Male Sex Is an Independent Predictor of Recurrence-Free Survival in Middle Eastern Papillary Thyroid Carcinoma

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Background: Disparity between sexes with regard to incidence, disease aggressiveness, and prognosis has been documented in several cancers. Although various reports have documented the association between male sex and aggressive papillary thyroid carcinoma (PTC), the prognostic impact of sex on PTC has been inconsistent. The role of sex in PTC aggressiveness and outcome in Middle Eastern PTC remains unknown. Therefore, our study retrospectively analyzed the data of a large cohort of Middle Eastern PTC patients to address this issue.

Methods: We compared men and women with respect to clinico-pathological characteristics, disease persistence, structural recurrence, risk stratification, and prognosis. We included 1,430 patients—1,085 (75.9%) women and 345 (24.1%) men.

Results: The median follow-up was 9.3 years. At diagnosis, 27% (93/345) of men were ≥55 years, compared with 17.8% (193/1085) of women (p = 0.0003). Men had significantly more advanced disease at presentation: higher stage (p = 0.0074), larger tumor size (p = 0.0069), higher rates of lymphovascular invasion (p = 0.0129), extrathyroidal extension (p = 0.0086), regional lymph node metastasis (p = 0.0279), and distant metastasis (p = 0.0101). There was a higher rate of recurrence (p < 0.0001) and TERT mutations (p = 0.0003) in male PTC patients than in female patients. Additionally, radioactive refractoriness was higher in male PTC patients (p = 0.0014). In multivariate analysis, male sex was an independent prognostic factor for poor recurrence-free survival (RFS) (hazard ratio = 1.58; 95% confidence interval = 1.20–2.06; p = 0.0011).

Conclusions: Men with PTC are more likely to present with more advanced and aggressive disease. Importantly, male sex was an independent prognostic factor for RFS. Thus, men may benefit from more aggressive management and therapeutic interventions.

Keywords: papillary thyroid carcinoma, male sex, recurrence-free survival, prognosis, clinico-pathological associations
INTRODUCTION

Papillary thyroid carcinoma (PTC) is the most common endocrine malignancy (1). The incidence of PTC is on the rise over the past two decades (2, 3). In Saudi Arabia, PTC is the second most common cancer affecting women, after breast cancer (4). PTC is an indolent disease with favorable prognosis in majority of patients. However, a subset of PTC patients (approximately one-third of all cases) will relapse (5–7), which could impact the quality of life for these patients. Thus, identification of clinical markers that could help to predict patients at high risk for recurrence is of great clinical importance for effective therapeutic interventions.

PTC is known to affect women more than men (1, 8). In fact, in Saudi Arabia, the age standardized incidence rate of thyroid cancer in women and men was 8.4 and 2.5 per 100,000 persons, respectively (4). The prognostic significance of sex in PTC remains controversial. While many studies have demonstrated the correlation between male sex and advanced stage, higher death rate, poor prognosis, and higher risk of recurrence in PTC (9–12), others have failed to identify prognostic difference between male and female PTCs when adjusting for age, stage, tumor size, and other influencing factors (13–15). Furthermore, current guidelines for risk stratification issued by the American Thyroid Association (ATA) does not include patient’s sex factor that could affect the risk of recurrence (16).

Despite the high incidence of PTC in Saudi Arabia and relatively high recurrence rate (17–19), the impact of sex on recurrence risk in PTC from Middle Eastern ethnicity remains unknown. Thus, we carried out this study on a large cohort of Middle Eastern adult PTC to investigate the impact of sex on clinico-pathological characteristics and patients’ prognosis. We also assess if male sex is an independent risk factor for recurrence of PTC from Middle Eastern ethnicity.

MATERIALS AND METHODS

Patient Selection
One thousand four-hundred and thirty consecutive unselected adult PTC patients (≥18 years) diagnosed between 1988 and 2018 at King Faisal Specialist Hospital and Research Centre (Riyadh, Saudi Arabia) were included in the study. Cases were identified based on clinical history followed by fine needle aspiration cytology for confirmation. The Institutional Review Board of the hospital approved this study and the Research Advisory Council (RAC) provided waiver of consent under project RAC # 2110 031 and #2211168.

Clinico-Pathological Data
Baseline clinico-pathological data were collected from case records and have been summarized in Table 1. Staging of PTC was performed using the eighth edition of the American Joint Committee on Cancer (AJCC) staging system. Based on the ATA guidelines, tall cell, hobnail, columnar cell, diffuse sclerosing, and insular variants were classified as aggressive variants, whereas classical and follicular variants were classified as non-aggressive variants (16). Prophylactic central lymph node dissection (PCLND) was performed in patients with clinically uninvolved central neck lymph nodes (cN0) who had either advanced primary tumors (T3 or T4) or clinically involved lateral neck nodes (cN1b), in accordance with the 2015 ATA guidelines (16). Of the 942 patients with cN0 PTC, 213 patients underwent PCLND. However, 343 patients who were eligible for PCLND did not undergo the procedure, based on the treating surgeon’s discretion. Only structural recurrence (local, regional, or distant) was considered for analysis. Recurrence was defined as any newly detected tumor (local or distant) or metastatic regional lymph node (LN), based on ultrasound and/or imaging studies in patients who had been previously free of disease following initial treatment. Regional lymph node metastases were further confirmed by cytological and/or histological examination. Persistent disease was defined as the presence of serum Tg at detectable levels, persisting/ increasing Tg antibody levels, or occurrence of structural disease within 1 year after surgery. Localized PTC was defined as tumor confined to the thyroid without any extrathyroidal extension, LN metastasis, or distant metastasis, at the time of diagnosis. Radioactive iodine (RAI) refractory disease and risk categories were defined based on 2015 ATA guidelines (16).

BRAF and TERT Mutation Analysis
BRAF and TERT mutation data were assessed in our laboratory by Sanger sequencing and have been published by us previously (20, 21).

Follow-Up and Study Endpoint
Patients were regularly followed up by both physical examinations and imaging studies to identify tumor recurrence. The median follow-up was 9.3 years (range, 1.0–30.1 years). Recurrence-free survival (RFS) was defined as the time (in months) from date of initial surgery to the occurrence of any tumor recurrence (local, regional, or distant). In case of no recurrence, date of last follow-up was the study endpoint for RFS.

Statistical Analysis
The associations between clinico-pathological variables and sex were performed using contingency table analysis and Chi square tests. Mantel–Cox log-rank test was used to evaluate RFS. Survival curves were generated using the Kaplan–Meier method. Cox proportional hazards model was used for multivariate analysis. Two-sided tests were used for statistical analyses with a limit of significance defined as p-value < 0.05. Data analyses were performed using the JMP14.0 (SAS Institute, Inc., Cary, NC) software package.

RESULTS

Patient and Tumor Characteristics
Median age of the study population was 39.2 years (range: 18–88 years), with a male-to-female ratio of 1:3. The majority of tumors were classical variants of PTC (66.0%; 943/1,430); 31.2% (446/1,430) of tumors were bilateral and 48.7% (697/1,430) were multifocal; 42.6% (609/1,430) of tumors exhibited extrathyroidal
Clinico-Pathological Associations of Male Sex in PTC
In our cohort, 24.1% (345/1430) of patients were male and 75.9% (1085/1430) were female. Male sex was associated with aggressive clinico-pathological characteristics such as older age (p = 0.0003), extrathyroidal extension (p = 0.0086), lymphovascular invasion (p = 0.0129), advanced T stage (p = 0.0069), LN metastasis (p = 0.0279), distant metastasis (p = 0.0101), and stage IV tumors (p = 0.0074). Male sex was also associated with tumor recurrence (p < 0.0001). To further corroborate the association of male sex with tumor recurrence, we analyzed the association of sex with ATA risk categories. Indeed, male sex was significantly associated with ATA high risk tumors (p = 0.0001). In addition, we found male sex to be associated with RAI refractoriness (p = 0.0014). Since BRAF and TERT mutation have been shown to be associated with RAI refractoriness, we sought to see if these mutations had a predilection for male sex. Although TERT mutation was associated with male sex (p = 0.0003), BRAF was not (p = 0.0938) (Table 2).

Since our cohort had a high rate of high-risk patients and we found a significant association between male sex and high-risk PTC, we sought to further analyze the clinico-pathological associations of male sex stratified by ATA risk categories. We found that male sex was associated with tumor recurrence in high-risk PTC (p = 0.0031), which stands true even on multivariate analysis (HR = 2.79, 95% CI = 1.45–5.76, p = 0.0016). In addition, male sex was associated with RAI refractoriness (p = 0.0085) and TERT mutation (p = 0.0341) in high-risk PTC. In intermediate-risk cases, male sex was found to be associated with other aggressive clinico-pathological characteristics, such as bilateral tumors (p = 0.0374) and advanced T stage (p = 0.0443). However, in both intermediate- and low-risk PTC, male sex was not associated with recurrence (Supplementary Tables 1–3).

Recurrence Rate in Male and Female PTC Stratified by Stage
Since stage of tumor is an important prognostic factor, we sought to determine the recurrence rate in male and female PTCs among early-stage (stage I and II) and late-stage (stage III and IV) tumors.
We found a significantly higher recurrence rate among men than women in early-stage tumors (24.2% vs. 14.4%; \(p < 0.0001\)), whereas the difference was not significant between male and female sex in late-stage PTC (57.1% vs. 40.0%; \(p = 0.1529\)) (Figure 1).

**Prognostic Significance of Sex in PTC**

We next analyzed the prognostic significance of sex in PTC. Male sex was associated with poor RFS (\(p < 0.0001\); Figure 2). On multivariate analysis using Cox proportional hazards model, male sex was found to be an independent predictor of poor RFS (hazard ratio = 1.58; 95% confidence interval = 1.20–2.06; \(p = 0.0011\)), when adjusted for other clinico-pathological parameters. In addition, we also found age, tumor laterality, LN metastasis, distant metastasis, tumor stage, and ATA risk category to be independent predictors of RFS (Table 3).

Since age is an important determinant of prognosis, we stratified the patients into younger age (<55 years) and older age (≥55 years).
to analyze the prognostic differences with regard to sex. Interestingly, we found male sex to be associated with poor RFS ($p < 0.0001$; Figure 3A) only in the younger age PTCs but not in the older age PTCs ($p = 0.1659$; Figure 3B). We also analyzed the prognostic significance of sex in localized PTCs and found that male sex was associated with poor RFS ($p = 0.0015$; Figure 3C).

**DISCUSSION**

While sex disparity in the incidence of PTC and its clinical impact have been well documented, detailed analysis of prognostic impact of sex on PTC from Middle Eastern ethnicity has not been fully illustrated. Our study of more than 1,400 adult PTCs documented their clinico-pathological characteristics and demonstrated significantly more aggressive disease in men than women. The presence of extrathyroidal extension and lymphovascular invasion was seen significantly more commonly in men than women. There was a higher rate of distant metastasis and regional LN metastasis in men than women. Moreover, a higher rate of advanced disease (stage II, III, and IV according to the latest AJCC staging system) and a higher rate of patients with intermediate- or high-risk disease were also observed in male PTC patients. Interestingly, our subgroup analysis showed that aggressive PTC was more common in men even at young age. This further supports the notion that men inherently have more aggressive PTC behavior, which may not be attributable solely to delay in diagnosis. Several previous studies have shown the association between male sex and advanced disease (9, 10, 13, 22, 23).
TABLE 3 | Multivariate analysis using Cox proportional hazard model for recurrence-free survival.

| Clinico-pathological variables | Recurrence-free survival |
|-------------------------------|--------------------------|
|                               | Hazard ratio | 95% Confidence interval | p-value |
| Age ≥55 years (vs. <55 years) | 2.66         | 1.91–3.64               | <0.0001 |
| Sex Male (vs. Female)         | 1.58         | 1.20–2.06               | 0.0011  |
| Histology Aggressive variants (vs. non-aggressive variants) | 0.98 | 0.66–1.41 | 0.9003 |
| Tumor laterality Bilateral (vs. Unilateral) | 1.56 | 1.03–2.44 | 0.0366 |
| Tumor focality Multifocal (vs. Unifocal) | 0.73 | 0.47–1.10 | 0.1325 |
| Extrathyroidal extension Present (vs. Absent) | 1.20 | 0.87–1.66 | 0.2616 |
| Lymphovascular invasion Present (vs. Absent) | 0.96 | 0.68–1.33 | 0.7948 |
| pT T3–4 (vs. T1–2) | 1.02 | 0.76–1.35 | 0.9093 |
| Lymph node metastasis Present (vs. Absent) | 1.76 | 1.31–2.40 | 0.0002 |
| Distant metastasis Present (vs. Absent) | 5.34 | 3.46–8.09 | <0.0001 |
| TNM stage III–IV (vs. I–II) | 0.50 | 0.28–0.86 | 0.0123 |
| ATA risk category Low risk Reference | | | |
| Intermediate risk | 1.47 | 0.76–3.01 | 0.2579 |
| High risk | 2.79 | 1.45–5.76 | 0.0016 |

FIGURE 3 | Recurrence-free survival stratified by age and disease localization. (A) Kaplan–Meier survival curve showing poor recurrence-free survival in male sex compared to female sex in patients aged <55 years (p < 0.0001). (B) Kaplan–Meier survival curve showing no significant difference in recurrence-free survival between male and female sex in patients aged ≥55 years (p = 0.1659). (C) Kaplan–Meier survival curve showing poor recurrence-free survival in male sex compared to female sex in patients with localized PTC (p = 0.0015).
Median age of the study population was 39.2 years. This finding is similar to studies from other Middle Eastern ethnicities (24–27), but lower than that seen in Western population (28). This most likely represents the inherent aggressive nature of PTC in the Middle Eastern ethnicity. Another consideration that needs to be taken into account is the age of the general population. In Saudi Arabia, the population pyramid is skewed toward younger age groups, showing a cone-shaped pattern. Indeed, nearly 60% of the Saudi population are under the age of 30 years. It has been shown previously that age of the population could partly explain the variability of age of onset for cancer, whereby younger populations tended to have a higher incidence of early-onset cancer (29, 30).

The rate of recurrence was 18.2% (260/1,430) in the overall cohort, which is relatively higher than what has been reported previously (31–33). The long follow-up duration and the low rate of PCLND may have contributed to the relatively high rate of recurrence in our study. The long median follow-up of 9.5 years might increase the likelihood to detect more recurrence in PTC patients than other studies with shorter median follow-up. In addition, PCLND has not been routinely performed in our center but rather it was performed based on tumor size and LN status, according to ATA guidelines (16). However, we have found that 343 PTC patients met the criteria for PCLND and yet did not undergo the procedure. In fact, 21.9% (75/343) of these patients developed recurrence during the follow-up period, which further contributed to the relatively high recurrence rate in our study. Furthermore, our study showed a higher recurrence risk in men than women. The recurrence risk was 1.7-fold higher in men presenting with AJCC stage I and II, compared to women. However, recurrence risk does not show significant difference between men and women for AJCC stage III and IV.

Our study findings showed that men had significantly poor RFS even in multivariate analysis where tumor stage and other influencing factors were considered. Moreover, significant prognostic differences between men and women was noted even when PTC was localized to the thyroid gland, which may suggest a truly aggressive PTC behavior in Middle Eastern men, even with small tumor size. Some previous studies have shown that sex was associated with poor prognosis (12, 23, 34, 35), whereas others found no prognostic difference between men and women (13–15). The lack of consensus among previous studies could be attributed to cohort size, classification used, and the inability to differentiate persistent disease from recurrent disease.

Another important finding is the significant association between male PTC and RAI refractoriness (RAIR). We attempted to explore the molecular features that might contribute to RAIR in male PTC patients, especially BRAF and TERT mutations. A large body of evidence have documented the correlation between BRAF and/or TERT mutation and poor RAI response (36–38). BRAF mutation data were available for 1,369 patients while TERT mutations were available in 1,288 patients of the study cohort. Interestingly, no correlation between BRAF mutations and male PTC patients was noted. However, a significantly higher rate of TERT mutations was observed in male PTC patients compared to female patients. A large meta-analyses, involving 32 studies, also found a significant association between TERT promoter mutations and male sex (39).

Our study has certain limitations. First, it has a historical, retrospective nature, it lacks complete information on some tumor features including TERT and BRAF mutations, and 3% of the patients were lost to follow-up. Second, the study cohort was limited to Middle Eastern ethnicity and it is from a single center that could slightly impact the generalizability of our results to other populations. Thirdly, our study population included a high rate of high-risk patients, which could be attributed to genetics or differences in presentation owing to the unique ethnicity. Whether this could also be partly attributed to delay in seeking healthcare remains to be explored.

In summary, our study demonstrated that men present with more advanced stage of disease, at older age and with higher rate of aggressive molecular and histopathological features. Men have a higher rate of recurrence and a shorter recurrence-free survival. Moreover, male gender was an independent prognostic factor for RFS in Middle Eastern PTC patients. Overall, the results of this study strongly suggest that sex should be considered as an important predictor of prognosis and therefore men with PTC may benefit from more aggressive initial treatment and intense follow-up.

**DATA AVAILABILITY STATEMENT**

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

**ETHICS STATEMENT**

The studies involving human participants were reviewed and approved by the Research Ethics Committee, King Faisal Specialist Hospital and Research Centre. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

**AUTHOR CONTRIBUTIONS**

Study concept and design: KA-K, SP, and AS. Executed the study: SP, AS, PA, NS, SA-S, and FA-D. Statistical analysis: SP. Drafting the article: KA-K, AS, and SP. Critical revision of the article for important intellectual content, writing of the article, and approval of the final version: KA-K, SP, AS, PA, NS, SA-S, and FA-D. All authors contributed to the article and approved the submitted version.

**ACKNOWLEDGMENTS**

The authors would like to thank Felisa DeVera for her technical assistance.

**SUPPLEMENTARY MATERIAL**

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fendo.2022.777345/full#supplementary-material
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