REVIEW ARTICLE

Indications for the Surgical Management of Benign Goiter in Adults

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on behalf of the German Society for General and Visceral Surgery quality commission

Summary

Background: Thyroidectomy is still three to six times more common in Germany than in the USA, Great Britain, and the Scandinavian countries. Thus, the question is often asked whether thyroidectomy in Germany is being performed for the correct indications.

Methods: This review is based on studies and guidelines containing information on the indications for surgery in benign goiter and Graves' disease; these publications were retrieved by a systematic literature search in the Medline and Cochrane Library databases (1990–2016). The indications recommended here were determined by vote by the German Society for General and Visceral Surgery (Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie, DGAV).

Results: On the basis of the available evidence (levels 2–4), and in the absence of prospective studies, the indications for surgery in goiter include a well-founded suspicion of malignancy, local compressive symptoms, and, rarely, cosmesis. In hyperthyroid goiter and Graves' disease, surgery is a potential alternative to radioiodine therapy, particularly if the volume of the thyroid gland exceeds 80 mL, in patients with advanced or active orbitopathy, and in female patients who are, or plan to be, pregnant. Large, asymptomatic, euthyroid nodular goiter without any suspicion of malignancy and scintigraphically "cold" nodules without any other evidence of malignancy are not indications for surgery. Thyroid operations of higher levels of difficulty (e.g., recurrent goiter, retrosternal extension, Graves' disease) should be carried out in institutions with special expertise in thyroid surgery.

Conclusion: The decision to operate should be made on an interdisciplinary basis and in conformity with the relevant guidelines after all of the appropriate diagnostic studies have been performed. The radicality of any proposed surgical procedure should be weighed against its potential complications.

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The number of thyroid surgeries performed to treat benign goiter declined in Germany between 2005 and 2013 from 89 000 to 79 000 per year (1). However, it was still about 3 to 6 times higher compared to the numbers in the USA, England, and Scandinavian countries (2–4). A population-based cross-sectional study including 4310 adults without known thyroid disease from the Western Pomerania region in Germany found a prevalence of nodular goiter of 35.9% (5); a similar rate can be assumed for Germany. Thus, the question arises how to define the population of patients who require surgical management; even more so when considering the fact that 75% of operated patients had no preoperative symptoms and normal thyroid function (2). In Germany, about 25% of thyroid surgeries (approximately 20 000) is performed for the indication of "suspicious thyroid nodule" (2). The malignancy rate in "suspicious" thyroid nodules obtained by "diagnostic thyroid surgeries" (typically hemithyroidectomy) is in Germany 1:15 cases, in Italy 1:7 and in England and Scandinavian countries 1:5 cases (6–8). This is partially due to a lack in guideline compliance (e.g., fine needle aspiration cytology [FNAC] is not used frequently enough) (9, 10). However, since delayed treatment (>12 months) of a malignancy which is limited to the thyroid has the same prognosis as immediate surgery, a watchful-waiting approach can be adopted with no disadvantage to the patient (11). Many times it has been criticized that in Germany not all thyroid surgeries performed in patients with benign nodular thyroid disease are indicated and that the preoperative investigations to estimate the malignancy risk recommended in the guidelines are not fully exhausted (12). A retrospective data analysis including 25 600 AOK-insured patients (AOK, *Allgemeine Ortskrankenkasse*; a large general statutory health insurance company) with nodular goiter showed that in contrary to the guideline recommendations (13, 14) only in 9% of patients calcitonin was measured and in only 21% of patients FNAC was performed (2).

Other than "observation alone," the options for the management of euthyroid nodular goiter include pharmacotherapy, radioiodine therapy, and surgical resection. More recently, additional local ablative procedures have become available (e.g. high-frequency ultrasound), but their significance has yet to be determined in studies (15). The decision about the most suitable treatment strategy has to be made on the basis of a patient's individual characteristics. Even though prospective randomized

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PRISMA flow chart of article selection. Our analysis focused on indications for the surgical management of common benign thyroid conditions, including nodular goiter, solitary thyroid nodule, Graves' disease, and recurrent goiter. Less frequent indications for the surgical management of benign thyroid disease, such as thyroiditis (Hashimoto, deQuervain, Riedel), thyroid cysts and thyrotoxic crisis, were not within the scope of the analysis and recommendations. The following definitions were used:

- Goiter: thyroid enlargement >25 mL in men, >18mL in women
- Nodular goiter: thyroid enlargement with a single or multiple nodules
- Solitary nodule: solitary thyroid nodule in a non-enlarged thyroid
- Retrosternal goiter: extension of thyroid gland below sternal notch in patients in upright position, detected clinically or in imaging studies

PRISMA, preferred reporting items for systematic reviews and meta-analyses

comparative studies on the efficacy of the various treatment approaches in patients with euthyroid nodular goiter are not available, numerous pertinent medical societies have created evidence-based guidelines on the diagnosis and management of benign thyroid changes (13, 14, 16, 17, e1, e2). The differences between the guidelines are small, but are noticed when it comes to the use of various diagnostic methods, the evaluation criteria for malignancy in ultrasonography, and implementation in daily practice (18–20).

It is frequently argued that especially surgeons establish an indication for surgical management of benign goiter far too often. In support of this argument the above mentioned data analysis of 25 600 AOK-insured patients (2) is frequently quoted, among others, which showed that an indication for surgical management of patients with benign goiter is considerably more frequently established by surgeons (20% and 29% for uninodular and multinodular goiter, respectively) compared to the average of all specialist groups (5% and 8%, respectively). However, most patients are diagnosed by a specialist who then refers them to a surgeon. If the surgeon rejected the indication for surgical management, a conflict with the referring specialist could ensue.

Thus, it can be assumed that in case of a “questionable” indication for surgical management, the surgeon would be reluctant to contradict the referring specialist in order not to jeopardize the collaboration. Thus, internal medicine specialists, endocrinologists and nuclear medicine specialists should make use of the diagnostic investigations recommended in the guidelines. However, the surgeon is ultimately responsible (both as regards content and legally) for the indication for thyroid surgery and any morbidity that may result from the operation. Here, it is crucial to strike a balance between radicality of surgery and potential complications (21).

Therefore, we wrote a review under the “Chosing wisely” initiative of the German Society for General and Visceral Surgery (*Deutsche Gesellschaft für Allgemein- und Viszeralchirurgie*, DGAV; the members of the DGAV quality commission are listed in the *eBox*) based on a systematic search of the literature and developed recommendations for indications for the surgical management of common benign thyroid diseases in adults.

Material and methods

A systematic literature search (Medline, Cochrane Library) was performed using the following keywords: “benign goiter AND indication“, “multinodular goiter AND indication“, “thyroid nodule AND indication“, “hyperthyroidism AND indication“ as well as “Graves’ disease AND indication“. The identified 683 abstracts from studies, guidelines and reviews with information about indications for the surgical management of benign thyroid conditions in adults were then independently screened by two authors (DKB, PEG) for information about indications for surgery. Altogether 38 studies/original articles and 16 guidelines mentioning indications for surgical management were selected and analyzed. Based on this analysis, recommendations for the indications for surgical management were developed (PRISMA flow chart, *Figure*). This data analysis and recommendations derived from it were presented and discussed during 3 meetings of the DGAV quality commission. The final recommendations were presented to the members of the quality commission and subsequently adopted in an open vote with strong consensus.

The following recommendations only apply to the indications for surgical management in adults. Detailed assessment of the preoperative workup and the choice of surgical technique was not within the scope of this analysis and the resulting recommendations.

Results

Goiter with or without nodules

According to the systematic literature search, reasonable suspicion of malignancy and compression were clear indications for surgical management (*Box 1*). It should be noted that a nonfunctioning “cold“ nodule on scintigraphy alone without further indicators of malignancy or other reasons to operate does not constitute

BOX 1

Clear and relative indications for the surgical management of goiter with or without nodules

Indications for surgery in patients with goiter with or without nodules include:

- Reasonable suspicion of malignancy, especially with
 - hard, firm, potentially fast growing fixed nodule(s)
 - cervical lymphadenopathy
 - ultrasound high-risk lesion classified as category 4c and 5 of TI-RADS classification (23, *Table 1*)
 - FNAC class suspicious/positive according to Schmid classification (28, *Table 2*) or class 4–5 according to Bethesda classification (27)
 - FNAC class requiring further investigations according to Schmid classification (28) or FNAC class 3 according to Bethesda classification (27), especially in the presence of indicators of malignancy in the patient's history or clinically
 - basal calcitonin serum level increase >26 pmol/L in women and 60 pmol/L in men (warning: assay-dependent)
- Presence of compression symptoms

Surgery may be indicated:

- In case of ultrasound lesions with moderate risk according to TI-RADS classification (23), if the patient does not wish to undergo regular follow-up
- In patients with past (years ago, especially in youth) exposure to external radiation or past radiation treatment
- In case of FNAC class suspicious/requiring further investigations according to Schmid classification (28) or class 3 according to Bethesda classification (27), as an alternative to monitoring at close intervals, even if no other indicators of malignancy (in the patient's history or clinically) are present
- In case of thyroid nodules and positive family history (1st degree relatives) for well-differentiated thyroid carcinoma
- In case of subclinical or overt hyperthyroidism based on functional autonomy as an alternative to radioiodine therapy, if the latter is contraindicated or not reasonable or refused by the patient
- For prevention of complications with progressive retrosternal growth (tracheal compression >35%, superior vena cava syndrome)
- For cosmetic reasons with visible goiter

Surgery is NOT indicated:

- In asymptomatic euthyroid nodular goiter without suspicion of malignancy
- For "cold" nodule on scintigraphy without further indicators of malignancy or other reasons to operate

FNAC, fine needle aspiration cytology; TI-RADS, thyroid imaging, reporting and data system

an indication for surgery. On the other hand, there are relative indications for surgery (*Box 1*). In case of a relative indication, treatment alternatives should be discussed with the patient and documented in the surgical informed consent form.

According to various guidelines, the individual risk of malignancy is determined by a combination of data from the patient's medical history, clinical examination findings, thyroid hormone levels, as well as ultrasound, scintigraphy and, if required, FNAC findings (13, 14, 16, 17, e1, e2). With regard to the medical history, the statistical probability of a malignant nodule is increased by factor 1.5–5 in case of:

- Status post head/neck radiation
- Positive family history of medullary thyroid carcinoma, of multiple endocrine neoplasia, Type 2a or papillary thyroid carcinoma
- Age <14 years and >70 years
- Fast-growing nodule and
- Persistent dysphonia, dysphagia or dyspnea (22).

Clinical examination findings indicative of malignancy include a hard, firm, fixed thyroid nodule and cervical lymphadenopathy (14). High-resolution ultrasound is the most important investigation for

assessing thyroid morphology and nodular changes. In the meantime, ultrasound criteria—so-called TI-RADS (thyroid imaging, reporting and data system) criteria (23)—have been established; based on 5 ultrasound features, the risk of malignancy of a thyroid nodule can relatively reliably be determined (*Table 1*). However, due to its comparatively high complexity, this classification has only found limited adoption in clinical practice. As an alternative, the ultrasound malignancy criteria described in the guidelines of the American Thyroid Association may be used (17). In case of medium- to high-risk lesions according to ultrasound morphology criteria, FNAC is recommended (13, 14, 17). The malignancy risk of a "cold" nodule detected with technetium scintigraphy is associated with a malignancy risk of about 1–5% (24) and alone, without other reasons, does not justify surgical management. While methoxy-isobutyl-isonitrile (MIBI) scintigraphy, a comparatively new imaging technology, continues to gain in importance in thyroid diagnosis (25), the data currently available do not allow to draw final conclusions on the role of this technology in Germany where goiter is endemic. At the most, it should only

BOX 2

Clear and relative indications for the surgical management of Graves' disease

- **Surgery is indicated in case of:**
 - Reasonable suspicion of malignancy (for criteria see Box 1)
 - Compression symptoms (especially dyspnea, stridor, dysphagia)
 - Concomitant active Graves' orbitopathy
 - Concomitant hyperparathyroidism
 - Pregnancy
 - Female patients with the desire to have a child which shall not be postponed
 - Requirement of immediate treatment effect (serious side effects of an antithyroid drug, pregnancy with high use of antithyroid medication, thyrotoxic crisis)
 - Short-term need for contrast exposure (e.g. cardiac catheterization)
 - Refusal of radioiodine therapy
- **Surgery may be indicated in case of:**
 - Moderate or large goiter (organ volume >60–80 mL), especially in the presence of nodules and moderate to severe Graves' orbitopathy
 - High recurrence risk, persistence after 6–12 months of pharmacotherapy, or recurrence after conservative management

be used on an individual basis as a supplementary investigation to establish the indication. Likewise, elastography, a method being increasingly adopted, can be a valuable supplement to the diagnostic workup, facilitating risk stratification of thyroid lesions (26).

Ultrasonographically confirmed thyroid nodules associated with medium to high risk of malignancy represent an indication for surgical management, especially if FNAC findings indicate uncertain cytology/requirement of further investigations or are classed as suspicious. In recent years, the Bethesda system for reporting thyroid cytopathology (27) has internationally been adopted; however, we prefer the German classification system (28) (Table 2) as it has no class 3 (atypia or follicular lesion of uncertain significance) which is of little informational value.

Patients with thyroid nodules and positive family history (1st degree relatives) for well-differentiated thyroid carcinoma have an increased risk of cancer (odds ratio [OR], 5.4; 95% confidence interval [CI]: [4.4; 6.5]) (e3). Molecular genetic markers from fine-needle aspiration cytology (e.g. BRAF mutations) can help to establish an indication for surgery; however, in Germany they play only a minor role in clinical routine. Calcitonin screening prior to goiter surgery is recommended in the clinical (S2k) guideline of the Surgical Working Group of Endocrine Surgery (CAEK) of the German Society of General and Visceral Surgery (14) to preoperatively establish the diagnosis of medullary thyroid carcinoma (MTC). When interpreting calcitonin levels, the sex-specific

prevalence of C cells and the potential effects of various medications, such as proton pump inhibitors, or diseases, such as Hashimoto's thyroiditis, need to be taken into account. Basal calcitonin levels of >26 pg/L in women and >60 pg/L in men are indicative of MTC with a probability of >95% (29).

The recommendations mentioned above also apply to solitary nodules in a thyroid that is not enlarged. Dyspnea or shortness of breath occur in 10–50% of goiter patients and are immediately resolved by surgical treatment (30, 31). Dyspnea was reported in up to 75% of patients with substernal goiter (32). In a retrospective study on 188 goiter patients with dyspnea due to tracheal compression, Stang et al. observed significant improvement of dyspnea in 82% of patients after goiter resection (31). There was a correlation between level of improvement and weight of resected thyroid tissue. Resection of >100 g of thyroid tissue improved dyspnea in 97% of patients after thyroidectomy. Interestingly, 59 (76.6%) of 77 snorers reported marked improvement in snoring and 77.1% of patients with obstructive sleep apnea syndrome (OSAS) reported improved positional dyspnea (31). In another retrospective study on 28 patients with OSAS and benign goiter, apnea/hypopnea indices (AHI) decreased significantly after thyroidectomy, resulting in postoperative de-escalation of the previously required therapy in almost all patients; in some cases, continuous positive airway pressure (CPAP) therapy was no longer necessary (32). However, larger prospective controlled studies are needed to further support the positive effect of thyroid resection in patients with OSAS and goiter.

Tracheal compression was described in 13% of all patients with benign goiter and in up to 97% of patients with retrosternal goiter (30, 31). In patients with narrowing of the tracheal lumen <35%, improvement in positional dyspnea after thyroidectomy was observed in 60% of patients studied, while 98% of patients with narrowing of the tracheal lumen >35% improved after thyroidectomy (31).

Furthermore, retrosternal goiter with mediastinal growth can cause displacement and/or compression of large intrathoracic vessels, resulting in superior vena cava syndrome (in 43 [22%] of 196 retrosternal/intrathoracic goiters operated at the Lukas Hospital Neuss, Germany, between 2001 and 2015); thus, an indication for goiter resection can be established in patients with mediastinal goiter.

In patients with autonomous thyroid adenoma(s), the risk of manifestation of hyperthyroidism is approximately 4% per year (33). According to the guidelines of the American Thyroid Association (34) and the slightly older recommendations of the Thyroid Section of the German Society of Endocrinology (35), uni- or multifocal autonomy of thyroid function with subclinical or overt hyperthyroidism should be treated definitively with radioiodine therapy (RIT) or surgery. After adequate information about the advantages and disadvantages of both treatment options, the

final decision ultimately rests with the patient. RIT is contraindicated in pregnant and nursing women. According to the guideline of the German Society of Nuclear Medicine (36), surgery is to be preferred over RIT in patients with suspicion of malignancy, large cysts (>10 mL in our view), compression syndrome, large goiter (>80 mL), intrathoracic goiter and in patients requiring immediate relief (e.g. serious side effects of antithyroid drugs, thyrotoxic crisis). In addition, individual patient characteristics and circumstance have always to be taken into account when making a decision for surgery or RIT (age of patient, comorbidities, recurrent goiter, pre-existing recurrent laryngeal nerve paralysis, working as a teacher or singer).

Benign goiter, especially with ventral growth pattern, may have a negative impact on quality of life if patients feel unhappy about their appearance. Thus, goiter resection for cosmetic reasons is indicated if it is the wish of the patient after they have been comprehensively informed about the risk associated with the surgical procedure.

Graves' disease

If definitive treatment of Graves' disease is indicated, two alternative treatment options—radioiodine therapy versus surgery—are available; however, many cases (small goiter, no suspicion of malignancy, no Graves' orbitopathy) represent classical indications for RIT. Adequate information about the advantages and disadvantages of both methods should be provided to the patient and documented. The clear and relative indications for surgical management are listed in Box 2. The recommendations mentioned are based on the guidelines of the German Society of Nuclear Medicine (36) and the American Thyroid Association (34). The only absolute indication for surgical management of Graves' disease is simultaneous reasonable suspicion of malignancy. A recently published meta-analysis found a cancer rate of 0.07% [0.04; 0.12] in patients with Graves' disease, based on 33 analyzed studies (37). Patients with Graves' disease and thyroid nodules had an almost 5-fold increased risk (23% versus 5%) of thyroid cancer compared to patients without nodule(s).

The question whether surgical treatment should be favored in patients with non-active Graves' orbitopathy (GO) cannot be conclusively answered at present. The risk of first manifestation of GO following RIT or deterioration of an existing GO is up to 20% and especially high in smokers (e4). An older randomized controlled trial (38) and a retrospective long-term study (e5) found that the risk of deterioration of GO after thyroidectomy is significantly lower compared to that after RIT. Thus, various guidelines recommend that RIT should not be used in patients with active or moderate to severe GO (14, 34, 35). One of the definitions used for moderate EO was proptosis (bulging of the eye anteriorly) >3 mm beyond the normal upper-limit value and the presence of periorbital soft-tissue inflammation.

TABLE 1

Ultrasound criteria according to TI-RADS classification (23) to determine risk of malignancy of thyroid nodules

Category	Ultrasound features*	Malignancy risk
1	Negative, no nodule	<0.1%
2	Benign nodule	<0.1%
3	Probably benign, no suspicious features on US	1.7%
4a	Low suspicion of malignancy with 1 suspicious feature on US	3.3%
4b	Intermediate suspicion of malignancy with 2 suspicious features on US	9.2%
4c	Moderate suspicion with 3 or 4 suspicious features on US	44.2–72.4%
5	Highly suggestive of malignancy with 5 suspicious features on US	87.5%

* The 5 suspicious sonographic features of malignancy are: solid component, hypoechoic or markedly hypoechoic nodule, microlobulations or irregular margins, microcalcifications, taller-than-wider shape. TI-RADS, thyroid imaging, reporting and data system; US, cervical ultrasound

TABLE 2

Classification of thyroid cytology (28, e7)

Finding	Criteria
Inadequate	Material containing few or no thyrocytes from solid or partly liquid nodules (exception: colloid nodules)
Negative	Any or all of the changes found in normal or hyperplastic thyroid glands, including follicular adenomas containing large/medium-sized follicles, including regressive changes, cysts, hemorrhagic cysts, and colloid nodules
Uncertain histology, in need of further evaluation*	Changes that are seen in highly cellular adenomas or follicular carcinomas, including oncocyctic variants; corresponds to follicular/oncocyctic neoplasia; moreover, some of the criteria of other types of malignant tumor may be present, e.g., papillary carcinoma
Suspicious for malignancy	Changes highly indicative of malignancy, although not all of the corresponding criteria are met
Positive	Changes meeting the criteria for papillary, medullary, undifferentiated thyroid carcinoma, or for other specific malignancies

* corresponds to 2 criteria of the Bethesda classification (27)

Recurrent goiter

The indications for the surgical management of recurrent goiter are the same as those for benign goiter. The increased risk of complications and the possibility of previous injury (e.g. recurrent laryngeal nerve paralysis) should be taken into account. The surgical treatment of recurrent goiter is challenging and the complication rate is increased compared to the initial surgery (13, 14). A meta-analysis found a rate of permanent damage to the recurrent laryngeal nerve of 3.7% (e6).

KEY MESSAGES

- In Germany, inconsistency in establishing the indication for thyroid surgery to treat benign nodular goiter is of concern.
- The preoperative investigations recommended in the guidelines to estimate the risk of malignancy are often not fully exhausted.
- Asymptomatic euthyroid nodular goiter without suspicion of malignancy and also a “cold” nodule on scintigraphy without further indicators of malignancy are not indicators for surgical management.
- The recommendations concerning the indications for the surgical management of benign goiter are based on data of mostly retrospective analyses or prospective surveys without external quality control.
- The recommendations made here are intended to further improve indication quality in thyroid surgery in Germany.

General recommendations

The respective indication for surgery should be established separately for each half of the thyroid gland and clearly explained in the operative report. Being associated with an increased risk of injury to the vocal cord nerves and parathyroid glands, more challenging surgical procedures for certain benign thyroid conditions, such as recurrent goiter, large retrosternal goiter and Graves’ disease, should be performed in centers with proven expertise in this field (significant numbers of cases and/or certification) (e6). The study of Adam et al. including 16 954 patients with thyroidectomy showed that the outcome of surgery was associated with the number of thyroidectomies performed by the respective surgeon (39). After adjustment, patients operated by a low-volume surgeon (<25 cases/year) were at a statistically increased risk of experiencing complications (OR 1.51; $p = 0.002$). Furthermore, a routine data analysis of 66 902 patients who underwent thyroid surgery showed that after risk adjustment the hospital volume for thyroid surgery had a significant effect on the indicator “recurrent laryngeal nerve paralysis” (40). The rate of permanent recurrent laryngeal nerve paralysis was 1.9% in category I (low case number, <50 operations/year) and 0.9% in category V (high case number, >385 operations/year).

Discussion

Recommendations based on a systematic search of the literature are conclusions drawn from data of mainly retrospective analyses or prospective surveys without external quality control; thus, they have to be worded in a relatively open way. They should always be viewed in the context of individual patient characteristics, weighing the risks and benefits of the surgical procedure. The implementation of these recommendations is intended to further improve indication quality in thyroid surgery in Germany. It is expected to be accompanied with a further reduction in the number of thyroid surgeries.

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Conflict of interest statement

The authors declare that no conflict of interest exists.

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► Supplementary material

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Supplementary material to:

Indications for the Surgical Management of Benign Goiter in Adults

by Detlef K. Bartsch, Markus Luster, Heinz J. Buhr, Dietmar Lorenz, Christoph-Thomas Germer, and Peter E. Goretzki on behalf of the German Society for General and Visceral Surgery quality commission

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