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Prognosis and prognostic factors of patients with papillary thyroid carcinoma requiring resection of recurrent laryngeal nerve due to carcinoma extension

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Abstract. The recurrent laryngeal nerve (RN) is one of the most common organs to which papillary thyroid carcinoma (PTC) extends. However, the prognosis and prognostic factors for patients with PTC extending to the RN remain unclear. In this study, we investigated this issue in 298 patients who underwent initial and locally curative surgery for PTC requiring RN resection due to carcinoma extension. Preoperative vocal cord paralysis was detected in 179 patients (60.1%), and directly linked to significant extension to other organs, large tumor size, and advanced age. However, it did not have a significant prognostic impact on uni- or multivariate analyses. On multivariate analysis, independent prognostic factors were large node metastasis and advanced age for lymph node recurrence, significant extension to other organs for distant recurrence, and significant extension to other organs, large node metastasis, extranodal tumor extension, and advanced age for carcinoma death, respectively. Most prognostic factors identified in the entire series of patients also had a strong prognostic impact on the subset of patients requiring RN resection, together with significant extension to other organs. Preoperative vocal cord paralysis reflected the aggressive characteristic of PTC to some extent, but did not have a significant prognostic value.

Key words: Papillary thyroid carcinoma, Prognosis, Recurrent laryngeal nerve

PAPILLARY THYROID CARCINOMA (PTC) is the most common thyroid malignancy. Although it is generally indolent, several clinicopathological factors predicting a poorer prognosis in PTC patients have been identified. Among them, extrathyroid extension is prominent. Several studies demonstrated that PTC patients with extrathyroid extension show a significantly poorer prognosis than those without extrathyroid extension, and they were therefore classified as being at high risk [1-5].

The recurrent laryngeal nerve (RN) is one of the most common organs to which PTC extends. The RN can be preserved when carcinoma extension is partial and the preoperative vocal cord function is normal [6]. However, RN resection is required when it is completely involved with the carcinoma and/or vocal cord paralysis is preoperatively detected. When the RN is resected, permanent vocal cord paralysis causing

hoarseness and aspiration occurs, but recovery in phonation is expected if nerve reconstruction is performed by end-to-end anastomosis with other nerves such as the ansa cervicalis [7-9].

We previously showed that PTC extending only to the RN showed a better prognosis than that extending to other posterior organs such as the trachea and esophagus [1]. Furthermore, more recently, we proposed that T4a in the UICC TNM classification [10] can be subdivided into two categories and extension to the RN should be downgraded compared to extension to deeper extension, such as extension to the tracheal and/or esophageal mucosa [11]. In contrast, Sugitani *et al.* demonstrated that symptomatic papillary microcarcinoma (PTC measuring 1 cm or less) patients showing preoperative vocal cord paralysis or large node metastasis were likely to die [12]. Also, for the subset of PTC larger than 1 cm, they regarded PTC having preoperative vocal cord paralysis as being high risk, together with PTC extending to the tracheal and/or esophageal mucosa [4].

To date, however, no studies have been published about the prognosis and prognostic factors regarding

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PTC extending to the RN. In this study, we investigated this issue, including the prognostic significance of preoperative vocal cord paralysis, in 298 PTC patients who underwent surgery and required RN resection due to carcinoma extension in our hospital.

Patients and Methods

When we encounter PTC extending to the RN, we try to preserve it by shaving, if extension is partial and the preoperative vocal cord function is normal. However, when PTC completely involves the RN and/or preoperative vocal cord paralysis is present due to carcinoma extension, we cut the RN and resect it together with primary lesions. Between 1987 and 2006, 334 of 7214 patients (5%) with PTC underwent initial surgery, thyroidectomy with RN resection because of carcinoma extension, in Kuma Hospital. Of these, 298 underwent preoperative vocal cord evaluation by bronchoscopy, fiberoptic laryngoscopy, or direct laryngoscopy, and these patients were enrolled in this study. They consisted of 38 males and 260 females, and their average age was 58.6 years (17-87 years). Patients who underwent locally non-curative surgery, those who had distant metastasis at surgery, those who could not be observed for one year or more after surgery, who did not undergo preoperative examination of vocal cords, and those with coexistent other thyroid malignancies such as anaplastic, follicular, and medullary thyroid carcinomas and malignant lymphoma were excluded from our series. Our series did not include T4b patients in the UICC classification [10].

Total thyroidectomy was performed in 244 patients (82%), and the remaining 54 underwent limited thyroidectomy such as subtotal thyroidectomy and lobectomy with isthmectomy. All patients except for one underwent at least central node dissection. Two hundred and eighty-four patients also underwent modified radical neck dissection (70 bilateral and 214 unilateral). Three underwent dissection also of the upper mediastinal compartment. One hundred and eighty-four patients (61.7%) underwent RN reconstruction using various methods [7-9].

Ninety-eight patients underwent whole body scans using 3-13 mCi of radioactive iodine (RAI) around one month after surgery at our outpatient clinic. RAI therapy or ablation using 30 mCi or more of RAI in our hospital was performed for 12 patients. None of these patients demonstrated an abnormal uptake of RAI

except for the thyroid bed.

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. Postoperative follow-up ranged from 12 to 279 months (median: 116 months). We regarded a patient as showing recurrence when recurrence was apparent on imaging studies such as an ultrasonography, CT scan, roentgenography, and PET-CT and also cytology.

To date, 56 patients (18.8%) have shown recurrence to the regional lymph nodes, and 44 (14.8%) have demonstrated recurrence to distant organs such as the lung, bone, and brain. Twenty-one patients (7.0%) have died of PTC.

Fisher's exact test was employed to compare variables. The Kaplan-Meier curve with a log rank test was adopted for univariate analysis of patients' prognoses. The Cox-hazard regression model was used for multivariate analysis. A *p*-value smaller than 0.05 was considered significant, and that of 0.05 or greater but less than 0.1 was regarded as marginally significant.

Results

Clinical significance of preoperative vocal cord paralysis

Of 298 patients, 179 (60.1%) had vocal cord paralysis on preoperative examination. Table 1 summarizes the relationship between preoperative vocal cord paralysis and various clinicopathological features. In our series, 59 patients (25%) showed significant extension to other organs such as tracheal mucosa, esophageal mucosa, and internal jugular vein. Two patients showed tumor extension only to the RN and jugular vein. Preoperative vocal cord paralysis was directly linked to significant extension to other organs, a tumor size larger than 4 cm, and age 55 years or older that independently showed prognostic significance in the entire series of PTC patients [13-15]. We then analyzed the difference in prognosis of patients with and without preoperative vocal cord paralysis using the Kaplan-Meier method. However, as shown in Table 2, lymph node and distant organ relapse-free survival (RFS) rates and cause-specific survival (CSS) rates of patients with preoperative vocal cord paralysis did not significantly differ from those of patients without preoperative vocal cord paralysis (*p*-values were 0.49862, 0.64731, and 0.66057, respectively). We also analyzed the same issue using a subset of patients, who did not

Table 1 Relationships between preoperative vocal cord paralysis and clinicopathological features (%)

	Paralysis (+)	Paralysis (-)	Total
Significant extension to other organs (+/-)	49(27)/130(73)	10(8)/109(92)	59/239 $p = 0.0006$
Lymph node metastasis ($\geq 3\text{cm}/<3\text{ cm}$)	16(9)/163(91)	14(12)/105(88)	30/268 $p = 0.43659$
Extranodal tumor extension (+/-)	27(15)/152(85)	15(13)/104(87)	42/256 $p = 0.54699$
Tumor size ($> 4\text{cm}/\leq 4\text{cm}$)	41(23)/138(77)	42(34)/77(66)	83/215 $p = 0.01946$
Gender (M/F)	26(15)/153(85)	12(10)/107(90)	38/260 $p = 0.31111$
Age ($\geq 55\text{yrs}/< 55\text{yrs}$)	124(69)/55(31)	68(57)/51(43)	192/106 $p = 0.03216$

Table 2 Survival rates of patients with and without preoperative vocal cord paralysis

	5-year	10-year
Lymph node RFS rates (%)		
Paralysis (+)	88.7 ± 2.4	79.3 ± 3.6
Paralysis (-)	88.0 ± 3.1	77.4 ± 4.3
		$p = 0.49862$
Distant organs RFS rates (%)		
Paralysis (+)	92.3 ± 2.1	83.3 ± 3.4
Paralysis (-)	94.5 ± 2.1	84.7 ± 3.8
		$p = 0.64731$
CSS rates (%)		
Paralysis (+)	96.3 ± 1.4	91.5 ± 2.9
Paralysis (-)	100	92.2 ± 2.6
		$p = 0.66057$

have high-risk features, that is, significant extension to other organs, lymph node 3 cm or larger, and extranodal tumor extension [13-15] (206 patients), but the survival rates did not differ between patients with and without preoperative vocal cord paralysis (p -values were 0.30562, 0.76044, and 0.41513, respectively).

Prognostic factors of PTC patients who underwent RN dissection

In order to identify prognostic factors of patients who underwent RN dissection, we performed multivariate analysis for prognostic factors identified in our previous studies using the entire series of PTC patients, such as age 55 years or older, male gender, tumor size larger than 4 cm, lymph node metastasis 3 cm or larger, and extranodal tumor extension [13-16], together with

preoperative vocal cord paralysis and significant extension to other organs.

Table 3 summarizes the results of multivariate analysis for lymph node recurrence. Age 55 years or older and lymph node metastasis 3 cm or larger were recognized as independent predictors for lymph node recurrence. Male gender has a marginal significance. As shown in Table 4, only significant extension to other organs was an independent prognostic factor for distant recurrence. However, lymph node metastasis 3 cm or larger and age 55 years or older also had a marginal significance for distant recurrence. Furthermore, significant extension to other organs, lymph node metastasis 3 cm or larger, extranodal tumor extension, and age 55 years or older independently reflected a poorer CSS of patients (Table 5). Tumor size larger than 4 cm was also a marginal predictor of carcinoma death. Preoperative vocal cord paralysis also did not have any prognostic impact on multivariate analysis.

Discussion

In this study, we investigated the prognostic factors of PTC patients who required RN resection at surgery because the RN was completely involved in carcinoma and unable to be preserved and/or preoperative vocal cord paralysis was present. We demonstrated that preoperative vocal cord paralysis had a direct relationship with other clinicopathological features such as significant extension to other organs, tumor size larger than 4 cm, and age 55 years or older, which were recognized as having significant prognostic impacts in our previous studies [13-16]. However, preoperative vocal

Table 3 Multivariate analysis for predictors of lymph node recurrence in PTC patients with extension to the RN

	<i>P</i> -values	Relative risks	95% CI
Significant extension to other organs	0.35790	1.35644	0.70806-2.59934
Preoperative vocal cord paralysis	0.33133	1.32229	0.75180-2.32764
Lymph node metastasis ≥ 3 cm	0.03693*	2.32008	1.05236-5.11495
Extranodal tumor extension	0.66098	1.10738	0.70199-1.76877
Tumor size > 4 cm	0.60481	1.16891	0.64724-2.11109
Male gender	0.05371	1.96146	0.98930-3.88896
Age 55 years or older	0.00474*	2.66049	1.34918-5.24631

P*<0.05 CI, confidence intervalTable 4** Multivariate analysis for predictors of distant recurrence in PTC patients with extension to the RN

	<i>P</i> -values	Relative risks	95% CI
Significant extension to other organs	0.00513*	2.69096	1.34541-5.38216
Preoperative vocal cord paralysis	0.67963	1.15676	0.58919-2.25114
Lymph node metastasis ≥ 3 cm	0.08622	2.07424	0.90134-4.77345
Extranodal tumor extension	0.58739	1.13005	0.72662-1.75748
Tumor size > 4 cm	0.55592	1.15168	0.62560-2.39166
Male gender	0.17778	1.71756	0.78210-3.77191
Age 55 years or older	0.07470	1.93611	0.93628-4.00352

P*<0.05 CI, confidence intervalTable 5** Multivariate analysis for predictors of carcinoma death in PTC patients with extension to the RN

	<i>P</i> -values	Relative risks	95% CI
Significant extension to other organs	0.00021*	6.46122	2.40736-17.3415
Preoperative vocal cord paralysis	0.21026	1.85663	0.70523-4.88782
Lymph node metastasis ≥ 3 cm	0.02932*	3.14903	1.12229-8.83586
Extranodal tumor extension	0.03764*	1.81147	1.03452-3.17191
Tumor size > 4 cm	0.09692	2.11582	0.87334-5.12584
Male gender	0.11511	2.54523	0.79622-8.13621
Age 55 years or older	0.00139*	9.31185	2.36995-36.5898

**P*<0.05 CI, confidence interval

cord paralysis did not correlate with patients' prognoses in our series both on uni- and multivariate analyses. Therefore, it is concluded that preoperative vocal cord paralysis has little prognostic impact regarding PTC extending to the RN and requiring RN resection, although it reflects the biologically aggressive characteristic of PTC to some extent, possibly because of the strong invasive character. Sugitani *et al.* defined PTC patients as being high risk when extending to the tracheal and/or esophageal mucosa and RN causing vocal cord paralysis, because 10-year disease-free survival rates and CSS rates of these patients were only 66 and 86%, respectively [4]. The incidence of extrathyroid extension in their patient series was 11%, which was higher than that in our series. In contrast, only 46% of

high risk patients underwent total thyroidectomy and the incidence was much lower than that of our series. This may influence the detection of recurrence especially to distant organs. Furthermore, they analyzed extension to RN and other organs as a single group. The difference in selection criteria and characteristics of patients, and difference in extent of surgery may be reasons for the discrepancy between their study and ours regarding the prognostic significance of preoperative vocal code paralysis.

On multivariate analysis, significant extension to other organs had a strong prognostic value for distant recurrence and carcinoma death of patients. We previously showed that, among patients with PTC extension corresponding to T4a, extension to the tracheal

mucosa, esophageal mucosa, and jugular vein more significantly affected patients' prognoses than extension to superficial organs such as the RN [11]. These were not inconsistent with our findings in this study, and whether or not other significant extension is present is important to evaluate the prognosis of patients with PTC extending to the RN.

As indicated above, some important prognostic factors such as age 55 years or older, large node metastasis 3 cm or larger, extranodal tumor extension, and tumor size larger than 4 cm were identified in our previous studies of entire series of PTC patients [13-16]. Also, in the series of patients requiring RN resection, most of these factors independently had prognostic impacts. A lymph node larger than 3 cm significantly predicted local and distant recurrences and carcinoma death in the entire series [16]. Sugitani *et al.* also showed that such patients were likely to die of PTC [4]. Also, in the subset of patients who underwent RN dissection in this study, large node metastasis significantly predicted lymph node recurrence and carcinoma death.

Extranodal tumor extension independently reflected CSS of patients in this series in the same manner as entire series [13-16]. Patient age was a significant prognostic factor of local and distant recurrence and carcinoma death in the entire series of patients [13-16] and affected lymph node RFS and CSS also in this series. It is therefore suggested that most prognostic factors identified in the entire series of PTC patients also reflected the prognosis of patients with extension to the RN.

In summary, significant extension to other organs is an important factor to predict distant recurrence and carcinoma death of PTC patients with extension to the RN. Furthermore, most prognostic factors identified in the entire series of patients such as advanced age, large node metastasis, and extranodal tumor extension also had prognostic values in PTC requiring RN resection. Preoperative vocal cord paralysis may be a sign of a biologically aggressive characteristic, but it does not have a significant prognostic value in these patients.

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