Papillary thyroid microcarcinoma (PTMC): Prognostic factors, management and outcome in 403 patients

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Abstract

Aim: To investigate an “optimal” therapeutic management of patients with papillary thyroid microcarcinoma (PTMC).

Methods: We evaluated a group of 403 consecutive patients affected by PTMC operated on by the same surgeon. Prognostic factors were evaluated by uni- and multivariate statistical analysis.

Results: After a mean follow-up of 8.5 years, 372 patients were living without disease (undetectable serum thyroglobulin levels), 24 patients were living with disease (increased serum thyroglobulin levels), 6 patients were deceased due to causes different from thyroid cancer, and 1 patient was deceased due to metastatic thyroid cancer. No statistically significant prognostic factor was found at uni- and multivariate analysis. However, it is worth noting that in patients with a larger primary tumour (size ≥ 5 mm) and treated by partial thyroidectomy alone, the prevalence of recurrent disease was higher than in patients treated by total thyroidectomy and 131I administration.

Conclusion: It appears reasonable to perform total thyroidectomy (possibly associated with central compartment node dissection), 131I whole body scan (followed by 131I therapy when necessary) and TSH-suppressive hormonal therapy in patients with PTMC.

Keywords: Papillary thyroid microcarcinoma; Total thyroidectomy; Partial thyroidectomy; Outcome; Prognostic factors

Introduction

Papillary carcinoma is the most common histologic type of malignancy harbouring from the thyroid gland. Recently, the widespread use of ultrasonography (US) and US-guided fine needle aspiration cytology (FNAC) has strongly facilitated the preoperative detection and diagnosis of small papillary carcinoma ≤ 10 mm in greatest dimension. These tumours are defined as papillary thyroid microcarcinoma (PTMC) and are the most common form of thyroid cancer, detected in up to 36% of cases in autopsy studies.1

At present, PTMC is defined as “incidental” when discovered at histologic analysis of a thyroid gland removed for a preoperative diagnosed benign disease. Instead, PTMC is defined as “occult” when it is undetectable at clinical examination and indirectly diagnosed because of

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examination and measuring less than 10 mm in maximum diameter. These observations have been receipted by the WHO classification of thyroid tumours, in which PTMC is defined as “a papillary carcinoma sized 10 mm or less in its maximal diameter”.

In patients affected by differentiated thyroid carcinoma, the prognostic importance of tumour size has been investigated: at multivariate statistical analysis, no increased mortality has been demonstrated for tumours with greatest dimension less than 1.5 cm. The high incidence of PTMC in autopsy studies (up to 35–50%) suggests that most of them had a benign behaviour. Conservative surgery has been advocated for patients with PTMC. However, loco-regional recurrences have been reported in 0–11% of PTMC patients, and some cases of distant metastases have also been described.

The aim of the present study was to investigate possible prognostic factors involved in disease outcome in a large series of 403 consecutive patients affected by PTMC operated on by the same surgeon.

Patients and methods

Patients

We considered 403 consecutive patients affected by PTMC, operated on by the same surgeon between January 1990 and December 2004: they were part of the whole series of 1164 patients with papillary thyroid carcinoma treated in our surgical centre by the same surgeon in the same period. There were 337 females and 66 males, with a female to male ratio of 5:1. Age was <45 years in 170 patients, and ≥45 years in 233 patients.

A thyroid dysfunction was diagnosed in 167 patients: 53 patients were receiving methimazole to cure hyperthyroidism and 67 patients L-thyroxine to restore hypothyroidism. These observations have been receipted by the examination and measuring less than 10 mm in maximum diameter. These observations have been receipted by the examination and measuring less than 10 mm in maximum diameter. These observations have been receipted by the examination and measuring less than 10 mm in maximum diameter. These observations have been receipted by the examination and measuring less than 10 mm in maximum diameter. These observations have been receipted by the examination and measuring less than 10 mm in maximum diameter.

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A thyroid dysfunction was diagnosed in 167 patients: 53 patients were receiving methimazole to cure hyperthyroidism and 67 patients L-thyroxine to restore hypothyroidism before operation. Co-existing nodular goitre was present in 195 patients: it was a cervico-mediastinal goitre in 49 patients and it was toxic in 53 patients. PTMC was occult in 23 patients, incidental in 237 patients, and it was diagnosed pre-operatively by US and US-guided FNAC in 143 patients.

Surgical treatment consisted of total thyroidectomy in 359 patients, and loboisthmectomy in 44 patients. In these 44 patients PTMC was “incidental” (i.e. these patients had been operated on for a preoperative diagnosed benign disease while the diagnosis of PTMC was obtained only at definitive histologic analysis). Moreover, considering the excellent prognosis generally reported in literature for PTMC and the absence of controlateral thyroid nodes at high resolution US examination, these patients were not re-operated to obtain total thyroidectomy.

Node dissection was associated in 127 patients in whom a diagnosis of PTMC was obtained pre-operatively or in whom suspected loco-regional lymph node metastases were found at intervention: in 95 patients node dissection involved the omolateral central compartment and in 32 patients both the central and omolateral laterocervical compartments.

Primary tumour was ≥5 mm in 234 patients and <5 mm in 169 patients. PTMC was unifocal in 343 patients, multifocal in 60 patients: 27 patients had multiple tumoral foci in 1 lobe, 33 patients had tumoral foci in both lobes. Extracapsular thyroid invasion was diagnosed in 16 patients. Furthermore, at histopathologic examination co-existing nodular goitre was found in 207 patients, follicular adenoma in 52 patients, Hurthle adenoma in 5 patients and thyroiditis in 79 patients.

At operation, lymph node metastases were found in 47 patients, in 23 cases involving the omolateral central compartment and in 24 cases both the central and omolateral laterocervical compartments.

After surgery 89 cases of transient hypocalcemia were observed, 87 in patients who underwent total thyroidectomy, 2 in patients who underwent lobectomy, while no case of larynx nerve palsy was recorded. Permanent hypoparathyroidism was observed in only 3 patients with co-existing parathyroid glandular hyperplasia, in whom a subtotal parathyroidectomy was performed together with total thyroidectomy.

All patients who had been treated by total thyroidectomy underwent 131I treatment because of presence of (a) thyroid remnants in 185 cases, (b) lymph node metastases in 75 cases, and (c) distant metastases in 1 case. Then, all patients received TSH-suppressive doses of L-thyroxine.

Patients were followed up at 3, 6 and 12 months after treatment and then on a yearly basis. The mean follow-up after first treatment was 8.5 years (range 9 months to 14 years). Follow-up consisted of clinical examination, measurement of serum thyroid hormones, serum TSH, serum thyroglobulin and anti-thyroglobulin antibodies levels and neck high resolution US. In the absence of detectable serum anti-thyroglobulin antibodies, patients with serum thyroglobulin level < 2 ng/dl on and off hormonal therapy were considered disease-free. Conversely, patients with serum thyroglobulin levels > 2 ng/ml, in the presence or not of macroscopically recurrent disease depicted by currently available imaging modalities, were considered living with disease. Other radiological and nuclear-medicine investigations were performed when necessary.

Patients of this study could be considered at low risk on the basis of preoperative FNAC and definitive histopathology diagnosis of a well-differentiated PTMC, with minimal extracapsular thyroid invasion in only 3.9% of cases.

At the last control (mean follow-up = 8.5 years), 372 patients were living without disease (undetectable serum thyroglobulin levels), 24 patients were living with disease (increased serum thyroglobulin levels), 6 patients were deceased due to causes different from thyroid cancer, and 1 patient was deceased due to metastatic thyroid cancer.
Statistical analysis

For the statistical analysis of prognostic factors, the following binary variables were considered: gender; age at initial diagnosis (<45 years or ≥45 years); presence of lymph node metastases; co-existence of thyroid diseases; concurrent treatment with L-thyroxine or methimazole; extent of surgery (total thyroidectomy versus partial thyroidectomy); performance of lymphadenectomy; histopathological findings (tumour size, multifocality, and thyroid capsular invasion); 131I whole body scan; and 131I therapy. Disease recurrence (both macro- or microscopic) and cancer-related death (unfavourable events) were taken as the endpoints of statistical analysis. Multivariate statistical analysis was performed by the Cox model and uni-variate statistical analysis by Fisher’s exact test. Chi-squared test was used to compare frequencies. \( P < 0.05 \) was considered to be statistically significant.

Results

The main characteristics of our patients’ population and the investigated prognostic factors are summarised in Table 1.

Patients living with disease (increased Tg levels) and cases with macroscopic recurrence

Regarding the 24 patients living with disease (increased serum thyroglobulin levels), there were 19 females and 5 males, with a female to male ratio of 3.8; 13 patients were ≥45 years old; a pre-operatively thyroid dysfunction was present in 3 cases. Considering this patient’s sub-group, surgical treatment consisted of total thyroidectomy in 8 patients and loboisthmectomy in 16 patients. Node dissection was associated in 6 cases: in 4 cases of the central compartment, in 2 cases both of the central and laterocervical compartments. The primary tumour was ≥5 mm in 18 patients and <5 mm in 6 patients. PTMC was monofocal in 14 patients and multifocal in 10 patients. Extracapsular thyroid invasion was diagnosed in 2 patients. At operation, lymph node metastases were found in 5 patients, in 2 patients involving the central compartment and in 3 patients both the central and laterocervical compartments.

During follow-up, 6 patients experienced loco-regional macroscopic recurrent disease detected by neck US: all were females, and 3 were ≥45 years old. Moreover, in 5 out of these 6 cases the initial surgical treatment consisted of a loboisthmectomy; the primary tumour was ≥5 mm in 5 patients, and it was monofocal in 4 cases. The disease recurrence occurred in the thyroid bed in 4 cases, in the laterocervical nodes in 1 case, in the subcutaneous neck tissue in 1 case. Only 1 of these patients had received 131I therapy after initial surgical treatment.

Outcome

All patients who had been treated by total thyroidectomy underwent (within 4–6 weeks from surgery) 131I whole body scan and 260 of them subsequently received 131I treatment: of these 260 patients, 249 cases are living without disease, 7 cases are living with disease, 3 cases are deceased without disease and 1 case is deceased due to thyroid cancer. No case of side-effect related to 131I treatment was recorded in our patient series.

Discussion

In our study, after a mean follow-up of 8.5 years, 6 cases of recurrent disease were recorded: surgical treatment consisted of a loboisthmectomy in almost all these cases (\( n = 5 \)) as well as the primary tumour was ≥5 mm in the majority of them (\( n = 5 \)). Moreover, in the “recurrent patient’s sub-group” only 1 patient received 131I therapy after initial surgery.

Considering all the patients with increased serum thyroglobulin levels during follow-up (i.e. patients affected both by macroscopic recurrent disease and by microscopic disease), at last control a total of 24 cases were considered living with disease. Of note, the majority of these patients received loboisthmectomy alone (\( n = 16 \)), and the primary tumour was ≥5 mm in 18 of them; moreover, only a minority of these 24 patients (\( n = 7 \)) received 131I treatment after surgery.

No factors were found to be significantly related with unfavourable events both at uni- and multivariate statistical analysis probably due to the small number of unfavourable events (recurrences and deaths) occurred during follow-up in our series. However, it is worth noting that patients who were treated by total thyroidectomy had a higher probability of being living disease-free (66.6%) against the 33.3% of patients treated by partial thyroidectomy alone. Moreover, a tumour size greater than 5 mm was more frequently observed in patients living with disease (75% of cases) in comparison with patients considered tumour free (43% of cases). Furthermore, the prevalence of lymph node metastases was not negligible (\( n = 47 \) patients; 11.6% of all cases) despite the small size of the primary tumour.

In a recent study Hay et al.\(^8\) reported their experience in a group of 535 patients affected by PTMC. They identified, by multivariate statistical analysis, 2 independent prognostic factors: (a) the presence of node metastases at diagnosis and (b) the extent of primary surgery. At 20-year follow-up, the loco-regional recurrence rates for node-negative and node-positive patients in their experience were significantly different (\( p < 0.0001 \)), in particular 1% and 18%, respectively. Furthermore, the loco-regional recurrence rate in patients who had undergone unilateral lobectomy only in comparison with those who had undergone
bilateral lobectomy was 5% and 20%, respectively ($p < 0.0001$).

Baudin et al.\(^\text{11}\) described the Gustave-Roussy Institute experience derived from a group of 189 patients affected by PTMC. The authors identified, by multivariate analysis, 2 independent prognostic factors: (a) the multifocality of the tumour and (b) the extent of primary surgery. They concluded that conservative surgery should be offered only to PTMC patients with unifocal disease, whereas total thyroidectomy, combined with node dissection of the central neck compartment (plus $^{131}$I treatment when appropriate), should be given to patients with multifocal disease.

In our large series of patients affected by PTMC, despite no significant prognostic factor was identified both at univariate and multivariate statistical analysis, it is worth noting that: (a) patients treated by partial thyroidectomy experienced a double percentage of recurrent tumour than patients treated by total thyroidectomy and $^{131}$I therapy, (b) patients who had recurrent disease showed a primary tumour greater than patients who had not, and (c) the prevalence of lymph node metastases, even if lower than in classical papillary thyroid carcinoma, was not negligible accounting for 11.6% of all cases.

### Limitations

One limitation of our study is that the group of patients who had been treated by partial thyroidectomy is rather little when compared with the group of patients who had been treated by total thyroidectomy. Moreover, it needs to be pointed out that considering the group of patients who had been treated by total thyroidectomy alone versus the group of patients who had been treated both by total thyroidectomy and $^{131}$I therapy, no significant differences in the outcome were observed. Despite these observations, we observed a trend towards a higher prevalence of recurrent disease in the relatively little group of patients who had been treated by partial thyroidectomy alone in comparison with patients who had been treated by total thyroidectomy. We believe that total thyroidectomy (possibly combined with central compartment node dissection), $^{131}$I whole body scan (followed by $^{131}$I therapy when necessary), and TSH-suppressive hormonal therapy might be considered as an adequate strategy for the management of PTMC patients. However, further randomised multicentric studies involving greater patient numbers with longer follow-up are necessary to clarify this aspect.

<table>
<thead>
<tr>
<th>Patients’ population characteristics</th>
<th>Total patients</th>
<th>Living without disease</th>
<th>Living with disease</th>
<th>Deceased without disease</th>
<th>Deceased due to thyroid cancer</th>
<th>Uni-variate statistical analysis ($p$ value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>403</td>
<td>372</td>
<td>24</td>
<td>6</td>
<td>1</td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Females</td>
<td>337</td>
<td>311</td>
<td>19</td>
<td>5</td>
<td>1</td>
<td>N.S.</td>
</tr>
<tr>
<td>Males</td>
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<td>61</td>
<td>5</td>
<td>1</td>
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<td></td>
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<td>Age at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>&lt;45 years</td>
<td>170</td>
<td>166</td>
<td>13</td>
<td>0</td>
<td>0</td>
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<tr>
<td>≥45 years</td>
<td>233</td>
<td>145</td>
<td>11</td>
<td>6</td>
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<td>N.S.</td>
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<td>Partial thyroidectomy</td>
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<td>25</td>
<td>16</td>
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<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Total thyroidectomy</td>
<td>359</td>
<td>347</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>N.S.</td>
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<tr>
<td>Lymph node dissection</td>
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<td></td>
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<td></td>
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<tr>
<td>CC</td>
<td>95</td>
<td>88</td>
<td>4</td>
<td>3</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>CC + LC</td>
<td>32</td>
<td>30</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td></td>
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<tr>
<td>Tumour size</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 mm</td>
<td>234</td>
<td>212</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>≥5 mm</td>
<td>169</td>
<td>160</td>
<td>18</td>
<td>4</td>
<td>0</td>
<td>N.S.</td>
</tr>
<tr>
<td>Unifocal tumour</td>
<td>343</td>
<td>329</td>
<td>14</td>
<td>2</td>
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<td>N.S.</td>
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<td>Multifocal tumour</td>
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<td>43</td>
<td>10</td>
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<tr>
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<td>12</td>
<td>2</td>
<td>2</td>
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<td>N.S.</td>
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<td>Lymph node metastases, of whom</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CC</td>
<td>23</td>
<td>20</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>N.S.</td>
</tr>
<tr>
<td>CC + LC</td>
<td>24</td>
<td>20</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Distant metastases</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
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<tr>
<td>$^{131}$I whole body scan</td>
<td>359</td>
<td>347</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>N.S.</td>
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<tr>
<td>$^{131}$I treatment</td>
<td>260</td>
<td>249</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

CC = central compartment.
LC = laterocervical compartment.
References


