Malignancy Rate in Sonographically Suspicious Thyroid Nodules of Less than a Centimeter in Size Does Not Decrease with Decreasing Size

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INTRODUCTION
The development of high-resolution ultrasound has made it possible to detect many nonpalpable thyroid nodules. The incidence of thyroid nodules is known to be about 70% in the general adult population, and about 5%-15% of the nodules are malignant (1). Especially, the increasing thyroid cancer incidence in the recent decade has been thought resulting from the increased detection of small subcentimeter-sized thyroid cancers (microcarcinoma) by ultrasound (2, 3). However, still controversies exist any cut-off size to discriminate the malignancy risk or prognosis in subcentimeter thyroid cancers.

Some previous studies showed that thyroid cancers larger than 5 mm had more lymph node metastasis than those 5 mm or smaller in papillary thyroid microcarcinoma (4, 5), and papillary carcinomas of sizes up to 5 mm showed significantly better recurrence-free survival rates compared to those between 6 and 10 mm (6). Based on these results, in the revised American Thyroid Association Guidelines, they recommend performing fine needle aspiration cytology (FNAC) on thyroid nodules larger than 5 mm with suspicious sonographic features for patients with high-risk histories. However, there is still controversy surrounding the management of subcentimeter thyroid nodules with suspicious sonographic features. To make recommendations about the indication of FNAC in subcentimeter thyroid nodules, it is also important to know the malignancy rates and the diagnostic yields of ultrasound-guided FNAC as well as the prognosis of subcentimeter-sized thyroid cancer.

To evaluate whether there exist any valuable cut-off size predicting the malignancy in subcentimeter-sized thyroid nodules with suspicious sonographic findings, we compared the malignancy rate and the diagnostic yields upon FNAC results according to the subdivided size.
ed FNAC was performed on a total of 9,861 thyroid nodules at Seoul National University Bundang Hospital. We retrospectively reviewed the medical records of all subjects and collected demographic data and information about the size of the nodules on which FNAC was performed and their FNAC results. The mean size of the nodules was 1.72 ± 1.13 cm (median 1.38 cm; range 0.14-9.92 cm). The mean age of the patients was 51.1 ± 12.1 yr. Of the nodules, 2,756 (27.9%) were smaller than 1 cm with a mean size of 0.70 ± 0.18 cm (median 0.71 cm; range 0.14-0.99 cm), and the mean age of the patients with these nodules was 50.3 ± 11.4 yr.

The US-guided FNAC was performed by several radiologists with the use of a Philips IU 22 (Royal Philips Electronics, Amsterdam, The Netherlands), which employs electronically focused near-field probes with a bandwidth of 7-12 MHz. For the nodules that had not undergone FNAC previously, FNAC was performed in thyroid nodules of 1 cm or more in size or in the subcentimeter nodules that had at least one sonographic finding suggestive of malignancy. Sonographic characteristics associated with malignancy were defined as hypoechoogenicity, an orientation taller-than-wide, the presence of calcification or irregular margins (7). In the nodules that were confirmed to be benign by the previous FNAC results, repeated FNACs were taken only for the nodules showing either 2 or more suspicious features or an increase in size during the follow-up examination. We treated the FNAC results for the nodules that underwent repeated FNACs as different nodules in this study. For the FNAC, 23-gauge needles were used without local anesthesia. A 26-gauge needle was used if profuse bleeding occurred.

Cytologic examination

Aspiration samples were dispersed onto slides and fixed by air-drying. Samples were then stained with either hematoxylin and eosin or Giemsa and evaluated by the pathology department of our hospital. The cytology findings of the nodules were reviewed by experienced pathologists and categorized as “benign”, “indeterminate”, “suspicious of follicular or Hürthle cell neoplasm”, “suspicious of malignancy”, “malignancy” or “nondiagnostic” (8). We defined the malignancy rate as the proportion of findings classified as both “suspicious of malignancy” and “malignancy” because the expected true malignancy rates were reported to be 60%-75% and 97%-99%, respectively (8). Thus, physicians usually recommend surgery in both cases. Benign nodules included adenomatous goiters, nodular hyperplasia, lymphocytic thyroiditis, degenerative nodules and other benign conditions.

Statistical analysis

To compare the cytologic findings, the chi-square test was performed using the SPSS software (SPSS, Inc., Chicago, IL, USA). A two-tailed P value of less than 5% was considered statistically significant. Univariate odds ratios (OR), with relative 95% confidence intervals (CI), were calculated to assess the ability of clinical characteristics to predict the results of FNAC.

Ethics statement

The institutional review board of Seoul National University Bundang Hospital approved this study protocol (B-1006-103-121) and waived the informed consent requirement for retrospective evaluation of the medical record.

RESULTS

The malignancy rate of subcentimeter sized thyroid nodules with sonographically suspicious findings

The malignancy rate was higher in subcentimeter-sized nodules with suspicious sonographic features than in nodules sized 1 cm or more (malignancy rate 19.7% vs 7.8%, P < 0.001; the rate of “malignancy” 16.0% vs 7.0%, P < 0.001; the rate of “suspicious for malignancy” 3.6% vs 0.8%, P < 0.001). The nondiagnostic rate in subcentimeter nodules was higher than the rate in nodules sized 1 cm or larger (19.3% vs 13.8%, P < 0.001) (Table 1).

Table 1. Cytological diagnosis according to nodule sizes

| Size of nodules | < 1.0 cm* | ≥ 1.0 cm | P       |
|----------------|----------|----------|---------|
| Number         | 2,756    | 7,105    |         |
| Age (yr)       | 50.3 ± 11.4 | 51.5 ± 12.4 | < 0.001 |
| Sex (M/F)      | 550/2,206 | 1,526/5,579 | 0.096   |
| Size nodule; mean ± SD (ranges) | 0.70 ± 0.18 | 2.11 ± 1.10 | < 0.001 |
| (0.14-9.92)    | (1.00-9.92) |         |         |
| Malignancy rate (n) | 19.7% (642) | 7.8% (533) | < 0.001 |
| Cytologic results |          |          |         |
| Benign         | 47.9% (1,318) | 68.4% (4,862) | < 0.001 |
| Atypia of undetermined significance | 12.1% (334) | 7.3% (517) | < 0.001 |
| Suspicious for follicular neoplasm | 1.1% (31) | 2.7% (190) | < 0.001 |
| Suspicious for malignancy | 3.6% (100) | 0.8% (56) | < 0.001 |
| Malignant      | 16.0% (442) | 7.0% (497) | < 0.001 |
| Nondiagnostic | 19.3% (531) | 13.8% (983) | < 0.001 |

*Thyroid nodules showed one or more sonographically suspicious findings; hypoechoigenicity, an orientation taller-than-wide, presence of calcification or irregular margin.

Table 2. Cytological diagnosis according to the nodule sizes in subcentimeter nodules with suspicious sonographic features

| Size of nodules | <= 0.5 cm | 0.6-0.9 cm | P       |
|----------------|-----------|------------|---------|
| Number         | 514       | 2,242      |         |
| Age (yr)       | 50.1 ± 11.1 | 50.3 ± 11.5 | 0.688   |
| Sex (M/F)      | 864/428   | 464/1,778  | 0.043   |
| Size nodule; mean ± SD | 0.43 ± 0.07 | 0.76 ± 0.13 | < 0.001 |
| Malignancy rate (n) | 25.1% (129) | 18.4% (413) | 0.001   |
| Cytologic results |          |          |         |
| Benign         | 35.6% (183) | 50.6% (1,135) | < 0.001 |
| Atypia of undetermined significance | 14.0% (72) | 11.7% (262) | 0.146   |
| Suspicious for follicular neoplasm | 1.0% (5) | 1.2% (26) | 0.717   |
| Suspicious for malignancy | 6.8% (35) | 2.9% (65) | < 0.001 |
| Malignant      | 18.3% (94) | 15.5% (348) | 0.123   |
| Nondiagnostic | 24.3% (125) | 18.1% (406) | 0.001   |

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The malignancy rates in subcentimeter-sized thyroid nodules

When we compared the rate of “malignant”, “suspicious of malignant” or malignancy rate among the mm-sized groups, we could not find any difference and there was no cut-off size to discriminate the difference (data not shown). Because some papers have suggested the use of 0.5 cm as a size threshold for determining whether or not surgical treatment is indicated (4, 6), we divided the subcentimeter nodules arbitrarily into groups consisting of nodules that were 5 mm or smaller (n = 514) and nodules that were larger than 5 mm (n = 2,242) (Table 2). The rate of “malignant” was similar between those two groups (18.3% vs 15.5%, $P$ = 0.123), while the rate of “suspicious for malignancy” was higher in smaller group (6.8% vs 2.9%, $P < 0.001$). In univariate or multivariate analysis, including both “suspicious malignancy” and “malignant” results, the malignancy rate was higher in smaller nodules (Table 3).

Age of patients associated with a high risk of malignancy in subcentimeter-sized thyroid nodules

We analyzed the malignancy rates according to the size, age or sex of the subjects to determine whether or not these clinical parameters could be useful in deciding when to perform an ultrasound-guided FNAC. Sex was not associated with an increased risk of malignancy in subcentimeter-sized thyroid nodules. When age was expressed as either categorical variables or continuous variables, both univariate and multivariate analysis revealed that younger age than 45 yr was associated with an increased risk of malignancy in subcentimeter nodules undergone FNAC (Table 3).

The rate of nondiagnostic results of FNAC

Nondiagnostic cytology findings also occurred more frequently in the 5 mm or smaller group (24.3% vs 18.1%, $P = 0.001$) (Table 2), and there exists a trend of increasing nondiagnostic results with its size decrement ($P$ value for trend $< 0.001$) (Fig. 1). The rate of nondiagnostic results of FNAC was highest (28.4%) in the 0.4-0.49 mm sized nodules.

DISCUSSION

Our data showed that the malignancy rate in nodules that underwent FNAC did not decrease with decreasing size for subcentimeter nodules with suspicious sonographic features. The overall malignancy rate was 16.0% in subcentimeter nodules, which is higher than 7.6% in nodules that were 1 cm or larger. A direct comparison of these two groups was not possible because FNAC was performed regardless of sonographic features in cases of nodules with size 1 cm or more, while in subcentimeter nodules, the FNAC was performed only in nodules showing one or more sonographically suspicious findings. The sonographic criteria for malignant thyroid nodules are more sensitive than the size criteria for prediction of thyroid cancer (9), resulting the higher malignancy rate in subcentimeter nodules. However, it is still unclear whether the malignancy rate among sonographically-suspicious subcentimeter nodules differs according to their size. With the development of high-resolution ultrasound, there increases the prevalence of thyroid micro-nodules, so it is im-

Table 3. Univariate and multivariate analysis of clinical characteristics for malignancy rate in patient with subcentimeter thyroid nodule

| Variables | Group % (n) | Malignancy rate % (n) | $P$ | Odds ratio (95% CI) | Corrected $P$ | Odds ratio (95% CI) |
|-----------|------------|-----------------------|-----|--------------------|---------------|--------------------|
| Size      | ≤ 0.5 cm   | 25.1 (129)            |     |                    |               |                    |
|           | 0.6-0.9 cm | 18.4 (413)            | 0.001 | 0.674 (0.537-0.845) | 0.001         | 0.669 (0.533-0.839) |
|           | Continuous variable | < 0.001 | 0.347 (0.206-0.586) | < 0.001 | 0.354 (0.209-0.598) |
| Sex       | Female     | 21.5 (118)            | 0.238 | 1.148 (0.913-1.444) | 0.175         | 1.173 (0.931-1.477) |
|           | Male       | 19.2 (424)            |       |                    |               |                    |
| Age       | < 45       | 22.8 (205)            | 0.004 | 0.754 (0.620-0.916) | 0.004         | 0.752 (0.618-0.915) |
|           | ≥ 45       | 18.2 (337)            |       |                    |               |                    |
|           | Continuous variable | 0.001 | 0.985 (0.977-0.994) | 0.001 | 0.986 (0.978-0.994) |

Fig. 1. The nondiagnostic rate of FNAC was increased by decreasing nodules in subcentimeter sized thyroid nodules.
important to know the cut-off size discriminating an increasing risk of malignancy. However little is known at date. To evaluate this, we categorized the subcentimeter nodules with 1 mm intervals, and found that in subcentimeter nodules showing any of suspicious sonographic features, the malignancy rates were quite similar regardless of their size. Statistically, the malignancy rate (the total rate of suspicious of malignancy and malignant) in the small nodules sized 5 mm or less was resulted even higher than the larger nodules. Because of the high nondiagnostic result in the smaller nodules, we could not say whether the actual malignancy rate is really higher in the smaller nodules, but we can conclude at least that the malignancy rate is not lower in the smaller nodules than the larger. Thus, nodular size itself could not be used as a predictive factor of malignancy, and it is reasonable to consider the malignancy risk of thyroid nodule depend on its sonographic finding or other clinical risk factors, but not on its size.

To determine whether or not FNAC is indicated for subcentimeter nodules, it is important to know not only about the malignancy risk but also the prognosis of thyroid microcarcinoma. The prognosis of thyroid cancer according to tumor size has been debated for years. In some studies, they reported the influence of the size of the primary tumor on survival among patients with papillary cancer was negligible for tumors less than 4 cm in diameter (10, 11). Other investigators have reported that tumor-related deaths are rare in patients with papillary thyroid tumors smaller than 1.0 cm (12), suggesting that microcarcinomas may not require immediate surgical treatment (13). However, despite the excellent overall prognosis for patients with papillary microcarcinoma, this type of microcarcinoma was associated with a 1.0% disease-related mortality rate, a 5.0% lymph node recurrence rate, and a 2.5% distant metastasis rate in other studies. We also reported that clinicopathological features, long-term prognosis, and immunohistochemical findings did not differ between patients with papillary microcarcinoma and papillary thyroid cancer (14, 15). All these results support the contrary opinion of papillary microcarcinoma should be treated in the same manner as conventional papillary thyroid cancer (16). Although cancer-related death has rarely been reported in patients with papillary microcarcinoma, tumor recurrence may be associated with tumor size in papillary microcarcinoma (17). Recurrences require another surgery, additional radioactive iodine treatment, or both, which lowers the quality of life and incurs additional costs. Considering this, it is also important to reduce the risk of recurrence as well as mortality in patients with papillary microcarcinoma. Therefore there existed some efforts to find the adequate cut-off size to be evaluated, but still show controversy. Thus, we tried to know then whether there existed a cut-off size to predict malignancy, but could not find. Even the malignancy rate was similar between nodules sized 0.5 cm or less and those with diameters between 0.6 and 0.9 cm (Table 2).

In addition to the malignancy risk and prognosis, the cost-effectiveness of FNAC should be carefully considered. There are only a few published reports regarding the adequacy of FNAC for diagnosing thyroid nodules smaller than 1 cm in maximum diameter (18-21). Thus, we also evaluated the diagnostic yield in the same subjects. The overall nondiagnostic rate was 19.3% and the nondiagnostic rate was increased with decreasing nodule size (Fig. 1). In the literature, the adequacy rate of ultrasound-guided FNAC ranges from 68% (22) to over 90% (23). Similar to our study, a study reported that the adequacy rate of FNAC was associated with the size of the nodule (24). Thus we should consider and explain to patients about the possibility of nondiagnosis before performing FNAC. However, in our study, the maximum nondiagnosis rate did not exceed 30% in the subdivided groups. Although the adequacy rate of FNAC is quite dependent on the experience of the radiologist, FNAC at our institute was performed by several different radiologists, thus we can assume the nondiagnostic rate in subcentimeter nodules might be similar in many other hospitals. Therefore, the diagnostic yield of small nodules should not be an absolute reason to avoid performing FNAC in subcentimeter nodules.

In addition, we investigated age or sex could impact the likelihood of malignancy of the nodules. Berker et al. (18) reported that thyroid cancer affects more women than men, however the gender of patients did not predict the malignancy of subcentimeter nodules that undergone FNAC in this study. Meanwhile younger age was associated with an increased risk of malignancy. Compared with patients older than 45 yr of age, patients younger than 45 yr were more likely to have malignant nodules diagnosed with FNAC (OR, 1.327; 95% CI, 1.091-1.613). These results suggest that we should pay an attention to the management of subcentimeter nodules in younger patients.

We believe that our study is very relevant because of its large number of including subjects but has some limitation. Our study is performed by reviewing medical record retrospectively, and FNAC were performed by several different radiologists. Thus we could not analyze the detailed sonographic features to predict the malignancy rate using them, because, for the informative results, it should be ruled out any possible inconsistency of each radiologist’s opinion, even if it is not so big. We expect that further analysis with detailed sonographic features by single expert radiologist in categorized subcentimeter nodules will provide more useful information.

In summary, the malignancy rates of nodules did not decrease with decreasing size in subcentimeter nodules which were showing one or more sonographically suspicious findings, while the rate of nondiagnostic results was increased with decreasing size. However, the inadequacy rate was not so high at the aspect of cost-effectiveness. Therefore when we decide to perform FNAC in subcentimeter-sized nodules, sonographic findings and other clinical risk factors should be considered, but we should not
deal with the nodular size itself as a predictor of malignancy risk. To make a consensus about cut-off size of FNAC for subcentimeter-sized thyroid nodules, a large-scaled prospective study examining recurrence, survival and the quality of life in patients of papillary microcarcinoma is warranted.

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AUTHOR SUMMARY

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We evaluated the malignancy and nondiagnostic rates using FNAC results in 2,756 thyroid nodules smaller than 1 cm according to the subdivided size. Subcentimeter nodules had at least one sonographic finding suggestive of malignancy. The malignancy rates of nodules did not decrease with decreasing size in subcentimeter nodules. The rate of nondiagnostic results was increased with decreasing size. Therefore when we decide to perform FNAC in subcentimeter-sized nodules, we should consider sonographic findings and other clinical risk factors but not the nodular size itself.