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Prognosis and prognostic factors of papillary thyroid carcinoma in patients under 20 years

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Abstract. Age is an important prognostic factor of papillary thyroid carcinoma (PTC). In this study, we investigated the prognosis and prognostic factors of PTC in patients younger than 20 years. We enrolled 110 patients who underwent initial surgery at Kuma Hospital between 1987 and 2008. Tumor size > 4 cm, metastatic node ≥ 3 cm, and significant extrathyroid extension were more frequently detected in 8 patients with distant metastasis at diagnosis than in 102 patients without distant metastasis. Ten- and 20-year lymph node recurrence-free survival (LN-RFS) and distant recurrence-free survival (DRFS) rates were 84 and 80%, and 95 and 89%, respectively. Metastatic node ≥ 3 cm, age ≤ 16 years, tumor size > 4 cm, and male gender affected LN-RFS, and the former two had an independent prognostic value in multivariate analysis. Metastastic node ≥ 3 cm, significant extrathyroid extension, age ≤ 16 years, tumor size > 4 cm, and a male gender predicted a poor DRFS, and the former two were independent prognostic factors. To date, only 2 patients have died of PTC. These findings suggest that, in the subset of PTC patients younger than 20 years, metastatic node ≥ 3 cm, significant extension, and age ≤ 16 were important signs of aggressiveness of carcinoma, and careful treatment is necessary for patients with these characteristics, although the cause-specific survival was excellent.

Key words: Papillary thyroid carcinoma, Prognosis, Age

PAPILLARY THYROID CARCINOMA (PTC) generally has an indolent character. However, PTC displaying certain clinicopathological features is progressive and lead to a dire prognosis. Old age is one of the important prognostic factors, and has been adopted in various staging systems such as the UICC TNM classification, AMES, MACIS, and CIH classification [1-4]. We also demonstrated that an age of 55 years or older is the strongest predictor of carcinoma death of PTC patients [5]. In contrast, it has been reported that PTC in children and young adults has a different biological character from PTC in old patients. Radiation exposure, including the Chernobyl disaster, in childhood is known to significantly increase the risk of PTC [6-10]. The clinicopathological features and prognosis of PTC in young patients with no history of radiation exposure have also been intensively investigated. PTC in young patients exhibited aggressive clinicopathological features such as distant metastasis, lymph node metastasis, multifocality, and a large tumor size more frequently than in old patients [11-19]. Mazzaferri *et al*. showed that the recurrence rate of PTC in patients under 20 years was higher than that of PTC patients aged 20-59 years, but carcinoma death was only occasional [20]. Similarly, Zimmerman *et al*. showed the likeliness of postoperative recurrence to the neck lymph nodes in young patients, but the cause-specific survival (CSS) of patients in their series was excellent [11]. Other studies also demonstrated an excellent prognosis for CSS of patients [15, 19].

Two studies have been published on this topic from Japan to date. Wada *et al*. analyzed 120 patients, and showed that patients with palpable lymph node metastasis showed a poorer disease-free survival (DFS) [21]. Enomoto *et al*. analyzed the prognosis after long-term follow-up (over 20 years in average), and DFS of patients under 16 years was significantly poorer than that of those 16 years or older [22]. However, in these studies, patients who underwent surgery in the

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1960s and 1970s before the modern diagnostic level were adopted. From the end of the 1980s, preoperative ultrasound significantly facilitated the accurate evaluation of not only size and location of primary lesions but also of lymph node metastasis. Furthermore, ultrasound is also useful to detect lymph node recurrence in postoperative follow-up. In this study, we analyzed 110 patients who underwent initial surgery in Kuma Hospital between 1987 and 2008 to elucidate the prognosis and prognostic factors of PTC in patients younger than 20 years.

Patients and Methods

Patients

We enrolled 110 PTC patients younger than 20 years with no history of radiation exposure who underwent initial surgery in Kuma Hospital, between 1987 and 2008. They consisted of 12 males and 98 females. Patients' ages ranged from 7 to 19 years, and were 17 years on average. Eight patients (7%) had distant metastasis at initial surgery and were classified as M1 in the UICC TNM classification [1]. The metastatic lesions were detected on preoperative imaging studies in 5 patients and on postoperative scintigraphy in 3 patients. The extent of thyroidectomy was total or near total (estimated remnant thyroid 1 gram or less) thyroidectomy in 59 patients and more limited thyroidectomy such as subtotal thyroidectomy and lobectomy with isthmectomy in the remaining 51 patients. Lymph node dissection was performed in 104 patients, and all these patients underwent central node dissection (CND). Uni- or bilateral modified radical neck dissection (MND) was also performed in 91 patients. Findings of the preoperative evaluation such as the location and size of primary lesions and lymph node metastasis, were predominantly obtained by ultrasound. Patients who had other thyroid malignancies such as follicular carcinoma, medullary carcinoma, anaplastic carcinoma, and malignant lymphoma, and patients who could not be followed for 12 months or less after surgery were excluded from our series.

Evaluation of extrathyroid extension and clinical lymph node metastasis

Extrathyroid extension of primary lesions was evaluated intraoperatively. We regarded T4a cases in the UICC TNM classification [1] as having significant extrathyroid extension. Our series did not include T4b patients in the TNM classification. Clinical lymph node metastasis (N) was divided into three groups: N0, no clinical node metastasis; N1, clinical node metastasis smaller than 3 cm; and N2, clinical node metastasis 3 cm or larger.

Postoperative follow-up

All patients were diagnosed with PTC on postoperative pathological examination. No patients were diagnosed as poorly differentiated carcinoma on WHO classification [23]. None of the M0 patients in our series underwent high-dose radioactive iodine (RAI) administration for ablation immediately after initial surgery, although scintigraphy using a small amount of RAI (3-13 mCi) at our outpatient clinic was performed in 34 patients. Abnormal uptake to distant organs was detected in 3 patients, as indicated above, and these patients were classified as M1.

We followed patients by ultrasound once per year to monitor them for signs of local recurrence. We performed fine needle aspiration biopsy (FNAB) for suspicious nodes and thyroglobulin measurement of the wash-out from needles used for FNAB to diagnose lymph node recurrence [24]. Either chest roentgenography or a CT scan was also performed once per year. The postoperative follow-up ranged from 17 to 296 months, and was 149 months on average. We regarded a patient as showing recurrence when it was apparent on imaging studies such as ultrasound, CT scan, roentgenography, and PET-CT.

Clinical outcomes of patients

To date, of the 102 M0 patients, lymph node recurrence has been detected in 16 patients (16%). Two patients (2%) showed recurrence to the remnant thyroid, which was not studied here. Distant recurrence was observed in 6 patients (6%). All these patients showed lung recurrence and one showed bone recurrence also. To date, 2 patients (one M0 and one M1) (2%) have died of PTC.

Statistical analysis

The chi-squire test was used for comparing variables. The Kaplan-Meier curve with a log rank test was adopted for univariate analysis. The Cox-Hazard regression model was employed for multivariate analysis. A p-value smaller than 0.05 was considered significant. A p-value between 0.05 and 0.1 was regarded as having a marginal significance.

Results

Comparison between M0 and M1 patients

We compared the clinicopathological features between 102 M0 and 8 M1 patients (Table 1). N grade was significantly higher in M1 patients than in M0 patients ($p = 0.0002$). The incidences of extrathyroid extension ($p = 0.0014$) and a tumor size larger than 4 cm ($p = 0.0028$) in M1 patients were significantly higher than in M0 patients. Age and gender did not significantly differ between these two groups.

Lymph node recurrence-free survival (LN-RFS) of 102 M0 patients

We analyzed the LN-RFS rate and prognostic factors affecting LN-RFS of 102 M0 patients (Table 2). Of 16 patients who showed lymph node recurrence, 7 (44%) had a tumor larger than 4 cm, 6 (38%) were graded as N2, but only 1 (6%) was classified as having significant extrathyroid extension. Nine patients (56%) were 16 years or younger. With the Kaplan-Meier method, 5, 10- and 20-year LN-RFS rates of these patients were 89, 84, and 80%, respectively (Fig. 1). We then analyzed the prognostic significance of various clinicopathological features. Patients with an age of 16 years or younger ($p = 0.0345$), N2 ($p < 0.0001$), a male gender ($p = 0.0285$), and tumor size larger than 4 cm ($p = 0.0159$) showed a significantly higher rate of lymph node recurrence than patients without these features. Extrathyroid extension did not affect LN-RFS in univariate analysis. In multivariate analysis, N2 ($p = 0.0004$) and an age 16 years or younger ($p = 0.0410$) independently reflected a poor LN-RFS (Table 2).

Distant recurrence-free survival (DRFS) of 102 M0 patients

Of 6 patients who showed distant recurrence during follow-up, 4 (67%) had a tumor larger than 4 cm, 4 (67%) were graded as N2, and 2 (33%) showed significant extrathyroid extension. Only 1 patient had none of these factors, but this patient was classified as N1. In our series, none of the N0 patients have shown distant recurrence to date. Five-, 10-, and 20-year DRFS rates were 99, 95, and 89%, respectively (Fig. 2). In univariate analysis, an age of 16 years or younger ($p = 0.0369$), N2 ($p < 0.0001$), a male gender ($p = 0.0424$), tumor size larger than 4 cm ($p = 0.0038$), and extrathyroid extension ($p = 0.0004$) significantly affected DRFS of the patients. In multivariate analysis, extrathyroid extension ($p = 0.00388$) and N2 ($p = 0.0323$) independently reflected a poor DRFS (Table 3).

Carcinoma death of patients

To date, 2 male patients aged 15 and 16 years at the time of initial surgery have died of PTC. One M0 patient died of the growth of lung and bone recurrences 187 months after surgery. He had a primary lesion measuring 6 cm and was classified as N2, although the primary tumor showed no extrathyroid extension. Another patient was diagnosed as M1 because of multiple lung metastases at the time of surgery. His PTC showed significant extrathyroid extension and he was also classified as N2. He underwent postoperative RAI therapy but died of PTC 28 months after surgery.

Discussion

In this study, we investigated the clinicopathological features, prognosis, and prognostic factors in PTC patients younger than 20 years. We demonstrated that: 1) the incidences of patients having aggressive features such as metastatic node larger than 3 cm and tumor larger than 4 cm were high, 2) lymph node recurrence was observed at a high incidence, and a metastatic node 3 cm or larger and age 16 years or younger were independent predictors, 3) a metastatic node 3 cm or larger and significant extrathyroid extension independently affected distant recurrence, and 4) their CSS was excellent.

Table 1 Difference in clinicopathological features between M0 and M1 PTC patients under 20 years (%)

		M0	M1	Total	
Extrathyroid extension	(Yes/No)	5(5)/97(95)	4(50)/4(50)	9/101	$p = 0.0013$
Tumor > 4 cm	(Yes/No)	22(22)/80(78)	6(75)/2(25)	28/82	$p = 0.0033$
Gender	(M/F)	11(11)/91(89)	1(13)/7(87)	12/98	N.S.
Age	(≤16/>16)	38(37)/64(63)	5(62)/3(38)	43/67	N.S.
N grade	(2/1/0)	11(9)/26(25)/65(64)	4(50)/4(50)/0	15/30/65	$p = 0.0002$

N.S., not significant

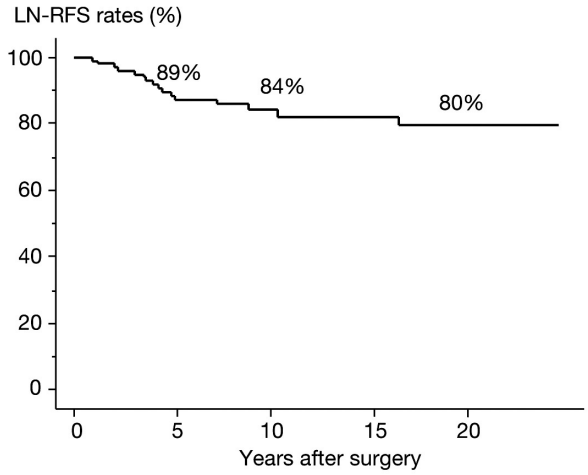

Fig. 1 LN-RFS of 101 PTC patients under 20 years.

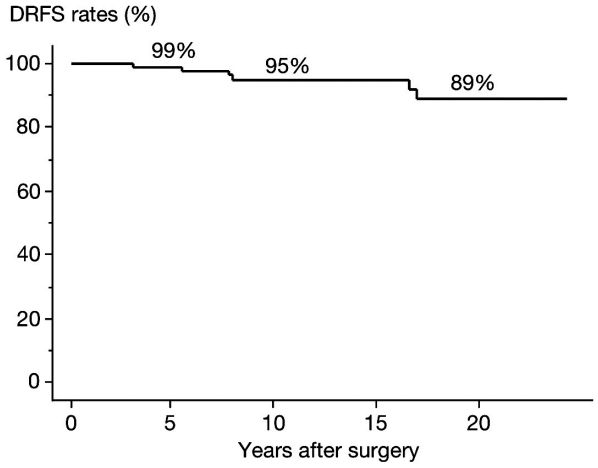

Fig. 2 DRFS of 101 PTC patients under 20 years

Table 2 Uni- and multivariate analyses for LN-RFS of 102 patients under 20 years

	Univariate *p*-values	Multivariate *p*-values	Hazard ratio (95% confidence interval)
Tumor > 4 cm	0.0159	0.5887	1.37 (0.44-4.26)
Male gender	0.0285	0.4394	1.63 (0.47-5.59)
N2	< 0.0001	0.0007	8.93 (2.53-31.25)
Age ≤ 16 years	0.0345	0.0410	3.14 (1.05-9.38)

Table 3 Uni- and multivariate analyses for DRFS of 102 patients under 20 years

	Univariate *p*-values	Multivariate *p*-values	Hazard ratio (95% confidence interval)
Tumor > 4 cm	0.0038	0.9236	1.13 (0.07-10.99)
Male gender	0.0416	0.8752	1.21 (0.11-13.70)
N2	< 0.0001	0.0323	14.50 (1.25-166.67)
Age ≤ 16 years	0.0369	0.1049	9.14 (0.63-132.58)
Extrathyroid extension	0.0004	0.0388	15.63 (1.15-200.00)

Our series included 7% M1 patients, which was higher than in the series of Enomoto *et al*. [22], but was similar to that in the study of Zimmerman *et al*. [11], which was 6.9%. M1 patients were more likely to show significant extrathyroid extension, a large tumor size, and high N grade, which is reasonable because M1 is a definite sign of an aggressive character. Also, in M0 patients, the incidences of a tumor larger than 4 cm and metastatic node 3 cm or larger were 22 and 9%, respectively, which were larger than those in our entire series of 5,768 M0 patients [5]: 10 and 3%, respectively, indicating that young patients are more likely to show these aggressive features than old patients. However, the incidence of significant extrathyroid extension of M0 patients was only 5%, which was even lower than that in the entire series (13%). It is therefore suggested that the biological character of PTC in young patients significantly differs from that in old patients.

Sixteen percent of patients in our series showed recurrence to the regional lymph nodes, which was higher than that in our entire series (8%) [5]. Ten- and 20-year lymph node recurrence rates of our series were also high, at 16 and 20%, respectively. We demonstrated that a metastatic node 3 cm or larger, extrathy-

roid extension, and a large tumor size were independent prognostic factors for recurrence to the lymph nodes in the entire series [5]. Also in this series, a metastastic node 3 cm or larger was an independent predictor of LN-RFS, and a tumor larger than 4 cm showed a prognostic value in univariate analysis. However, extrathyroid extension did not show a prognostic significance for lymph node recurrence even in univariate analysis, which was in sharp contrast to PTC in old patients [5].

In our series, 6% of patients showed recurrence to distant organs, which was not discrepant with a previous study in Japan [22]. Interestingly, in contrast to lymph node recurrence, extrathyroid extension was an independent prognostic factor for distant recurrence together with a metastatic node 3 cm or larger, and a tumor size larger than 4 cm also had a prognostic significance. These findings were not discrepant with our previous data for the entire PTC series [5, 25]. Furthermore, as indicated above, a metastatic node 3 cm or larger, significant extrathyroid extension, and a large tumor size were frequently detected in M1 patients. Thus, we can conclude that these factors are significantly related to distant metastasis of PTC in patients younger than 20 years.

We previously showed that a male gender moderately affected carcinoma recurrence and carcinoma death of PTC patients in entire series [10, 25, 26]. Also, in this series younger than 20 years, a male gender affected carcinoma recurrence in univariate analysis. Our series included only 2 patients who died of PTC, and they were males. Therefore, it is suggested that a male gender has a prognostic significance to some extent also in PTC patients younger than 20 years.

Age is a very important prognostic factor of PTC. The incidence of recurrence rate significantly elevated in old patients, and, in our series, an age of 55 years or older was the strongest prognostic factor for CSS of the entire series of PTC patients [5]. In contrast, in the subset of PTC patients younger than 20 years, an age of 16 years or younger was an independent predictor for LN-RFS and showed a prognostic value for DRFS in univariate analysis. Furthermore, the 2 patients, who died of PTC in our series were aged 16 years or younger. Then, in contrast to the entire series, younger patients are likely to show a dire prognosis with PTC under 20 years, which was not discrepant with the findings of Enomoto *et al*. [22].

To date, a few studies have published data on the difference in gene mutations between young and old PTC patients. Kumagai *et al*. showed a low frequency of $BRAF^{T1796A}$ mutations [27] and Fenton *et al*. demonstrated common *ret/PTC* mutations in young PTC [28]. Many studies showed that *BRAF* mutations reflect a dire prognosis of patients [29, 30], but negative results were presented in Japanese patients [31]. Furthermore, the relationship between *ret/PTC* mutations and the prognosis remains controversial [32-35]. Therefore, these findings cannot clearly explain the difference in prognosis of PTC patients younger than 20 years and old patients.

In our series, 51 patients did not undergo total thyroidectomy at the initial surgery. Of these, only 2 (4%) showed recurrence to the remnant thyroid. Furthermore, none of the M0 patients in our series underwent high-dose RAI administration immediately after the initial surgery. In our series, only 6 patients showed distant recurrence. Five of these had aggressive features, that is, a tumor larger than 4 cm, significant extrathyroid extension, and a metastatic node 3 cm or larger, and the remaining one was also graded N1. Previous studies from Western countries recommended routine total thyroidectomy with postoperative RAI therapy [36-39]. However, Hay *et al*. showed that 73% of PTC patients younger than 21 years at the initial surgery, who died from nonthyroid malignancy during follow-up, underwent postoperative therapeutic irradiation, and they have issued warnings about routine RAI administration of the therapeutic dose [40]. The incidence of carcinoma death was extremely low in our series, and distant recurrence occurred in none of the N0 patients. It is therefore suggested that high-dose RAI administration immediately after surgery should be avoided and routine total thyroidectomy is not mandatory for patients with no aggressive features.

In summary, we demonstrated that aggressive characteristics such as distant metastasis at diagnosis, a large tumor size, and large node metastasis were frequently detected in PTC patients younger than 20 years, although significant extrathyroid extension was not. Node metastasis 3 cm or larger and an age of 16 years or younger independently predict a poor LN-RFS, and node metastasis 3 cm or larger and significant extrathyroid extension were independent prognostic factors for DRFS. Patients exhibiting these clinicopathological features should be treated carefully, although CSS of PTC patients younger than 20 years is excellent.

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