

Does the Risk of Malignancy Increase When a Thyroid Nodule Is Larger Than 2 cm?

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SUMMARY ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ●

Background

In the evaluation of thyroid nodules for malignancy, the size of the nodule has been a cause for concern, mainly because the size—if it is a carcinoma—directly influences the staging. In addition, larger nodules in other organs, such as the adrenal gland, are more likely to be malignant. However, the data on size as a determinant of carcinoma in a thyroid nodule are conflicting (1-3). The current study assesses the impact of nodule size on the risk of cancer by analyzing a large clinical database.

Methods

The records of 4955 consecutive patients referred to Brigham and Women's hospital for evaluation of thyroid nodules during 1995–2009 were reviewed. Nodule size was measured in three dimensions by ultrasonography in all patients. The nodules were biopsied by fine-needle aspiration (FNA), and a cytopathologic diagnosis was made using the Bethesda classification. When patients underwent surgery, the final diagnosis was based on the surgical pathology.

Results

A total of 9339 nodules ≥ 1 cm were identified, and 7348 (78%) were evaluated by FNA. Those excluded usually had a high cystic component. The mean nodule size was 2.6 cm. The nodules were subdivided into the following groups by size: 1 to 1.9, 2 to 2.9, 3 to 3.9,

and ≥ 4 cm and the percent of nodules in each group was 49%, 27%, 14%, and 11%, respectively. Nodule size had no influence on the distribution of cytology aspirates in each Bethesda category: the percentage of benign aspirates was 72% of nodules 1.0 to 1.9 cm; 67% of nodules 2.0 to 2.9 cm, 65% of nodules 3.0 to 3.9 cm, and 64% of nodules ≥ 4 cm. The nodules in 5% of each size group were classified as malignant. Six percent of the nodules 1 to 1.9 cm were considered suspicious, as were 8 to 9% of nodules in the larger size groups.

Based on surgical pathology, 927 of 7348 nodules (13%) were cancers. Papillary cancers made up 86% and follicular or Hürthle-cell carcinomas 8% of the cancers, the remainder being other cell types. The prevalence of cancer in relation to nodule size was 10.5% of those 1.0 to 1.9 cm, 13.5% of those 2.0 to 2.9 cm, 16.3% of those 3.0 to 3.9 cm, and 15.0% of those ≥ 4.0 cm. When the nodules 1.0 to 1.9 cm were compared with those ≥ 2.0 cm, the difference was statistically significant ($P < 0.01$), but there were no differences in prevalence between the larger three groups. Increasing nodule size was associated with a lower proportion of papillary and a higher proportion of follicular or Hürthle-cell cancers as well as the rarer types (anaplastic, medullary, and lymphoma).

Conclusions

Increasing thyroid nodule size impacts cancer risk in a nonlinear manner with a threshold of 2.0 cm.

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ANALYSIS AND COMMENTARY ● ● ● ● ●

This large body of data has been analyzed very carefully and provides more concern for malignancy when the nodule is larger than 2 cm. In addition, the data suggest that larger solid nodules are more likely to be follicular carcinoma as compared with the smaller nodules. However, the literature concerning the size of nodules and the risk of malignancy is controversial. McHenry et al. evaluated 1023 patients with nodules; 673 underwent surgery (3). The mean (\pm SD) size of the benign nodules was larger, 4.4 ± 2.4 cm as compared with 3.3 ± 2.2 cm for malignant nodules ($P < 0.05$). In an estimate of probability of malignancy based on size, their analysis showed that the likeli-

hood of malignancy significantly decreased nonlinearly with increasing nodule size. The recent paper by Shrestha et al. (reviewed in the November 2012 issue of *Clinical Thyroidology*) found malignancy in 19.3% of 533 nodules 1.0 to 3.9 cm and 14.3% of 127 nodules ≥ 4 cm (4).

Another reason for concern in evaluating FNA results in large nodules is the possibility of a false negative result due to sampling error. The current study of Kamran et al found that the false negative rate was 1.3% in larger nodules and only slightly less in smaller nodules. Shrestha et al. also reported that false negative rates did not differ significantly based on nodule size (4).

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