



Complete Summary

GUIDELINE TITLE

Thyroid carcinoma.

BIBLIOGRAPHIC SOURCE(S)

Working Group Thyroid Carcinoma. Thyroid carcinoma. Utrecht, The Netherlands: Association of Comprehensive Cancer Centres (ACCC); 2007 Jun 1. 146 p. [599 references]

GUIDELINE STATUS

This is the current release of the guideline.

COMPLETE SUMMARY CONTENT

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SCOPE

DISEASE/CONDITION(S)

Nonmedullary differentiated thyroid carcinoma:

- Papillary thyroid carcinoma
- Follicular thyroid carcinoma

GUIDELINE CATEGORY

Diagnosis
Evaluation
Management
Risk Assessment
Treatment

CLINICAL SPECIALTY

Endocrinology
Family Practice
Internal Medicine
Nuclear Medicine
Nursing
Nutrition
Oncology
Otolaryngology
Pathology
Pharmacology
Radiation Oncology
Radiology
Surgery

INTENDED USERS

Advanced Practice Nurses
Dietitians
Pharmacists
Physician Assistants
Physicians
Social Workers

GUIDELINE OBJECTIVE(S)

To improve the following aspects regarding the care of patients with differentiated thyroid carcinoma:

- Diagnosis, referral, and treatment
- Overall and disease-free survival
- Quality of life

TARGET POPULATION

Children and adults with differentiated (nonmedullary) thyroid carcinoma

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation/Follow-up

1. Patient history
2. Physical examination
3. Laboratory tests (calcitonin thyroid stimulating hormone [TSH] radioiodine [¹³¹I] uptake assays; thyroglobulin [Tg] and anti-Tg antibodies levels; Tg messenger ribonucleic acid [mRNA - not recommended])
4. Imaging (scintigraphy [not recommended for primary diagnosis], ultrasound, computed tomography [CT], magnetic resonance imaging [MRI])
5. Cytology (fine needle aspiration cytology [FNAC], ultrasound-guided or palpation-guided cytological biopsy)

6. Perioperative frozen section assessment (not recommended for diagnosis of thyroid tumours)
7. No further investigation for incidentally found impalpable thyroid nodules

Management/Treatment

1. Surgery (hemithyroidectomy, total thyroidectomy plus ¹³¹I ablation)
2. Radioablation (preablation scintigram with ¹²³I or ¹³¹I, ablation dose, preablation recombinant human TSH (rhTSH), iodine restriction diet prior to ¹³¹I ablation, scintigraphy, or therapy)
3. Management after initial therapy
 - Vocal cord assessment
 - Management of vocal cord paralysis (tracheotomy, logopaedia)
 - Peri- and postoperative care of parathyroid glands
 - Adjuvant treatment (external radiotherapy or TSH suppression following radioablation)
4. Treatment of local recurrence (locoregional surgery or radiotherapy)
5. Treatment of distant metastases (surgery, radiotherapy)
6. Other treatment options (radiofrequency ablation, bisphosphonates, embolization, chemotherapy, fixed-dose administration of ¹³¹I, rhTSH during ¹³¹I therapy)

Special Considerations

1. Diagnosis and treatment of pregnant patients with thyroid carcinoma
2. Treatment of pediatric patients with thyroid carcinoma
3. Organization of care
4. Supportive care

MAJOR OUTCOMES CONSIDERED

- Overall and disease-free survival rates
- Rate of local recurrence
- Rate of distant metastases
- Quality of life
- Sensitivity and specificity of diagnostic methods

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Hand-searches of Published Literature (Secondary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The recommendations in this guideline are based as much as possible on evidence from published scientific research. Relevant articles were found by performing systematic searches in the Cochrane Library and Medline, and as necessary in Embase, Cinahl, and Psycinfo. Language was limited to English, German, French,

and Dutch. Manual searches were also performed. Searches covered 1966 to January 2004. Some more recent articles were also included. The following search terms were used to identify the patient population: thyroid* near (neoplasm* or cancer* or malignan* or tumo?r*), differentiated thyroid* cancer*, thyroid* neoplasm*, thyroid* nodule*, carcinoma papillary follicular, Hürthle cell, and the Medical Subject Headings (MeSH) terms "Thyroid-Neoplasms", "Carcinoma-Papillary-Follicular", and "Adenoma-Oxyphilic". Some articles identified in the reference list of the obtained articles were also selected. Other guidelines for differentiated thyroid carcinoma were consulted. Secondarily, articles were selected based on inclusion/exclusion criteria. One important selection criterion was comparative studies with sufficient level of evidence, such as meta-analyses, systematic reviews, randomised controlled trials (RCTs), and controlled trials (CTs). If these were not available, comparative cohort studies, comparative patient-control studies, and non-comparative studies were considered. Case reports were excluded. Other important criteria included were: sufficient volume and follow-up, sufficient exclusions with regard to selection bias, and an application to the situation in the Netherlands. The quality of the selected articles was evaluated by working group members using evidence-based guideline development (evidence-based richtlijnontwikkeling, EBRO) evaluation forms. Articles of mediocre or poor quality were excluded.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

For articles regarding intervention	
A1	Systematic reviews covering at least some A2-level studies in which the results of the individual studies are consistent
A2	Randomised comparative clinical studies of good quality (double-blind, controlled), sufficient size and consistency
B	Randomised clinical trials of moderate quality or insufficient size, or other comparative studies (non-randomised, comparative cohort studies, patient-control studies)
C	Non-comparative studies
D	Expert opinion from, for example, working group members
For articles regarding diagnosis	
A1	Studies on the effects of diagnosis on clinical outcomes in a prospectively followed, well-defined patient population with a predefined protocol based on the

	results of the study test, or decision theory studies on the effects of diagnosis on clinical outcomes based on the results of A2-level studies with sufficient consideration given to the interaction between diagnostic tests
A2	Studies that include a reference test with predefined criteria for the study test and the reference test and a good description of the test and the clinical population studied; a sufficiently large series of consecutive patients must be included, predefined cut-off values must be used and the results of the test and the gold standard must be evaluated independently. For situations in which multiple diagnostic tests are involved, there is in principle interaction and the analysis should take this into account by using, for example, logistical regression
B	Comparison with a reference test and description of the study test and population, but lacking the other characteristics of A-level studies
C	Non-comparative studies
D	Expert opinion from, for example, working group members

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

After the selection process, the remaining articles were used as the basis for the various conclusions stated in the guideline. The selected articles were graded according to the level of evidence. In the conclusion sections of each chapter in the original guideline document, the level of evidence and the most important related articles are mentioned.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus
Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Composition of the Working Group

In December 2002 a multidisciplinary working group was formed that consisted of representatives of all relevant specialities involved in the diagnosis and treatment of patients with differentiated thyroid carcinoma. The working group included members of medical and paramedical disciplines, a medical decision theory specialist, a representative from the thyroid patient organization 'Schildklierstichting Nederland', and colleagues from the Association of Comprehensive Cancer Centres (Vereniging van Integrale Kankercentra, VIKC) and the Dutch Institute for Healthcare Improvement (Kwaliteitsinstituut voor de Gezondheidszorg Centraal Begeleidings Orgaan [CBO]).

In creating the working group, consideration was given to the geographic distribution of the group members, the proportional representation of various concerned associations and authorities, as well as distribution among those working or not working in an university hospital. Working group members acted independently mandated by their associations.

Methods of the Working Group

The working group met 18 times in the period December 2002 - January 2006 to develop the draft guideline. The first step was identification of areas of weakness. A large group of specialists from various disciplines involved in the diagnosis and treatment of differentiated thyroid carcinoma were asked to identify areas of weakness in care, the organisation of care, and healthcare procedures.

Basis questions were formulated from the list of identified areas of weakness (see appendix 13 in the original guideline document).

Given the scale of the task, subgroups were formed with representatives of relevant disciplines. The basis questions were divided among the subgroups to compose a description of the optimal care for patients with differentiated thyroid carcinoma. Members of the subgroups performed systematic literature searches and judged the quality of the evidence found. They subsequently wrote a section or chapter of the draft guideline based on the literature found and, when necessary, after consultation of experts. These texts were presented during the plenary sessions. All working group members had the opportunity to discuss and contribute to all sections and chapters. The texts were revised by the authors based on the commentary received, and were then assessed and adjusted as necessary by the editorial board to obtain a coherent draft. This text formed the draft guideline that was submitted to scientific associations for commentary in early 2006.

On 11 April 2006, a national consensus meeting was held in which the draft guideline was officially presented to the relevant professional organisations.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Level of Evidence for Conclusions	
1	At least one systematic review (A1) or two independently conducted A2-level studies
2	At least two independently conducted B-level studies
3	At least one A2-, B- or C-level study
4	Expert opinion from, for example, working group members

COST ANALYSIS

The increased emphasis on healthcare costs underscores the need for guidelines that promote efficient procedures. It is therefore important to avoid unnecessary diagnostic testing and assess the efficiency and cost-effectiveness of various

treatment and diagnostic options. Attention is given to this topic at various points throughout the original guideline document.

METHOD OF GUIDELINE VALIDATION

External Peer Review
Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

After incorporating the comments from the consensus conference, the final draft was approved by the complete working group at the final plenary session and submitted to the relevant professional organisations for authorisation.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

General

Heredity

The working group recommends that patients with a hereditary burden resulting in thyroid carcinoma must be referred to a level 1 or 2 hospital.

Staging

The working group recommends that the information needed for tumor/node/metastasis (TNM) classification in the pathology report must be recorded in all cases.

Diagnosis

Patient History and Physical Examination

If a thyroid nodule is highly suspected to be malignant, based on clinical grounds (either or not supported by additional diagnostics, e.g., ultrasound or fine needle aspiration cytology [FNAC]) the patient should be treated by a multidisciplinary team in order to guarantee quality.

Laboratory Tests

Calcitonin

Thyroid stimulating hormone (TSH) should be determined in all patients with thyroid nodules.

A calcitonin assay is recommended if the FNAC results are inconclusive, if clinically the conclusion is suspicious or unclear, or if the preoperative diagnosis is unclear

for other reasons. If the suspicions are confirmed by an elevated calcitonin value, the patient should be referred to a level 1 hospital.

It is recommended to treat patients with medullary thyroid carcinoma a level 1 hospital, given the greater therapeutic experience that can be found there as well as the better insight into the relative benefits of surgical and non-surgical treatments.

Routine assessment of calcitonin level in patients with a solitary thyroid nodule is not recommended at the moment. In cases with atypical cytological findings (spindle-shaped or plasmacytoid cells without colloid), the calcitonin value can provide additional value, particularly when determining the surgical approach. The same is true for immunohistochemical assessment of imbedded FNAC material.

Imaging

Scintigraphy

Scintigraphy is not recommended for use in the primary diagnosis of thyroid carcinoma.

Ultrasound

The following features should be described during ultrasonographic investigation of palpable thyroid nodule: cystic/solid, hypoechoic/echogenic, borders regular/irregular, microcalcifications present/absent, halo present/absent, vascularisation intra/extranodular, positive cervical lymph nodes present/absent.

The working group advises using ultrasound-guided FNAC for all palpable thyroid nodules and to correlate the clinical, ultrasonographic, and cytological evidence.

A national multicentre study to evaluate the diagnostic value and cost-effectiveness of ultrasound and FNAC in patients with a thyroid nodule warrants recommendation to establish in patients with clinically and ultrasonographically unsuspected nodules FNAC may be avoided.

Ultrasound assessment prior to FNAC can be used to:

- Detect or exclude extrathyroidal disease
- Describe the ultrasonographic features of the index nodule

Cytology

Fine Needle Aspiration Cytology (FNAC)

FNAC plays a central role in the diagnosis of palpable thyroid disorders and is recommended as the first microinvasive diagnostic test.

Immediate assessment of representativity of the sample by a cytopathologist is advised to limit the number of nondiagnostic biopsy sessions as much as possible.

Thyroid biopsies must be performed by physicians who:

- Have adequate technical skills and routinely perform thyroid aspirations
- Can interpret the cytology results correctly
- Can recommend management or treatment based on the cytology results

Thyroid biopsies must be assessed by:

- A pathologist with interest and experience in thyroid cytology and histology, who can recommend management or treatment based on the cytology results
- If an experienced pathologist is not available locally, the sample should be sent to a pathologist that does have expertise in this field

Treatment decisions and any necessary further diagnostic testing should be determined only after discussion with the:

- Treating specialist
- Pathologist
- Radiologist

Ultrasound-Guided Versus Palpation-Guided Cytological Biopsy

If cytological assessment of a thyroid nodule is to be performed, it is preferable that ultrasound guidance is used. Ultrasound guidance is recommended for all patients in the following situations:

- Lack of biopsy experience among other specialists
- Insufficient material obtained during the first FNA
- Semisolid nodules, to obtain material from the solid component
- Nodules that are difficult to identify by palpation

This enhances the yield of the cytological biopsy and facilitates an optimal correlation between the ultrasonographic features and the cytological diagnosis of the nodule.

Fine Needle Aspiration (FNA) for Multinodular Goitres

Sampling of clinically suspicious nodules identified by ultrasound is recommended when performing FNAC in clinical multinodular goitres.

Frozen Section Assessment

Perioperative frozen section assessment does not play a role in the diagnosis of thyroid tumours.

Impalpable Thyroid Nodules

The working group recommends no further investigation be performed for impalpable thyroid nodules found incidentally in the absence of predisposing clinical factors.

Treatment

Hemithyroidectomy is recommended for unifocal papillary thyroid carcinoma <1 cm if there is no indication of lymph node metastases. Total thyroidectomy followed by ¹³¹I ablation is preferred if the resection is not radical, multifocal papillary carcinoma is found in the resected specimen from hemithyroidectomy, or if there is an increased risk of malignancy in the contralateral thyroid lobe. Hemithyroidectomy is recommended for unifocal papillary thyroid carcinoma <1 cm if there is no indication of lymph node metastases. Total thyroidectomy followed by ¹³¹I ablation is preferred if the resection is not radical, multifocal papillary carcinoma is found in the resected specimen from hemithyroidectomy, or if there is an increased risk of malignancy in the contralateral thyroid lobe.

Minimally Invasive Follicular Carcinoma

From the perspective of optimal long-term control, total thyroidectomy followed by ¹³¹I ablation is recommended for minimally invasive follicular thyroid carcinoma.

Ablation

Preablative Scintigram

Obtaining a preablative scintigram after total thyroidectomy is preferable for patients with differentiated thyroid carcinoma. For the scintigram, ¹²³I or low-dose ¹³¹I (< 75 MBq or < 2 mCi) should be used. A second operation should be considered for patients with high thyroid bed uptake (> 5-10%). The preablative scintigram may be omitted in centres with demonstrated and recognised surgical expertise resulting in consistently low thyroid bed uptake.

The working group recommends conducting a nationwide prospective study to compare the efficacy of ¹³¹I ablation in centres that obtain a preablative scintigram, those that use fixed dosing, and those that use extensive tumour dosimetry.

Ablation Dose

For the ablation of residual thyroid tissue following thyroidectomy, ¹³¹I doses of 1,850 to 3,700 MBq are recommended. For the sake of standardisation, the working group recommends using 3,700 MBq. A dose of 3,700 MBq should always be used when recombinant human TSH (rhTSH) is given as preparation rather than thyroid hormone withdrawal.

Standard doses of 3,700 to 7,400 MBq are recommended for patients with lymph node metastases found by preablative scintigraphy and those who underwent nonradical resection of the primary thyroid tumour. However, surgery should be considered first for patients with high iodine uptake in the thyroid bed or uptake in multiple lymph nodes according to preablative scintigraphy. For patients with confirmed metastases and a high thyroid bed uptake, it may be considered to first ablate the thyroid remnant using a lower ablative dose and, after a few months, treat the metastases with high standard doses of ¹³¹I.

The working group recommends conducting a nationwide prospective study to compare the results of ^{131}I ablation and ^{131}I treatment for lymph node metastases and nonradically resected thyroid carcinoma among centres who obtain a preablative scintigram, those who use fixed dosing, and those who perform extensive dosimetry.

Preparation with rhTSH Before Ablation

Hypothyroidism is the gold standard for preparation for ^{131}I ablation. In the subgroup of patients with a relatively low risk of residual or recurrent thyroid carcinoma (stage T2N0-1M0 or T0-1N1M0; see the original guideline document for staging definitions), preparation with rhTSH may be considered as an alternative. In this case, the ablation dose should be 3,700 MBq (100 mCi).

Iodine-Restricted Diet Prior to I Scintigraphy, ^{131}I ablation, or ^{131}I therapy

The working group strongly suggests considering prescribing an iodine-restricted diet for patients with low ^{131}I uptake in thyroid remnants or metastases prior to ^{131}I ablation of thyroid remnants, ^{131}I treatment for thyroid carcinoma metastases, or ^{131}I diagnostic whole body scintigraphy.

(Adjuvant) Treatment after Initial Treatment

Vocal Cords and Parathyroid Glands

Vocal Cord Assessment

Preoperative vocal cord assessment using laryngoscopy is indicated for patients with voice alterations or prior surgery in the thyroid region.

- Postoperative vocal cord assessment, occurring approximately one week after thyroid surgery, is indicated for patients with voice alterations or pronounced shortness of breath

Management of Postoperative Vocal Cord Paralysis

- Patients with bilateral nervus recurrens paresis and inspiratory stridor and dyspnoea may require acute tracheotomy. For patients with bilateral nervus recurrens paresis and less severe symptoms or unilateral nervus recurrens paresis, watchful waiting with a laryngoscopic check-up every 6 to 12 months is justified, given the chance of spontaneous recovery
- Logopaedia is recommended for patients with unilateral nervus recurrens paralysis. If the results are unsatisfactory and permanent paresis is diagnosed, corrective surgery at a specialised centre may be considered

Peri- and Postoperative Care of Parathyroid Glands

The working group recommends that it is important that at least one viable parathyroid gland is identified and spared during total thyroidectomy. The removed thyroid specimen should always be examined for the presence of

parathyroid glands that were also removed. All removed, non-vital parathyroid tissue should be re-implanted.

The Role of External Radiotherapy Following Ablation

External radiotherapy after surgery and ^{131}I ablation is not indicated for papillary or follicular thyroid carcinoma. External radiotherapy is indicated for patients aged >45 years with macroscopically nonradical tumour resection; it may be considered for those with microscopic residual disease.

Suppression Therapy Following Ablation

It is recommended that a TSH value <0.1 mU/l should be targeted in all patients with thyroid carcinoma until the first evaluation following ablation therapy, and for patients with the following:

- High risk
- Thyroglobulin (Tg) greater than cut-off during thyroxine and/or TSH stimulation
- Persistent tumour

For low-risk patients with thyroid carcinoma, it is recommended that, after 2 years of TSH suppression (TSH <0.1 mU/L), treatment is adjusted to roughly target the median TSH value of 1 mU/l.

Follow-Up

Follow-up Low Risk

Diagnostic Evaluation during Follow-up

The working group recommends that follow-up of low-risk patients with thyroid carcinoma can occur as described in the 'Flowchart for follow-up of low risk patients' (see original guideline document).

Low-Risk Group

The working group defines low-risk patients as those aged 20 to 45 years with minimally invasive follicular thyroid carcinoma or stage pT1-2 papillary carcinoma and excluding tall-cell, columnar cell, or diffuse sclerosing variants. Patients must also meet the following criteria:

- No evidence of lymph node and/or distant metastases
- Post-ablation scan shows uptake in the thyroid bed only
- Tg <1 ng/mL during TSH suppression after 3 months of follow-up
- No anti-Tg antibodies

Follow-up Non Low Risk

The working group recommends that the follow-up flowchart should not be used for patients with thyroid carcinoma who are not considered low-risk. These

patients should be monitored more frequently with Tg assessment during T4 substitution, neck ultrasound, diagnostic ¹³¹I scintigraphy, and Tg following TSH stimulation, preferably induced by thyroxine withdrawal.

The suggested frequency of Tg assessment during T4 substitution and neck ultrasound is every 3 to 6 months in the first 2 years with annual Tg assessment and diagnostic ¹³¹I scintigraphy following TSH stimulation. Depending on the diagnostic findings, the interval between check-ups may be increased over the course of the follow-up.

Thyroglobulin Assessment

Thyroglobulin during Follow-up as a Determinant of Further Management

For patients with thyroid carcinoma and non stimulated Tg concentration greater than 1 ng/mL (1.5 pmol/L), a 50%-increase in Tg concentration should always be followed by diagnostic imaging.

Detectable Tg in the first year after treatment for thyroid carcinoma must be interpreted in relation to the original condition of the patient following initial treatment.

If the likelihood of recurrent or metastatic disease is considered low, Tg assessment during T4 substitution should be repeated after 3 to 6 months before considering additional diagnostic testing.

If the repeat test indicates a Tg concentration greater than 1 ng/ml (1.5 pmol/L) during T4 substitution, diagnostic imaging should be performed, including neck ultrasound and, if necessary, 100 mCi ¹³¹I diagnostic testing, or therapy as needed.

Quality Requirements in Thyroglobulin Assessment

Assessment of anti-Tg antibodies should occur in parallel with Tg assessment.

If anti-Tg antibodies are present, it should be reported that they interfere with the Tg assessment. Laboratories should not report undetectable levels of Tg in patients with anti-Tg antibodies if the Tg concentration is determined using immunometric methods that may be susceptible to negative interference from anti-Tg antibodies.

Discussion with a nuclear medicine physician and an internist/endocrinologist regarding the reporting of Tg in samples that are positive for anti-Tg antibodies is recommended.

Clinical Relevance of Anti-Tg Antibodies

The working group is of the opinion that patients with thyroid carcinoma and anti-Tg antibodies require more comprehensive monitoring, depending in part on other clinical parameters. These patients should be considered high-risk until the antibodies become undetectable during follow-up. If antibodies develop during

follow-up, a thorough evaluation for the presence of recurrent thyroid carcinoma should occur.

The Value of Tg Messenger Ribonucleic Acid (mRNA) During Follow-Up

The working group does not recommend Tg mRNA assessment in patients with thyroid carcinoma.

Imaging Techniques

The Value of Neck Ultrasound During Follow-Up

Neck ultrasound is a standard diagnostic test used in combination with TSH-stimulated Tg assessment 6 months after surgery and ablative ¹³¹I therapy in low-risk patients. Neck ultrasound should also be performed in high-risk patients and those suspected of having recurrent or metastatic thyroid carcinoma. Patients with suspicious lymph nodes identified by ultrasound (low Solbiati index, irregular echostructure, calcifications, irregular vascularisation, or loss of hilar structure) should undergo ultrasound-guided cytological diagnostic assessment.

For further follow-up of low-risk patients, neck ultrasound with Tg assessment during thyroid hormone substitution is a sensitive diagnostic approach.

Chest X-Ray

The working group does not recommend routine chest x-ray in the follow-up of patients with differentiated thyroid carcinoma.

Nuclear Imaging

Scintigraphy with sestamibi/tetrofosmin, thallium, octreotide, and 18-fluoro-deoxy-glucose positron emission tomography (FDG-PET) do not have a role in the routine follow-up of patients with differentiated thyroid carcinoma. These tracers may be useful in patients suspected of having recurrent or metastatic disease based on increased serum thyroglobulin concentrations but for whom no disease can be localised with ¹³¹I whole body scintigraphy (preferably using therapeutic doses).

Skeletal scintigraphy does not have a role in the routine follow-up of patients with differentiated thyroid carcinoma.

The working group recommends that octreotide scintigraphy should be considered in the follow-up of patients with thyroid carcinoma only if experimental treatment with labelled octreotide is considered after conventional therapies have failed.

The Value of Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) During Follow-Up

If nuclear imaging provides inconclusive results regarding the presence, location, or amount of tumour tissue, CT or MRI can be performed. The choice between CT and MRI depends on local expertise and availability.

Treatment of Local Recurrence

Locoregional Treatment

Lymph node metastases >1 cm are preferably removed surgically. For clinically occult locoregional tumour recurrence in the neck that is smaller than 1 cm and accumulates radioiodine, treatment with ^{131}I is effective.

For local recurrence of thyroid carcinoma, the most complete resection possible should be performed. The radicality of the intervention should be weighed against the morbidity associated with radical resection. Tumour type and location, patient condition, and life expectancy should also be considered.

Locoregional recurrence of thyroid carcinoma should be treated by a multidisciplinary team in a centre for thyroid surgery.

The working group recommends that radiotherapy for thyroid carcinoma should be considered for extranodal tumour invasion and tumour-positive resection margins in which there is limited or no radioiodine uptake.

Treatment of Distant Metastases

Surgical treatment for distant metastases of thyroid carcinoma is indicated for solitary or a limited number of metastases, and should be followed by ^{131}I or external radiotherapy.

If surgical intervention is not possible or undesirable, iodine-accumulating metastases of thyroid carcinoma should be treated with ^{131}I .

Treatment with ^{131}I may be continued until the post-treatment scintigram no longer detects ^{131}I uptake.

The working group recommends that external radiotherapy can be given for metastases of papillary and follicular thyroid carcinoma when the metastases no longer accumulate ^{131}I or demonstrate insufficient regression during ^{131}I therapy.

Other Treatment Options

Radiofrequency Ablation

Radiofrequency ablation is a treatment option that may be considered for recurrent thyroid carcinoma that is inoperable and insufficiently sensitive to ^{131}I . Treatment should take place in a treatment centre with experience with radiofrequency ablation.

Bisphosphonates

Monthly treatment with pamidronate given intravenously at a dose of 90 mg is recommended for patients with otherwise untreatable painful bone metastases of differentiated thyroid carcinoma to relieve pain and improve quality of life.

Embolisation

Embolisation should be considered for symptomatic bone metastases of thyroid carcinoma, possibly in combination with external radiotherapy or ^{131}I . The procedure should be performed in a specialized treatment centre.

Chemotherapy

Chemotherapy may be considered for patients with metastatic thyroid carcinoma who have failed all other therapeutic options and have indications of rapidly progressing disease. Chemotherapy should be given in a referral centre after discussion with an internist/oncologist and preferably in the context of a clinical trial.

Fixed-Dose Administration of ^{131}I

If recurrent or metastatic thyroid carcinoma is suspected based on increasing thyroglobulin concentrations, and neck ultrasound shows no evidence of disease, a fixed dose of 3,700 to 7,400 MBq of ^{131}I during TSH stimulation is recommended. Performing a whole body scan (WBS) 4 to 7 days after this dose is recommended. If the WBS indicates ^{131}I uptake, further targeted localisation of the disease can be considered and other treatment, such as surgery, can be considered as necessary. Repeating therapy with 3,700 to 7,400 MBq of ^{131}I during TSH stimulation should also be considered.

rhTSH during ^{131}I Therapy

Recombinant TSH prior to ^{131}I therapy can be considered as an alternative to thyroxine withdrawal for patients with thyroid carcinoma and contraindications to thyroxine withdrawal and for those who may not tolerate thyroxine withdrawal.

Lithium Preparation Prior to ^{131}I Therapy

Treatment with lithium during ^{131}I therapy for metastatic thyroid carcinoma is not recommended.

Management of Patients with Negative Post-Therapy Scans but Detectable Tg and Positive Results with Other Diagnostic Imaging

If metastases of thyroid carcinoma do not accumulate ^{131}I but are detectable with radiological assessment, surgical treatment is preferred. If surgery is not possible, treatment with radiolabeled lutetium (^{177}Lu)-octreotate can be considered in the context of a clinical trial.

Pregnancy

Pregnancy and Differentiated Thyroid Carcinoma

For pregnant patients with a thyroid nodule that is not suspected of being malignant, diagnostic assessment and treatment can be postponed until after delivery. The nodule, however, should be followed carefully. For nodules

suspected of being malignant based on clinical or cytological features, surgical treatment can be performed during the second trimester without increased risk to mother and child.

Pregnancy during Follow-Up of Thyroid Carcinoma

Pregnancy is contraindicated in patients with active, progressing thyroid carcinoma for whom treatment is indicated.

During pregnancy of low-risk patients with thyroid carcinoma without active disease, targeting a serum TSH value of 1 mU/l with thyroid hormone substitution is recommended.

Pediatric Patients

Pediatric Patients with Differentiated Thyroid Carcinoma

Given the low incidence and relatively high morbidity, the working group recommends that children with differentiated thyroid carcinoma should undergo surgery in a level 1 hospital.

Monitoring of children with thyroid carcinoma should be performed by a paediatrician with specific knowledge and experience in endocrinology.

Organisation of Care

It is recommended that diagnosis, treatment and follow-up is performed by a multidisciplinary team.

The working group recommends a team including the following specialists:

- Internist/endocrinologist*
- Surgeon
- Pathologist
- Nuclear medicine physician
- Radiologist
- Radiation oncologist
- Nurse specialists and, if necessary, psychosocial professional
- Laboratory physician/clinical chemist

All team members should have expertise and interest in the management of differentiated thyroid carcinoma.

*In some treatment centres, this may be an internist/oncologist.

Key Points from the Guideline

The working group recommends that patients for whom diagnostic surgery (hemithyroidectomy) is indicated based on thyroid pathology should undergo surgery in a hospital where at least 10 to 15 thyroid operations are performed per surgeon each year. In the absence of cervical lymph node metastases and if there

were no complications from the first operation, a contralateral hemithyroidectomy can in principle take place in the same treatment centre.

The working group recommends that patients with preoperatively confirmed thyroid carcinoma should undergo surgery in at least a level 2 hospital. If the presence of cervical lymph node metastases is confirmed or highly suspected before surgery, the working group recommends performing the operation in a level 1 hospital.

The working group recommends that patients with confirmed malignancy and complications (nonradical first resection) and those who require a second operation in a previously explored region should be referred to a level 1 hospital.

Management of patients with medullary or anaplastic thyroid carcinoma is beyond the scope of this guideline. These patients should always be treated in a level 1 hospital.

The first 6 months of follow-up after initial therapy and ablation should take place in the hospital where ¹³¹I was administered, given the complexity involved in determining the level of risk. Subsequently, low-risk patients can be followed in a regional hospital by an internist/endocrinologist with experience with this type of follow-up.

A protocol for follow-up is required.

See the original guideline document for recommendations for psychosocial care and dietary considerations.

CLINICAL ALGORITHM(S)

The original guideline document contains the clinical algorithm "Flowchart for follow-up of low risk patients."

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not identified or graded for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Early diagnosis, referral, and treatment may result in higher rates of overall and disease-free survival, and improved quality of life.

POTENTIAL HARMS

- The relatively good quality of life in patients with metastatic thyroid carcinoma should be weighed against the adverse effects and potential benefit of chemotherapy.
- Like other medications, Thyrogen® can cause side effects. A small number of patients have side effects at the injection site, including redness, discomfort, itching, local pain or stinging.
- There is a risk of surgical complications following resection and total thyroidectomy.
- The reported risk of transient hypocalcaemia following total thyroidectomy is around 60%.
- Permanent hypoparathyroidism, in which parathyroid hormone levels remain very low after 1 year, is a very serious complication that occurs in approximately 0.5 to 4% of patients. The risk of hypoparathyroidism is increased by extensive surgery, e.g., for large tumours or the removal of lymph nodes in the central neck compartment. The location of the parathyroid glands, which is not always predictable, also plays a role. Given the serious consequences of hypoparathyroidism, all parathyroid tissue that is damaged or removed should be re-implanted to prevent long-term complications.
- Treatment of metastatic disease with radioiodine can result in fatal complications, such as cerebral oedema and intracerebral haemorrhage.

Special Populations

Children

Complications following thyroid surgery (hypoparathyroidism and recurrent nerve paralysis) occur relatively frequently in children.

CONTRAINDICATIONS

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Pregnancy is contraindicated in patients with active, progressing thyroid carcinoma for whom treatment is indicated.

QUALIFYING STATEMENTS

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Guidelines are not legal requirements, but rather scientifically founded and widely accepted views and recommendations to which healthcare providers would have to adhere to provide quality care. Given that guidelines are based on 'average' patients, healthcare providers can deviate from the recommendations in the guideline as necessary in individual cases. Deviation from the guideline is in fact sometimes necessary if the patient's situation requires it. When there is deviation from the guideline, however, it must be rationalised, documented and, when necessary, discussed with the patient.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

Implementation was considered throughout the various phases of development of the draft guideline. Particular attention was given to factors that may accelerate or hinder the introduction of the guidelines in daily practice. The guideline will be distributed through scientific organisations and hospital staff, as well as hospital oncology boards and Comprehensive Cancer Centres (Integrale Kankercentra). A summary of the guideline will also be published in the Dutch Journal of Medicine (Nederlands Tijdschrift voor Geneeskunde) and attention will be given to the guideline in various specialty journals. In addition, the guideline will be reproduced on the Centraal Begeleidingsorgaan (CBO) website and www.oncoline.nl.

Indicators need to be developed to evaluate the implementation of the guideline and its effects. Indicators are measurable characteristics of healthcare that may be used as a marker for quality of care. Indicators give healthcare providers the opportunity to assess whether they are providing the desired level of care. They can also be used to identify areas for improvement. These indicators will be established based on the recommendations in this guideline in conjunction with scientific societies and other professional organisations.

IMPLEMENTATION TOOLS

Foreign Language Translations
Personal Digital Assistant (PDA) Downloads

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Getting Better
Living with Illness

IOM DOMAIN

Effectiveness
Timeliness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Working Group Thyroid Carcinoma. Thyroid carcinoma. Utrecht, The Netherlands: Association of Comprehensive Cancer Centres (ACCC); 2007 Jun 1. 146 p. [599 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Working group members behaved as independently as possible with regard to external commercial influences related to the guideline topic. Details on the declared conflicts of interest from working group members are available upon request from the Dutch Institute for Healthcare Improvement (Kwaliteitsinstituut voor de Gezondheidszorg Centraal Begeleidingsorgaan [CBO]).

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in English and Dutch from the [Association of Comprehensive Cancer Centres Web site](#).

Print copies: Available from Association of Comprehensive Cancer Centres PO Box 19001, 3501 DA Utrecht, The Netherlands

AVAILABILITY OF COMPANION DOCUMENTS

A version of the guideline for Personal Digital Assistants (PDAs) is also available at the [Association of Comprehensive Cancer Centres Web site](#).

PATIENT RESOURCES

None available

NGC STATUS

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