European Review for Medical and Pharmacological Sciences 2017; 21: 234-238

Surgical safety analysis of retaining the glands in papillary thyroid microcarcinoma

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Abstract. – OBJECTIVE: The objective of the present study was to analyze the surgical safety of retaining the glands in papillary thyroid microcarcinoma (mPTC).

PATIENTS AND METHODS: 156 cases of mPTC were retrospectively reviewed and divided into four groups according to the treatment: group A (conservative follow-up group, 30 cases), group B (total resection of unilateral gland combined with isthmic resection, 48 cases), group C (total resection of unilateral gland combined with subtotal resection of contralateral gland, 47 cases), and group D (total resection of bilateral glands, 31 cases). The average follow-up time was 34.5 months.

RESULTS: The occurrence rate of hypothyroidism, hypoparathyroidism, hypocalcemia, injury of the recurrent laryngeal nerve and total occurrence rate in the group B were significantly lower than in the group C and group D, and the differences were statistically significant ($p<0.05$). The 75% survival time was 33 months in group A, 35 months in group B, and 34 months in group D. The survival time of group A was significantly less than in the other groups, and the difference was statistically significant ($p<0.001$). There was no significant difference in the comparison of total mortality rate and recurrence rate ($p>0.05$).

CONCLUSIONS: The total resection of the unilateral gland combined with isthmic resection, which conserves gland functionality, reduces complications and maintains survival time. It is, therefore, worthy of further clinical application.

Key Words:
Papillary thyroid microcarcinoma, Total resection of unilateral gland, Complication, Survival time, Recurrence rate.

Introduction

Papillary thyroid microcarcinoma (mPTC) is defined as a tumor with diameter ≤ 10 mm, slow growth, low invasiveness, favorable prognosis, and lack of typical clinical symptoms[1,3]. With improvements in physical examination, development of high-frequency ultrasound, fine needle aspiration cytology (FNAC) and pathological diagnosis, the detection rate of mPTC has increased. In 2010, the incidence rate of thyroid cancer in men and women in South Korea was 24.9/10 million and 119.6/10 million, respectively. Thyroid cancer was first among all malignant tumors, and over half of new thyroid cancer cases were mPTC[4].

The basic goals for surgical treatment of mPTC include maximal resection of the tumor, preservation of glandular function, reduction of recurrence rate and improvement of survival rate[5]. Treatment regimens differ according to the country. The latest guidelines from the American Thyroid Association (ATA) and European Society for Medical Oncology stress that total thyroidectomy should be the primary treatment option, as the results from other procedures including subtotal thyroidectomy, lobectomy, and conservative surgery remain unclear[6,7]. Clinical studies from China have concluded that total resection of the unilateral gland combined with isthmic resection, conducted following a strict screening of low-risk groups was both safe and effective[8]. Researchers from Japan have proposed that some microcarcinomas do not require treatment and that observation was sufficient[9]. There were also different opinions about the cleaning scope of neck lymph nodes, unified standards on whether the prophylactic dissection of ipsilateral and contralateral central lymph nodes should be conducted, and the groups who benefited the most from these treatments[10,11]. In the present work, follow-up observation was applied in mPTC patients who underwent different treatments to compare the survival and recurrence rates, thereby providing a reference for clinical treatment.

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Patients and Methods

Patients

156 patients with mPTC who were diagnosed in our hospital from January 2012 to January 2016 were retrospectively analyzed. All patients were definitely diagnosed by iconography or FNAC and pathology. The inclusion criteria were: 1. Single lesions and no group VI lymph node metastasis; 2. Patients received postoperative thyroid hormone therapy to inhibit thyroid stimulating hormone (TSH) production; and 3. Complete medical history/clinical information was available. The exclusion criteria were: 1. The pathological type was non-papillary or combined with other thyroid diseases; 2. Pregnant and lactating women; 3. Radiotherapy, chemotherapy or other treatment regimens were conducted; 4. Dysfunction of other organs; 5. Surgery could not be tolerated; 6. Cervical injury; and 7. History of radiotherapy or other surgeries. This study was carried out under the approval of the Ethics Committee of The Central Hospital of Zhumadian City. All patients and their families signed the informed consent. The 156 patients were divided into four groups according to treatment as follows: group A (conservative follow-up group, 30 cases), group B (total resection of unilateral gland combined with isthmic resection, 48 cases), group C (total resection of unilateral gland combined with subtotal resection of contralateral gland, 47 cases) and group D (total resection of bilateral glands, 31 cases). Group A included seven males and 23 females. The average age was 46.3 ± 8.4 years old; the maximum tumor diameter was 3-10 mm with an average of 6.6 ± 2.3 mm. Thirteen cases had tumor location on the left and 17 were on the right. Group B included 14 males and 34 females, and the average age was 46.6 ± 8.5 years. The maximum tumor diameter was 4-10 mm, with an average of 6.8 ± 2.2 mm. Twenty-two cases had tumor location of the left and 25 were on the right. Group C included 12 males and 35 females, and the average age was 45.5 ± 7.6 years. The maximum tumor diameter was 4.5-10 mm with an average of 6.8 ± 2.5 mm. Twenty cases had tumor location on the left and 27 were on the right. Group D included eight males and 23 females, and the average age was 46.2 ± 8.2 years. The maximum tumor diameter was 4-10 mm with an average of 6.3 ± 2.4 mm. Fourteen cases had tumor location on the left and 17 were on the right. There were no significant differences in sex, age, tumor diameter or tumor position between the two groups (p>0.05).

Therapeutic Methods

The patients in the group A received no specific treatment and were followed by a conservative observation. They were not administered any drugs, and opted for therapy via lifestyle changes, such as avoiding radiation and adjusting diet. Concerning the 2015 ATA guidelines, the low-risk population was strictly screened, such as those complicated with minor lymph node metastasis (≤ five micrometastases in the lymph nodes by pathological examination). The maximum diameter of metastasized tumors was less than 0.2 cm, the papillary thyroid carcinoma subtype was follicular, and the condition was papillary microcarcinoma regardless of being positive for BRAF gene mutations. Patients in all of the other groups underwent the standard operation process, combined with high-frequency ultrasound guidance when necessary. Nanocarbon staining was used to identify the normal parathyroid glands and lymph nodes as well as to carefully identify neurovascular structures, thus preventing accidental injury. Intraoperative pathological examinations were immediately conducted, and patients with suspicious positive margins or suspicious lymph nodes were considered for whether the scope of operation needed to be expanded.

Observational Indexes

The average follow-up time was 34.5 months. The differences in the occurrence rates of hypothyroidism, hypoparathyroidism, hypocalcemia, injury of the recurrent laryngeal nerve, survival time, survival rate and recurrence were compared.

Statistical Analysis

SPSS20.0 software (SPSS Inc., Chicago, IL, USA) was used to analyze and process data. Measurement data are presented as mean ± standard deviation. The comparison between groups was done using One-way ANOVA test followed by Post Hoc Test (LSD). Qualitative data were expressed as case number or percentage. Chi-squared test or Fisher's exact probability test was performed between the groups. Kaplan-Meier method (Log-Rank test) was used in the analysis of survival time. A value of p>0.05 was considered statistically significant.

Table I. The comparison of the incidence rate of complications [cases (%)].

Group	Cases	Hypothyroidism		Hypocalcemia	The injury rate of recurrent laryngeal nerve	The total incidence
Group B	48	4 (8.3)	5 (10.4)	3 (6.3)	5 (10.4)	7 (14.6)
Group C	47	11 (23.4)	12 (25.5)	10 (21.3)	13 (27.7)	16 (34.0)
Group D	31	9 (29.0)	10 (32.3)	8 (25.8)	11 (35.5)	14 (45.2)
χ^2		6.156	6.086	6.334	7.592	9.281
p		0.046	0.048	0.042	0.022	0.010

Note: group B (total resection of unilateral gland combined with isthmic resection), group C (total resection of unilateral gland combined with subtotal resection of contralateral gland), group D (total resection of bilateral gland).

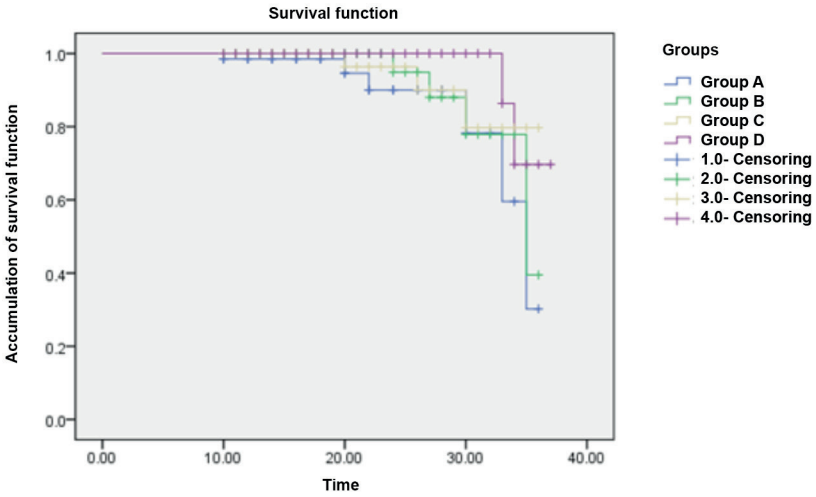

Figure 1. Survival curve (Kaplan-Meier method).

Results

Comparison of the Occurrence Rate of Complications

In the group A, tumor diameter was 3.5-10 mm (average: 6.9 ± 2.6 mm), and compared with diameters recorded before the follow-up visits; the differences were not statistically significant (p=0.326, p=0.421). There were two cases of hypothyroidism (normally treatable with thyroxine supplement therapy). Hypoparathyroidism and hypocalcemia did not occur. In the group B, the occurrence rates of hypothyroidism, hypoparathyroidism, hypocalcemia, injury of the recurrent laryngeal nerve and the total occurrence rate were significantly lower than the other two groups (p>0.05) (Table I).

Comparison of the Survival Time and Survival Rate

The 75% survival time in the group A was 33 months, 35 months in the group B and 34 months in the group D. The survival time of the group A was significantly lower than in the other groups (χ^2=87.740, p<0.001) (Figure 1). In the group A, one case died within one year, three cases died within two years, and six cases died within three years. In the group B, no cases died within one year, one case died within two years, and four cases died within three years. In the group C, no cases died within one year, one case died within two years, and three cases died within three years. In the group D, no cases died within one or two years, and two cases died within three years. The differences were not statistically significant in the comparison of total mortality within three years (χ^2=4.058, p=0.255).

Comparison of Recurrence Rate

There was no significant difference in the comparison of recurrence rate among the different groups (p>0.05) (Table II).

Table II. The comparison of the recurrence rate [cases (%)].

Group	Cases	Recurrence in situ	Metastasis	The total recurrence rate
Group A	30	3	1	4 (13.3)
Group B	48	3	1	4 (8.3)
Group C	47	2	0	2 (4.3)
Group D	31	1	1	2 (6.5)
χ^2				2.141
p				0.544

Discussion

Microcarcinoma is not clinically equivalent to low-risk thyroid cancer, and the biological behavior of microcarcinoma does not always predict a positive prognosis. Clinically, patients in which a primary tumor was small enough such that conventional imaging examination failed to detect the primary lesion, and where the emergence of neck metastases and systemic metastasis have already occurred, are often found[1]. Researchers from different countries propose different solutions for this issue. Ito et al[9] from Japan excluded patients with tumors that were adjacent to the trachea and located on the back side of the thyroid. At this point, the tumor may have invaded the recurrent laryngeal nerve, and fine needle aspiration biopsy showed a higher degree of malignancy, given the presence of lymph node metastasis. During the follow-up time, progress occurred. A total of 340 cases of mPTC were included in the study. The mean follow-up time was 74 months. Compared with the control group that underwent total resection of bilateral glands, there were no significant differences in lymph node metastasis or prognosis in the observation group. American and European guidelines stress[6,7] that total resection of the unilateral gland combined with isthmic resection should be conducted only in low-risk patients with the inner gland, single lesions; without a history of radiation exposure to the head and neck; or cervical lymph node metastasis. Furthermore, the pathological types should comply with typical follicular variants of papillary carcinoma or micro infiltrating follicular carcinoma. In our country, the following situations are regarded as absolute indication for total resection of the unilateral gland combined with isthmic resection: the single small thyroid papillary carcinoma is limited to one side of the gland, there is a low risk of recurrence, there is no childhood history of radiation exposure to the head and neck, there is no cervical lymph node metastasis or distant metastasis, and there are no nodules on the contralateral gland. The rate of operation is 60-5%[8]. An increasing amount of studies has found that expanding the range of thyroid surgery in patients with mPTC does not provide a survival advantage, and increases the risk of complications related to surgery. A choking cough after drinking caused by superior laryngeal nerve injury, hoarseness and difficulty breathing caused by recurrent laryngeal nerve injury, hypocalcemia induced numbness or convulsions, and other symptoms caused by parathyroid injury have a strong impact on quality of life following surgery[12,13].

Regarding the cleaning scope of lymph nodes, ATA guidelines suggest that central lymph node dissection should not be conducted on patients that have no invasion and lymph node involvement. Furthermore, the guidelines maintain that prophylactic dissection of central lymph nodes did not reduce mortality in this patient population, and increases the probability of injury to the recurrent laryngeal nerve and parathyroid. Concurrently, postoperative ^{131}I therapy in most patients improved the cure rate[10] to varying degrees. Chinese and Korean scholars[11] reported that the dissection of the ipsilateral central lymph node, regardless of the size of primary lesions, could clear the disease stage and guide treatment and follow-up.

New minimally invasive surgeries, such as total endoscopic surgery and Miccoli surgery, are also being increasingly applied clinically[14]. It should be noted that minimally invasive surgery may increase the probability of injury of the recurrent laryngeal nerve, cause larger trauma to subcutaneous tissue, and has group VII lymph node sweeping limitations. Percutaneous ablation of mPTC by ultrasound guidance has also been explored[15]. The ability to screen populations with minimal surgical intervention will benefit a large number of patients with mPTC. However, this will depend on further development of molecular etiology and molecular imaging. The high-frequency ultrasound has become a first choice method for diagnosis of thyroid diseases. The typical mPTC ultrasound manifests as a hypoechoic lesion with a rough edge, an aspect ratio over one, and calcification in nodules can be seen. Enlargement of neck lymph nodes, unclear corticomedullary line, and calcification in lymph nodes are important indications for the diagnosis of cervical lymph node metastasis of mPTC[16].

In the present study, we found that the occurrence rates of hypothyroidism, hypoparathyroidism, hypocalcemia, injury of the recurrent laryn-

geal nerve and total occurrence rate in the group B were significantly lower than in the group C and the group D, and the differences were statistically significant ($p<0.05$). The survival time of the group A was significantly less than in the other groups, which suggested that conservative observation as the only intervention may decrease long-term survival time. However, there was no significant difference in the comparison of the total mortality rate and recurrence rate over three years, which may be a reflection of the small sample size and short follow-up time.

Conclusions

The total resection of the unilateral gland combined with isthmic resection can maintain gland functionality, can reduce complications and does not decrease survival time. It, therefore, merits further clinical application.

Conflict of interest

The authors declare no conflicts of interest.

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