Clinicopathological characteristics and prognosis of thyroid cancer in northwest China: A population-based retrospective study of 2490 patients

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Keywords
Clinicopathological characteristic; Northwest China; prognosis; retrospective study; thyroid cancer.

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Introduction
Thyroid cancer is a common malignancy of the endocrine system and occurs more frequently in women than men.1 Over the past few decades, the incidence of thyroid cancer has increased in different countries, including the United States, United Kingdom, France, Canada, and Australia.2 In China, the annual incidence appreciably increased by 14.51% in women during 2003–2007.3 Rahib et al. reported that thyroid cancer will become the fourth most common cancer by 2030 in the United States if recent trends are maintained.4 The burden of thyroid cancer is substantial, thus proper preventive measures and treatment are urgently required.

Among the Chinese population, the features of thyroid cancer differ across various regions. For example, Yang et al. showed a gender ratio of 1:3 (1185 men: 3698 women), while Li et al. reported 1:3.56.5–7 Other features, such as pathological distribution and BRAF mutations, are diverse. In this study, we investigated thyroid cancer cases in northwest China from August 2015 to June 2018 and provide information from specific areas to predict the burden of thyroid cancer in northwest China.

Abstract
Background: The specific clinical features of thyroid cancer patients in northwest China are unclear; therefore, we analyzed the clinicopathological characteristics and prognosis of this population.

Methods: Clinical characteristics including age, gender, blood type, histological type, and BRAFV600E gene mutation; and incidence; risk factors; surgical treatment; and prognosis were recorded.

Results: A total of 2490 thyroid cancer patients were included; 98% were diagnosed with papillary thyroid cancer (PTC). Weight, blood type, histological type, and BRAFV600E gene mutation rates were significantly different. Pediatric thyroid cancer patients had higher lymph node metastasis, lower BRAFV600E mutation, and 6.2–9.2% greater recurrence rates than adult patients. PTC and papillary thyroid microcarcinoma displayed similar features, while in other types, such as follicular and medullary thyroid cancer, there were variations. Multiple logistic analyses showed that age (odds ratio [OR] 0.957, 95% confidence interval [CI] 0.944–0.970; P < 0.001), focal status (OR 16.174, 95% CI 9.257–28.262; P < 0.001), pathology (OR 0.642, 95% CI 0.473–0.871; P = 0.004) and lymph node metastasis (OR 0.059, 95% CI 0.033–0.107; P < 0.001) were independent factors for BRAFV600E mutation.

Conclusion: Most real world clinicopathological features, treatment, and prognosis of thyroid cancer are similar to reported data, such as the higher incidence of disease in women and the larger proportion of PTC. However, the results in pediatric patients and those with BRAF gene mutations are controversial and require more clinical incidence.
Methods

Data collection

Patients newly diagnosed with thyroid carcinoma between August 2015 and June 2018 were enrolled in the study. Clinical characteristics were collected from the thyroid database established by Xijing Hospital. Two independent researchers performed data collation and entry. In cases of disagreement, another researcher was consulted for judgment until a consensus was reached. The study was conducted in accordance with The Code of Ethics of the Declaration of Helsinki and the ethical standards of the ethics committee of Air Force Medical University. We guaranteed that the personal information of the participants was protected.

Pathological diagnostic criteria

The pathological outcome was determined by at least two experienced pathologists from the Pathology Department of Xijing Hospital, based on standard definitions set by the World Health Organization (WHO). Thyroid cancer was classified into papillary thyroid cancer (PTC), follicular thyroid cancer (FTC), anaplastic thyroid cancer (ATC), and medullary thyroid cancer (MTC), based on histopathological characteristics.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0 (IBM Corp., Armonk, NY, USA). A Pearson’s chi-squared ($\chi^2$) test was performed to determine the differences in clinicopathological factors between the groups. Continuous outcomes were analyzed using independent t-tests for groups of two and one-way analysis of variance among groups of three of more. $P < 0.05$ was considered significant. Multiple logistic regression analysis was applied to identify risk factors for $BRAF^{V600E}$ mutation.

Results

Patients

A total of 2490 patients (1884 women: 606 men = 3.1:1) were included in the study. The average age of patients was $43.3 \pm 11.19$ years (range: 5–80). The patients were all from northwest China, including Shaanxi, Shanxi, Xinjiang, Ningxia, and Gansu. As indicated, 98% (2440/2490) of thyroid cancer patients were identified with PTC, and more than half of these PTC patients (1295/2440) were diagnosed with papillary thyroid microcarcinoma (PTMC). Other histological types, including FTC, ATC, and MTC accounted for 0.8%, 0.04%, and 0.5%, respectively. In regard to $BRAF^{V600E}$ gene expression, 68.6% of participants were detected with the $BRAF$ gene and 84.5% of them showed gene mutation. The baseline features of the patients are presented in Table 1.

Clinicopathological features of patients of different ages

To investigate the influence of patient age on clinicopathological features, we divided all patients into a children/
adolescent group (≤ 20 years old) and adult groups of various age ranges (21–45, 46–59, ≥ 60 years) (Table 2). Weight ($F = 10.609$, $P < 0.001$), blood type ($\chi^2 = 131.724$, $P < 0.001$), lymph node metastasis ($\chi^2 = 57.654$, $P < 0.001$), surgical method ($\chi^2 = 10.103$, $P = 0.018$), and BRAF$^{V600E}$ mutations ($\chi^2 = 37.511$, $P < 0.001$) differed among the groups. Using 45 years of age as cutoff value, we found that patients aged ≤ 45 weighed the least (Table 3). In regard to blood types, differences were observed between patients aged ≤ 45 and > 45 years ($P < 0.001$): 65.4% of patients aged ≤ 45 had A or B blood types, while 60.0% of those aged > 45 years had A or O blood types. Regarding the distribution of histological types, the proportions of patients with PTC and PTMC were 51.1% versus 39.4% in the group aged ≤ 45, and 47.7% versus 57.6% in the group aged > 45 years, respectively. Similarly, the BRAF$^{V600E}$ gene mutation rate in all patients was 80%, but patients aged > 45 years had a 7.6% greater mutation rate than the other groups. There were no differences in the distributions of gender, lesions, lymph node metastasis, surgery method, or recurrence rate. After a medium follow-up duration of 24 months (range: 1–34), the rate of recurrence in thyroid carcinoma patients was ≤ 10%. The lung and bones were common locations for recurrence.

Clinical features of thyroid cancer in children

In the 65 pediatric thyroid cancer patients, the ratio of girls to boys was 3.64:1. The distributions of blood type, histological type, and lesions are shown in Table 2. In contrast to adult patients, younger patients possessed higher lymph node metastasis and lower BRAF$^{V600E}$ mutation rates (Table 2). In respect to surgical treatment, children with thyroid cancer were treated following the same guidelines

### Table 2 Characteristics of thyroid cancer patients by age group

| Characteristics | < 21 (n = 65) | 21–45 (n = 1343) | 46–59 (n = 905) | ≥ 60 (n = 177) | $\chi^2/F$ | $P$ |
|-----------------|---------------|-----------------|-----------------|---------------|----------|-----|
| Gender          |               |                 |                 |               |          |     |
| Male (n = 606)  | 14 (21.5%)    | 335 (24.9%)     | 209 (23.1%)     | 48 (27.1%)    | 2.048    | 0.562|
| Female (n = 1884) | 51 (78.5%)   | 1008 (75.1%)    | 696 (76.9%)     | 129 (72.9%)   |          |     |
| Weight          | 52.17 ± 13.54 | 63.9 ± 11.71    | 65.2 ± 10.61    | 63.12 ± 9.89  | 10.609   | < 0.001|
| Blood type      |               |                 |                 |               |          |     |
| A (n = 718)     | 22 (33.8%)    | 401 (29.9%)     | 244 (27.0%)     | 51 (28.8%)    | 153.656  | < 0.001|
| B (n = 754)     | 12 (18.5%)    | 487 (36.3%)     | 195 (21.5%)     | 60 (33.9%)    |          |     |
| AB (n = 382)    | 17 (26.2%)    | 198 (14.7%)     | 122 (13.5%)     | 45 (25.4%)    |          |     |
| O (n = 636)     | 14 (21.5%)    | 257 (19.1%)     | 344 (38.0%)     | 21 (11.9%)    |          |     |
| Lesion          |               |                 |                 |               |          |     |
| Unilateral (n = 1473) | 37 (56.9%) | 803 (59.8%)    | 540 (59.7%)    | 93 (52.5%)    | 3.661    | 0.3  |
| Bilateral (n = 1017) | 28 (43.1%)   | 540 (40.2%)    | 365 (40.3%)    | 84 (47.5%)    |          |     |
| Histological type |           |                 |                 |               |          |     |
| PTC (n = 1145)  | 48 (73.8%)    | 671 (50.0%)     | 338 (37.3%)     | 88 (49.7%)    | 131.724  | < 0.001|
| PTMC (n = 1295) | 11 (16.9%)    | 661 (49.2%)     | 544 (60.1%)     | 79 (44.6%)    |          |     |
| FTC (n = 20)    | 5 (7.7%)      | 6 (4.0%)        | 6 (7.0%)        | 3 (1.7%)      |          |     |
| MTC (n = 12)    | 1 (1.5%)      | 4 (0.3%)        | 5 (0.6%)        | 2 (1.1%)      |          |     |
| Others (n = 18) | 0             | 1 (0.1%)        | 12 (13.3%)      | 5 (2.8%)      |          |     |
| LN metastasis   |               |                 |                 |               |          |     |
| Yes (n = 1174)  | 59 (90.8%)    | 605 (45.0%)     | 441 (48.7%)     | 69 (39.0%)    | 57.654   | < 0.001|
| No (n = 1316)   | 6 (9.2%)      | 738 (55.0%)     | 464 (51.3%)     | 108 (61.0%)   |          |     |
| Surgery         |               |                 |                 |               |          |     |
| Total thyroidectomy (n = 2087) | 54 (83.1%) | 1142 (85.1%)  | 733 (81.0%)     | 157 (88.7%)   | 10.103   | 0.018|
| Near-total thyroidectomy (n = 403) | 11 (16.9%) | 200 (14.9%)  | 172 (19.0%)     | 20 (11.3%)    |          |     |
| BRAF detection rate (n = 1708/2490) | 30/65 (46.2%) | 947/1343 (70.5%) | 614/905 (67.8%) | 117/177 (66.1%) | 18.237   | < 0.001|
| BRAF mutation   |               |                 |                 |               |          |     |
| Yes (n = 1444)  | 16/30 (53.3%) | 778/947 (82.2%) | 544/614 (88.6%) | 106/117 (90.6%) | 37.511   | < 0.001|
| No (n = 264)    | 14/30 (46.7%) | 169/957 (17.7%) | 70/617 (11.3%)  | 11/117 (9.4%) |          |     |
| Follow-up rate  |               |                 |                 |               |          |     |
| Yes (n = 56/65) | 10 (15.4%)    | 123 (9.2%)      | 78 (8.6%)       | 11 (6.2%)     | 5.135    | 0.162|
| No (n = 55/64)  | 55 (84.6%)    | 1220 (90.8%)    | 827 (91.4%)     | 166 (93.8%)   |          |     |

FTC, follicular thyroid cancer; LN, lymph node; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma.
as adults. Postoperatively, 83.1% (54/65) of children underwent radioactive iodine (RAI) ablation with iodine-131 (131I) to detect metastatic disease, treat residual tumors and metastases, and to ablate any remaining normal thyroid tissue. Excluding 9 patients lost to follow-up, 10 (15.4%) patients developed recurrence, a rate 6.2–9.2% higher than in adult patients. The most common sites of recurrence were the lungs, wall of the chest, and claviculate.

**Correlation between histological type and clinical features**

We analyzed the specific pathological features of each histological type, which are summarized in Table 4. As shown, 59.7% of patients with PTC had unilateral lesions, 42.6% were multifocal, 72.1% had lymph node metastasis, and 84.6% had \( \text{BRAF}^{\text{V600E}} \) mutations. Similarly, in PTMC patients, 58.1% had unilateral lesions, 51.7% were multifocal, 76.0% had lymph node metastasis, and 85.3% had \( \text{BRAF}^{\text{V600E}} \) mutations. However, for other types of thyroid cancer, predominantly FTC, the clinical features were different: 76.0% of patients with PTC had unilateral lesions, 38.0% were multifocal, 24.0% had lymph node metastasis, and 42.1% had \( \text{BRAF}^{\text{V600E}} \) mutations. There were no differences in local recurrence among the thyroid cancer types.

**Correlation between \( \text{BRAF} \) status and clinical features**

More than 80% of patients had \( \text{BRAF}^{\text{V600E}} \) mutations, but these occurred more often in women than in men. To investigate the relationship between clinicopathological features and \( \text{BRAF}^{\text{V600E}} \) expression, all patients were divided into \( \text{BRAF}^{\text{V600E}} \) positive and negative groups. As shown 5,
there were significant differences in age (P = 0.019), lesions (P < 0.001), focal status (P = 0.001), histological type (P < 0.001), and lymph nodes (P < 0.001) between patients with or without BRAFV600E mutations. Multiple logistic analyses showed that age (odds ratio [OR] 0.957, 95% confidence interval [CI] 0.944–0.970; P < 0.001), focal status (OR 16.174, 95% CI 9.257–28.262; P < 0.001), pathology (OR 0.642, 95% CI 0.473–0.871; P = 0.004), and lymph node metastasis (OR 0.059, 95% CI 0.033–0.107; P < 0.001) were independent factors for BRAFV600E mutation.

Discussion

The incidence of thyroid cancer has been steadily increasing in recent years and several studies have identified gender or racial/ethnic differences in incidence, clinicopathologic variables, gene expression, and prognosis.9–11 In 2013, Rose et al. reported regional differences in thyroid cancer presentation and survival rates, but not within separate racial/ethnic groups.12 We investigated the features of thyroid cancer in northwest China. Consistent with the results of previous reports, we found a higher incidence of thyroid cancer in women, at a ratio of 3:1. A vast majority of patients in our sample were diagnosed with PTC, while other types, primarily FTC or MTC, accounted for only 2% of cases; contrary to our result, previous studies have indicated an incidence rate in other types of 5%.13,14 Although FTC and MTC are more aggressive types, they are associated with a lower rate of lymph node recurrence. Distant metastasis was the main cause of death and the most common locations were the lungs and bones in both our study sample and in previous reports.15,16

Cancer of the thyroid gland in pediatric patients is a rare and more aggressive disease.17 Patients aged ≤ 20 years account for 2.75% of all patients with thyroid cancer, but unfortunately the incidence appears to be increasing.18,19 In this study, 2.6% (65/2490) of thyroid cancer patients were aged < 21. The low incidence and limited availability of prospective randomized trials means that there is currently a lack of evidence-based understanding of thyroid cancer in children. In 2009, Hogan et al. reported that in 1753 cases in children, 83% were PTC, 10% were FTC, 5% MTC, and 2% were other types.20 In our sample, PTC and PTMC accounted for 90.7% of all younger patients; 7.7% and 1.5% had FTC and MTC, respectively.

Table 4 Correlation between histological type and clinical features

| Characteristics               | PTC (n = 1145) | PTMC (n = 1295) | Other (n = 50) | χ²/F | P   |
|-------------------------------|---------------|----------------|--------------|------|-----|
| Gender                        |               |                |              |      |     |
| Male (n = 606)                | 308 (26.9%)   | 283 (21.9%)    | 15 (30%)     | 9.292| 0.01|
| Female (n = 1884)             | 837 (73.1%)   | 1012 (78.1%)   | 35 (70%)     |      |     |
| Age                           |               |                |              |      |     |
| Average age                   | 42.2 ± 11.89  | 44.2 ± 10.22   | 47.0 ± 12.93 | 14.1 | < 0.001|
| Median age                    | 42 (5–80)     | 45 (13–76)     | 47 (8–71)    |      |     |
| Weight                        | 64.8 ± 12.32  | 63.6 ± 10.35   | 62.9 ± 9.80  | 3.794| 0.023|
| Blood type                    |               |                |              |      |     |
| A (n = 718)                   | 312 (27.2%)   | 397 (30.7%)    | 9 (18.0%)    | 19.793| 0.003|
| B (n = 754)                   | 325 (28.4%)   | 408 (31.5%)    | 21 (42.0%)   |      |     |
| AB (n = 382)                  | 184 (16.1%)   | 186 (14.4%)    | 12 (24.0%)   |      |     |
| O (n = 636)                   | 324 (28.3%)   | 304 (23.5%)    | 8 (16.0%)    |      |     |
| Lesion                        |               |                |              |      |     |
| Unilateral (n = 1473)         | 683 (59.7%)   | 752 (58.1%)    | 38 (76.0%)   | 6.62 | 0.037|
| Bilateral (n = 1017)          | 462 (40.3%)   | 543 (41.9%)    | 12 (24.0%)   |      |     |
| Focal                         |               |                |              |      |     |
| Unifocal (n = 1370)           | 714 (62.4%)   | 625 (48.3%)    | 31 (62.0%)   | 20.596| < 0.001|
| Multifocal (n = 1120)         | 488 (42.6%)   | 670 (51.7%)    | 19 (38.0%)   |      |     |
| LN metastasis                 |               |                |              |      |     |
| Yes (n = 1174)                | 826 (72.1%)   | 984 (76.0%)    | 12 (24.0%)   | 67.426| < 0.001|
| No (n = 1316)                 | 319 (27.9%)   | 311 (24.0%)    | 38 (76.0%)   |      |     |
| BRAF mutation                 |               |                |              |      |     |
| Yes (n = 1444)                | 644/761 (84.6%)| 792/928 (85.3%)| 8/19 (42.1%) | 36.646| < 0.001|
| No (n = 264)                  | 117/761 (15.4%)| 136/928 (14.7%)| 11/19 (57.9%)|      |     |
| Recurrence                    |               |                |              |      |     |
| Yes                           | 90 (7.9%)     | 94 (7.3%)      | 4 (8.0%)     | 0.330| 0.848|
| No                            | 1055 (92.1%)  | 1201 (92.7%)   | 46 (92.0%)   |      |     |

LN, lymph node.
guidelines for the treatment of adult patients are used to treat children with thyroid neoplasia, but these may not be appropriate. When choosing a treatment regimen, pediatric patients undergo total or near-total thyroidectomy, considering the child’s growth and the need for a second operation. Repeated radioactive iodine therapy or re-operation in cases of recurrence are reported to have negative effects on children’s development. Prophylactic lymph node dissection is also debated and is not currently recommended. RAI ablation with 131I is often used after surgery to detect metastatic disease, treat residual tumors and metastases, and to ablate any remaining normal thyroid tissue to allow more accurate monitoring for recurrent disease. In our patient sample, 83.1% of children were treated with RAI ablation. However, the ideal adjuvant treatment for children with thyroid cancer following primary surgery is unclear. Moreover, it is important to note that attention should be paid to the psychological health of children with cancer. If necessary, regular psychological intervention should be considered.

BRAF mutations are correlated with more aggressive and iodine-resistant phenotypes and represent the most common oncogenic event in thyroid cancer, providing valuable prognostic information. BRAF mutations are associated with other clinicopathological parameters, which may prove to be predictive biomarkers of therapeutic response; however, more studies are needed to confirm the viability of these potential biomarkers. In 2012, Kurtulmus et al. reported a BRAFV600E mutation rate of 39.45% in thyroid cancer patients. In 2013, Fernandez et al. reported that BRAFV600E mutations occurred in 77.4% of classic PTC patients, 31.9% of the follicular variant, and 72.2% of high tall cell PTCs. In our sample, 84.5% of patients had BRAFV600E mutations: 84.6% in classic PTCs, 85.3% in PTMCs, and 42.1% in the other types. These mutations were associated with age, multicentricity, histologic subtype, and lymph node metastasis. In 2013, Lim et al. demonstrated that BRAFV600E mutations were significantly associated with large tumor size, extrathyroidal extension, and lymph node metastasis. In contrast, Ming et al. found no significant association between BRAFV600E mutations and gender, tumor size, histological subtype, multifocality, or accompanying nodular goiter and Hashimoto’s; however, in thyroid cancer patients < 21 years, the BRAFV600E mutation rate was 53.3%, approximately 30% lower than in older patients. By contrast, Henke et al. observed BRAFV600E mutations in 63% of pediatric thyroid cancer patients, which occurred more often in male than in female patients. Thus, the clinical significance of BRAFV600E gene mutation in thyroid cancer is unresolved and more evidence is needed to establish guidelines.

The overall prognosis of thyroid cancer patients, particularly those with differentiated thyroid cancer, is excellent. Factors associated with recurrent thyroid cancer include extrathyroidal extension of the primary tumor, bulky nodal

| Table 5 Correlation between BRAF status and clinical features |
| --- |
| Index | BRAF positive | BRAF negative | \( \chi^2/F \) | P |
| Gender | | | | |
| Male (n = 418) | 351 | 67 | 0.139 | 0.71 |
| Female (n = 1290) | 1093 | 197 | | |
| Age | | | | |
| Average | 44.1 ± 10.76 | 39.4 ± 11.60 | 5.547 | 0.019 |
| Median | 44 (14–80) | 39 (6–69) | | |
| Lesion | | | | |
| Unilateral (n = 1389) | 1153 | 236 | 13.392 | < 0.001 |
| Bilateral (n = 319) | 291 | 28 | | |
| Focal | | | | |
| Unifocal (n = 919) | 753 | 166 | 10.343 | 0.001 |
| Multifocal (n = 789) | 691 | 98 | | |
| Histological type | | | | |
| PTC (n = 725) | 605 | 120 | 35.7 | < 0.001 |
| PTMC (n = 952) | 827 | 125 | | |
| FTC (n = 13) | 5 | 8 | | |
| MTC (n = 1) | 0 | 1 | | |
| Others (n = 7) | 4 | 3 | | |
| LN metastasis | | | | |
| Yes (n = 1059) | 943 (65.3%) | 116 (43.9%) | 43.245 | < 0.001 |
| No (n = 649) | 501 | 148 | | |

FTC, follicular thyroid cancer; LN, lymph node; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer; PTMC, papillary thyroid microcarcinoma.
metastatic lesions, macroscopic local invasion, and aggressive histologic subtypes. In this study, the recurrence rates of participants in various age groups were similar at approximately 8%, except for pediatric thyroid cancer patients who had a relatively higher probability of recurrence. In 2014, Mehanna et al. reported a recurrence rate in PTMC patients of 7.9%. In 2015, Joo et al. reported a 7.4% regional lymph node recurrence rate in PTC patients. Meanwhile, Pedrazzini et al. suggested that total or near-total thyroidectomy might reduce the risk of local recurrences in non-incidental PTMC, while prophylactic dissection of central compartment nodes in the absence of clinically evident metastases did not seem to change the risk of recurrence. Moreover, RAI ablation of thyroid remnants should only be considered in young patients with multifocal tumors and histologically proven metastatic lesions, macroscopic local invasion, and aggressive histologic subtypes. In this study, the recurrence rates of participants in various age groups were similar at approximately 8%, except for pediatric thyroid cancer patients who had a relatively higher probability of recurrence. In 2014, Mehanna et al. reported a recurrence rate in PTMC patients of 7.9%. In 2015, Joo et al. reported a 7.4% regional lymph node recurrence rate in PTC patients. Meanwhile, Pedrazzini et al. suggested that total or near-total thyroidectomy might reduce the risk of local recurrences in non-incidental PTMC, while prophylactic dissection of central compartment nodes in the absence of clinically evident metastases did not seem to change the risk of recurrence. Moreover, RAI ablation of thyroid remnants should only be considered in young patients with multifocal tumors and histologically proven metastatic lymph nodes with a significantly higher risk of recurrence.

In conclusion, this retrospective study revealed the real world clinicopathological features, treatment, and prognosis of thyroid cancer from a single medical center located in northwest China. Most of our results are similar to reported data, such as the higher incidence of disease in women and the larger proportion of patients with PTC. However, there is insufficient evidence to conclude which factors are associated with prognosis in pediatric patients and in patients with BRAF gene mutations.

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Disclosure

No authors report any conflict of interest.

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