

# Postoperative Findings and Risk for Malignancy in Thyroid Nodules with Cytological Diagnosis of the so-called "Follicular Neoplasm"

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**Background** : Malignant follicular lesion is not differentiated from benign lesions cytologically. The objective of this study was to assess the rate and the risk of malignancy in thyroid nodules which were cytologically diagnosed as follicular neoplasm by fine-needle aspiration (FNA) cytology.

**Methods** : All the patients who had undergone surgery with cytological diagnosis of follicular neoplasm from January 1996 through December 2001 in Asan Medical Center were studied retrospectively. Patients' and nodule characteristics were analyzed for factors associated with the presence of cancer. Two hundred and fifteen patients (196 females, 19 males) were included and their mean age was 39.4 years (range: 12~76).

**Results** : About half of the patients (102 out of 215, 47.4%) had malignancy with 29 papillary carcinomas, 57 follicular carcinomas, 15 Hürthle cell carcinomas and 1 medullary carcinoma. Previously suggested factors associated with risk for malignancy, such as male gender, large tumor size (>4 cm) or age of patients (>45 years), were not associated with increased risk. Diagnosis of Hürthle cell neoplasia on FNA was also not associated with increased risk. Only the extremes in age of the patients (below 20 or above 60 years) were associated with increased risk for malignancy.

**Conclusion** : In our findings, prevalence of carcinoma in thyroid nodule patients with cytological diagnosis of follicular neoplasm was much higher than those reported. Clinical characteristics, such as male gender, age and nodule size, are not useful predictors for the presence of malignancy. Thyroid nodules with cytological diagnosis of follicular neoplasm warrant immediate surgery.

**Key Words** : Follicular neoplasm, Cytology, Thyroid Cancer

## INTRODUCTION

Cytological diagnosis of thyroid papillary carcinoma is not difficult when it shows a characteristic nuclear pattern and papillary structure of cell nests. In contrast, malignant follicular lesion is not easily differentiated from benign lesions cytologically. If follicular cells are seen with macrophages and

degenerated cells in the colloid background, cytological diagnosis of nodular hyperplasia is entertained and the lesion is usually considered as benign, although some might turn out to be malignant after resection. The term follicular neoplasm has been applied to the presence of abundant follicular epithelial cells in sheets, in microfollicles or a trabecular pattern with scanty or no colloid. The important issue is the concern that such a lesion might be follicular carcinoma. The

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definition of a follicular carcinoma is primarily based on histologic evidence of capsular or vascular invasion extra-thyroidal tissue invasion, or nodal or distant metastasis<sup>11</sup>. However, the cytological pattern of "follicular neoplasm" which is identified at fine-needle aspiration (FNA) may be seen in follicular adenoma, follicular carcinoma, nodular goiter or in the follicular variant of papillary carcinoma<sup>2, 3)</sup>. Since the cytological diagnosis of follicular neoplasm includes various benign and malignant conditions, it seems crucial to see if there are any characteristics that suggest the presence of malignancy in those cases for optimal care. In the literature, the probability of malignancy in thyroid nodules with cytological diagnosis of follicular neoplasm is approximately 20~30%<sup>4-7)</sup>.

The aim of this study was to evaluate the prevalence of malignancy and to assess the risk of malignancy in patients with cytological diagnosis of follicular neoplasm.

## MATERIALS AND METHODS

Subjects for this study were composed from a retrospective search of patients who underwent thyroidectomy with a diagnosis of follicular neoplasm on FNA cytology from January 1996 through December 2001 at Asan Medical Center. Two hundred and fifteen patients (196 females, 19 males) were included and their mean age was 39.4 years (range: 12~76). FNA was performed by an experienced pathologist (G.G), the aspirates were stained with Papanicolaou staining and reviewed by at least two expert cytopathologists. Diagnosis of follicular neoplasm was entertained when the aspirates showed high cellularity and/or microfollicles with minimal colloid. Indeterminate class was considered as follicular neoplasm and any suspicious cases were excluded although there were certainly some vague gray zones.

Total thyroidectomy was performed in several patients with proven or suspected malignancy on frozen section diagnosis during operation. However, in most cases lobectomy and isthmectomy were performed initially for pathologic confirmation of nodules. For those with malignancy in pathologic examination, completion thyroidectomy was done usually within 4 weeks after the first operation and followed by radioiodine ablation as necessary.

The results of the histopathologic examination by permanent section slides concerning the main nodule were compared with the preoperative cytology and incidentally found micro-papillary carcinomas were not considered. In all cases cytology slides were retrospectively reviewed again after histologic confirmation.

The two-tailed *t*-test and chi-square test were used for comparisons of numerical and categorical variables,

respectively. Risk for thyroid malignancy in follicular neoplasm was described by the relative risk, and 95% confidence intervals (CI) for the relative risk were calculated. *p* values of less than 0.05 (two-tailed) were considered statistically significant.

## RESULTS

The final pathologic diagnosis for the 215 patients with follicular neoplasm on FNA cytology are shown in Table 1. One hundred and two of the patients (47.4%) had carcinoma, consisting of 29 papillary carcinomas, follicular variant in all of them (13.5%), 57 follicular carcinomas (26.5%), 15 Hürthle cell carcinomas (7%) and 1 medullary carcinoma (0.5%). Otherwise, 113 of the patients (52.6%) had benign lesions, consisting of 81 follicular adenomas (37.7%), 30 nodular hyperplasia (14%) and 2 Hashimoto's thyroiditis (0.9%).

The clinical characteristics of patients with benign and those with malignancy based on pathologic exam were compared (Table 2). The mean age of patients with carcinoma was  $39.4 \pm 11.6$  years (range, 12~66 years) compared with  $39.5 \pm 14.3$  years (range, 13~76 years) in patients without carcinoma ( $p > 0.05$ ). Thyroid carcinoma was diagnosed in 91 of 196 women, compared with 11 of 19 men ( $p > 0.05$ ). The mean tumor size in patients with carcinoma was  $3.2 \pm 1.3$  cm (range, 0.7~8.1 cm) compared with  $3.2 \pm 1.5$  cm (range, 0.8~8.0 cm) in patients without carcinoma ( $p > 0.05$ ). Diagnosis of Hürthle cell neoplasia on FNA was noted in 42 (19.5%) among 215 patients. Malignancy was found in 15 of 42 (35.7%). There was no significant difference in the probability of malignancy in the cytological diagnosis of Hürthle cell neoplasia groups ( $p > 0.05$ ).

**Table 1. Histologic diagnosis in 215 patients who underwent surgery under the diagnosis of follicular neoplasm on FNA cytology**

Histologic diagnosis	Number	Percent of total specimens
Adenoma	81	37.7%
Nodular hyperplasia	30	14.0%
Hashimoto's thyroiditis	2	0.9%
<b>Total benign nodules</b>	<b>113</b>	<b>52.6%</b>
Papillary carcinoma	29	13.5%
Follicular carcinoma	57	26.5%
Hürthle cell carcinoma	15	7.0%
Medullary carcinoma	1	0.5%
<b>Total malignant nodules</b>	<b>102</b>	<b>47.4%</b>

**Table 2.** Clinical features of patients with benign and malignant nodules confirmed by surgery

	Benign (n=113)	Malignancy (n=102)	p
Sex (male : female)	8 : 105	11 : 91	NS
Age (years)	39.4±11.6	39.5±14.3	NS
Size of lesion (cm)	3.2±1.3	3.2±1.5	NS
Hürthle cell neoplasia on FNA (n=42)	27 (23.9%)	15 (14.7%)	NS

NS, Not Significant.

**Table 3.** Relative risk for malignancy in thyroid nodules diagnosed as "follicular neoplasm" in FNA cytology according to the patients' characteristics

	Relative risk	95% confidence interval
Male gender	1.49	0.56~3.96
Age ≥ 45 years	1.03	0.57~1.83
Age ≥ 60 years	3.98	1.25~12.6
Age ≤ 20 years	3.98	1.07~14.9
Size of lesion ≥ 4 cm	1.28	0.70~2.33

Multivariate analysis was performed to find risk factors for the presence of malignancy. Male gender (RR: 1.49, 95% CI: 0.56~3.96), tumor size above 4 cm (RR: 1.28, 95% CI: 0.70~2.33) and age above 45 years (RR: 1.03, 95% CI: 0.57~1.83) did not increase the risk of malignancy (Table 3). But age above 60 years (RR: 3.98, 95% CI: 1.25~12.6) and age below 20 years (RR: 3.98, 95% CI: 1.07~14.9) were significantly associated with increased risk of malignancy. Patients age above 60 years had a risk of malignancy of 76.5% (13/17) while those patients younger than 60 years had a risk of 44.9% (89/198). Patients of below 20 years had a risk of malignancy of 76.9% (10/13) while those patients older than 20 years had a risk of 45.5% (92/202).

## DISCUSSION

We studied 215 patients with follicular neoplasm by FNA and found 102 carcinomas (47.4%), which is a much higher rate of malignancy than previously reported results in the literature<sup>4-7</sup>. This might be due to more strict criteria for the diagnosis of follicular neoplasm by our cytopathologists when follicular cells are seen on aspirates since all the suspicious cases were excluded. Interestingly, the size of the nodule was not a predictor for the presence of malignant thyroid nodule.

The diagnosis of follicular carcinoma is usually made after examination of permanent sections following surgical treatment

because FNA is not sensitive for distinguishing between adenoma and carcinoma. The accuracy of FNA cytology depends on the skills of the pathologist and of those who perform the FNA. The overall rate of malignancy in nodules with cytologic diagnosis of follicular neoplasm has been reported as approximately 20~30%. But in our current study, about 50% of patients were diagnosed as malignancy. One of the reasons might be the fact that our institution is a tertiary care referral center. Thus, patients with suspicious malignancy on clinical and cytological features might have been referred from a primary care clinic, causing a bias in patient selection.

In our study, nodule size greater than 4 cm was not associated with an increased risk of malignancy. Raber *et al.* and McHenry *et al.* also reported a similar result to ours<sup>7, 8</sup>. But Tuttle *et al.* revealed that male gender, nodule size greater than 4 cm and the finding of a solitary nodule by palpation were associated with a significantly increased risk of malignancy<sup>9</sup>. A Mayo Clinic report demonstrated that 20% of lesions larger than 4 cm in diameter were follicular cancers, in comparison with 6% of smaller ones<sup>10</sup>.

Patients younger than 20 and older than 70 years of age have been reported to have the highest incidence of carcinoma<sup>11</sup>. On the contrary, the Mayo Clinic report reported that the risk of cancer varies with the patient's age and that for every increase of 10 years in age, the risk of cancer decreased 0.7 times<sup>10</sup>. Other studies have suggested that advancing age may be a risk factor for malignancy in thyroid nodules found to have follicular neoplasm by FNA. Tyler *et al.* demonstrated that age greater than 50 years was a significant risk factor for malignancy<sup>12</sup>. In our study, the mean age was similar in both benign and malignant groups. But an age below 20 years (10/13) and an age above 60 years (13/17) had a significant increased risk for malignancy.

It has been suggested that a male patient is more likely to have malignant lesion among those with follicular neoplasm diagnosed by FNA cytology. In a large series with cold thyroid nodules, the risk of malignancy was higher in men, especially at the extremes of age and was also associated with a higher risk of carcinoma in patients with follicular lesions<sup>11</sup>. However, we and others have not found male gender to be an independent predictor of carcinoma<sup>7</sup>.

Of the malignant lesions in our series, 57 (55.8%) were follicular carcinomas, 15 (14.7%) were Hürthle cell neoplasms and 29 (28.4%) were papillary carcinoma follicular variants. That incidence of follicular carcinoma was similar to that reported by Chen *et al.*<sup>6</sup>, but significantly higher than that reported by Goldstein *et al.* and by Udelsman *et al.*<sup>13, 14</sup>. The fact that there was such a large proportion of follicular carcinomas and that follicular carcinomas were more frequent than papillary carcinomas may reflect a patient grouping for

the lesions that were follicular neoplasms. The frequency of follicular carcinoma among thyroid cancers is as low as approximately 10% in countries with adequate iodine intake<sup>13</sup>. The rate of follicular carcinoma among thyroid cancers in Korea was reported to be 15%<sup>15</sup>.

For the malignant potential of Hürthle cell neoplasm, there is a controversy in the literature. Some authors suggest that Hürthle cell neoplasm is generally a benign lesion and not likely to have a malignant course<sup>16</sup>, and its size per se cannot be correlated with the risk for malignancy<sup>17</sup>. However, the majority of Hürthle cell neoplasms are larger than 5 cm and the presence of aneuploid DNA is frequently associated with recurrence. These findings led to an opposite opinion that all patients with Hürthle cell neoplasm in large size should undergo an operation<sup>7, 17</sup>.

Interestingly, there were two cases of Hashimoto's thyroiditis without true neoplasm. Their cytology was reviewed after histologic confirmation and showed mainly numerous oxyphilic cells with only scanty numbers of lymphocytes mimicking Hürthle cell neoplasm.

Recently, biochemical and cytological studies, such as flow cytometric nuclear DNA analysis or computer-assisted cell morphometry analysis of immune staining for galectin-3<sup>18, 19</sup>, have been assessed as potential predictors of the presence of a malignant tumor, but their true clinical implication remain still unclear.

In summary, in our findings the prevalence of carcinoma in patients identified as follicular neoplasm by FNA was about half, quite higher than those that had been reported. Male gender, age and nodule size were not helpful to predict the presence of malignancy. However, age below 20 years or above 60 years showed increased risk of malignancy. Therefore, we conclude that patients with thyroid nodules diagnosed as follicular neoplasm by FNA cytology should undergo surgery regardless of clinical features, especially when patients are younger than 20 years or older than 60 years.

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