

Cases of pN1b and pM1 Papillary Microcarcinoma of the Thyroid

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Abstract

Introduction Papillary thyroid carcinoma has a relatively good prognosis among malignant tumors of the thyroid. Therefore, a “wait and see” strategy is often adopted for patients with micropapillary thyroid carcinoma. On the other hand, patients with papillary thyroid carcinoma with N1b or M1 disease are known to show a poor prognosis. Here, we investigated the differences in the characteristics between patients with papillary thyroid microcarcinoma with and without N1b metastatic nodes/distant metastases to identify the risk factors for metastasis.

Methods The retrospective study was performed in patients with thyroid microcarcinoma who were treated at the Kobe City Medical Center General Hospital from 2007 to 2017. The characteristics of the patients with thyroid microcarcinoma who were classified as having N1b or M1 disease (N1b/M1 group) were compared with those of patients with the same cancer classified as having N0, N1a, or M0 disease (N0/N1a group).

Results A total of 65 patients were enrolled in this study; 12 were classified into the N1b/M1 group and 53 were classified into the N0/N1a group. The proportion of males was significantly higher in the N1b/M1 group than in the N0/N1a group. There were no statistically significant differences in the distribution of the tumor sites, the ultrasonographic findings, or the frequency of the presence of multiple carcinomas. Although three patients died due to other causes, there were no patients who died due to papillary thyroid carcinoma.

Conclusion No significant predictors were identified for classifying patients with papillary thyroid microcarcinoma into the N1b/M1 group in this study. However, our findings suggested that male patients with papillary thyroid microcarcinoma require more careful follow-up in comparison to female patients with this cancer.

Keywords

- ▶ thyroid microcarcinoma
- ▶ papillary carcinoma
- ▶ metastasis
- ▶ male patients
- ▶ risk factor

Introduction

The prognosis for differentiated thyroid cancer is said to be comparatively favorable,¹ and T4, N1b, and M1 are considered to be poor prognostic factors for papillary thyroid adenocarcinoma.^{2,3} Normally, surgery was the first choice for treating papillary thyroid adenocarcinoma. However, as the disease gradually progresses and many cases have a favorable prognosis, some facilities are now selecting a conservative

approach with regular follow-up observations.⁴ However, in cases of papillary carcinoma, metastasis to the neck lymph nodes is most frequently identified,⁵ and even some cases of microcarcinomas lead to death. Herein, we first examined whether there were cases of thyroid microcarcinoma with either N1b or M1. We also compared cases with either N0 or N1 to retrospectively investigate whether it is possible to predict microcarcinomas, which metastasize easily.

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Subjects and Methods

This study included patients who underwent surgery for thyroid tumors at the Department of Otolaryngology-Head and Neck Surgery, Kobe City Medical Center General Hospital between January 1, 2007, and April 30, 2017, and were diagnosed with thyroid microcarcinoma according to histopathological examination. The seventh edition of the Thyroid Cancer Treatment Guidelines defines a microcarcinoma as “a focus with a maximum diameter of 1 cm, many of which are papillary carcinomas, but which may also describe other tissue types.”⁶ Conforming to this definition, papillary carcinomas with a diameter of ≤ 1 cm were examined. pN1b or pM1 cases were designated as the pN1b/M1 cohort and all other pN0 or pN1 cases and cM0 or pM0 cases were designated as the pN0/N1a cohort to comparatively examine whether there were trend differences in both cohorts. The following variables were evaluated: age, sex, chief complaint, tumor site, ultrasound findings, surrounding infiltration, multiple occurrences of tumors within the gland, and outcomes. Data between the two groups were compared using the chi-square test, and $p < 0.05$ was considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 24. This study was approved by our hospital's institutional review board.

Results

A total of 65 patients were diagnosed with papillary thyroid microcarcinoma. N classification indicated that there were 36 pN0 cases, 18 pN1a cases, and 11 pN1b cases. M classification resulted in 64 cM0 cases and 1 pM1 case. The pM1 case was designated as pN0. The pN1b and pM1 cases were designated as the pN1b/M1 cohort and the remaining N0 or N1a and cM0 cases were allocated into the N0/N1a cohort for comparative investigation. There were 12 patients in the pN1b/M1 cohort, and 53 patients in the pN0/N1a cohort. A comparison of patient characteristics between the pN1b/M1 and pN0/N1a cohorts is shown in ► **Table 1**.

Age

Patients in the pN1b/M1 cohort were aged from 32 to 77 years (average age: 57 years, median age: 60 years), with 6 patients younger than 55 years (50%). Patients in the pN0/N1a cohort were aged from 29 to 80 years (average age: 59 years, median age: 62 years), with 17 patients younger than 55 years (32%). No statistically significant differences were found between the two cohorts ($p = 0.241$).

Sex

There were 8 males and 4 females in the pN1b/M1 cohort, and 9 males and 44 females in the pN0/N1a cohort, indicating that there was a significantly higher percentage of males in the pN1b/M1 cohort ($p = 0.001$).

Chief Complaints

The chief complaints of the pN1b/M1 cohort were neck swelling (six cases), thyroid tumors incidentally detected via imaging examinations such as CT and PET (five cases), and

Table 1 Comparison between pN1b/M1 and pN0/N1a cohorts

	pN1b/M1 cohort	pN0/N1a cohort	p-Value
No. of cases	12	53	
Age (y)	32–77	29–80	
< 55	6 cases (50%)	17 cases (32%)	0.241
Sex			
Male	8 cases (67%)	9 cases (17%)	0.001 ^a
Female	4 cases (33%)	44 cases (83%)	
Chief complaint			
Detected upon testing	5 cases (42%)	32 cases (60%)	0.417
Neck swelling	6 cases (50%)	16 cases (30%)	
Other	1 case (8%)	5 cases (9%)	
Tumor site			
Right lobe	9 cases (75%)	26 cases (49%)	0.218
Left lobe	3 cases (25%)	22 cases (41%)	
Isthmus	0 cases (0%)	5 cases (9%)	
Adjacent to thyroid capsule	8 cases (67%)	33 cases (62%)	0.775
Ultrasound findings			
Hypoechoic	5 cases (46%)	13 cases (28%)	0.272
Hyperechoic	3 cases (27%)	8 cases (17%)	
Acoustic shadow	3 cases (27%)	25 cases (54%)	
Surrounding infiltration			
Ex0	9 cases (75%)	29 cases (55%)	0.198
Ex1	3 cases (25%)	24 cases (45%)	
Multiple lesions in gland	6 cases (50%)	16 cases (30%)	0.190

Notes: The pN1b/M1 cohort included cases of either pN1b or pM1, whereas the pN0/N1a cohort included cases of either pN0 or pN1a and cM0. The p -value was obtained using a chi-square test to compare the pN1b/M1 and pN0/N1a cohorts.

^aStatistically significant difference.

ambulatory impairment caused by thoracic metastasis (one case). Of the neck swelling cases, two cases were thyromegaly and four cases were neck lymphadenopathy. In the pN0/N1a cohort, 32 cases were identified by examination, of which 31 cases were identified by imaging examinations and 1 case was identified by serological examination. There were 16 cases of neck swelling, of which 13 cases were thyromegaly and 3 cases were neck lymphadenopathy. There were four cases of pharyngeal discomfort, and one case of hoarseness. The thyromegaly cases were due to adenomatous goiter, chronic thyroiditis, Graves' disease, and other benign illnesses. The cases of neck lymphadenopathy in the pN1b/M1 cohort were due to lymph node metastasis, but in the pN0/N1a cohort, lymphadenopathy was due to inflammation.

Tumor Site

The thyroid was classified into the right lobe, isthmus, and left lobe, and the cancer was examined at sites where the tumor had a maximum diameter. In the pN1b/M1 cohort, there were nine cases of microcarcinoma in the right lobe and three cases of microcarcinoma in the left lobe. In the pN0/N1a cohort, there were 26 cases of microcarcinoma in the right lobe, 22 cases of microcarcinoma in the left lobe, and 5 cases of microcarcinoma in the isthmus. Although there were more right-lobe tumors in the pN1b/M1 cohort, no statistically significant difference was identified ($p = 0.218$). Furthermore, cases in which preoperative ultrasound identified thyroid capsules and tumors with their closest parts as 1 mm or less were examined as proximal cases. A biopsy was conducted only for cases in which the ultrasound observation was unclear. There were 8 proximal cases in the pN1b/M1 cohort (67%) and 33 proximal cases in the pN0/N1a cohort (62%); no statistically significant difference was observed ($p = 0.775$).

Characteristics of Ultrasound Findings

Tumors were classified into the following three groups for examination: (1) hypoechoic tumors, that is, tumors without concomitant hyperechoic bright spots; (2) hyperechoic tumors, that is, tumors including either fine or macular hyperechoic bright spots without concomitant acoustic shadows; and (3) acoustic shadow tumors, that is, tumors with concomitant acoustic shadows. Cases of tumors that could not be identified as a microcarcinoma were excluded because there were multiple tumors with different observations, and cases that did not undergo ultrasound observation were also excluded. In total, there were 18 cases of hypoechoic tumors, 11 cases of hyperechoic tumors, 28 cases of acoustic shadow tumors, and 8 cases that were excluded. In the pN1b/M1 cohort, there were five cases of hypoechoic tumors, three cases of hyperechoic tumors, and three cases of acoustic shadow tumors. In the pN0/N1a, there were 13 cases of hypoechoic tumors, 8 cases of hyperechoic tumors, and 25 cases of acoustic shadow tumors. Statistical analysis of data between the two cohorts revealed no significant difference ($p = 0.272$).

Surrounding Infiltration

In the pN1b/M1 cohort, there were 9 Ex0 cases and 3 Ex1 cases. In the pN0/N1a cohort, there were 29 Ex0 cases and 24 Ex1 cases, with no Ex2 cases identified. No statistically significant difference was identified between the two cohorts ($p = 0.198$).

Multiple Occurrences of Tumors within the Thyroid Gland

There were 6 cases of multiple microcarcinomas identified in the thyroid gland in the pN1b/M1 cohort (50%), and 16 such cases were identified in the pN0/N1a cohort (30%); however, no statistically significant difference was identified ($p = 0.190$).

Outcomes

The follow-up period for the pN1b/M1 cohort was 4 to 121 months (median: 16 months), in which there were nine cases of non-tumor-bearing survival, two cases of tumor-

bearing survival, and one case of death by other causes. Total thyroidectomy was performed for all cases. The follow-up period for the pN0/N1a cohort was 1 to 116 months (median: 47 months), with 50 cases of non-tumor-bearing survival, 1 case of tumor-bearing survival, and 2 cases of death by other causes. Total thyroidectomy was performed for 46 cases, and one lobe was resected in 7 cases. There were no cases of cause-specific death.

Discussion

Thyroid papillary adenocarcinoma is associated with a comparatively favorable prognosis, and surgery is the first choice of treatment. The disease is often identified during regular health check-ups, and more microcarcinomas are increasingly being detected.⁴ Latent cancers have been detected in only 0.5 to 5.2% of autopsy cases;⁷ therefore, there appear to be many cases in which the mortality factors are not directly affected even when such carcinomas are left untreated. In recent years, the number of cases in which active surveillance has been chosen for thyroid microcarcinomas has increased.⁴ However, thyroid cancers can metastasize easily to the lymph nodes, and prognosis in N1b and M1 cases is poor.^{2,3} Furthermore, the Thyroid Tumor Treatment Guidelines state, "Lymph node metastasis, remote metastasis, and papillary microcarcinomas concomitant with infiltration outside the thyroid gland that are clarified by preoperative diagnosis are suitable for absolute resection, and observation over time is not recommended. If a patient who shows no signs of these metastases or infiltrations desires conservative treatment with regular follow-up observations after receiving a thorough explanation and giving their consent, they are eligible to receive such treatment."² Herein, we searched for findings that could be used as a reference to determine the eligibility of cases of microcarcinoma for surgery through comparative analysis of microcarcinoma pN1b/M1 cases and other cases.

Our examinations did not identify any statistically significant difference based on age between the pN1b/M1 and pN0/N1a cohorts. Age had little effect on the percentage of metastases. However, a conservative approach with regular follow-up examinations for microcarcinoma cases has been reported to result in a strong tendency for tumor growth among younger patients,⁸ and although there was no statistically significant difference, the percentage of patients younger than 55 years in the pN1b/M1 cohort was higher. Thyroid cancers require long-term observation, and it appears that if such an approach is selected, younger patients require more careful follow-up over time.

Approximately half of the male cases were placed in the pN1b/M1 cohort, indicating that microcarcinoma was more progressive in men. Male sex also appeared to be a critical prognostic factor for papillary carcinoma. It might also be necessary to implement testing and treatment during the follow-up period at different intensities for microcarcinomas based on sex.

As the chief complaint was microcarcinoma, cases were often incidentally discovered during tests for other purposes. In many cases, thyromegaly was detected during treatment for

benign tumors such as adenomatous goiter. There were also cases detected during neck lymph node metastasis, and if neck lymph node swelling is identified with an unknown origin, it is necessary to consider the possibility of not only malignant pharyngeal tumors but also thyroid cancer metastasis.

The tumor site was mainly the right lobe, but no statistically significant difference was identified. Furthermore, percentages of remote metastasis according to proximity to the capsule were unchanged. While cases of multiple occurrences within the gland were more numerous in the pN1b/M1 cohort than in the pN0/N1a cohort (46 vs. 30%), no statistically significant difference was identified. Multiple occurrences of tumors in the gland were often unrecognized as tumors in ultrasound examinations. Regarding the scope of surgery, thyroid lobe resection is often recommended for T1N0M0 cases, and total thyroid gland resection is recommended for high-risk patients; microcarcinomas often fall into the gray zone. As multiple occurrences of tumors in the gland are also common for cases of microcarcinomas, we believe that such cases could also be eligible for total thyroidectomy.

In terms of ultrasound findings, one previous report classified hyperechoic bright spots into five types and examined the characteristics of microcarcinomas, which can easily become enlarged during follow-up observations.⁹ Massive hyperechoic bright spots, which are said to show calcification, are classified into five types: minute, macular, and coarse accompanied by acoustic shadow (fragmented, mass-like, eggshell-shaped). We classified minute and macular tumors as hyperechoic tumors, and the three types of coarse hyperechoic bright spots with acoustic shadow as acoustic shadow tumors. It is reported that continuous observations over time are possible for coarse echo bright spots and minute hyperechoic bright spots with acoustic shadows that show no tumor growth.⁹ Our results also showed that the percentage of hypoechoic tumors in the pN1b/M1 cohort was high and that of acoustic shadow tumors was low, but no statistically significant difference was identified. The percentage of tumors with acoustic shadows was low in the pN1b/M1 cohort, but there were also cases in which metastasis was identified. Thus, if a conservative approach with regular follow-up examinations over time is selected, it appears that in addition to the thyroid gland, the lymph nodes should also be closely examined.

Investigation of postoperative follow-up did not identify a specific cause of death. Considering the favorable survival rates in the pN1b/M1 cohort, such cases might be controlled even by treatment after manifestation of metastasis. Consequently, when examined from the viewpoint of survival, a conservative approach with regular follow-up observations may be the first choice. However, as cases of microcarcinomas are also associated with the possibility of cancers other than papillary carcinomas, such as medullary carcinomas and low differentiation cancers, it is ideal to definitively diagnose the papillary carcinoma through cytology or serum examinations even if a conservative approach is selected.

Herein, only surgical cases were investigated, and there was a bias toward surgery selection, which may have resulted in the percentage of cases with microcarcinoma metastasis being

even lower. However, given that remote metastasis clearly worsens survival, metastasis to the brain or bone clearly reduces the patient's quality of life due to the occurrence of neurological symptoms. To create a standard for choosing either observations over time or surgical treatment by predicting future worsening, we investigated the characteristics of microcarcinoma metastasis. However, we were unable to identify any predictive factors other than male sex. Even with microcarcinomas, it is necessary to thoroughly examine the patient's background, such as age and social environment, and directly consult the patient before choosing whether to take a conservative or a surgical approach. If a conservative approach is selected, testing for metastasis should be implemented as considered appropriate.

Conclusion

This study investigated thyroid gland microcarcinomas. A large percentage of male cases were assigned to the pN1b/M1 cohort. It was difficult to predict metastasis using only thyroid tumor imaging findings. A conservative approach may be selected in the short term for papillary thyroid microcarcinomas, and selection of either a conservative or surgical approach for thyroid microcarcinomas should be based on informed consent.

Conflict of Interest

None declared.

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