

ORIGINAL ARTICLE

Clinical features and prognostic factors in papillary thyroid microcarcinoma depends on age

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Purpose: Clinical outcomes of papillary thyroid microcarcinoma (PTMC) vary. In general, age at diagnosis is an independent prognostic factor in conventional papillary thyroid carcinoma. However, it is unclear in patients of PTMC. The purpose of this study was to identify clinicopathologic features and prognostic factors of PTMC according to patients' age. **Methods:** Five hundred twenty-seven patients who received thyroid surgery and diagnosed as having PTC between January 2001 and December 2009 were included. The clinical data were retrospectively analyzed. **Results:** We divided the patients into two groups; group I who were younger than 45 years, and group II who were 45 years old or older. The mean tumor size and incidences of neck lymph nodes involvement of group I was larger than group II. In group II, however, there were more patients who had multiple cancer foci and were body mass index ≥ 25 kg/m². The overall incidence of recurrent disease was 3.2%. The incidence of recurrence was higher in group II (2.0% vs. 4.0%), without a statistical difference. In multivariate analysis, the significant risk factors of recurrence were male gender and multifocality in group I, and lymph node metastasis and multifocality in group II. In particular, the male gender and multifocality showed the highest odds ratio (OR) on each group (OR, 4.721 and 6.177). **Conclusion:** The patients with PTMCs had different clinical features and prognostic factors according to age. Hence, clinicians should consider a different strategy for therapy and plan for follow-up according to age.

Key Words: Papillary thyroid cancer, Microcarcinoma, Prognosis, Age

INTRODUCTION

Papillary thyroid microcarcinoma (PTMC) is defined as a papillary thyroid cancer measuring 10 mm or less in maximum diameter [1]. Advances in ultrasonography-guided fine needle aspiration cytology have resulted in a marked increase in the number of patients diagnosed with PTMC [2].

Clinical outcomes of PTMC vary. Most PTMCs have an

indolent course and excellent prognosis [3-6]. However, some PTMCs result in recurrence, distant metastasis, or mortality [3,7,8]. Therefore, the optimal management of PTMC remains controversial, ranging from conservative treatment to more aggressive treatment as with other malignancies of the thyroid [2,3,6,9-12]. To date, there are no confirmative factors to predict the prognosis of PTMCs, although the BRAF^{V600E} mutation with aspiration specimen is associated with poor prognostic factors such as lymph

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node metastasis, tumor size, extrathyroid extension and multifocality [13-18].

In general, age at diagnosis is an independent prognostic factor in conventional papillary thyroid carcinoma (PTC). Older patients tend to have more locally aggressive tumors and a higher incidence of distant metastases at diagnosis and more aggressive histologic variant, factors that locally portend a more dismal outlook. However, it is unclear whether these findings hold among patients of PTMC. We therefore examined the clinicopathologic features and prognostic factors of PTMC according to patient age.

METHODS

We reviewed the charts of the patients who underwent thyroid surgery for malignancy from January 2001 to December 2009 in Gyeongsang National University Hospital. Among these, patients who were diagnosed with PTMC after operation were selected for this study. And the patients with other malignancies or history of previous thyroidectomy were excluded from the study.

Of the 1,145 patients with PTC, 539 patients were diagnosed as having PTMC. Of these patients, 12 patients were excluded because 8 patients were diagnosed with other malignancies before or after operation, and 4 patients were already had hemi-thyroidectomies due to benign disease of the thyroid. Thus, the remaining 527 patients were included in this study.

The epidemiologic factors and pathologic reports after operation were examined based on chart review. For each patient, height and weight was used to calculate body mass index (BMI) according to its determined formula (i.e., $BMI = \text{weight, kg} / [\text{height, m}]^2$).

In our institution, methods of operation were selected by tumor characteristics. If the patients had no bilateral tumor foci, lymph node metastasis and grossly soft tissue invasion, we would perform a hemi-thyroidectomy as an initial operation. If lymph node metastasis was observed after the hemithyroidectomy, completion thyroidectomy was recommended, and these patients were considered to have undergone total thyroidectomy in the analysis. But

the five patients who were recommended to undergo completion thyroidectomy were followed up without receiving it. After surgery, most patients received thyroid hormone suppressive therapy for at least 6 months. Among the patients who had neck lymph node metastasis or three or more multiple cancer foci after receiving total thyroidectomy, post-operative radio-active iodine (RAI) therapy was performed. But, the patients who refused to undergo RAI due to such reasons as their general condition, even though they met the criteria and were recommended to undergo treatment, were also included in the analysis.

Postoperative investigation usually consisted of thyroid ultrasonography, thyroid function test, and/or ^{131}I whole-body diagnostic scanning. Postoperative investigation was performed 6 months after surgery and at 6 to 12-month intervals thereafter.

Chi-square test and Fisher's exact test were used to analyze the significance of difference in the clinical features. Logistic regression analysis was performed for multivariate analysis to determine significant factors associated with recurrence among the age's group. In addition, survival rates were calculated by the Kaplan-Meier method and were compared by the log-rank test. All statistical analyses were performed using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA) and P-value < 0.05 were considered statistically significant.

RESULTS

The mean age of the patients with PTMCs was 47.67 ± 11.452 years old (range, 15 to 73 years). We divided the patients with PTMCs into two groups according to age. Group I was patients who were younger than 45 years old at the time of diagnosis, and group II was patients who were 45 years old or older. Two hundred five patients (38.9%) belonged to group I and 322 belonged to group II.

Clinicopathologic features

The clinicopathologic features of patients with PTMC according to age group are given in Table 1.

There was no significant difference of sex in two groups. The mean tumor size of PTMCs of group I was larger than

Table 1. The clinicopathologic features of patients with papillary thyroid microcarcinoma

| | Group I (n = 205) | Group II (n = 322) | P-value |
|-----------------------------|-------------------|--------------------|---------|
| Male:female | 38:167 | 51:271 | 0.474 |
| Cancer size (cm) | 0.71 ± 0.24 | 0.67 ± 0.24 | |
| <0.5 | 56 (27.3) | 116 (36.0) | 0.045 |
| ≥0.5 | 149 (72.7) | 206 (64.0) | |
| Capsular invasion | 72 (35.1) | 135 (41.9) | 0.121 |
| Neck LN involvement | 45/81 (55.56) | 49/128 (38.28) | 0.016 |
| Lateral neck LN involvement | 3 | 2 | 0.874 |
| Multiplicity | | | |
| Solitary | 175 (85.4) | 236 (73.3) | 0.001 |
| Multiple | 30 (14.6) | 86 (26.7) | |
| Unilateral | 16 | 33 | 0.002 |
| Bilateral | 14 | 53 | |
| Operation methods | | | 0.000 |
| Total thyroidectomy | 88 (42.9) | 206 (64.0) | |
| Hemithyroidectomy | 117 (57.1) | 116 (36.0) | |
| RAI therapy | 14 (6.8) | 51 (15.8) | 0.003 |
| BMI (kg/m ²) | | | 0.031 |
| <25 | 145 (70.7) | 198 (61.5) | |
| ≥25 | 60 (29.3) | 124 (38.5) | |
| Recurrence | 4 (2.0) | 13 (4.0) | 0.216 |

Values are presented as mean ± SD or number (%).

Group I, patient's age < 45 years; Group II, patient's age ≥ 45 years.

SD, standard deviation; LN, lymph node; RAI, radio-active iodine; BMI, body mass index.

group II. The incidences of neck lymph nodes involvement were higher in group I (22.0% vs. 15.2%, $P = 0.033$), and the patient ratio of BMI ≥ 25 kg/m² was lower in group I than group II (29.3% vs. 38.5%, $P = 0.031$). In group II, however, there were more patients who had multiple cancer foci, especially in both thyroid lobes. The capsular invasion of cancer was also higher in group II, but there was no significant difference between the groups.

Total thyroidectomy and radioactive iodine ablation treatment were more frequently performed in patients of group II ($P = 0.000$ and 0.003).

Tumor recurrence

The follow-up period ranged from 5.6 to 120.0 months and mean period was 48.2 ± 24.6 months. After that period, there was no distant metastasis or death related to PTMC.

The overall incidence of recurrent disease was 3.2%. One patient developed a recurrent mass on the remnant thyroid after hemithyroidectomy, one had recurrence on both the thyroid bed and lateral neck lymph node, and the other 15 patients had only lateral neck lymph node

recurrence.

The incidence of recurrence was higher in group II (2.0% vs. 4.0%), without being statistically difference ($P = 0.216$).

The interval from initial surgery to recurrence ranged from 5.1 to 81.3 months. No difference was identified in the interval periods of recurrence among the two groups.

Risk factors of recurrence

In group I, male gender, multifocality and BMI were significantly associated with recurrence at univariate analysis. However, in group II, the capsular invasion, neck lymph node metastasis, multifocality at diagnosis and RAI treatment after operation were independent risk factors for recurrence (Table 2).

For each group, a univariate analysis was performed and the factors that were deemed meaningful in the analysis were further analyzed through a multivariate analysis. At multivariate analysis, the significant risk factors of recurrence were male gender and multifocality in group I ($P = 0.03$ and 0.04), and lymph node metastasis and multifocality in group II ($P = 0.01$ and 0.01). In particular, male

Table 2. Risk factors of recurrence of patients with papillary thyroid microcarcinoma according to age group

| | Group I | | P-value | Group II | | P-value |
|--------------------------|------------|-----------|---------|------------|------------|---------|
| | Non-recur | Recur | | Non-recur | Recur | |
| Sex | | | 0.021 | | | 0.235 |
| Male | 35 (17.4) | 3 (75.0) | | 51 (16.5) | 0 (0) | |
| Female | 116 (82.6) | 1 (25.0) | | 258 (83.5) | 13 (100.0) | |
| Cancer size (cm) | | | 0.577 | | | 1.000 |
| <0.5 | 56 (27.9) | 0 (0) | | 111 (35.9) | 5 (38.5) | |
| ≥0.5 | 145 (72.1) | 4 (100.0) | | 198 (64.1) | 8 (61.5) | |
| Capsular invasion | 71 (35.3) | 1 (25.0) | 1.000 | 126 (40.8) | 9 (69.2) | 0.049 |
| Neck LN involvement | 43 (21.4) | 2 (50.0) | 0.210 | 42 (13.6) | 7 (53.8) | 0.001 |
| Multiplicity | | | 0.044 | | | 0.001 |
| Solitary | 173 (86.1) | 2 (50.0) | | 232 (75.1) | 4 (30.8) | |
| Multiple | 28 (13.9) | 2 (50.0) | | 77 (24.9) | 9 (69.2) | |
| Unilateral | 16 | 0 | 0.002 | 31 | 2 | 0.001 |
| Bilateral | 12 | 2 | | 46 | 7 | |
| Operation methods | | | 1.000 | | | 0.557 |
| Total thyroidectomy | 86 (42.8) | 2 (50.0) | | 199 (64.4) | 7 (53.8) | |
| Hemithyroidectomy | 115 (57.2) | 2 (50.0) | | 110 (35.6) | 6 (46.2) | |
| RAI therapy | 14 (7.0) | 0 (0) | 1.000 | 46 (14.9) | 5 (38.5) | 0.039 |
| BMI (kg/m ²) | | | 0.042 | | | 0.773 |
| <25 | 144 (71.6) | 1 (25.0) | | 189 (61.2) | 9 (69.2) | |
| ≥25 | 57 (28.4) | 3 (75.0) | | 120 (38.8) | 4 (30.8) | |

Values are presented as number (%).

Group I, patient's age < 45 years; Group II, patient's age ≥ 45 years.

SD, standard deviation; LN, lymph node; RAI, radio-active iodine; BMI, body mass index.

Table 3. Multivariate analysis of factors affecting the recurrence in each age group of papillary thyroid microcarcinomas

| Group | Factor | Odds ratio | P-value | 95% CI |
|-------|------------------------------|------------|---------|---------------|
| I | Sex (male) | 4.721 | 0.030 | 0.005-0.763 |
| | Multiple | 4.072 | 0.044 | 1.070-106.886 |
| | BMI (≥25 kg/m ²) | 1.885 | 0.170 | 0.485-61.075 |
| II | Capsular invasion | 1.902 | 0.168 | 0.680-9.167 |
| | LN metastasis | 5.498 | 0.019 | 1.322-22.629 |
| | Multiple | 6.177 | 0.013 | 1.397-16.956 |
| | RAI therapy | 0.089 | 0.766 | 0.168-3.714 |

CI, confidence interval; BMI, body mass index; LN, lymph node; RAI, radio-active iodine.

gender and multifocality showed the highest odds ratio (OR) in each group (OR, 4.721 and 6.177) (Table 3).

By the Kaplan-Meier survival analysis, recurrence-free survival was higher in group I (98.0% vs. 95.9%), but there was no significant difference between the groups (log-rank = 0.078) (Fig. 1). Of group I, the recurrence-free survival of male was lower than female, it was significant (M : F = 92.1% : 99.4%; log-rank = 0.010) (Fig. 2A). Also, of group II, the recurrence-free survival of the patients with solitary PTMCs was higher than the others (solitary : mul-

tiple = 98.3% : 88.9%; log-rank = 0.000) (Fig. 2B).

DISCUSSION

Recently, several papers have focused on the clinical significance, the appropriate treatment, and the prognostic features of PTMC [6,19,20]. Obviously, the increasing interest in this disease worldwide has resulted in more frequent diagnosis. Grodski and Delbridge [20] have demon-

strated that the incidence of PTC has almost doubled over the last three decades, mainly due to the higher incidence of PTMC.

According to the seventh edition of tumor, node, metastasis system classification by the American Joint Committee on Cancer, age is an important prognostic factor [21]. Of the PTMCs, if the patient's age is younger than 45 years old; the stage is just I regardless of extrathyroid extension and lymph node metastasis. If the patient's age is 45 years old or older, their stages might be upgraded according to tumor characteristics. Recently, Yu et al. [22] reported that an age greater than 45 years was poor survival factor in PTMC, so they stated that older patients should

be considered for more aggressive treatment. However, other studies reported that age was not a prognostic factor of PTMC. Similarly, in this study, the recurrence rate was higher in older group, but there was also no significant difference between the groups. Therefore, we sought to examine the clinical impact according to age rather than age as prognostic factor.

According to studies, the recurrence rate of PTMC ranges from 3 to 16.7%, and they reported the prognostic factors; tumor size, postoperative Tg level, presence of lymph node metastases at diagnosis, sex, and extent of surgery [3,10,11,14,17,18]. The lateral neck lymph node metastases have been considered a confirmative prognostic factor of PTMC, but there is considerable debate concerning central neck lymph node metastases [14,15]. Also, routine prophylactic central neck lymph node dissection for PTMC has been debated because prophylactic node dissection seems to have little prognostic benefit [6,23,24]. So et al. [25] reported that the lymph node metastasis was not associated with age, but Lombardi et al. [17] reported that the patients who had lymph node metastasis were younger than others. In our study, the incidence of lateral neck lymph node metastases at the time of diagnosis was too low at 0.9%, so it might be difficult to analyze the significance of lateral lymph nodes on PTMC. Of all, the incidence of neck lymph node metastases was higher in patients whose age was less than 45 years. Patients with lymph node metastases showed higher recurrence rates

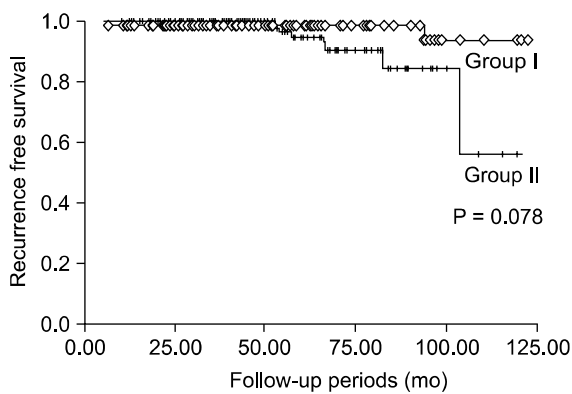


Fig. 1. Recurrence-free survival rate of papillary thyroid microcarcinoma according to age group by the Kaplan-Meier survival analysis. The recurrence-free survival was higher in group I, but there was no significant difference between the groups.

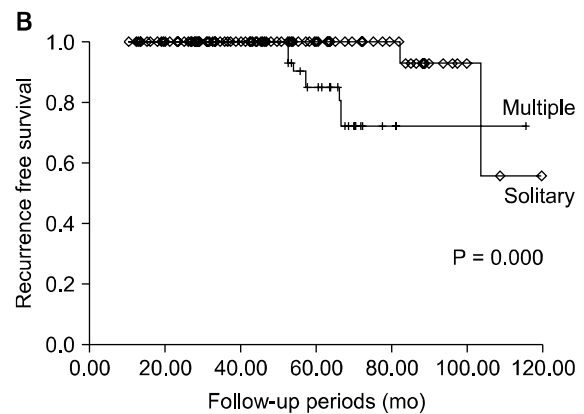
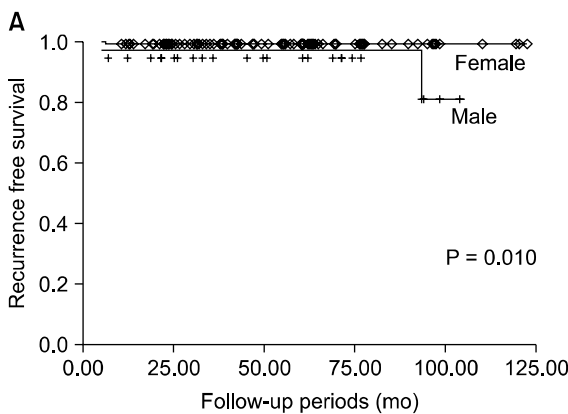


Fig. 2. Recurrence-free survival rate of papillary thyroid microcarcinoma (PTMC) according to sex in group I patients. (A) Stratified by sex in the group I. The recurrence-free survival of male was lower than female (log-rank = 0.010). (B) Stratified by multiplicity in the group II. The recurrence-free survival of the patients with solitary PTMCs was higher than the others (log-rank = 0.000).

than patients without them. However, lymph node metastases revealed significant prognostic factors for recurrence in only the patients whose ages were 45 years or older.

Multifocal lesions in PTMC are not an unusual finding like conventional PTC. In general, the incidence of multifocality has been reported to be 19 to 32%. In our study, 22% of the PTMC patients had multifocal cancers and 57.8% of them had bilateral cancer. Multifocality was the only significant prognostic factor on both age groups (OR: group I, -4.072 and group II, -6.177; P-value < 0.05). Therefore, the multifocality of PTMC was considered to be one of the most significant prognostic factors regardless of age.

The association with sex and prognosis of PTMC has been debated. Recently, Roh et al. [26] reported that there was no association between sex and lymph node metastasis. Unexpectedly, Besic et al. [27], and So et al. [25] reported that the male gender had a tendency toward node metastasis. However, there was little evidence for the relationship between sex and the recurrence or survival in patients with PTMC. In this study, of the patients aged less than 45 years, males were revealed to be a significant factor affecting to recurrence, and the OR was 4.721 on multivariate analysis.

Positive associations between BMI and thyroid cancer have been reported in large prospective studies and meta-analysis [28-30], but there has been no evidence whether these findings hold among patients of PTMC. In our study, the patients with a BMI of ≥ 25 kg/m² showed the tendency to have poor prognosis in univariate analysis but not in multivariate analysis. Further studies on this issue are needed.

Our study had some limitations. The first limitation of this study is the fact that it was a retrospective study with patients from a single institution. The second limitation is that this study resulted from short periods of follow-up (mean, 48.2 \pm 24.6 months). So, if we follow-up over long periods, we may have a higher recurrence rate than now along with different prognostic factors. Hence, we think that it is necessary to perform a prospective study on disease recurrence and survival for the two groups with long-term follow-up periods.

In this study, we found that although age itself was not independent prognostic factor of recurrence in PTMC, the different age groups had different clinical features and prognostic factors. Sex and multifocality of cancer were the significant factors determining recurrence in patients aged <45; and the lymph node metastases and multifocality in patients aged ≥ 45 years old. Therefore clinicians should consider a different strategy of therapy and plan for follow-up according to age.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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