

ORIGINAL

Prognostic significance of young age in papillary thyroid carcinoma: Analysis of 5,733 patients with 150 months' median follow-up

Yasuhiro Ito, Akira Miyauchi, Minoru Kihara, Takuya Higashiyama, Kaoru Kobayashi and Akihiro Miya

Department of Surgery, Kuma Hospital, Kobe 650-0011, Japan

Abstract. Among the several prognostic factors of papillary thyroid carcinoma (PTC), age is the most prominent. It is well known that elderly PTC patients have poorer prognoses. Here we investigated the prognostic impact of young age in univariate and multivariate analyses. We retrospectively analyzed 5,733 PTC patients without distant metastasis at presentation, who underwent initial surgery at Kuma Hospital. The median follow-up period was 150 months. We classified the patients into three groups: young (< 30 years), middle-aged (30–59), and older patients (≥ 60 years). The tumor size was larger and clinical node positivity was higher in the young patients, and significant extrathyroid extension was higher in the older patients compared to the other two groups. In the univariate analysis, the young patients showed poorer extrathyroidal locoregional and distant recurrence rates than the middle-aged patients, but not cause-specific survival rates. In the multivariate analysis, age < 30 years was an independent or marginal predictor of extrathyroidal locoregional and distant recurrence, but not of carcinoma-related death. Age ≥ 60 years independently affected PTC recurrence and death. Taken together, we should carefully treat young PTC patients because of the likeliness of extrathyroidal locoregional and distant recurrence, which may not be life-threatening.

Keywords: Young age, Papillary thyroid carcinoma, Prognostic value

PAPILLARY THYROID CARCINOMA (PTC) is the most common malignancy arising from thyroid follicular cells. Although it is an indolent disease displaying a good prognosis, several factors have been identified that are associated with worse prognoses of PTC patients, among which age is the most prominent. Age has been adopted in various PTC staging systems with various cutoffs: 45 years in the UICC TNM (tumor, node, metastases) classification [1], 41 years for males and 51 years for females in the AMES (age, metastases, extent and size) classification [2], 40 years in the MACIS (metastases, age, completeness of resection, invasion, size) scoring system [3], 50 years in the Cancer Institute Hospital (CIH) classification [4], and 55 years in our intraoperative staging system [5]. These staging systems indicate that older age is a strong predictor of a poor prognosis of patients.

In contrast, Mazzaferri *et al.* showed that recurrence rates of PTC were high in patients < 20 years and > 59 years, although they did not perform a time-series comparison [6]. We also showed, using the Kaplan-Meier method, that the lymph node recurrence rate was high in patients ≤ 20 years and > 60 years, although the carcinoma death rate was elevated in patients > 60 years [7].

Miyauchi *et al.* [8, 9] recently showed that the incidence of biochemically persistent disease (BPD: detectable thyroglobulin [Tg] level after total thyroidectomy) was higher in patients < 40 years and ≥ 60 years compared to middle-aged patients, although in BPD patients, the percentage of short Tg-doubling time (< 2 years), which is a strong predictor of carcinoma-related death [8], increased with patient age [9]. It is thus suspected that young age also has a strong prognostic value for carcinoma recurrence. This point was not adopted by various staging systems, probably because their endpoint is carcinoma-related death.

In the present study, therefore, we investigated the prognostic significance of young age in PTC using a large number of patients with long follow-ups in uni-

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Correspondence to: Dr. Akira Miyauchi, Department of Surgery, Kuma Hospital, 8-2-35, Shimoyamate-dori, Chuo-ku, Kobe 650-0011, Japan. E-mail: miyauchi@kuma-h.or.jp

variate and multivariate analyses.

Patients and Methods

Patients

We retrospectively analyzed 5,733 patients (605 males and 5,128 females, average age 50.0 ± 13.7 years) with PTC without distant metastasis at presentation. They underwent initial surgery for PTC between January 1987 and March 2005 at Kuma Hospital, Kobe, Japan. Total or near total thyroidectomy was performed for 2,953 patients. The remaining 2,780 underwent limited thyroidectomy such as subtotal thyroidectomy (537 patients), lobectomy with or without isthmectomy (2,191 patients) and isthmectomy (52 patients). Lymph node dissection was performed in 5,503 patients, and all of these 5,503 patients underwent central node dissection. Therapeutic or prophylactic, unilateral or bilateral lateral node dissection was also performed in 4,371 patients. Eleven patients underwent upper mediastinum compartment dissection in addition to central and lateral compartment dissection.

Age classification

In this study, we classified the patients in three categories based on age at surgery: young patients (younger than 30 years; $n=529$ patients, 9%), middle-aged patients (30–59 years; $n=3,722$, 65%) and older patients (60 years or older; $n=1,482$, 27%). We set the cutoff age between the young and middle-aged patients at 30, 35, 40 years in the same analyses, and we found that using 30 years as the cutoff age showed resulted in the clearest data. When the cutoff age of 35 or 40 was used, the distant recurrence rate of the young patients did not significantly differ from that of the middle-aged patients in the univariate analysis, and age younger than 35 or 40 was not recognized as a predictor of distant recurrence in the multivariate analysis (data not shown). The 60-years cutoff age for older patients was chosen based on our previous study [9].

Definitions of Ex and N

We regarded patients as being extrathyroid extension (Ex)-positive when their primary lesions extended to adjacent organs corresponding to T4a, but not T3, based on intraoperative findings [10]. Our series did not include T4b patients. In our series, 738 patients (13%) were regarded as Ex-positive on intraoperative findings.

“N” indicates lymph node metastasis detected on preoperative imaging studies. In this study, we classified N into three grades: N0, no clinical node metastasis; N1, clinical node metastasis but smaller than 3 cm; and N2, clinical node metastasis measuring 3 cm or larger. In our series, 182 (3%) and 999 (17%) patients were classified as N2 and N1, respectively.

Postoperative follow-up

Scintigraphy or postoperative ablation using a small amount of radioactive iodine (RAI) (30 mCi or less) was performed in 1,011 patients. None of the patients in our series had any abnormal uptake in distant organs; patients who showed abnormal uptake in distant organs were excluded from this study.

We followed patients by ultrasonography once per year to monitor them for signs of local recurrence. Either chest roentgenography or a CT scan was also performed once per year. Thyroglobulin (Tg) and its antibody (Tg-Ab) were monitored in the patients who underwent total thyroidectomy, but we regarded patients as having recurrence only when it apparent on imaging studies such as ultrasonography, CT scan and PET-CT. For patients who changed hospitals for whatever reason, we used mailed questionnaires to determine their disease condition. The median follow-up period was 150 months (12–318 months) in the entire group and it was longer ($p < 0.0001$) in the middle-aged (158 months) and young patients (159 months) than in the old patients (131 months).

Statistical analysis

We use the Kaplan-Meier curve method with a log rank test for the univariate analysis, and we performed a multivariate analysis using the Cox proportional hazard regression model. Statview 5.1 software was employed for these analyses. A p -value < 0.05 was considered significant, and that between 0.05 and 0.1 was considered marginal.

Results

Difference in clinicopathological features of young, middle-aged and older patients

The clinicopathological features of the patients in the three age groups are summarized in Table 1. Tumor size was significantly larger and N was more frequently positive in the young patients. However, the older patients were more likely to be Ex-positive than oth-

Table 1 Relationship between clinicopathological features and 3 patient groups based on age at surgery among 5,733 patients with PTC (Papillary thyroid carcinoma)

	The number of patients		
	Young	Middle-aged	Old
Gender (Male/Female)	57(11%)/472(89%)	374(10%)/3,378(90%)	174(12%)/1,308(88%)
	Not significant		
Tumor size (≥ 4 cm/ < 4 cm)	86(16%)/443(84%)	305(8%)/3,417(92%)	169(11%)/1,325(89%)
	$p < 0.0001$		
Ex (+/-)	26(5%)/503(95%)	367(10%)/3,555(90%)	345(23%)/1,137(77%)
	$p < 0.0001$		
N (2/1/0)	23(4%)/116(22%)/390(74%)	100(3%)/640(17%)/2,982(81%)	59(4%)/243(16%)/1,180(80%)
	$p = 0.0014$		

Table 2 Relationship between the extent of thyroidectomy and 3 patient groups based on age at surgery among 5,733 patients with PTC

	The number of patients		
	Total or near total	Less than total or near total	Total
Young	258 (49%)	271 (51%)	529
Middle-aged	1,880 (51%)	1,842 (49%)	3,722
Old	815 (55%)	667 (45%)	1,482

Old vs. Middle-aged; $p = 0.0035$ Old vs. Young; $p = 0.0148$ Middle-aged vs. Young: Not significant

Table 3 Relationship between recurrence to the remnant thyroid and 3 patient groups based on age at surgery among 2,780 patients with PTC who underwent less than total or near total thyroidectomy

	Recurrence to the remnant thyroid		
	Yes	No	Total
Young	8 (3%)	263 (97%)	271
Middle-aged	36 (2%)	1,806 (98%)	1,842
Old	5 (1%)	662 (99%)	667

Old vs. Middle-aged; $p = 0.0321$ Old vs. Young; $p = 0.0138$ Middle-aged vs. Young: Not significant

ers. The male/female ratio did not differ significantly among the three groups.

Recurrence to the thyroid

Table 2 indicates the relationship between the extent of thyroidectomy and the three groups. Total or near total thyroidectomy was performed more frequently in the old patients than in the middle-aged and young patients. Of the 2,780 patients who underwent less than total or near total thyroidectomy, the young and middle-aged patients were more likely to show recurrence to the remnant thyroid (Table 3).

Extrathyroidal locoregional recurrence-free survival of patients

To date, 478 patients (8%) showed an extrathyroidal

locoregional recurrence such as to the regional lymph nodes, perithyroid fat tissue, and thyroid bed. The incidence of extrathyroidal locoregional recurrence in the three groups was 12% (172 of 1,482 patients) in the older group, 7% (244 of 3,722 patients) in the middle-aged group and 12% (62 of 529 patients) in the young group.

Fig. 1 shows the Kaplan-Meier curves of the patients' extrathyroidal locoregional recurrence-free survival. The middle-aged patients' extrathyroidal locoregional recurrence-free survival rate was significantly better than that of both the older ($p < 0.0001$) and young patients ($p = 0.0001$), and those of the young and older patients did not differ.

Table 4 provides the results of the multivariate analysis for extrathyroidal locoregional recurrence. Age < 30 years ($p = 0.0006$) was an independent predictor of

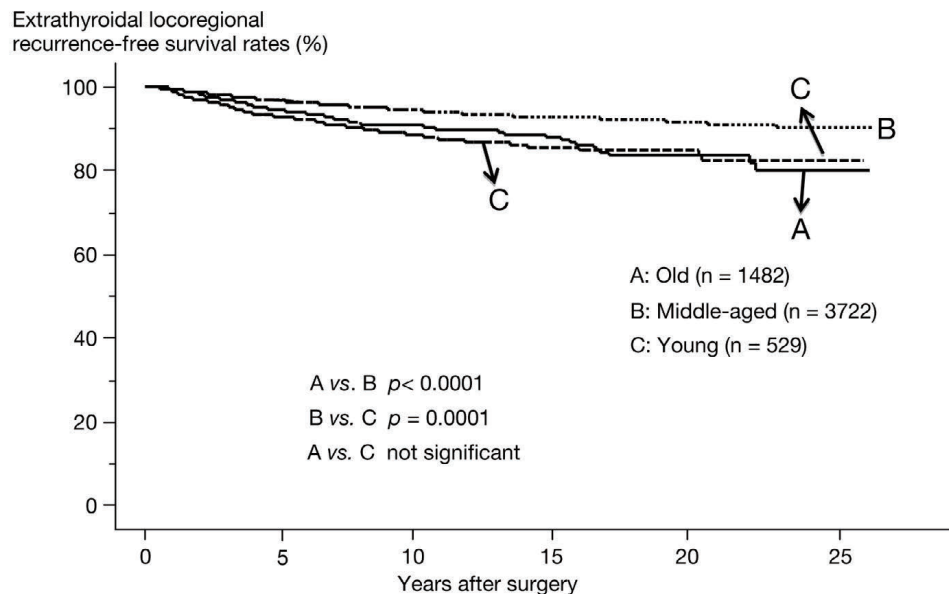


Fig. 1 Kaplan-Meier curves of extrathyroidal locoregional recurrence-free survival of young, middle-aged and older patients with PTC

Table 4 Multivariate analysis for extrathyroidal locoregional recurrence in PTC patients

Variable	<i>p</i> -value	Hazard ratio (95% CI)
Age < 30 years	0.0006	1.639 (1.645-2.174)
Age ≥ 60 years	< 0.0001	1.736 (1.420-2.123)
Male gender	0.0022	1.445 (1.142-1.828)
N1	< 0.0001	2.770 (2.257-3.401)
N2	< 0.0001	4.926 (3.663-6.579)
Tumor size > 4 cm	< 0.0001	1.969 (1.580-2.451)
Ex	< 0.0001	2.331 (1.890-2.882)

CI: confidence interval

extrathyroidal locoregional recurrence, as was age ≥ 60 years ($p < 0.0001$).

Distant recurrence-free survival of patients

In the entire series, 202 patients (4%) had a recurrence to distant organs such as the lung, bone, and brain: 102 older patients (7%), 80 middle-aged patients (2%) and 20 young patients (4%).

As shown in Fig. 2, middle-aged patients had the best distant recurrence-free survival rate of the three groups. The distant recurrence-free survival rate of the young patients was significantly better ($p < 0.0001$) than that of the older patients, but significantly poorer ($p = 0.0168$) than that of the middle-aged patients.

In the multivariate analysis (Table 3), age < 30 years had a marginal prognostic impact ($p = 0.516$) of distant recurrence. Age ≥ 60 years was an independent predictor of distant recurrence ($p < 0.0001$).

Cause-specific survival of patients

To date, 79 of the 5,733 patients (1.3%) died of PTC. The incidence of carcinoma-related death in the three groups was 4% (53 of 1,482 patients) in the older group, 0.7% (25 of 3,722 patients) in the middle-aged group and 0.2% (1 of 529 patients) in the young group.

In the univariate analysis, the cause-specific survival rate in the older patients was significantly poorer ($p < 0.0001$) than that of the middle-aged and young patients. The rate did not differ significantly between the middle-aged and young patients (Fig. 3).

Table 4 shows the results of the multivariate analysis of carcinoma-related deaths in the PTC patients. Unlike extrathyroidal locoregional and distant recurrence, age < 30 years was not recognized as an independent predictor of carcinoma-related death ($p = 0.1272$). Age ≥ 60 years, in contrast, had a strong prognostic impact ($p < 0.0001$) for cause-specific survival.

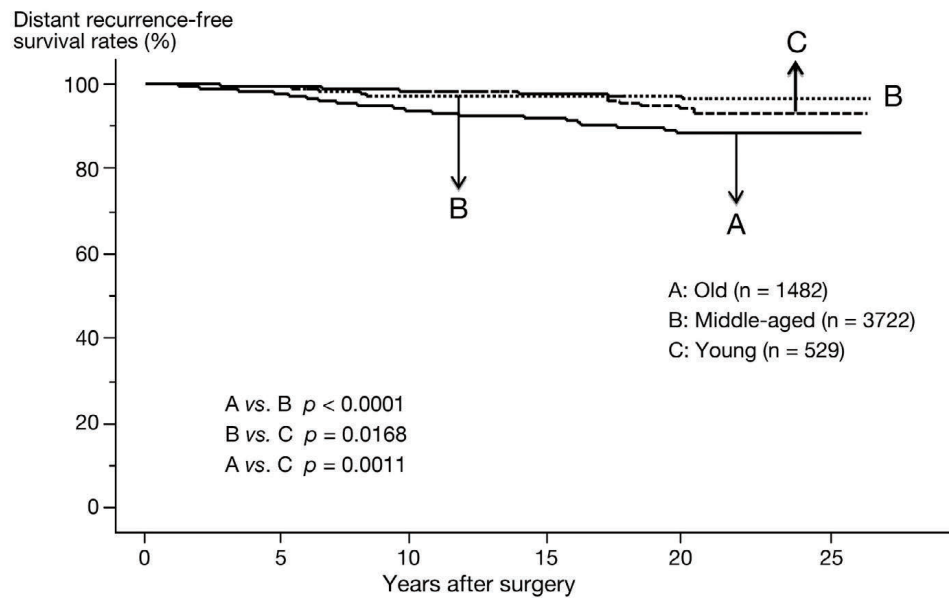


Fig. 2 Kaplan-Meier curves of distant recurrence-free survival of young, middle-aged and older patients

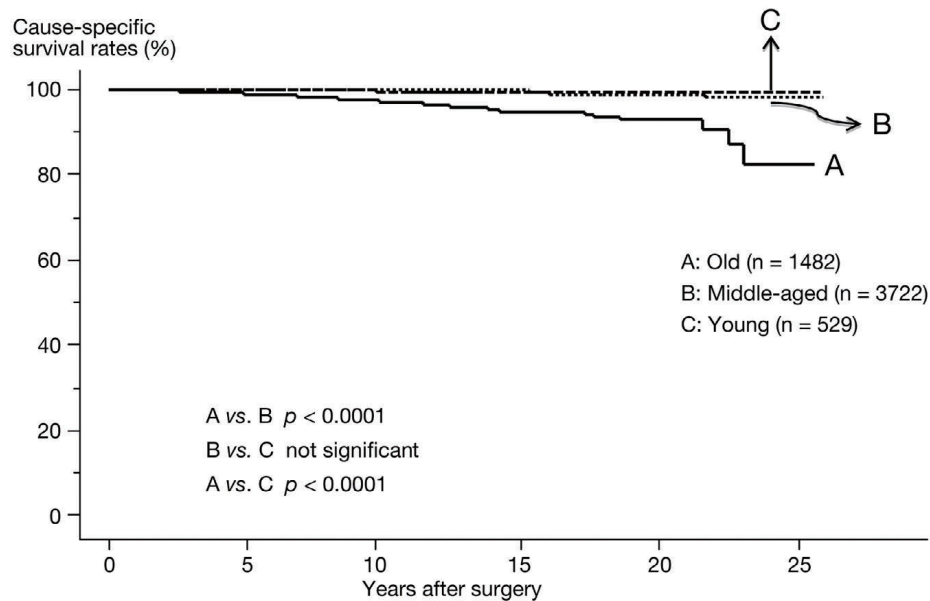


Fig. 3 Kaplan-Meier curves of cause specific-free survival of young, middle-aged and older patients

Discussion

In this study, we demonstrated that (1) the young (< 30 years) and older (≥ 60 years) patients had a poorer prognosis for extrathyroidal locoregional and distant recurrence compared to the middle-aged patients, (2) the cause-specific survival in the young and middle-aged patients was better than that in the older patients, (3) in the multivariate analysis, young age was an inde-

pendent predictor of extrathyroidal locoregional and distant recurrence (as was older age), but not of carcinoma-related death.

As shown in Table 1, the clinicopathological features of PTC vary according to patient age. The tumor size in the young patients was larger than those in the middle-aged and older patients. The N factor is a very important prognostic factor [4, 5], and young patients are more likely to be N-positive than older and middle-aged

Table 5 Multivariate analysis for distant recurrence in PTC patients

Variable	p-value	Hazard ratio (95% CI)
Age < 30 years	0.0516	1.637 (0.996-2.688)
Age ≥ 60 years	< 0.0001	2.967 (2.183-4.032)
Male gender	0.9081	1.023 (0.690-1.520)
N1	< 0.0001	3.413 (2.475-4.707)
N2	< 0.0001	6.993 (4.673-10.526)
Tumor size > 4 cm	< 0.0001	1.923 (1.393-2.653)
Ex	< 0.0001	4.016 (2.941-5.495)

CI: confidence interval

Table 6 Multivariate analysis for carcinoma-related death of PTC patients

Variable	p-value	Hazard ratio (95% CI)
Age < 30 years	0.1272	0.210 (0.028-1.563)
Age ≥ 60 years	< 0.0001	5.917 (3.571-9.804)
Male gender	0.0601	1.715 (0.978-3.003)
N1	0.0008	2.506 (1.462-4.292)
N2	< 0.0001	7.194 (3.953-12.987)
Tumor size > 4 cm	0.0003	2.463 (1.513-4.016)
Ex	< 0.0001	5.000 (2.994-8.333)

CI: confidence interval

patients. The Ex status also has a significant prognostic impact, especially for large tumors [11], and in the present study the older patients were more frequently Ex-positive than the other age groups. The incidence of these important prognostic factors was not very high in the middle-aged patients, which may explain, at least in part, the good prognosis of these patients.

Since the prognosis of a patient is determined by a complex combination of various prognostic factors, we performed a multivariate analysis including other conventional prognostic factors to investigate whether young age independently affects the prognosis. Conventional prognostic factors such as Ex, large tumor size, and N factor independently reflected carcinoma recurrence and carcinoma-related death in PTC, as shown in Tables 4–6. Interestingly, young age was also recognized as an independent prognostic factor of extrathyroidal locoregional and distant recurrence. In cases of PTC, carcinoma recurrence may not immediately become life-threatening, but it is definitely a stressor for both patients and physicians. Therefore, we should carefully treat young PTC patients because of the likeliness of carcinoma recurrence.

We set the cutoff age at 30 after performing the same analyses using candidates such as 30, 35, and 40. The cutoff age at 30 showed the clearest results. Cho *et al.* performed a similar study, and they set the cutoff ages

at 35 and 55 years [12], but their median follow-up periods were short, and thus the number of patients with recurrence was too small to draw any conclusions.

It remains an open question regarding why, although young patients are likely to show extrathyroidal locoregional and distant recurrence, they are unlikely to die of PTC. Miyauchi *et al.* also demonstrated that a short Tg-doubling time was more likely to be seen in older patients [9]. One explanation may be that the recurred lesions of young patients are easier to control than those of older patients; for example, RAI therapy for distant metastasis is more effective and the reoperation for recurred extrathyroidal locoregional lesions is easier.

Older patients are likely to die of PTC, possibly because their recurred lesions are progressive and difficult to control. However, the pathobiological and molecular mechanisms underlying the difference in the mortality rate between older and young patients remain unknown.

There are some limitations of this retrospective study. Firstly, the median follow-up period of the old group was shorter than others. This might be because old patients are likely to die not only of thyroid carcinoma but also of other diseases. Secondly, the incidence of recurrence to the remnant thyroid in the three groups did not show the same tendency as that of extrathyroid locoregional recurrence. This may be due

to the fact that the indication of total or near total thyroidectomy was changed between 1987 and 2005 and especially in the past, varied according to surgeons.

In summary, young age (< 30 years) was an independent prognostic factor of extrathyroidal locoregional and distant recurrence, but not carcinoma-related death. Older age (≥ 60 years) independently reflected not only

carcinoma recurrence but also carcinoma death. The difference in the biological features of PTC between the young and older patients has yet to be elucidated. When a young PTC patient is being treated, the likelihood of extrathyroidal locoregional and distant recurrence should be borne in mind.

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