

Thyroid Nodules in Graves Disease and the Risk of Thyroid Carcinoma

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Background: The risk of thyroid carcinoma in patients with Graves disease has been particularly emphasized when nodules coexist with thyroid hyperplasia; a surgical approach has been suggested.

Objectives: To detect thyroid nodules early in patients with Graves disease and to evaluate the risk of carcinoma.

Methods: The study group included 315 consecutive outpatients with Graves hyperthyroidism not previously treated with surgery or radioiodine therapy. Thyroid ultrasonography was performed at the time of enrollment and repeated annually in all patients; fine-needle aspiration (FNA) was carried out in those patients with nodules and repeated after 2 years or at shorter intervals.

Results: One hundred six of 315 patients with Graves disease had thyroid nodules 8 mm in diameter or larger

detected by ultrasonography. In 49 patients, nodules were present at the time of the first examination; in 57 patients, nodules developed during follow-up. Fine-needle aspiration cytology results revealed features of carcinoma in only 1 patient; this was confirmed by histologic examination of excised thyroid tissue. The nodules with normal cytologic features at the time of the first examination did not show any clinical and/or cytologic evolution toward malignancy during follow-up.

Conclusions: Ultrasonographic evidence of nodules was frequently found among our patients with Graves disease, but malignant FNA cytologic findings of the examined nodules were rare at the time of diagnosis and throughout the course of the disease. When FNA cytologic evaluation does not indicate malignancy, the presence of thyroid nodules in patients with Graves disease does not indicate an aggressive therapeutic approach.

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SINCE SHAPIRO et al¹ identified thyroid carcinoma in 9% of the thyroids removed to treat Graves disease, numerous studies have been performed to clarify the relationships between Graves disease, thyroid-stimulating hormone (TSH) receptor antibodies (TRAb), and thyroid carcinoma. A high incidence of carcinoma in patients with Graves disease who underwent thyroidectomy was confirmed in many²⁻⁹ but not all¹⁰⁻¹⁵ studies, with frequencies varying from 0%¹⁵ to 9.8%.⁶ A striking increase in the risk of carcinoma was reported in patients with Graves disease with palpable nodules, with incidences up to 22.2%³ and 45.8%⁶ in the excised nodules. Moreover, increased aggressiveness of thyroid carcinoma in patients with Graves disease was reported in some studies.^{5,6,16}

Although other authors have failed to confirm a high likelihood of finding thyroid carcinoma in palpable nod-

ules,^{8,10,17,18} the discovery of nodules in patients with Graves disease still arouses concern. The issue cannot be fully resolved by fine-needle aspiration (FNA) cytologic evaluation, since thyroid cancer in patients with Graves hyperthyroidism has been described as multifocal and metastatic to regional lymph nodes, even when the primary lesion is small.^{5,6} Therefore, the treatment of nodules in patients with Graves disease is still controversial, because the choice between a conservative and an aggressive approach is not based on clear clinical evidence. We are not aware of any studies evaluating the frequency of malignant nodules in patients with Graves disease examined by ultrasonography and FNA cytologic evaluation or the long-term outcome of nodules with benign FNA cytologic findings.

This study was therefore undertaken to detect thyroid malignant neoplasms early in patients with Graves disease through a systematic search for

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PATIENTS AND METHODS

PATIENTS

From January 1983 through January 1997, we studied 315 consecutive patients with Graves hyperthyroidism who were not previously treated with surgery or radioiodine therapy (265 women and 50 men; mean \pm SD age, 42 ± 15 years [range, 11-77 years]; mean \pm SD follow-up, 7.0 ± 3.7 years [range, 1.5-15.5 years]). None of the patients had previously received external irradiation to the neck. Informed written consent was obtained from all patients. The diagnosis of Graves disease was based on history, signs of hyperthyroidism, and the commonly accepted laboratory criteria (ie, elevated serum free thyroxine levels, free triiodothyronine levels, undetectable or clearly suppressed TSH levels, and diffusely increased radionuclide uptake at scintiscan). In the group of patients with Graves disease with a coexisting nodule, the scintigraphic image showed a cold area in only 31 cases, while in the remainder ($n = 75$), the nodule was not clearly distinguishable from the surrounding tissue. High serum concentrations of TRAb and/or antiperoxidase antibodies were found at the time of diagnosis and/or relapse. The patients with Graves disease were treated with antithyroid drugs (ie, methimazole or propylthiouracil). Two patients with FNA cytologic findings suspicious for malignancy underwent thyroidectomy. Forty-seven patients had a poor response to medical treatment; 29 received radioiodine treatment and 18 (9 with nodules) underwent near-total thyroidectomy. In this last group, the pathological examination of the resected thyroid did not reveal malignancy.

STUDY PROTOCOL

A careful evaluation of the thyroid was done at the time of admission and in the clinical examinations during follow-up. The presence of nodules was confirmed by at least 2 experienced examiners. Thyroid ultrasonography was done for all patients at the time of admission and repeated annually. Fine-needle aspiration was repeated biennially or at shorter intervals when a nodule was detected by ultrasonography and/or physical examination. Thyroid scintiscan was done at the time of enrollment and repeated in the patients with Graves disease who developed nodules during follow-up.

The patients with Graves disease without nodules and the patients with nodules showing benign FNA cytologic findings were evaluated with clinical examinations and hormonal and immunological assays repeated at appropriate intervals (≥ 6 months). The patients with FNA cytologic

findings that suggested or revealed malignancy underwent thyroidectomy.

ASSAYS

Free thyroid hormones were separated by a chromatographic method using Sephadex LH-20 columns and measured with a solid-phase radioimmunoassay (Technogenetics, Milan, Italy). Normal values are 4.3 to 8.9 pmol/L (279-480 pg/dL) for free triiodothyronine and 9.1 to 20.7 pmol/L (0.7-1.6 ng/dL) for free thyroxine. Plasma TSH values were determined by a sensitive immunoassay using monoclonal antibodies (Allegro HS-TSH; Nichols Institute Diagnostics, San Juan Capistrano, Calif). The TSH standards are calibrated in accordance with the World Health Organization (second international reference preparation 80/558). The range of normal values in our laboratory is 0.4 to 4.6 mIU/L; the assay has a calculated sensitivity of 0.04 mIU/L. Antiperoxidase antibodies were detected by a radioimmunoassay (AB-TPO; Sorin Biomedica, Saluggia, Italy); levels greater than 20 U/mL were regarded as significant. The kit standards are calibrated against the National Institute for Biological Standards and Control 66/387 serum thyroid microsomal antibodies reference preparation. Serum TRAb levels were measured by a radioreceptor assay (TRAK assay; Henning, Berlin, Germany); values greater than 14 U/L (calibrated with Medical Research Council standard LATS-B 65/122 and World Health Organization thyroid-stimulating antibodies standard 90/672) were considered positive.

ULTRASONOGRAPHY AND FNA

Thyroid ultrasonography was done with ATL Ultramark 9 DP and HDI scanners (Advanced Technology Laboratories, Bothell, Wash) and 5- and 10-mHz linear transducers provided by the manufacturer to be used for small body parts. Thyroid ultrasonography was done by a physician who did not know the thyroid status of the patients. The same ultrasonographer carried out thyroid ultrasonography at enrollment and during the annual examination.

Fine-needle aspiration of the nodules was performed with a 21-gauge needle. Cytologic examination was done by the standard method. When the material obtained by FNA was inadequate, the procedure was repeated. Ultrasonography guidance was routinely employed for nodules less than 2.0 cm in diameter; FNA was not done for very small nodules (< 8 mm thick). The patients in our study were examined by the same team of cytologists.

nodular lesions with ultrasonography and FNA of the nodules, and to evaluate the clinical outcome of the nodules without malignant or suspect cytologic features in patients with Graves disease who did not undergo thyroidectomy.

RESULTS

Ultrasonography results revealed thyroid nodular lesions of sufficient size (≥ 8 mm) for FNA in 106 of 315 patients with Graves disease. In 49 patients, the nodules were present at the onset of the disease. In the other 57,

the nodules developed later during follow-up (during medical treatment in 38 patients, at relapse in 2, and during remission in 17) (**Figure**). Nodules were palpable in 44 (14.0%) of 315 patients. In 18 patients, the nodules completely regressed throughout follow-up (13 during medical therapy and 5 during remission).

The presence of nodules was not associated with more severe disease. The patients with Graves disease with nodules at the onset of the disease did not show more serious alterations of hormonal values or higher TRAb levels (**Table**). When nodules appeared during the course of the disease, they were not associated with a signifi-

cant increase of TRAb levels (mean \pm SD, 20.8 \pm 31.0 U/L; median, 8.6 U/L; range, 5-145 U/L at the discovery of the nodule vs 10.6 \pm 7.1, 7.1, and 5-26 U/L, respectively, in the previous measurement; $P = .20$). No nodules appeared during the spontaneous evolution to hypothyroidism in any of our patients. In regard to the evolution of cytologic features or spontaneous regression, no differences were found between palpable nodules and those detected only by ultrasonography. Nine (20%) of 44 palpable nodules and 12 (19%) of 62 detected only by ultrasonography disappeared during follow-up. Spontaneous regression of the nodules was associated with stable remission of the disease in 7 of 18 patients.

Among the 106 patients with Graves disease with nodules who underwent FNA, the cytologic examination showed atypical features arousing suspicion of carcinoma in only 2 patients with palpable nodules. Both underwent surgery and in 1 the pathological examination confirmed the diagnosis of mixed follicular carcinoma. In the 104 patients with Graves disease with ultrasonographic evidence of nodular lesions and normal FNA cytologic findings, the nodular lesions did not demonstrate any tendency to clinical and/or cytologic evolution toward malignancy. The follow-up period after the first FNA examination ranged from 2.3 to 13.8 years (median, 5.8 years).

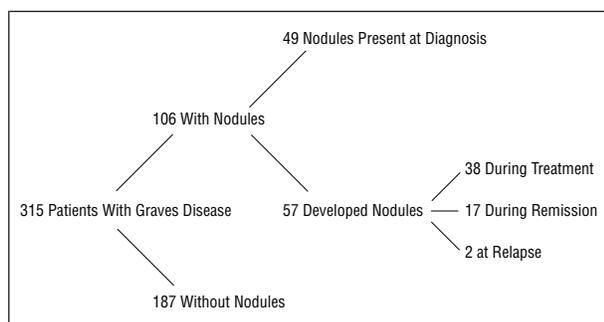
COMMENT

The coexistence of thyroid nodules and Graves disease is widely described, but its significance is uncertain in regard to the potential risk of malignancy. In our series, 14.0% of patients presented with palpable nodules, comparable to the 15.8% found by Dobyns et al¹⁰ in a very large series. The incidence of nodules was higher when ultrasonography was used. Nodules with a diameter of 8 mm or larger were found in 33.6% of our patients with

Graves disease, and the figure was higher (40.6%) when smaller lesions were included, a frequency comparable in magnitude to that observed when ultrasonography was used in the general population of different countries in Europe^{19,20} and North America.²¹⁻²⁴

In spite of the high risk of carcinoma reported in patients with Graves disease with nodules,^{3,6} we found only 1 patient with positive FNA cytologic findings confirmed by histological diagnosis. Moreover, in the patients with benign cytologic findings, the nodular lesions did not show any evidence of cytologic transformation into carcinoma during follow-up. The natural course of differentiated thyroid carcinoma is characterized by very slow progression, so the observation period of our study may have been too short to detect the evolution from silent carcinoma to overt clinical disease. However, in patients regularly examined who underwent repeated ultrasonography and FNA, the follow-up should be long enough to detect local growth and/or cervical node metastasis of tumors that are, according to some researchers, characterized by increased aggressiveness when coexisting with Graves disease.^{5,6,16}

Several factors may explain the high incidence of carcinoma in these studies, which is not in line with our results or with common clinical experience. First, all of the previous studies retrospectively examined patients with Graves disease who were surgically treated, and the results deserve to be examined in some detail. In the earliest reports, thyrotoxicosis was considered insurance against thyroid cancer, a conclusion based mainly on the results of Beahrs et al²⁵ and Sokal,²⁶ who reported incidences of carcinoma in patients with Graves disease of 0.5% and 0.15%, respectively. Shapiro et al¹ and subsequent reports²⁻⁹ indicated that the coexistence of Graves disease and thyroid carcinoma was not rare. The differences between studies carried out in different decades probably reflect to some degree the changing criteria in the selection of patients with Graves disease for thyroidectomy. In the 1950s, thyroidectomy was the usual therapy for Graves disease; thereafter, a tendency toward medical and radioiodine therapy emerged, causing a progressive decline in the number of patients referred for thyroidectomy.²⁷ Thus, in recent years, patients with Graves disease who receive surgical treatment constitute a select group with more serious forms of the disease and are not representative of the whole population of patients with Graves disease. Second, in some studies a number of patients with carcinoma had been previously treated with external radiation.¹⁻³ Third, the high frequency of thyroid carcinoma in the surgical series of patients with Graves disease is probably caused by occult and clinically inconsequential cancers uncovered at thyroidec-



Thyroid nodules 8 mm or larger in diameter in patients with Graves hyperthyroidism at diagnosis and during the course of the disease. Twenty-two of 315 patients with Graves disease had nodules less than 8 mm in diameter that are not included in the Figure.

Patients With Graves Disease With and Without Nodules at Onset: Comparison of Hormonal and Antibody Patterns*

	No. of Patients	FT ₃ , pmol/L (pg/dL)†	FT ₄ , pmol/L (ng/dL)†	FT ₃ /FT ₄ Ratio†	TSH, mIU/L	TRAb, U/L‡	Ophthalmopathy, No. (%)
With nodules	49	27.3 \pm 17.6 (1773 \pm 1143)	51.4 \pm 28.0 (4.0 \pm 2.2)	0.53 \pm 0.1	0.13 \pm 0.10	26 (5-135)	8 (16)
Without nodules	266	25.7 \pm 13.6 (1669 \pm 883)	55.8 \pm 28.8 (4.3 \pm 2.4)	0.46 \pm 0.2	0.09 \pm 0.07	22.2 (5-405)	44 (17)

*FT₃ indicates free triiodothyronine; FT₄, free thyroxine; TSH, thyroid-stimulating hormone; and TRAb, TSH receptor antibodies. $P > .05$ for all comparisons.

†Mean \pm SD.

‡Median (range).

tomy. The difference between pathologically and clinically identified thyroid carcinomas is well known. While thyroid microcarcinomas are found in 5% to 36% of adults at autopsy, clinically detectable thyroid carcinomas constitute less than 1% of all human cancers, while the annual incidence rate in various parts of the world ranges from 0.5 to 10 cases per 100 000.²⁸ The possibility of a bias related to the pathological examination of the excised thyroid is supported by studies in which the incidence of carcinoma can be compared between patients with Graves disease who have undergone thyroidectomy and those who have not undergone surgery. Behar et al³ found thyroid carcinoma in 10 (5.2%) of 194 patients who underwent thyroidectomy, but only 1 (0.3%) of 303 patients treated with radioiodine therapy developed thyroid carcinoma during a 9-year follow-up. Pacini et al⁴ found thyroid carcinoma in 6 (7%) of 86 patients with Graves disease who underwent thyroidectomy, but among 1137 patients treated with methods other than surgery, only 1 developed thyroid carcinoma. In the same study, 4 (22%) of 18 patients with Graves disease and palpable thyroid nodules had carcinoma, while none of the 147 patients who did not undergo surgery developed thyroid carcinoma during 15 years of follow-up.

A possible role of TRAb in the development and the progression of thyroid cancer was suggested on the basis of in vitro experiments²⁹ and confirmed in clinical studies by Belfiore et al⁶ and Ozaki et al⁵ but not by others.^{13,18} We cannot draw any conclusion on this point on the basis of our series. However, we did consider the possible relationship between TRAb levels and the presence of nodules in patients with Graves disease and found no significant increase of TRAb levels preceding or accompanying the growth of nodules.

In view of the conflicting evidence on the frequency and heightened aggressiveness of thyroid carcinoma in patients with Graves disease, a surgical approach has been empirically suggested when a cold nodule is found.^{30,31} Our study indicates that thyroid ultrasonography can reveal nodules in a significant number of patients with Graves disease that are free of malignancy when FNA cytologic evaluation is performed; even in patients with large, cold nodules, the risk of malignancy appears reasonably low. On the basis of our experience, in patients with Graves disease as well as other patients with thyroid nodules, thyroid ultrasonography provides information on the size, structure, and evolution of the nodules; however, thyroid nodules incidentally discovered when ultrasonography is performed have limited clinical relevance. Therefore, thyroid ultrasonography appears to provide limited information in the evaluation of patients with Graves disease.

In conclusion, when FNA cytologic findings do not suggest or reveal malignancy, the coexistence of nodules and Graves disease does not indicate a more severe prognosis, nor does it warrant shifting to an unnecessarily aggressive surgical approach for lesions that are likely to follow a benign course.

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