# Determining the Malignancy of a Thyroid Nodule: When Is Total Thyroidectomy Indicated?

**Ronald Rubin, MD—*Series Editor***

A 53-year-old man presented to the practice after noticing what he described as a lump in his neck area. He had detected the mass to one side of his Adam's apple while shaving. It was not tender, nor had there ever been tenderness in the area. His current health was otherwise quite good, with no new complaints. Specifically, he had experienced no palpitations, sweating, unexplained weight loss, or fatigue. There had been no change in his appearance or eyes. He worked in a trucking business but had no industrial or other exposures.

His family history was positive for hyperthyroidism—"the kind with the eyes," as he put it—in his mother and sister. He had received a diagnosis of Hodgkin disease at age 20 and had undergone splenectomy as part of the staging process. He received local radiotherapy to his chest and neck, with no evidence of recurrence since then.

Physical examination findings of the head, eyes, ears, nose, and throat were unremarkable, including the absence of elicited exophthalmos. Examination of the neck revealed a roughly 2-cm, essentially round mass on the right side of his larynx. It was firm, nontender, and freely movable. Careful palpation revealed no enlarged lymph nodes in the neck, axillae, or supraclavicular areas. The chest was clear to auscultation, and heart sounds were normal. There were no abdominal masses. The skin was normal without rashes or petechiae. Neurologic examination findings were nonfocal.

Results of a complete blood cell count and a comprehensive metabolic panel, including the serum calcium level, were normal. The sedimentation rate was 18 mm/h. A chest radiograph was negative for adenopathy in the thorax. Results of 2 thyrotropin tests were normal.

He underwent fine-needle aspiration (FNA) with 5 passes through the mass. Cytologic analysis of the samples revealed areas of nuclear enlargement, which was read as atypia of undetermined significance, according to the American Thyroid Association guidelines.[1,2] An ultrasonography study of the mass revealed it to be a 2.3-cm lesion within the right lobe of the thyroid near the midline. There was no associated cervical lymphadenopathy. The nodule was hypoechoic and had blurred edges on one side.

**WHICH ONE OF THIS PATIENT'S FINDINGS WOULD CONSTITUTE A FIRM INDICATION FOR PROCEEDING TO TOTAL THYROIDECTOMY?**

**A. A triple negative pattern for *BRAF*, *RAS*, and *TERT* oncogenes on mutation analysis in cytology specimens.**
**B. Consistently undetectable levels of thyrotropin.**
**C. A history of radiation to the neck during adolescence.**
**D. A strong family history of hyperthyroidism in a first-degree relative.**

## Answer: C, a history of radiation to the neck during adolescence.

The case presented here is typical of a thyroid nodule, a quite common clinical entity that affects 50% of the population and whose significance lies in the fact that 8% to 16% harbor malignancy, which can be effectively managed or cured with early diagnosis.[1,3] As technical advances accrue, thyroid nodule management is reviewed at regular intervals to incorporate diagnostic advances into practice.

The epidemiology of thyroid nodules reveals clinical findings

## TAKE-HOME MESSAGE

Thyroid nodules are an extremely common finding. The major concern is whether or not a nodule harbors malignancy. A variety of procedural and laboratory evaluation techniques exist (and continue to evolve toward the goal of greater predictive value and accuracy), offering a very useful clinical approach to a thyroid nodule. Classically, this involves measurement of thyrotropin, detailed ultrasonography evaluation, and ultimately FNA of the nodule for routine pathology and genetic tests. If definitive benignity or malignancy is not determined after these studies, specific strong clinical suggestions for aggressive therapy—namely, total thyroidectomy—have been developed and include a history of thyroid irradiation as a child or young adult.

that are linked to a statistically increased cancer risk, which include a history of thyroid cancer in a first-degree relative; a history of external beam irradiation as a child or adolescent; male sex; and several other less common endocrinopathies that involve the thyroid.[1]

### DIAGNOSTIC TESTS

After a thorough history and physical examination, a simple but effective diagnostic strategy will involve 3 studies.

The thyrotropin level should be measured. If it is found to be low, it needs be pursued as to whether the nodule is hyperfunctioning, which suggests hyperthyroidism and is an unusual finding in cases of neoplasm. This situation makes **Answer B** an incorrect choice.

Ultrasonography is the initial study indicated and will reveal the size of the nodule, which itself probably is an independent risk factor, with a size less than 1 cm being unlikely to be cancer, and a size of 4 cm or larger being very likely malignant.[2,3] Additionally, the ultrasonography characteristics of thyroid nodules have been studied over time in large numbers of patients. Specific characteristics are associated with increased malignancy risk and include hypoechogenicity; indistinct, blurred margins of the nodule; non-uniform and irregular dimensions; and microcalcifications.[2,3]

Once the ultrasonogram has been examined and a normal thyrotropin level is present, FNA is indicated and usually is easily and safely done and is definitive (along with ancillary cytologic and molecular study of the biopsy tissue) in a majority of cases. Two to five FNA passes are suggested so as to obtain adequate sites and sufficient tissue for analysis.

### MALIGNANCY RISKS

The Bethesda System is used for uniform reporting of cytologic analysis.[2,3] The categories are as follows: nondiagnostic, with a 20% malignancy risk; benign, with a 2.5% malignancy risk; atypia of undetermined significance, with a 14% malignancy risk; follicular neoplasm, with a 25% malignancy risk; suspicions for malignancy, with a 70% malignancy risk; and malignant, with a 99% malignancy risk.

A new refinement still in the early stages is the additional use of molecular testing of the cytology specimens. Studies have indicated as high as 100% specificity for thyroid cancer when, for example a *BRAF* mutation is found and 80% to 90% specificity when a *RAS* mutation is present. Conversely, in indeterminate nodules by cytology alone, when all mutations associated with malignancy are negative, a negative predictive value approaching 95% is seen.[4] These facts are opposite of what is proposed in **Answer A**, which is not correct. This testing requires more experience, but clearly in this era of genetic medicine, such analyses will become more accurate, useful, and commonplace in the evaluation of thyroid nodules.

Nodules judged to be benign are followed with ultrasonography, checking for size and characteristic changes, at intervals the length of which remain under study, with opinion ranging from 1 to 4 years.

### THYROID NODULE TREATMENT

Finally, as the major purpose of these schemes is to determine which nodules harbor a potentially dangerous neoplasm, some comments on management are needed. Nodules judged to be benign are followed with ultrasonography, checking for size and characteristic changes, at intervals the length of which remain under study, with opinion ranging from 1 to 4 years.[5]

If the malignancy of a nodule is still indeterminate after all

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the above studies have been done, many experts will proceed to thyroidectomy.[5]

Our patient's nodule was indeterminate cytologically, but with some worrisome ultrasonography findings of hypoechogenicity and some margin blurring. However, he had one of the very high-risk characteristics for thyroid cancer for which total thyroidectomy is almost always recommended when malignancy cannot be definitively excluded—a history of thyroid radiation as a young man for his Hodgkin disease (**Answer C**).

Of note, other strong clinical suggestions for this aggressive but definitive therapy include finding a high-predictive-value oncogene; finding malignancy in one nodule of a multinodular thyroid; and a family history of thyroid cancer in a first-degree relative. **Answer D** tries to link cancer in a nodule to a family history of hyperthyroidism and is not correct.

### PATIENT FOLLOW-UP

The detailed evaluation of this patient's thyroid nodule was considered inconclusive and could not achieve definitive characterization of the nodule as either benign or malignant.

Since he had a history of radiation to the neck during adolescence as treatment of Hodgkin disease, the decision was made to perform total thyroidectomy, which revealed a 2.2-cm solid nodule containing papillary carcinoma. All local lymph nodes were negative for metastases, as was a subsequent metastatic workup.

He experienced no adverse sequelae from surgery, and 1 year later is well and on lifelong levothyroxine therapy. ■

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