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# The surgical dilemma of primary surgery for follicular thyroid neoplasms

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Follicular thyroid carcinoma is the second most prevalent form of differentiated thyroid carcinoma, following papillary thyroid carcinoma. Preoperative diagnosis is hampered by the fact that fine-needle aspiration cytology as well as supplemental molecular analysis cannot unambiguously distinguish between follicular thyroid carcinoma and benign follicular thyroid adenoma. The 2017 WHO classification defines three histological subtypes of follicular thyroid carcinoma: minimally invasive (excellent prognosis), encapsulated angioinvasive, and widely invasive type (higher risk of recurrence and metastatic spread). The fact that definite characterization of follicular neoplasms is predominantly a postoperative histological diagnosis (core criteria: capsular, vascular and adjacent tissue invasion) translates into the challenge for the thyroid surgeon to plan preoperatively for presence of malignancy and, if required, to adapt the surgical strategy according to intraoperative (frozen section) or postoperative histological findings. Until improved tools for pre-/intraoperative diagnosis are available, the malignant potential of a follicular thyroid lesion can be assessed by stratifying the patient according to clinical risk factors (presence of metastases, advanced patient age, tumor size). A stepwise, escalating surgical approach with restricted primary resection (hemithyroidectomy) and completion surgery based on the definite histopathology is another option to solve this dilemma. The currently recommended surgical

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treatment strategies for FTCs as published by ATA, BTA, CAEK and ESES are discussed. There is consensus that prophylactic lymphadenectomy is not required for FTCs and that hemithyroidectomy is sufficient in low-risk FTCs (capsular invasion only) whereas thyroidectomy with postoperative radioiodine therapy is indicated in high-risk FTCs (angioinvasion; widely invasive FTC).


## Background

Even though, in comparison to papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC) is relatively rare, it requires close attention for an adequate, entity-adapted surgical treatment. In fact, diagnosis of a suspicious follicular lesion in the thyroid gland poses a challenge to the thyroid surgeon: in contrast to other thyroid malignancies such as PTC or medullary thyroid carcinoma (MTC), fine-needle aspiration cytology (FNAC) as well as supplemental molecular genetic analysis – such as the *BRAF* hot-spot analysis for PTC – or laboratory findings – such as increased plasma calcitonin for MTC - do not prove to be helpful in pre-operative surgical decision-making. Up to now, there are still no dependable and cost-effective means to preoperatively distinguish between follicular adenoma and the three variants of follicular thyroid carcinoma, as described in the 2017 WHO classification. Moreover, the value of intraoperative frozen section is debated in case of preoperatively diagnosed "follicular neoplasia". In absence of identified metastasis, only the frozen section finding of tumor infiltration beyond the tumor capsule, into vessels, or into adjacent tissues may intraoperatively redirect the surgical strategy, e.g. from intended hemithyroidectomy to thyroidectomy.

Almost always, therefore, the definite characterization of a follicular neoplasm remains a post-operative histopathological diagnosis, hampering targeted preoperative surgical planning or intra-operative adaptation of the surgical strategy, as is nowadays common for other thyroid carcinomas.

Current guidelines of international expert associations as well as numerous studies published in the literature address this surgical dilemma on follicular thyroid neoplasms. The recent changes of the WHO 2017 classification of endocrine neoplasms - which differentiates three distinct FTC subtypes with different prognoses - implicate that an optimized resection strategy could avoid unnecessary radical resection with associated higher operative risks. Prerequisites would be either improvement of tools for pre-/intraoperative diagnosis, and/or patient stratification depending on clinical risk factors (advanced patient age, tumor size, and presence of metastases) and/or a stepwise, escalating surgical approach with restricted primary resection and completion surgery, if advisable.

### *Epidemiology*

Within the dichotomous classification of differentiated thyroid carcinoma, follicular thyroid carcinoma is represented with a frequency of 10–15%, following papillary thyroid carcinoma [1,2]. An increased incidence of FTC is registered in geographical regions with high prevalence of iodine deficiency [3,4]. The majority of patients diagnosed with FTC is female (ratio approximately 2.5:1), with an age peak in the fifth and sixth decade of life [4–7]. Yet, the onset of the minimally invasive FTC subgroup is usually earlier than that of the widely invasive form of FTC [8]. Whereas locoregional lymphatic spread is rare in FTC (1–7%) [9–11], hematogenous metastases to the lung and bone are observed more frequently (6–20%) [5,12]. Lymph node metastases are primarily observed in widely invasive FTCs, usually in combination with distant metastases [8,13,14].

### *Histopathology*

FTC is defined as a malignant epithelial tumor of the thyroid gland with follicular differentiation, in absence of the nuclear features typical of papillary thyroid carcinoma. The definition published in 2016 by the American Registry of Pathology (ARP) denominates two main types: minimally invasive FTC and widely invasive FTC [15]. Approximately 2/3 of FTC are considered minimally invasive [13]. The definition includes a subdivision of “minimally invasive FTC” into “minimally invasive FTC with capsular invasion (not obvious invasion)”, “minimally invasive FTC with limited vascular invasion (<4 vessels)” and “minimally invasive FTC with extensive vascular invasion (≥4 vessels)”.

In comparison, the current 2017 World Health Organization (WHO) classification of tumors of endocrine organs divides FTC into three histological subtypes, emphasizing the distinction between minimally invasive FTC with capsular invasion but absent vascular invasion and the encapsulated variant of FTC with angioinvasion [16]:

1. Minimally invasive follicular thyroid carcinoma with capsular invasion only (miFTC)
2. Encapsulated angioinvasive follicular thyroid carcinoma (eaFTC)
   - with limited vascular invasion (<4 vessels)
   - with extensive vascular invasion (≥4 vessels)
3. Widely invasive follicular thyroid carcinoma (wiFTC)

The treatment guidelines published by the American Thyroid Association (ATA) refer to FTC with vascular invasion into >4 vessels as “high risk” thyroid carcinoma, justifying a more aggressive approach towards total thyroidectomy and postoperative radio-iodine (RAI) therapy [17] (Table 1).

*Genetic background*

Whereas the preoperative diagnosis of PTC is confirmed by the detection of a *BRAFV600E* mutation and is supported by the detection of specific *RET/PTC* gene fusions in fine needle aspirates, the finding of *RAS (NRAS, HRAS, KRAS)* mutations and/or a *PAX8-PPARγ* gene fusion gives only a hint for the presence of FTC [18–20], since also follicular thyroid adenomas can harbor the latter molecular alterations [21,22]. A potential adenoma-carcinoma sequence is postulated for FTCs, especially for *RAS*-mutant tumors [19]. Whereas *PAX8-PPARγ* was found to be associated with FTC onset at lower patient age (4th decade) and “overtly invasive histology” (i.e., tumors confined to the thyroid gland and harboring at least three, typically more than five areas of capsular and vascular invasion), *RAS* mutations were detected in FTCs with a varying range of invasiveness, in association with a later onset of disease [19,21]. Patients with coexistence of *HRAS, NRAS* or *KRAS* mutations and a *TERT* promoter mutation were shown to harbor advanced disease at time of diagnosis, and an onset of disease at older age [23]. Depending on the analyzed patient cohort, *RAS* mutations are detected in 40–50% of FTC, whereas *PAX8-PPARG* fusion is present in 25–63% [19,24,25].

Moreover, the following genes were described to potentially carry driver mutations for FTC: *BRAF, BRIP1, CNOT1, DICER1, EIF1AX, EZH1, IDH1, IGF2BP3, KDM5C, KMT2C, MAP4K3, NF1, PTEN, PI3KCA, SOS1, SPOP, STAG2, TCF12, TP53* and *TSHR* [20,23,24,26].

Microsatellite instability (MSI) as a result of DNA mismatch repair (MMR) inactivation was described to be present in 2.5% of FTC cases, and nearly absent in other malignant tumors deriving from the thyroid [27]. The coincidence of MSI and loss of heterozygosity (LOH) in several, different loci (= “overall frequency of allelic loss”, OFAL) was postulated as a biomarker to distinguish FTC and follicular thyroid adenoma from PTC and nodular goiter [28]. Furthermore, in FTC, OFAL correlated with advanced American Joint Committee on Cancer (AJCC) stages, indicating its relevance for tumor progression [28].

mRNA expression analyses of multiple, thyroid- or tumor-associated molecular genetic alterations by microarray gene expression classifier (GEC, based on Affymetrix Human Exon 1.0 GeneChip) [29] are available nowadays, without reimbursement of cost in most health insurance systems; the added value in the treatment of patients with suspicious follicular thyroid nodules remains to be proven [30].

In conclusion, - and in contrast to PTC and MTC - no pathognomonic biomarker or molecular genetic finding has been identified to date which can reliably and cost-effectively be used for preoperative diagnosis of FTC, or to improve the distinction between benign and malignant follicular thyroid lesions in fine needle aspirates.

**Table 1**
Recommendations for the treatment of FTC subtypes according to international expert societies.

| Entity | International Expert Society recommendations | | | |
|---|---|---|---|---|
| WHO Definition 2017 [16] | German Association of Endocrine Surgeons (CAEK) 2013 [4] | European Society of Endocrine Surgeons (ESES) 2014 [58] | British Thyroid Association (BTA) 2014 [44] | American Thyroid Association (ATA) 2015 [17] |
| | **Recommended thyroid resection strategy** | | | |
| Minimally invasive FTC, capsular invasion only (miFTC) | lobectomy or total thyroidectomy<br>specification for total thyroidectomy[1] | lobectomy or total thyroidectomy<br>specifications for both lobectomy[1]<br>and total thyroidectomy[2] | lobectomy or total thyroidectomy<br>specification for total thyroidectomy[1] | lobectomy or near-total/total thyroidectomy<br>specifications for both lobectomy[1] and near-total/total thyroidectomy[2] |
| Encapsulated angioinvasive FTC (eaFTC) | total thyroidectomy | total thyroidectomy | total thyroidectomy | near-total/total thyroidectomy[3] |
| Widely invasive FTC – grossly invasive (wiFTC) | total thyroidectomy | total thyroidectomy | total thyroidectomy | near-total/total thyroidectomy[3] |
| | **Recommended lymph node dissection strategy** | | | |
| All FTC types | no prophylactic lymph node dissection;<br>therapeutic lymph node dissection in case of evidence of lymph node metastasis before or during the operation<br>Specification for lymphadenectomy[2] | no prophylactic lymph node dissection;<br>therapeutic lymph node dissection in case of evidence of lymph node metastasis before or during the operation | no prophylactic lymph node dissection;<br>therapeutic lymph node dissection in case of evidence of lymph node metastasis before or during the operation<br>Specification for lymphadenectomy[2] | no prophylactic lymph node dissection;<br>therapeutic lymph node dissection in case of evidence of lymph node metastasis before or during the operation<br>Specification for central and lateral lymphadenectomy[4] |
| | **Recommended postoperative radioiodine (RAI) treatment** | | | |
| All FTC types | RAI recommended for FTC with angioinvasion (independent from number of vessels affected) and for wiFTC | RAI indicated for elderly patients (>45 years), large tumor size (>40 mm), extensive vascular invasion, presence of distant synchronous or metachronous metastasis, positive nodes and if recurrence is noted in follow-up | no indication for RAI if all criteria are met: follicular carcinoma, tumor <1cm, unifocal or multifocal, minimally invasive without angioinvasion, no invasion of thyroid capsule (extra thyroidal extension)<br>Definite indication if one criterion is met: tumor >4cm, any tumour size with gross extra thyroidal extension, distant metastases present<br>Uncertain indication if one of following criteria is met: large | RAI recommended for high-risk DTC (e.g. eaFTC with >4 vessels affected), if the primary thyroid carcinoma is >4 cm, if there is gross extrathyroidal extension, or regional or distant metastasis, older age (>45 years), contralateral thyroid nodules, a personal history of radiation therapy to the head and neck or familial differentiated thyroid carcinoma |

| | | | | |
|---|---|---|---|---|
| | | | tumor size, extra-thyroidal extension, widely invasive histology, multiple lymph node involvement, large size of involved lymph nodes, high ratio of positive to negative nodes, extracapsular nodal involvement. | |
| **Additional information** | | | | |
| | [1] decision depending on multinodular disease<br>[2] extent of lymph node dissection (central, uni/bilateral) dependent on localization of proven lymph node metastases | [1] if patients <45 years old at presentation, tumor size <40 mm, without vascular invasion, without any node or distant metastases.<br>[2] if patients ≥45 years at presentation, tumor size ≥40 mm, vascular invasion present, positive nodes, positive distant metastases. | [1] in absence of risk factors: age >45, widely invasive histology, lymph node/distant metastases, angioinvasion, tumor size >4 cm<br>[2] If there is preoperative or intraoperative suspicion of nodal disease, FNAC or frozen section should be performed prior to therapeutic node dissection | [1] for low- to intermediate-risk: unifocal tumors <4 cm, no evidence of extrathyroidal extension or lymph node metastases<br>[2] if overall strategy includes RAI therapy. Tumors between 1 and 4 cm: bilateral procedure recommended if risk factors are present: older age (>45 years), contralateral thyroid nodules, a personal history of radiation therapy to the head and neck, familial differentiated thyroid carcinoma (because of plans for RAI therapy or to facilitate follow-up strategies or address suspicions of bilateral disease)<br>[3] high risk: >4 vessels with angioinvasion<br>[4] therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central nodes should accompany total thyroidectomy. Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy. |

## Diagnosis

On a radionuclide scan, FTCs usually appear as cold thyroid nodules [4]. FTC and follicular thyroid adenoma share a highly similar ultrasound pattern. Yet, larger lesion size, lack of sonographic halo, hypoechoic appearance and absence of cystic changes favor the diagnosis of a follicular carcinoma [31]. A standardized analysis of suspicious thyroid nodules - e.g., using the European Thyroid Association (ETA) Guidelines for Ultrasound Malignancy Risk Stratification (“Eu-TIRADS”) [32] or the ATA Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer [17] - should be performed, to facilitate the selection of patients with a potential benefit from undergoing FNAC.

It is a fact that FNAC analysis frequently leads to indeterminate results (Bethesda category: III “atypia of undetermined significance or follicular lesion of undetermined significance”, IV “follicular neoplasm or suspicious for follicular neoplasm” [33]), since the method cannot provide a conclusive evaluation of FTC core criteria: capsular and vascular invasion [34,35]. Only one third of patients harboring thyroid nodules of Bethesda category III actually represent malignant diagnoses [36].

In patients with indeterminate FNAC results and the suspicion of FTC, additional immunostaining of the FNA material indicating positivity for HBME-1 and galectin-3 may be helpful to select patients for surgery [37,38]. Galectin-3 (a member of the β-galactosidase-binding lectin family) expression appears to be upregulated especially in association with a *PAX8-PPARγ* rearrangement [19]. To rule out potential malignancy in thyroid nodules with indeterminate results in FNAC, evaluation of mRNA expression using microarray gene expression classifier (GEC) may hold diagnostic value [29]. Drawbacks of the method – in addition to cost - are that long-term outcome data of patients excluded from surgery due to negative results in GEC are not yet available, and that the predictive value is dependent on the prevalence of malignancy in the analyzed cohorts [30,39]. The ETA recommends the evaluation of *BRAF, RET/PTC, PAX8-PPARγ* and *RAS* for suspicious thyroid nodules [30]. At present, in case of follicular thyroid neoplasms, molecular genetic analysis cannot serve to establish an indication for need and especially not for the extent of thyroid surgery, due to the ambiguous results regarding potential malignancy.

For suspicious follicular thyroid lesions, all preoperatively available results including clinical features, sonographic and radionuclide imaging, elastography results as well as cytological and molecular genetic findings have to be interpreted as a complex framework for diagnosis and indication for thyroid surgery.

The value of intraoperative frozen sections, as an additional diagnostic tool, is discussed controversially in case of follicular neoplasms. Similar to the methodological limitation of FNAC, a conclusive evaluation of capsular and vascular invasion is not ensured [40,41]. However, if vascular invasion is diagnosed in frozen sections, it is usually associated with widely invasive FTC. To aggravate the situation, the differentiation between FTC and the follicular variant of a PTC is impaired in frozen section analysis. Only the histopathological evaluation of formalin-fixed, paraffin-embedded tissue slices allow for the indisputable diagnosis of FTC, as well as for the characterization of its subtypes [34,42,43].

Whereas the British Thyroid Association (BTA) considered frozen section not appropriate for the intraoperative diagnosis of FTC [40,41,44], the German Association of Endocrine Surgeons (CAEK) attached importance to frozen section analysis for the scope of ruling out other malignant diagnoses in case of preoperatively diagnosed follicular neoplasms [4,45–47]. For example, a frozen section diagnosis of follicular variant of PTC can redirect the extent of surgery to thyroidectomy and/or lymph node dissection, to spare the patient a secondary surgery.

## Prognostic factors

In comparison to PTC and to the follicular variant of PTC, a higher tumor-specific mortality rate was demonstrated for FTC [48]. An analysis published in 2004 reported the overall utility to provide prognostic information about the survival of FTC patients for different scoring systems: Tumor, Node, Metastases (TNM); European Organization for Research and Treatment of Cancer (EORTC); Age, Grade, Extent, Size (AGES); Age, Metastases, Extent, Size (AMES); and Metastases, Age, Completeness of resection, Invasion, Size (MACIS); the latter revealed the highest accuracy for prediction of survival [49].

Independently performed multivariate analyses led to the identification of risk factors, which are associated with a significantly poorer outcome in FTC, i.e., the development of metastases, or a lowered disease-free or cancer-specific survival. These risk factors include tumor size, patient age, widely invasive FTC type, lymph node/distant metastases, angioinvasion, and extrathyroidal extension [8,50–54] (Table 2).

In absence of these risk factors, for miFTC, an excellent long-term prognosis was demonstrated, with survival rates being similar to the average US population [8]. Development of metastases is rarely observed in patients with minimally invasive FTC without risk factors (<10%) [13]. Potential metastasis appears to be related to an existing angioinvasion [53]. Yet, the literature suggests that "limited" vs. "extensive vascular invasion" has a different impact on prognosis [17,55].

In contrast, wiFTC is associated with a significantly worse carcinoma-specific survival and disease-free survival than minimally invasive FTC [13,53]. Whereas carcinoma-specific survival (10 years) was shown to be 93.5% for minimally invasive FTC (ARP definition, comprising miFTC and eaFTC), 53.6% was registered for wiFTC [13]. This highly aggressive subgroup of FTC is more often diagnosed at a higher patient age and with advanced initial T-stages, fulfilling the abovementioned risk factors for a poorer outcome [56,57]. Metastases are present in one third of cases at the time of diagnosis [13]. Long-term survival rates in patients with metastatic FTC range from 31% to 43% [5].

Differences in the biological behavior of FTC subgroups may be associated with the genetic background of the entities. While patients with *PAX8-PPARγ* present with younger age (4th decade), lower T-stages and with primarily minimally invasive/angioinvasive histology, the patient group with FTC and an underlying *RAS* mutation has a varying range of invasiveness with an onset at older age, suggesting that at least two distinct molecular pathways are responsible for FTC tumorigenesis [19,21].

In the last ten years, proven risk factors for a poorer outcome of FTC were confirmed, and novel predictors were detected (Table 1). For example, mutational burden – a biomarker measuring the total number of present mutations – was identified as a predictor for mortality and recurrence, independent from the histological subgroup of FTC [20]. Furthermore, the presence of a *TERT* promoter mutation was observed as a prognostic factor for an impaired disease-free survival in miFTC and eaFTC [23].

However, most analyses of prognostic factors relevant for FTC are still based on the histological subgroups according to the ARP definition (Table 1). The subgroup eaFTC, added by the WHO in 2017, is not yet broadly represented as an independent category of analysis, nor as a potential prognostic factor for FTC itself. An analysis of 39 cases of FTC, published in 2018, showed that - compared to miFTC and eaFTC -, wiFTC had significantly higher AJCC stages at time of surgery and were more likely to recur, or be the cause of death [20]. Though not significant, 10-year-disease-specific survival was impaired in cases of eaFTC and wiFTC, but not in miFTC [20].

Less aggressive therapy is already proposed for so-called low-risk FTCs in current expert recommendations, although only further large-scale follow-up analyses will be able to prove adequateness of the surgical treatment options for the particular subgroups of FTC in the future. Since histological FTC subtypes and clinical risk factors were shown to be associated with dissimilar prognosis and course of disease, as a consequence, different surgical treatment strategies are required, once the diagnosis on the subtypes is available. Addressing the issue, international expert societies have published recommendations based on FTC histology and clinical risk factors [4,17,44,58].

## Surgical treatment of follicular thyroid carcinoma

In case of a solitary thyroid nodule with an indeterminate result in FNAC (Bethesda category III-IV [33]) and/or the clinical suspicion of malignancy (tumor size, accelerated growth, elastography results, ultrasound or other imaging indicators, lymphadenopathy, distant lesions suspicious of metastases etc.), comprehensive information about the therapeutic options should be offered to the patients concerned. This should include the information about the limitation of frozen section for the intraoperative distinction between follicular thyroid adenoma and follicular carcinoma, as well as the limitation to intraoperatively identify minimally invasive, angioinvasive and widely invasive subtypes [4]. Hence, the patient should be made aware during informed consent that both the surgeon may

**Table 2**
Prognostic factors in follicular thyroid carcinoma (studies published between 2008 and 2019)

| Authors | Year | Endpoint | | | | | | | Prognostic factor | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Survival | | | | | Metastasis | | Advanced patient age | Male sex | Female sex | Tumor size | Postoperative histology | |
| | | Disease-free survival | Overall survival | Cause-specific death | Cause-specific survival | Distant metastasis-free survival | Lymph node metastasis | Distant metastasis | | | | | Widely invasive histology | Angioinvasion |
| **Category: Follicular Thyroid carcinoma - general** | | | | | | | | | | | | | | |
| Alfalah et al. [9] | 2008 | | | | | | $X_{pr}$ | | - | - | - | + | | |
| Asari et al. [13] | 2009 | | | | | | $X_{pr}$ | | - | - | - | - | + | |
| | | | | | | | | $X_{pr}$ | + | - | - | + | + | |
| | | X | | | | | | | + | - | | ⊕ | ⊕ | |
| O'Neill et al. [53] | 2011 | | | | | | | $X_f$ | ⊕ | - | - | - | | ⊕ |
| Sugino et al. [57] | 2011 | | | | | | | $X_{pr}$ | + | - | - | + | + | - |
| | | | | | X | | | | ⊕ | | | + | + | - |
| | | | | | | X | | | ⊕ | | | ⊕ | ⊕ | - |
| | | | | | | | | $X_f$ | + | - | - | + | - | - |
| Kim et al. [60] | 2014 | | | | X | | | | + | - | | + | ⊕ | - |
| Podda et al. [61] | 2015 | X | | | | | | | | | | ⊕ | | |
| Rios et al. [62] | 2015 | X | | | | | | | + | + | | + | + | + |
| Su et al. [63] | 2018 | | X | | | | | | ⊕ | | | ⊕ | | |
| | | | | X | | | | | + | ⊕ | | - | | |
| Nicolson et al. [20] | 2018 | | | | X | | | | + | - | - | - | + | + |
| Duan et al. [23] | 2018 | X | | | | | | | - | - | - | - | + | |
| **Category: Minimally invasive follicular thyroid carcinoma** [15] | | | | | | | | | | | | | | |
| Asari et al. [13] | 2009 | X | | | | | | | + | - | | + | | |
| | | | | | X | | | | - | - | | - | | |
| Sugino et al. [54] | 2012 | | | | | | | $X_f$ | + | - | - | + | | - |
| | | | | | | | | $X_{pr}$ | + | - | - | - | | - |
| | | | | | X | | | | ⊕ | | | + | | - |
| | | | | | | X | | | ⊕ | | | + | | - |
| Ito et al. [55] | 2013 | X | | | | | | | ⊕ | - | | ⊕ | | ⊕ |
| | | | | | X | | | | - | - | | ⊕ | | ⊕ |
| Kim et al. [60] | 2014 | X | | | | | | | - | - | | - | | ⊕ |
| Stenson et al. [64] | 2016 | | | X | | | | | + | ⊕ | | - | | + |
| **Category: Widely invasive follicular thyroid carcinoma (wiFTC)** [15,16] | | | | | | | | | | | | | | |
| Asari et al. [13] | 2009 | X | | | | | | | + | + | | - | | |
| | | | | | X | | | | + | - | | ⊕ | | |
| Ito et al. [65] | 2013 | X | | | | | | | - | - | - | ⊕ | | |
| | | | | | X | | | | - | - | - | - | | |
| Kim et al. [60] | 2014 | X | | | | | | | - | - | | - | | - |

Factors with proven prognostic relevance marked with "+"; if confirmed in multivariate analysis, prognostic factor is highlighted as "⊕".
Factors analyzed, but not confirmed as prognostically relevant, are marked with "-".
Analyzed endpoints are marked with "X". The endpoint "metastasis" includes "$X_{pr}$" (diagnosis preoperatively, or immediately after primary surgery) and "$X_f$" (diagnosis during follow-up).

decide during the primary surgery to adapt the extent of surgical resection, and that a secondary surgery may need to be carried out.

*Thyroid resection*

BTA as well as ATA published distinct recommendations for the surgical treatment of FTC, based on the criterion "tumor size" in combination to clinical and histological risk factors. For FTCs with a diameter >4 cm, total thyroidectomy is suggested (Table 1) [17,44]. For FTCs with a tumor diameter >1 and ≤ 4 cm, hemithyroidectomy is considered a sufficient treatment, if the following risk factors (BTA) are absent: age >45 years, widely invasive histology (as judged visually in the operative situs, or by frozen section), lymph node/distant metastases, angioinvasion [44]. The ATA guidelines refer to the following risk factors: older age (>45 years), contralateral thyroid nodules, a personal history of radiation therapy to the head and neck, as well as familial differentiated thyroid carcinoma, which - because of plans for radioiodine therapy or to facilitate follow-up strategies - should favor

| | | | Metastasis | | Genetic disorder | | | | | | Patients included | Median/ *Mean* follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Capsular invasion | Multifocality | Extrathyroidal extension | Lymph node metastasis | Distant metastasis | Mutational burden | Driver gene mutation for FTC [20] | Driver genes for cancer [59] | *EIF1AX* mutation | *TERT* promoter mutation | *H/N/K-RAS* mutation | | |
| | | | | - | | | | | | | 70 | *52* |
| | + | | | | | | | | | | 207 | 86 |
| | - | | | | | | | | | | | |
| | + | | + | ⊕ | | | | | | | | |
| | | | ⊕ | | | | | | | | 124 | 40 |
| + | | | + | | | | | | | | 134 | 150 |
| | | | | ⊕ | | | | | | | | |
| | | | | | | | | | | | | |
| - | | | - | | | | | | | | 121 | |
| | | | + | ⊕ | | | | | | | 204 | 55 |
| | | | | | | | | | | | 71 | *113/125* |
| | | ⊕ | | | | | | | | | 66 | *99* |
| | - | - | + | ⊕ | | | | | | | 204 | 77 |
| | | + | + | ⊕ | | | | | | | | |
| | | | | | ⊕ | + | + | | | | 39 | 69 |
| | | | + | | | | | + | + | - | 51 | 56 |
| | | | | | | | | | | | | |
| | - | | | | | | | | | | 127 | 86 |
| | - | | | + | | | | | | | | |
| - | | | - | | | | | | | | 244 | 86 |
| + | | | - | | | | | | | | 251 | |
| - | | | | + | | | | | | | | |
| - | | | | | | | | | | | | |
| - | - | | | | | | | | | | 285 | *117* |
| - | - | | | ⊕ | | | | | | | 292 | |
| | | | - | ⊕ | | | | | | | 165 | 55 |
| | | | | | | | | | | | 58 | 140 |
| | | | | | | | | | | | | |
| | - | | - | | | | | | | | 80 | 86 |
| | - | | - | ⊕ | | | | | | | | |
| | | | | | | | | | | | 70 | *117* |
| | | | | ⊕ | | | | | | | 79 | |
| | - | | - | ⊕ | | | | | | | 39 | 55 |

thyroidectomy [17]. The latter evaluation of ATA risk factors is of course easier to carry out preoperatively, while the BTA risk factors may necessitate an expert frozen section.

A consensus statement by the European Society of Endocrine Surgeons (ESES) recommends (completion) thyroidectomy followed by radioiodine treatment (RAI) in minimally invasive FTC only in case of tumor size ≥4 cm, patients ≥45 years of age and in case of vascular invasion and/or nodal/distant metastases [58].

In contrast, the German Association of Endocrine Surgeons (CAEK) practice guidelines for the surgical management of malignant thyroid tumors are primarily histology-oriented: for minimally invasive FTC with capsular invasion only, independent from tumor size, hemithyroidectomy is recommended [4]. For this histological subtype, also the ESES considered hemithyroidectomy a sufficient treatment (in absence of risk factors: >45 years at presentation, tumor size >4 cm and angioinvasion or nodal/distant metastasis) [58]. Yet, - not uncommon in countries with a high prevalence of multinodular goiter - multinodular disease can be a reason for total thyroidectomy in patients with minimally invasive FTC with capsular invasion only [4]. The CAEK recommends total thyroidectomy (including postoperative RAI treatment) in patients harboring FTC with proven angioinvasion as well as for widely invasive FTC [4,17,44]. To facilitate RAI treatment, in case of an initially performed lobectomy, a completion thyroidectomy should be performed in these patients [4,17]. Minimally invasive FTC with capsular invasion only, due to a low risk of metastasis, does not require completion thyroidectomy, independent from tumor size (Table 1) [4]. If completion thyroidectomy is needed involving a previously explored/resected side the timing should be in the first

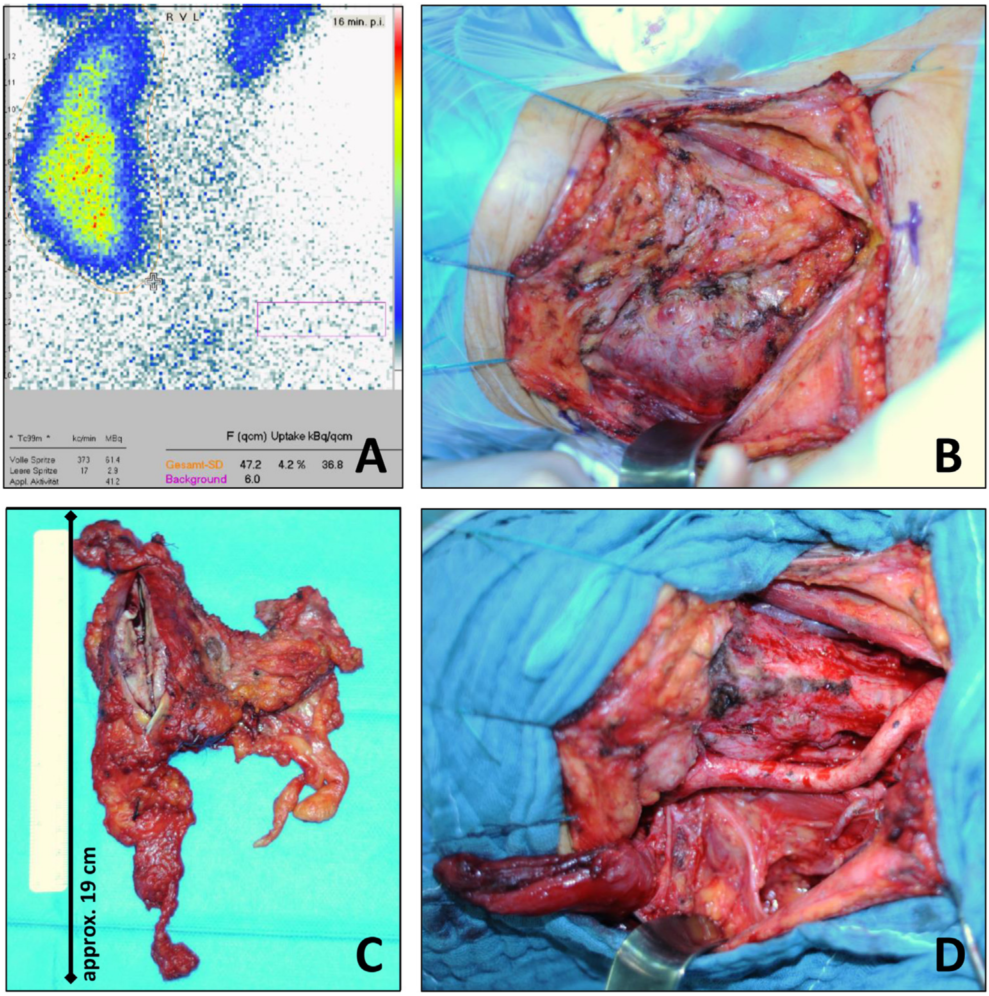


**Fig. 1.** Adequate surgery for widely invasive follicular thyroid carcinoma includes multivisceral en-bloc resections.
**Description:** Postoperative tumor persistence in the right cervical region was identified in a 79-year-old female patient following staged thyroidectomy for wiFTC. After referral to the University Medical Center Mainz, a pretherapeutic scan (A) revealed a large persistent tumor mass. Cervical re-exploration was performed. The figure depicts the anatomical situs before (B) and after (D) resection of the FTC, that included an extensive tumor thrombus in the right internal jugular vein. To achieve complete removal of the tumor (C), en-bloc resection of the central and right lateral lymph node compartments (K1a + b, K2 [66]) as well as resection of the infrahyoid muscles and the right internal jugular vein was carried out.

days following primary surgery or in an interval of three month in case. In other cases, e. b. only contralateral lobectomy following hemithyroidectomy, timing is usually not associated with increased risk.

In case of widely invasive FTC with extrathyroidal spread, the presence of invasion of the infrahyoid muscles or into perithyroidal veins and sometimes internal jugular veins can be identified preoperatively or intraoperatively. The veins can be filled with large tumor thrombi, sometimes extending to the upper chest; the surgical resection is performed with palliative intent in these difficult situations. In addition, wiFTCs might proceed to poorly differentiated histological patterns, further worsening patient outcome.

A key factor for complete and successful locoregional tumor resection (local R0) is the timely recognition of the advanced tumor growth. Multivisceral en-bloc resections of the thyroid, and infiltrated vessels and strap muscles can prevent invasion of the esophago—tracheal axis while the usually present distant metastases can be controlled with adjuvant radio-iodine treatment or targeted therapy concepts (Fig. 1).

### *Lymph node dissection*

Acknowledging the fact that the driving prognostic factor for FTC is considered the presence of distant hematogenous metastases instead of lymph node metastases, current recommendations of expert societies emphasize the limited value of a prophylactic central lymph node dissection, while therapeutic lymph node dissection is indicated (Table 1) [4,17,44,58]. The BTA recommends frozen section analysis of suspicious lymph nodes to evaluate the necessity of lymphadenectomy [44]. According to the German CAEK, central lymphadenectomy may be performed in cases with intraoperative verification of thyroid carcinoma due to the fact that the differentiation between follicular variant of PTC and FTC is incorrect in many cases of frozen section [4]. However, the new “low-risk” categorization of the follicular variant of PTCs and the equally excellent prognosis of the encapsulated follicular variant of PTCs will prompt a revision of this recommendation, which is currently defined by an interdisciplinary expert panel. The ATA argues for a central and lateral lymph node dissection, in case that biopsy-proven lymph node metastases are present [17].

## Summary

The 2017 WHO classification defines three histological subtypes of follicular thyroid carcinoma: the minimally invasive, encapsulated angioinvasive and widely invasive type. Current preoperative methods of analysis, including fine-needle aspiration cytology and supplemental molecular analysis cannot unambiguously distinguish between follicular adenoma and the three variants of follicular thyroid carcinoma. Moreover, the value of intraoperative frozen section is debated in case of preoperatively diagnosed “follicular neoplasia”. Resulting uncertainties are hampering the adaption of the surgical strategies. The complete characterization of follicular neoplasm is almost always a postoperative diagnosis. The recommended surgical treatment strategy is stratified depending on tumor histology and clinical risk factors (advanced patient age, tumor size, presence of metastases). The ATA, BTA, ESES and CAEK agree, that hemithyroidectomy is sufficient in low-risk FTC with capsular invasion only. Minor differences arise in the appraisal of risk factors, e. g. the arbitrary cut-off for patient age with of 45years, that prompt the recommendation for total thyroidectomy with postoperative radioiodine therapy in FTC with angioinvasion and widely invasive FTC. Uniformly, all cited surgical societies state that prophylactic lymphadenectomy is not required for FTC.

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**Practice Points**

- Comprehensive informed consent discussions with the patient about surgical treatment options are required in cases of follicular neoplasms of the Bethesda categories III-IV
- The WHO 2017 defines three types of follicular thyroid carcinoma (FTC) with different prognoses, and therefore divergent histology-dependent treatment strategies
- Hemithyroidectomy is sufficient in low-risk FTC with capsular invasion only (miFTC)
- Total thyroidectomy with postoperative radioiodine therapy is indicated in FTC with angioinvasion, and in widely invasive FTC
- Prophylactic lymphadenectomy is not required for FTC

**Research agenda**

- "Encapsulated angioinvasive histology" (WHO Definition 2017) should be critically evaluated as an independent prognostic factor for FTC in multivariate analyses
- Studies on real-world quality of the correct histopathological characterization of miFTC vs. eaFTC, e.g., via second opinion assessment by a reference pathologist, or via diagnostic quality assessment schemes ("ring trials") using digital images of thyroid tissue histological slides
- Novel biomarkers for preoperative diagnosis of FTC subtypes are required to refine preoperative diagnosis
- Large cohorts of FTC subgroups should undergo molecular analysis, with correlation of molecular genetic findings to the clinical course of the disease

Aims:

o Improving the preoperative diagnosis in fine needle aspiration material
o Supporting the histopathological differentiation of the FTC types and/or between follicular adenoma and miFTC
o Identification of molecular genetic risk factors
o facilitating the assessment, based on prospective risk factors, whether completion surgery/radioiodine treatment should be performed in an individual patient

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