Male sex is not an independent risk factor for recurrence of differentiated thyroid cancer: a propensity score-matching study

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Male patients have a significantly higher prevalence of advanced-stage thyroid cancer. However, sex differences in the risk of differentiated thyroid carcinoma (DTC) recurrence have not been fully elucidated. Therefore, the present study aimed to investigate male sex as a prognostic factor for DTC. We assessed 5566 patients with DTC who underwent thyroid surgery between January 2009 and December 2015 at Seoul St. Mary’s Hospital (Seoul, Korea). Clinicopathological characteristics and long-term oncologic outcomes between female and male patients with DTC were compared using propensity score matching to reduce selection bias. The mean follow-up duration was 99.9 ± 18.7 months. The recurrence rate was significantly higher in male patients than female patients before matching (3.3% vs. 2.2%, p = 0.030), and there was no significant difference in recurrence rates between the matched groups after matching (3.0% vs. 2.5%, p = 0.591). Based on Kaplan–Meier analysis, the two groups did not significantly differ in disease-free survival after matching. Multivariate analysis revealed that male sex was not an independent prognostic factor of DTC recurrence. Male sex did not have a significant effect on DTC recurrence. Further studies with larger cohorts are required to validate the findings of this study.

Thyroid cancer is one of the most common endocrine malignancies. The incidence of thyroid cancer has substantially increased worldwide in the last several decades¹–³. Differentiated thyroid carcinoma (DTC), including papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), and Hurthle cell carcinoma, is the most common malignancy of the thyroid gland¹. In terms of overall incidence, DTC accounts for 1%–1.5% of all cases of cancer, and its incidence is three times higher in female patients than male patients²,⁵,⁶.

Generally, DTC has an excellent prognosis because of its indolent features. According to a Surveillance, Epidemiology, and End Results report, patients with DTC have an overall survival rate of 90%–95%⁷. However, some clinicopathological risk factors, including age, tumor size, lymph node (LN) metastasis, and extrathyroidal extension (ETE), are associated with the aggressive nature and high recurrence of DTC⁸. The American Thyroid Association (ATA) management guidelines have proposed a clinicopathological risk stratification system that can be used for classifying patients as those who are at low, intermediate, or high risk. Using this system, several factors, such as ETE, LN metastasis, aggressive histology, vascular invasion, and multifocality were found to be associated with increased risk of recurrence⁹. However, sex is not considered a risk factor for recurrence.

DTC is more prevalent in women than men but the cause is not fully elucidated¹⁰. Li et al. reported that male patients had a 0.78-fold risk of developing malignancy and larger tumor size than female patients¹¹. Moreover, male patients had a significantly higher prevalence of advanced-stage thyroid cancer, LN metastasis, and ETE¹². Some studies have reported that sex, age, tumor size, aggressive histology, ETE, and LN metastasis were significant prognostic factors for thyroid cancer¹³–¹⁷. The impact of sex on the risk of DTC recurrence is controversial, and results pertaining to this concept vary in the literature¹⁴,¹⁶,¹⁸–²¹. Toniato et al. and several other studies have concluded that sex does not significantly contribute to recurrence and survival¹⁶,²⁰. By contrast, Zahedi et al. studied patients with DTC who were > 18 years old and showed that the recurrence rate was higher in males than in females, a finding supported by other studies¹⁴,¹¹,¹⁹. In another novel study, Choi H. et al. summarized secular trends by analyzing results to date and found that the poor outcome of PTC associated with men decreased over time, whereas aggressive pathological features remained the same or increased over time²¹.

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Therefore, the current study aimed to compare the clinicopathological characteristics and long-term oncologic outcomes between females and males with DTC using propensity score matching to reduce selection bias.

## Results

Comparison of clinicopathological characteristics between female and male patients before and after propensity score matching. Table 1 shows the baseline clinicopathological characteristics of female and male patients before and after propensity score matching. In terms of age, males were significantly younger than females (45.8 ± 11.8 years vs. 46.8 ± 12.2 years, p = 0.017). The surgical extent was significantly more extensive in males than females (0.001). Tumor size was significantly larger in males than females (1.1 ± 0.8 cm vs. 0.9 ± 0.7 cm, p < 0.001). The incidence of lymphatic and vascular invasions was significantly higher in males than females (34.3% vs. 24.6%, p < 0.001 and 4.0% vs. 1.9%, p < 0.001, respectively). Female patients had a significantly higher prevalence of ETE that male patients (5.7% vs. 3.9%, p = 0.022). Moreover, the proportion of harvested and positive LNs was higher in males than females (12.6 ± 16.7 vs. 10.7 ± 12.1, p < 0.001 and 3.1 ± 4.9 vs. 1.7 ± 3.4, p < 0.001, respectively). Males had significantly more advanced N and TNM stage than females.

### Table 1

Comparison of clinicopathological characteristics between females and males before and after propensity score matching. Data are expressed as patient's number (%), or mean ± SD. A statistically significant difference was defined as p < 0.05.

| Feature                  | Before matching | After matching | p-value | Before matching | After matching | p-value |
|--------------------------|-----------------|----------------|---------|-----------------|----------------|---------|
| Age (years)              | Female (n = 4420) 46.8 ± 12.2 (range, 12–88) | Male (n = 1146) 45.8 ± 11.8 (range, 11–81) | 0.017 | Female (n = 1040) 46.5 ± 12.4 (range, 14–79) | Male (n = 1040) 46.2 ± 11.8 (range, 11–81) | 0.535 |
| Extent of operation      | 0.001           | 0.376          |         | 0.823           | 0.986          |         |
| Less than TT             | 3313 (75.0%)    | 805 (70.2%)    |         | 764 (73.5%)     | 745 (71.6%)   |         |
| TT and/or mRND           | 1107 (25.0%)    | 341 (28.9%)    |         | 276 (26.5%)     | 295 (28.4%)   |         |
| Type of carcinoma        | 0.823           | 0.986          |         |                 |                |         |
| PTC                      | 4333 (98.0%)    | 1124 (98.1%)   |         | 1018 (97.9%)    | 1019 (98.0%)  |         |
| FTC                      | 75 (1.7%)       | 18 (1.6%)      |         | 18 (1.7%)       | 17 (1.6%)     |         |
| HTC                      | 12 (0.3%)       | 4 (0.3%)       |         | 4 (0.4%)        | 4 (0.4%)      |         |
| Tumor size (cm)          | 0.9 ± 0.7 (range, 0.2–9.0) | 1.1 ± 0.8 (range, 0.2–5.5) | <0.001 | 1.1 ± 0.8 (range, 0.2–6.5) | 1.1 ± 0.8 (range, 0.2–5.5) | 0.933 |
| ETE                      | 250 (5.7%)      | 45 (3.9%)      |         | 39 (3.8%)       | 40 (3.8%)     | 0.809  |
| Multifocality            | 1708 (38.6%)    | 446 (38.9%)    | 0.865   | 398 (38.3%)     | 390 (37.5%)   | 0.752  |
| Bilaterality             | 414 (9.4%)      | 101 (8.8%)     | 0.607   | 101 (9.7%)      | 82 (7.9%)     | 0.163  |
| Lymphatic invasion       | 1086 (24.6%)    | 393 (34.3%)    | <0.001  | 326 (31.3%)     | 325 (31.3%)   | 0.962  |
| Vascular invasion        | 83 (1.9%)       | 46 (4.0%)      | <0.001  | 35 (3.4%)       | 35 (3.4%)     | 1.000  |
| Perineural invasion      | 81 (1.8%)       | 24 (2.1%)      | 0.544   | 21 (2.0%)       | 20 (1.9%)     | 0.875  |
| BRAFV600E positive       | 2871/3650 (78.7%) | 748/929 (80.5%) | 0.223   | 659/866 (76.1%) | 675/846 (79.8%) | 0.071  |
| Harvested LNs            | 10.7 ± 12.1     | 12.6 ± 16.7    | <0.001  | 10.8 ± 12.3     | 11.7 ± 15.2   | 0.109  |
| Positive LNs             | 1.7 ± 3.4       | 3.1 ± 4.9      | <0.001  | 2.4 ± 3.8       | 2.6 ± 3.9     | 0.355  |
| T stage                  | 0.710           | 0.779          |         |                 |                |         |
| T1                       | 3911 (88.5%)    | 991 (86.5%)    | 924 (88.8%) | 909 (87.4%)    |                |         |
| T2                       | 218 (4.9%)      | 91 (7.9%)      | 64 (6.2%) | 74 (7.1%)      |                |         |
| T3a                      | 41 (0.5%)       | 19 (1.7%)      | 13 (1.3%) | 17 (1.6%)      |                |         |
| T3b                      | 238 (5.4%)      | 44 (3.8%)      | 37 (3.6%) | 39 (3.8%)      |                |         |
| T4a                      | 12 (0.3%)       | 1 (0.1%)       | 2 (0.2%) | 1 (0.1%)       |                |         |
| N stage                  | <0.001          | 0.502          |         |                 |                |         |
| N0                       | 2351 (53.2%)    | 471 (41.1%)    | 456 (43.8%) | 455 (43.8%)    |                |         |
| N1a                      | 1880 (42.5%)    | 597 (52.1%)    | 533 (51.3%) | 522 (50.2%)    |                |         |
| N1b                      | 189 (4.3%)      | 78 (6.8%)      | 51 (4.9%) | 63 (6.1%)      |                |         |
| M stage                  | 0.471           | 0.530          |         |                 |                |         |
| M1                       | 2 (0.0%)        | 0 (0.0%)       | 0 (0%)   | 0 (0%)         |                |         |
| TNM stage                | 0.021           |                |         |                 | 0.530          |         |
| Stage I                  | 3903 (88.3%)    | 983 (85.8%)    | 887 (85.3%) | 898 (86.3%)    |                |         |
| Stage II                 | 516 (11.7%)     | 163 (14.2%)    | 153 (14.7%) | 142 (13.7%)    |                |         |
| Stage III                | 1 (0.0%)        | 0 (0%)         | 0 (0%)   | 0 (0%)         |                | 0.530  |
| Recurrence               | 96 (2.2%)       | 38 (3.3%)      | 0.030   | 26 (2.5%)       | 31 (3.0%)     | 0.591  |
A significantly higher recurrence rate was observed in males than females before matching (3.3% vs. 2.2%, \( p = 0.030 \)).

Propensity score matching yielded 1040 matched pairs of patients. There were no significant differences in clinicopathological characteristics, including the recurrence rate, between the matched groups (Table 1).

### Univariate and multivariate analyses of the risk factors for recurrence before propensity score matching

| Risk Factor                  | Univariate HR (95% CI) | p-value | Multivariate HR (95% CI) | p-value |
|------------------------------|-------------------------|---------|--------------------------|---------|
| Gender                       |                         |         |                          |         |
| Female                       | Ref.                    |         |                          |         |
| Male                         | 1.552 (1.066–2.259)     | 0.022   |                          |         |
| Age (years)                  |                         |         |                          |         |
| > 45                         | Ref.                    |         | Ref.                     |         |
| ≤ 45                         | 2.192 (1.537–3.125)     | < 0.001 | 1.841 (1.278–2.652)      | 0.001   |
| Extent of operation          |                         |         |                          |         |
| Less than TT                 | Ref.                    |         |                          |         |
| TT and/or mRND               | 1.821 (1.286–2.577)     | 0.001   |                          |         |
| Tumor size                   |                         |         |                          |         |
| < 1 cm                       | Ref.                    |         |                          |         |
| ≥ 1 cm                       | 2.136 (1.522–2.998)     | < 0.001 |                          |         |
| ETE                          | 3.409 (2.140–5.432)     | < 0.001 | 2.196 (1.305–3.695)      | 0.003   |
| Multifocality                | 1.563 (1.114–2.193)     | 0.010   |                          |         |
| Bilaterality                 | 1.744 (1.084–2.805)     | 0.022   |                          |         |
| Lymphatic invasion           | 3.202 (2.281–4.496)     | < 0.001 |                          |         |
| Vascular invasion            | 3.471 (1.822–6.611)     | < 0.001 | 2.504 (1.286–4.876)      | 0.007   |
| Perineural invasion          | 3.335 (1.632–6.815)     | 0.001   |                          |         |
| Harvested LNs                | 1.021 (1.014–1.028)     | < 0.001 |                          |         |
| Positive LNs                 | 1.076 (1.063–1.088)     | < 0.001 | 1.062 (1.041–1.083)      | < 0.001 |
| T stage                      |                         |         |                          |         |
| T1                           | Ref.                    |         |                          |         |
| T2                           | 2.488 (1.445–4.285)     | 0.001   |                          |         |
| T3b                          | 3.649 (2.256–5.903)     | < 0.001 |                          |         |
| T4a                          | 3.928 (0.548–28.173)    | 0.173   |                          |         |
| N stage                      |                         |         |                          |         |
| N0                           | Ref.                    |         |                          |         |
| N1a                          | 4.350 (2.797–6.765)     | < 0.001 | 3.159 (2.015–4.955)      | < 0.001 |
| N1b                          | 7.002 (3.738–13.116)    | < 0.001 | 1.488 (0.630–3.512)      | 0.364   |

\( p < 0.001 \) and \( p = 0.021 \), respectively.

### Table 2. Univariate and multivariate analyses of risk factors for recurrence before propensity score matching.

Data are expressed as hazard ratio (HR) and 95% confidence interval (CI). A \( p \) value < 0.05 was considered statistically significant. TT total thyroidectomy, mRND modified radical neck dissection, ETE extrathyroidal extension, LN lymph node, T tumor, N node.

Univariate and multivariate analyses of the risk factors for recurrence before and after propensity score matching. Table 2 presents the univariate and multivariate Cox regression analysis results for the risk factors of recurrence before propensity score matching. Age ≤ 45 years (hazard ratio (HR) 1.841; 95% confidence interval (CI) 1.278–2.652; \( p = 0.001 \)), ETE (HR 2.196; 95% CI 1.305–3.695; \( p = 0.003 \)), vascular invasion (HR 2.504; 95% CI 1.286–4.876; \( p = 0.007 \)), and number of positive LNs were considered to be significant predictors of recurrence (HR 1.062; 95% CI 1.041–1.083; \( p < 0.001 \)). Among the various risk factors, N1a stage was the most significant predictor of recurrence (HR 3.159; 95% CI 2.015–4.955; \( p < 0.001 \)).

After propensity score matching, the number of positive LNs (HR 1.193; 95% CI 1.129–1.260; \( p < 0.001 \)) and N1a stage (HR 2.401; 95% CI 1.010–5.708; \( p = 0.047 \)) were found to be significant predictors of recurrence (Table 3). In the Kaplan–Meier analysis, disease-free survival (DFS) was significantly differed between the two groups before matching (\( p = 0.021 \), Fig. 1). However, there was no significant difference in DFS between the two groups after matching (\( p = 0.492 \), Fig. 2).

Subgroup analysis between female and male patients aged between 20 and 45 years before and after propensity score matching. The baseline clinicopathological characteristics of female and male patients aged between 20 and 45 years are summarized in Table 4. Before propensity score matching, age was considered to be a significant factor. That is, males were significantly older than females (36.8 ± 5.2 vs. 35.8 ± 6.2 years, \( p = 0.001 \)). Moreover, males underwent significantly more extensive surgeries than females.
The incidence of lymphatic invasion was significantly higher in males than in females (36.8% vs. 30.3%, \( p = 0.003 \)). Male patients had a significantly higher proportion of harvested and positive LNs than female patients (13.9 ± 16.9 vs. 11.4 ± 13.0, \( p < 0.001 \) and 3.6 ± 5.3 vs. 2.2 ± 3.8, \( p < 0.001 \), respectively). N stage was significantly more advanced in males than females (\( p < 0.001 \)). However, there were no significant differences in recurrence rates between the two groups (\( p = 0.086 \)).

Propensity score matching yielded 515 matched pairs of patients. There were no significant differences in clinicopathological characteristics between the matched groups (Table 4).

Table 5 depicts the risk factors for recurrence among patients aged between 20 and 45 years after propensity score matching. Lymphatic invasion (HR 2.214; 95% CI 1.118–4.381; \( p = 0.023 \)) and the proportion of positive LNs (HR 1.071; 95% CI 1.028–1.115; \( p < 0.001 \)) were considered to be significant predictors of recurrence.

### Table 3. Univariate and multivariate analyses of risk factors for recurrence after propensity score matching.

Data are expressed as hazard ratio (HR) and 95% confidence interval (CI). A \( p \) value < 0.05 was considered statistically significant. ETE extrathyroidal extension, LN lymph node, T tumor, N node.

|                        | Univariate   | Multivariate |
|------------------------|--------------|--------------|
|                        | HR (95% CI)  | p-value      | HR (95% CI)  | p-value      |
| **Tumor size**         |              |              |
| < 1 cm                 | Ref.         |              |              |              |
| ≥ 1 cm                 | 2.155 (1.281–3.624) | 0.004        |              |              |
| ETE                    | 4.330 (2.050–9.144) | < 0.001      |              |              |
| **Bilaterality**       |              |              |
|                       | 2.259 (1.141–4.471) | 0.019        |              |              |
| **Lymphatic invasion** | 4.185 (2.429–7.210) | < 0.001      |              |              |
| **Perineural invasion**| 3.787 (1.370–10.464) | 0.010        |              |              |
| **Harvested LNs**      | 1.022 (1.012–1.032) | < 0.001      |              |              |
| **Positive LNs**       | 1.152 (1.115–1.190) | < 0.001      | 1.193 (1.129–1.260) | < 0.001      |
| **T stage**            |              |              |
| T1                     | Ref.         |              |              |              |
| T2                     | 3.079 (1.494–6.346) | 0.002        |              |              |
| T3b                    | 5.077 (2.376–10.847) | < 0.001      |              |              |
| **N stage**            |              |              |
| N0                     | Ref.         |              | Ref.         |              |
| N1a                    | 5.432 (2.444–12.077) | < 0.001      | 2.401 (1.010–5.708) | 0.047        |
| N1b                    | 8.255 (2.895–23.542) | < 0.001      | 0.545 (0.121–2.464) | 0.431        |

**Figure 1.** Disease-free survival curves of female and male groups before propensity score matching (log-rank \( p = 0.021 \)).
Subgroup analysis between female and male patients aged over 45 years before and after propensity score matching. Table 6 presents the baseline clinicopathological characteristics of females and males aged over 45 years before and after propensity score matching. The tumor size was significantly larger in males than in females (1.1 ± 0.9 vs. 1.0 ± 0.7 cm, \( p < 0.001 \)). Males had a significantly higher prevalence of ETE than females (4.5% vs 7.5%, \( p = 0.024 \)). The incidence of lymphatic and vascular invasions was significantly higher in males than in females (31.2% vs. 19.7%, \( p < 0.001 \) and 4.5% vs. 1.7%, \( p < 0.001 \), respectively). Males had a significantly higher proportion of positive LNs than females (2.4 ± 4.2 vs. 1.3 ± 2.6, \( p < 0.001 \)). Further, male patients had a significantly higher T, N, and TNM stage than female patients (\( p < 0.001 \) and \( p < 0.001 \), respectively). The recurrence rate was significantly higher in males than in females (2.9% vs 1.3%, \( p = 0.012 \)). After matching, the recurrence rate did not significantly differ between the two groups (\( p = 0.301 \)).

The risk factors for recurrence in patients aged > 45 years after propensity score matching are shown in Table 7. Multifocality (HR 3.438; 95% CI 1.143–10.342; \( p = 0.028 \)) and the proportion of positive LNs (HR 1.259; 95% CI 1.117–1.429; \( p < 0.001 \)) were found to be significant predictors of recurrence.

**Discussion**

DTC is the most common endocrine malignancy, and it usually has a favorable prognosis, with a 10-year disease-specific survival rate of > 90%2,22–24. However, some patients can develop local recurrence or distant metastasis to the lung and/or bone, resulting in death. This finding indicates that DTC can progress via different clinical pathways. Several clinicopathological factors, including age, tumor size, ETE, multifocality, LN metastasis, and histologic type, were found to be significant prognostic factors for DTC25–28. The ATA management guidelines have proposed a risk stratification system based on significant prognostic factors9. The American Joint Committee on Cancer/Union for International Cancer Control TNM staging system has been widely used for predicting the prognosis of DTC29. However, sex has not been considered a prognostic factor in the commonly used staging systems.

Male sex was associated with a lower DFS and disease-specific survival based on previous studies18,30–33. However, some reports showed that the overall survival was not affected by sex34,35. A prognostic factor correlated with sex is not a consistent finding, and the effect of sex on DFS has not yet been validated. Recently, Zahedi et al. reported that the risk of DTC recurrence is higher in men than in women18. Thus, this study aimed to evaluate the effect of sex on long-term prognosis of DTC.

This study compared the clinicopathological characteristics and long-term oncologic outcomes of male and female patients with DTC. Results showed that compared with females, males had significantly larger tumor sizes, higher prevalence of ETE and lymphatic and vascular invasions and greater proportions of positive LNs and TNM stage. This result is consistent with that of previous studies showing that men were more likely to present with more aggressive disease characteristics11,12,36,37. The recurrence rate was significantly higher in males than in females (3.3% vs. 2.2%, \( p = 0.030 \)). However, this result may not be accurate with respect to disease severity.

In this study, the impact of sex was assessed in patients with DTC. However, a significant difference was observed between males and females in terms of several clinicopathological characteristics. That is, males were significantly younger than females. Furthermore, male sex was significantly associated with more aggressive tumor characteristics, including larger tumor size, higher incidence of ETE and lymphatic and vascular invasion,
and greater TNM stage and proportion of positive LNs. Therefore, the findings of this study were affected by several confounding factors, including selection bias, between the two groups. To minimize the effects of these factors, propensity score matching analysis was performed to adjust for several clinicopathological characteristics. After matching, the recurrence rates between female and male patients did not significantly differ (2.5% vs. 3.0%, \( p = 0.591 \)).

We performed multivariate Cox regression and Kaplan–Meier analyses to identify whether sex was independently associated with DFS before and after propensity score matching. Before matching, male sex was considered to be a significant predictor of recurrence (HR 1.552; \( p = 0.022 \)) based on the univariate analysis. A statistically significant difference was also observed in the Kaplan–Meier analysis (log-rank test, \( p = 0.021 \)). However, sex was not an independent prognostic factor for recurrence in multivariate analysis. Several studies have reported that male sex was not an independent risk factor for survival in DTC20,37. After matching, our analyses confirmed that sex was not a significant predictor of DTC recurrence.

It is difficult to explain why the DFS did not significantly differ between male and female patients with DTC in the current study. However, this result may be attributed to the long-term decreasing prognostic potential of male sex. Choi et al. have assessed secular trends in the prognostic factors for PTC. They reported that the risk for poor outcomes associated with male sex decreased over time in PTC. However, the risk associated with pathologic characteristics remained the same or increased over time21. Further, another study has shown that young women had a better prognosis, and the outcomes were similar between men and those aged > 55 years33. Therefore, a subgroup analysis was conducted to evaluate the differences in prognosis between male and female

|                      | Before matching | After matching |
|----------------------|-----------------|---------------|
|                      | Female (n = 1948) | Male (n = 587) | p-value   | Female (n = 515) | Male (n = 515) | p-value   |
| Age (years)          | 35.8 ± 6.2 (range, 20–45) | 36.8 ± 5.2 (range, 20–45) | 0.001 | 36.8 ± 6.0 (range, 20–45) | 36.7 ± 5.2 (range, 20–45) | 0.722 |
| Extent of operation  | 0.001           |               |         | 0.946           |               |         |
| Less than TT         | 1470 (75.5%)    | 402 (68.5%)   |         | 356 (69.1%)     | 355 (68.9%)   |         |
| TT and/or mRND       | 478 (24.5%)     | 185 (31.5%)   |         | 159 (30.9%)     | 160 (31.1%)   |         |
| Type of carcinoma    | 0.283           |               |         | 0.155           |               |         |
| PTC                  | 1915 (98.3%)    | 576 (98.1%)   |         | 510 (99.0%)     | 504 (97.9%)   |         |
| FTC                  | 30 (1.5%)       | 8 (1.4%)      |         | 5 (1.0%)        | 8 (1.6%)      |         |
| HTC                  | 3 (0.2%)        | 3 (0.5%)      |         | 0 (0%)          | 3 (0.6%)      |         |
| Tumor size (cm)      | 1.0 ± 0.7 (range, 0.2–9.0) | 1.0 ± 0.7 (range, 0.2–5.5) | 0.072 | 1.0 ± 0.8 (range, 0.2–9.0) | 1.0 ± 0.7 (range, 0.2–5.5) | 0.589 |
| ETE                  | 71 (3.6%)       | 19 (3.2%)     |         | 20 (3.9%)       | 18 (3.5%)     |         |
| Multifocality        | 653 (33.5%)     | 206 (35.1%)   | 0.486   | 174 (33.8%)     | 172 (33.4%)   | 0.947   |
| Bilaterality         | 136 (8.0%)      | 47 (8.0%)     | 0.999   | 50 (9.7%)       | 37 (7.2%)     | 0.178   |
| Lymphatic invasion   | 590 (30.3%)     | 216 (36.8%)   | 0.003   | 186 (36.1%)     | 180 (35.0%)   | 0.745   |
| Vascular invasion    | 40 (2.1%)       | 18 (3.1%)     | 0.157   | 15 (2.9%)       | 15 (2.9%)     | 1.000   |
| Perineural invasion  | 26 (1.3%)       | 11 (1.9%)     | 0.330   | 7 (1.4%)        | 9 (1.7%)      | 0.802   |
| BRAFV600E positive   | 1250/1608 (77.7%) | 388/476 (81.5%) | 0.234  | 322/416 (77.4%) | 337/417 (80.8%) | 0.798  |
| Harvested LNs        | 11.4 ± 13.0     | 13.9 ± 16.9   | < 0.001 | 13.0 ± 15.2     | 13.1 ± 15.4   | 0.798   |
| Positive LNs         | 2.2 ± 3.8       | 3.6 ± 5.3     | < 0.001 | 3.2 ± 5.1       | 3.1 ± 4.5     | 0.816   |
| T stage              | 0.219           |               |         | 0.748           |               |         |
| T1                   | 1745 (89.6%)    | 519 (88.4%)   |         | 460 (89.3%)     | 455 (88.3%)   |         |
| T2                   | 116 (6.0%)      | 47 (8.0%)     |         | 32 (6.2%)       | 40 (7.8%)     |         |
| T3a                  | 16 (0.8%)       | 2 (0.3%)      |         | 3 (0.6%)        | 2 (0.4%)      |         |
| T3b                  | 67 (3.4%)       | 19 (3.2%)     |         | 20 (3.9%)       | 18 (3.5%)     |         |
| T4a                  | 4 (0.2%)        | 0 (0%)        |         | 0 (0%)          | 0 (0%)        |         |
| N stage              | < 0.001         |               |         | 0.847           |               |         |
| N0                   | 921 (47.3%)     | 210 (35.8%)   |         | 194 (37.7%)     | 197 (38.3%)   |         |
| N1a                  | 917 (47.1%)     | 327 (55.7%)   |         | 277 (53.8%)     | 279 (54.2%)   |         |
| N1b                  | 110 (5.6%)      | 50 (8.5%)     |         | 44 (8.5%)       | 39 (7.6%)     |         |
| TNM stage            |               |               | 1.000   |               |               |         |
| Stage I              | 1946 (99.9%)    | 587 (100%)    | 0.590   | 514 (99.8%)     | 515 (100%)    |         |
| Stage II             | 2 (0.1%)        | 0 (0%)        | 1 (0.2%) | 0 (0%)         |               |         |
| Recurrence           | 63 (3.2%)       | 21 (3.6%)     | 0.086   | 23 (4.5%)       | 20 (3.9%)     | 0.756   |

Table 4. Subgroup comparison between female and male participants aged 20–45 years before and after propensity score matching. Data are expressed as patient's number (%), or mean ± SD. A statistically significant difference was defined as \( p < 0.05 \). TT total thyroidectomy, mRND modified radical neck dissection, PTC papillary thyroid carcinoma, FTC follicular thyroid carcinoma, HTC Hürthle cell thyroid carcinoma, ETE extrathyroidal extension, LN lymph node, T tumor, N node, M metastasis.
patients according to age. The patients were divided into two groups, which were as follows: young age group (≤ 45 years) and old age group (> 45 years). We validated that sex was not an independent prognostic factor for recurrence in both age groups in the multivariate analysis after propensity score matching. The cause of the difference in DTC presentation between males and females is unclear. However, the increased number of screening tests might be correlated to these changes. In the past, men were less likely to visit hospitals than women; thus, they present with more aggressive stages of thyroid cancer. In addition, since a high proportion of women present with benign thyroid disease, such as thyroiditis, screening is faster due to serial follow-up. Therefore, women with thyroid cancer could be diagnosed at earlier stage. However, with the higher number of health examinations performed, the number of male patients with incidentally detected thyroid cancer has been increasing recently. Machens et al. emphasized the need for earlier diagnosis and intervention in men to validate whether male sex with thyroid cancer could be diagnosed at earlier stage. However, with the higher number of health examinations performed, the number of male patients with incidentally detected thyroid cancer has been increasing recently. Another study showed that sex was an age-specific effect modifier for the incidence of PTC. Thus, the sex gap in the incidence of PTC decreased with age33,38. Since the proportion of elderly male patients is relatively higher, age might be an important confounding factor when conducting a comparison between two groups according to sex. Hence, sex might not be an independent prognosis factor39.

Table 5. Univariate and multivariate analyses of risk factors for recurrence in patients aged 20–45 years after propensity score matching. Data are expressed as hazard ratio (HR) and 95% confidence interval (CI). A p value < 0.05 was considered statistically significant. TT total thyroidectomy, mRND modified radical neck dissection, ETE extrathyroidal extension, LN lymph node, N node.

| Extent of operation | Univariate | Multivariate |
|---------------------|------------|--------------|
| HR (95% CI) | p-value | HR (95% CI) | p-value |
| Less than TT | Ref. | Ref. | |
| TT and/or mRND | 2.380 (1.309–4.329) | 0.004 | 1.071 (1.028–1.115) | 0.001 |
| ETE | 2.916 (1.042–8.163) | 0.042 |  |
| Bilaterality | 2.259 (1.141–4.471) | 0.019 |  |
| Lymphatic invasion | 3.217 (1.732–5.972) | < 0.001 | 2.214 (1.118–4.381) | 0.023 |
| Vascular invasion | 4.446 (1.748–11.305) | 0.002 |  |
| Harvested LNs | 1.015 (1.001–1.029) | 0.041 |  |
| Positive LNs | 1.094 (1.056–1.133) | < 0.001 | 1.071 (1.028–1.115) | < 0.001 |
| N stage |  |
| N0 | Ref. | Ref. | |
| N1a | 3.148 (1.383–7.169) | 0.006 |  |
| N1b | 4.255 (1.429–12.671) | 0.009 |  |

In conclusion, compared with females, male patients were more likely to present with more aggressive disease characteristics, including larger tumor size, higher prevalence of ETE and lymphatic and vascular invasions, greater proportion of positive LNs, higher grade of TNM stage, and higher recurrence rate. However, after propensity score matching, no significant difference was observed in the recurrence rates between the matched
groups. Therefore, male sex was not found to be an independent prognostic factor for DTC recurrence. Further studies with larger cohorts should be conducted to validate this result.

### Methods

#### Patients.

We retrospectively analyzed 5827 patients with DTC who underwent thyroid surgery from January 2009 to December 2015 at Seoul St. Mary’s Hospital (Seoul, Korea). In total, 198 patients with incomplete data and 63 who were lost to follow-up were excluded from the analysis. The medical charts and pathology reports of 5566 patients were reviewed and analyzed. According to sex, patients were categorized into two groups (female and male groups). The mean follow-up duration was 99.9 ± 18.7 (range 66–137) months. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the institutional review board of Seoul St. Mary’s Hospital, The Catholic University of Korea (IRB No: KC20RISI0829). The need for informed consent was waived due to the retrospective nature of this study.

#### Preoperative workup.

The preoperative workup included physical examination, serum thyroid function test, neck ultrasonography (US), and computed tomography (CT) scan. Thyroid nodules were diagnosed based on preoperative US-guided fine needle aspiration cytology (FNAC). FNAC was performed by experienced radiologists. The diagnoses made by using FNAC were based on the Bethesda system. To validate the size and extent of the thyroid malignancy, all patients underwent complete staging investigations including total thyroidectomy, modified radical neck dissection, and systematic lymph node dissection.

#### Table 6

Subgroup comparison between females and males aged > 45 years before and after propensity score matching. Data are expressed as patient's number(%), or mean ± SD. A statistically significant difference was defined as p < 0.05. TT total thyroidectomy, mRND modified radical neck dissection, PTC papillary thyroid carcinoma, FTC follicular thyroid carcinoma, HTC Hurthle cell thyroid carcinoma, ETE extrathyroidal extension, LN lymph node, T tumor, N node, M metastasis.
location of tumors, presence/absence of ETE, LN status, and other abnormal findings in the neck. All patients diagnosed with DTC were evaluated via preoperative US and neck CT scan. If there were palpable LNs or suspicious LNs were found on preoperative US or neck CT, FNAC and washout thyroglobulin testing were performed. The surgical extent was decided in accordance with the ATA management guideline.

Postoperative management and follow-up. Postoperative care and follow-up were conducted according to the ATA management guidelines regardless of sex. Patients underwent physical examination, neck US, and serum thyroid function testing at 3–6-month intervals and annually thereafter. All patients took suppressive doses of L-thyroxine and were regularly followed up by physical examination, thyroid function testing, Tg and anti-Tg antibody concentration measurements, and neck US at 3–6-month intervals and annually thereafter. Radioactive iodine (RAI) ablation was performed at 6–8 weeks postoperatively, and whole body scans were performed at 5–7 days after RAI ablation in patients who underwent total thyroidectomy.

Those with recurrence or distant metastasis on routine follow-up evaluations underwent additional diagnostic imaging, including CT scan, positron emission tomography/CT scan, and/or radioactive iodine whole body scan, to determine the location and extent of suspected recurrence. In cases of suspected recurrence in the remnant thyroid, resection bed, or lymph nodes, diagnosis was confirmed via histologic examination using FNAC or a surgical biopsy specimen.

Primary and secondary endpoints. The primary endpoint was DFS between males and females after propensity score matching, and the secondary endpoint was the clinicopathological characteristic differences between males and females before and after propensity score matching.

Statistical analysis. Continuous variables were presented as means with standard deviations and categorical variables were presented as numbers with percentages. Student’s t-test and the Pearson’s chi-square test or Fisher’s exact test were used to compare continuous and categorical variables, respectively. Univariate and multivariate Cox regression analyses were performed to validate the predictors of DFS, and HRs with 95% CIs were calculated. DFS was compared by performing Kaplan–Meier survival analysis with the log-rank test.

To reduce the effects of selection bias and potential confounding factors, propensity score matching was performed using various clinicopathological characteristics: age, extent of operation, tumor size, ETE, lymphatic invasion, vascular invasion, harvested LNs, positive LNs, N stage, and TNM stage. Individual patient propensity scores were calculated via logistic regression analysis and used to validate the predictors of DFS, and HRs with 95% CIs were calculated. DFS was compared by performing Kaplan–Meier survival analysis with the log-rank test.

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Table 7. Univariate and multivariate analyses of risk factors for recurrence in patients aged >45 years after propensity score matching. Data are expressed as hazard ratio (HR) and 95% confidence interval (CI). A p value < 0.05 was considered statistically significant. ETE extrathyroidal extension, LN lymph node, N node.
Data availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Author contributions
K.K. designed the study, participated in data collection, data interpretation, and revised the manuscript. J.P. participated in the interpretation of the data and drafted and revised the manuscript. D.J.L., J.S.B., and J.S.K. participated in data analysis, interpretation of data and revised the manuscript. All authors approved the final version of the manuscript.

Competing interests
The authors declare no competing interests.

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