NICE National Institute for Health and Care Excellence

NICE guideline

Thyroid cancer: assessment and management

NICE guideline
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Your responsibility

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals and practitioners are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or the people using their service. It is not mandatory to apply the recommendations, and the guideline does not override the responsibility to make decisions appropriate to the circumstances of the individual, in consultation with them and their families and carers or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Local commissioners and providers of healthcare have a responsibility to enable the guideline to be applied when individual professionals and people using services wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with complying with those duties.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

Overview

This guideline covers diagnosis and management of thyroid cancer in people aged 16 and over. It aims to reduce variation in practice and increase the quality of care and survival for people with thyroid cancer.

Who is it for?

- Healthcare professionals
- Commissioners and providers of thyroid cancer services
- People with thyroid cancer, their families and carers.

Recommendations

People have the right to be involved in discussions and make informed decisions about their care, as described in NICE's information on making decisions about your care.

Making decisions using NICE guidelines explains how we use words to show the strength (or certainty) of our recommendations, and has information about prescribing medicines (including off-label use), professional guidelines, standards and laws (including on consent and mental capacity), and safeguarding.

1.1 Information and support

Information for people with suspected thyroid cancer

1.1.1 When providing information, follow the recommendations on enabling patients to actively participate in their care in NICE's guideline on patient experience in adult NHS services and putting shared decision making into practice in NICE's guideline on shared decision making.

1.1.2 Explain to people with suspected thyroid cancer:

- that not all lumps, nodules or swellings in the thyroid are cancer
- what the diagnostic pathway involves and what tests they may need.

1.1.3 Advise people where to find reliable high-quality information and support after consultations, from sources such as national and local support groups, networks and information services.

Information for people having surgery

1.1.4 Offer people with suspected or confirmed thyroid cancer, and their family and carers if appropriate, written and verbal information on what hemithyroidectomy or total thyroidectomy involves. Explain the benefits and risks of treatment, including long-term implications such as:

- the effects of having part or all of your thyroid removed
- the potential for and possible consequences of:
  - hypothyroidism and the subsequent need for lifelong thyroid hormone replacement
  - the need for treatment for low parathyroid hormone
  - voice change and swallowing disorders.

Information for people with thyroid cancer

1.1.5 When giving people with thyroid cancer their diagnosis, even for low-risk thyroid cancers, it is important to acknowledge that this is a cancer diagnosis and allow the person time to ask questions and be fully informed.

1.1.6 Do not refer to thyroid cancer as a 'good cancer' because many people do not find this reassuring and it can cause them to feel that their diagnosis is unimportant.

1.1.7 Consider further appointments if they will benefit a person's psychological wellbeing, even if they are not indicated for physical reasons.

1.1.8 Give people with thyroid cancer, and their family and carers if appropriate, written and verbal information on:

- who their key worker is and who to contact for more information
- their thyroid cancer and its likely cure rate, effect on their life expectancy and likelihood of recurrence

- the role and function of the thyroid gland and the need for long-term monitoring of thyroid function
- how treatment may affect conception, pregnancy, breast feeding and fertility
- the risks, benefits and uncertainties of treatment and its potential effects on their quality of life, energy, weight and mood
- the roles of those involved in their treatment and follow up, and the composition of the multidisciplinary team
- where to get reliable further information.

1.1.9 At follow up give people with thyroid cancer, and their family and carers if appropriate, information on:

- follow up and how it is likely to be done
- what thyroglobulin is, how it is measured and why
- lifelong thyroid hormone replacement
- lifelong monitoring of thyroid function
- when to seek advice from a healthcare professional, who that healthcare professional should be and how to contact them.

Information for people having radioactive iodine

1.1.10 Offer people with suspected or confirmed thyroid cancer, and their family and carers if appropriate, written and verbal information on the benefits, and short- and long-term risks of radioactive iodine (RAI). Explain that:

- the aim of RAI is to destroy any residual thyroid tissue, including tissue that may be malignant, and allows effective monitoring for recurrence by a blood test
- precautions may be needed when taking RAI which may temporarily affect conception, pregnancy, breast feeding and fertility

- although uncommon, there is the potential for dry mouth and salivary gland inflammation, both of which are temporary in most people
- there is a potential but very low risk of RAI causing new primary second cancers.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on information and support.

Full details of the evidence and the committee's discussion are in evidence review R: information, education and support needed by people with suspected and confirmed thyroid cancer, and their families and carers.

1.2 Assessment and diagnosis

1.2.1 See the recommendation on referral for suspected thyroid cancer in the NICE guideline on suspected cancer.

Blood tests

1.2.2 See the recommendations on thyroid function tests in the NICE guideline on thyroid disease.

1.2.3 Do not use calcitonin testing to assess thyroid nodules unless there is a reason to suspect medullary thyroid cancer (MTC), such as a family history or a nodule with an appearance on ultrasound that suggests MTC.

1.2.4 Do not routinely measure thyroid peroxidase antibody (TPO).

1.2.5 Consider TPO measurement when interpreting indeterminate cytopathology.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on blood tests.

Full details of the evidence and the committee's discussion are in evidence review B: indications for blood tests.

Ultrasound

1.2.6 See the section on investigating thyroid enlargement in the NICE guideline on thyroid disease, and the recommendation on referral for suspected thyroid cancer in the NICE guideline on suspected cancer.

1.2.7 Offer greyscale ultrasound with an established system for grading ultrasound appearance as the initial diagnostic test when investigating thyroid nodules for malignancy.

1.2.8 See the recommendations on grading and reporting ultrasound findings when investigating thyroid enlargement in the NICE guideline on thyroid disease.

Management options based on ultrasound results

1.2.9 Offer fine needle aspiration cytology (FNAC) to people who meet the threshold using an established system for grading ultrasound appearance.

1.2.10 Consider FNAC or active surveillance for people who do not meet the threshold for FNAC on ultrasound grading alone if there are other reasons for clinical concern.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on ultrasound.

Full details of the evidence and the committee's discussion are in evidence review A: ultrasound accuracy and threshold of nodule size and classification.

FNAC testing

Performing and reporting FNAC

1.2.11 See the recommendation on using ultrasound guidance when performing FNAC in the NICE guideline on thyroid disease.

1.2.12 Use liquid-based cytology, direct smear or both when processing FNAC samples.

1.2.13 Use the Royal College of Pathologists modification of the British Thyroid Association (BTA) reporting system to report cytology results.

1.2.14 Consider rapid on-site evaluation of FNAC adequacy rates to improve the diagnostic yield of samples if the Thy1 (inadequate) rate for the centre or individual clinicians is higher than 15% (when Thy1c is excluded).

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on performing and reporting FNAC.

Full details of the evidence and the committee's discussion are in evidence review D: diagnostic accuracy of fine needle aspiration cytology.

Management and further sampling after initial FNAC

1.2.15 Use the initial FNAC results to determine further management and sampling options, as shown in table 1.

Table 1 Management options after initial fine-needle aspiration cytology

Initial fine-needle aspiration cytology result	Management and further sampling
Thy1 (inadequate)	Offer repeat sampling Consider core-needle biopsy (CNB) or fine-needle aspiration cytology (FNAC) with rapid on-site evaluation (ROSE) as the first choice Consider FNAC alone if ROSE is unavailable and CNB is unavailable or inappropriate Consider diagnostic hemithyroidectomy if the repeat sample is also Thy1
Thy1c (cystic lesion)	Offer repeat sampling with FNAC Consider diagnostic hemithyroidectomy if the repeat sample is also Thy1c and the ultrasound appearances are concerning
Thy2 and Thy2c (benign)	Consider repeat ultrasound Offer repeat sampling with FNAC if the second ultrasound also reaches the threshold for FNAC Consider CNB as an alternative to FNAC Discharge people if there is no evidence of malignancy after all investigations are complete, unless there are other reasons for clinical concern
Thy3a (atypia, neoplasia possible)	Offer repeat sampling Consider CNB (or FNAC if CNB unavailable or inappropriate) Consider diagnostic hemithyroidectomy or active surveillance if repeated samples are still Thy3a
Thy3f (suggesting follicular neoplasm)	Consider diagnostic hemithyroidectomy
Thy4 (suspicion of malignancy) and Thy5 (malignant)	Offer diagnostic hemithyroidectomy, or treatment with therapeutic hemithyroidectomy or total thyroidectomy

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on management and further sampling after initial FNAC.

Full details of the evidence and the committee's discussion are in evidence review E: efficacy of repeat FNAC, active surveillance or discharge and evidence review F: molecular testing.

Radioisotope scans

1.2.16 Do not routinely use radioisotope scans for the initial diagnosis of thyroid cancer.

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on radioisotope scans.

Full details of the evidence and the committee's discussion are in evidence review C: radioisotope scans.

Imaging for further staging

1.2.17 Do not routinely use cross-sectional imaging (CT or MRI) in people with T1 or T2 disease and no other indications.

1.2.18 Consider cross-sectional imaging (CT of neck and chest, or MRI of neck and CT of chest) for people with thyroid cancer that is T3 or T4, any N1 or M1 thyroid cancer or other clinical suspicion of metastases.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on imaging for further staging.

Full details of the evidence and the committee's discussion are in evidence review G: imaging for further staging.

1.3 Initial treatment of differentiated thyroid cancer

Surgery and active surveillance for primary tumours

1.3.1 When discussing surgical options with a person with differentiated thyroid cancer, take into account their preferences, comorbidities and all the available evidence regarding their tumour.

1.3.2 Offer hemithyroidectomy or total thyroidectomy to people with differentiated thyroid tumours larger than 1 cm or multifocal disease (T1a [m] to T2N0M0).

1.3.3 Offer total thyroidectomy to people who have:

- a T3 or T4 stage primary tumour
- regional lymph node involvement (N1)
- adverse pathological features
- distant metastatic disease (M1).

1.3.4 Offer completion thyroidectomy to people who have had a hemithyroidectomy if it is indicated on review of the histological features of the initial specimen.

1.3.5 Consider hemithyroidectomy or active surveillance for people with a solitary microcarcinoma (T1a) without evidence of nodal involvement.

Surgery for nodal disease

1.3.6 Offer a compartment-orientated lateral neck dissection for people with structural nodal disease in the lateral neck.

1.3.7 Consider a prophylactic ipsilateral central neck dissection when doing the compartment-orientated lateral neck dissection for people with structural nodal disease in the lateral neck.

1.3.8 Offer a compartment-orientated central neck dissection for people with structural nodal disease in the central neck.

1.3.9 Do not offer prophylactic central or lateral neck dissection (except in the circumstances in recommendation 1.3.7).

Surgery during pregnancy

1.3.10 Consider deferring surgery until after pregnancy, taking into account:

- the risk of delaying surgery
- the risk to the pregnancy
- the rate of disease progression.

The obstetrician, surgeon and endocrinologist should discuss these factors and a joint decision should be reached in discussion with the pregnant woman.

1.3.11 When surgery cannot be delayed until after pregnancy, it should be done during the second trimester if possible.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on surgery and active surveillance for primary tumours.

Full details of the evidence and the committee's discussion are in evidence review H: initial treatments for differentiated thyroid cancer.

Thyrotropin alfa

1.3.12 Offer thyrotropin alfa for pretherapeutic stimulation for people with thyroid cancer (including those with distant metastases; see recommendation 1.3.13) who are having RAI ablation.

In December 2022 this use of thyrotropin alfa as a treatment for thyroid cancer in people with distant metastases was off-label. See NICE's information on prescribing medicines.

1.3.13 Use thyrotropin alfa with caution in people with thyroid cancer who have brain or spinal metastases, because there is a risk of clinically significant tumour flare.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on thyrotropin alfa.

Full details of the evidence and the committee's discussion are in evidence review I: thyrotropin alfa.

RAI for initial ablation

1.3.14 Offer RAI to people who have had a total or completion thyroidectomy based on the criteria in the recommendation on offering total thyroidectomy in the section on surgery and active surveillance for primary tumours.

1.3.15 Do not offer RAI to people with T1a or T1b tumours including those with multifocal disease, unless there are adverse features, regional lymph node involvement, or evidence of other metastatic disease.

1.3.16 Consider RAI for people with T2 disease who have had a total or completion thyroidectomy, but whose disease does not show any of the features in the recommendation on offering total thyroidectomy in the section on surgery and active surveillance for primary tumours.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on RAI for initial ablation.

Full details of the evidence and the committee's discussion are in evidence review J: radioactive iodine versus no radioactive iodine.

RAI activity for initial ablation

1.3.17 Consider RAI with an activity for initial ablation of 3.7 GBq for people with high-risk features such as T4, N1b or M1 disease or aggressive subtypes, or people for whom multiple ablations should be avoided because they have one or more of the following characteristics:

- significant comorbidities such as cardiovascular disease
- mobility issues
- complex social concerns.

1.3.18 Offer RAI with an activity for initial ablation of 1.1 GBq to people who are not having 3.7 GBq.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on RAI activity.

Full details of the evidence and the committee's discussion are in evidence review K: activity of radioactive iodine after thyroidectomy.

External beam radiotherapy

1.3.19 Consider external beam radiotherapy (EBRT) if there is macroscopic disease after surgery or local disease that is unlikely to be controlled with RAI.

1.3.20 Consider EBRT for symptom control for people receiving palliative care.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on external beam radiotherapy.

Full details of the evidence and the committee's discussion are in evidence review L: external beam radiotherapy versus no external beam radiotherapy.

1.4 Ongoing treatment with thyroid stimulating hormone suppression for differentiated thyroid cancer

When to offer thyroid stimulating hormone suppression

1.4.1 Do not offer thyroid stimulating hormone (TSH) suppression to people who:

- do not meet the threshold for RAI (see the section on RAI for initial ablation)
- have significant comorbidities that mean low TSH levels should be avoided.

1.4.2 Offer thyroid hormone at doses that will suppress TSH to below 0.1 mIU/litre, to people who have had total or completion thyroidectomy and RAI. TSH suppression should be continued until follow-up review at 9 to 12 months after initial treatment has been completed.

Assessing and managing response to TSH suppression

1.4.3 Use dynamic risk stratification to determine further management at 9 to 12 months after completion of initial RAI ablation, as follows:

- Reduce TSH suppression to achieve a TSH level of between 0.3 mIU/litre and 2.0 mIU/litre and continue this for life in people with an excellent response to treatment.
- Continue TSH suppression to achieve a TSH level of between 0.1 mIU/litre and 0.5 mIU/litre in people who have an intermediate response to initial treatment.

1.4.4 Continue to suppress TSH to less than 0.1 mIU/litre in people who have biochemical or structural evidence of persistent or recurrent disease.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on thyroid stimulating hormone suppression.

Full details of the evidence and the committee's discussion are in evidence review M: TSH suppression versus no TSH suppression.

Long-term duration of TSH suppression

1.4.5 Offer a review to people who have had ongoing TSH suppression for more than 10 years. Decide whether the TSH suppression can be reduced after an individualised assessment of risks and benefits, and explain that:

- lifelong suppression is not necessary unless they have high-risk or metastatic disease
- reducing TSH suppression may lower the risk of developing bone and cardiac problems.

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on long-term duration of TSH suppression.

Full details of the evidence and the committee's discussion are in evidence review N: duration of TSH suppression.

1.5 Post-thyroidectomy monitoring of differentiated thyroid cancer

Measuring thyroglobulin and thyroglobulin antibodies

1.5.1 Be aware that:

- the presence of thyroglobulin antibodies, above the laboratory threshold, can

interfere with the measurement of thyroglobulin levels

- detectable thyroglobulin levels in people without thyroglobulin antibodies suggest the presence of either residual thyroid tissue or residual or recurrent thyroid cancer.

1.5.2 Offer thyroglobulin measurement alongside measurement of thyroglobulin antibodies in people with differentiated thyroid cancer who have had total or completion thyroidectomy and RAI. Measure at:

- 3- to 6-month intervals in the first 2 years after RAI ablation **and**
- 6- to 12-month intervals thereafter.

1.5.3 Consider further investigations if a person has had total thyroidectomy and RAI, and:

- has detectable thyroglobulin levels without thyroglobulin antibodies
- investigations have not shown recurrent or residual cancer in the presence of detectable thyroglobulin without thyroglobulin antibodies, and now the thyroglobulin levels without thyroglobulin antibodies are rising.

1.5.4 Consider further investigations if a person has had a total thyroidectomy without RAI and has rising thyroglobulin levels without thyroglobulin antibodies.

1.5.5 Do not routinely measure thyroglobulin levels in people who have not had total or completion thyroidectomy.

1.5.6 Consider further investigation when thyroglobulin antibodies are first detected above the laboratory threshold or at any point if the levels of thyroglobulin or thyroglobulin antibodies are rising.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on measuring thyroglobulin and thyroglobulin antibodies.

Full details of the evidence and the committee's discussion are in evidence review O: measurement of thyroglobulin.

Stimulated thyroglobulin and highly sensitive thyroglobulin testing

1.5.7 Consider either a stimulated thyroglobulin test or highly sensitive thyroglobulin test if thyroglobulin is undetectable on a standard assay in people who have had a total or completion thyroidectomy and RAI, and have no evidence of structural persistent disease.

1.5.8 Consider the following if using a stimulated thyroglobulin test:

- less frequent follow up, where appropriate, and more relaxed TSH suppression if stimulated thyroglobulin is below 1 microgram/litre (low risk)
- continuing TSH suppression if stimulated thyroglobulin is between 1 microgram/litre and 10 microgram/litre (indeterminate risk)
- further investigations and treatment if stimulated thyroglobulin is 10 microgram/litre or more and there is no resectable disease.

1.5.9 Consider the following if using a highly sensitive assay that can detect thyroglobulin levels lower than 0.2 microgram/litre:

- less frequent follow up, where appropriate, and more relaxed TSH suppression if the thyroglobulin level is lower than 0.2 microgram/litre
- stimulated thyroglobulin, which can be helpful in separating people into lower- and higher-risk groups if the thyroglobulin level is between 0.2 microgram/litre and 1 microgram/litre.

1.5.10 Use caution when interpreting results in the presence of thyroglobulin antibodies

because they may cause false-positive or negative findings.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on stimulated thyroglobulin and highly sensitive thyroglobulin testing.

Full details of the evidence and the committee's discussion are in evidence review P: stimulated or highly sensitive thyroglobulin assays.

1.6 Follow up of differentiated thyroid cancer

1.6.1 Do not routinely follow up people with thyroid cancer who have a solitary microcarcinoma (T1a) that has been surgically removed.

1.6.2 Consider an ultrasound at 6 to 12 months initially then annual clinical follow up for up to 5 years for people with T1a (m) or T1b stage or greater thyroid cancer, who have had a hemithyroidectomy or total thyroidectomy without RAI.

1.6.3 Consider a risk-stratified approach to follow up for any person who has had total or completion thyroidectomy and RAI, as shown in table 2.

Table 2 Risk-stratified follow up for people who have had a total or completion thyroidectomy and radioactive iodine

Risk group	Follow up
Low risk (no evidence of disease on imaging and thyroglobulin of less than 0.2 microgram/litre, or stimulated thyroglobulin of less than 1 microgram/litre)	Consider (at least annually) follow up of 2 to 5 years with thyroglobulin testing Use ultrasound if needed
Medium risk (thyroglobulin between 0.2 and 1.0 microgram/litre, or stimulated thyroglobulin of between 1 and 10 microgram/litre)	Consider (at least annually) 5 to 10 years follow up with thyroglobulin testing Use ultrasound if needed

Risk group	Follow up
High risk (thyroglobulin of greater than 1.0 microgram/litre, or stimulated thyroglobulin of greater than 10 microgram/litre)	Consider (at least annually) 10 years follow up with thyroglobulin testing Use ultrasound if needed
Anyone with biochemical or structural evidence of disease	Consider (at least annually) lifelong follow up with thyroglobulin testing Use ultrasound if needed

1.6.4 Discuss at the multidisciplinary team meeting any person who has had a total or completion thyroidectomy and RAI and has evidence of structural persistent disease.

For a short explanation of why the committee made these recommendations and how they might affect practice, see the rationale and impact section on follow up.

Full details of the evidence and the committee's discussion are in evidence review Q: length and frequency of follow up.

Terms used in this guideline

This section defines terms that have been used in a particular way for this guideline.

Active surveillance

Active surveillance involves monitoring the person's thyroid cancer with periodic appointments that include investigations such as blood tests and ultrasound. The duration and frequency of further appointments and investigations should be a clinical decision that considers the risks for the person.

Completion thyroidectomy

A completion thyroidectomy relates to when someone who has had a hemithyroidectomy has the rest of their thyroid gland removed. In this guideline, recommendations related to

treatment and monitoring for total thyroidectomy also apply to people who have had a completion thyroidectomy.

Dynamic risk stratification

Following initial risk assessment at diagnosis, the risk of recurrence is re-assessed at follow up by evaluating the person's response to treatment. This re-evaluation of risk constitutes a 'dynamic risk stratification' allowing the follow-up strategy to be modified according to risk. This is an established system and the response to treatment is based on measurement of serum thyroglobulin Tg (and anti-thyroglobulin antibody TgAb) and ultrasound imaging.

Radioactive iodine

A radioactive form of iodine used to treat thyroid cancer by killing thyroid cells and thyroid cancer cells after surgery. It is usually taken in a capsule or liquid.

Thyroid cytology specimens

This guideline uses the Royal College of Pathologists guidance on the reporting of thyroid cytology specimens published in 2016 (see table 3) for recommendations related to reporting FNAC results.

Table 3 Royal College of Pathologists thyroid cytology categories

Thy category	Description
Thy1	Inadequate or non-diagnostic Thy1: inadequate Thy1c: cystic lesion
Thy2	Benign or non-neoplastic
Thy3	Indeterminate or neoplasm possible Thy3A: neoplasm possible (atypical features) Thy3F: follicular neoplasm
Thy4	Suspicious of malignancy
Thy5	Malignant

TNM classification

This guideline uses the tumour, node, metastasis (TNM) classification developed by the Union for International Cancer Control (UICC) to describe the stage of the cancer. Please refer to the TNM Classification of Malignant Tumours, 8th Edition for further information.

Recommendations for research

The guideline committee has made the following recommendations for research.

Key recommendations for research

1 Molecular tests

In fine-needle aspiration cytology (FNAC) samples that are adequate but cannot differentiate between benign and malignant samples, what is the clinical and cost effectiveness of molecular testing for thyroid cancer?

For a short explanation of why the committee made this recommendation for research, see the rationale section on management and further sampling after initial FNAC.

Full details of the evidence and the committee's discussion are in evidence review F: molecular testing.

2 Duration of follow up

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

For a short explanation of why the committee made this recommendation for research, see the rationale section on follow up.

Full details of the evidence and the committee's discussion are in evidence review Q: length and frequency of follow up.

3 Active surveillance compared with surgery

For people with stage 1 differentiated thyroid cancer, what is the clinical and cost effectiveness of active surveillance compared with surgery?

For a short explanation of why the committee made this recommendation for research, see the rationale section on surgery and active surveillance for primary tumours.

Full details of the evidence and the committee's discussion are in evidence review H: initial treatments for differentiated thyroid cancer.

4 Duration of thyroid stimulating hormone suppression

For people with differentiated thyroid cancer who have had surgery and radioactive iodine (RAI), what is the optimal duration of thyroid stimulating hormone suppression?

For a short explanation of why the committee made this recommendation for research, see the rationale section on long-term duration of TSH suppression.

Full details of the evidence and the committee's discussion are in evidence review N: duration of TSH suppression.

Other recommendations for research

5 Radioactive iodine

What is the clinical and cost effectiveness of RAI after total or completion thyroidectomy for people with T2 disease and no adverse pathological features?

For a short explanation of why the committee made this recommendation for research, see the rationale section on RAI for initial ablation.

Full details of the evidence and the committee's discussion are in evidence review J: radioactive iodine versus no radioactive iodine.

6 Thyroid peroxidase antibody testing

For people with indeterminate cytopathology, what is the clinical and cost effectiveness of thyroid peroxidase antibody testing?

For a short explanation of why the committee made this recommendation for research, see the rationale section on thyroid peroxidase antibody testing.

Full details of the evidence and the committee's discussion are in evidence review B: indications for blood tests.

7 Imaging for further staging

For people with differentiated thyroid cancer who have initial ultrasound evidence of extensive local spread (T2N1), what is the clinical and cost effectiveness of CT, MRI or F-18 FDG PET-CT scanning, with or without ultrasound, as part of a further staging strategy?

For a short explanation of why the committee made this recommendation for research, see the rationale section on imaging for further staging.

Full details of the evidence and the committee's discussion are in evidence review G: imaging for further staging.

8 External beam radiotherapy compared with usual care

What is the clinical and cost effectiveness of external beam radiotherapy for people with

residual or recurrent thyroid cancer?

For a short explanation of why the committee made this recommendation for research, see the rationale section on external beam radiotherapy.

Full details of the evidence and the committee's discussion are in evidence review L: external beam radiotherapy versus no external beam radiotherapy.

Rationale and impact

These sections briefly explain why the committee made the recommendations and how they might affect practice.

Information and support

Recommendations 1.1.1 to 1.1.10

Why the committee made the recommendations

The committee agreed that the NICE guidelines on patient experience in adult NHS services and shared decision making give important advice on enabling people to participate in their care.

The committee agreed that it is important to give information on what to expect with investigations and treatments, and to deliver it at an appropriate time to support people in managing their condition. The committee were aware that people often look for information themselves and therefore it is important to direct them to sources that are good quality and reliable.

The committee also agreed it is important to explain to people with signs of thyroid cancer that not all swellings are cancerous and what any investigations may entail. This included the implications of surgery on thyroid function and what the consequences are.

Evidence showed that telling people with thyroid cancer that it is a 'good cancer', was generally not reassuring. It caused them to feel that the diagnosis was being dismissed as unimportant and, as a result, they felt undeserving of seeking support. Therefore, the committee recommended that healthcare professionals should avoid telling people they have a 'good cancer'. Instead, they should give the person time to acknowledge they have cancer and to ask any questions. For some people this may mean further appointments are beneficial.

The committee agreed that a lot of people with newly diagnosed thyroid cancer might not know what the thyroid gland does. Therefore, it is important to give them information on the thyroid gland, how their condition will be managed, any consequences of treatment

and the long-term follow-up requirements.

How the recommendations might affect practice

Giving people information and support and including further appointments for some people, is current practice. Therefore, the recommendations are unlikely to have a big impact.

Return to recommendations

Blood tests

Recommendations 1.2.2 to 1.2.5

Why the committee made the recommendations

The very early part of the pathway for suspected thyroid cancer is covered in other NICE guidance. NICE's guideline on suspected cancer covers when to refer people with an unexplained thyroid lump and NICE's guideline on thyroid disease covers the initial tests to use when investigating suspected thyroid dysfunction or thyroid enlargement. For this guideline, the committee looked at additional blood tests that could be used for the diagnosis of thyroid cancer. The committee made recommendations in this area based on consensus because no evidence was identified.

Calcitonin testing

The committee discussed the high rate of false positives from calcitonin testing, which can cause serious harm from unnecessary treatments. For example, the committee were aware of evidence that suggested that borderline raised calcitonin can be caused by Hashimoto's disease or certain drugs. This can in turn cause over-treatment and high levels of morbidity. The false positives may cause a particularly low positive-predictive value because of the relative rarity of medullary thyroid cancer (MTC), with only 100 to 150 new cases per year in the UK. The committee therefore agreed that for most people it would be more useful and less harmful not to use calcitonin testing. Instead, other methods of assessment should be used, such as fine-needle aspiration cytology (FNAC).

However, the committee agreed that there were some people for whom the benefits of

calcitonin testing might outweigh its harms. This would include people at higher risk of MTC, for whom the risks of false negatives would outweigh the risks of false positives at a population level. This includes people with a family history of MTC; those with multiple endocrine neoplasms; those with suspected MTC or MTC diagnosed by cytopathology, core biopsy, or other histopathology; and people with C-cell hyperplasia.

Therefore, a recommendation was made that calcitonin should not be tested routinely unless there are prior reasons to suspect MTC.

Thyroid peroxidase antibody testing

The committee discussed from their experience how results from thyroid peroxidase antibody (TPO) tests can facilitate interpretation of FNAC results. For example, if the FNAC result is suggestive of benign thyroiditis, then a positive TPO test may help to confirm this. A positive TPO test may also allow an indeterminate result to be downgraded to benign. Therefore, the committee agreed that TPO should be used to facilitate interpretation in cases where the FNAC result is uncertain. However, where there is little uncertainty about the FNAC result, the committee did not think the benefits of TPO testing justified its use. Therefore, the recommendation was made that TPO should not be routinely measured but could be considered when there was indeterminate cytopathology. Given the uncertainty in this area the committee also made a recommendation for research on thyroid peroxidase antibody testing.

How the recommendations might affect practice

The recommendation to not offer calcitonin testing unless MTC is suspected largely reflects current practice in the UK. It also represents a targeted use of NHS resources due to the rarity of MTC and high cost of the test. The recommendation on TPO may lead to an additional use of resources but was considered important to avoid unnecessary surgeries in people with benign nodules and indeterminate cytopathology (for example, people with Hashimoto's disease). It is therefore expected to lead to fewer unnecessary thyroidectomies and ultimately improve the efficiency of the NHS.

Return to recommendations

Ultrasound

Recommendations 1.2.6 to 1.2.10

Why the committee made the recommendations

After considering the diagnostic accuracy evidence, the committee eliminated all index tests that had sensitivity and specificity benchmarks below 0.9 and 0.5, respectively. These were the minimum pre-hoc standards for first-line diagnostic tests. Given that there was evidence for simpler techniques, such as greyscale ultrasound, the committee also excluded techniques that were impractical, unsuitable for most people or invasive. This included elastography and contrast enhanced ultrasound. The committee also considered a simple combination of greyscale characteristics and a doppler test that used blood-velocity measurement. However, evidence for both tests was taken from single studies, which raised questions of representativeness, and the doppler test had imprecision in the sensitivity result. The only index tests remaining that fulfilled all criteria of accuracy and clinical appropriateness were the ordinal scales of greyscale characteristics. Therefore, the committee recommended that greyscale ultrasound should be offered as the initial test. The data available did not provide evidence to suggest one system for grading ultrasound was better than another. Therefore, the committee agreed with the recommendation in the NICE guideline on thyroid disease that the decision to do FNAC should be made using an established system for grading ultrasound.

The committee were also aware that none of the established systems have perfect sensitivity. Therefore, some people with malignancy might 'slip through the net' and not receive further investigation. So, another recommendation was made that people whose results do not meet the threshold could still have further investigations with FNAC or active surveillance if there are still clinical concerns.

Overall, the committee agreed with the recommendations on investigating thyroid enlargement in the NICE guideline on thyroid disease. They discussed the importance of using a classification system that considers:

- echogenicity
- microcalcifications
- border
- shape in transverse plane
- internal vascularity **and**
- lymphadenopathy.

They also agreed that reports of ultrasound findings should:

- specify which grading system has been used for the assessment
- include information on the characteristics of the nodule
- provide an overall assessment of malignancy
- confirm that both lobes have been assessed **and**
- document assessment of cervical lymph nodes.

This can help improve diagnosis by ensuring all the data is available to clinicians when assessing the person.

How the recommendations might affect practice

Recommending an established system for grading ultrasound appearance is not expected to affect current practice significantly. This is because the recommendation does not state which system to use and therefore it is unlikely to persuade clinicians to adopt a new system.

Instituting FNAC or active surveillance for people who do not meet the threshold for FNAC or who have small nodules does not represent a change to current practice.

Return to recommendations

Performing and reporting FNAC

Recommendations 1.2.11 to 1.2.14

Why the committee made the recommendations

The committee recommended that FNAC should be offered with either liquid-based cytology, direct smear or both. They agreed that the evidence did not show that one technique was better than the other. Current practice varies with some centres using one technique and others using both. The committee agreed that the Royal College of Pathologists modification of the BTA reporting system (RCPath BTA) is widely used in the UK. Therefore, they made a recommendation, based on consensus, to use the RCPath BTA

reporting system.

An estimation of the data from the evidence review suggested that rapid on-site evaluation (ROSE) reduced non-diagnostic results by 55%. It is likely to be cost effective when offered where there is a concerningly high inadequacy rate. The Royal College of Pathologists notes that an inadequacy rate of more than 15% (excluding Thy1c) is problematic. Therefore, the committee agreed that centres or individual clinicians with high inadequacy rates might benefit from ROSE if this is implemented and routinely used. Thy1c was excluded from the threshold because it would not benefit from ROSE. This is because Thy1c indicates a non-diagnostic for cystic lesion which is not operator- or technique-dependent.

How the recommendations might affect practice

Although direct smear is commonly used with FNAC, liquid-based cytology is less commonly used in smaller centres. If a centre adopts liquid-based cytology, then some changes in training and provision of equipment may be needed. However, most large centres already use liquid-based cytology and some centres use both as part of a quality assurance process to get better results. The overall impact on practice is likely to be small.

Use of ROSE, specifically for centres or individual clinicians with high inadequacy rates, was thought to represent a change in practice. It would require auditing the adequacy rates of samples and personnel would be needed to provide such services. However, it likely represents a cost-effective use of NHS resources if used where there is a concerningly high inadequacy rate, particularly those with a medium or high volume of FNACs. The committee also agreed it may be beneficial in all centres with a high inadequacy rate. Furthermore, a persistent, low inadequacy rate of FNAC (with or without ROSE) may be achieved due to the training provided by cytopathologists, thus improving the diagnostic efficiency of the NHS in the long-term.

Return to recommendations

Management and further sampling after initial FNAC

Recommendation 1.2.15

Why the committee made the recommendation

For people who have an inadequate (Thy1) FNAC results, the committee recommended that sampling should be repeated. This was because an unsatisfactory aspirate is often a random technical failure that might not be repeated. The preferred approach for repeat sampling is a core-needle biopsy (CNB) or FNAC with ROSE. This was because the diagnostic clinical review of FNAC and CNB, and the studies informing the health economic model, found that CNB and FNAC with ROSE are more accurate than repeat FNAC and associated with a lower rate of unsatisfactory results. The committee recommended that, in some cases, FNAC alone could be performed instead. For example, if CNB and ROSE are not available locally, or if the nodule is near a blood vessel that would make the use of CNB with large needles inappropriate. Should this further test still be Thy1, then the committee thought the best way to determine malignancy is by diagnostic hemithyroidectomy.

For people with a cystic lesion (Thy1c), FNAC should be repeated. This is because neither CNB or FNAC with ROSE were considered useful for non-diagnostic cystic samples. If the second FNAC is also Thy1c and the initial ultrasound appearances are concerning, then the committee agreed that a diagnostic hemithyroidectomy should be considered to establish the diagnosis.

To optimise the sensitivity of FNAC testing, which was fractionally below the target of 0.95, the committee recommended repeating tests that are benign (Thy2 or Thy2c). In the first instance, the committee agreed that repeating ultrasound should be considered. If this still produces a suspicious result, then the next step would be to repeat the FNAC. CNB could be considered as an alternative to repeating FNAC, because although it is invasive and more expensive than FNAC, it can extract more material. Benign FNAC tests should be repeated because sampling error can sometimes cause false negatives. Therefore, if the initial Thy2 result was caused by sampling error, a repeat test is likely to return a positive result but, if it was not, the repeated test will also be Thy2. The committee therefore recommended that people who have had repeated investigations, and there is no evidence of malignancy after these are complete, can be discharged unless there are other clinical concerns.

The committee made a repeat sampling recommendation for people with Thy3a results. The preferred approach is CNB, which reflects the findings of the economic evaluation and clinical review. A consider recommendation was made, because in some cases a Thy3a sample may suggest a follicular lesion, which would not benefit from repeat sampling with

CNB. FNAC is recommended as an alternative when CNB is unavailable or inappropriate. In case of a further Thy3a results, a recommendation was made to use diagnostic hemithyroidectomy or active surveillance.

For people with Thy3f results, the committee recommended that diagnostic hemithyroidectomy be considered. This reflected the committee's view that repeat sampling with FNAC or CNB is less useful after a suspected follicular lesion (Thy3f) and that diagnostic hemithyroidectomy is justified by the high risk of malignancy in this group (around 30%). There were also concerns that, if not followed up with surgery, final diagnosis after Thy3f could take longer. This would delay treatment for a potentially malignant tumour, create uncertainty for the person, and in some centres lead to a longer delay than is allowed by NHS cancer targets. Although the committee agreed that this is current practice, a consider recommendation was made. This reflects the uncertainty in the evidence and the committee agreed that there may be some cases, for instance in older people with severe comorbidities, where a hemithyroidectomy for a Thy3f may not be appropriate.

For people with Thy4 or Thy5 cytology, the committee recommended diagnostic or therapeutic hemithyroidectomy, or total thyroidectomy. The recommendation that people in these groups should be sent straight to surgery was based on evidence that the groups would contain a significant proportion of people with malignancy.

The economic model suggested that molecular testing could be cost effective in certain cytologies, particularly after a suspected follicular lesion (Thy3f), which would not benefit from repeat sampling. However, molecular tests are not widely available in the NHS and are mostly produced outside the UK. The committee agreed that molecular tests could help reduce the number of unnecessary diagnostic hemithyroidectomies in people with indeterminate FNAC results and made a recommendation for research for molecular tests.

How the recommendation might affect practice

The recommendation to offer CNB or FNAC with ROSE after a non-diagnostic Thy1 cytology result is considered a change from current practice. Some centres could have preference for, or availability of, only one of the two techniques, so the recommendation ensures flexibility in the management of Thy1. In centres where neither technique is available, the implementation of CNB or FNAC with ROSE could require additional resources for training and resourcing in the short term. However, the reduction of non-adequate cytologies, repeat sampling and unnecessary surgeries is expected to offset the

initial investments.

The recommendation to consider repeat ultrasound and repeat FNAC with Thy2 reflects current practice and it is not expected to have an impact on NHS resources.

The recommendations to repeat sampling with CNB after a Thy3a cytology is a significant change from current practice. FNAC has generally been the preferred method for repeat sampling in the NHS, so some changes in training for biomedical scientists, radiologists and pathologists and provision of equipment in centres where CNB is rarely offered or not available are expected. However, as shown in the health economic analysis, this is likely a cost-effective use of NHS resources, which would reduce unnecessary diagnostic surgeries and improve efficiency.

The recommendations to offer diagnostic hemithyroidectomy to people with Thy3f and either diagnostic or therapeutic surgery to people with Thy4 and Thy5, reflect the current approach and are not likely to have an impact on practice or resources.

Return to recommendation

Radioisotope scans

Recommendation 1.2.16

Why the committee made the recommendation

In the absence of evidence from the review, the committee formed a recommendation by consensus. The committee agreed that there is a potential harm from radioisotope scans and, based on clinical experience, agreed that they are no more accurate than FNAC. Therefore, the benefits of radioisotope scans would normally not outweigh the harms and they would not be considered.

However, the committee did not have enough evidence to recommend that radioisotope scans should never be used. Therefore, the word 'routinely' was used to indicate that they might be useful in very rare and specific circumstances, although the committee did not provide examples. This was because any such examples would be extremely context-dependent and would not demonstrate the complexity of such decision making.

The committee agreed that there may be value in using radioisotope scans when

assessing recurrent thyroid cancer, however this was not part of this review question. Therefore, this recommendation relates to the initial diagnosis of thyroid cancer.

How the recommendation might affect practice

The recommendation largely reflects current practice because radioisotope scans are only used rarely, and it is therefore not expected to have a significant effect on practice.

Return to recommendation

Imaging for further staging

Recommendations 1.2.17 and 1.2.18

Why the committee made the recommendations

In the absence of evidence, the committee used consensus to form the recommendations. The committee agreed that for people with T1 or T2 thyroid cancer and no other indications, cross-sectional imaging is not needed. The ultrasound results obtained when the thyroid was first assessed should provide enough detail for further staging. Other indications that would suggest cross-sectional imaging may be useful, include signs of metastases or a suspicious symptom such as a cough. This decision was based on the agreement that ultrasound would be sensitive enough to pick up the relatively superficial structural lesions that might occur in most of this group. It was also agreed that the potential harms of deeper imaging techniques would not be outweighed by the benefits in this group. For example, CT carries radiation risks, particularly to younger people, and some people find the experience of MRI distressing.

For people at even higher levels of risk, such as those with T3 or T4 thyroid cancer, or with any local spread to nodes or distant metastases, cross-sectional imaging techniques should be considered, as well as the initial ultrasound, to help define the stage of cancer.

The committee agreed that cross-sectional imaging would be useful either before surgery, to help inform the procedure, or after surgery, to inform subsequent management. However, the committee noted that clinicians would need to balance the benefit of additional information gained from CT contrast, against the potential need to delay RAI as a result of having a CT scan.

How the recommendations might affect practice

The impact of the recommendations on practice is expected to be small, because the recommendations reflect current practice.

Return to recommendations

Surgery and active surveillance for primary tumours

Recommendations 1.3.1 to 1.3.11

Why the committee made the recommendations

Surgery and active surveillance for primary tumours

Evidence from the randomised control trial (RCT) showed total thyroidectomy led to less cancer recurrence than hemithyroidectomy. Weighing up the benefits and harms, using this evidence and their experience, the committee agreed that total thyroidectomy should be recommended over hemithyroidectomy if there are definite indications for postoperative radioactive iodine (RAI), such as a large primary tumour or bilateral disease. This is because definite indications for postoperative RAI suggest that the risk of recurrence is high enough that the benefits of total thyroidectomy outweigh its potential harms. However, where the risk of recurrence is lower, the committee agreed that a hemithyroidectomy would be as beneficial and potentially less harmful, and might also allow people to maintain normal thyroid function. The committee also agreed that, although a hemithyroidectomy might be chosen, some people might need a completion thyroidectomy later if it is indicated by a histological review or during later surveillance.

No randomised evidence was found for active surveillance. Observational evidence showed that surgery led to lower overall mortality compared with active surveillance in people with stage 1 disease. However, the committee were aware of the lack of adjustment for likely confounding by comorbidity. In this population there were no other outcomes reported and so it was difficult to establish a full picture of benefits and harms.

In contrast, observational evidence from adults with cytologically confirmed papillary thyroid microcarcinoma favoured active surveillance over hemithyroidectomy. This was

because people on active surveillance had fewer surgical scar problems, neuromuscular symptoms, throat and mouth symptoms and loss of interest in sex. However, measurements of other quality of life outcomes were largely inconclusive.

The committee agreed that the evidence base suggested that active surveillance should not be used for most people with thyroid cancer. Instead, it should only be considered for people who have a small (less than 1 cm) solitary microcarcinoma, with the person's preferences taken into account after a full discussion. This was because, in the committee's experience, there is a low risk of the tumour adversely affecting the person's quality of life. Therefore the committee made a recommendation to consider either hemithyroidectomy or active surveillance for people with a microcarcinoma.

Given the lack of RCT evidence and low quality of the observational data for active surveillance, the committee also made a recommendation for research comparing active surveillance with surgery.

Surgery for nodal disease

No evidence was found for treatment of existing nodal disease, and so the committee drew upon their clinical experience to form recommendations. The committee agreed that any nodal disease should be dealt with at the time of the total thyroidectomy. Despite the lack of evidence, the committee agreed that a strong 'offer' recommendation was justified because it is in the best interests of the person to ensure no cancerous material is left behind. Leaving it in situ is likely to mean the person would have to have an additional invasive procedure, and also there would be additional cost to the NHS. The committee also noted that there were no alternative procedures to those recommended. Therefore the committee agreed that if nodal disease is present in the lateral neck, a compartment-orientated lateral neck dissection should be offered, and, if nodal disease is present only in the central neck, a compartment-orientated central neck dissection should be offered. They also discussed that carrying out an ipsilateral central neck dissection at the same time may also benefit the person. Because the cancer has already spread to the neck and surgery of the neck is already being performed, carrying out this procedure at the same time may help avoid future surgery. This is a 'consider' recommendation because it was not based on evidence and the procedure is prophylactic and not for the removal of known cancer.

Prophylactic surgery for nodal disease

RCT evidence suggested that people who have had a total thyroidectomy and prophylactic central compartment lymph node dissection (PCCND) needed fewer additional RAI treatments but had a higher risk of permanent hypoparathyroidism. Evidence was inconclusive in terms of recurrent laryngeal nerve palsy. Overall, the committee thought that the benefits from having fewer additional ablations were outweighed by the risks of permanent hypoparathyroidism. Therefore, in conjunction with the limited and poor-quality evidence, the committee agreed that PCCND should not be offered. No evidence was found for prophylactic lateral lymph node dissection, but the committee agreed that, while the benefits would be similar, the harms would exceed those observed for central lymph node dissection. Therefore, the committee agreed that prophylactic lateral lymph node dissection should also not be offered.

Surgery during pregnancy

Finally, the committee agreed that there could be risks to the foetus if operating on pregnant women, although the risks are unclear. The concern in the first trimester is largely about preventing birth defects from the anaesthetic drugs. The concern in the later trimesters is about loss of the pregnancy. Therefore the committee agreed that it would be better to defer any surgical treatment until after pregnancy. However, they also noted that in the rare event of there being clinical or radiological evidence of progression (local invasion or regional disease development) then surgery should be done during the second trimester if possible. The committee recommended that a joint decision should be reached with the mother about whether to defer surgery during pregnancy, after a discussion by the obstetrician, surgeon and endocrinologist.

How the recommendations might affect practice

The committee agreed that the recommendations were unlikely to change current practice.

Return to recommendations

Thyrotropin alfa

Recommendations 1.3.12 and 1.3.13

Why the committee made the recommendations

Evidence showed that thyrotropin alfa (also known as recombinant human thyroid stimulating hormone) had short-term benefits over RAI with thyroid hormone withdrawal (THW) and did not demonstrate any harms. The relative benefits from thyrotropin alfa were improved quality of life, wellbeing, social, emotional and general function and reduced fatigue. The committee also agreed that thyrotropin alfa is better tolerated than THW.

Economic evidence showed mixed results when thyrotropin alfa was compared with THW. Three studies showed thyrotropin alfa to be either cost effective or to dominate THW. One study, based on the latest evidence, found thyrotropin alfa not to be cost effective. Therefore the committee agreed to take into account some original analysis that found a cost per quality-adjusted life year of thyrotropin alfa between £20,000 and £30,000.

Overall, the committee agreed that thyrotropin alfa should be offered to everyone. They noted that some people might be harmed by THW. People vulnerable to the detrimental effects of THW include those with psychiatric or mental health conditions, cardiac conditions, older-age, chronic kidney disease and a higher risk of falls. The committee made a strong recommendation, because they agreed a weaker recommendation would be inappropriate when the aim is to avoid direct harm.

The committee also agreed that thyrotropin alfa is better than THW for those who are not 'lower stage', or people for whom THW was not contraindicated. Thyrotropin alfa enables people to return to normal activities within 2 or 3 days of treatment, whereas THW is taken for 4 to 6 weeks before treatment with RAI, and people typically need to take at least 2 to 3 weeks off work. This means that THW was also considered to disadvantage those from lower socioeconomic groups, in whom a loss of earnings could adversely affect their quality of life, and those who have caring responsibility for children or the elderly. Unpaid carers may also struggle to find or afford someone to do their role while they are unable to do normal activities.

The committee also discussed the harms associated with THW and noted that the person will become acutely hypothyroid. This means they may experience mood changes such as anxiety, depression, lethargy and difficulty concentrating. This is particularly important for people with pre-existing mental health problems. The committee acknowledged that in most people the harm caused by THW is temporary. However, they agreed that the degree of short-term harm was so great that a change in practice to THW could not be recommended without clear and certain evidence of THW being cost effective.

Because thyrotropin alfa is an established and accepted current practice, a change in practice could disrupt RAI treatment. The committee noted that the preparation with thyrotropin alfa ensures flexibility for periods of RAI shortage, whereas THW could cause disruption and harm to people if providers are not able to offer the treatment at the end of the withdrawing period. Therefore, taking these factors into account, the committee made a recommendation for thyrotropin alfa.

In December 2022, using thyrotropin alfa as a treatment for thyroid cancer in people with distant metastases was an off-label use. However, the committee agreed that in their experience thyrotropin alfa still offered benefits to people with distant metastases if carefully managed because it avoided a short-term reduction in their quality of life.

Finally, any rise in TSH has the theoretical risk of causing flare of thyroid cancer. Due to the sharp rise and high levels of TSH following treatment with thyrotropin alfa, particular caution should be taken. This is of most concern in people with metastases in the brain or spine. The committee agreed that in these cases thyrotropin alfa can still be used by giving pre-treatment steroids or external beam radiotherapy (EBRT).

How the recommendations might affect practice

The committee noted that using thyrotropin alfa has become standard practice, so the recommendation is not expected to have any impact on current practice.

Return to recommendations

RAI for initial ablation

Recommendations 1.3.14 to 1.3.16

Why the committee made the recommendations

In the absence of evidence, the committee made a consensus recommendation that RAI should be offered after a total or completion thyroidectomy, if a person has a primary tumour at stage T3 or T4, regional lymph node involvement, pathological findings associated with a poor prognosis (including multifocal disease), or evidence of distant metastases. This recommendation is strong because there was consensus that, based on clinical experience, the benefits would significantly outweigh any harms for people who

fulfil these criteria. The committee were also aware that trials that are currently ongoing do not cover people in these groups.

There was also agreement that RAI should not be offered for T1a or T1b tumours after thyroidectomy, unless there are adverse features such as prognostically poor histological subtypes or an R1 resection margin. This decision was based on evidence that there was no difference in outcome and a consensus that the harms from RAI might outweigh the benefits unless adverse prognostic features or evidence of metastatic disease are present.

Having defined the situations in which RAI would and would not be offered, the committee agreed that a recommendation to consider RAI for clinical presentations that fit neither of the former recommendations would be appropriate. On balance they agreed that RAI would be of benefit for this group, and they made a consider recommendation. Given the uncertainty, a recommendation for research was made to address the clinical and cost effectiveness of RAI after total or completion thyroidectomy for people with T2 disease and no adverse pathological features. The committee agreed that this is important to establish the precise balance of benefits and harms so that appropriate clinical decisions can be made.

How the recommendations might affect practice

There are currently variations in how RAI is used in practice. However, this is gradually reducing, particularly for people considered to be at intermediate risk of thyroid cancer recurrence. By defining 3 distinct sets of clinical presentations, the recommendations offer new clarity on when RAI should and should not be offered, and when it should be considered. They are therefore likely to change practice leading to a more transparent decision-making process.

Return to recommendations

RAI activity for initial ablation

Recommendations 1.3.17 and 1.3.18

Why the committee made the recommendations

The evidence suggested that higher activity RAI only provides a small benefit to a small

number of people. The committee agreed that given the legal requirement to minimise radiation exposure (The Ionising Radiation [Medical Exposure] Regulations, 2017), this did not warrant giving higher activity RAI to everyone. Therefore the committee recommended that most people should have RAI with an activity for initial ablation of 1.1 GBq.

However, the committee recognised that some people in high-risk groups should be considered for RAI with an activity of 3.7 GBq for their initial ablation. High-risk groups include people with advanced or aggressive disease and people with significant comorbidities such as cardiovascular disease, mobility issues or complex social concerns, who should therefore avoid multiple ablations. For these people, the benefits of more complete ablation after a single exposure would probably outweigh the harms of higher activity RAI. The committee therefore recommended that these high-risk groups could have higher activity RAI.

How the recommendations might affect practice

The committee agreed that the evidence supports current practice, where lower activity RAI is generally preferred to high activity. It is likely that the recommendation would further increase the number of people having lower activity RAI instead of high activity, which would reduce NHS costs and potentially prevent second malignancies caused by radiation exposure.

Return to recommendations

External beam radiotherapy

Recommendations 1.3.19 and 1.3.20

Why the committee made the recommendations

The committee discussed the benefits and risks of EBRT. They agreed that it is only used in a small subgroup of people with thyroid cancer when there is no alternative treatment. In people with well-differentiated thyroid cancer there was evidence that EBRT reduced recurrence and prevented local disease progression. There was also evidence of increased death at 10 years. However, the committee agreed that despite this observational evidence adjusting for confounders, there was still likely to be some residual confounding within the analysis. In their experience, the committee agreed that EBRT showed benefit

without increased mortality. Although they acknowledged that mortality is likely to be higher in people selected for EBRT because of the advanced nature of their disease. Therefore the committee decided that EBRT should be carefully considered on a person-by-person basis that minimises risk and maximises benefit. The committee agreed that people with macroscopic disease or histological appearances that may indicate more aggressive disease, and people with tumours that have not taken up RAI, may benefit most from EBRT. This is because their tumours would not usually respond well to other treatments.

Similarly, the committee agreed that EBRT may benefit people who are having palliative care, in whom cancer metastases or local residual disease can cause symptoms such as ulceration due to skin invasion, pressure symptoms or pain. The committee therefore recommended that EBRT should be considered in these cases.

Overall, the committee agreed that the observational evidence was of low quality, but suggested that EBRT can provide benefit by reducing recurrence and local progression. However, they did not believe the mortality data reflected their experience and, given their view that the observational data was likely to be biased, they also made a recommendation for research for an RCT for EBRT.

How the recommendations might affect practice

Less than 5% of people with well-differentiated thyroid cancer currently have EBRT. The recommendation is unlikely to increase workload or referrals and therefore the resource impact should be minimal or non-existent. It is possible that the recommendations will lead to a more careful and appropriate selection of people for EBRT, reducing both the costs of EBRT use and of avoidable adverse effects.

Return to recommendations

Thyroid stimulating hormone suppression

Recommendations 1.4.1 to 1.4.4

Why the committee made the recommendations

The evidence suggested that thyroid stimulating hormone (TSH) suppression with thyroid

hormone reduces cancer recurrence and mortality when compared with no TSH suppression. However, this evidence was from a single, small study graded as very low quality. There was also no accompanying evidence that assessed potential harms or risks associated with TSH suppression, such as osteoporosis or cardiac complications. Because the evidence base was weak, and lacked information on harms, the committee decided to form recommendations largely through consensus. The recommendations reflect current practice.

When to offer TSH suppression

It was agreed that people who do not need RAI, should not be offered TSH suppression. In this group, the risks of recurrence, spread or mortality were believed to be so low that TSH suppression would benefit only a very small number of people. Given that the adverse effects on bone and cardiac health would affect a far greater proportion, it was agreed that the balance of benefits and harms strongly indicated avoidance of TSH suppression in this group.

In contrast, the committee agreed that the situation would be different for people who have had total or completion thyroidectomy and RAI. These treatments are only given when the perceived risks of recurrence, spread or mortality are higher. For these people, the balance of benefits and harms shifts towards an overall benefit from TSH suppression. Therefore for such people TSH suppression may be offered to maintain TSH levels below 0.1 mIU/litre.

Assessing and managing response to TSH suppression

After starting treatment, the person's response to the suppression should be monitored. After 9 to 12 months, if they have an excellent response to treatment, suppression can be reduced to achieve a TSH level of between 0.3 IU/litre and 2.0 IU/litre. If there is an intermediate response, suppression should be continued to achieve a TSH level of between 0.1 IU/litre and 0.5 IU/litre. This is on the basis that initial treatments and TSH suppression have probably eliminated the cancer and that further high levels of suppression could do more harm than good. However, if their response has been poor, they should continue to receive high levels of suppression. This is because the potential harms from the uncontrolled disease outweigh the harms of TSH. The committee agreed that achieving the target TSH levels may not be possible in all people but should be for most.

How the recommendations might affect practice

The recommendations to avoid TSH suppression in low-risk cancers might change practice. Avoidance of inappropriate TSH suppression would be expected to reduce long-term adverse effects. This would in turn have a favourable effect on resources, because most thyroid cancers diagnosed at present are low risk.

Return to recommendations

Long-term duration of TSH suppression

Recommendation 1.4.5

Why the committee made the recommendations

There was no evidence found for the optimal duration of TSH suppression. Previously, people would have TSH suppression indefinitely. However, with regular monitoring and risk assessment, this is no longer the case. Now TSH suppression is stopped if the perceived risk from TSH suppression outweighs the likely benefit in preventing cancer recurrence. The recommendations reflect that change in practice by highlighting the importance of an individualised assessment of risks and benefits. The committee also emphasised that some people may not want to suddenly stop or reduce TSH suppression because of the anxiety related with such a change. Therefore people on TSH suppression for more than 10 years should have a clinical review to assess their ongoing treatment, as well as the risks and benefits of TSH suppression.

In the past, people with thyroid cancer would have been told that TSH suppression is for life. However, the current thinking is that this not usually necessary. The committee agreed that it was important to explain this to people with thyroid cancer and reassure them that they will still be monitored if their suppression is relaxed.

Because of the lack of evidence, a recommendation for research was also made on the duration of TSH suppression.

How the recommendations might affect practice

The recommendations reflect current practice and so are not likely to have an impact on practice or resources.

Return to recommendation

Measuring thyroglobulin and thyroglobulin antibodies

Recommendations 1.5.1 to 1.5.6

Why the committee made the recommendations

In the absence of evidence, recommendations were made by consensus. The committee discussed how measuring thyroglobulin antibodies alongside thyroglobulin was important because the presence of thyroglobulin antibodies can affect thyroglobulin levels. This can increase the number of false positive or false negative results. They also noted that detectable thyroglobulin levels in people without thyroglobulin antibodies suggests the presence of either residual thyroid tissue or residual or recurrent thyroid malignancy. They agreed that the harms of thyroglobulin measurement, such as false positives leading to over investigation, did not outweigh the clinical benefits from early detection of recurrence or progression. In the absence of a feasible alternative method for measuring recurrence, the committee recommended measurement of thyroglobulin following a total or completion thyroidectomy with RAI. Frequency of thyroglobulin measurement was recommended, in line with current practice, at 3- to 6-month intervals for the first 2 years, followed by 6- to 12-month intervals after that.

The committee agreed that if thyroglobulin antibodies are not detected, then thyroglobulin levels can be interpreted at face value. In such a case, this initial evidence of recurrence from thyroglobulin testing should lead to further investigations, either to confirm or refute recurrence. They also recommended that people who have previously been cleared of having recurrence after a thyroglobulin test, but now have rising thyroglobulin levels, should also have further investigations for recurrence. This is because the rise in thyroglobulin levels might be a 'new' sign of recurrence that requires investigation. Further investigations could include neck ultrasound, CT scan of neck and chest or MRI scan of the neck. The choice often depends on local availability, and a prior knowledge of what happened with the patient in assessing where in the body recurrence is most likely to be.

The committee noted that there may be some cases where a person has had a total thyroidectomy without RAI. However, there may be additional factors that suggest more detailed follow up is needed. In these circumstances, the clinician may have decided to

measure thyroglobulin as part of the follow up. If the person's levels rise, then further investigations should be considered. A detectable level of thyroglobulin that is not rising is not usually an indication for further investigations as often there will be a small amount of residual thyroid tissue following total thyroidectomy without RAI.

For people who have not had a total thyroidectomy, there would rarely be a need to measure thyroglobulin levels and interpretation of results can be difficult. This is because the person would still have functioning thyroid. Therefore the committee recommended that thyroglobulin levels should not be routinely measured.

The committee also considered the more complex scenario of what should happen if thyroglobulin antibodies are detected above the laboratory threshold. Initially, the clinician would be expected to investigate how the assay might be affected by antibodies, and if it might cause an increase or decrease in measured thyroglobulin levels. This would influence how the thyroglobulin levels are interpreted and, if there was enough uncertainty, prompt a move to other investigations to confirm or refute recurrence. It was also agreed that there should be further investigations if, at a later point, either the thyroglobulin levels or thyroglobulin antibodies start to rise. This was because each of these scenarios could, directly or indirectly, indicate recurrence. Therefore the committee made a recommendation to consider further investigation in the presence of thyroglobulin antibodies when they are first detected or at any point if thyroglobulin or thyroglobulin antibody levels are rising.

How the recommendations might affect practice

The committee did not think that the recommendations would have an impact on current practice, because the recommendations reflect current and established practice.

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Stimulated thyroglobulin and highly sensitive thyroglobulin testing

Recommendations 1.5.7 to 1.5.10

Why the committee made the recommendations

The committee agreed to form recommendations by consensus because no evidence was available from the literature. When thyroglobulin is undetectable on a standard assay, the committee agreed that further investigation should be considered with either a stimulated or highly sensitive thyroglobulin assay. They also suggested strategies for what to do depending on the results obtained from using each method.

When using stimulated thyroglobulin, there were 3 levels of response suggested. A reading of below 1 microgram/litre was considered low risk, and led to the recommendation that follow up and TSH suppression could be relaxed. A reading of between 1 microgram/litre and 10 microgram/litre was considered an indeterminate response, and led to the recommendation to consider continuation of TSH suppression. Finally, a reading of 10 microgram/litre or more led to a recommendation to consider further investigations and treatment. The type of treatment would depend on what the further investigations revealed. This gradation of actions, from a relaxation to a strengthening of vigilance, was based on the changing perception of recurrence risk associated with the stimulated thyroglobulin measurements.

When using a highly sensitive assay that can detect thyroglobulin levels lower than 0.2 microgram/litre, there were 2 levels of response suggested. A reading of below 0.2 microgram/litre was considered low risk and led to the recommendation that follow up and TSH suppression could be relaxed. A reading of between 0.2 microgram/litre and 1.0 microgram/litre led to a recommendation to consider stimulated thyroglobulin, which can be helpful in separating people into lower- and higher-risk categories. If a person was shown to be at medium risk on stimulated thyroglobulin, this would suggest continuing with the same strategy and not relaxing TSH suppression. But, if they were at high risk, this would indicate the consideration of further investigations and treatment.

With all these recommendations, the committee stressed that the presence of anti-thyroglobulin antibodies can distort both stimulated and highly sensitive thyroglobulin measurements, and caution should therefore be used when interpreting results in this situation.

How the recommendations might affect practice

The impact of the recommendations on practice is expected to be small, because the recommendations reflect current practice.

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Follow up

Recommendations 1.6.1 to 1.6.4

Why the committee made the recommendations

The available evidence on follow-up strategy included people with very early-stage thyroid cancer. The committee agreed that the evidence was therefore not representative of much of the population, so they used consensus to make the recommendations. They agreed the strategy should be set according to the severity of disease and the treatment given. For people with T1a disease that has been surgically removed with no local (N0) or distant (M0) spread, the committee agreed that the risks of further spread or recurrence were so low that the harms of further follow up would outweigh any benefits. Such harms include the anxiety caused by the investigations and the radiation risks of some forms of detection.

For people with thyroid cancer that is stage T1a(m), T1b or greater, and who have had a hemithyroidectomy or total thyroidectomy without RAI, an ultrasound at 6 to 12 months was recommended, followed by an annual clinical follow up for 5 years. This group was regarded as having a small but real risk of recurrence and spread. Therefore the benefits of follow up, such as better prognosis resulting from early detection and treatment, starts to outweigh the previously outlined harms. The timing of the initial follow up was based on current practice. The frequency was based on the committee's understanding of how quickly recurrences and spread may occur. They also considered at what point it tends to be safe to assume that further problems are unlikely, provided no recurrence or spread has yet occurred. The committee agreed that the need for ultrasound at these annual clinical follow ups would need to be decided on a case-by-case basis. The committee also acknowledged that there may occasionally be instances when it is appropriate to measure thyroglobulin in those cases, but detectable thyroglobulin alone did not indicate recurrence of cancer. The trend in thyroglobulin over several measurements was therefore considered more useful in these people.

For people who have had both a total or completion thyroidectomy and RAI, the duration and frequency of follow up was based on the assumed level of risk and response to treatment. Low risk was defined as no evidence of disease on imaging and a thyroglobulin level of less than 0.2 microgram/litre (or a stimulated thyroglobulin level of less than

1 microgram/litre). Medium risk was defined as thyroglobulin between 0.2 microgram/litre and 1.0 microgram/litre, or stimulated thyroglobulin of between 1 microgram/litre and 10 microgram/litre. High risk was defined as thyroglobulin of greater than 1.0 microgram/litre, or stimulated thyroglobulin of greater than 10 microgram/litre. The annual frequencies were again based on the committee's understanding of how quickly recurrences and spread may occur. The committee acknowledged that, while annual follow up is recommended, there may be cases in which more frequent follow up is needed. The increasing duration of total follow up with the level of presumed risk was based on the committee's experience that late recurrence and spread increases with risk. Therefore more prolonged vigilance is needed, and the benefit outweighs any potential harms from follow up, such as anxiety about radiation.

For anyone at the highest levels of risk, with persistent biochemical or structural disease, there is the potential for disease progression. Therefore the committee recommended that follow up should occur annually for an indefinite period, and potentially for life. Finally, the committee discussed how thyroglobulin measurement is designed to identify recurrence that may not yet be structurally evident. Therefore if structural recurrence is detected in people who have been treated with total or completion thyroidectomy and RAI, further thyroglobulin measurement is unnecessary. Such people should be discussed in the multidisciplinary team meeting with the surgeon.

There was no evidence for how long people should be followed up, so the committee set minimum periods and wrote a recommendation for research on the duration of follow up.

How the recommendations might affect practice

The impact of the recommendations on practice is expected to be small, because the recommendations reflect current practice.

Return to recommendations

Context

Cancer of the thyroid, a small gland at the base of the neck, is uncommon and can occur at any age. It is most often diagnosed in people from their 20s through to their 60s. Almost all thyroid cancers (about 97%) are differentiated and have a good prognosis. When deaths do occur, they tend to arise from the spread of the cancer to the bones or lungs. There has been an increase of over 150% in the incidence of thyroid cancer in the UK over the past 30 years. It is unclear if this is because of more effective diagnosis or more people developing thyroid cancer. The rise in incidence has not been matched by a rise in mortality, but raises questions about assessment for people with suspected thyroid cancer and about appropriate treatment.

There is particular uncertainty about the management of nodules of small and intermediate size and classification, and practice varies internationally.

Thyroid cancer is usually treated by partial (hemi-) or total thyroidectomy, sometimes followed by radioactive iodine. Since thyroid cancer can occur in young adults and has a good prognosis, many who have this surgery will spend most of their lives without a thyroid gland. The long-term implications of this include lifelong treatment with replacement thyroid hormone, and possible complications such as hypoparathyroidism and vocal cord palsy. Internationally, very small thyroid tumours are sometimes managed with active surveillance.

Once thyroid cancer has been treated, there is still a chance it might recur. Recurrence is uncommon in well-differentiated cancers, but it can be more serious than the original occurrence. There are questions about the risk of recurrence and how this risk should be translated into a long-term follow-up strategy.

Finding more information and committee details

To find NICE guidance on related topics, including guidance in development, see the NICE topic pages on thyroid cancer and thyroid disorders.

For full details of the evidence and the guideline committee's discussions, see the evidence reviews. You can also find information about how the guideline was developed, including details of the committee.

NICE has produced tools and resources to help you put this guideline into practice. For general help and advice on putting our guidelines into practice, see resources to help you put NICE guidance into practice.

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