

Diagnosis and treatment of small follicular thyroid carcinomas

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Background: Follicular thyroid microcarcinomas (mFTCs) of 10 mm or less in size rarely manifest clinically and their clinical significance is controversial. This study assessed their characteristics and incidence, and analysed treatment modalities used for mFTC.

Methods: Members of the German Association of Endocrine Surgeons were asked to review patients with mFTC operated on between 1990 and 2005.

Results: Data for 90 patients from 26 institutions were reported. Histopathological slides were available for re-evaluation in 35 patients. Most initial diagnoses had to be revised because of incorrect size assessment or incorrect diagnosis (benign adenoma, papillary thyroid carcinoma (PTC), follicular variant of PTC). The diagnosis of mFTC was confirmed in only four patients. As a result of the incorrect histopathological diagnosis, unnecessary completion thyroidectomy and radioiodine ablation were performed in 17 and 20 patients respectively. The incidence of mFTC was calculated to be 0.12 per million population per year.

Conclusion: mFTC is exceptionally rare. Such tumours are overdiagnosed, resulting in unnecessary treatment associated with avoidable morbidity. Histopathological re-evaluation by an experienced pathologist is recommended before embarking on further treatments when a diagnosis of mFTC is made.

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Introduction

Thyroid microcarcinomas originating from the follicular epithelium, or C cells, are usually defined as thyroid tumours of 10 mm or less, corresponding to pathological tumour category 1 (pT1) of the tumour node metastasis (TNM) classification of malignant tumours (fifth edition)¹. Clinically, thyroid tumours of this size are often diagnosed incidentally in specimens resected predominantly for benign indications such as goitre or Graves' disease. These procedures are often subtotal resections of the thyroid gland with varying extent of thyroid remnants. Usually, no concomitant lymph node dissection is performed as the indication for thyroidectomy is benign disease.

According to the latest guidelines, total (or near-total) thyroidectomy with lymph node dissection in the central cervical compartment is the treatment of choice

for papillary thyroid cancer^{2,3}. The aim of this surgical strategy is to remove the tumour, provide accurate staging, prepare the optimal conditions for radioiodine ablation, and reduce the risk of local recurrence.

Papillary thyroid microcarcinoma (mPTC) is a common condition and has been well studied^{4–8}. If resected incidentally, the patient does not require any additional therapy in a low-risk situation (unifocal lesion, no invasion of the thyroid capsule, no histological subtype with more aggressive behaviour)⁴. Otherwise, a completion thyroidectomy and central lymph node dissection is recommended. Patients with mPTCs in a low-risk setting have excellent recurrence-free and overall survival rates, regardless of the extent of thyroid resection^{9–12}.

In contrast to the well documented incidence, biological behaviour and prognosis of mPTC, little is known about follicular thyroid carcinoma with a size of 10 mm or

less (mFTC). There is considerable controversy among clinicians and pathologists regarding the incidence and clinical significance of this apparently rare tumour.

The aim of this study was to investigate the characteristics and incidence of mFTC as well as the clinical management of patients diagnosed with this microcarcinoma.

Methods

In 2006, a survey was performed among the members of the German Association of Endocrine Surgeons (Chirurgische Arbeitsgemeinschaft Endokrinologie, CAEK). They were asked to review the records of patients operated on between 1990 and 2005 to identify those with mFTC. Identified patients were entered into a database that included information on predisposing factors, underlying thyroid pathology, tumour characteristics and clinical management.

To validate the diagnosis of mFTC, available histopathological slides were reviewed by three expert pathologists with particular knowledge of thyroid pathology, according to a standard protocol.

The German cancer registries of Bavaria, Saarland, Bremen, and the former German Democratic Republic and Berlin (Gemeinsames Krebsregister der Länder Berlin, Brandenburg, Mecklenburg-Vorpommern, Sachsen-Anhalt und der Freistaaten Sachsen und Thüringen), as well as the Swiss cancer registry of St Gallen and Appenzell, provided the number of patients with T1 follicular carcinomas. As the majority of these patients were registered while the fifth edition of the TNM classification was still in use, the numbers provide a close approximation of the incidences of mFTC. Population data for German states were obtained from the Statistical Yearbook 2007 for the Federal Republic of Germany¹³ using population data at 31 December 2004. Population data for the Swiss cantons were obtained from the websites of the cantons^{14,15} and the yearly population count was averaged for the observation period. Incidence was calculated by dividing the case numbers by number of years of observation and population.

Statistical analysis

Ninety-five per cent confidence intervals (c.i.) were calculated using R (version 2.6.2) and Excel (adopting the algorithm from R), employing the method of Clopper and Pearson¹⁶.

Results

Twenty-six institutions in Germany, Austria and Switzerland contributed clinical and histopathological data for 90 patients operated on between 1990 and 2005 (Germany, 65; Austria, 14; Switzerland, 11). Histological slides could be retrieved for 46 patients, although slides from 11 patients were of insufficient quality to permit re-evaluation. Thus, the histological appearance for 35 patients could be re-evaluated by three expert pathologists (one from each participating country evaluating the slides of their country).

A diagnosis of mFTC could be verified in only four of these 35 patients. Median tumour size was 6.5 (range 5–7) mm. Vascular infiltration was found in all four tumours and penetration of the capsule in two. Patient characteristics, primary indications for surgery and types of resection are shown in *Table 1* for the four patients with confirmed mFTC, and for the 31 patients with a revised histopathological diagnosis.

In seven patients, malignancy was excluded and the diagnosis of benign follicular adenoma established. In seven instances, follicular tumours were larger than 10 mm. PTC and the follicular variant of PTC were identified in two and 15 patients respectively. In addition, two of these PTCs were larger than 10 mm (both 12 mm). There were considerable differences in the diameter estimates between the initial assessment and the expert review for the 11 cases of FTC (*Fig. 1*).

All four patients with confirmed mFTC were women (median age 47.5 (range 32.8–75.2) years). None had undergone previous neck irradiation. In three patients the

Table 1 Patient characteristics, indication and type of surgery

	mFTC excluded (n = 31)	mFTC confirmed (n = 4)
Median (range) age (years)	54 (29–76)	47 (33–75)
Sex ratio (M:F)	10:21	0:4
Indication for surgery		
Euthyroid goitre	17	3
Hyperthyroid goitre	3	0
Graves' disease	2	1
Suspected malignancy (mFTC)	1	0
Suspected malignancy (other)	2	0
Other	6	0
Primary resection		
Subtotal lobe resection	10	0
Hemithyroidectomy	9	1
Subtotal or Dunhill resection	4	1
Near-total thyroidectomy	0	1
Total thyroidectomy	5	1
Other	3	0

mFTC, follicular thyroid carcinoma of 10 mm or less in size.

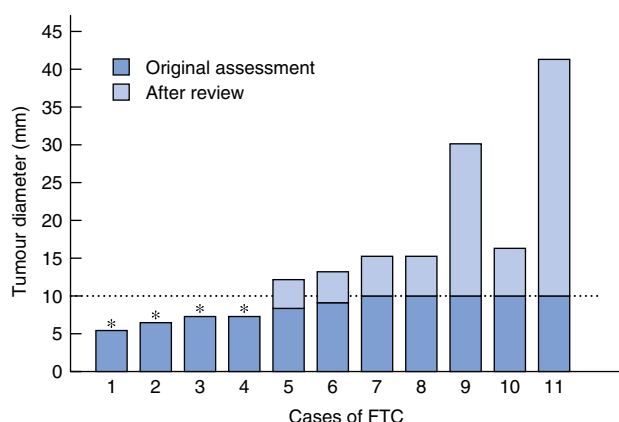


Fig. 1 Size determination of follicular thyroid carcinomas (FTCs) at the original assessment and at the review for this study. *Size of microcarcinoma confirmed at review. The dotted line at 10 mm indicates the threshold for a diagnosis of microcarcinoma

indication for surgery was goitre and in one Graves' disease. Two patients had total or near-total thyroidectomy and did not undergo completion surgery; the other two patients requiring a second procedure initially had a Hartley–Dunhill resection and a hemithyroidectomy. Only

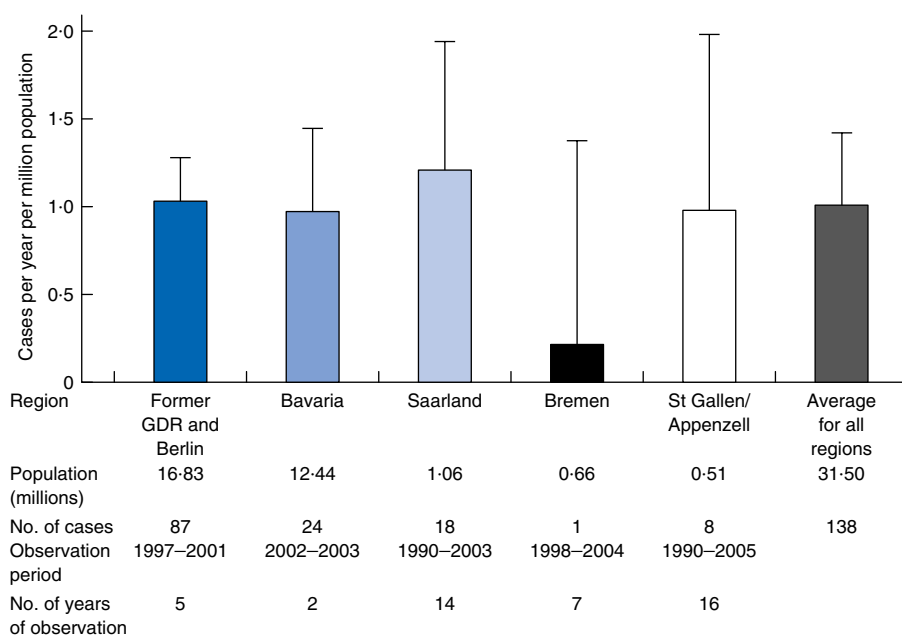
three of the four patients received radioiodine ablation after surgery.

Of seven patients rediagnosed with a benign adenoma, all had had a completion thyroidectomy and been subjected to at least one radioiodine ablation (maximum three).

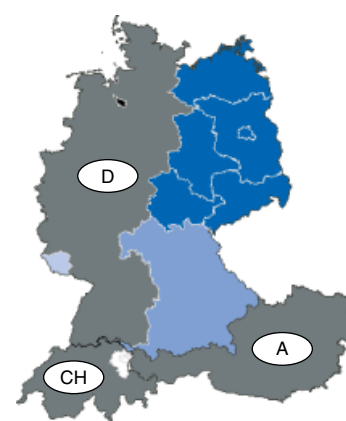
At least 15 of the 17 patients with PTC could have been considered correctly treated with a limited resection with no need for additional radioiodine ablation in a low-risk setting. Incorrect diagnosis of FTC led to ten unnecessary completion thyroidectomies and to radioiodine ablation in 13 of the 17 patients.

Incidence of follicular thyroid microcarcinoma

The incidence of diagnosis of mFTC was assessed using data from four cancer registries in Germany and one in Switzerland (*Fig. 2*). In all five registries the annual incidence was approximately one patient per million inhabitants. For the cancer registry of St Gallen and Appenzell (covering the north-eastern part of Switzerland), a complete histological review of all eight patients registered with mFTC during the period 1990–2005 could be performed. Only one of the eight patients had



a Incidence of T1 FTC



b Map showing incidence data

Fig. 2 a Incidence of T1 (tumour size 10 mm or less) follicular thyroid carcinoma (FTC) in various regions in Germany and Switzerland, derived from regional cancer registries. Error bars indicate 95 per cent confidence intervals. The average incidence is the mean for all regions weighted according to population size and observation period. GDR, German Democratic Republic. **b** Map of Germany (D), Switzerland (CH) and Austria (A) showing regions from which incidence data were obtained; the colours correspond to those used for the five regions in **a**

a confirmed mFTC. This indicates an actual incidence of 0.12 patients per million inhabitants per year.

Discussion

In the recently published guidelines of the American Thyroid Association² and the European Thyroid Association³, fine-needle aspiration is recommended only for solitary thyroid nodules larger than 10 mm. Therefore, microcarcinomas of the thyroid are nearly always recognized as incidentally discovered tumours in a thyroid specimen that has usually been removed for benign disease. As surgeons are usually unaware of the presence of malignancy, the procedure often leaves behind variable amounts of thyroid tissue, and omits lymphadenectomy. The strategy for the treatment of incidentally discovered cancer can be determined only after surgery.

The standard procedure for thyroid carcinoma of the follicular epithelium is total thyroidectomy with lymph node dissection in the central cervical compartment. Only for mPTCs in a low-risk situation do the guidelines not require completion thyroidectomy. Although there is evidence that mFTCs without vascular invasion have an excellent prognosis even with limited thyroid resection^{17,18}, there are no exceptions or specific regulations in the guidelines for the surgical treatment of such carcinomas. Thus, clinicians adhering to the guidelines will treat mFTCs with a completion thyroidectomy, unless total thyroidectomy has already been performed, and administer radioiodine ablation.

Given the importance of a correct diagnosis for guideline-compliant patient management, the results of the histopathological re-evaluation in the present study are sobering. In 31 of 35 patients, the initial diagnosis of mFTC had to be revised. It is therefore hardly surprising that many patients underwent treatments that would not have been performed had the initial pathological diagnosis been accurate.

For only seven patients with an inaccurate assessment of FTC size would therapy not have changed with the correct diagnosis. In 24 patients who did not have FTC, an initially correct diagnosis would have altered their management. Two-thirds of these patients (17 of 24) underwent completion thyroidectomy and 20 had additional radioiodine ablation. This is of concern for two reasons. Patients received unnecessary thyroxine replacement, which impairs quality of life¹⁹. The morbidity associated with reoperation is much greater than that of the primary intervention, with an increased risk of permanent postoperative hypoparathyroidism and recurrent laryngeal nerve palsy. The present study did not, however, examine

morbidity in the 17 patients who underwent unnecessary reoperation.

Difficulties in the pathological assessment of follicular thyroid lesions and observer variation have been described previously^{20,21}, but it was surprising to see that not only was the assessment of tumour type subject to such great variation but so too was tumour size. The marked disagreement of PTC diameter estimates between the original assessment and the review are a cause for concern. The decision whether an incidentally diagnosed FTC can be managed with a limited resection is essentially based on the diameter of the tumour and the presence of specific risk factors. Given the observed inaccuracy of the initial measurements, clinicians should be aware of the difficulties pathologists have in making this measurement accurately.

At the outset of data collection for this study, the fifth edition of the TNM classification was in use, the sixth edition that puts the limit for a pT1 tumour at a maximum of 20 mm being published in 2002. It is likely that this change had minimal impact on the estimated incidence of mFTC. The registry with the largest population base (Berlin and the former German Democratic Republic) reported patients only for 1997–2001. Two further registries provided data up to 2003 and it is reasonable to assume that the sixth edition had not been implemented. Only two registries reported data after 2003. These registries had the smallest population base (each about 0.5 million) and at least 70 per cent of the observation period was before 2003. In any event, application of the sixth edition of the TNM classification with the higher threshold should lead to a higher incidence of T1 tumours. The incidence of T1 FTCs in the two registries reporting cases after 2003, however, was no higher than in the other registries.

Considering the heterogeneity of the cancer registries, the observed incidence rates were remarkably similar. After reviewing the literature, only one publication was found from which the incidence rate could be deduced²². In that study, the population of Luxembourg (408 000 inhabitants) was observed for 10 years and nine patients with FTC of 9 mm or less were identified.

The annual incidence rate there was 1.5 per million. In the present study it was possible to review histopathologically all diagnosed cases of T1 FTC in only a relatively small area in north-eastern Switzerland. Just one of eight patients could be confirmed as having mFTC with a diameter of 10 mm or less. The actual annual incidence of this completely analysed population was 0.12 cases per million inhabitants.

Although this survey has methodological limitations, clinically and histopathologically mFTCs are extremely

rare and the probability that a surgeon or pathologist will encounter a patient with such a tumour during his or her lifetime is very low. This tumour type seems to be overdiagnosed and therefore overtreated. It is strongly recommended that clinicians confronted with the diagnosis of FTC of 10 mm or less should have the diagnosis verified by an independent expert pathologist.

Collaborators

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The authors declare no conflict of interest.

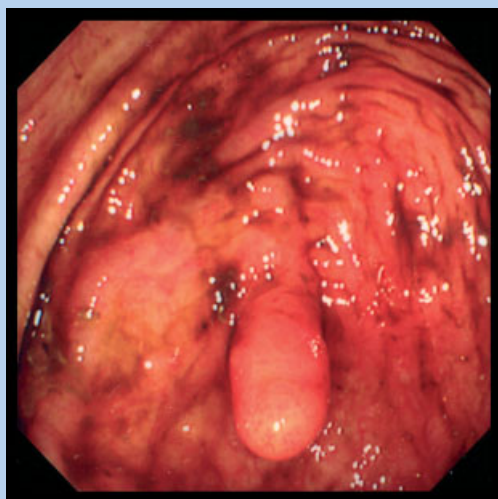
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Inverted appendix masquerading as a “virtual” polyp

A 56-year-old woman presented for colonoscopy following a Lifescan which had identified two caecal polyps. At colonoscopy a long ‘finger-like’ structure, with normal overlying mucosa, was found within the caecum (*Fig. a*). A diagnosis of inverted appendix was made and the structure was not snared. Subsequent review of her CT revealed the corresponding polyp-like structure and the absence of an extra-luminal appendix (*Fig. b*). Complete inversion/intussusception of a normal appendix is rare, with an incidence of 0.01 per cent.



a



b

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