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Relationship between prognosis of papillary thyroid carcinoma patient and age: A retrospective single-institution study

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Abstract. Age is an important prognostic factor in papillary thyroid carcinoma (PTC). In this study, we investigated the difference in prognosis of 7 subsets of PTC patients without distant metastasis at presentation or a history of radiation exposure (20 years or younger, 21-30 years, 31-40 years, 41-50 years, 51-60 years, 61-70 years, and older than 70 years). The lymph node recurrence rate was high in patients 20 years or younger and those older than 60 years. Distant recurrence and carcinoma death rates significantly elevated in patients older than 60 years. The incidence of significant extrathyroid extension markedly increased with age, although that of large node metastasis or extranodal tumor extension did not differ much among the 7 subsets. With the Kaplan-Meier method, lymph node recurrence rate was poor in patients 20 years or younger and in those older than 60 years. Poor distant recurrence-free and cause specific survivals of patients older than 60 years were identified in the series of PTC patients with and without these aggressive features. It is therefore suggested that 1) Lymph node recurrence rate was high in patients 20 years or younger and those older than 60 years and 2) prognosis, including distant recurrence-free survival and cause-specific survival, of patients older than 60 years was poor regardless of clinicopathological features of PTC at initial surgery.

Key words: Papillary thyroid carcinoma, Prognosis, Age

PAPILLARY THYROID CARCINOMA (PTC) is the most common malignancy arising from thyroid follicular cells. Generally, it is an indolent disease, but certain factors indicating a poor prognosis have been identified to date. Age is one of the important prognostic factors in PTC, and has been adopted in prominent staging systems such as the UICC TNM classification [1], AMES [2], MACIS [3], and Cancer Institute Hospital (CIH) classification [4].

Previous studies showed that PTC of old patients was more likely to show unfavorable clinicopathological features such as advanced stage, large tumor size, extrathyroid extension, clinical node metastasis, high mitotic activity, nuclear polymorphism and lack of iodine avidity [5-10]. Wada *et al.* showed that, in the subset of PTC with palpable node metastasis, old patients were significantly more likely to show recurrence than young patients [11], and Voutilainen *et al.* demonstrated patients with old age at initial surgery were likely to die of PTC after lymph node recurrence [12]. Furthermore, old age was regarded as an independent predictor of prognosis of PTC patients in multivariate analysis [13, 14]. In adolescents and young adults, lymph node metastasis, distant metastasis, and tumor multiplicity were more frequently detected than old patients [15-20]. Although patients were likely to show a recurrence, their cause-specific survival was reported to be excellent [19-25]. Indeed, Mazzaferri *et al.* showed that, in their cohort study, recurrence rates of PTC were high in patients under 20 and over 60 years, while the carcinoma death rate increased with old age [26]. To date, no studies using a series containing a large number of patients in a single institution in Japan have been published regarding the relationship between age and the prognosis of PTC patients. In this study, therefore, we investigated the difference in prognosis of patients according to age using the Kaplan-Meier method.

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Patients and Methods

Patients

We enrolled 5,784 patients with PTC without distant

metastasis at presentation who underwent initial surgery in Kuma Hospital, between 1987 and 2005. They consisted of 609 males and 5,175 females, and the age of the patients was 50.1 ± 14.0 years on average. None of these patients had a history of radiation exposure in childhood. The extent of thyroidectomy was total or near total (estimated remnant thyroid 1 gram or less) thyroidectomy in 2,955 patients and more limited thyroidectomy such as subtotal thyroidectomy and lobectomy with isthmectomy in the remaining 2,829 patients. The extent of lymph node dissection was uni- or bilateral modified radical neck dissection (MND) with central node dissection (CND) in 4,373 patients, CND only in 1,137 patients, and no or only partial dissection in the remaining 274 patients. All patients were diagnosed with PTC on postoperative pathological examination. Findings of the preoperative evaluation such as the location and size of primary lesions and lymph node metastases, were predominantly obtained by ultrasonography. Patients who had other thyroid malignancies such as follicular carcinoma, medullary carcinoma, anaplastic carcinoma, and malignant lymphoma, and those who could not be followed for 12 months or more after surgery were excluded from our series.

Evaluation and classification of extrathyroid extension and clinical node metastasis

Extrathyroid extension of primary lesions was evaluated intraoperatively. We regarded cases corresponding to T4a in the UICC TNM classification as having significant extrathyroid extension, and those corresponding to T3 as having minimal extension [1]. Our series did not include T4b patients in the TNM classification. Clinical lymph node metastasis (N) was divided into three groups, as described previously [27]: N0, no clinical node metastasis; N1, clinical node metastasis smaller than 3 cm and without extranodal tumor extension requiring at least partial excision of adjacent organs for node dissection; and N2, clinical node metastasis 3 cm or larger or showing extranodal tumor extension. We regarded significant extrathyroid extension and N2 as aggressive features in this study.

Postoperative follow-up

Scintigraphy using a small amount of radioactive iodine (RAI) (3-13 mCi) and/or postoperative ablation using 30 mCi or more of RAI was performed at our outpatient clinic 1-2 months after total or near total thyroidectomy in 1,031 patients with tumors showing aggressive characteristics such as massive extrathyroid extension, or multiple clinically apparent lymph node metastases. None of these patients showed abnormal uptakes.

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. The postoperative follow-up ranged from 12 to 280 months, and was 129 months on average. We regarded a patient as showing recurrence when it was apparent on imaging studies such as ultrasonography, CT scan, roentgenography, and PET-CT.

Statistical analysis

The Kaplan-Meier curve with a log rank test was adopted for univariate analysis. A p-value smaller than 0.05 was considered significant.

Results

Aggressive features and prognosis of PTC patients according to patient age

In our series, 753 and 237 patients (13.1% and 4.1%) showed significant extrathyroid extension and N2, respectively. In the subset of patients 20 years or younger, the incidence of significant extension was only 3.8%. The incidence increased with patient age and 33.7% of patients older than 70 years showed significant extension. In contrast, the incidence of N2 did not much differ in all subsets ranging from 3.1 to 7.3%.

To date, 394 (6.8%) and 156 (2.7%) patients were shown recurrence to lymph nodes and distant organs, respectively, and 64 (1.1%) have died of PTC. Lymph node recurrence was detected in 17.3% of patients aged 20 years or younger. However, the incidence ranged from 4.6 to 7.3% in the 4 subsets from 21 to 60 years old. It again elevated to 9.4 and 11.8% in patients aged from 61 to 70 years and those older than 70 years, respectively. Distant recurrence ranged from 1.4 to 2.3% in the 5 subsets of patients aged 60 years or younger. It increased to more than 5% in the 2 subsets of patients older than 60 years. The carcinoma death rate elevated to 2.9 and 3.9% in the 2 subsets of patients older than 60 years, while it was only 1.0% or even less in the 5 subsets of patients aged 60 years or younger. These findings are summarized in Table 1.

Table 1 Number of patients with aggressive characteristics, lymph node and distant recurrences and carcinoma death according to age at initial surgery (%)

Age (yrs)	Number of patients	Significant extension	N2	LN recurrence	Distant recurrence	Carcinoma death
≤ 20	104	4 (3.8)	7 (6.7)	18 (17.3)	3 (2.9)	1 (1.0)
21-30	515	28 (5.4)	16 (3.1)	33 (6.4)	11 (2.1)	0
31-40	832	57 (6.9)	31 (3.7)	61 (7.3)	12 (1.4)	1 (0.1)
41-50	1,296	138 (10.6)	55 (4.2)	59 (4.6)	18 (1.4)	4 (0.3)
51-60	1,686	201 (11.9)	56 (3.3)	87 (5.2)	38 (2.3)	15 (0.9)
61-70	995	204 (20.5)	46 (4.6)	94 (9.4)	53 (5.3)	29 (2.9)
> 70	356	120 (33.7)	26 (7.3)	42 (11.8)	21 (5.9)	14 (3.9)
Total	5,784	753 (13.1)	237 (4.1)	394 (6.8)	156 (2.7)	64 (1.1)

Table 2 Ten-year LN-RFS rates, DRFS rates, and CSS rates of PTC patients according to age (standard error)

Age (yrs)	LN-RFS rates	*p*-values	DRFS rates	*p*-values	CSS rates	*p*-values
≤ 20	89.8 (3.7)	0.00370	97.7 (1.7)	N.S.	100	N.S.
21-30	95.2 (1.2)	N.S.	97.4 (0.8)	N.S.	100	N.S.
31-40	93.4 (1.1)	0.00090	98.4 (0.5)	N.S.	99.8 (0.1)	N.S.
41-50	97.7 (0.5)	0.02287	98.8 (0.4)	0.03502	98.7 (0.2)	0.01382
51-60	97.2 (0.5)	0.00000	97.7 (0.4)	0.00000	98.2 (0.3)	0.00000
61-70	92.3 (1.1)	0.00000	94.5 (0.8)	N.S.	97.5 (0.6)	0.00603
> 70	82.6 (3.3)		90.3 (2.3)		94.3 (1.9)	

N.S., not significant

Prognosis of PTC patients according to age

We then analyzed the lymph node relapse-free survival (LN-RFS), distant organ relapse-free survival (DRFS), and cause specific survival (CSS) of PTC patients using the Kaplan-Meier method. As shown in Table 2, LN-RFS of patients aged 20 years or younger was significantly poorer than that of those 21-30 years. LN-RFS of patients 41-50 years was better than that of those 31-40 years, but it became successively poorer in the 3 subsets of patients older than 50 years. Especially, 10-year LN-RFS rates of patients aged 61-70 years and older than 70 years were low, at 92.3 and 82.6%, respectively. DRFS of patients in the 5 subsets of patients aged 60 years or younger were excellent, and their 10-year DRFS rates ranged from 97.4 to 97.7%. However, it became significantly lower in the 2 subsets of patients older than 60 years. Similarly, CSS of PTC patients 60 years or younger was excellent in the 5 subsets 60 years or younger, but it became significantly poorer successively in the two subsets of patients older than 60 years: 10-year CSS rates were 97.5 and 94.3%, respectively.

Relationship between prognosis of PTC patients with and without aggressive features

Significant extrathyroid extension and N2 were identified as important prognostic factors in PTC [25, 28, 29]. As shown in Table 3, In PTC patients with significant extension, LN-RFS of patients in the 5 subsets aged 60 years or younger was generally favorable, but it became significantly poorer in patients in the 2 subsets older than 60 years: 10-year LN-RFS rates were 87.2 and 71.9%, respectively. Similarly, DRFS and CSS became poorer in the 2 subsets patients older than 60 years. Also in PTC without significant extension, LN-RFS rate was poor in patients 20 years or younger and older than 60 years (Table 4). DRFS did not significantly differ among the 7 subsets, but 10-year DRFS rates tended to be lower in the 2 subsets older than 60 years. CSS of patients in the 4 subsets aged 50 years

Table 3 Ten-year LN-RFS rates, DRFS rates, and CSS rates of PTC patients with significant extrathyroid extension according to age (standard error)

Age (yrs)	LN-RFS rates	*p*-values	DRFS rates	*p*-values	CSS rates	*p*-values
≤ 20	100	N.S.	75.0 (21.7)	N.S.	100	N.S.
21-30	100	N.S.	81.5 (8.7)	N.S.	100	N.S.
31-40	88.6 (5.7)	N.S.	93.5 (3.7)	N.S.	97.9 (2.1)	N.S.
41-50	97.2 (1.6)	N.S.	94.8 (2.1)	N.S.	99.0 (1.0)	N.S.
51-60	97.3 (1.3)	0.00000	92.2 (2.1)	0.00625	97.0 (1.4)	0.01042
61-70	87.2 (3.2)	N.S.	82.1 (3.0)	N.S.	91.9 (2.2)	N.S.
> 70	71.9 (8.8)		77.8 (6.4)		84.7 (5.3)	

N.S., not significant

Table 4 Ten-year LN-RFS rates, DRFS rates, and CSS rates of PTC patients with no or minimal extrathyroid extension according to age (standard error)

Age (yrs)	LN-RFS rates	*p*-values	DRFS rates	*p*-values	CSS rates	*p*-values
≤ 20	89.2 (3.4)	0.00303	98.9 (21.7)	N.S.	100	N.S.
21-30	95.0 (1.2)	N.S.	98.4 (0.6)	N.S.	100	N.S.
31-40	94.3 (1.1)	N.S.	98.8 (0.4)	N.S.	100	N.S.
41-50	97.8 (0.5)	0.01087	99.1 (0.3)	N.S.	100	0.03304
51-60	97.0 (0.5)	0.00000	98.4 (0.4)	N.S.	99.5 (0.2)	0.01055
61-70	93.1 (1.1)	0.00009	97.6 (0.6)	N.S.	99.0 (0.4)	N.S.
> 70	84.3 (3.7)		96.0 (0.2)		99.4 (0.5)	

N.S., not significant

or younger was excellent, but it became poorer in the 3 subsets of patients older than 50 years.

LN-RFS of N2 patients was good in the 5 subsets of patients 60 years or younger, but it was poorer in the 2 subsets older than 60 years. Also, DRFS and CSS of patients became poor in the subsets older than 60 years (Table 5). In the subset of N0 or N1 patients, LN-RFS was poor in patients 20 years or younger and older than 60 years (Table 6). DRFS and CSS also became poor in the subsets of patients older than 60 years.

Discussion

In this study, we investigated the difference in prognosis of PTC patients according to age. The incidence of lymph node recurrence was high in patients 20 years or younger and in those older than 60 years, indicating that the lymph node recurrence showed a biphasic pattern in the age distribution of patients. Distant recurrence and carcinoma death markedly increased in patients older than 60 years. These findings were not discrepant with those in a previous cohort study by Mazzaferri *et al*. [26].

Also with the Kaplan-Meier method, LN-RFS, DRFS and CSS rates became poor in the subsets of patients older than 60 years. Therefore, we can conclude that PTC in old patients has a more aggressive character. The cutoff age varies according to classification systems: 45 years in the UICC classification [1], 41 years for males and 51 years for females in the AMES [2], 50 years in the CIH classification [4], and 55 years in our iStage system [27]. Our findings indicated above were not discrepant with those in our previous study [27].

Previous studies showed that old patients more frequently had aggressive characteristics than young

Table 5 Ten-year LN-RFS rates, DRFS rates, and CSS rates of PTC patients with N2 according to age (standard error)

Age (yrs)	LN-RFS rates	*p*-values	DRFS rates	*p*-values	CSS rates	*p*-values
≤ 20	100	N.S.	57.1 (24.9)	N.S.	100	N.S.
21-30	100	N.S.	76.7 (12.0)	N.S.	100	N.S.
31-40	92.3 (7.4)	N.S.	87.1 (7.4)	N.S.	100	N.S.
41-50	98.1 (1.8)	N.S.	91.7 (4.0)	N.S.	97.7 (2.3)	N.S.
51-60	100	0.00211	82.1 (6.5)	0.02993	94.7 (3.9)	0.02985
61-70	78.7 (1.1)	N.S.	61.3 (8.3)	N.S.	71.7 (8.1)	N.S.
> 70	69.0 (3.7)		90.0 (6.7)		78.1 (7.3)	

N.S., not significant

Table 6 Ten-year LN-RFS rates, DRFS rates, and CSS rates of PTC patients with N0 or N1 according to age (standard error)

Age (yrs)	LN-RFS rates	*p*-values	DRFS rates	*p*-values	CSS rates	*p*-values
≤ 20	89.3 (3.4)	0.00427	100	N.S.	100	N.S.
21-30	95.3 (1.2)	N.S.	98.2 (0.7)	N.S.	100	N.S.
31-40	94.0 (1.1)	0.00088	98.8 (0.4)	N.S.	99.9 (0.2)	N.S.
41-50	97.9 (0.5)	0.01618	99.1 (0.3)	0.03606	100	N.S.
51-60	96.9 (0.5)	0.00000	98.1 (0.4)	0.00019	99.4 (0.3)	0.03985
61-70	92.9 (1.0)	0.00002	95.9 (0.7)	0.00803	98.8 (0.4)	N.S.
> 70	85.4 (3.1)		90.3 (2.5)		94.8 (2.0)	

N.S., not significant

patients [5-10]. Also in our series, although the incidence of N2 patients did not differ according to age, the incidence of significant extension definitely elevated in the subsets of patients older than 60 years, which might worsen the prognosis of these patients. However, we also demonstrated that LN-RFS, DRFS, and CSS of patients older than 60 years were poor not only in patients with these aggressive features but also in those without these features. It is therefore suggested that PTC older than 60 years shows a poor prognosis regardless of whether they have aggressive clinicopathological features at initial surgery.

In our series, patients aged 20 years or younger showed a poor LN-RFS, which was not discrepant with a previous finding [26]. However, we analyzed the prognosis of 104 patients aged 20 years or younger without distant metastasis at presentation, and showed that distant recurrence during postoperative follow-up was detected only in 2.9% of patients, and only 1.0% of patients died of PTC. It is therefore suggested that PTC in patients 20 years or younger generally shows a favorable outcome regarding distant recurrence and carcinoma death despite the frequent lymph node recurrence.

The organ to which PTC most frequently recurs is the regional lymph nodes [29]. Also in this series, the incidence of lymph node recurrence (6.8%) was higher than that of distant recurrence (2.7%). With the Kaplan-Meier method, LN-RFS rate was poorer than DRFS rate in patients without aggressive features in all age groups (Tables 4 and 6). However, in the subsets of patients having aggressive features, DRFS rate was even poorer than LN-RFS rate in many age groups (Tables 3 and 5). We previously showed that significant extension and large node metastasis were strong predictors of lung and bone recurrences [14]. Our find-

ings also indicate that distant recurrence is much more likely to occur in patients with aggressive features than in those without such features. Such patients should be carefully treated considering the high incidence of distant recurrence after surgery.

In summary, we showed that lymph node recurrence rate was high in patients 20 years or younger and those older than 60 years and that prognosis of patients older than 60 years were poor regardless of clinicopathological features of PTC at initial surgery. Further studies are needed to elucidate the molecular mechanisms of the difference in prognosis according to patient age.

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