National Institute for Health and Care Excellence

NICE guideline on Thyroid cancer: assessment and management
Document cover sheet

Date	Version number	Editor	Action
	1	BP	First edit
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17/6/22	3	BP	Post GE changes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

Thyroid cancer: assessment and management

Draft for consultation, June 2022

This guideline covers diagnosis and management of thyroid cancer in people aged 16 and over. It provides recommendations on diagnosis with ultrasound, fine-needle aspiration cytology and cross-sectional imaging, as well as guidance on treatment with surgery, thyrotropin alfa, radioactive iodine, and external beam radiation. There are also recommendations on TSH suppression, monitoring and follow up, and information for people with thyroid cancer and their families and carers.

Who is it for?

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

What does it include?

- the recommendations
- recommendations for research
- rationale and impact sections that explain why the committee made the recommendations and how they might affect practice
- the guideline context.

Information about how the guideline was developed is on the guideline's webpage. This includes the evidence reviews, the scope, details of the committee and any declarations of interest.

Contents

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 people 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, including the:

- risks
- implications of having part or all of your thyroid removed
- potential for hypothyroidism

- potential need for thyroid hormone replacement and its possible consequences
- potential need for treatment for low parathyroid hormone and its possible consequences.

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 this will be beneficial for 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
- their underlying condition, including the role and function of the thyroid gland and the need for long-term monitoring of thyroid function
- their likely cure rate, effect on their life expectancy and likelihood of recurrence
- how treatment may affect conception, pregnancy and fertility
- the risks, benefits and uncertainties of treatment and its potential effects on their quality of life, energy, weight and mood
- who will be involved in their treatment and follow up
- where to get reliable further information
- who to contact for more information.

1.1.9 At follow up, give people with thyroid cancer, 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, and who that healthcare professional should be.

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 and support.

1.2 Diagnosis

Blood tests

1.2.1 See recommendations on investigating thyroid dysfunction and 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.

1.2.2 Do not use calcitonin testing to assess thyroid nodules unless there is suspicion of medullary thyroid cancer, for example family history or a nodule with ultrasound appearances suspicious of medullary thyroid cancer.

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

1.2.4 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: blood tests.

Ultrasound

1.2.5 See the section on investigating thyroid enlargement in the NICE guideline on thyroid disease: assessment and management, and the recommendation on referral for suspected thyroid cancer in the NICE guideline on suspected cancer.

1.2.6 Offer greyscale ultrasound with a structured scoring system as the initial diagnostic test when investigating thyroid nodules for malignancy.

1.2.7 See the recommendations on grading and reporting ultrasound findings when investigating thyroid enlargement in the NICE guideline on thyroid disease: assessment and management.

Management options based on ultrasound results

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

1.2.9 If using EU-TIRADS, consider using a score of 4 or more as a threshold for who should have fine needle aspiration cytology (FNAC).

1.2.10 Consider FNAC, Active surveillance or diagnostic hemithyroidectomy for people who do not meet the threshold for FNAC on ultrasound criteria 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.

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 Consider using cytospin and cell block in addition to, or instead of, smear 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 a period of rapid onsite assessment of FNAC adequacy rates to improve the diagnostic yield of samples if the Thy 1 (inadequate) rate for individual clinicians is higher than 15%.

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: FNAC testing or biopsy.

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 FNAC result	Management and further sampling
Thy 1 (inadequate)	Offer repeat sampling with core-needle biopsy (CNB) (or fine-needle aspiration cytology [FNAC] if CNB is unavailable or inappropriate) Consider diagnostic hemithyroidectomy if the repeat sample is also Thy 1
Thy 2 (benign)	Consider repeat ultrasound Consider repeat sampling with CNB or FNAC if the second ultrasound reaches the threshold for FNAC

	Discharge people if their needle biopsy results are benign and all investigations are complete, unless there are other reasons for clinical concern
Thy 3a (indeterminate)	Offer repeat sampling with CNB (or FNAC if CNB unavailable or inappropriate) Consider diagnostic hemithyroidectomy or Active surveillance if repeated samples are still Thy 3a.
Thy 3f (indeterminate)	Consider diagnostic hemithyroidectomy
Thy 4 (suspicion of malignancy) and Thy 5 (malignant)	Offer diagnostic hemithyroidectomy or consider 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: repeat FNAC 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 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 T2 thyroid cancer if there are aggressive features on histopathology or their age or sex puts them at a higher risk.

1.2.19 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 , or any N1 or M1 thyroid cancer.

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.

1.3 Initial treatment

Surgery and active surveillance for primary tumours

1.3.1 When discussing surgical options with the person take into account the person's 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] and above).

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 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 1.3.7).

Surgery during pregnancy

1.3.10 Consider deferring surgery until the end of pregnancy, taking into account the risk of delaying surgery and the risk to pregnancy.

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

Full details of the evidence and the committee's discussion are in evidence review H: initial treatment.

Thyrotropin alfa (recombinant human thyroid stimulating hormone)

1.3.11 Offer thyrotropin alfa for pretherapeutic stimulation to people with thyroid cancer (including those with distant metastases; see recommendation

1.3.14) who are having radioactive iodine (RAI) ablation or treatment, if thyroid hormone withdrawal (THW) is contraindicated because the person has 1 or more of the following:

- cardiac conditions
- psychiatric or mental health conditions
- frailty
- a higher risk of falling
- chronic kidney disease.

1.3.12 Consider thyrotropin alfa for pretherapeutic stimulation for any people with thyroid cancer who can have THW (including those with distant metastases; see recommendation 1.3.14) who are having RAI ablation or treatment.

In June 2022 use of thyrotropin alfa in people who have distant metastases was off-label. See NICE's information on prescribing medicines for more information.

1.3.13 Be aware that people having THW often need to take at least 2 to 3 weeks off work. This can disadvantage people for whom a loss of earnings could adversely affect their quality of life.

1.3.14 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 pretherapeutic recombinant human thyroid stimulating hormone.

Full details of the evidence and the committee's discussion are in evidence review I: pretherapeutic recombinant human thyroid stimulation.

RAI therapy

1.3.15 Offer RAI to people who have had a total or completion thyroidectomy based on the criteria in recommendation 1.3.3

1.3.16 Do not offer RAI to people with a solitary microcarcinoma (T1a), unless there are adverse features.

1.3.17 Consider RAI for people who have had a total or completion thyroidectomy, but whose disease does not show any of the features in recommendation 1.3.15.

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 therapy.

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

RAI activity

1.3.18 Consider RAI with an activity of 3.7 GBq for high-risk groups, such as people with T4, N1b or M1 disease or aggressive subtypes, or for whom multiple ablations should be avoided. This includes people with significant comorbidities such as cardiovascular disease, mobility issues or complex social concerns.

1.3.19 Offer RAI with an activity of 1.1 GBq to people with thyroid cancer who do not meet the criteria in recommendation 1.3.18.

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 radiation therapy

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

1.3.21 Consider external beam radiotherapy 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 radiation therapy.

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

1.4 Ongoing treatment with thyroid stimulating hormone suppression with thyroid hormone

Who 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 recommendation 1.3.15)
- 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 for at least 1 year 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, 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 who respond well to initial treatment.
- Continue TSH suppression to achieve a TSH level of 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 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 Review 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.

For a short explanation of why the committee made this recommendation and how it might affect practice, see the rationale and impact section on 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 Monitoring post-thyroidectomy

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
- positive thyroglobulin levels in people with negative thyroglobulin antibodies indicate the presence of either residual thyroid tissue or residual or recurrent thyroid malignancy.

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 **and**
- 6-to-12-month intervals thereafter.

1.5.3 Consider further investigation if a person has had:

- RAI and a positive thyroglobulin test with negative thyroglobulin antibodies
- a previous negative thyroglobulin test, but thyroglobulin levels are now rising
- a total thyroidectomy without RAI and where thyroglobulin levels are now rising.

1.5.4 Do not routinely measure thyroglobulin levels in people who have not undergone total or completion thyroidectomy.

1.5.5 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 monitoring 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

1.5.6 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.

1.5.7 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 2 microgram/litre (low risk)
- continuing TSH suppression if stimulated thyroglobulin is between 2 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.

1.5.8 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 categories if the thyroglobulin level is between 0.2 microgram/litre and 1 microgram/litre

1.5.9 Use caution when interpreting results in the presence of anti-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

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

1.6.2 Consider an ultrasound at 6 to 12 months initially then annual 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 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 and a combination of ultrasound and thyroglobulin testing
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 and a combination of ultrasound and thyroglobulin testing
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 and a combination of ultrasound and thyroglobulin testing
Anyone with biochemical or structural evidence of disease	Consider (at least annually) lifelong follow up and a combination of ultrasound and thyroglobulin testing

1.6.4 Discuss with a surgeon if the person 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 taking into account 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 on ultrasound imaging.

Radioactive iodine

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

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
Thy 1	Inadequate or non-diagnostic
Thy 2	Benign or non-neoplastic
Thy 3	Indeterminate or neoplasms possible Thy 3a: neoplasms possible (atypical features) Thy 3f: follicular neoplasms
Thy 4	Suspicious of malignancy
Thy 5	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

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 people with thyroid cancer?

For a short explanation of why the committee made this recommendation see the rationale section on repeat testing and discharge.

Full details of the evidence and the committee's discussion are in evidence review E: repeat FNAC.

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 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.

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 see the rationale section on initial treatment.

Full details of the evidence and the committee's discussion are in evidence review H: initial treatment.

Duration of thyroid stimulating hormone suppression

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

For a short explanation of why the committee made this recommendation see the rationale section on duration of thyroid stimulating hormone suppression.

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

Other recommendations for research

Radioactive iodine

What is the clinical and cost effectiveness of RAI after total or completion thyroidectomy for people with tumours at stages 2b or 3, with no adverse pathological features?

For a short explanation of why the committee made this recommendation see the rationale section on radioactive iodine.

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

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 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.

Imaging for further staging

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

For a short explanation of why the committee made this recommendation 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.

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 see the rationale section on external beam radiation therapy.

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

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 1.1.9

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 was 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 was important to direct them to sources that are good quality and reliable.

The committee agreed it was 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 shows that telling people that thyroid cancer was a 'good cancer' was generally not reassuring to people with thyroid cancer. It caused them to feel that the diagnosis was being dismissed as unimportant and, as a result, they felt unworthy of seeking support. Therefore, the committee recommended that health care professionals avoid telling people they had a 'good cancer' and that they 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 would be managed, any consequences of treatment and the long-term follow-up requirements.

How the recommendations might affect practice

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

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Blood tests

Recommendations 1.2.1 to 1.2.4

Why the committee made the recommendations

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 some 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, but to rely instead on other methods of assessment, 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 were prior reasons to suspect MTC.

Thyroid peroxidase antibody

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 were sufficient to justify 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 research recommendation in this area.

How the recommendations might affect practice

The recommendation to not offer calcitonin testing unless medullary cancer is suspected, largely reflects current practice in the UK. It also represents a targeted use of NHS resources due to the rarity of medullary cancer 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.

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Ultrasound

Recommendations 1.2.5 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 the majority of people or invasive, such as 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. Of these, the committee agreed that the studies assessing malignancy using an EU-TIRADS score of 4 or more had the best combination of sensitivity, specificity and simplicity of use. However, they acknowledged that this is still from very low quality evidence, and that changing to EU-TIRADS would be a significant change in practice. Therefore, the committee agreed that the decision to do FNAC should be made using an established system for grading ultrasound and if EU-TIRADS is used then a score of 4 or above should be considered as the threshold for doing FNAC. The EU-TIRADS score is based on the EU Thyroid Imaging and Reporting Data System (TIRADS) scale.

However, the committee were aware that this scale and threshold does not have perfect sensitivity, and that therefore some people with malignancy might 'slip through the net' and not receive further investigation. Therefore, a further recommendation was made that people whose results do not exceed the threshold could still have further investigations with an FNAC, be placed on active surveillance, or have a diagnostic hemithyroidectomy if the clinician believed there were extenuating clinical reasons.

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 takes into account echogenicity, microcalcifications, border, shape in transverse plane, internal vascularity and lymphadenopathy and noted that the British Thyroid Association (BTA) and EU TIRADS do this. 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 are available to clinicians when assessing the person.

How the recommendations might affect practice

The classification system widely used in current practice is the BTA U classification. Recommending an established system for grading ultrasound appearance is not expected to affect current practice significantly. This is because it does not state which system to use and, therefore, it is unlikely to persuade clinicians to adopt a new system. The recommendation for an optimal threshold for the EU TIRADS, which is expected to improve the accuracy of clinicians who are already using this system to classify nodules, may increase the number of people getting FNAC. This is because the current system also uses size of nodule as part of the threshold.

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

Return to recommendations

UltrasoundFNAC testing

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 considered with cytospin and cell block. This was based on evidence that showed that including these techniques alongside smear leads to a high sensitivity (0.937) and specificity (0.825) for identifying nodules as 3 and above on the Bethesda classification scheme. The committee agreed that the Royal College of Pathologists modification of the BTA reporting system (RCPath BTA) aligns with Bethesda, and any differences are superficial, and nomenclature based. For example, RCPath BTA grade Thy 3a is equivalent to Bethesda grade 3. Therefore, they made a consensus recommendation to use the RCPath BTA reporting system.

An estimation of the data from the evidence review suggested that rapid on site assessment (ROSA) reduced non-diagnostic results by 55% and is likely to be cost saving. The Royal College of Pathologists notes that an inadequacy rate of greater than 15% is problematic. Therefore the committee agreed that certain sites, where inadequacy rates were high, might benefit from ROSA.

How the recommendations might affect practice

Although smear is commonly used with FNAC, cytospin and cell block are less commonly used in smaller centres. These recommendations may therefore require some changes in training and provision of equipment in these centres. However, most large centres already use cytospin and cell block and so the overall impact on practice is likely to be small.

Institution of ROSA, specifically for individual clinicians with high inadequacy rates, was thought to represent a change in practice. This would require auditing the adequacy rates of samples and personnel would be needed to provide such services. However, as shown in the economic analysis, it represents a cost-effective use of NHS resources and would lead to important savings due to less need for repeat FNAC. Furthermore, in centres where ROSA is added, even if it is for a

limited period of time, a persistent low inadequacy rate due to the training provided by cytopathologists may be achieved, thus improving the diagnostic efficiency of the NHS in the long-term.

Return to recommendations

Management and further sampling after initial FNAC

Recommendations 1.2.15

Why the committee made the recommendations

For people who have an inadequate (Thy 1) FNAC results, the committee recommended that sampling should be repeated, because an unsatisfactory aspirate is often a random technical failure that might not be repeated. The preferred approach for repeat sampling was a core-needle biopsy (CNB). This was because the diagnostic clinical review of FNAC and CNB and the studies informing the health economic model found it to be more accurate than repeat FNAC and associated with a lower rate of unsatisfactory results. The committee were aware that, in some cases, FNAC could be performed instead. For example, if there was not local availability of CNB or the nodule was in an area of the neck that is more easily accessed with FNAC. Therefore, the recommendation includes FNAC if CNB is unavailable or inappropriate. Should this further test still be inadequate (Thy 1) then the committee thought the best way to find determine malignancy was for a diagnostic hemithyroidectomy.

To optimise the sensitivity of FNAC testing, which was fractionally below the target of 0.95, the committee recommended repeating tests that were benign (Thy 2 on RCPath classification). In the first instance the committee agreed that repeating ultrasound should be considered. If this still shows a suspicious result then the next step would be to consider repeat sampling with FNAC or CNB. Benign FNAC tests should be repeated because random sampling error can sometimes cause false negatives. Therefore, if the initial Thy 2 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 Thy 2. The committee therefore recommended that people who have had repeated FNAC tests and still have a Thy 2 result can be discharged unless there are other clinical concerns.

The committee made a repeat sampling recommendation in people with Thy 3a results. CNB was, again, the preferred approach, reflecting the findings of the economic evaluation and clinical review. As with Thy 1, the recommendation allows FNAC when CNB is unavailable or inappropriate. In case of a further Thy 3a results, a recommendation was made to use diagnostic hemithyroidectomy or active surveillance.

For people with Thy 3f results, the committee recommended that they should have diagnostic hemithyroidectomy. This reflects the committee's view that repeat sampling is less useful after Thy 3f 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 Thy 3f could take longer to happen. 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.

For people with Thy 4 or Thy 5 cytology, the committee recommended diagnostic hemithyroidectomy or therapeutic hemithyroidectomy or total thyroidectomy. The recommendation that people in these groups should be sent straight to surgery is 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. However, molecular tests are largely unavailable in the NHS and are mostly produced outside the UK. The committee agreed that they could help reduce the number of unnecessary diagnostic hemithyroidectomies in people with indeterminate FNAC results and made a research recommendation in this area.

How the recommendations might affect practice

The recommendation to repeat FNAC with Thy 2 if there are clinical concerns represents current practice and it is not expected to have an impact on NHS resources.

The recommendations to repeat sampling with CNB after a Thy 1 and Thy 3a result, is a significant change from current practice. This is because FNAC has generally been the preferred method for repeat sampling in the NHS. These recommendations

are expected to require some changes in training for radiologists and provision of equipment in centres where CNB is rarely offered or not available. Therefore, the recommendations are expected to increase NHS resource use in the short-term. However, the lower inconclusive rates and better accuracy of CNB will lead to fewer unnecessary hemithyroidectomies and possibly shorten the diagnosis time for many people. This will therefore improve NHS efficiency and reduce overall costs.

The recommendations to offer diagnostic hemithyroidectomy to people with Thy 3f and either diagnostic or therapeutic surgery to people with Thy 4 and Thy 5, reflect the current approach and so are not likely to have an impact on practice or resources.

Return to recommendations

Radioisotope scans

Recommendation 1.2.16

Why the committee made the recommendations

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 were 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, the committee made it clear that this recommendation relates to the initial diagnosis of thyroid cancer.

How the recommendations might affect practice

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

Return to recommendation

Imaging for further staging

Recommendations 1.2.17 to 1.2.19

Why the committee made the recommendations

In the absence of evidence, the committee used consensus to form recommendations. The committee agreed that for people with stage T1 thyroid cancer and no other indications, based on initial diagnostic investigations, ultrasound should be the main imaging used to inform further staging. Other indications would 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 of people. For example, CT carries radiation risks, particularly to younger people, and some people find the experience of MRI traumatic.

However, for people at stage T2 with high-risk features, the committee agreed that imaging capable of surveying at greater depth should be considered, because spread may be more extensive. Therefore, the benefits for these people would outweigh the harms and cross-sectional imaging techniques such as CT or MRI should be considered as it will help with surgical planning. The committee agreed that age and sex should be included in the decision-making process, because greater age and male sex have both been shown to increase the risk of spread and recurrence. Given the uncertainty in this area the committee also made a research recommendation for this group.

For people at even higher levels of risk, such as those at stage T3 or T4, 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 any 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

Initial treatment

Recommendations 1.3.1 to 1.3.10

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, while there were no differences between treatments in terms of hoarseness. Weighing up the benefits and harms, the committee agreed that total thyroidectomy should be recommended over hemithyroidectomy if there were 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 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, loss of interest in sex and throat and mouth symptoms. However, measurements of other quality of life outcomes were largely inconclusive.

The committee agreed that the evidence base for active surveillance suggested it 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 is because in their experience there is a low risk of the tumour adversely affecting the person's quality of life. Therefore, they 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 research recommendation comparing active surveillance with surgery.

Surgery for existing 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 additional cost to the NHS. The committee also noted that there are 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 the need for future surgery. This was a consider recommendation because it was not based on evidence and the procedure is prophylactic and is 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 recommended. 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, prophylactic lateral lymph node dissection was also not recommended.

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 during 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 they would consider surgery after discussion with the mother and an obstetrician.

How the recommendations might affect practice

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

Return to recommendations

Pretherapeutic thyrotropin alfa (recombinant human thyroid stimulating hormone)

Recommendations 1.3.11 to 1.3.14.

Why the committee made the recommendations

Evidence showed that thyrotropin alfa (also known as recombinant human thyroid stimulating hormone (rhTSH)) 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 comparing thyrotropin alfa with THW. Three studies showed thyrotropin alfa to be either cost effective or to dominate THW while 1 study, based on 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 QALY of thyrotropin alfa between £20,000 and £30,000. As a result, different strengths of recommendations depending on the patient group were made.

The committee agreed that some people might be harmed by THW and therefore should be offered thyrotropin alfa. People vulnerable to the detrimental effects of THW would 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 was to avoid direct harm.

The committee also agreed that thyrotropin alfa would be the treatment choice for all people with thyroid cancer including those who were not ‘lower stage’, or people for

whom THW was not contraindicated. This is a consider recommendation because thyrotropin alfa was not shown be cost-effective over THW at the £20,000 threshold. Also, using thyrotropin alfa in people with distant metastases is off-label use. However, the committee agreed that in their experience thyrotropin alfa still offered benefit in this group if carefully managed because it avoided a short-term reduction in their quality of life.

The committee also agreed that thyrotropin alfa enabled 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 needed to take at least 2 to 3 weeks off work. This meant 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. 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 patients with pre-existing mental health problems. Therefore, the committee made a be aware recommendation to highlight this point.

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 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 with steroids or external beam radiotherapy (EBRT).

How the recommendations might affect practice

The committee noted that using thyrotropin alfa has become standard practice. Should THW be used instead then this may involve a change in practice.

Return to recommendations

RAI therapy

Recommendations 1.3.15 to 1.3.17

Why the committee made the recommendations

In the absence of evidence, the committee made consensus recommendations. They agreed that RAI should be offered after a total or completion thyroidectomy, if a person has a primary tumour at stage T3b, T4a or T4b, regional lymph node involvement, pathological findings associated with a poor prognosis (including multifocal disease), or evidence of distant metastases. This was a strong recommendation 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 consensus that RAI should not be offered for solitary microcarcinoma (T1a) after thyroidectomy, unless there are adverse features such as prognostically poor histological subtypes or an R1 resection margin. This decision was based on the consensus opinion that the harms from RAI might outweigh the benefits unless adverse prognostic features are present. Furthermore, it was agreed that this approach reflects current practice.

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 research recommendation was made to address the clinical and cost effectiveness of RAI after total or completion thyroidectomy for people with tumour stages 2b or 3 and no adverse pathological features. The committee agreed that this was important to establish the precise balance of benefits and harms so that appropriate clinical decisions can be made.

How the recommendations might affect practice

The use of RAI is currently subject to variation 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 likely, therefore, to change practice leading to a more transparent decision-making process.

Return to recommendations

Radioactive iodine activity

Recommendations 1.3.18 to 1.3.19

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, this did not warrant giving higher activity RAI to everyone. Therefore, the committee recommended that the majority of people should have RAI with activity of 1.1 GBq.

However, the committee recognised that some people in high-risk groups should initially be considered for RAI with an activity of 3.7 GBq. 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 sub-groups could have higher activity RAI.

How the recommendations might affect practice

The committee agreed that the evidence confirmed 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 receiving 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 radiation therapy

Recommendations 1.3.20 to 1.3.21

Why the committee made the recommendations

The committee discussed the benefits and risks of EBRT. They agreed that 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 though they acknowledged that mortality is likely to be higher in this group because of the advanced nature of their disease. EBRT is only offered to people if there is no alternative treatment. 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 tend to respond well to other treatments.

Similarly, the committee agreed that EBRT may benefit people receiving palliative care where 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 and suggested the benefit of reduction 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 research recommendation for a randomised controlled trial for EBRT.

How the recommendations might affect practice

Between 5% and 7% of people with well-differentiated thyroid cancer currently receive 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

Ongoing treatment

TSH suppression with thyroid hormone

Recommendations 1.4.1 to 1.4.4

Why the committee made the recommendations

The evidence suggested that 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 assessing 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, which reflects current practice.

Who 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 are 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 indicates 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 for TSH suppression. This is because, although the risks of recurrence, spread and mortality might be lower with TSH suppression than the risk of adverse effects, the impact of thyroid cancer progression outweighs the potential treatment risks. 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 responded well, 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. If on the other hand, their response has been poor, they should continue to receive high levels of suppression, because the potential harms from the uncontrolled disease outweigh the harms of suppression.

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 that the majority of thyroid cancers diagnosed at the present time are low risk.

Return to recommendations

Duration of TSH suppression

Recommendation 1.4.5

Why the committee made the recommendations

There was no evidence found for the optimal length of TSH suppression. Previously, people would have TSH suppression indefinitely. However, with regular monitoring and risk assessment, this has changed recently, with TSH suppression being 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 factoring in people's comorbidities. 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. Because of the lack of evidence, a research recommendation was also made in this area.

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

Monitoring post-thyroidectomy

Measuring thyroglobulin and thyroglobulin antibodies

Recommendations 1.5.1 to 1.5.5

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 positive thyroglobulin levels in people with negative thyroglobulin antibodies indicate the presence of either residual thyroid tissue or residual or recurrent thyroid malignancy. Therefore, the committee agreed that thyroglobulin antibodies should always be measured alongside thyroglobulin. Harms of thyroglobulin measurement, such as false positives leading to over investigation, were not regarded as sufficient to negate the clinical benefits from early detection of recurrence or progression of disease. 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 monthly intervals for the first 2 years, followed by 6 to 12 monthly 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 whether there has been recurrence. In addition, they recommended that there should also be further investigation of recurrence in people who have previously been cleared of having actual recurrence

after a positive thyroglobulin test, but for whom thyroglobulin levels are rising. This is because the rise in thyroglobulin levels might denote a 'new' potential sign of recurrence that requires investigation.

The committee also noted that there may be a few cases where a person may have been treated with a total thyroidectomy without RAI. However, there may be additional factors that suggest more detailed follow up is indicated. In these circumstances the clinician may have decided to measure thyroglobulin as part of the follow-up regime. Should their levels rise, then further investigations should be considered.

For people who have not had a total thyroidectomy there would rarely be a need to measure thyroglobulin levels as the person would still have some functioning thyroid. Therefore, the committee recommended that thyroglobulin levels are not 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 whether it might cause a shift upwards or downwards in measured thyroglobulin levels. This would influence how the thyroglobulin levels are interpreted, and, if there was sufficient 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 third recommendation suggested further investigation in the presence of thyroglobulin antibodies when they are first detected and at also any point later if the levels of thyroglobulin or thyroglobulin antibodies 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.

Return to recommendations

Stimulated or highly sensitive thyroglobulin assays

Recommendations 1.5.6 to 1.5.9

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 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 2 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 of vigilance to a strengthening of it, 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 0.1 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 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.

Return to recommendations

Follow up

Recommendations 1.6.1 to 1.6.4

Why the committee made the recommendations

The committee agreed that the available evidence was biased by very early disease and was therefore not representative of much of the population. Therefore, 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, with no local (N0) or distant (M0) spread, which has been surgically removed, 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 around the investigations involved and the radiation risks of some forms of detection.

For people with stage T1a(m) or T1b or greater, who have had a hemithyroidectomy or total thyroidectomy without RAI, an ultrasound at 6 to 12 months followed by an annual follow up for 5 years was recommended. This group was regarded as having a small but real risk of recurrence and spread, and therefore the benefits of follow up, such as better prognosis resulting from early detection and treatment, would start to outweigh the 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, as well as at what point it tends to be safe to assume that further problems are unlikely, provided no recurrence or spread has occurred up to that point.

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. For people at low risk 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) annual follow up was recommended for 2 to 5 years. For people at medium risk defined as thyroglobulin between 0.2 and 1.0 microgram/litre, or stimulated thyroglobulin of between 1 and 10 microgram/litre then annual follow up was recommended for 5 to 10 years. For people at high risk defined as thyroglobulin of greater than 1.0 microgram/litre, or stimulated thyroglobulin of greater than 10 microgram/litre then an annual follow up was recommended for 10 years. The annual frequencies were again based on the committee's understanding of how quickly recurrences and spread may occur. The committee acknowledged that, while annual follow up is recommended, there may be cases in which a more frequent follow-up period is required. 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.

Finally, 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 lifelong. 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, and such people should be immediately referred back to their surgeon.

There was no evidence for how long people should be followed up, so the committee set minimum periods and wrote a research recommendation 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, but 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 webpage on thyroid cancer and the NICE webpage on thyroid disorders.

For details of the guideline committee see the committee member list.