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# Minimally invasive follicular thyroid cancer: treat as a benign or malignant lesion?

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## ABSTRACT

**Background:** Follicular thyroid cancer is the second most common thyroid cancer, accounting for 10%-15% of all cases. Follicular thyroid carcinomas (FTCs) can be classified into two subtypes: classic (C), which exhibit both vascular and capsular invasion and minimally invasive (MI), which only has limited capsular invasion. Both types, like most well-differentiated thyroid cancers, are traditionally treated the same: a completion thyroidectomy usually followed by radioiodine ablation. We hypothesize that MI-FTC may behave more like a benign follicular adenoma rather than C-FTC and may not require total thyroidectomy/radioiodine.

**Methods:** A prospective thyroid database was screened for patients with follicular cell tumors. Data on recurrence rates, disease-free survival, and requirement for follow-up surgery and/or radioiodine were compared. Disease-free survival was determined by the Kaplan–Meier method. Analysis of variance and chi-square test were used to evaluate other factors.

**Results:** In total, there were 419 benign adenomas (87%), 21 MI-FTCs (4.5%), and 41 C-FTCs (8.5%). Patients with adenomas were younger ( $P = 0.035$ ) and were more likely to be female ( $P = 0.001$ ). Importantly, the 16-y disease-free survival was 100% in the adenoma group, 100% in the MI-FTC group, and 36.6% in the C-FTC group ( $P < 0.0001$ ).

**Conclusions:** MI-FTCs behave similar to adenomas with 100% disease-free survival with up to 16 y of follow-up. These data suggest MI-FTCs could be potentially treated by thyroid lobectomy alone like follicular adenomas and perhaps should be classified as a distinct clinical entity.

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## Introduction

Follicular thyroid carcinoma (FTC) is the second most common type of thyroid cancer, comprising 10%-15% of all thyroid carcinomas.<sup>1–8</sup> Although the second most common type, its incidence has decreased over the past few years.<sup>5</sup> It is generally more aggressive than its more common counterpart,

papillary thyroid cancer, because it typically presents at a later disease stage.<sup>2</sup> Hurthle cell carcinomas are often considered a subtype of FTC and are therefore included as part of the study.<sup>9</sup>

Like most well-differentiated thyroid cancers, FTCs > 1 cm are treated with total/completion thyroidectomy with radioactive iodine.<sup>10</sup> FTCs are classified into two subtypes: classic

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(C), which exhibit both vascular and capsular invasion, and minimally invasive (MI), which only has limited capsular invasion.<sup>11</sup> Both have traditionally been treated the same. However, the two entities may behave in distinctly different manners.<sup>5</sup>

We hypothesize that MI-FTC may behave more like a benign follicular adenoma rather than C-FTC and therefore may not require total thyroidectomy and radioactive iodine.<sup>2</sup> Avoidance of completion/total thyroidectomy and/or radioiodine ablation would spare a portion of the thyroid, preserving normal function, and minimize risk to the parathyroid glands. The recurrent laryngeal nerve, primarily responsible for vocal motor function, would also be put at no risk if a follow-up surgery was not required.<sup>4,12</sup>

## Methods

Institutional approval was obtained and waived informed consent. A prospective thyroid database dating back up to 23 y was reviewed to include patients with follicular and Hurthle cell tumors. Permanent histology was used as the final diagnosis. MI tumors were any carcinomas deemed “minimally invasive” on the pathology report (minimal/zero tumor capsule invasion). MI carcinomas had no vascular/lymph invasions. Moderate to heavy tumor capsule invasion or obvious tumor capsule extension was categorized as classic tumors. Any venous/lymphatic invasion or extrathyroidal extension was also described as a classic tumor.

Data on recurrence rates, disease-free survival, requirement for follow-up surgery and/or radioiodine ablation, and lesion type were compared among the groups. Disease-free survival was determined by the Kaplan–Meier method with log-rank analysis. Analysis of variance and chi-square analysis were used to evaluate age (at time of surgery) and gender, respectively. A significant *P* value was set at  $\leq 0.05$ .

Disease recurrence was defined as a confirmed case of follicular or Hurthle cell thyroid cancer that had originated after a patient was clinically determined to be cancer free. Evaluation of the following data was used as indicators of confirmed disease recurrence: clinical notes, ultrasound, total body scans with radioiodine, and thyroglobulin levels. A thyroglobulin threshold was set at 2 ng/mL, with  $> 2$  ng/mL indicating recurrence. Patients with persistent disease ( $n = 10$ ) were not included in the analysis; 100% of the patients with persistent disease had C-FTC. Disease-free survival was calculated based on date of operation to date of latest clinical follow-up.

## Results

### Patient data

About 481 patients met criteria for inclusion: 349 were classified as follicular and 132 as Hurthle cell tumors. In total, there were 419 benign adenomas (87%), 21 MI-FTCs (4.5%), and 41 C-FTC cancers (8.5%). Table 3 shows that patients with adenomas were younger ( $P = 0.035$ ) and patients overall were more likely to be female ( $P = 0.001$ ).

**Table 1 – Procedure versus diagnosis.**

Follicular	Procedure	
	Thyroid lobectomy	Completion/total thyroidectomy
Adenoma	337 (80.5%)	82 (19.5%)
Minimally invasive	13 (61.9%)	8 (38.1%)
Classic	16 (38.1%)	25 (61.9%)
Total, $P < 0.0001$	366	115

A comparison of the diagnosis of adenoma, minimally invasive follicular thyroid carcinoma, and classic follicular thyroid carcinoma versus the procedure performed to treat.

### Surgical data

The average nodule size was 1.88 ( $\pm 0.43$ ) centimeters. The rates of total thyroidectomy were 19.8% for adenomas, 38.1% for MI-FTC, and 61.9% for C-FTC ( $P < 0.0001$ ). Table 1 demonstrates the overall distribution of the type of procedure, categorizing into either thyroid lobectomy or completion/total thyroidectomy. Most patients underwent thyroid lobectomy. After surgery, some patients received radioiodine treatment to ablate any remaining thyroid tissue. These data are shown in Table 2. Overall radioiodine rates, according to date of latest endocrine follow-up, were determined to be 33.3% for MI-FTC and 63.4% for C-FTC ( $P < 0.0001$ ).

### Outcomes

There was no difference in outcomes when stratifying Hurthle cell and FTCs versus combining the two groups, so the data are presented as combined Hurthle cell and FTCs. The Kaplan–Meier disease-free survival plot depicted a pattern of recurrence that was similar in adenomas and MI-FTC, whereas the C-FTC group was significantly different than both of the others. Figure 1 demonstrates the significant recurrence rates in C-FTC up to 16 y of follow-up. Figure 2 demonstrates disease-free survival with C-FTC in lobectomy versus total thyroidectomy, which showed three recurrences in lobectomy and five cases in total thyroidectomy. Figure 3 demonstrates that there was greater recurrence in males (5,  $n = 19$ ) when compared with females (3,  $n = 23$ ). There was no difference in recurrence with age ( $P = 0.49$ ). Nodules size had

**Table 2 – Radioiodine versus diagnosis.**

Follicular	Radioactive iodine	
	No	Yes
Adenoma	419 (100%)	0 (0%)
Minimally invasive carcinoma	14 (66.7%)	7 (33.3%)
Classic carcinoma	15 (36.5%)	26 (63.4%)
Total, $P < 0.0001$	448	33

The use of radioactive iodine or not as part of the treatment for follicular adenoma, minimally invasive follicular thyroid carcinoma, or classic follicular thyroid carcinoma.

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