

# Clinicopathologic Characteristics of Papillary Microcarcinoma in the Elderly

Won Jin Kim<sup>1</sup>, Min Jung Bae<sup>1</sup>, Yang Seon Yi<sup>1</sup>, Yun Kyung Jeon<sup>1,2</sup>, Sang Soo Kim<sup>1,2</sup>, Bo Hyun Kim<sup>1,2</sup> and In Joo Kim<sup>1,2</sup>

Division of Endocrinology and Metabolism, Department of Internal Medicine<sup>1</sup>, Biomedical Research Institute, Pusan National University Hospital<sup>2</sup>, Busan, Korea

**Background and Objectives:** Older patients show more aggressive features in papillary thyroid carcinoma (PTC). However, data about clinicopathologic features of older patients in papillary thyroid microcarcinoma (PTMC) are limited. Presently, we investigated the difference of clinicopathologic features in PTMC according to age.

**Materials and Methods:** A total of 820 PTMC patients (82 males, 10%; 738 females, 90%) who underwent total thyroidectomy at Pusan National University Hospital were enrolled. The patients were divided into three age groups: group 1 (44 years or younger, n=230), group 2 (45-64 years, n=513), and group 3 (65 years or older, n=77). **Results:** Extrathyroidal extension was 33% in group 1, 32.2% in group 2, and 31.2% in group 3 (p=0.948). There was no significant difference of lymph node metastasis between the groups: N0 (59.1% vs. 67.8% vs. 70.1%), N1a (37.4% vs. 28.8% vs. 26%), and N1b (3.5% vs. 3.3% vs. 3.9%) (p=0.159). Of the 820 patients, 526 (64.1%) were diagnosed as early stage (stage I, II) PTMC and 294 (35.9%) were diagnosed as advanced stage (stage III, IV) PTMC. The proportion of patients with each stage was significantly different between the groups (p<0.001). However, there was no significant difference in the stage over 45 years old. Of the 820 patients, 517 were evaluated BRAF<sup>V600E</sup> mutation. There was no difference in prevalence between each group.

**Conclusion:** There was no statistically significant difference of clinicopathologic features between the groups, indicating that old age itself was not associated with unfavorable clinicopathologic features in PTMC.

**Key Words:** Papillary thyroid microcarcinoma, Age, Clinicopathologic features

## Introduction

Papillary thyroid carcinoma (PTC) is the most common type of thyroid malignancy and comprises up to 80% of the malignancies arising from thyroid follicular cells.<sup>1,2)</sup> Papillary thyroid microcarcinoma (PTMC) is defined by the World Health Organization (WHO) as a PTC measuring  $\leq 10$  mm in the greatest dimension. Most PTMC are not detectable upon physical examination.<sup>3)</sup> The increased use of thyroid ultrasonography and technical improvements associated with fine-needle

aspiration biopsy (FNAB) have resulted in rapidly increase in the rate of PTMC patients.<sup>4,5)</sup> It is estimated that PTMC accounts for up to 30% of total PTC.<sup>6,7)</sup> In South Korea, the incidence of PTMC patients have increased markedly over the past 5 years.<sup>8)</sup>

PTC patients show a variety clinical courses and long-term outcomes. In general, PTC has a good prognosis with a 5-year survival rate of 97–99% and 10-year survival rate of 98%.<sup>1,9)</sup> Similarly, most PTMC have excellent prognosis. However, some studies have shown loco-regional recurrence, distant metastasis, and mortality.<sup>7,10,11)</sup> One study suggested that

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Correspondence: In Joo Kim, MD, PhD, Division of Endocrinology and Metabolism, Department of Internal Medicine, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 602-739, Korea  
Tel: 82-51-240-7224, Fax: 82-51-254-3127, E-mail: injkim@pusan.ac.kr

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long-term recurrence rate was 60% at 20 years in PTMC patients.<sup>12)</sup> Many factors affect outcome for PTC patients, including age, gender, tumor histology, presence of lymph node, or distant metastasis.<sup>13)</sup> Among them, older patients tend to have more aggressive courses and poor prognosis. However, data about the prognostic factors in PTMC are limited.

In the present study, we investigated the difference of clinicopathologic features in PTMC according to age. We hypothesized that older patients were not associated with unfavorable features in PTMC.

## Materials and Methods

### Patients

We reviewed the records of 1415 patients who underwent total thyroidectomy for PTC between January 2009 and December 2011 at Pusan National University Hospital. Of these 1415 patients, 820 PTMC patients were enrolled. The medical records of PTMC patients with pathological reports were reviewed retrospectively. They consisted of 82 males (10%) and 738 females (90%). The mean age of the patients was  $50 \pm 11.297$  years (range, 16–83). The study patients were divided into three groups according to age: group 1 (44 years or younger,  $n=230$ ), group 2 (45–64 years,  $n=513$ ), and group 3 (65 years or older,  $n=77$ ). The study protocol was approved by the Institutional Research Board of Pusan National University Hospital.

### Clinicopathologic characteristics

Our database included age at the time of surgery, gender, methods of operation, clinicopathological

characteristics, including background Hashimoto's thyroiditis, multifocality, extrathyroidal extension, cervical lymph node metastasis, stage, and BRAF<sup>V600E</sup> mutational status. Patients included in study underwent a standard total thyroidectomy. Concomitant central neck compartment lymph node dissection was performed in all patients. Background Hashimoto's thyroiditis was defined as cytologic confirmation. Tumors were considered to be multifocal if two or more foci were found in one or both lobes. Tumors were classified histologically according to International Union Against Cancer (UICC) tumor, node, metastasis (TNM) classification. Study patients also were divided into two stage groups by early stage (stage I, II) PTMC and advanced stage (stage III, IV) PTMC. BRAF<sup>V600E</sup> mutation status was analyzed on the tissue after surgical operation. In our institution, dual priming oligonucleotide (DPO)-based multiplex polymerase chain reaction (PCR) (SeeGene, Seoul, Korea) was used to detect BRAF mutation.

### Statistical analyses

The statistical analyses were performed using the SPSS (SPSS ver. 15.0 for Windows, Chicago, IL, USA) software package. Numeric data were expressed as the mean  $\pm$  SD. Categorical data were presented as frequency and percentage. Chi-square test was used to compare innominal variables of clinicopathologic characteristics between groups. Kruskal-Wallis test was used to compare stage between groups. Statistical significance was defined as a  $p < 0.05$ .

## Results

Table 1 summarizes the baseline characteristics of

**Table 1.** Baseline characteristics of patients with papillary thyroid microcarcinoma

	Group 1 ( $n=230$ )	Group 2 ( $n=513$ )	Group 3 ( $n=77$ )
Age (years)			
Mean $\pm$ SD	$35.93 \pm 5.840$	$53.32 \pm 5.223$	$69.90 \pm 3.747$
Range	(16–44)	(45–64)	(65–83)
Gender (F/M)	204/26 (88.7/23)	465/48 (90.6/9.4)	69/8 (89.6/10.4)

Values are presented as mean  $\pm$  SD or number (%). Group 1, patient's age  $< 45$  years; Group 2, patient's  $45 \leq \text{age} < 65$ ; Group 3, patient's age  $\geq 65$  years. F: female, M: male

patients with PTMC according to the age group. Two hundred thirty patients (28.04%) belonged to group 1, 513 patients (62.56%) belonged to group 2, and 77 patients (9.3%) belonged to group 3. Gender distribution was not statistically significantly different between groups. Table 2 presents the histopathological features in PTMC patients. Background Hashimoto's thyroiditis was present in 15 (6.5%) group 1 patients, 19 (3.7%) group 2 patients, and 2 (2.6%) group 3 patient ( $p=0.161$ ). Multifocality did not differ between groups (23% vs. 25.1% vs. 27.3%,  $p=0.717$ ). Extrathyroidal extension was present in 76 patients (33%) in group 1, 165 patients (32.2%), and 24 patients (31.2%) in group 3 ( $p=0.948$ ). There were no statistically significant differences of lymph node metastasis between groups: positive lymph node metastasis (40.9% in group 1 vs. 32.1% in group 2 vs. 29.9% in group 3). Among in patients with positive lymph node metastasis, there was no significant difference in distribution between groups: N1a (37.4% vs. 28.8% vs. 26%), N1b (3.5% vs. 3.3% vs. 3.9) ( $p=0.159$ ). Of the 820

patients, 396 (64.1%) were diagnosed early stage (stage I, II) PTMC and 294 (35.9%) were diagnosed advanced stage (stage III, IV) PTMC. The proportion of patients with each stage were 100% versus 0% in group 1, 49.7% versus 50.3% in group 2, and 53.2% versus 46.8% in group 3 ( $p<0.001$ ). A post hoc analysis was performed for the stage distribution of group 2 and group 3, there was no significant difference between two groups ( $p=0.563$ ). Of the 820 patients, 517 (63%) were performed BRAF<sup>V600E</sup> mutation analysis, 140 in group 1, 326 in group 2, and 51 in group 3. BRAF<sup>V600E</sup> mutation was detected in 81 (35.8%) of group 1, 193 (37.6%) of group 2, and 25 (32.5%) of group 3 ( $p=0.598$ ). There was no difference in prevalence between each group. Distant metastasis was not detected in all patients.

## Discussion

According to staging systems, age is one of the most powerful prognostic factors. Older age is identi-

**Table 2.** Histopathological characteristics of patients with papillary thyroid microcarcinoma

	Group 1 (n=230)	Group 2 (n=513)	Group 3 (n=77)	p value
Hashimoto's thyroiditis				0.161
Present	15 (6.5)	19 (3.7)	2 (2.6)	
Absent	215 (93.5)	494 (96.3)	75 (97.4)	
Multifocality				0.717
Present	53 (23)	129 (25.1)	21 (27.3)	
Absent	177 (77)	384 (74.9)	56 (72.7)	
Extrathyroidal extension				0.948
Present	76 (33)	165 (32.2)	24 (31.2)	
Absent	154 (67)	348 (67.8)	53 (68.8)	
LN grade				0.159
N0	136 (59.1)	348 (67.8)	54 (70.1)	
N1a	86 (37.4)	148 (28.8)	20 (26)	
N1b	8 (3.5)	17 (3.3)	3 (3.9)	
TNM stage				<0.001
I	230 (100)	255 (49.7)	40 (51.9)	
II	0 (0)	0 (0)	0 (0)	
III	0 (0)	242 (47.2)	34 (44.2)	
IV	0 (0)	16 (3.1)	3 (3.9)	
Stage				<0.001
Early (stage I, II)	230 (100)	255 (49.7)	41 (53.2)	
Advanced (stage III, IV)	0 (0)	258 (50.3)	36 (46.8)	
BRAF <sup>V600E</sup> mutation	81 (35.2)	193 (37.6)	25 (32.5)	0.589

Values are presented as number (%). Group 1, patient's age <45 years; Group 2, patient's 45 ≤ age <65; Group 3, patient's age ≥65 years

fied a poor prognostic factor for PTC patients. Previous studies showed that older patients had aggressive features than young patients.<sup>14)</sup> Ito et al.<sup>14)</sup> showed that lymph node recurrence was high and survival was poor in patients older than 60 years. The age criterion varies according to classification systems: 45 years in the UICC TNM classification,<sup>3)</sup> 41 years for males and 51 years for females in the Age, Metastasis, Extent, and Size (AMES) classification,<sup>15)</sup> and 50 years in the Cancer Institute Hospital (CIH) classification.<sup>16)</sup> UICC TNM classification system is used as universal. In Korean society, an age of over 65 years is considered as elderly. So, we divided patients into three groups based on this age value. Except age, many other factors affect outcome for PTC patients, such as histology, tumor size, lymph node metastasis, extrathyroidal extension, distant metastasis, BRAF<sup>V600E</sup> mutation, gender, and treatment options. In this study, we investigated the difference of prognostic variables in PTMC according to age and the impact of age on these variables. There were no significant differences of Hashimoto's thyroiditis, multifocality, extrathyroidal extension, lymph node metastasis, and BRAF mutation in all ages. There was no significant difference in the stage aged 45 years or older.

Recently, Cho et al.<sup>17)</sup> reported that PTMC patients had different clinical features and prognostic factors according to age. Based on the age of 45 years, patients were divided into two groups. Sex and multifocality of PTMC were the significant factors determining recurrence in younger than 45 years and the lymph node metastases and multifocality in older than 45 years. The authors reported that age was not an independent prognostic factor of recurrence in PTMC.<sup>17)</sup> Kim et al.<sup>18)</sup> reported that there was no association between age and subclinical central lymph node metastasis in PTMC. This result is consistent with our report and some other studies.<sup>18-20)</sup>

The coexistence of PTC and Hashimoto's thyroiditis has been reported to range from 10% to 58%.<sup>21)</sup> The coexistence of Hashimoto's thyroiditis with PTC is associated with a better outcome.<sup>22,23)</sup> A previous study reported that patients with PTC and lymphocytic thyroiditis had a good prognosis. The authors reported

lower frequencies of extrathyroidal extension, nodal metastasis, and distant metastasis.<sup>24)</sup> Kim et al.<sup>21)</sup> suggested that coexisting Hashimoto's thyroiditis in patients with PTC is a negative predictive factor for central lymph node metastasis. However, other studies showed that coexistence of Hashimoto's thyroiditis has no protective effect on prognosis.<sup>25)</sup> The pathogenesis of the coexistence of PTC and Hashimoto's thyroiditis remains unclear. There have been few reports of studies on the effects of coexisting Hashimoto's thyroiditis with PTMC patients. In this study, the result showed no statistically significant difference between three groups in the prevalence of background Hashimoto's thyroiditis (15 [6.5%] in group 1 vs. 19 [3.7%] in group 2 vs. 2 [2.6%] in group 3,  $p=0.161$ ).

PTC is frequently multifocal. Shattuck et al.<sup>26)</sup> suggested that multifocality is not a manifestation of intraglandular metastasis. Multifocal tumors in PTC are the result of the generation of multiple independent origins. Multifocality of PTC was considered a significant prognostic factor. Multifocality has been associated with increased lymph node and distant metastasis, persistence residual disease after initial treatment, and recurrence.<sup>26)</sup> Similarly, multifocality in PTMC is associated with lymph node metastasis and capsular invasion.<sup>7,27)</sup> Patients with multifocality should receive aggressive treatment.<sup>28)</sup> Multifocality in PTMC is not unusual.<sup>17)</sup> In this study, the incidence of multifocality was 24.8%. The incidence of multifocality in PTMC has been reported to be 19 to 32%.<sup>17)</sup>

The presence of a BRAF<sup>V600E</sup> mutation has been a more aggressive and poor clinical course. A prior study reported that BRAF<sup>V600E</sup> mutation was associated with advanced tumor stage and metastasis in PTC.<sup>29)</sup> There is still a controversy about the relationship between the BRAF<sup>V600E</sup> mutation in PTMC and the prognosis. Lee et al.<sup>29)</sup> suggested that presence of BRAF<sup>V600E</sup> mutation showed significantly more aggressive features (advanced stage, extrathyroidal extension, and nodal metastasis). Of the 820 patients, 517 were evaluated BRAF<sup>V600E</sup> mutation in this study. BRAF<sup>V600E</sup> mutation was detected 57.83% of PTMC patients. There was no difference in prevalence according to age. However, these data should be in-

interpreted with caution because of missing data.

The results of this study are subject to some limitations. The study was retrospective and the records of patients were from a single institution. Another limitation is that we enrolled the patients who underwent surgery between January 2009 and December 2011. So, we analyzed the data of a short period. We have no data about disease recurrence and survival for the each group. Follow-up for a prolonged period is needed.

Despite these limitations, it is notable that this study enrolled a relatively large number of PTMC patients. Another advantage is that the data has consistency about clinicopathologic characteristics, especially lymph node dissection because of two surgeons performed total thyroidectomy with central compartment node dissection according to same protocol.

There has been debate whether PTMC patients should be managed as aggressively as other PTC patients. In our institution, total thyroidectomy is the preferred option. One study suggested that observation only without treatment is safe for small intrathyroidal PTMCs.<sup>6)</sup> Other authors favor lobectomy<sup>6)</sup> while yet other authors prefer total thyroidectomy, I-131 whole body scan, and thyroid stimulating hormone (TSH) suppressive therapy.<sup>30)</sup> No prospective and randomized clinical trials have been performed to determine the proper treatment for PTMC.

In this study, there was no statistically significant difference of clinicopathologic features between groups. We consider that if old age is a poor prognostic factor in PTMC, they have aggressive clinicopathologic characteristics at the time of diagnosis or initial surgery. However, we concludes that old age itself is not associated with unfavorable clinicopathologic features in PTMC. There was no significant difference in the stage older than 45 years. However, long-term follow-up is needed to observe the recurrence and survival.

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