Thyroid Cancer Prevalence After Radioiodine Treatment of Hyperthyroidism

Tiziana Angusti, Alessandra Codegone, Riccardo Pellerito, and Alessandro Favero

Unità Operativa Autonoma di Medicina Nucleare, Dipartimento di Oncologia, Ospedale Mauriziano Umberto I Torino, Torino, Italy

The definitive treatment of hyperthyroidism in Europe is quite different from that in the United States. In Europe, the surgical approach is often preferred and considered safer than radioiodine treatment. European doctors usually prefer to surgically remove the thyroid and perform a pathologic examination of it. They consider it to be an essential diagnostic tool to identify possible diseases that might be associated with hyperthyroidism and even to detect the rare thyroid tumors that might be associated with thyroid hyperfunction. The aim of this study was to evaluate whether radioiodine therapy could be a risk factor for the misdiagnosis of thyroid cancer. **Methods:** We performed a retrospective revision of data we collected from 6647 patients (1171 [17.5%] men, 5476 [82.5%] women), all of whom underwent ^{131}I therapy for hyperthyroidism from 1970 to 1997. Of the whole group, 6.5% were younger than 40 y, 33.5% were 40–60 y old, and 60% were older than 60 y. Moreover, 5061 (76%) patients had either an autonomously functioning node or a toxic multinodular goiter. The other 1586 (24%) patients had Graves' disease. **Results:** After treatment, thyroid cancer was discovered in 10 (0.15%) patients, none of whom belonged to the group of patients with Graves' disease. Five of these patients were treated during a period from 1970 to 1980, when sonography was not routinely available. The incidence of thyroid cancer in the series of radioiodine-treated patients (150/100,000 over a 27-y period) was not significantly different from its incidence in the general population. The expected rate is 124.88 per 100,000 over a 27-y period. **Conclusion:** An accurate preliminary evaluation (clinical examination, sonography, and cytologic evaluation of fine-needle aspiration) is fundamental for a proper choice between radioiodine and surgical therapy.

Key Words: hyperthyroidism; radioiodine treatment; thyroid cancer

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The definitive treatment of hyperthyroidism is still a matter of debate. Some European doctors consider surgery the treatment of choice because it drastically resolves hyperthyroidism and implies a lower rate of relapse. Moreover, surgery permits the possibility of making a neck exploration and pathologically evaluating thyroid specimens to rule out the presence of associated disorders and unexpected thyroid tumors.

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For correspondence or reprints contact: Alessandro Favero, MD, Department of Nuclear Medicine, Mauriziano Hospital, Corso Turati 46, Turin 10128, Italy.

Recently, increasing attention has been focused on the possible presence of thyroid cancer associated with either Graves' disease or autonomously functioning nodules (AFNs). A high prevalence (3.3%–19%) of occult tumors has been found in the thyroid glands that were examined after a thyroidectomy had been performed for hyperthyroidism (*1,2*).

On the other hand, surgical treatment may be associated with the risks of anesthesia and surgery, which can be either immediate (hemorrhage and vocal cord paralysis) or late (hypoparathyroidism). In the case of AFNs treated by surgery, hypothyroidism can be considered an adverse effect. Alternatively, hypothyroidism represents the goal in the case of Graves' disease or multinodular goiter (MNG). The rate of hypothyroidism associated with surgery for AFNs can be considerable, as reported by Ferrari et al. (*3*) and others (*4*). Furthermore, surgery is more expensive than other nonsurgical treatments (^{131}I therapy and percutaneous ethanol injection therapy) (*5,6*).

In Europe, in the case of hyperthyroidism, radioiodine treatment is considered a second option. On the contrary, in the United States, this is the treatment of choice unless there are specific contraindications, such as previous neck irradiation or suspicious nodules. Radioiodine administration is also preferred because it does not require hospitalization and is generally well tolerated. It has an adequate success rate, a low incidence of side effects, and a lower cost than surgery (*7*). Moreover, additional doses can be administered until the euthyroid condition is achieved. The late development of hypothyroidism has been reported as a side effect after this kind of treatment of AFNs, but its incidence is not significantly different from that of surgical treatment (*3*).

Over the past decades, it has been speculated that radioiodine administration could lead to a higher incidence of thyroid tumors because external neck radiation is considered a risk factor for thyroid cancer (*8*). However, no increase in the relative risk of thyroid cancer was reported in patients who underwent radioiodine therapy for hyperthyroidism (*9*).

Nevertheless, even if thyroid cancer is not frequently associated with hyperthyroidism, thyroid cancer might be underestimated after radioiodine therapy. For instance, after successful radioiodine therapy, AFNs might still be detectable on clinical examination and appear as nodes without significant levels of radioactivity on scintigrams. Further-

more, both sonography and cytologic examination of fine-needle aspiration biopsy display a suspicious pattern after radioiodine therapy (*10,11*). On this basis, one could question whether a diagnosis of cancer might be missed or whether it might be delayed after radioiodine therapy for hyperthyroidism.

To assess the prevalence of unsuspected thyroid cancers and their clinical relevance, we performed a retrospective study on a large cohort of patients who had undergone radioiodine treatment for hyperthyroidism.

MATERIALS AND METHODS

We reviewed the data of 6647 consecutive patients (1171 [17.5%] men, 5476 [82.5%] women), all of whom received a radioiodine treatment for Graves' disease, AFNs, or toxic MNG from 1970 to 1997. Of the whole group, 432 (6.5%) were younger than 40 y, 2232 (33.5%) were 40–60 y old, and 3983 (60%) were older than 60 y. Among them, 5061 (76%) patients had either an AFN or a toxic MNG, and the remaining 1586 (24%) patients had Graves' disease.

The ^{131}I dose that was administered had been calculated on the basis of the assessment of the thyroid's volume through clinical examination as well as the 24-h uptake of ^{131}I and the effective biologic half-life ($t_{1/2}$). The dose range was 185–740 MBq (5–20 mCi). Of the whole group, 962 (14.5%) patients needed a second ^{131}I dose, and 312 (4.7%) needed 3 or more doses.

Each patient underwent a follow-up protocol that consisted of a clinical examination and a serum measurements of free triiodothyronine (FT_3), free thyroxine (FT_4), thyroid-stimulating hormone (TSH), thyroid peroxidase antibody, and thyrotoxin receptor antibody. This same protocol was followed 3 times, at 3, 6, and 12 mo after the treatment. Thereafter, we repeated the clinical evaluation and the FT_3, FT_4, and TSH measurements once a year.

The follow-up period ranged from 3 to 25 y (median, 7 y). Ten percent of the patients were lost to follow-up. The incidence of thyroid malignancies in the radioiodine-treated group was compared with the incidence in the general Italian population. We obtained the latter value from the database of EUCAN90 (International Agency for Research on Cancer, 1996) (*12*) and calculated this value over a 27-y period. Comparison was made using the χ^2 test. Statistical analysis was performed using the Windows version of the STATISTICA program (release 4.5, 1993; StatSoft, Inc., Tulsa, OK).

RESULTS

Thyroid cancer was diagnosed in 10 (0.15%) patients during the follow-up period. This percentage is not significantly different from that observed in the general population ($P = 0.7$ by χ^2 test), independently of age. The characteristics of patients affected by thyroid malignancy are summarized in Table 1. Five (50%) of 10 patients were ≥65 y old.

Five patients (patients 1, 2, 4, 6, and 7) were treated for toxic goiter, whereas the other 5 patients (patients 3, 5, and 8–10) had an AFN. None of these patients was treated for Graves' disease. In 3 of the 5 patients (patients 3, 9, and 10) who were treated for an AFN, cancer developed in the opposite lobe, whereas in patient 8 cancer arose from the same lobe of the AFN. The fifth patient (patient 5) can probably be classified as having a hot cancer (Fig. 1). This patient became euthyroid after the radioiodine therapy, whereas the node that had been hyperfunctioning was still detectable. He had been free of disease for 5 y. The node suddenly increased in size and became painful. A near-total thyroidectomy was then performed. Pathologic examination showed a poorly differentiated mixed papillary-follicular thyroid carcinoma within the node that was previously functioning autonomously as well as lymph node involvement. Staging after surgery also reflected bone metastases on the sacrum, the left hemipelvis, and the body of T11. He died of an arrhythmia 3 d after the administration of 3.7 GBq ^{131}I for ablation of thyroid remnants (Fig. 2).

No relationship was found between the less differentiated

TABLE 1
Characteristics of Patients with Thyroid Malignancy

Patient no.	Sex	Disease	Year of treatment	Age at ^{131}I treatment (y)	Dose (MBq)	Time between treatment and cancer diagnosis (y)	Pathology
1	F	MNG	1990	70	407	7	Follicular pT4
2	F	Toxic MNG	1981	38	407	11	Mixed Hürthle-papillary pT1
3	F	Hot node, right	1989	78	740	2	Anaplastic* pT4
4	F	Toxic MNG	1976	68	444	14	Follicular poorly differentiated pT4
5	M	Hot node, left	1980	54	814	7	Mixed papillary-follicular
6	F	Hot node in MNG	1972	62	814	6	Anaplastic follicular
7	M	Toxic MNG	1972	60	629	8	Medullary
8	M	Hot node, right	1989	65	296	6	Hürthle pT4
9	F	Hot node, left	1987	65	222	10	Follicular Hürthle pT4
10	F	Hot node, right	1969	56	814	13	Follicular pT4 pN1 pM+
Median†				63.5 (38–78)	518 (222–814)	7.5 (2–14)	

*Anaplastic thyroid carcinoma.
†Range in parentheses.

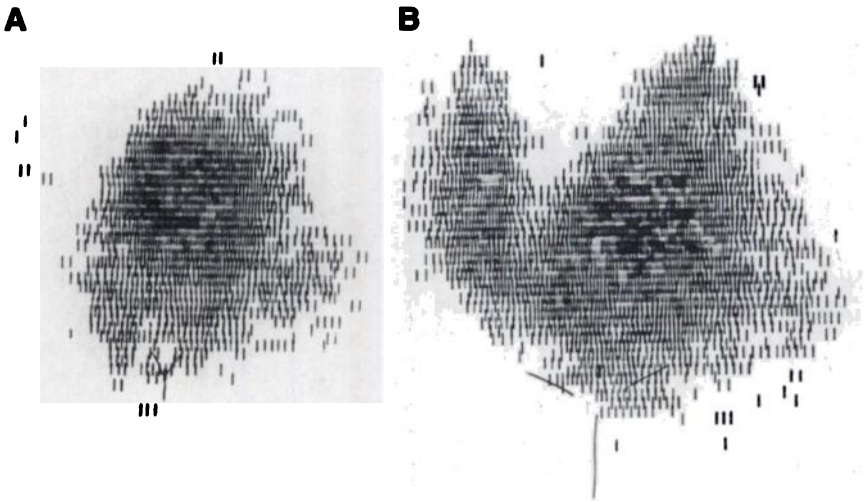

FIGURE 1. Rectilinear thyroid ^{131}I scan of patient 5. (A) Hot nodule on left lower pole. Extranodal thyroid tissue is suppressed. (B) Extranodal thyroid tissue becomes evident after TSH stimulation.

neoplasms and the period of time after the treatment in which these cancers developed. Also, the young age, during the treatment period, did not seem to represent a risk factor for the development of cancer.

In addition, pathologic examination revealed a great prevalence (7/10) of follicular tumors, whereas papillary thyroid cancers were not present if 1 patient (patient 5) with poorly differentiated mixed papillary-follicular carcinoma is excluded. Five patients (patients 3–5, 7, and 10) died of thyroid cancer soon after the diagnosis of malignancy (within 1 y). Among these 5 tumors, 3 were follicular carcinomas (2 were poorly differentiated and 1 was classified as pT4). One of the 5 tumors was a medullary carcinoma (patient 7), and the fifth tumor was anaplastic (patient 3). Four of the initial group of 10 patients are still alive, and the median follow-up is 2 y. The last patient was lost to follow-up in 1983.

FIGURE 2. Rectilinear thyroid ^{131}I scan of patient 5 shows thyroid remnants after thyroidectomy for thyroid cancer.

DISCUSSION

The frequency of the concurrence of thyroid carcinomas and hyperthyroidism has been reported to vary from 2% to 19% (*1,10*). In an autopsy series, the prevalence of occult thyroid tumors was reported to be about 13% (*13*). Most of these occult tumors usually remain clinically silent for an entire lifetime. Moreover, the association between thyroid carcinoma and Graves' disease was reported to be 10 times higher in patients who underwent surgery than in patients who were treated with ^{131}I (*14*). The explanation for this might rely on an effective destruction of small cancerous foci as a consequence of the ^{131}I therapy.

The incidence of clinically evident thyroid cancers in the general population is considerably lower than is the incidence of occult cancers (*15*). On this basis, one could speculate that the incidental finding of a neoplastic focus during an autopsy does not imply that this tumor would have had clinical consequences.

The widespread use of sonographic and fine-needle aspiration techniques has led to an increase of sensitivity in the early diagnosis of thyroid tumors. We can hypothesize that if these techniques had been available, they would have enabled us to detect the neoplastic evolution in patients 4–7 and 10. Also, their use could have favorably influenced the clinical course of the disease in these patients.

The prevalence of thyroid cancer in the overall population is estimated to be 4.625 per 100,000 per year; in a period of 27 y we would expect $4.625 \text{ per } 100{,}000 \times 27 = 124.88$ per 100,000 cases. In our series, this figure is 150 per 100,000, a rate that is not statistically different from the former ($P = 0.7$ on χ^2).

We also must consider that we work in Piedmont, an Italian region in which the average prevalence of goiter is high but not uniformly distributed. Similarly, in Italy, the prevalence of thyroid diseases and goiter is not uniform, even if not known exactly. Contrary to all expectations, supplementation of iodine is insufficient in many areas in

Italy. For this reason, in this country, the prevalence of goiter is definitely higher than is its occurrence in Northern Europe and in the United States. As a consequence, we treated more patients with toxic goiter (76%) than patients with Graves' disease (24%).

In a large series of thyroid tumors, we observed that most of them (1414/2012 [70.3%]) developed in the context of MNG (*16*). If we compare goiter endemic regions with regions that are not endemic, a higher prevalence of follicular or less differentiated carcinomas has been reported (*17*).

In this series, thyroid malignancies are mainly follicular carcinomas, and the most probable explanation is that this is more related to the high prevalence of goiter among our patients (*18*) rather than to radioiodine treatment. Moreover, this finding could explain the absence of papillary neoplasms in our series, even if this absence is fortuitous.

As reported by others (*14*), our data highlight the absence of cancers associated with Graves' disease. This finding is consistent with an effective destruction of small cancerous foci, which might be a consequence of ^{131}I therapy.

CONCLUSION

As far as the possibility of misdiagnosis of associated thyroid cancer is concerned, we conclude that ^{131}I therapy for hyperthyroidism is a safe procedure to treat Graves' disease. Alternatively, with respect to AFNs and MNG, attention must be focused on the presence of nodes with suspicious patterns. An accurate clinical work-up through physical examination, sonography, and cytologic evaluation on fine-needle aspiration should permit the selection of patients who could benefit from a surgical treatment.

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