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Evaluation of recurrence risk in patients with papillary thyroid cancer through tumor-node-metastasis staging: A single-center observational study in Taiwan

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ABSTRACT

Background: Many patients with papillary thyroid cancer (PTC) demonstrate satisfactory outcomes. However, 8%–28% of patients with PTC show tumor recurrence, which may affect prognosis. Therefore, identifying factors associated with tumor recurrence in patients with PTC may be helpful to refine therapeutic strategies.

Methods: To identify factors associated with PTC recurrence, we retrospectively reviewed demographic features (sex and age), operation method, image character, serum thyroglobulin (Tg), accumulated radioactive iodine (I-131) therapeutic dose, I-131 uptake, and metastases at diagnosis in 829 patients with PTC. Patients were grouped into early (stage I and II; n = 698) and advanced (stage III and IV; n = 131) tumor-node-metastasis (TNM) stages. Recurrence rate, mortality rate, risk factors of recurrence, recurrent free survival and overall survival curve were compared between two groups.

Results: Patients in the early stage demonstrated a lower recurrence rate (7.2%) than did those in the advanced stage (28.2%, $p < 0.05$). The mortality rate of patients with recurrence in the advanced stage was higher than that of those in the early stage (51.4% vs. 12.0%). The major impact factors on tumor recurrence in early TNM stage were distant metastasis and lymph node metastasis, while in advanced TNM stage were distant metastasis, male gender, total thyroidectomy with limited lymph node dissection, and a high serum Tg level.

Conclusions: Strategies to monitor tumor recurrence might be refined according to the TNM stages of PTC patients.

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At a glance of commentary

Scientific background on the subject

Risk factors for tumor recurrence and cancer-specific mortality were different between patients with early- and advanced-stage PTC.

What this study adds to the field

The major impact factors on tumor recurrence in early TNM stage were distant metastasis and lymph node metastasis, while in advanced TNM stage were distant metastasis, male gender, total thyroidectomy with limited lymph node dissection, and a high serum Tg level.

Papillary thyroid cancer (PTC) is the most common endocrine malignancy, comprising approximately 85%–90% of all thyroid cancers [1,2]. In general, PTC is considered an indolent tumor with low-grade malignancy and satisfactory prognosis [3]. However, tumor recurrences are still observed in 8%–28% of patients with PTC [1,4,5]. These tumor recurrences considerably deteriorate quality of life and increase medical expenses [6,7]. Furthermore, patients have to undergo therapies for recurrence, including repeat surgical intervention, radioactive iodine (I-131) therapy, local radiotherapy, or target therapy with tyrosine kinase inhibitors for local regional invasion and distant metastasis [8–11]. Therefore, strategies to identify patients with PTC at a high recurrence risk are crucial.

Several factors such as sex, age, tumor, extrathyroid extension, and distant metastasis have been reported to increase the risk of recurrence of PTC [12,13]. So, the current guidelines have suggested to classify the disease into low-, moderate-, high-risk group based on clinicopathological factors after diagnosis of well-differentiated thyroid cancer [9]. Unfortunately, some of the patients' postoperative clinicopathological records are incomplete or unavailable to be evaluated according to the current guidelines. To find a better follow-up strategy for patients with PTC unsuitable for classifying recurrence risk by American Thyroid Association (ATA) risk stratification, we explored the risk factors of recurrence after first thyroid surgery through different TNM stage.

Patients and methods

From 1977 to 2013, 3495 patients with thyroid cancer, including 2798 PTC patients (80.1%), received regular follow-up care at Chang Gung Medical Center in Linkou, Taiwan [14]. We retrospectively recruited 829 patients with PTC having a disease-free status at least 6 months after their first thyroidectomy before 2004. Pathologic diagnosis of PTC was confirmed according to the World Health Organization criteria [15]. The staging for PTC at the time point of recruitment was defined by The Union for International Cancer Control Tumor-Node-Metastasis (TNM) Criteria (6th ed.) [16].

Demographic data, clinicopathological features, thyroid operation procedures, and serum thyroglobulin (Tg) level, uptake, and accumulated dose determined through I-131 whole-body scan (WBS) after first thyroidectomy and duration for disease free at least 6 months were collected for analyses. Patients were categorized as disease free as following criteria: 1) they showed negative results in I-131 WBS, undetectable Tg levels without thyroxine treatment, thyroid-stimulating hormone (TSH) level >30 IU/mL: 2) except for non-stimulated thyroglobulin <1 ug/L, there was no local recurrence or remote metastasis through non-invasive examination during follow up [17]; 3) they were with biochemical incomplete response, defined as repeated stimulated thyroglobulin >1 ug/L but without localized recurrence or distant metastasis [18]. Recurrence was defined as the detection of residual PTC after 6 months of disease-free status, which was determined from the pathological report of the surgical specimen or from the presence of I-131 uptake on diagnostic/therapeutic scans in patients with an elevated serum Tg level [17].

Total thyroidectomy was performed for tumors >1 cm or tumors <1 cm with lymph node metastasis or extrathyroid extension. With the evolutional change of the guidelines, surgeons have different principles of lymph node dissection for PTC during these periods; thus, radical and central neck dissection was not routinely performed in our hospital. However, at least limited lymph node dissection would be performed for PTC patients with grossly enlarged lymph nodes detected before or during surgical intervention [17]. Therefore, we classified the surgical methods into total thyroidectomy, total thyroidectomy plus limited lymph node dissection and total thyroidectomy plus radical lymph node dissection to facilitate statistical analysis.

In patients with PTC recurrence, thyroid remnant ablation was performed after withdrawal of thyroxine suppression therapy for 4 weeks after surgery. The I-131 ablation dose for most patients was 1.1–3.7 GBq (30–100 mCi). A WBS was performed 1 week after I-131 administration by using a dual-head gamma camera (Dual Genesys; ADAC, USA) equipped with a high-energy collimator. The whole-body image was acquired through continuous-mode scanning at a speed of 5 cm/min. In addition, a thyroid scan was performed with a pinhole collimator (4-mm aperture) placed at a distance of 7 cm over the neck for a total of 50,000 counts or 30 min. Participants with I-131 foci extended beyond the thyroid bed were classified as having metastatic cancer. Patients with metastatic cancer were treated with high therapeutic doses [3.7–7.4 GBq (100–200 mCi)]. A repeat therapeutic dose of 3.7–7.4 GBq was used at an interval of 6–12 months according to the degree of disease progression [17].

In view of incomplete postoperative clinicopathological records of all the subjects, we calculated the recurrence rate of thyroid cancer based on different TNM stages and compared the differences in the demographic and clinical data; then further analyzed the major risk factors for recurrence through multivariate regression analysis in different TNM stages. All causes of death are based on the final diagnosis in the medical

record. The most common causes of death related to PTC were respiratory insufficiency, followed by circulatory failure, hemorrhage, and airway obstruction.

Continuous variables were expressed as the median with the range. The Mann–Whitney U test was used to compare continuous variables. Categorical data were presented as numbers with percentages and compared using Fisher's exact or chi-square test. Recurrence-free survival (RFS) was defined as the time from the first thyroidectomy until the first evidence of any recurrence, whereas overall survival (OS) was defined as the time from the first thyroidectomy to death due to any cause or to the last follow-up date. The univariate Cox proportional hazard model was used to evaluate a potential relationship between demographic and clinical variables and RFS; the statistics of cox regression variable items were carried out in Allen-Cady model [19]. The estimated hazard ratios (HRs) and 95% confidence intervals (CI) were calculated. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. Statistical significance was defined as two-sided p-value <0.05. All statistical analyses were performed using IBM SPSS software version 21.0 (IBM Corp., Armonk, NY).

Results

Among 829 patients with PTC, the recurrence rates of different TNM stages were as follows: stage I, 7.30% (46/631); stage II, 6.0% (4/67); stage III, 22.90% (8/35); and stage IV, 30.20% (29/96). In view of similar recurrence rates and for increasing statistical power, we merged patients into two groups, namely early (stage I and II) and advanced (stage III and IV) stages. Fig. 1 presents the recurrent rate of PTC in patients at early and advanced stages (early stage: 7.2% (50/698) vs. advanced stage: 28.2% (37/131), $p < 0.001$).

Table 1 presents demographic and clinicopathological characteristics of PTC patients in early and advanced TNM stage. In the early stage, patients with recurrence demonstrated younger age at diagnosis, large tumor sizes, a high serum Tg level, a high I-131 uptake after first thyroidectomy, a high accumulated I-131 dose, and high proportion of multicentric intrathyroid lesions, metastasis at lymph node, soft tissue invasion, and distant metastasis compared with those without recurrence. In the advanced stage, patients with recurrence demonstrated older age at diagnosis, male sex, a high serum Tg level, a high accumulated I-131 dose, high proportion of metastasis at lymph node and distant metastasis, and low proportion of total thyroidectomy plus limited lymph node dissection compared with those without recurrence. The time to first recurrence was 5.5 years in the early TNM stage and 5 years in the advanced TNM stage. In the early TNM stage, the median follow-up period was 17.1 years in recurrence group and 16.1 years in disease free group. In the advanced TNM stage, the median follow-up period was 12.1 years in recurrence group and 15.7 years in disease free group. The most common site of recurrence was the lymph node (early stage: 78%, advanced stage: 56%) in patients at all stages, followed by the mediastinum (18%) and lung (29.7%) in early and advanced stages, respectively. The proportion of bone metastasis is low (4.0% in the early stage and 10.8% in the advanced stage). As expected, patients in the advanced stage demonstrated higher total (early stage vs. advanced stage, 1.3% vs. 15.3%, $p < 0.001$) and thyroid-related (early stage vs. advanced stage, 12.0% vs. 51.4%, $p < 0.001$) mortality than did those in the early stage.

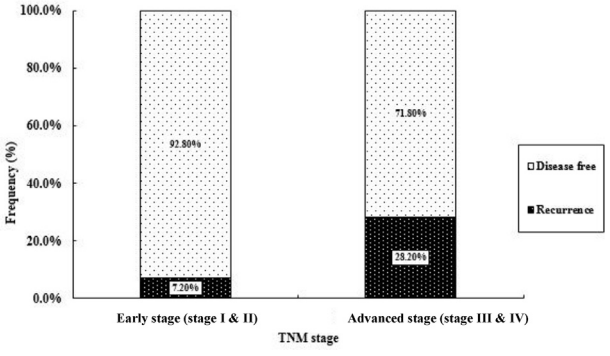

Fig. 1 Recurrence rate of patients at different stages of papillary thyroid cancer. Frequency of disease-free survival and recurrence between early- and advanced-stage PTC. Chi-square test, $p < 0.001$.

In the univariate analysis, younger age at diagnosis (HR: 0.968, CI: 0.942–0.944, $p = 0.016$), large tumor size (HR: 1.530, CI: 1.308–1.789, $p < 0.001$), multicentric intrathyroid lesions (HR: 2.049, CI: 1.069–3.927, $p = 0.031$), a high serum Tg level (HR: 1.002, CI: 1.001–1.003, $p < 0.001$), a high accumulated I-131 dose (HR: 1.005, CI: 1.004–1.005, $p < 0.001$), soft tissue invasion (HR: 3.424, CI: 1.934–6.063, $p < 0.001$), lymph node metastasis (HR: 3.112, CI: 1.746–5.544, $p < 0.001$), and distant metastasis (HR: 14.371, CI: 8.100–25.499, $p < 0.001$) were associated with recurrence in patients in the early stage. However, only a high accumulated I-131 dose (HR: 1.005, CI: 1.004–1.006, $p < 0.001$), lymph node metastasis (HR: 2.532, CI: 1.348–4.757, $p = 0.004$), and distant metastasis (HR: 4.877, CI: 2.606–9.129, $p < 0.001$) repeatedly demonstrated statistical significance in the multivariate analysis [Table 2]. In patients in the advanced stage, the univariate analysis showed that older age at diagnosis (HR: 1.065, CI: 1.028–1.105, $p = 0.001$), male sex (HR: 2.351, CI: 1.225–4.514, $p = 0.010$), a large tumor size (HR: 1.199, CI: 1.032–1.393, $p = 0.018$), high serum Tg levels (HR: 1.005, CI: 1.003–1.008, $p < 0.001$), a high accumulated I-131 dose (HR: 1.003, CI: 1.002–1.004, $p < 0.001$), lymph node metastasis (HR: 2.042, CI: 1.070–3.897, $p = 0.030$), and distant metastasis (HR: 13.335, CI: 6.413–27.730, $p < 0.001$) were associated with recurrence. Thyroidectomy plus limited lymph node dissection (HR: 0.480, CI: 0.232–0.992, $p = 0.047$) was associated with a decreased recurrence risk. In the multivariate analysis, male sex (HR: 3.984, CI: 1.912–8.301, $p < 0.001$), high serum Tg levels (HR: 1.009, CI: 1.006–1.012, $p < 0.001$), a high accumulated I-131 dose (HR: 1.002, CI: 1.001–1.003, $p < 0.001$), and distant metastasis (HR: 27.265, CI: 10.520–70.662, $p < 0.001$) were associated with recurrence, whereas thyroidectomy plus limited lymph node dissection was associated with a decreased recurrence risk (HR: 0.328, CI: 0.152–0.708, $p = 0.005$) [Table 3].

Patients with early-stage PTC had higher RFS and OS than did those with advanced-stage PTC [Fig. 2]. The RFS of different stages (early vs. advanced) of PTC was as follows:

Table 1 Clinical features of patients with early- and advanced-stage PTC.

	Early stage (n = 698)			Advanced stage (n = 131)		
	Recurrence	Disease free	*p*-value	Recurrence	Disease free	*p*-value
Number (n (%))	n = 50 (7.2%)	n = 648 (92.8%)		n = 37 (28.2%)	n = 94 (71.8%)	
Age at diagnosis (year-old)[a]	30 (13–57)	36 (11–72)	**0.01**	58 (53–64)	52 (45–78)	**0.01**
Sex (male/female)	(12/38)	(101/547)	0.12	(16/21)	(21/73)	**0.02**
Tumor size (cm)	3.0 (1.1–10.0)	2.3 (1.1–7.0)	**<0.001**	3.2 (2.2–4.2)	2.6 (2.0–4.0)	0.169
Operation method (n (%))			0.18			**0.04**
Total thyroidectomy	25 (50%)	380 (60%)		19 (51.4%)	37 (39.4%)	
Total thyroidectomy + limited lymph node dissection	22 (44%)	251 (38.7%)		12 (32.4%)	51 (54.3%)	
Total thyroidectomy + radical lymph node dissection	3 (6%)	15 (2.3%)		6 (16.2%)	6 (6.3%)	
Multicentric vs. single intrathyroid lesion (n (%))	12/38 (24%)	88/560 (13.6%)	**0.043**	12/25 (32.4%)	25/69 (26.6%)	0.500
Serum Tg[b] level after first thyroidectomy and disease free for 6 months (ng/ml)	30.2 (6.9–85.8)	3.5 (0–12.9)	**<0.001**	15.8 (3.8–37.4)	3.9 (0–12)	**<0.001**
I-131 uptake after first operation (%)	2.54 (0–26.2)	0.91 (0–60.8)	**0.007**	0.8 (0–4.0)	0.1 (0–2.7)	0.292
Accumulated I-131 dose after first thyroidectomy (mCi)[c]	495.9 (0–1199.5)	89.8 (0–731)	**<0.001**	301 (170.1–669.3)	120 (60–210)	**<0.001**
Follow-up period (years)	17.1 (10.8–33.5)	16.1 (0.1–31.7)	0.342	12.1 (1.3–29.4)	15.7 (1.97–26.5)	**0.000**
Metastasis at diagnosis						
Soft tissue invasion (n (%))	19 (38.0%)	92 (14.2%)	**<0.001**	27 (73.0%)	68 (72.3%)	0.942
Lymph node (n (%))	18 (36.0%)	93 (14.3%)	**<0.001**	18 (48.6.0%)	27 (28.7%)	**0.031**
Distant metastasis (n (%))	19 (38%)	18 (2.6%)	**<0.001**	22 (59.5%)	4 (4.3%)	**<0.001**
Recurrence site						
Brain (n (%))	2 (4.0%)			1(2.7%)		
Lymph node (n (%))	39 (78.0%)			21 (56.8%)		
Mediastinum (n (%))	9 (18.0%)			7 (18.9%)		
Lung (n (%))	4 (8.0%)			11 (29.7%)		
Bone (n (%))	2 (4.0%)			4 (10.8%)		
Time to recurrence (years)	5.5 (1.1–32.3)			5.0 (1.1–28.1)		
Mortality						**<0.001**[d]
Total (n (%))	9/698 (1.3%)			20/131 (15.3%)		
Thyroid-related (n (%))	6/50 (12.0%)			19/37 (51.4%)		
Thyroid-unrelated (n (%))	3/50 (6.0%)			1/37 (2.7%)		

Abbreviations: PTC: papillary thyroid cancer; I-131: radioactive iodine.

[a] Categorical variables were presented as the total number (%); continuous variables were presented as the median (range); the comparison between categorical and continuous variables was performed using the chi-square test and Mann–Whitney *U* test, respectively; bold and italics indicate p value < 0.05, which is considered statistically significant.

[b] The serum thyroglobulin (Tg) level was obtained after first thyroidectomy and duration for disease free at least 6 months.

[c] Regarding the impact of the I-131 therapeutic dose on the subjects in this study, the frequency and dosage of I-131 therapy might vary depending on the physician, so we adopted the accumulated I-131 dose before this study was analyzed.

[d] Comparison of mortality between early- and advanced-stage recurrence groups.

96.7% vs. 86.2% (5 year), 94.4% vs. 74.7% (10 year), 92.9% vs. 71.5% (15 year), and 92.1% vs. 70.0% (20 year) (log-rank test, $p < 0.001$). The OS of different stages (early vs. advanced) of PTC was as follows: 100% vs. 97.7% (5 year), 100% vs. 91.5% (10 year), 99.7% vs. 85.5% (15 year), and 98.8% vs. 80.1% (20 year) (log-rank test, $p < 0.001$).

Discussion

The results of this study suggested that patients with different stages of PTC had different rates of recurrence risk (early vs. advanced stage: 7.2% vs. 28.2%). These results were consistent with those of other studies, which also showed a high tumor recurrence in patients at an advanced stage [20,21]. The overall mortality rate (3.5%) of our cohort was lower than that of other studies (4.9%–7%) [22,23]. This difference was probably due to the exclusion of patients with PTC with persistent disease status. The risk of thyroid-related mortality was higher in patients at an advanced stage (51.4%) than in patients at an early stage (12.0%) of PTC, which was also compatible with the suggestions of current guidelines for managing thyroid cancer [24]. Therefore, patients with advanced-TNM-stage PTC not only had a high recurrence rate but also a high cancer-specific mortality.

Local lymph node metastasis is usually one of the early manifestations in the progression of PTC to distant metastasis

Table 2 Analysis of risk factors for recurrence in patients with early-stage PTC.

	Univariate		Multivariate	
	HR (95% CI)	*p*-value[a]	HR (95% CI)	*p*-value[b]
Age at diagnosis (years)	0.968 (0.942–0.994)	**0.016**		
Sex (male/female)	1.675 (0.875–3.205)	0.120		
Tumor size (cm)	1.530 (1.308–1.789)	**<0.001**		
Operation method				
Total thyroidectomy	1			
Total thyroidectomy + limited lymph node dissection	1.269 (0.714–2.253)	0.417		
Total thyroidectomy + radical lymph node dissection	2.678 (0.808–8.872)	0.107		
Multicentric vs.single intrathyroid lesions	2.049 (1.069–3.927)	**0.031**		
Serum Tg[c] level after first thyroidectomy and disease free for 6 months (ng/ml)	1.002 (1.001–1.003)	**<0.001**		
I-131 uptake after first operation (%)	1.031 (0.999–1.065)	0.059		
Accumulated I-131 dose after first thyroidectomy (mCi)	1.005 (1.004–1.005)	**<0.001**	1.005 (1.004–1.006)	**<0.001**
Metastasis at diagnosis				
Soft tissue invasion	3.424 (1.934–6.063)	**<0.001**		
Lymph node metastasis	3.112 (1.746–5.544)	**<0.001**	2.532 (1.348–4.757)	**0.004**
Distant metastasis	14.371 (8.100–25.499)	**<0.001**	4.877 (2.606–9.129)	**<0.001**

Abbreviations: PTC: papillary thyroid cancer; I-131: radioactive iodine; HR: hazard ratio; CI: confidence interval.
[a] Cox proportional hazards regression with bold and italics indicating *p* value < 0.05, which was considered statistically significant.
[b] Cox proportional hazard regression analyses were performed with backward elimination (Allen-Cady model) from variables with *p* values < 0.05 on univariate analyses.
[c] The serum thyroglobulin (Tg) level was obtained after first thyroidectomy and duration for disease free at least 6 months.

[1,25]. Besides, lymph node metastasis is associated with a high recurrence rate and a high disease-specific mortality [26]. Our results consistently suggested lymph node metastasis as a major risk factor for recurrence in patients with early-stage PTC. Kluijfhout et al. report that positive incidental lymph nodes are independently associated with recurrence in patients with PTC [27]. Therefore, a neck lymph node survey with palpation and periodical ultrasonography follow-up for detecting tumor recurrence is crucial for patients with PTC, particularly at the early stage.

Our results indicated that male sex was associated with a high recurrence risk in patients with advanced-stage PTC. Consistent with our findings, Lamartina et al. report that male sex is an independent risk factor for tumor recurrence following complete remission achieved with reoperation [28]. Moreover, Lee et al. demonstrate that male sex is a risk factor

Table 3 Analysis of risk factors for recurrence in patients with advanced-stage PTC.

	Univariate		Multivariate	
	HR (95% CI)	*p*-value[a]	HR (95% CI)	*p*-value[b]
Age at diagnosis (years)	1.065 (1.028–1.105)	**0.001**		
Sex (male/female)	2.351 (1.225–4.514)	**0.010**	3.984 (1.912–8.301)	**<0.001**
Tumor size (cm)	1.199 (1.032–1.393)	**0.018**		
Operation method				
Total thyroidectomy	1			
Total thyroidectomy + limited lymph node dissection	0.480 (0.232–0.992)	**0.047**	0.328 (0.152–0.708)	**0.005**
Total thyroidectomy + radical lymph node dissection	1.756 (0.700–4.404)	0.230		
Mulicentric vs.single intrathyroid lesions	1.334 (0.669–2.658)	0.413		
Serum Tg[c] level after first thyroidectomy and disease free for 6 months (ng/ml)	1.005 (1.003–1.008)	**<0.001**	1.009 (1.006–1.012)	**<0.001**
I-131 uptake after first thyroidectomy (%)	1.044 (0.998–1.091)	0.061		
AccumulatedI-131 dose after first thyroidectomy (mCi)	1.003 (1.002–1.004)	**<0.001**	1.002 (1.001–1.003)	**<0.001**
Metastasis at diagnosis				
Soft tissue invasion	1.074 (0.520–2.219)	0.847		
Lymph node metastasis	2.042 (1.070–3.897)	**0.030**		
Distant metastasis	13.335 (6.413–27.730)	**<0.001**	27.265 (10.520–70.662)	**<0.001**

Abbreviations: PTC: papillary thyroid cancer; I-131: radioactive iodine; HR, hazard ratio; CI, confidence interval.
[a] Cox proportional hazards regression with bold and italics indicating *p* value < 0.05, which were considered statistically significant.
[b] Cox proportional hazard regression analyses were performed with backward elimination (Allen-Cady model) from variables with *p* values < 0.05 on univariate analyses.
[c] The serum thyroglobulin (Tg) level was obtained after first thyroidectomy and duration for disease free at least 6 months.

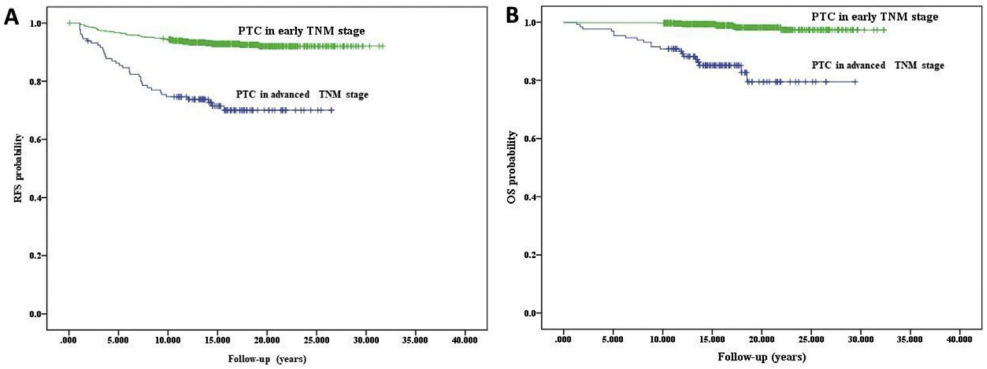

Fig. 2 Recurrence-free and overall survival curves of patients with early- and advanced-stage papillary thyroid cancer. (A) Kaplan–Meier curves for recurrence-free survival (RFS) in patients with early- and advanced-stage PTC. Log-rank test, $p < 0.001$. (B) Kaplan–Meier curves for overall survival (OS) in patients with early- and advanced-stage PTC. Log-rank test, $p < 0.001$.

for distant recurrence [29]. Therefore, intensive monitoring is necessary to discover tumor recurrence, particularly in male patients with advanced-stage PTC.

Our results showed that patients with advanced-stage PTC receiving thyroidectomy and limited lymph node dissection were at a lower risk of recurrence than did those receiving thyroidectomy only. Prophylactic central compartment neck dissection with total thyroidectomy in clinically node-negative PTC uncovers occult lymph node metastasis [30]. Numerous studies have repeatedly reported that central neck lymph node dissection reduced local recurrence and distant metastasis [31–33]. By contrast, central neck lymph node dissection is not suggested in patients with early-stage PTC [34]. Both in early- and advanced-stage, our analyses demonstrated high recurrence rates in patients receiving total thyroidectomy plus radical lymph node dissection; such results were probably due to small patient number and selection bias. However, the statistical outcomes were insignificant. Moreover, a higher recurrence rate encountered in patients with initially more advanced locoregional disease requiring radical lymph node dissection may be predictable to happen; and this may also be the case in the early stage young PTC patients who had advanced locoregional metastases. The same situation was also noted in patients with early-stage PTC, who receiving total thyroidectomy plus limited lymph node dissection. For patients with advanced-stage PTC who only received total thyroidectomy during first thyroid surgery, more intension might be warranted to identify possible early tumor recurrence.

The serum level of Tg after TSH stimulation is the most sensitive test for early detection of PTC recurrence [35]. The serum Tg level, proportional to the volume of thyroid mass [36], could be correlated with the volume of the remnant thyroid tissue after thyroidectomy or PTC recurrence. A high serum Tg level has been suggested to be an indicator of PTC recurrence after thyroidectomy [26,37]. Our study further indicated that elevated levels of serum Tg in patients with PTC, particularly in the advanced stage after thyroidectomy, were associated with recurrence. Frequent assays of stimulated serum Tg levels in patients with advanced-staged PTC are mandatory to monitor tumor recurrence.

Our results revealed that a high accumulated I-131 dose used for thyroid ablation was associated with recurrence. Patients who given relatively high doses of I-131 are often in more serious disease status. Therefore, although higher accumulated doses of radioactive iodine can reduce patient's overall survival [38], due to its slow ablation effect, it might have a limited effect on the reduction of recurrence rate of some more aggressive cancer subtypes such as tall cell type or insula type. We were unable to further confirm the above inference due to incomplete clinicopathological data. This was also one of the main limitations of this study.

Distant metastasis increases not only the recurrence risk but also death risk [1]. Our results consistently demonstrated that distant metastasis was associated with tumor recurrence in patients with PTC at all stages. The 10-year survival rate of patients with recurrent PTC is 70%–85% [14,39,40], whereas that of patients with distant metastatic PTC is 57% [39]. Therefore, intensive follow-up is imperative for patients with distant metastatic PTC for early verification of tumor recurrence.

Our study has some limitations. First, owing to the retrospective nature of the study, skewed results due to selection bias are likely. Second, missing data, such as Tg antibody data, details of operation record and pathological subtypes, may have influenced the analysis. This is also why we could not revise the patient's tumor staging according to the latest version of ATA risk stratification for well differentiated thyroid cancer. Third, treatment characteristics, such as the extent of surgical procedure, dosing of I-131 therapy, and follow-up frequency of each patient, were inconsistent. Nevertheless, our results disclosed that risk factors for tumor recurrence and cancer-specific mortality were different between patients with early- and advanced-stage PTC. In short, the major impact factors on tumor recurrence in early TNM stage were distant metastasis and lymph node metastasis, while in advanced TNM stage were distant metastasis, male gender, total thyroidectomy with limited lymph node dissection, and a high serum Tg level. Although the high cumulative I-131 therapeutic dose is related to recurrence at all stages, the correlation strength is weak. Therefore, strategies to monitor tumor recurrence might be refined according to the TNM

stages of PTC patients unsuitable for classifying recurrence risk by ATA risk stratification.

Conflicts of interest

The authors have no financial or ethical conflicts of interest to report.

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