Second Primary Cancer in Patients with Papillary Thyroid Carcinoma

CARLES ZAFON, GABRIEL OBIOLS and JORDI MESA

Department of Endocrinology, Hospital Universitari Vall d’Hebron, Universitat Autònoma de Barcelona, Barcelona, Spain

Abstract. Background and Aim: There is an increased incidence of secondary primary cancer (SPC) in patients with papillary thyroid carcinoma (PTC). The risk is stronger in the first year after the first malignancy (synchronous tumours). The aim of this study was to assess the prevalence of SPC in patients with PTC, and to analyse whether the timing of tumour presentation influenced the clinicopathological characteristics of PTC. Patients and Methods: A total of 184 patients with PTC were included in the study. Results: There were 24 patients with SPC and nine with PTC and two other primary tumours (42 additional malignancies in total). Additional tumours were more prevalent in male and older patients. In 11 cases (33%), the two carcinomas were synchronous. PTCs from synchronous cases were significantly larger than those from non-synchronous cases. Conclusion: Patients with PTC were at an elevated risk for SPC. In one third of patients, both neoplasms were diagnosed within the same year. Male and older patients were more likely to have SPC.

Differentiated thyroid carcinoma (DTC) is the most frequent endocrine malignancy and its incidence is increasing worldwide (1). The most common type of DTC is papillary thyroid carcinoma (PTC). PTC has a relatively benign prognosis; the 10-year survival rate is close to 95%. Several studies have shown an increase in incidence of second cancer after, as well as before, thyroid carcinoma. Bi-directional association has been confirmed by large epidemiological studies and a meta-analysis (2-5). The relationship has been attributed to exposure to a common risk factor, genetic susceptibility, a treatment effect, or surveillance bias. In a significant proportion of cases, DTC and the second primary tumour are diagnosed within the same year (synchronously). Ronckers et al. (3), using the Surveillance Epidemiology and End Results (SEER) Cancer Registry Program with a cohort of more than 2,000,000 patients, reported that for many types of cancer, the risk of the second primary cancer (SPC) was stronger in the initial 12 months after the first malignancy. Sandeep et al. (4) found that for all cancers combined and for several specific malignancies, the risk of the second cancer was significantly higher within a year of diagnosis of the primary neoplasm. Ömür et al. (6) reported that a third of patients with multiple primary tumours had concurrent DTC and an SPC. However, few reports have compared the clinicopathological features of DTC between patients with synchronous and non-synchronous (metachronous) SPCs. Lang et al. (7) reported that patients with synchronous second malignancy had more advanced DTC and were more likely to die from thyroid cancer than those with a metachronous second tumour.

The aim of the present retrospective cohort study was to assess the prevalence of SPC in patients with PTC, and to analyse whether the timing of tumour presentation (synchronous versus metachronous) influenced the clinicopathological characteristics of PTC.

Patients and Methods

Patients with PTC diagnosed and treated in our hospital between 2000 and 2010 were selected for the cohort. We excluded cases that (i) were lost to follow-up, (ii) had incomplete clinical data, and (iii) had follow-up for less than one year. Cancer additional to PTC was classified as synchronous when both tumours were diagnosed within one year, whereas it was metachronous when the difference in diagnosis was more than one year.

The following clinicopathological variables were considered in the analysis: age, sex, mode of detection, extent of disease, maximum diameter of the primary tumour, multifocality, bilaterality, extrathyroid extension, and lymph node metastases. Data were summarized using the mean (standard deviation) or median (Q1–Q3) for continuous variables and proportions for categorical variables. Statistical analysis was performed using the χ2-test and Fisher’s exact test for categorical variable analysis, and by Student’s
t-test and Mann–Whitney U-test to compare continuous variables between groups. All tests were two-tailed. A p-value <0.05 was considered to be statistically significant.

**Results**

From 2000 to 2010, 208 patients with PTC were diagnosed at our institution. Table I summarizes the baseline characteristics of the 184 patients who were finally included in the study. The clinical records of these patients indicated 24 cases with SPC. Nine patients had PTC and two primary tumours. Thus, 33 (18%) patients were affected with PTC and another malignancy.

Patients with PTC but without additional malignancies were younger than those with SPC, 46.5 (14.5) versus 56 (14.4) years old (p=0.001). Moreover additional malignancies were more prevalent in male than in female patients. There were 27/151 (18%) male patients in the group with PTC-alone and 12/33 (36%) in the group of patients with a second neoplasm (p=0.025). Moreover, there were no differences in tumour characteristics and patient outcome (Table II).

There were a total of 42 additional malignancies in the cohort of patients with PTC. Breast cancer was the most common (10 cases). Lympho-haematological malignancies (including Hodgkin’s disease, chronic lymphatic leukaemia, acute lymphatic leukaemia and acute myeloid leukaemia) and cutaneous basocellular carcinoma were observed in five cases in each group. Other tumours included: four lung, three prostate, three bladder, and three colorectal cancer, two melanoma, and two stomach and two renal cancer, and one each of pleural, neuroendocrine and myxofibrosarcoma.

In 11 patients (33%) the two carcinomas were synchronous, whereas in the remaining 22 (66%), malignancies were diagnosed more than one year later. Among patients with synchronous cancer, seven cases of PTC were secondly diagnosed, and in four of them, thyroid carcinoma was found by positron-emission tomography during an extension study of the primary tumour. Additional malignancies were three cases of breast and three of lung cancer, and one of prostate, colon, stomach and urinary bladder cancer.

In 11 out of 42 (26%) additional carcinomas, PTC was diagnosed in the same year as the SPC. In the remaining cases, PTC was the first tumour to be diagnosed in 11 patients with a mean time interval until the next tumour of 3.8 (1.9) years, and PTC was not the first tumour in 20 cases, with a mean time interval from the first tumour to PTC of 9.6 (6.6) years (p=0.002).

Differences in the characteristics of patients with PTC according to synchronous or metachronous malignancies are shown in Table III. There were no differences in the majority of clinicopathological characteristics. However, it is interesting to note that synchronous tumours were significantly larger than metachronous tumours, 15 (8-20) mm versus 12 (4.25-11.75) mm (p=0.01). Thus, microcarcinomas (<1 cm) comprised of 14 out of 22 (63%) metachronous tumours but only three out of 11 (27%) synchronous tumours (p=0.04).

**Discussion**

Treatment of DTC includes surgery, with total thyroidectomy in most cases, $^{131}$I ablation of remnant thyroid tissue, and long-term thyrotropin-suppressive therapy with supraphysiological doses of levothyroxine (8). DTC has a relatively benign prognosis, and the 10-year survival rate is close to 95%. Several reports have shown that patients with DTC are at elevated risk for SPC. Non-thyroid malignancy can occur before, after, or at the same time as DTC.

The risk of non-thyroid malignancy in survivors of DTC has been extensively studied. Ronckers et al. (3) reported an 11% elevated risk compared to that in the general population.
patients with invasive melanoma (14). after primary melanoma, in a cohort of more than 70,000 malignancies. Thyroid cancer was the second most prevalent, increased risk of thyroid cancer after many types of primary cancer. Synchronous malignancies are currently defined as those diagnosed within the same year. Ronckers et al. (3) reported that a third of patients with multiple primary tumours had concurrent DTC and SPC. Moreover, Lang et al. (7) have reported that patients with synchronous second malignancy had more advanced DTC and were more likely to die from thyroid cancer than those with metachronous SPC. In this regard, we report that PTC in the synchronous tumour group was larger than in the metachronous group. Hence, the number of papillary microcarcinomas was higher in patients with non-synchronous than in those with synchronous tumours. All these findings support the idea that far from being a detection bias motivated by close medical surveillance, a common risk factor or a temporary predisposition may play a role in the concurrence of both tumours.

In conclusion, patients with DTC are at elevated risk for SPC. In a third of cases, both neoplasms were diagnosed within the same year. Additional primary tumours were most frequent in male and older patients. Breast cancer is the most frequent tumour associated with thyroid carcinoma. Finally, PTC in patients with synchronous tumours is larger than in those with metachronous tumours.

Table III. Clinical and histological characteristics of papillary thyroid carcinoma in patients with synchronous and metachronous second primary neoplasm.

<table>
<thead>
<tr>
<th></th>
<th>Synchronous</th>
<th>Metachronous</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>11</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>61 (11.7)</td>
<td>53.4 (15.2)</td>
<td>0.12</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>6 (54)</td>
<td>6 (27)</td>
<td>0.12</td>
</tr>
<tr>
<td>Median size, mm (q1-q3)</td>
<td>15 (8-20)</td>
<td>7.5 (4.2-11.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Microcarcinomas, n (%)</td>
<td>3 (27)</td>
<td>14 (63)</td>
<td>0.04</td>
</tr>
<tr>
<td>Lymph node metastases, n (%)</td>
<td>6 (54)</td>
<td>15 (70)</td>
<td>0.34</td>
</tr>
<tr>
<td>Multifocality, n (%)</td>
<td>5 (45)</td>
<td>11 (50)</td>
<td>0.71</td>
</tr>
<tr>
<td>Mean $^{131}I_{Na}$, dose (SD)</td>
<td>103(50)</td>
<td>81(66)</td>
<td>0.34</td>
</tr>
<tr>
<td>Patients in remission, n (%)</td>
<td>9 (81)</td>
<td>19 (86)</td>
<td>0.87</td>
</tr>
</tbody>
</table>

population. Sandeep et al. (4), in a multinational study with >30,000 patients with DTC, found that the risk of SPC was 1.31. A systematic review and meta-analysis performed by Subramanian et al. (5) in 2007 concluded that the standardised incidence ratio of SPC in thyroid cancer survivors was 1.20 (95% confidence interval, 1.17-1.24). In a multinational European cohort, the increased risk of SPC was quantified as >27% (9). Other studies with smaller case numbers have confirmed these data. However, whether the risk of SPC after DTC is the consequence of radioiodine treatment, as has been suggested, remains controversial. Fallahi et al. (10) reported that a cumulative dose of $^{131}I_{Na}$ of >1.08 Ci was associated with an increase in SPC. Ronckers et al. (3) also found a two-fold increased risk of additional cancer in organs that concentrate $^{131}I_{Na}$ among patients with thyroid carcinoma. However, other authors have not found such an association. For example, Bhattacharyya and Chien (11) compared patients with DTC treated with or without $^{131}I_{Na}$ and did not find any difference in the risk of SPC. In addition, Berthe et al. (12) and Verkooijen et al. (13) did not find any causal relation with iodine therapy.

Conversely, the risk of DTC after non-thyroid primary malignancy has also been demonstrated. In the study of Ronckers et al. (3), the overall risk was 42% higher than expected. In the study of Sandeep et al. (4), there was an increased risk of thyroid cancer after many types of primary malignancies. Thyroid cancer was the second most prevalent, after primary melanoma, in a cohort of more than 70,000 patients with invasive melanoma (14).

Finally, DTC can be concurrently diagnosed with another primary cancer. Synchronous malignancies are currently defined as those diagnosed within the same year. Ronckers et al. (3) reported that for many types of cancer, the risk of DTC was stronger in the first year after, or before, the other malignancy. Sandeep et al. (4) found that for all cancers combined and for several specific malignancies, a significant risk of SPC was highest within a year of diagnosis of the primary neoplasm. The results of the present study are in agreement with the findings of Ömür et al. (6), who reported that a third of patients with multiple primary tumours had concurrent DTC and SPC. Moreover, Lang et al. (7) have reported that patients with synchronous second malignancy had more advanced DTC and were more likely to die from thyroid cancer than those with metachronous SPC. In this regard, we report that PTC in the synchronous tumour group was larger than in the metachronous group. Hence, the number of papillary microcarcinomas was higher in patients with non-synchronous than in those with synchronous tumours. All these findings support the idea that far from being a detection bias motivated by close medical surveillance, a common risk factor or a temporary predisposition may play a role in the concurrence of both tumours.

References


