Prognostic significance of patient age in papillary thyroid carcinoma with no high-risk features

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Abstract. Older age is recognized as a predictor of poor prognosis in papillary thyroid carcinoma (PTC) patients. However, young age is associated with disease progression of PTC measuring 1 cm or smaller in patients on active surveillance. In this study, we investigated the relationship between patient age and prognosis of PTC belonging to very low-, low-, and intermediate-risk groups based on the guidelines published by the Japan Association of Endocrine Surgery in 2018. We enrolled 4,870 PTC patients with no high-risk features and assigned each to one of three categories: very low risk (N = 1,161), low risk (N = 1,746), and intermediate risk (N = 1,963). In very low-risk patients, the local recurrence-free survival (RFS) rate of young patients (<55 years) was significantly worse (p = 0.0437) than that of older patients (≥55 years). In low-risk patients, although age did not affect local recurrence, older patients were more likely to show distant recurrence on univariate (p = 0.0005) and multivariate analyses (p = 0.0017). In the intermediate-risk series, the local RFS rate of older patients tended to be poor (p = 0.0538), and older age was significantly associated with distant RFS (univariate, p = 0.0356; multivariate, p = 0.0439) and carcinoma death (univariate, p < 0.0001; multivariate, not done because of no other suitable factors). The prognostic significance of patient age depends on risk classification: younger age significantly predicts local recurrence in very low-risk PTC, while older age predicts worse prognosis in low- and intermediate-risk patients. These findings indicate that young age is related to rapid growth in early-phase PTC.

Key words: Papillary thyroid carcinoma, Surgery, Patient age, Prognosis

PAPILLARY THYROID CARCINOMA (PTC) is the most common malignancy of the thyroid. Although the prognosis of PTC is generally favorable, cases having some background and clinical features are aggressive and show dire prognosis. In the guidelines published by the Japan Association of Endocrine Surgeons [1], PTC was divided into four categories: very low-risk, tumor size (T) ≤1 cm without extrathyroid extension and lymph node and/or distant metastasis (T1aN0M0); low-risk, T measuring 1.1–2 cm and negative for lymph node and/or distant metastasis (T1bN0M0); high-risk, PTC having one or more of the following, 1) T >4 cm, 2) extrathyroidal extension to adjacent structures except for the sternothyroid muscle (Ex) or extra-nodal extension of tumor in metastatic lymph node(s) (LN-Ex), 3) clinical node metastasis (N1) ≥3 cm, or 4) distant metastasis (M1); and intermediate-risk, PTC not belonging to the very low-, low-, or high-risk classes.

Note that patient age is not part of this classification system. Previous studies have demonstrated that age is an important prognostic factor in PTC [2-8]. Also, age is part of the Tumor-Node-Metastasis (TNM) staging system defined by the American Joint Committee on Cancer (AJCC) [9]. We previously demonstrated that older age (>55 years) significantly affected patients’ cause-specific survival (CSS) in high- and intermediate-risk patients, but not in T1N0M0 patients (very low-risk and low-risk patients were analyzed as a single group) [10]. However, young age was associated with disease progression of PTC measuring 1 cm or smaller in patients on active surveillance [11]. Therefore, the prognostic impact of age might vary according to the risk stage of the disease. In this study, we investigated the prognostic significance of age in PTC with no high-risk features (i.e., very low-, low-, and intermediate-risk patients), not only for CSS, but also for recurrence-free survival (RFS) by univariate and multivariate analyses.
Patients and Methods

Between Jan 1988 and Dec 2005, 6,211 patients underwent initial surgery for PTC at Kuma Hospital. Of these, 1,341 had one or more high-risk features; T >4 cm, N1 >3 cm, Ex, LN-Ex, or M1 and were thus ineligible for the study. We enrolled the remaining 4,870 PTC patients in this study. All diagnoses of PTC were based on postoperative pathological examination. We deleted patients having incidentally detected PTC not identified on preoperative imaging studies, those for whom medical records were insufficient, and those with other coexisting thyroid malignancies. All patients underwent thyroidectomy with or without lymph node dissection. After surgery, patients were asked to visit our hospital at least once a year for blood tests and imaging studies (mainly ultrasound). For patients who were referred to other hospitals for various reasons, we consistently (once a year) sent questionnaires to inquire about their current circumstances. In this study, we considered a lesion a PTC recurrence only when a structural lesion was detected by imaging studies. We analyzed local recurrence (recurrence to the remnant thyroid and/or regional lymph nodes) and distant recurrence (recurrence to distant organs such as the lung and bone) separately.

We used StatFlex (Artec, Osaka, Japan) for univariate and multivariate analyses. A Kaplan-Meier method with log-rank test was adopted for univariate analysis. A multivariate analysis was performed using the Cox regression hazard model. For multivariate analyses, we selected factors showing p-values <0.15 on univariate analysis. A p-value <0.05 was considered statistically significant.

This study was approved by the ethical committee at Kuma Hospital (No. 20200709-1).

Results

Patient profiles

Table 1 shows the clinicopathological features of the 4,870 patients in the present series. Total thyroidectomy was performed for 39.3% of patients, and radioactive iodine (RAI) was administered for ablation or adjuvant therapy in only 0.7% of patients. A small dose of RAI
(3–13 mCi) was administered to 11.6% of patients for the purpose of whole-body scintigraphy. Postoperative follow-up periods ranged from 12 to 404 months (median 219 months). The numbers of patients with very low risk, low risk, and intermediate risk were 1,161, 1,746, and 1,963, respectively.

**RFS of very low-risk patients**

To date, 49 (4.2%) of the 1,161 very low-risk patients have shown local recurrence. The 10- and 20-year local RFS rates were 97.4% and 94.4%, respectively. Fig. 1 shows Kaplan-Meier curves for local RFS for patients age ≥55 years and those age <55 years. The local RFS rate of patients age <55 years was significantly worse (p = 0.0437) than that of those age ≥55 years. Gender was not related to local RFS rate (p = 0.2266). One patient aged 57 at initial surgery, in whom local recurrence (regional lymph nodes) was found 47 months after surgery, also showed distant recurrence (bone and lung) 180 months after surgery. To date, none of the patients have died of thyroid carcinoma.

We performed further subset analyses. Recurrence to the remnant thyroid and lymph nodes was detected in 25 and 26 patients, respectively (2 showed both). Remnant thyroid recurrence-free and lymph node recurrence-free survival did not significantly differ (p = 0.2068, and p = 0.1403, respectively) between patients age ≥55 years and those age <55 years. We also performed subgroup analysis for patient age (50–54 years, 40–49 years, 30–39 years, and <30 years) and for tumor size (9–10 mm, 7–8 mm, and <6 mm), but no significant difference could be observed among the subgroups (data not shown).

**RFS of low-risk patients**

To date, 77 (4.4%) and 16 (0.9%) of the 1,746 patients have shown local recurrence and distant recurrence, respectively; of these, 11 (0.6%) have shown both. Only three patients (0.2%) have died of thyroid carcinoma. The 10- and 20-year local RFS rates were 97.5% and 95.1%, respectively. As shown in Fig. 2a, patient age did not affect local recurrence. The 10- and 20-year distant RFS rates were 99.7% and 99.0%, respectively. Fig. 2b shows the Kaplan-Meier curves for distant recurrence of patients aged <55 years and ≥55 years. Patients aged ≥55 years showed a significantly worse (p = 0.0005) distant RFS rate than those aged <55 years. Also, male gender significantly affected (p = 0.0373) distant recurrence on univariate analysis. Table 2 shows the multivariate analysis for distant recurrence. Age ≥55 years was recognized as an independent predictor of distant recurrence (p = 0.0017) while male gender was not.

**RFS and CSS of patients with intermediate-risk PTC**

In the series of 1963 intermediate-risk PTC patients, 230 (11.7%) and 39 (2.0%) showed local and distant recurrence, respectively. The 10- and 20-year local RFS rates were 97.5% and 95.1%, respectively. As shown in Fig. 3a, patient age did not affect local recurrence. The 10- and 20-year distant RFS rates were 99.7% and 99.0%, respectively. Fig. 3b shows the Kaplan-Meier curves for distant recurrence of patients aged <55 years and ≥55 years. Patients aged ≥55 years showed a significantly worse (p = 0.0005) distant RFS rate than those aged <55 years. Also, male gender significantly affected (p = 0.0373) distant recurrence on univariate analysis. Table 2 shows the multivariate analysis for distant recurrence. Age ≥55 years was recognized as an independent predictor of distant recurrence (p = 0.0017) while male gender was not.
recurrences, respectively, and 21 (1.1%) showed both. Twenty-three patients (1.2%) died of thyroid carcinoma.

The 10- and 20-year local RFS rates were 91.2% and 87.1%, respectively. As shown in Fig. 3a, the local RFS rate of patients aged ≥55 tended to be worse ($p = 0.0538$) than that of those aged <55. We then performed multivariate analysis of patient age with other factors having $p$-values <0.15 on univariate analysis (N1; $p = 0.0003$, and male gender; $p = 0.1316$). N1 was found to be an independent prognostic factor for local recurrence ($p = 0.0001$) while the other two factors were not (Table 3).

The 10- and 20-year distant RFS rates were 98.7% and 97.5%, respectively. Age ≥55 years significantly affected distant RFS of patients ($p = 0.0356$) on univariate analysis (Fig. 3b). On multivariate analysis together with N1 (univariate analysis, $p = 0.0665$), only age ≥55 years independently affected distant RFS ($p = 0.0439$) (Table 4).

**Table 2** Multivariate analysis of distant recurrence of T1bN0M0 PTC

| Variables       | $p$-values | Odds ratio (95% CI) |
|-----------------|------------|---------------------|
| Age ≥55 years   | 0.0017     | 6.559 (2.029–21.205) |
| Male gender     | 0.0630     | 3.318 (0.937–11.752) |

PTC, papillary thyroid carcinoma; CI, Confidence interval

**Fig. 3** (a) Kaplan-Meier curves for local RFS rates of intermediate-risk PTC in patients aged <55 years and ≥55 years. (b) Kaplan-Meier curves for distant RFS rates of intermediate-risk PTC in patients aged <55 years and ≥55 years. (c) Kaplan-Meier curves for CSS rates of intermediate-risk PTC in patients aged <55 years and ≥55 years.

**Table 3** Multivariate analysis of local recurrence of intermediate-risk PTC

| Variables       | $p$-values | Odds ratio (95% CI) |
|-----------------|------------|---------------------|
| N1              | 0.0001     | 1.715 (1.323–2.224) |
| Age ≥55 years   | 0.0878     | 1.267 (0.966–1.662) |
| Male gender     | 0.1797     | 1.276 (0.893–1.523) |

PTC, papillary thyroid carcinoma; CI, Confidence interval

**Table 4** Multivariate analysis of distant recurrence of intermediate-risk PTC

| Variables       | $p$-values | Odds ratio (95% CI) |
|-----------------|------------|---------------------|
| Age ≥55 years   | 0.0439     | 1.925 (1.018–3.639) |
| N1              | 0.0790     | 1.763 (0.936–3.639) |

PTC, papillary thyroid carcinoma; CI, Confidence interval
The 10- and 20-year CSS rates were 99.6% and 98.7%, respectively. Patients aged ≥55 years showed a significantly worse CSS ($p < 0.0001$) than those aged <55 years (Fig. 3c). Multivariate analysis was not performed because no other factors had $p$ values <0.15 on univariate analysis.

**Discussion**

In this study, we investigated the prognostic significance of patient age in PTC with no high-risk features. Generally, older age is known as a predictor of poor prognosis in PTC patients [2-8]. Indeed, in our previous study, older age (≥55 years) was recognized as an independent and very strong predictor of carcinoma death [12].

In this study, however, we performed subset analyses of PTC patients and demonstrated that the prognostic impact of age was not uniform but significantly varied according to classifications of very low, low, and intermediate risk. In the subset of very low-risk patients (corresponding to low-risk papillary thyroid microcarcinoma [PTMC]), young patients were more likely to show local recurrence than older patients. In the low-risk group, older age was a predictor of distant recurrence, but not of local recurrence. In the intermediate-risk group, older patients tended to have a poor local RFS, and were significantly more likely to show distant recurrence and die of thyroid carcinoma. These findings indicate that young age implies rapid PTC growth in early-phase PTC, while older age is significantly related to further carcinoma progression thereafter.

In a series of PTC and follicular thyroid carcinoma patients, Mazzaferri et al. demonstrated that the carcinoma recurrence rate showed biphasic change according to patient age: the recurrence rate was high in young patients, became low in middle-age patients, and increased again in those 60 years and older. The carcinoma death rate remains low in young patients, despite the high recurrence rate, and elevated in those 60 years and older [13, 14]. Indeed, PTMCs in young patients are more likely to grow during active surveillance, and growth activity successively decreases with advanced age [11, 15]. Also, Miyauchi et al. demonstrated that on calculation, estimated tumor volume doubling rates of low-risk PTMCs before presentation was significantly higher than those after presentation and during active surveillance [16]. These findings are not discrepant with our results that young low-risk PTMC patients are more likely to show recurrence than old patients after surgery. However, since the mechanisms for enlargement of primary lesions, metastasis to the lymph nodes, and growth of metastatic lesions might differ, we analyzed recurrence to the remnant thyroid and node metastasis separately. However, we could not obtain any significant associations between these recurrence rates and patient age. This is possibly because of the small number of patients having recurrence to the thyroid (25 patients) and to the lymph nodes (26 patients). Further studies enrolling larger number of patients with longer follow-up periods are necessary to elucidate this point, but our data show that very low-risk PTCs in young patients are more progressive and more likely to recur after surgery than those in old patients, which is in sharp contrast to PTCs in other risk classifications.

In our series of very low-risk patients, only one patient showed distant recurrence 180 months after surgery. This patient, however, was found to have local recurrence before then (47 months after surgery). None of the very low-risk patients showed distant recurrence with no local recurrence or died of thyroid carcinoma, indicating that our results in the present study do not affect the appropriateness and safety of active surveillance for very low-risk PTC patients.

Our study has some limitations. This is a retrospective study. Our patient series underwent surgery quite some time ago when therapeutic strategies, including surgical designs and RAI administration, significantly differed from those today. Lateral node dissection was performed for 68.1% of patients, while only 39.3% underwent total thyroidectomy. The incidence of patients who underwent RAI ablation or adjuvant therapy was only 0.7%, which was significantly lower than today’s rates. In contrast, our study has the strength of comprising a large number of patients (4,870 patients in total) with very long-term follow-up (median 219 months).

In conclusion, the prognostic impact of patient age significantly differs according to risk classifications. Young age is a significant predictor of local recurrence in very low-risk PTC, which could be related to the rapid PTC growth in the early phase. Low- and intermediate-risk patients showed the opposite trend, with old age being directly related to recurrence rates.

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**Disclosure Statement**

The authors declare they have no competing financial interests.

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