

The Natural History of Benign Thyroid Nodules

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IMPORTANCE Detection of asymptomatic thyroid nodules has increased. Consensus is lacking regarding the optimal follow-up of cytologically proven benign lesions and sonographically nonsuspicious nodules. Current guidelines recommend serial ultrasound examinations and reassessment of cytology if significant growth is observed.

OBJECTIVE To determine the frequency, magnitude, and factors associated with changes in thyroid nodule size.

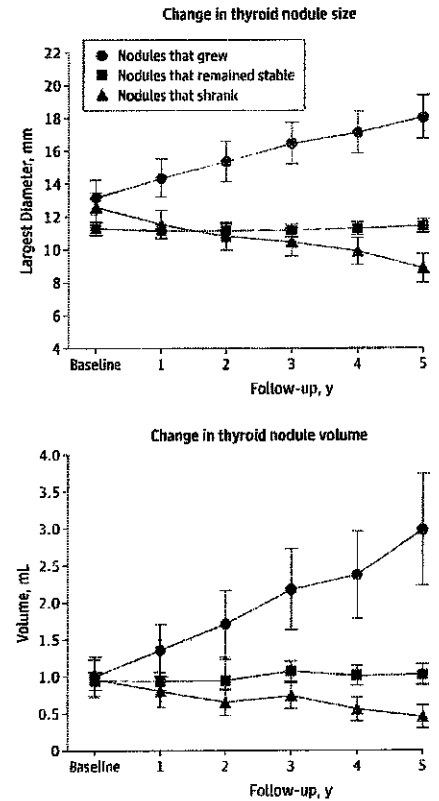
DESIGN, SETTING, AND PARTICIPANTS Prospective, multicenter, observational study involving 992 consecutive patients with 1 to 4 asymptomatic, sonographically or cytologically benign thyroid nodules. Patients were recruited from 8 hospital-based thyroid-disease referral centers in Italy between 2006 and 2008. Data collected during the first 5 years of follow-up, through January 2013, were analyzed.

MAIN OUTCOMES AND MEASURES Baseline nodule growth (primary end point) was assessed with yearly thyroid ultrasound examinations. Size changes were considered significant for growth if an increase of 20% or more was recorded in at least 2 nodule diameters, with a minimum increase of 2 mm. Baseline factors associated with growth were identified. Secondary end points were the sonographic detection of new nodules and the diagnosis of thyroid cancer during follow-up.

RESULTS Nodule growth occurred in 153 patients (15.4% [95% CI, 14.3%-16.5%]). One hundred seventy-four of the 1567 original nodules (11.1% [95% CI, 10.3%-11.9%]) increased in size, with a mean 5-year largest diameter increase of 4.9 mm (95% CI, 4.2-5.5 mm), from 13.2 mm (95% CI, 12.1-14.2 mm) to 18.1 mm (95% CI, 16.7-19.4 mm). Nodule growth was associated with presence of multiple nodules (OR, 2.2 [95% CI 1.4-3.4] for 2 nodules; OR, 3.2 [95% CI, 1.8-5.6 for 3 nodules; and OR, 8.9 [95% CI, 4.4-18.0] for 4 nodules), main nodule volumes larger than 0.2 mL (OR, 2.9 [95% CI, 1.7-4.9] for volumes >0.2 to <1 mL and OR, 3.0 [95% CI, 1.8-5.1] for volumes ≥1 mL), and male sex (OR, 1.7 [95% CI, 1.1-2.6]), whereas an age of 60 years or older was associated with a lower risk of growth than age younger than 45 years (OR, 0.5 [95% CI 0.3-0.9]). In 184 individuals (18.5% [95% CI, 16.4%-20.9%]), nodules shrank spontaneously. Thyroid cancer was diagnosed in 5 original nodules (0.3% [95% CI, 0.0%-0.6%]). Only 2 had grown. An incidental cancer was found at thyroidectomy in a nonvisualized nodule. New nodules developed in 93 patients (9.3% [95% CI, 7.5%-11.1%]), with detection of one cancer.

CONCLUSIONS AND RELEVANCE Among patients with asymptomatic, sonographically or cytologically benign thyroid nodules, the majority of nodules exhibited no significant size increase during 5 years of follow-up and thyroid cancer was rare. These findings support consideration of revision of current guideline recommendations for follow-up of asymptomatic thyroid nodules.

Figure 1. Changes in Thyroid Nodule Size and Volume During the First 5 Years of Follow-up



No. of nodules that	174	174	170	157	144	131
Grew	174	174	170	157	144	131
Remained stable	1188	1188	1170	1155	1115	1096
Shrank	205	205	197	188	173	161
No. of patients	992	992	963	946	902	875

Nodule growth occurred in 174 (11.1%) of the 1567 nodules present at baseline; 1188 (75.8%) remained stable and 205 (13.1%) shrank. Graphs represent the estimated mean with 95% CIs of the maximum diameters and volumes of thyroid nodules. An analysis of variance for repeated measures was carried out to evaluate the change in thyroid nodule size over 5 years of follow-up.