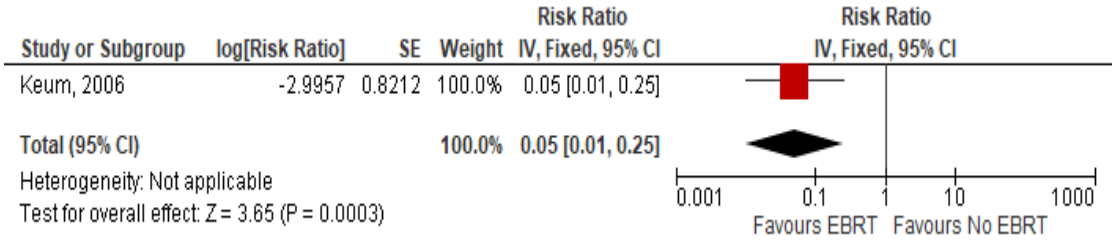


Figure 11: Progression of disease (HR)

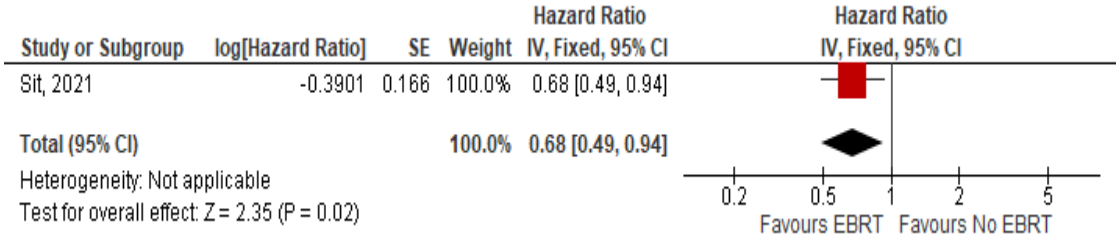
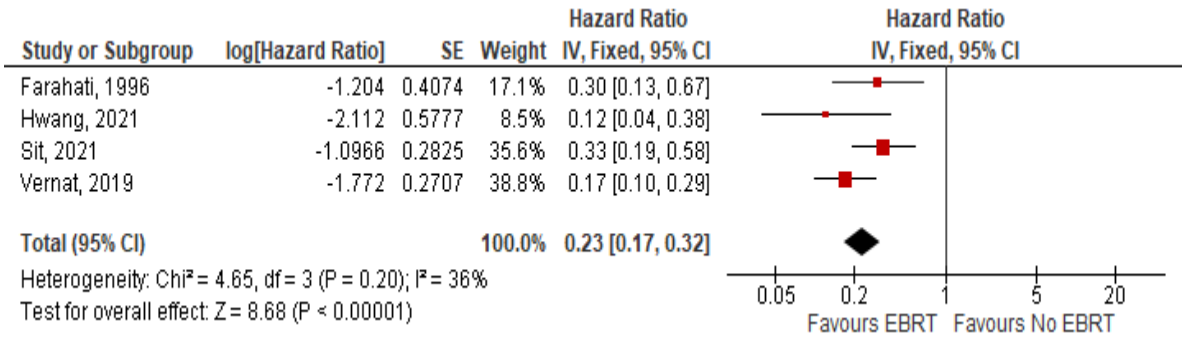


Figure 12: Local/regional recurrence.



Appendix F – GRADE and/or GRADE-CERQual tables

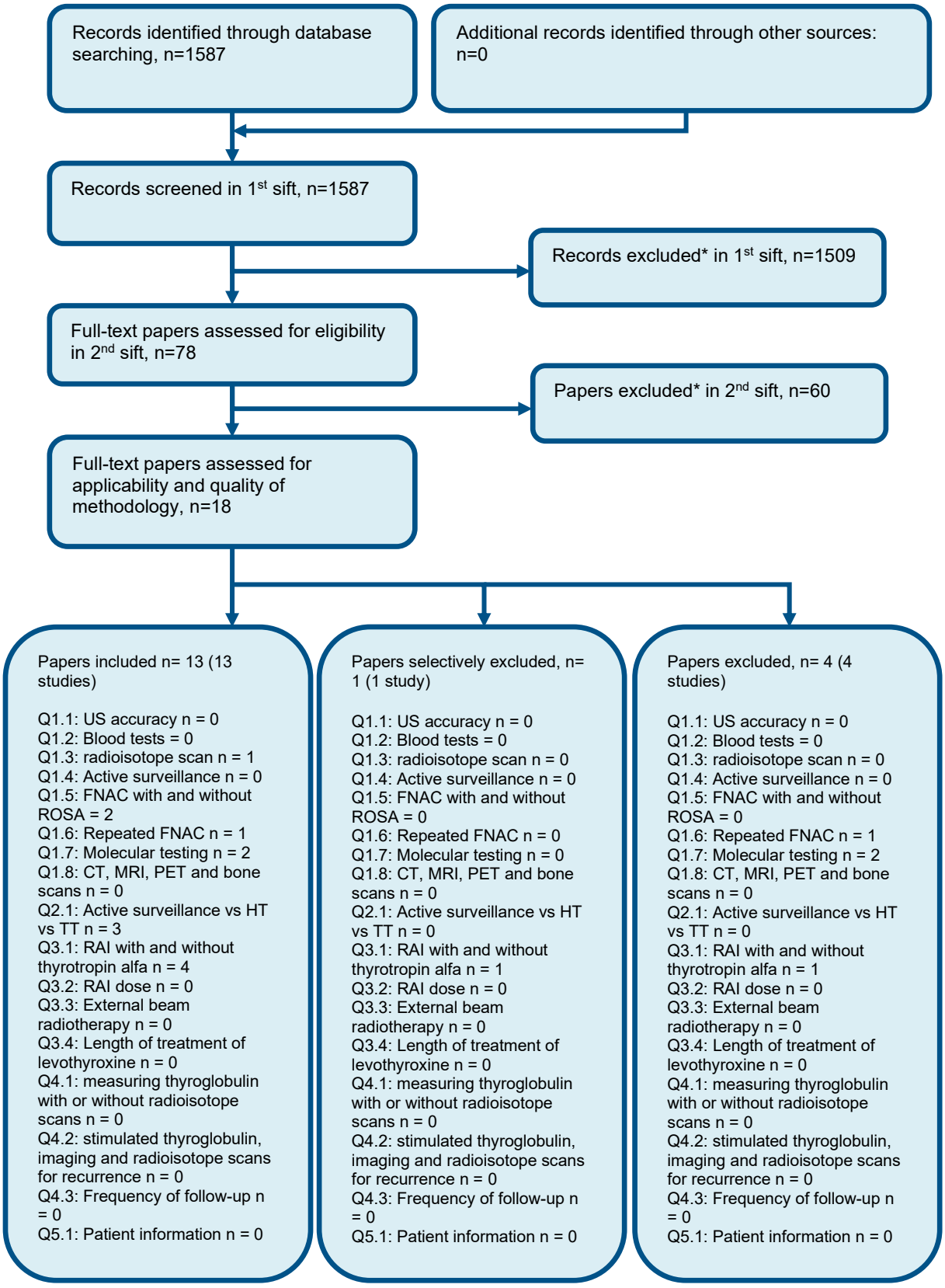
Table 5: Clinical evidence profile: External-Beam radiotherapy versus no External-beam radiotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	EBR	No EBR	Relative (95% CI)	Absolute		
Mortality: Follicular 10 years IV-A												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	Very serious imprecision[2]	none	816	8038	Adjusted HR: 1.14 [0.53, 2.46]	Not assessable	VERY LOW	CRITICAL
Mortality: Follicular 10 years IV-B												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	Very serious imprecision[2]	none	816	8038	Adjusted HR: 0.28 [0.05, 1.51]	Not assessable	VERY LOW	CRITICAL
Mortality: Follicular 10 years IV-C												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	Very serious imprecision[2]	none	816	8038	Adjusted HR: 0.90 [0.58, 1.38]	Not assessable	VERY LOW	CRITICAL
Mortality: Papillary 10 years IV-A												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	Serious imprecision[2]	none	816	8038	Adjusted HR: 1.29 [0.93, 1.79]	Not assessable	VERY LOW	CRITICAL
Mortality: Papillary 10 years IV-B												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	Serious imprecision[2]	none	816	8038	Adjusted HR: 1.74 [1.16, 2.70]	Not assessable	VERY LOW	CRITICAL

Mortality: Papillary 10 years IV-C												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	Very serious imprecision[2]	none	816	8038	Adjusted HR: 1.25 [0.76, 2.08]	Not assessable	VERY LOW	CRITICAL
All-cause Mortality (RR)												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	Very serious imprecision[2]	none	25	43	Adjusted RR: 1.20 [0.40, 4.2]	Not assessable	VERY LOW	CRITICAL
All-cause mortality (HR)												
3	Observational	very serious risk of bias[1]	no serious inconsistency	No serious indirectness	Serious imprecision[2]	none	572	957	Adjusted HR: 1.36 [1.08, 1.71]	Not assessable	VERY LOW	CRITICAL
Disease-specific mortality (HR)												
3	Observational	very serious risk of bias[1]	no serious inconsistency	no serious indirectness	Serious imprecision[2]	none	508	1071	Adjusted HR: 1.57 [1.19, 2.07]	Not assessable	VERY LOW	CRITICAL
Progression of disease (RR)												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	No serious imprecision	none	25	43	Adjusted RR: 0.05 [0.01, 0.25]	Not assessable	LOW	CRITICAL
Progression of disease (HR)												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	Serious imprecision[2]	none	211	194	Adjusted HR: 0.68 [0.49, 0.94]	Not assessable	VERY LOW	CRITICAL
Local/regional recurrence (HR)												
1	Observational	very serious risk of bias[1]	NA	no serious indirectness	No serious imprecision	none	550	335	Adjusted HR: 0.23 [0.17, 0.32]	Not assessable	LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G – Economic evidence study selection



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

Appendix H – Economic evidence tables

None.

Appendix I – Excluded studies

I.1 Clinical studies

Table 6: Studies excluded from the clinical review

Study	Exclusion reason
Alanis 2000[1]	Not review population
Ampil 1985[2]	Systematic review: study designs inappropriate
Arora 2014[3]	Systematic review: literature search not sufficiently rigorous
Augustin, 2021[4]	Did not compare EBR to no EBR
Brierley 1996[7]	Not review population
Brierley 1998[6]	Inappropriate comparison
Brierley 2005[5]	Systematic review: study designs inappropriate
Briggs 2002[8]	Not guideline condition
Carrillo, 2020[9]	EBR versus EBR with rescue surgery. As both arms have EBR, this study cannot evaluate the effects of EBR ; instead, any differential effects between arms will be due to the addition of rescue surgery, which is not the topic under scrutiny.
Cetinayak 2008[10]	Not guideline condition
Chen 2009[11]	Non-English language studies
Chougule 2011[12]	Not guideline condition
Chow 2002[13]	Systematic review is not relevant to review question or unclear PICO
Compagnon 2016[14]	Non-English language studies
Corral 2020[15]	Systematic review is not relevant to review question or unclear PICO
Corrigan 2019[16]	Systematic review is not relevant to review question or unclear PICO
De crevoisier 2004[17]	Systematic review: study designs inappropriate
Esik 1994[18]	Not review population
Farina 2017[20]	Systematic review: study designs inappropriate
Gal 2013[21]	Not review population
Gao, 2021[22]	abstract
Gkountouvas 2010[23]	Systematic review: study designs inappropriate

Groen, 2022[24]	No adjustments made for confounding in analysis
Hadjieva 2001[25]	Systematic review: study designs inappropriate. Systematic review is not relevant to review question or unclear PICO
Hallquist 1993[26]	Systematic review is not relevant to review question or unclear PICO
Han 2020[27]	Systematic review is not relevant to review question or unclear PICO
Kebebew 2005[30]	Not review population
Kiess 2016[32]	Conference abstracts
Kim 2010[33]	Not review population
Kim 2017[34]	Not review population
Kukulska, 2021[35]	No adjustments made for confounding in analysis
Kus 2010[36]	Not review population
Kwon 2013[37]	Inappropriate comparison
Lee 2006[38]	Systematic review: methods are not adequate/unclear
Levendag 1993[39]	Systematic review: literature search not sufficiently rigorous
Lin 1997[40]	Not review population
Mangoni 2017[41]	Systematic review: literature search not sufficiently rigorous
Meadows 2006[42]	Inappropriate comparison
O'connell 1994[45]	Not review population
Phlips 1993[46]	Not review population
Romesser 2014[47]	Systematic review is not relevant to review question or unclear PICO
Romesser, 2021[48]	EBR versus EBR with chemotherapy. As both arms have EBR, this study cannot evaluate the effects of EBR ; instead, any differential effects between arms will be due to the addition of chemotherapy, which is not the topic under scrutiny. No adjustments for confounding
Ron 2012[49]	Systematic review is not relevant to review question or unclear PICO. Systematic review: study designs inappropriate. Systematic review: literature search not sufficiently rigorous
Ryu, 2021[50]	abstract
Saeed 2020[51]	Not review population
Schwartz 2008[53]	Not review population
Schwartz 2009[52]	Not review population
Sekar, 2020[54]	Effects of EBR on outcome not analysed

Shaha 2017[55]	Not review population
Shete, 2020[56]	No adjustments for confounding
Shi 2018[57]	Not review population
Shokoohi 2020[58]	Not review population
Siraj, 2020[59]	Did not evaluate EBR
Smith 2012[61]	Not review population
Srikantia 2011[62]	Systematic review is not relevant to review question or unclear PICO
Sugino 2014[63]	Systematic review is not relevant to review question or unclear PICO
Tam 2017[64]	Not review population
Tariq 2014[65]	Not review population
Tell 1997[66]	Not review population
Terezakis 2009[67]	Not review population
Troch 2010[68]	Not review population
Tsang 1998[69]	Not review population
Tubiana 1985[70]	Not review population
van Velsen, 2021[71]	Did not evaluate EBRT
Wachter 2020[73]	Not review population
Wang 2006[74]	Not review population

I.2 Health Economic studies

Appendix J – Research recommendations – full details

J.1.1 Research recommendation

What is the clinical and cost effectiveness of external beam radiotherapy, for people with residual or recurrent thyroid cancer?

J.1.2 Why this is important

A research recommendation for a randomised trial comparing EBR and no EBR was considered to be important because of the conflicting information about the efficacy of EBR. Such a trial was not thought to present ethical problems because there is genuine uncertainty in the effects of EBR, and therefore being randomised to one group or another would not be considered to be 'good' or 'bad' based on current data. It was accepted that there would be difficulties in pursuing an RCT in this area, due to the need for a large number of consenting patients to enable adequate random mixing of the complex array of possible presentations that will occur by the time that EBR treatment would be used in the clinical pathway. A small RCT, even if carried out with impeccable methodology, might not achieve good random mixing of characteristics and therefore might yield a study with selection bias. The case of a previous attempt at an RCT in Europe 15 years was discussed, where the study was discontinued because of the difficulty in recruiting enough patients who would consent to randomisation. However, the committee did not feel that this meant that there were any fundamental reasons why an RCT would not be possible and given that it was an important issue the benefits of attempting to carry it out might be worth the logistic hurdles.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	EBRT may have the potential to offer patients a significant reduction in local symptoms and local progression, although there is also evidence that it may increase mortality. However, the current evidence base is not rigorous enough to confirm this. A better evidence base, in the form of a large, stratified RCT, is therefore important for patients to allow the possibility of safe and effective use of EBRT in patient groups where its benefits may outweigh harms and for EBRT to be avoided in patient groups where its harms may exceed benefits.
Relevance to NICE guidance	The efficacy of EBRT has been considered in this guideline, but we did not find any RCTs evaluating it. The development of such RCTs is therefore required.
Relevance to the NHS	A large, stratified RCT will enable more targeted provision of a modality that may improve quality of life and reduce mortality for some groups.
National priorities	None known

Current evidence base	No RCTs are available. Observational evidence (with adjustment for confounding) suggests a paradoxical picture, with EBR having some benefits on progression and recurrence but not mortality.
Equality considerations	None known

J.1.4 Modified PICO table

Population	People with localised residual, or locally recurrent thyroid cancer (not amenable to other treatments).
Intervention	EBRT
Comparator	Usual care
Outcome	Quality of life, progression, mortality
Study design	RCT
Timeframe	Long term
Additional information	None