**Prognosis and growth activity depend on patient age in clinical and subclinical papillary thyroid carcinoma**

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**Abstract.** In this review, we focused on the patient age as an indicator of tumor growth and prognostic significance in both clinical papillary thyroid carcinoma (PTC) and subclinical papillary microcarcinoma (PMC: PTC ≤ 1 cm). In clinical PTC, young age (< 30 years) and old age (≥ 60 years) significantly affected the disease-free survival of patients, and old age was a strong predictor of carcinoma death. In contrast, in subclinical PMC, growth activity significantly decreased with patient age, and young age (< 40 years) was an independent predictor of carcinoma growth, indicating that old patients with subclinical PMC are the best candidates for observation without immediate surgery. Taken together, our findings indicate that the role of patients’ age as an indicator of tumor growth differs significantly between clinical PTC and subclinical PMC.

Key words: Age, Prognostic factor, Papillary thyroid carcinoma

**PAPILLARY THYROID CARCINOMA (PTC)** is the most common malignancy arising from thyroid follicular cells. It is generally an indolent disease, but if certain characteristics are present, the prognosis of PTC is poor. Patient age is one of the important prognostic factors for PTC. Old age in particular has been used as an important component of various classification systems. Many reports have been published regarding the prognostic significance of patient age; most demonstrated that old age is associated with a poor disease-free survival (DFS) and, more importantly, cause-specific survival (CSS).

However, we note that most cases of PTC remain subclinical and harmless. Autopsy studies frequently detected latent PTC [1–3]. In a clinical study, small thyroid carcinoma was found in 3.5% of otherwise healthy women on ultrasonographic screening and ultrasonography-guided fine needle aspiration biopsy (FNAB) [4]. In 1993, Miyauchi et al. initiated the protocol of observation for subclinical papillary microcarcinoma (PMC: PTC ≤ 10 mm) without immediate surgery, and we published our promising results obtained with this protocol in 2003, 2010, and 2013 [5–7]. In the most recent study, we investigated the significance of age as an indicator of tumor growth and proliferation in PMC, but the results were not identical to those of clinical PTC.

In this review, we describe the differences in the prognostic significance of age and the growth activity associated with age between clinical PTC and subclinical PMC.

1. Prognostic significance of age in clinical PTC

1-1. Age in various staging systems

Many tumor staging systems have been published, and patient age is included as a cutoff parameter or in a formula in most of them. The most widely adopted staging system is the Union for International Cancer Control (UICC) TNM (tumor, node, metastasis) staging system, [8] which sets the cutoff age at 45 years. Similarly, the AMES (age, grade, extent of disease, size) system established by the Lahey clinic [9] and the GAMES (grade, age, metastases, extent, size) system by Memorial Sloan Kettering Hospital [10] set the cutoff ages at 41 for men and 51 for women and 45 years, respectively. In the MACIS (metastasis, age, completeness of surgical resection or removal of the tumor, invasion and size) score by the Mayo Clinic, age 40 years or older causes the elevation of score [11].

Two PTC staging systems were established by
Japanese institutions. One is the Cancer Institute Hospital (CIH) classification [12]. This classification is very simple. The high-risk group consist of patients < 50 yrs old with distant metastases at diagnosis and those ≥ 50 yrs with large (≥ 3 cm) node metastases, significant extrathyroid extension, or distant metastases. All others are classified into the low-risk group. Another is our modification of the UICC TNM classification of PTCs [13]. This system classifies PTC patients without distant metastases into three groups (high-, intermediate, and low-risk), and the cutoff age was set at 55 yrs. Table 1 summarizes the cutoff age in the current prominent staging systems.

It is notable that all of these systems use only old age as a risk factor. This may be because these staging systems set their end point as the carcinoma death rather than the carcinoma recurrence of the patients.

1-2. Difference in clinicopathological features of clinical PTC according to patient age

Since most of the PTC staging systems use patient age as a factor, it is apparent that old age is thought to relate to aggressive features of PTC. We therefore investigated the relationship between patient age and prominent clinicopathological features affecting patients’ prognoses.

A. Tumor size

To date, only a few studies have compared tumor size and patient age. Miccoli et al. classified 2,709 patients into three categories based on patient age and showed that the tumor sizes of the patients < 18 yrs old were the largest [18]. Considering the observation that most PTCs remain latent as indicated in the Introduction, PTCs in young patients are more likely to grow rapidly than those in old patients.

We analyzed 5,768 patients with PTC, who underwent initial surgery in our hospital between 1987 and 2004 (average follow-up period: 10.8 years [1-23 years]), and we found that the tumor sizes of the male patients were larger than those of the female patients [19]. We speculated that this difference occurred because male patients may have less opportunity to undergo medical screening, including thyroid ultrasound. However, since male gender is a prognostic factor of DFS in our series [19], it is also possible that the growth activity of PTCs in males may be higher than that of PTCs in females.

B. Lymph node metastasis

We showed previously that the incidence of latent node metastasis (undetectable on imaging studies but detectable on pathological examination) increased with tumor size [20–22]. Other research groups have investigated the relationship between lymph node metastasis and patient age. Sugino et al. evaluated the cases of 746 patients with “nonadvanced PTC” and reported that lymph node metastasis was more frequently observed in patients < 30 yrs [23]. Ahuja et al. showed that lymph node metastases were more frequently positive in patients ≤ 40 yrs [24].

We observed that clinical node metastasis detectable on preoperative imaging studies (N) was positive in 41% of patients < 20 yrs [25]. We also investigated the rate of lymph node metastasis together with other clinicopathological features in PTC patients without distant metastasis grouped into several age brackets (Table 2), and we found that 28.8% of the patients ≤ 20 yrs were N-positive [26]. This incidence decreased in middle age and rose again in old patients: 19.9 and 24.7% in those 61–70 yrs and > 70 yrs, respectively (Table 2). Patients aged 41–50 has the lowest incidence of N, at 14.7%.

The incidence of N was significantly higher in those ≤ 40 yrs (p < 0.0001) and those > 50 yrs (p = 0.0011) than the incidence of those 41–50 yrs. In addition, the incidence of N affecting prognosis (size ≥ 3 cm and/or extranodal tumor extension-positive) was high, at 6.7% and 7.3% of patients ≤ 20 yrs and those > 70 yrs, respectively, while its incidence was lower, 3.1%–4.6%, in other age groups (Table 2). These findings illustrate that the incidence of clinical node metastasis showed a biphasic pattern according to patient age.

C. Extrathyroid extension

Extrathyroid extension is divided into two categories

<table>
<thead>
<tr>
<th>Staging systems</th>
<th>Cutoff ages</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMES [9]</td>
<td>41 for men and 51 for women</td>
</tr>
<tr>
<td>MACIS [11]</td>
<td>Involved in the formula</td>
</tr>
<tr>
<td>UICC TNM staging system [8]</td>
<td>45</td>
</tr>
<tr>
<td>EORTC [14]</td>
<td>Involved in the formula</td>
</tr>
<tr>
<td>GAMES [10]</td>
<td>45</td>
</tr>
<tr>
<td>UAB &amp; MDA [15]</td>
<td>50</td>
</tr>
<tr>
<td>CIH classification [12]</td>
<td>50</td>
</tr>
<tr>
<td>Our classification system [13]</td>
<td>55</td>
</tr>
<tr>
<td>OSU [16]</td>
<td>Not included</td>
</tr>
<tr>
<td>Clinical Class [17]</td>
<td>Not included</td>
</tr>
</tbody>
</table>

Table 1 Cutoff age in prominent staging systems
in the UICC TNM classification: minimal extension and significant extension [8]. In our series, minimal extension did not affect patient prognosis [27], and we regard significant extension only as a prognostic factor. The incidence of significant extension increased with patient age [26]. In the series of patient ≤ 20 yrs, only 3.8% was significant extension-positive, but it gradually elevated to 33.7% in patients > 60 yrs (Table 3). The incidence of significant extension of patients ≤ 40 was significantly lower than that of the patients aged 41–60 (p < 0.0001). In addition, patients > 60 were significantly more frequently extension-positive (p < 0.0001) than those aged 41–60 yrs. It is therefore suggested that PTC became more invasive with increasing age.

D. Pathological and molecular findings

The majority of PTCs are the well-differentiated and conventional type among all age groups, but there is histology typical for young and for old ages. The most important histology is a tall cell variant that has an aggressive character, and this histology was an independent predictor of carcinoma death among the patients in our series [28]. Previous studies demonstrated that this histology was more frequently observed in old patients [18, 29–31].

In contrast, a diffuse sclerosing variant of PTC was detected at a higher incidence in young patients [31–36]. This variant has a higher incidence of unfavorable features such as lymph node and distant metastases and is widespread in the thyroid, indicating the likeliness of carcinoma recurrence. To date, its prognosis remains controversial [32–36], but some studies demonstrated that the CSS of this variant did not differ from that of conventional PTC [33–36]. A cribriform morular variant is almost typical in young female patients, many cases of which are hereditary and associated with familial polyposis of the colon. However, its prognosis is quite excellent and in our series, none of the patients died of thyroid carcinoma [37, 38].

The Ki-67 labeling index (LI) reflects cell-proliferating activity. A high Ki-67 LI was found to be a prognostic factor for both the DFS and the CSS of PTC patients, and it was directly related to patient age [39, 40].

BRAFV600E mutation is widely recognized as a strong prognostic marker for PTC in foreign countries [41, 42], but in Japan, its prognostic value is limited [43, 44]. The reason(s) for this discrepancy in prognostic value remain unknown, but this mutation was not related to patient age in these studies [41–44].

I-3. Influence of patient age on the prognosis of clinical PTC

A. DFS of patients

In 1994, Mazzaferri et al. demonstrated that in a series of papillary and follicular thyroid carcinoma, recurrence was most frequent in the patients < 20 and > 59 yrs [16]. Miyauchi et al. showed that the rate of persistent disease (thyroglobulin [Tg] detectable after total thyroidectomy) was higher in patients ≥ 60 yrs and those < 40 yrs than in middle-aged patients [45]. These findings suggest that PTC recurrence has bimodal peaks in patient age.

Sugino et al. showed that the rate of lymph node metastasis was high in patients < 30 yrs, and distant recurrence was frequently observed in patients > 50 yrs [23]. Table 4 provides the lymph node and distant recurrence rates of 5,784 patients according to patient age [26]. The lymph node recurrence rate was high
in the patients ≤ 20 yrs and > 60 yrs. Distant recurrence was slightly higher in the patients ≤ 30 yrs compared to the middle-aged patients and significantly elevated in the patients > 60 yrs. In addition, with the use of the Kaplan-Meier method, we found that the lymph node recurrence-free survival of the patients ≤ 20 yrs was poorer than that of the patients aged 21–30 (p = 0.0037), and it was significantly poorer in the patients in their 40s to 70s. The distant recurrence-free survival became poorer in patients > 50 yrs (40s vs. 50s, p = 0.0350: 50s vs. 60s, p < 0.0001). In our recent study, ages < 30 yrs and ≥ 60 yrs were independent predictors of locoregional and distant recurrence of PTC in a multivariate analysis (manuscript submitted).

Taken together, these findings demonstrate that young and old patients more frequently show carcinoma recurrence compared to middle-aged patients, and locoregional and distant recurrence are dominant in young and old patients, respectively.

Table 4 Number of patients and the incidence of lymph node and distant recurrences and carcinoma death according to age at initial surgery (%)

<table>
<thead>
<tr>
<th>Age (yrs)</th>
<th>Number of patients</th>
<th>LN recurrence</th>
<th>Distant recurrence</th>
<th>Carcinoma death</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 20</td>
<td>104</td>
<td>17.3</td>
<td>2.9</td>
<td>1.0</td>
</tr>
<tr>
<td>21-30</td>
<td>515</td>
<td>6.4</td>
<td>2.1</td>
<td>0</td>
</tr>
<tr>
<td>31-40</td>
<td>832</td>
<td>7.3</td>
<td>1.4</td>
<td>0.1</td>
</tr>
<tr>
<td>41-50</td>
<td>1,296</td>
<td>4.6</td>
<td>1.4</td>
<td>0.3</td>
</tr>
<tr>
<td>51-60</td>
<td>1,686</td>
<td>5.2</td>
<td>2.3</td>
<td>0.9</td>
</tr>
<tr>
<td>61-70</td>
<td>995</td>
<td>9.4</td>
<td>5.3</td>
<td>2.9</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>356</td>
<td>11.8</td>
<td>5.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Total</td>
<td>5,784</td>
<td>6.8</td>
<td>2.7</td>
<td>1.1</td>
</tr>
</tbody>
</table>

B. Cause-specific survival (CSS) of patients

To date, many studies have demonstrated that old age significantly affected the CSS of PTC patients, by setting the cutoff age at 40–55 yrs [13, 46–55]. We also showed that CSS showed a tendency similar to distant recurrence-free survival (40s vs. 50s, p = 0.0138): 50s vs. 60s, p < 0.0001: 60s vs. 70s, p = 0.0060) [23]. Miyazaki et al. showed that the Tg doubling-time (Tg-DT) is a dynamic prognostic factor after total thyroidectomy for Tg-antibody-negative PTC patients, and that Tg-DT more keenly predicts the CSS of patients than conventional prognostic factors [56]. They demonstrated that patients with short Tg-DT values (< 2 yrs) are likely to die of PTC. They also demonstrated that Tg-DT was shorter in patients ≥ 60 yrs than in those 40–59 yrs and <40 yrs [45]. These findings are consistent with Table 4, showing that the carcinoma death rate was markedly increased in the patients > 60, and they suggest that a cutoff age at 60 yrs for CSS is more suitable than younger ages, e.g., 40 and 45.

C. How do we interpret these data?

In the above sections, we showed that (1) PTCs in young patients frequently recur, but these patients are unlikely to die; (2) old age is a predictor not only of carcinoma recurrence but also carcinoma death, and (3) the optimal cutoff ages may be 30 and 60 yrs.

These findings might be due to the difference in the biological behaviors of PTCs between young and old patients. The incidence of clinical node metastasis showed a biphasic pattern, but that of significant extrathyroid extension increased with patient age (Tables 2 and 3). These might result in high lymph node recurrence rates in patients ≤ 20 yrs and > 60 yrs, high distant recurrence rates in those ≤ 30 yrs and > 60 yrs, and a high carcinoma death rate in those > 60 yrs (Table 4).

The difficulty in controlling recurred PTC lesions might be another reason for the likeliness of carcinoma death among old patients. For local recurrence, including lymph node recurrence, reoperation should be the first line of therapy. However, as shown in Table 3, PTC in old patients is more invasive than that in young patients, and curative resection for local recurrence might be difficult or even impossible. For distant recurrence and unresectable local recurrence, radioiodine (RAI) therapy is the standard therapy at present. However, recurred lesions of old patients are more frequently RAI-refractory than those of young patients [57, 58]. Although external beam radiotherapy may be effective for locoregional control as an alternative therapy [59], we can conclude that the difficulty in controlling recurred lesions causes the high incidence of carcinoma death of old patients. In the near future, the use of novel therapies with molecular-targeted agents such as sorafenib is expected to improve the prognosis of advanced thyroid carcinoma patients.

The method of classifying clinical PTC varies according to institutions. Many institutions adopt the UICC TNM classification, but others have their own. In our opinion, it might be better to set two cutoff ages to discriminate high-risk patients for carcinoma death and for carcinoma recurrence from others. Cho et al. set the cutoff ages at 35 yrs and 62.5 yrs to predict carcinoma recurrence and death [60]. In the past, we set
the cutoff age at only 55 [13], but we now think it better to set two cutoff ages at 30 and 60 based on our data, in order to more accurately evaluate the likeliness of carcinoma recurrence and death.

2. Age as an indicator of tumor growth and proliferation of subclinical PMC under observation

2-1. Background of subclinical PMC observation

As indicated in the Introduction, most PTCs remain latent and subclinical; only a small portion of them become clinical. However, the recent development of ultrasound technology has facilitated the detection of many subclinical PMC. We note that all PMCs are not harmless, although the total group includes high-risk cases. PMC with clinical node metastasis, distant metastasis or extension to adjacent organs should be treated immediately. Sugitani et al. demonstrated that the CSS of symptomatic PMC patients with clinical lymph node metastasis and hoarseness due to carcinoma extension to the recurrent laryngeal nerve is poor [61, 62]. We also showed that the 10-yr lymph node recurrence-free rate, distant recurrence-free rate, and CSS of PMC patients with lymph node ≥ 3 cm or extranodal tumor extension was poor, at 70%, 88%, and 90%, respectively [63]. These high-risk patients should be carefully and extensively treated, although the size of the primary lesion(s) is small.

In contrast, Davies et al. reported that the incidence of PTC showed a 2.9-fold increase between 1973 and 2002, and between 1988 (the first year SEER collected data on tumor size) and 2002, 49% of the increase consisted of carcinomas ≤ 1 cm, but mortality from thyroid carcinoma was stable between 1973 and 2002 [64]. This is definitely due to the increased detection of small and harmless PTCs, most of which are subclinical PMC. In addition, as indicated in the Introduction, a mass screening of ultrasonography detected thyroid carcinoma, mostly PMCs, in 3.5% of otherwise healtht women [4]. These findings suggest that many patients have undergone unnecessary surgery for harmless and subclinical PMCs.

2-2. Results of subclinical PMC observation

As indicated above, Miyauchi suggested observation trial for subclinical PMCs and he and his colleagues initiated it in 1993 [7]. However, immediate surgery was recommended for patients with tumors with high-risk features such as (1) tumor(s) located adjacent to the trachea, (2) tumor(s) located on the dorsal surface of the thyroid, possibly invading the recurrent laryngeal nerve (even though not symptomatic), (3) cytological findings suggesting high-grade malignancy, and (4) the presence of regional node metastasis or, although it is very rare, the presence of distant metastasis on imaging studies. Tumors with progression signs such as size enlargement and/or appearance of node metastasis during observation are also strong candidates for surgery at that point.

To date, two institutions have actively performed subclinical PMC observation and published favorable outcomes [5–7, 61]. These studies revealed that a certain proportion of subclinical PMCs show progression signs during observation. Sugitani et al. showed that 4% and 1% of low-risk PMC cases showed size enlargement and appearance of node metastasis during observation, respectively [61]. Our most recent study in a series of 1,235 patients found a 10-year carcinoma enlargement rate (enlargement by ≥ 3 mm compared to the initiation of observation) and an appearance rate of novel node metastasis of 8.0% and 3.8%, respectively [7].

However, two important issues are that (1) none of the patients in our series showed distant metastases or died of PTC during observation (average 60 months [18-227 months]), and (2) none of the 186 patients who underwent surgery after progression signs showed carcinoma recurrence except for one who underwent hemithyroidectomy and had a recurrence in the remnant thyroid [5, 7]. These findings suggest that observation without immediate surgery for subclinical PMC incidentally detected by ultrasonography is a workable and important alternative to surgery, and it is not too late to surgically treat these patients after the appearance of progression signs. This strategy prevents numerous unnecessary surgeries for these patients. Table 5 summarizes the recent patient outcomes of two institutions.

2-3. How does patient age influence the development of low-risk PMC?

Sugitani et al. showed that the subclinical PMCs of young patients tended to develop compared with old patients, but they did not perform a longitudinal data analysis [61]. We divided PMC patients into three categories: < 40 yrs (young group), 40–59 yrs (middle-aged group) and ≥ 60 yrs (old group) and analyzed the influence of age on carcinoma growth by the
Kaplan-Meier method. The young group was significantly more likely to show size enlargement compared to the middle-aged group ($p = 0.0315$). Surprisingly, the PMCs in the old group were significantly less frequently enlarged compared to the middle-aged group ($p = 0.0329$). The lymph node appearance rate in the old group was the lowest of the three groups [7]. Therefore, PMC progression might be inversely related to patient age.

We also performed a multivariate analysis and found that, in the series of all patients, age < 40 yrs was an independent predictor of both carcinoma enlargement and novel lymph node appearance. In the combined subset of middle-aged and old patients, middle age independently reflected carcinoma enlargement [7]. Therefore, subclinical PMC patients ≥ 60 yrs old might be strong candidates for observation. Although the PMCs of young patients may be more progressive than those of old or middle-aged patients, it might not be too late to perform surgery after the detection of progressive signs.

### 3. Difference in age as a prognostic factor and an indicator of tumor growth and proliferation between clinical PTC and subclinical PMC

In clinical PTC, old age is the strongest prognostic factor of the CSS of patients [55], and young and old patients are more likely to have a recurrence of the tumor compared to middle-aged patients [16, 26]. Also in subclinical PMC, young age is an independent predictor of carcinoma growth, which is consistent with the finding in clinical PTC. However, there is one significant discrepancy of age as a prognostic factor between clinical PTC and subclinical PMC. Unlike clinical PTC, subclinical PMCs in old patients are the most indolent of the three groups (young, middle-age, and old), and old subclinical PMC patients are strong candidates for observation without immediate surgery.

Previous autopsy studies showed that the incidence of latent carcinoma was higher in adulthood than childhood, but did not increase with age [65-67]. These findings suggest that PMCs arise when patients are young in age and, although the PMCs’ growth activity might be somewhat high while the patients are young, it is lost with age, and thus the PMCs remain subclinical for the patient’s lifetime. If PMC arises at any stage of adulthood, the incidence of latent PMC would increase linearly. It can therefore be speculated that only a small portion of PMCs regain their growth activity with aging and become aggressive (especially invasive), resulting in a poor prognosis.

Data from autopsy and clinical studies indicate that subclinical PMC is a common finding, especially in females. However, only a small portion of these PMCs develops; the vast majority remains subclinical. When the patients are young, some of their PMCs might have relatively high growth activity and become clinical, but most of them remain subclinical and their growth activity even decreases with patient age. However, when PMCs regain growth activity in old age for some reason, they will become aggressive (especially invasive), resulting in a poor prognosis. Further studies are needed to elucidate the differences in the biological behaviors of clinical PTC between old and young patients; that is, why clinical PTC in old patients is more aggressive and invasive than in young patients.

### Table 5 Outcomes of subclinical PMC patients under observation

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Outcomes of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugitani et al. (2010)</td>
<td>230</td>
<td>1. An increase in size and novel lymph node appearance were observed in 7% and 1%, respectively after 1–17 years’ observation. 2. PMC in young patients tended to develop. 3. None of the patients showed distant recurrence or died of carcinoma.</td>
</tr>
<tr>
<td>Ito et al. (2013)</td>
<td>1,235</td>
<td>1. The 10-year size enlargement and novel lymph node appearance rates were 8.0% and 3.8%, respectively after 1.5–19 years’ observation. 2. Young age (&lt; 40 years) was an independent predictor of carcinoma progression. 3. Carcinoma in old age (≥ 60 years) is the most indolent and a strong candidate of observation. 4. None of the patients showed distant recurrence or died of carcinoma.</td>
</tr>
</tbody>
</table>
References


35. Koo JS, Hong S, Park CS (2009) Diffuse sclerosing variant is a major subtype of papillary thyroid carcinoma in the young. *Thyroid* 19: 1225-1231.


