



ORIGINAL ARTICLE

The risk of recurrence within the first five years is very low in patients with papillary thyroid carcinoma treated with radioiodine

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Abstract

Introduction: In older studies, the frequency of recurrence was approximately 20% among patients with papillary thyroid carcinoma (PTC) treated with radioactive iodine (RAI), but it is possible that many of these cases actually correspond to persistent disease and that the frequency of recurrence is overestimated. **Objective:** To reevaluate the frequency of recurrence within the first five years in patients with PTC adequately operated upon and treated with RAI who did not exhibit persistent disease (postoperative ultrasonography and post-therapy whole-body scanning showing no apparent tumor). **Methods:** We selected 293 patients [51 low risk (17.4%) and 242 intermediate risk (82.6%)] submitted to thyroidectomy followed by RAI who did not have persistent disease. **Results:** Five years after RAI therapy, a tumor was detected in 10 patients (3.4%) (lymph node metastases in seven, pulmonary metastases in two, and bone metastases in one). Structural recurrence was observed in only 2% of low-risk patients and in 3.3% of intermediate-risk patients, with disease progression in none of the low-risk patients and in only one (0.4%) of the intermediate-risk patients. Survival was 100%. **Conclusion:** The results of this study suggest that, after adequate total thyroidectomy and in the absence of persistent disease, the frequency of recurrence within the first five years is very low in patients with PTC (not high risk) treated with RAI.

Keywords: carcinoma; papillary; follicular; ultrasonography; doppler; whole body imaging.

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Introduction

In patients with papillary thyroid carcinoma (PTC) in whom tumor resection was macroscopically complete and who do not exhibit an apparent tumor in the short term after surgery, subsequently diagnosed disease is defined as recurrence¹⁻³. Older studies report a frequency of recurrence of approximately 20% in patients treated with radioactive iodine (RAI)³⁻⁵. Routine post-therapy whole-body scanning (RxWBS) has shown that many metastases, which would probably only be detected later as recurrence, can already be diagnosed on the occasion of RAI administration as persistent disease². This sensitivity of RxWBS is optimized after adequate total thyroidectomy with discrete thyroid remnants^{6,7}. More recently, postoperative ultrasonography (US) was found

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to be able to identify cervical metastases not apparent on RxWBS⁸⁻¹⁰, also defined as persistent disease that would probably only be diagnosed later as recurrence. Although these imaging methods are already recommended¹¹, few studies have submitted a large number of patients to routine postoperative US (before RAI) and reported the frequency of recurrence specifically in those without persistent disease⁹. Thus, it is possible that many cases of recurrence among patients with PTC treated with RAI actually correspond to persistent disease and that the frequency of recurrence is overestimated.

The objective of this prospective study was to reevaluate the frequency of recurrence within the first 5 years in patients with PTC adequately operated upon and treated with RAI who did not exhibit persistent disease, including postoperative US and RxWBS in this definition.

Material and methods

Patients

This was a prospective study. The patients were treated at our service between 2006 and 2014. During this period, and until today, patients with PTC are routinely evaluated 3-4 months after surgery by US/Doppler. Patients submitted to total thyroidectomy followed by RAI, who did not have persistent disease according to the criteria in Table 1, were first selected. Patients with poorly differentiated carcinoma and extensive extrathyroid invasion (pT4) were excluded. Patients with antithyroglobulin antibodies (TgAb) were also excluded. Once included in the study, the patients were followed up for 5 years after RAI as described below.

Table 1. Definition of absence of persistent disease.

Macroscopically complete tumor resection in the neck reported by the surgeon
Clinical examination 3 months after surgery without suspicion of metastases
Uncompromised surgical margins
Chest X-ray obtained before or up to 3 months after surgery without distant metastases
Neck US/Doppler 3-4 months after surgery without abnormalities (see Methods)
RxWBS with uptake in the thyroid bed < 2% ^{6,7} and without ectopic uptake

US = Ultrasonography; RxWBS = Posttherapy whole body scanning.

The patients were submitted to ablation with RAI after levothyroxine withdrawal for 4 weeks or administration of recombinant human TSH (rhTSH) and administration of a low-iodine diet for 10 days prior to the procedure. Thirty, 50 or 100 mCi was administered. Anterior and posterior whole-body images were obtained 7 days after ablation with RAI (RxWBS).

Follow-up

The patients were evaluated 12 months after RAI administration by the measurement of unstimulated Tg (u-Tg), TgAb, and neck US. Imaging methods other than US [neck, chest and mediastinal computed tomography (CT),

fluorodeoxyglucose-positron emission tomography (FDG-PET)/CT] were performed if u-Tg \geq 1 ng/ml. The patients were followed up by clinical examination, measurement of u-Tg and TgAb at intervals of 6-12 months, and annual neck US. Imaging methods other than US (CT, FDG-PET/CT, RxWBS) were performed when u-Tg \geq 1 ng/ml. The time of follow-up was 60 months in all patients.

Imaging methods

US/Doppler was defined as negative in the absence of lymph nodes with (i) microcalcification, (ii) cystic degeneration, (iii) peripheral hypervascularization, or (iv) without a hilum with a long axis/short axis $<$ 2, and in the absence of a vascularized nodule in the thyroid bed^{12,13}. All suspected lesions apparent on the scans were evaluated by US-guided fine needle aspiration (cytology and Tg). CT with contrast was performed on 5-mm sequential sections. FDG-PET/CT was carried out after stimulation with rhTSH. All images were analyzed by experienced Radiology or Nuclear Medicine specialists.

Structural disease was defined based on the results of the imaging methods, cytology or histology, and/or unequivocal ectopic uptake (excluding false-positive results) on RxWBS or FDG-PET/CT.

Assays

Chemiluminescent assays were used for the measurement of Tg [Access Thyroglobulin Assay, Beckman Coulter, Fullerton, CA (functional sensitivity of 0.1 ng/ml)¹⁴] and TgAb [Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA (reference value of up to 40 IU/ml) or ARCHITECT Anti-Tg, Abbott Laboratories, IL, USA (reference value of up to 4.11 IU/ml)].

Results

A total of 293 patients met the selection criteria (Table 1), i.e., they did not have persistent disease, including 226 women (77.1%) and 67 men (22.9%) ranging in age from 16 to 78 years (mean 49 years). Fifty-one patients (17.4%) were classified as low risk¹¹ (none of them with microcarcinoma or with the noninvasive encapsulated follicular variant of papillary thyroid carcinoma [EFVPTC]¹⁵) and 242 (82.6%) as intermediate risk according to the American Thyroid Association¹¹.

Over the 5 years after RAI, structural disease was detected in 10 patients (3.4%) (cervical metastases in six, pulmonary metastases in two, mediastinal metastases in one, and bone metastases in another). The metastases were detected by US in four patients, by FDG-PET/TC in three, by CT and FDG-PET/CT in two, and by CT and RxWBS in one patient.

In addition to being maintained under TSH suppression, five of the patients with structural disease were treated exclusively with surgery, one with surgery and lymph node alcoholization, one exclusively with RAI, one with external radiotherapy and bisphosphonate, and one was only kept under observation. Finally, one patient is a candidate for treatment with tyrosine kinase inhibitor. At the end of the 5 years, five patients still had persistent

disease but progression was observed in only one and four had stable disease or a partial response. There was no death related to the disease.

Thus, in the first 5 years after RAI therapy, among patients adequately operated upon and without persistent disease, recurrence was observed in only 2% of low-risk patients and in 3.3% of intermediate-risk patients. Disease progression was not observed in any of the low-risk patients and in only one (0.4%) of intermediate-risk patients. Survival was 100%. Noteworthy, two patients had negative US and RxWBS but disease was detected already in the first year after RAI by FDG-PET/CT. According to some authors, these cases can also be considered persistent disease¹⁶.

Discussion

In the absence of persistent disease, the frequency of recurrence in the first 5 years among patients with PTC adequately operated upon and treated with RAI was very low in the present study. We attribute these results to the following facts. In addition to the surgical report, histology and clinical examination, postoperative US and RxWBS were also used to define persistent disease. RxWBS was always recommended after RAI therapy¹¹ and postoperative US (before RAI) is also currently recommended^{9,10}. US was performed by an experienced professional, was not obtained immediately after surgery to reduce the risk of artifacts that would compromise adequate assessment of the neck^{8,9,17}, and a criterion that previously showed high sensitivity was adopted to define negative US¹³. All patients were submitted to adequate total thyroidectomy, demonstrated by uptake in the thyroid bed < 2%. In addition to indicating the quality of surgery, this finding increases the sensitivity of RxWBS^{6,7}. On the other hand, we emphasize that SPECT/CT was not performed as currently preferred¹¹, which theoretically could increase sensitivity and further improve the negative predictive value of the initial evaluation.

Although the patients were only followed up for 5 years after RAI, it is known that most recurrences occur during this period^{1,4,5,18,19}. Furthermore, in older studies, even with most patients being low risk, the recurrence rate had already reached 10% five years after initial therapy^{4,5}. Therefore, although new recurrences are likely, we believe that the frequency will still be low, for example after 10-20 years. The few low-risk patients included had tumors > 1 cm, none had noninvasive EFVPTC¹⁵, and even separate analysis of intermediate-risk patients revealed a very low frequency of recurrence (3%). The follow-up protocol also appeared to be adequate because all patients with u-Tg ≥ 1 ng/ml were submitted to additional imaging methods and only in those who continued to have u-Tg < 1 ng/ml throughout follow-up were these methods not performed, but even these patients were evaluated by annual US. However, we recognize that the results cannot be extrapolated to high-risk patients¹¹.

In the only previous study of our knowledge in which postoperative US was routinely obtained in a significant number of patients, 16/468 patients (3.4%) with negative US and RxWBS without ectopic uptake developed recurrences after 6 to 170 months (median 42 months)⁹. Although that study was retrospective, with the limitations inherent to this design, all patients were

high or intermediate risk and the study agrees with our results of a very low frequency of recurrence after RAI when patients without persistent disease are specifically analyzed.

The results of the present study have some implications. First, in agreement with other studies^{2,9}, the findings suggest that most part of the structural disease detected in patients with PTC is already present at the time of RAI administration, reinforcing the importance of adequate surgery and the possibility that tumor persistence is detected early. Second, in the absence of apparent persistent disease, the recurrence risk after RAI seems to be much lower than traditionally reported³⁻⁵, especially in intermediate-risk patients. This offers the prospect that a less rigorous and less costly follow-up protocol is sufficient in these patients (intermediate risk without persistent disease). Third, also due to the low frequency of recurrence seen in intermediate-risk patients, application of the current risk stratification¹¹ could be revised since it does not distinguish persistent from recurrent disease and may be a better predictor of the former rather than the latter.

We did not evaluate patients not treated with RAI and we therefore cannot state the contribution of this therapy to the low frequency of recurrence observed here. Nevertheless, the results suggest that a good number of cases of the disease detected after initial therapy would be due to the non-treatment of persistent disease with RAI and not to its inefficiency in preventing recurrence. Nevertheless, we recognize that the above questions can only be answered with randomized studies comparing patients treated with RAI versus untreated patients.

Another limitation of the present study was the lack of postoperative Tg measurement, a parameter that could refine the recurrence risk, which may even be lower if, for example, postoperative Tg is < 2 ng/ml^{20,21}, or identify a higher risk subgroup if, for example, Tg is > 10 ng/ml^{9,20}. This factor may be as or more important than the current stratification in predicting recurrence in patients without persistent disease.

Conclusion

The results of this study suggest that, after adequate total thyroidectomy and in the absence of persistent disease, the frequency of recurrence within the first 5 years is very low in patients with PTC (not high risk) treated with RAI.

Compliance with Ethical Standards

The study was approved by the local Research Ethics Committee (CAAE 21968013.8.0000.5138 / Number 411.326) and the subjects gave written informed consent.

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