Impact of sex on the clinicopathological characteristics and prognosis of papillary thyroid cancer

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SUMMARY

Papillary thyroid cancer (PTC) is the most common endocrine malignancy. Observed clinical and pathological differences between the sexes of PTC patients have been reported. There is currently no consensus regarding the impact of sex on PTC prognostication. We studied 566 PTC patients and observed that there was a higher PTC incidence in women, that PTC diagnosis was more challenging in women, and that men tended to present with larger cancers. However, once PTC is diagnosed, both sexes have a similar cancer prognosis, as evaluated using the MACIS (Metastasis, Age, Completeness of Resection, Invasion, Size) score. Our observations suggest that research efforts should be especially directed at improving the diagnostic yield of preoperative fine needle aspiration biopsy in women who present with nodular thyroid disease.

Papillary thyroid cancer (PTC) is the most common endocrine malignancy; it accounts for more than 85% of all thyroid cancer cases,[1] and globally its incidence has been steadily rising. Despite the considerable progress that has been made in understanding the molecular pathways that underlie thyroid cancer development and progression, the influence of sex on PTC clinicopathological characteristics and prognosis is currently unclear. Some reports have suggested that mortality might be twice as high in men with PTC than in women.[2] However, other groups have reported that the only clinically significant prognostic factors for PTC are histopathologic subgroup, American Joint Commission on Cancer Stage (determined by patient age, cancer size and the presence of nodal or distant metastases), and the completeness of surgical resection.[3] Our objective was to characterize and compare the clinicopathological characteristics and prognosis of PTC between the sexes.

We studied 566 sequential patients with newly diagnosed primary PTC who presented to St. Paul's Hospital, Vancouver, B.C., between January 2000 and December 2013. Preoperative fine needle aspiration biopsy (FNAB) cytology was characterized as being either cancer, benign, indeterminate or inadequate. At our institution, the extent of thyroid surgery is consistent with American Thyroid Association (ATA) guidelines for management of adult patients with thyroid nodules and differentiated thyroid cancer. The MACIS score (Metastasis, Age, Completeness of Resection, Invasion, Size) was calculated for each patient as an estimation of PTC prognosis.

The clinical and pathological characteristics of the study population are summarized in Table 1. Most (77.6%) of the PTC patients were women. The average PTC size was significantly larger in men than women (1.98 cm v. 1.68 cm, $p = 0.002$). There was also a statistically significant difference in the proportion of women compared with men who underwent a total thyroidectomy as their initial operation (59.4% v. 81.3%, $p = 0.001$). Interestingly, there was no significant difference in PTC prognosis, as determined by the MACIS score, when comparing men to women (4.70 v. 4.58, $p = 0.08$). Similarly, we did not observe any statistically significant differences between the sexes with respect to mean age at PTC presentation, presence of vascular invasion by cancer, presence of lymph node metastasis, presence of distant metastasis and completeness of cancer resection. In addition, the incidence of papillary microcarcinoma (PMC; PTC < 1cm) was not

significantly different when comparing women and men (34.4% v. 33.9%, $p = 0.91$).

Some groups have suggested that thyroid cancer is more aggressive when diagnosed in men, with reduced survival rates in men compared with women. Our research focused on PTC, and although we observed that the average PTC size was significantly larger in men, this did not lead to a significant difference in their cancer prognosis. Our observations also suggest that PTC presents a greater diagnostic challenge in women. Women with an underlying PTC diagnosis were more likely than men to have an indeterminate preoperative cytological diagnosis (15.0% v. 4.7%, $p = 0.032$), which led to women undergoing more diagnostic thyroid lobectomies than men. After a pathological PTC diagnosis, the vast majority of these women also later went on to undergo a second operation for removal of their remaining thyroid lobe.

The ATA guidelines recommend that in the absence of prior head and neck irradiation or a history of familial thyroid cancer, a thyroid lobectomy is sufficient for treatment of PMCs without evidence of extrathyroidal cancer extension and/or the presence of lymph node metastases. We found the incidence of PMCs to be similar in both sexes. Thus, PMC should have had little influence on the type of operation initially performed, or on cancer prognosis, in our male and female patient population.

Thyroid stimulating hormone (TSH) is a known promoter of thyroid hyperplasia and may therefore be involved in thyroid tumorigenesis and progression. Women have more fluctuations than men in their TSH levels, with higher levels of TSH occurring during parts of the menstrual cycle, during pregnancy, or when using oral contraceptives.[4] Differences in the TSH levels of men and women have been suggested to contribute to differences in thyroid nodule incidence, size and pathology. Sex hormones may also contribute to the observed sex differences in PTC patients. Using a transgenic mouse model of follicular thyroid cancer, Zhang and colleagues[5] found that testosterone appeared to promote thyroid cancer progression through suppression of immune surveillance against cancer cells and reduction of tumour suppressor gene expression.

Table 1. Clinical and pathological characteristics of the PTC study population stratified by sex

Characteristic	Patient sex; mean ± SD (range) or %		
	Women ($n = 439$)	Men ($n = 127$)	p value
Age, yr	46.1 ± 13.5 (15.0–95.0)	47.6 ± 12.7 (21.0–78.0)	0.25
Cancer size, cm	1.68 ± 1.43 (0.03–13.0)	1.98 ± 1.74 (0.05–10.0)	0.002
MACIS score	4.58 ± 1.09 (3.13–9.44)	4.70 ± 1.21 (3.15–8.90)	0.08
PMC incidence, %	34.4	33.9	0.91
Presence of distant metastases, %	0	0	> 0.99
Presence of VI, %	19.6	20.5	0.86
Presence of LN metastases, %	37.8	40.2	0.67
Proportion of incomplete resections, %	7.3	7.9	> 0.99

LN = lymph nodes; PMC = papillary microcarcinoma; PTC = papillary thyroid cancer; SD = standard deviation; VI = vascular invasion.

Our research had several limitations. As our study was retrospective, the thyroid nodule cytology was not consistently reported using the diagnostic groups outlined in the Bethesda System for Reporting Thyroid Cytopathology (BSRTC). Thus, confirmation of our observations regarding the increased difficulty in preoperative PTC diagnoses in women, in a BSRTC-characterized population, would be important. In addition, the extent of thyroid surgery for PTC treatment in current ATA guidelines is based on patient and cancer characteristics, and so completion thyroid lobectomy may not be recommended as commonly now as in the past. Furthermore, study of PTC is challenging because it may recur over more than 20 years; therefore, we used a composite PTC prognosticator, the MACIS score, to determine patient prognosis.

Our observations suggest that once diagnosed the treatment of PTC in men and women should be similar. However, treating physicians should be aware that female patients with an indeterminate preoperative cytological diagnosis are more likely than male patients to have an underlying cancer diagnosis. While this difference does not impact their final cancer prognosis, it may influence preoperative patient counselling and the extent of the initial thyroid operation. We believe that research efforts should be especially directed at improving the diagnostic yield of preoperative FNAB in women who present with nodular thyroid disease. Thus, patient sex should be considered when formulating a plan for the management of thyroid nodules, with the ultimate goal of minimizing morbidity and improving outcomes.

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