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ORIGINAL ARTICLE

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Total thyroidectomy is superior for initial treatment of thyroid cancer

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Abstract

Purpose: The incidence of thyroid cancer has increased annually, and has a heavy psychological and economic burden on the society and individuals. Based on thyroid cancer data from patients treated in Liaocheng People's Hospital in 2017, with Chinese national and regional characteristics, in this study we addressed the controversy of which initial thyroid surgical mode, lobectomy, or total thyroidectomy is the most effective.

Patients and methods: Clinical and pathological data from 552 patients with thyroid cancer, who were initially diagnosed and treated surgically, were collected from the Department of Thyroid Surgery. Among them, 40 patients underwent endoscopic surgery, with resection, including lobectomy + central lymph node dissection of the affected lobe, while 512 cases underwent total thyroidectomy + central lymph node dissection.

Results: The metastasis rate for all patients was 59.42%, with lymph node metastasis of papillary thyroid microcarcinoma of 46.92%; however, for patients with tumors >2 cm, the proportion developing metastasis was increased to 77.53%.

Conclusion: In thyroid cancer, rates of neck lymph node metastasis are high, particularly among patients with risk factors for poor prognosis. Our data suggest that initial treatment should comprise at least total thyroidectomy + central lymph node dissection in China, at least in tumors larger than 1 cm, to avoid the risks associated with secondary surgery and effects on patient quality of life.

KEYWORDS

initial treatment, metastasis, real world, surgery, thyroid cancer

1 | BACKGROUND

In the past 30 years, the incidence of thyroid cancer has been increasing annually worldwide, with the incidence in China also rising. It is estimated that by 2019, thyroid cancer will become the third most common malignancy in women in the United States, representing a heavy economic burden on both society and individuals.[1]

Effective and appropriate surgical treatment of differentiated thyroid carcinoma is of great clinical significance. Differentiated thyroid carcinoma accounts for 80-90% of thyroid cancer incidence and the most common metastasis is to the cervical lymph nodes. Total thyroidectomy and lobectomy remain the main primary surgical interventions for thyroid carcinoma. There has been no large sample randomized controlled clinical trial to compare these two methods.[2,3] When thyroid cancer is associated with multiple risk factors, such as multiple, bilateral, and capsule invasion, the lymph node metastasis rate does increase.[4-6]

Chinese experts do not consider papillary thyroid microcarcinoma (PTMC; defined as a lesion with a nodule diameter of $\leq$1 cm^3) a low-risk carcinoma, as any advanced thyroid cancer is a development

from microcancer, and any cancer that initially occurs is not late-stage advanced PTC.[7,8] The incidence of lymph node metastasis in patients with central region PTC is 20-66%,[9,10] indicating that, although PTC progresses slowly, its ability and tendency to metastasize to lymph nodes, and even distant organs are unscientific to classify malignant tumors based on tumor size, as the invasiveness and distant metastatic ability of tumors are a consequence of evolution of the tumor genome.[11,12]

We collected clinical and pathological data from 552 patients undergoing treatment at the Department of Thyroid Surgery, Liaocheng People's Hospital, and analyzed their responses to current treatment approaches. We aimed to determine the most appropriate initial surgical intervention for patients in China with this condition.

2 | METHODS

2.1 | Patient selection

This study was a retrospective analysis of a total of 552 cases of PTC treated and undergoing surgery from January 1 to December 31, 2017 in the Department of Thyroid Surgery, Liaocheng People's Hospital. All patients underwent fine needle aspiration before surgery, and had pathological diagnoses of papillary carcinoma or suspected papillary carcinoma. No abnormal lymph nodes were found in preoperative color Doppler ultrasound and CT.

2.2 | Surgery

Surgical procedures were as follows: 40 cases underwent endoscopic surgery, with resection ranging from the lateral lobes of the affected side to central lymph node dissection of the affected side. The indications for endoscopic thyroidectomy were those with tumor diameter less than 2 cm, no nodules on contralateral imaging examination, and negative cervical lymph node examination. The essential factor is that the patient has cosmetic needs. The remaining 512 patients underwent total thyroidectomy and central lymph node dissection. For patients <18 years old, informed consent was obtained from both parents.

2.3 | Ethical approval

Surgical methods were based on the guidelines of Chinese Thyroid Cancer (CTA), following the experience of clinical professors. The study was conducted in accordance with the Declaration of Helsinki. The ethical approval number is 2016071.

2.4 | Data acquisition

Pathological data were obtained from the Department of Pathology, Liaocheng People's Hospital, and were based on postoperative analysis of paraffin-embedded tumor samples. Information on all patients was systematically coded in a single computer file. Data from this system were exported for statistical analyses.

3 | RESULTS

All patients were treated directly after discovery of the lesion, without any observation period. Cases included 105 males and 447 females, and were 13-72 years old, with 72 cases aged ≤35 years.

The pathological subtypes present among the 552 cases of PTC were classical (n = 537), follicular variant (n = 12), tall cell variant (n = 2), and solid variant (n = 1) (Figure 1).

The mean incidence of metastasis was 59.42%, and metastasis rate was positively correlated with tumor diameters ≤0.5 to >2 cm associated with rates from 44.68% to 77.53%, respectively (Table 1). The proportion of PTMC (≤1 cm) was 47.10%, with a lymph node metastasis rate of 46.92% (Table 2).

Among patients undergoing lobectomy and total thyroidectomy, the proportions with lymph node metastasis were 32.5% and 39.84%, respectively. Of patients receiving total thyroidectomy, 46.68% underwent cervical lateral lymph node dissection, and metastasis was detected in 83.26% (Table 3). Only 8.37% of the patients had negative lymph nodes in the central region, but metastasis in the lateral area of the neck, while 16.74% of patients had negative lymph nodes in both the central and the lateral neck areas (Table 4).

In addition, we enumerated the number of cases of surgery for thyroid cancer at our hospital from 2009 to 2018 and the results demonstrate that the number of cases generally rose annually by 4.72-18.16% (Table 5).

4 | DISCUSSION

According to the results of the SEER database of the National Cancer Center of the United States, the incidence of both PTC <1.0 cm and thyroid cancers 1.0-4.0 cm increased from 1980 to 2010, especially among highly educated groups.[13] Statistical data from the United States and South Korea show an increase in the incidence of thyroid cancer.[14] Further, the results of surveys in Denmark, Finland, Israel, Japan, Spain, and Switzerland also demonstrate increases in thyroid cancer incidence, which is mainly PTC, with significant sex differences in the relative extent of the rise. This phenomenon cannot be fully explained by improvements in the sensitivity of testing methods, nor increased awareness among doctors and patients of screening.[15] Scholars from other countries have actively researched the risk factors associated with thyroid cancer, and found that autoimmune disorders, ionizing radiation, iodine intake, estrogen, environmental endocrine disruptors, negative psychosocial factors, and heredity may contribute to increases in thyroid cancer incidence.[16,17]

It is generally recognized that, over time, the degree of malignancy and dedifferentiation of PTC tumors increases; however, when the level of malignancy changes, what causes changes in the tumor genome has not been fully or satisfactorily explained.[18-20]

As available therapies for thyroid cancer are effective, there is little drive for early diagnosis and surgical treatment, which is counterintuitive and violates the basic principles of pursuing early detection,

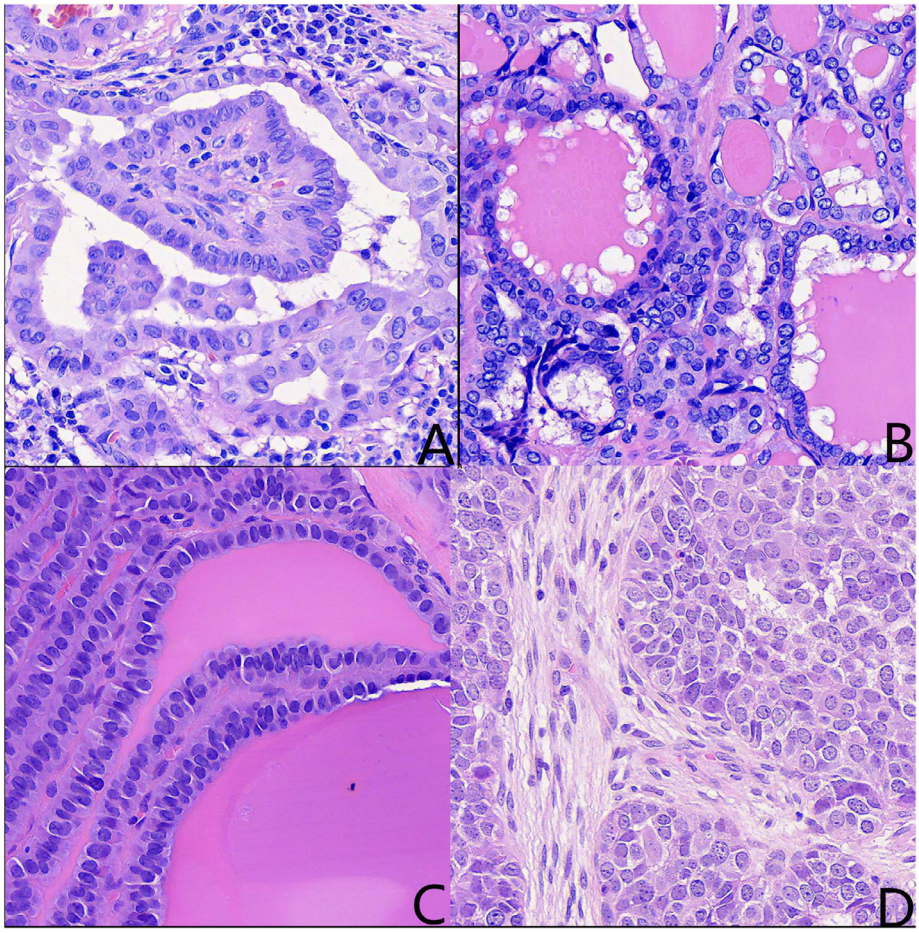

FIGURE 1 Histology types of thyroid cancer identified in this study. A, Classical type PTC. B, Follicular variant PTC. C, Tall cell variant PTC. D, Solid variant PTC. All images are 40× magnification [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 The diameter and metastasis of thyroid cancer

Diameter (cm)	Cases	Proportion	Metastasis	Proportion
≤0.5	94	17.03%	42	44.68%
≤1	166	30.07%	80	48.19%
≤2	191	34.60%	118	61.78%
>2	89	16.12%	69	77.53%
Total			328	59.42%

TABLE 4 The lymph node of thyroid cancer in lateral neck node dissection

Central lymph node	Lateral neck lymph node	Metastasis	Proportion
Positive	Negative	62	25.94%
Positive	Positive	117	48.95%
Negative	Negative	40	16.74%
Negative	Positive	20	8.37%

TABLE 2 The proportion of papillary thyroid microcarcinoma

Cases	Proportion	Metastasis	Proportion	Central lymph node	Proportion	Lateral neck lymph node	Proportion
260	47.10%	122	46.92%	114	43.85%	67	25.77%

TABLE 3 The surgery and high-risk factors of thyroid cancer

	Cases	Proportion	Metastasis	Proportion
Total thyroidectomy central lymph node dissection	512		204	39.84%
Lobectomy homogenous central node dissection	40		13	32.50%
Total thyroidectomy central lymph node dissection	279	54.49%	119	42.65%
Total thyroidectomy central lymph node dissection lateral neck node dissection	239	46.68%	199	83.26%

TABLE 5 Numbers of cases of thyroid cancer treated at our hospital in the past 9 years

Year	2009	2010	2011	2012	2013	2014	2015	2016	2017
Case	247	253	298	341	396	462	620	530	552

with the aim of early diagnosis and treatment of malignant tumors. In addition, the psychological pressure on patients of the uncertainty of following up while waiting for the diagnosis of malignancies to change before taking action is undoubtedly considerable. Cancer does not have specific Chinese characteristics. In 2014, the Memorial Sloan-Kettering Cancer Center in the United States launched a "wait-and-see" program for patients with thyroid cancer.[21] Patients diagnosed with microcarcinoma of the thyroid could choose not to have it removed for a while, but rather to have it checked regularly; however, the vast majority of patients with PTMC did not hesitate to choose surgical treatment. Further, some patients who chose the observation option eventually asked for surgery, and doctors feared being sued for missing the optimal treatment time. Early treatment is not only effective, but it is also associated with reduced risk and fewer complications.[22] Once lymphatic metastases, or distant lung and bone metastases, occur, the cost of medical care often increases considerably, which can even endanger the life of the patient.

According to our clinical and pathological data, as the diameter of the tumor mass increased from ≤ 0.5 to >2 cm, the proportion of lymph node metastasis rose from 44.68% to 77.53%, respectively. The proportion of micropapillary carcinoma ≤1 cm was 47.10%, with a corresponding lymph node metastasis rate of 46.92%, which is not consistent with the classification of microcarcinomas as low-risk tumors. Lymph node metastasis is also an indicator of malignancy. Over time, tumor size and the proportion and number of lymph node metastases will increase, leading to disease progression, increased difficulty and risk of surgery, and a gradual rise in the risk of recurrence and metastasis. While the diameter was 1.0-2.0 cm, the metastasis was 61.78%. When the mass was >2 cm, the proportion of patients with lymph node metastasis rose to 77.53%, indicating that PTC was progressing, including the level of malignancy and dedifferentiation, although there is no way to evaluate or predict such progression. Therefore, this study asserts that total thyroidectomy is beneficial for the initial treatment of thyroid cancer, at least in tumors larger than 1 cm.

Compared with the National Comprehensive Cancer Network (NCCN) and the American Thyroid Association (ATA) guidelines for the diagnosis and treatment of differentiated thyroid cancer, Chinese guidelines for patients undergoing thyroid surgery to remove all indications do not include any specific age-based requirements. The NCCN guidelines recommend that patients with PTC aged <15 or >45 years should undergo total thyroidectomy. While the ATA guidelines recommend total thyroidectomy for all patients with PTC with tumor diameters >1 cm, unlike Chinese guidelines. Further, total thyroidectomy is also recommended for all patients with thyroid nodules in the contralateral gland and for patients with PTC with tumor diameters 1.0-1.5 cm, aged >45 years. In addition, Chinese guidelines indicate that all patients with differentiated thyroid cancer should receive central region lymph node dissection, as this provides effective protection from recurrent laryngeal nerve and parathyroid gland involvement. The NCCN and ATA guidelines recommend no dissection of the central lymph node without involvement, except for abnormal palpation or clear metastasis diagnosed by puncture biopsy.[23] Total thyroidectomy can have advantages for patients, including: (a) single treatment of multiple lesions, particularly bilateral cancer lesions; (b) facilitates postoperative monitoring of tumor recurrence and metastasis; (c) beneficial for postoperative I131 treatment; (d) reduces the recurrence rate of tumors and the probability of reoperation, which avoids increasing the incidence of serious complications due to reoperation; (e) accurate assessment of postoperative staging and risk stratification of patients; and (f) prevention of recurrence of thyroid cancer from development into poorly differentiated thyroid cancer. In patients with PTC, thyroid globulin levels can be assessed postoperatively to determine whether there is residual tumor or recurrence.[24] For patients with all thyroid tissue removed, there should be no thyroid globulin present in the body, hence, if thyroid globulin is detected in the serum, it generally indicates that some lesion remains or has relapsed, which is also an important prognostic indicator.[25] Forty patients underwent endoscopic thyroidectomy, who were preoperatively evaluated as low-risk patients, with the lymph node metastasis rate of 32.50%. The rate of lymph node metastasis in patients with total thyroidectomy was 39.84%. Here, lobectomy did not show obvious superiority, indicating that total thyroidectomy was not inferior to lobectomy.

Total thyroidectomy increases the incidence of recurrent laryngeal nerve and parathyroid gland injury, and any complications will have a serious impact on the mental health and quality of life of patients postoperatively. Therefore, surgeons must receive strict guidance and training to reduce or avoid surgical complications. Doctors undergoing training who may conduct lateral + isthmus + contralateral subtotal thyroidectomy should ensure that very small amount of nontumor thyroid tissue is left on the contralateral glandular lobe only to avoid recurrent disease of the laryngeal nerve and around the parathyroid gland. Simultaneously, in combination with the application of nanocarbon and nerve monitoring during surgery, to avoid bilateral recurrent laryngeal nerve or parathyroid gland damage, residual thyroid tissue can be dealt with using radioactive I131 therapy following surgery.

Thyroidectomy can lead to complications, primarily parathyroid injury (3-5%) and recurrent laryngeal nerve injury (1-5%). It is accepted that patients who undergo total or partial thyroidectomy must use thyroxine replacement, or even suppression, therapy for the rest of their lives.[26,27] Data from our hospital related to hypocalcemia, hoarseness, and sensory dysfunction of the shoulder after thyroid surgery are currently undergoing statistical analysis and will be presented in future reports. The pathological characteristics of PTC mean that analysis of the influence of surgical approach on survival and prognosis will be a long-term project, and we will continue to analyze follow-up data for these patients. Only a small number of patients were found to have BRAF gene mutations in our study, as there is no comprehensive promotion of genetic testing in our hospital, hence not all patients were evaluated.

According to the CTA, endocrine inhibition therapy is essential, regardless of surgical approach. Hence, long-term endocrine suppression therapy was required for all patients with PTC, including those who underwent lobectomy + central lymph node dissection. Radioactive I131 therapy is also an important part of comprehensive treatment of thyroid cancer.[28,29] All patients with lymph node metastasis, whether in the central or cervical region, were treated with I131 administered at doses of 80-130 mCi, according to the risk stratification assessment, with additional rounds of treatment if needed, based on the results of follow-up observation.

The method of treatment of thyroid cancer is influenced not only by surgeons, but also by nuclear medicine, imaging, and other clinicians, and even by health insurance companies. Careful preoperative staging and risk stratification of thyroid carcinoma results in better outcomes for patients with thyroid carcinoma. This is because such an approach facilitates more accurate surgery, and individualized treatment, as well as allowing the collection of data on national trends in this disease. The authors consider that surgeons should fully embrace the principles of tumor prevention and treatment, and be mindful that thyroid cancer is a malignant tumor; hence, the scope of treatment should not be reduced unnecessarily, to avoid the need for reoperation several years later. Therefore, it is necessary to assess patients, according to the current scientific knowledge, to make a comprehensive judgment of the safety of surgery, the willingness of the patient, and medical resources available, together with the national considerations and regional factors in China, and the degree of acceptance of the operation and possible secondary surgery by the patient. Together, this information can inform implementation of rational diagnosis and treatment plans.

5 | CONCLUSIONS

The data from our department inform several important points. (a) The incidence of thyroid cancer cases in our hospital generally rose annually. (b) PTC, even PTMC, has a high rate of local metastasis (59.42% and 46.92%, respectively) as, although it is an inert tumor after recovery, high invasiveness can occur on evolution of the tumor genome, indicating that it cannot be considered to exhibit a low degree of malignancy. Therefore, this study asserts that total thyroidectomy is beneficial for initial treatment of thyroid cancer, at least in tumors larger than 1 cm. (c) With increased tumor size, local lymph node metastasis rates rose from 44.68% to 77.53%, indicating that tumor invasiveness is elevated in larger cancers. When tumor diameter was >2 cm, the rate of cervical lymph node metastasis rose to 77.53%, suggesting that more aggressive and thorough treatment is required for patients with such tumors, and dissection of lateral cervical lymph nodes may be a good option. Postoperative complications and long-term follow-up data will be reported in the future.

6 | LIMITATIONS

This study does have limitations, because we only count the single-center thyroid cancer data in one area, and cannot represent a general phenomenon. However, we believe that the single-center data can also be convincing to remind thyroid surgeons to pay attention to papillary thyroid cancer.

AUTHORS' CONTRIBUTIONS

All authors contributed equally, there is no sequence. Yongkun Wang and Lin Han were responsible for the study design. Yongkun Wang was responsible for data interpretation. Yingxue Li and Lin Han were responsible for writing the manuscript. Wenjuan Wen was responsible for conducting the literature search and data collection. Lin Han was responsible for data analyses. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

COMPLIANCE WITH ETHICAL STANDARDS

Written informed consent for participation in this study was obtained from each patient after full explanation of the purpose and nature of all procedures used. The study was conducted in accordance with the Declaration of Helsinki. The ethical approval number is 2016071.

Before surgery, patients and their families were fully informed and discussed the implications. For patients <18 years old, informed consent was obtained from both parents.

DATA AVAILABILITY STATEMENT

We confirm that we will share the data underlying the findings reported in this manuscript and allow researchers to verify the results presented, replicate the analysis, and conduct secondary analyses.

All medical records are legal and reasonable. The study was approved and supervised by the ethics committee of Liaocheng People's Hospital, affiliated to Shandong First Medical University.

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