Should a family history of papillary thyroid carcinoma indicate more aggressive therapy in patients with this tumor?

História familiar de carcinoma papilífero de tireoide deve indicar terapia mais agressiva em pacientes com este tumor?

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ABSTRACT

Objective: To determine whether the currently recommended therapy for papillary thyroid carcinoma (PTC) that show no classical factors indicating a poor prognosis is also effective in cases with a family history of this tumor. Subjects and methods: Forty-two patients were studied; 10 were submitted to lobectomy and 32 to total thyroidectomy, including 23 without lymph node dissection and 9 with lymph node dissection. None of the patients received radioiodine or was maintained under TSH suppression. Results: No case of recurrence was detected by imaging methods and there was no increase in thyroglobulin or antithyroglobulin antibodies during follow-up (24 to 72 months). Conclusion: The treatment usually recommended for patients with PTC does not need to be modified in the presence of a family history of this tumor if no factors indicating a poor prognosis are present (tumor ≤ 2 cm, non-aggressive histology, no extensive extrathyroid invasion or important lymph node involvement, complete tumor resection, no evidence of persistent disease after surgery). Arq Bras Endocrinol Metab. 2014;58(8):812-6

Keywords
Papillary thyroid carcinoma; familial history; radioiodine; TSH supression; elective lymph node dissection

RESUMO

Objetivo: Avaliar se a terapia atualmente recomendada para o carcinoma papilífero de tireoide (CPT) sem fatores clássicos de pior prognóstico é efetiva também nos casos em que existe história familiar deste tumor. Sujeitos e métodos: Foram avaliados 42 pacientes; dez foram tratados com lobectomia e 32 com tireoidectomia total, sendo 23 sem dissecção de linfonodos e 9 com dissecção linfonodal. Nenhum paciente recebeu radioiodo ou foi mantido com TSH suprimido. Resultados: Nenhuma recidiva nos métodos de imagem foi observada, nem incremento da tireoglobulina ou anticorpos antitireoglobulina durante o seguimento (24 a 72 meses). Conclusão: Em pacientes com CPT, sem fatores de pior prognóstico (tumor ≤ 2 cm, histologia não agressiva, sem invasão extratireoidiana extensa ou acometimento linfonodal importante, ressecção tumor completa, sem indícios de doença persistente após a cirurgia), o tratamento usualmente recomendado não precisa ser modificado quando há história familiar desse tumor. Arq Bras Endocrinol Metab. 2014;58(8):812-6

Descritores
Carcinoma papilífero de tireoide; história familiar; radioiodo; supressão do TSH; dissecção linfonodal eletiva
INTRODUCTION

Traditionally, the definition of recurrence risk in patients with papillary thyroid carcinoma (PTC) is based on histological data (size, number of foci and subtype of the tumor; extrathyroid and vascular invasion; metastases) and tumor resection (1-4). Some studies suggested the diagnosis of PTC in a relative(s) to be a risk factor for recurrence (5-10). Since this information has not been included in risk stratification (1-4) and one of the main objectives of this stratification is to guide therapy, it is important to know whether the diagnosis of PTC in a first-degree relative would influence (or modify) the current therapeutic recommendations.

With respect to treatment of PTC, there is agreement that total thyroidectomy is the most adequate initial procedure (1-4). In the presence of clinically apparent metastases (cN1), therapeutic lymph node dissection is also consensus (1-4). Similarly, treatment or adjuvant therapy with 131I and TSH suppression have been recommended for patients with incomplete tumor resection, persistent disease, or high risk for recurrence (1-4). Obviously, a family history does not modify these managements. Therefore, the controversy regarding the possible importance of family history for therapy lies in subjects who are at low risk of recurrence and for whom elective cervical lymph node dissection, ablation with 131I or TSH suppression have not been recommended (1-4).

The objective of this prospective study was to determine whether the currently recommended therapy for patients with PTC who show no classical factors indicating a poor prognosis (no cervical lymph node dissection, ablation with 131I or TSH suppression) is also effective when they have a family history of this tumor.

SUBJECTS AND METHODS

First, 723 siblings of 447 patients with PTC (a single case in the family until that time) were screened by ultrasonography (US) (11). This screening resulted in the diagnosis of PTC in one additional relative in 21 families and in two additional relatives in 11 families (11). These 43 cases detected by US screening were included in this prospective study. Family syndromes associated with PTC such as familial adenomatous polyposis, Gardner’s syndrome, Cowden disease, Werner’s syndrome, and Carney’s complex were excluded in all patients.

The extent of surgery was defined according to the criteria shown in table 1. Ten patients were submitted to lobectomy, 23 to total thyroidectomy without lymph node dissection, and 10 to total thyroidectomy and lymph node dissection.

In patients undergoing lobectomy, measurement of serum thyroglobulin (Tg) and anti-Tg antibodies (TgAb) during therapy with levothyroxine (L-T4) and neck US were performed 6 months after surgery and then annually.

In patients treated with total thyroidectomy, ablation with 131I was indicated according to the algorithm shown in figure 1. Only one patient received radioiodine due to the presence of 5 metastatic lymph nodes. This patient was excluded from the study. One year after total thyroidectomy, the patients were evaluated according to the algorithm shown in figure 2. After, the patients were followed up by serum measurement of basal Tg and TgAb and annual US.

Figure 1. Criteria for indication of 131I after total thyroidectomy.

Figure 2. Criteria for therapy after total thyroidectomy and therapeutic lymph node dissection.
The time of follow-up ranged from 24 to 72 months (median 50 months). The imaging methods did not detect apparent metastases in any of the patients during follow-up after surgery. The behavior of tumor markers (Tg and TgAb) during follow-up are shown in table 3.

### Table 3. Behavior of tumor markers (Tg and TgAb) during follow-up

<table>
<thead>
<tr>
<th>Initial surgery</th>
<th>Results of last assessment</th>
<th>Behavior of tumor markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobectomy (n = 10)</td>
<td>Negative TgAb and basal Tg &gt; 1 ng/mL (n = 8)</td>
<td>Tg reduction &gt; 30% compared to Tg 6 months after surgery</td>
</tr>
<tr>
<td>Positive TgAb and undetectable basal Tg (n = 2)</td>
<td>TgAb reduction &gt; 50% compared to the titers found 6 months after surgery</td>
<td></td>
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<tr>
<td>Total thyroidectomy with or without lymph node dissection (n = 32)</td>
<td>Negative TgAb and basal Tg &gt; 0.2 ng/mL (n = 11)</td>
<td>Initial stimulated Tg ≤ 1 ng/mL (n = 3) → Tg declining compared to Tg obtained 1 year after surgery. Last stimulated Tg was &lt; 2 ng/mL in 2 patients and 3.1 ng/mL in the othera</td>
</tr>
<tr>
<td>Positive TgAb and undetectable basal Tg (n = 3)</td>
<td>TgAb reduction &gt; 50% (n = 2) or stable TgAb (n = 1b) compared to the titers found 1 year after surgery</td>
<td></td>
</tr>
</tbody>
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- a US, CT and FDG-PET/CT, repeated in the last assessment, did not reveal disease.
- b US and CT repeated at the end of the study were negative for metastases.

### RESULTS

Thirty of the 42 patients included were women and 12 were men. Patient age ranged from 14 to 67 years (mean 35 years). TNM stage and risk stratification are shown in table 2. With respect to tumor size > 1 cm, multicentricity, extrathyroid invasion and clinically apparent lymph node metastases (cN1), 30 patients presented at least one finding and 14 had at least two of these findings.

All patients were maintained on an L-T4 dose sufficient to obtain TSH levels of 0.3 to 2 mIU/L. The study was approved by the Research Ethics Committee of our Institution.

Tg was measured by a chemiluminescent assay (Access Thyroglobulin Assay, Beckman Coulter, Fullerton, CA) with a functional sensitivity of 0.1 ng/mL. TgAb was measured by a chemiluminescent assay (Immulite 2000, Diagnostic Products Corporation, Los Angeles, CA) or ARCHITET Anti-Tg, Abbott Laboratories, IL (functional sensitivity of up to 4.11 IU/mL).

US was performed with a linear multifrequency 14 MHz transducer for morphological analysis and for power Doppler evaluation. US was defined as negative when no suspicious lesions were detected (12,13) or, in the presence of these lesions, when cytology and Tg measurement in the needle washout fluid obtained by US-guided fine-needle aspiration were negative. Chest and mediastinal computed tomography (CT) was performed on 5-mm sequential sections. FDG-PET/CT was carried out after stimulation with recombinant human TSH.

Figure 2. Assessment 1 year after total thyroidectomy.
DISCUSSION

Some studies have shown a higher risk of recurrence in the case of family aggregation of PTC compared to sporadic PTC (5-10), but this observation is not confirmed in all studies (14-20). There is even greater controversy to know whether the possible increased risk is due to the more aggressive initial presentation or whether a family history itself is an independent risk factor for recurrence (14). This information is important to define whether patients with a family history of PTC require more aggressive treatment than the one usually recommended, as proposed by some authors (6,21,22). More aggressive therapy (including 131I and TSH suppression) is already recommended for patients with incomplete tumor resection, persistent disease immediately after surgery or high risk of recurrence, irrespective of family history (1-4). Therefore, the controversy is restricted to cases that show no classical factors indicating a poor prognosis, which was the objective of this prospective study. The present results suggest that the common recommendation of total thyroidectomy without elective lymph node dissection, ablation with 131I or TSH suppression seems to be sufficient in these patients, even in the presence of a family history of PTC (1-4). Based on the characteristics of the patients included in the study, this conclusion only applies to those presenting the criteria shown in table 4, which were observed in all of them.

Table 4. Prognostic factors observed in all patients included in the study

| Tumor ≤ 2 cm | Non-aggressive histology | Absence of extensive extrathyroid invasion | < 5 lymph nodes affected and no metastases ≥ 3 cm | Apparently complete tumor resection | No signs of persistent disease immediately after surgery |

Another doubt is related to the question whether a poor prognosis of PTC exists only when three or more relatives are affected (5,7). Studies have shown a more aggressive behavior of the tumor even when there are only two relatives affected (6-10). In the present series, no recurrence was observed even in patients of families with three affected relatives.

The present study has some limitations. The first is the small number of patients included, but the lack of recurrence minimizes the relevance of sample size. The second limitation is the time of follow-up; however, it is known that approximately 80% of recurrences occur in the first 5 years of follow-up (23). In addition, the results found [US persistently showing no anomalies associated with basal Tg ≤ 0.2 ng/mL (24) or stimulated Tg < 1-2 ng/mL (24); stable or declining Tg (25-27), or TgAbs reduction > 50% (28)] make the occurrence of long-term recurrence rates that would modify the conclusion of the study unlikely. On the other hand, strengths of the study are its prospective design using pre-defined and uniform initial therapy and follow-up; inclusion of exactly the group of patients for which controversy exists; the therapy performed (no elective lymph node dissection, ablation with 131I or TSH suppression); and even the surprising result (absence of apparent recurrence). Specifically in this subgroup of patients (PTC ≤ 2 cm and no unfavorable risk factors), there is low risk of structural disease recurrence after less extensive surgery and without radioiodine (29). In fact, we reviewed the data of 58 patients seen at our institution, who were similar to the present patients (nonaggressive PTC ≤ 2 cm) and were submitted to the same therapy and follow-up, but who had sporadic tumors (30,31). None case of recurrence was also detected in this group (30,31).

In conclusion, the treatment usually recommended for patients with PTC who show no unfavorable risk factors (1-4) does not need to be modified in the presence of a family history of this tumor. Studies involving a larger number of patients are needed to confirm this conclusion.

Disclosure: no potential conflict of interest relevant to this article was reported.

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