Clinical importance of bilateral disease in patients with papillary thyroid cancer

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SUMMARY

A cancer-related factor that is not included in papillary thyroid cancer (PTC) prognostic scoring systems is bilaterality. While it may seem that bilaterality should be considered during the management of PTC, its clinical importance has been debated. This controversy exists because the extent of surgery for PTC has not been found to affect survival in low-risk individuals, despite their potential for PTC bilaterality. We sought to determine if PTC bilaterality is a cancer prognosticator based upon its association with known clinical and pathological PTC prognosticators, and MACIS scores. In this article we discuss our findings and their potential clinical implications.

Papillary thyroid cancer (PTC) is a highly prevalent endocrine malignancy with low recurrence rates and excellent prognosis. Many different prognostic scoring systems have been developed to predict outcomes for patients with PTC.[1] One cancer-related factor that is not included in PTC prognostic scoring systems is the presence of PTC bilaterality. Although intuitively it seems that PTC bilaterality should be a consideration during PTC management, its clinical significance has remained controversial. This debate exists because the extent of surgery for PTC (i.e., lobectomy v. total thyroidectomy) has not been found to affect survival in low-risk individuals, despite their potential for PTC bilaterality.[2] We sought to determine if PTC bilaterality is a cancer prognosticator based upon its association with known clinical and pathological predictors of PTC prognosis and MACIS scores.

We retrospectively reviewed all sequential PTC patients who underwent either total thyroidectomy or thyroid lobectomy and subsequent completion thyroid lobectomy at St. Paul's Hospital, Vancouver, Canada, between 2000 and 2012. Demographic and histopathological risk factors and MACIS scores were compared between patients with unilateral and bilateral PTC, and statistical significance was determined using χ^2 analysis.

Our study population consisted of 203 PTC patients. Of these individuals, 82 (40.4%) had bilateral PTC, and 121 (59.6%) had unilateral PTC. Several clinical and histopathological PTC characteristics that are known to correlate with cancer prognosis were investigated using χ^2 analysis and are presented in Table 1. By definition, all patients with bilateral PTC were also considered to have multifocal PTC. Only 3 patients in the unilateral PTC group (2.5%) had evidence of multifocal disease within their involved thyroid lobe.

Of the 8 clinicopathological characteristics studied, only PTC size and the presence of lymphovascular invasion correlated with cancer bilaterality (Table 1). Not surprisingly, PTC multifocality was significantly different between the 2 groups since all patients diagnosed with PTC bilaterality had more than 1 focus of PTC, and thus harbored multifocal disease (Table 1).

Multifocality, defined as the presence of greater than a single intrathyroidal PTC focus, was further studied to determine if the principal site of multifocal PTC in the bilateral cases was ipsilateral or contralateral to the largest PTC focus. The mean size and number of multifocal lesions were 0.7 cm and 2.2 cm,

respectively. Out of 81 bilateral PTC cases, the majority of patients had their principal site of cancer multifocality ipsilateral to their largest cancer focus, a significant observation (50 cases, 61.7%, $p = 0.035$). When individuals with predominantly ipsilateral multifocal PTC were compared with individuals with predominantly contralateral multifocal PTC, there were no significant differences observed. This finding is consistent with observations made by Hay and colleagues[1] from the Mayo Clinic during the development of the MACIS prognostic scoring. Multicentricity was not found to predict risk of thyroid cancer mortality, and was therefore not incorporated into the MACIS score.[1] Multivariate regression was also carried out considering all of the covariates, but none correlated with PTC bilaterality.

Perhaps the most surprising finding in our study was the association we observed between cancer size and lateralization. Specifically, PTC unilaterality was associated with larger cancer size (> 1 cm), and there also was a significantly higher proportion of individuals harbouring small PTCs in the bilateral group than in the unilateral group (26.8% v. 0%, $p < 0.001$). In addition, the majority of individuals with multifocal PTC in the bilateral group had their principal site of multifocality within the same lobe as the largest PTC focus (61.7%, $p = 0.035$). This is an important observation, because prior work has suggested that the presence of multifocal PTC predicts the presence of bilateral PTC, and thus suggests potential benefit from total thyroidectomy.[3] Based on our observations, individuals harbouring small and otherwise low-risk PTCs, if treated with lobectomy alone, may have residual PTC foci present in the remnant lobe up to 26.8% of the time.

Table 1. Incidence and associations of papillary thyroid carcinoma bilaterality with patient and cancer characteristics and with MACIS score

Characteristic	Group; no. (%)		*p* value
	Bilateral	Unilateral	
Sex			0.52
Female	55 (67.1)	90 (74.4)	
Male	27 (32.9)	31 (25.6)	
Age, yr			0.36
< 45	31 (37.8)	59 (48.8)	
≥ 45	51 (62.2)	62 (51.2)	
Extrathyroidal extension			0.78
No	49 (61.2)	78 (65.0)	
Yes	31 (38.8)	42 (35.0)	
Size, cm			< 0.001
≤ 1	22 (26.8)	0	
> 1	60 (73.1)	121 (100)	
Vascular extension			0.001
No	66 (80.5)	119 (98.3)	
Yes	16 (19.5)	2 (1.7)	
Multifocal disease			< 0.001
No	0	118 (97.5)	
Yes	82 (100)	3 (2.5)	
Lymph node metastases			0.36
No	46 (56.8)	82 (67.8)	
Yes	35 (43.2)	39 (32.2)	
Distant metastases			0.52
No	77 (96.3)	120 (99.2)	
Yes	3 (3.8)	1 (0.8)	
MACIS score			0.78
< 6	65 (82.3)	92 (76.7)	
6–6.99	7 (8.9)	17 (14.2)	
7–7.99	4 (5.1)	6 (5.0)	
> 8	3 (3.8)	5 (4.2)	
MACIS score			> 0.99
< 7	72 (91.1)	109 (90.8)	

A recent population-level analysis confirmed previous findings that total thyroidectomy for PTC resulted in a higher 10-year overall survival, and a lower 10-year recurrence risk than lobectomy alone. In this study, it was shown that after adjusting for variables related to complexity of disease, the apparent overall survival advantage attributable to total thyroidectomy was not reproducible.[2] Thus, even though current American Thyroid Association guidelines acknowledge that PTC has a predisposition for being both multifocal and/or bilateral, they stipulate that for cancers smaller than 4 cm with no evidence of gross extrathyroidal extension and no evidence of lymph node or distant metastatic disease, either near-total or total thyroidectomy or thyroid lobectomy may be considered adequate initial surgical treatment.[4]

An important consideration is the underlying mechanisms that lead to PTC multifocality. It has been postulated that multifocal PTCs either represent multiple synchronous primary cancers that arise from independent clones, or that they are the consequence of intraglandular dissemination of a single malignant clone.[5] The associations we observed between small PTC size, the presence of lymphovascular invasion and PTC bilaterality suggest we are either observing small, locally aggressive but independent cancer foci, or that they represent a single primary cancer that spreads early, through lymphovascular invasion, into the contralateral lobe. Even though the underlying pathophysiology of PTC bilaterality is currently controversial and further research is required, limited study of this question at the molecular level has supported the former theory.[5]

The incidence of bilateral PTC in our study population was 40.4%, which is consistent with prior reports in the current literature.[3] We found PTC bilaterality was associated with smaller cancer size and the presence of lymphovascular invasion. These observations suggest that the development of PTC bilaterality, regardless of the underlying mechanism, likely represents an early event that occurs during thyroid cancer development and progression. While our study does not necessarily suggest that individuals with small, otherwise low-risk PTCs should mandatorily undergo a total thyroidectomy, we believe that the propensity for bilateral disease should be clearly addressed in the discussion with thyroid cancer patients when planning the extent of their thyroid operation.

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