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# Salvage surgery for structural local recurrence of papillary thyroid cancer: recurrence patterns and surgical outcome

Naoki Otsuki, Hikari Shimoda, Naruhiko Morita, Tatsuya Furukawa, Masanori Teshima, Hirotaka Shinomiya and Ken-ichi Nibu

*Department of Otolaryngology-Head and Neck Surgery, Kobe University Graduate School of Medicine, 7-5-1, Kusunoki-Cho, Chuo-Ku, Kobe 650-0017, Japan*

**Abstract.** To clarify the patterns of the recurrence and to assess the oncological and functional outcomes after salvage surgery for the patients with structural local recurrence of papillary thyroid cancer (PTC), twenty-five patients who underwent salvage surgery for structural local recurrence of PTC were retrospectively reviewed. Structural recurrences were observed in the tracheal lumen in 5 patients, intraluminal or intramuscular esophagus in 5 patients, trachea, and cricoid cartilage in 9 patients, cricoid and thyroid cartilage in 2 patients, intra-lumen of the larynx in 1 patient and soft tissue around thyroid in 3 patients, respectively. Although all local disease was resected with macroscopically negative margin, 10 patients diagnosed as microscopically positive margin. Major surgical complications occurred in 6 patients, including common carotid artery injury ( $n = 1$ ), unintentional pharyngeal or esophageal injury ( $n = 2$ ), recurrent laryngeal nerve paralysis ( $n = 2$ ), and pharyngeal fistula resulting in common carotid artery rupture ( $n = 1$ ), and were successfully managed. During the follow-up periods, 6 patients were alive without disease, 15 patients survived with distant metastases and/or locoregional recurrence, and 4 patients died of the disease. While tracheocutaneous fistula remained in 7 patients, the vocal function was preserved in all patients but one who underwent total laryngectomy. Normal oral intake was retained in all patients. In conclusion, although salvage surgery for structural recurrence of PTC has a high risk of complications, it may be worthwhile when macroscopic curative resection is available. The decision should be made considering various factors including curability, risk of surgical procedure, functional outcome, and life expectancy.

**Key words:** Tracheal invasion, Esophageal invasion, Surgical complication, Postoperative function

**DESPITE** improvements in the surgical and medical treatment of papillary thyroid carcinoma (PTC), subsets of patients suffer from local and regional recurrence after initial surgery [1, 2]. Because local recurrence (LR) of PTC is commonly observed around the recurrent laryngeal nerve, trachea, larynx, esophagus, and carotid artery, intraoperative injury of the cranial nerves and/or great vessels during dissection can lead to lethal complications or decrease long-term quality of life (QOL), particularly by causing voice disorders and dysphagia. Additionally, patients with LR of PTC might display locally advanced primary tumor, multiple cervical LN metastases, and/or distant metastasis [3]. Therefore, the patterns of recurrence are variable, and their managements are often con-

troversial. Because of the low mortality and longer survival of patients with PTC, a balance between curability by surgery and expected postoperative QOL should be considered in the decision-making process for the treatment of LR disease [4]. In this study, we retrospectively reviewed the medical records of patients with LR of PTC to clarify the patterns of recurrence and to assess oncological and functional outcomes after salvage surgery for patients with structural LR of PTC.

## Patients and Methods

Between 2001 and 2018, 398 PTC surgeries were performed at the Kobe University Hospital. Among these procedures, 25 (6.3%) were performed in patients with structural LR. Twenty-one patients underwent initial surgery in other hospitals and were referred to our institution, and the remaining four patients underwent initial surgery in our institution. The characteristics of these 25 patients including age; sex; initial tumor, node, metastasis

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Correspondence to: Naoki Otsuki M.D., Ph.D., Kindai University, Faculty of Medicine, Department of Otolaryngology, 377-2, Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan.  
E-mail: naokies@med.kindai.ac.jp

sis (TNM) staging; duration from initial surgery to LR at the primary site; location of LR; surgical procedures; postoperative complications; pathological diagnosis; and functional and oncological outcomes were obtained from medical records. TNM staging was classified according to the Union for International Cancer Control 8<sup>th</sup> TNM classification [5]. The American Thyroid Association (ATA) risk category was classified according to the 2015 ATA management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer [6]. Vocal and swallowing functions were evaluated *via* video laryngoscopy with speech therapists. Patterns of LR were classified according to the invading structures as follows: (a) intraluminal invasion of the trachea, (b) intraluminal or intramuscular invasion of the esophagus, (c) trachea and cricoid cartilage involvement, (d) cricoid and thyroid cartilage involvement, (e) intraluminal invasion of the larynx, and (f) soft tissue around the thyroid.

Ethical approval was obtained from the Ethics Committee of the Kobe University Hospital (#180101) prior to enrolment. Informed consent was obtained from all individual participants included in this study.

### Statistical analysis

Survival time was determined as the number of days from the date of initial surgery or salvage surgery until an event (death for overall survival and death from PTC for disease-specific survival). All statistical analyses were performed using the JMP software package (version 9; SAS; Cary, NC, USA).

## Results

The patients' characteristics and their previous treatments are summarized in Tables 1 and 2. The initial stages of local disease were classified as T4a in 19 (83%) patients, T3 in 3 (13%) patients, and T2 in 1 (4%) patient. Distant metastasis was observed in two patients at the initial surgery. Shaving, window resection of the tracheal wall, and end-to-end anastomosis of the trachea were performed in five, seven, and three patients, respectively. Esophageal muscle resection and recurrent nerve laryngeal resection were also performed in 11 and 12 patients, respectively. Radioactive iodine treatment (RAI) was employed after total thyroidectomy in 10 (40%) patients. External beam radiotherapy was performed in one patient with bone metastasis.

The clinical course and recurrent/persistent tumor locations are listed in Table 3. LR was detected at times ranging from 21 to 186 months (median 72 months) after the initial surgery. LR was mostly identified by radiographic imaging such as computed tomography (CT) and positron emission tomography (PET) ( $n = 14$ ) and by an

**Table 1** Clinical features, initial stage and treatment of 25 patients with locally recurrent PTC

	<i>n</i> = 25	%
Gender		
Female	17	68
Male	8	32
Age		
<55 y	4	16
≥55 y	21	84
cT stage*	( <i>n</i> = 23)	
T1	0	0
T2	1	4
T3	3	13
T4a	19	83
cN stage*	( <i>n</i> = 23)	
N0	8	35
N1a	4	17
N1b	11	48
cM stage*	( <i>n</i> = 23)	
M0	21	91
M1	2	9
UICC stage*	( <i>n</i> = 23)	
Stage I	5	22
Stage II	2	9
Stage III	14	61
Stage IV	2	9
ATA risk group*	( <i>n</i> = 23)	
Low	2	9
Intermediate	3	13
High	18	78
Thyroid surgery		
Hemithyroidectomy	7	28
Subtotal thyroidectomy	2	8
Total thyroidectomy	16	64
Neck dissection		
Central	10	40
Central + ipsi. Lateral	12	48
Central + bil. Lateral	3	12
Tracheal treatment		
None	10	40
Shaving	5	20
Window resection	7	28
Anastomosis	3	12
Esophageal treatment*	( <i>n</i> = 24)	
None	13	54
Muscle resection	11	46
Recurrent nerve		
Preservation	11	44
Resection	14	56
Adjuvant radiotherapy		
None	15	60
Radioactive iodine (RAI)	10	40

\* Clinical data of initial treatment was not obtained in some patients.

**Table 2** Clinical features and initial treatment of 25 patients with locally recurrent PTC

Case	Initial Status			Initial Surgery					RAI after Surgery
	Age/Sex	TNM Stage		Thyroid	Neck Dissection	Trachea	Esophagus	RLN	
1	67 F	T4aN1bM0	III	ST	CND + ipsi. LND	S	—	Res	—
2	67 F	T4aN1bM0	III	TT	CND + ipsi. LND	A	—	Pre	—
*3	76 F	T4aN1aM0	III	HT	CND	S	—	Res	—
4	66 M	T4aN0M0	III	HT	CND	—	—	Res	—
5	65 M	NA		HT	CND + ipsi. LND	—	—	Res	—
6	51 F	T4aN1aM0	I	TT	CND	—	M	Res	—
7	66 F	T4aN1bM0	III	HT	CND + ipsi. LND	—	M	Res	+
8	60 F	T4aN0M0	III	TT	CND + bil. LND	A	M	Pre	—
9	64 F	T4aN1aM0	III	TT	CND	W	M	Res	+
10	50 F	T4aN1bM0	I	TT	CND + ipsi. LND	S	M	Res	+
11	64 F	NA		TT	CND	—	M	Pre	+
12	60 F	T4aN1bM0	III	TT	CND + bil. LND	W	M	Pre	—
*13	47 M	T4aN1bM0	I	TT	CND	W	M	Res	+
*14	53 M	T4aN1bM0	I	TT	CND + ipsi. LND	S	M	Res	—
15	60 F	T3N1bM0	II	TT	CND + ipsi. LND	—	—	Pre	+
16	68 M	T4aN0M0	III	TT	CND + bil. LND	W	M	Pre	—
17	70 M	T4aN1bM0	III	TT	CND + ipsi. LND	W	—	Res	+
18	63 F	T4aN0M0	III	HT	CND	—	—	Res	—
19	72 F	T4aN0M0	III	HT	CND	S	—	Res	—
20	65 F	T2N0M0	I	TT	CND + ipsi. LND	—	—	Pre	—
21	69 F	T4aN1aM0	III	TT	CND + ipsi. LND	W	M	Res	+
22	72 M	T4aN0M1	IV	HT	CND	A	NA	NA	—
*23	57 M	T3N1bM1	IV	TT	CND + ipsi. LND	—	—	Pre	+
24	75 F	T3N0M0	II	ST	CND	—	—	Pre	—
25	60 F	T4aN1bM0	III	TT	CND + ipsi. LND	W	—	Pre	+

\* Initial surgery in our institution

HT, Hemithyroidectomy; ST, Subtotal thyroidectomy; TT, Total thyroidectomy; CND, Central neck dissection; LND, Lateral neck dissection; ipsi, Ipsilateral; bil, bilateral; W, Window resection of trachea; S, shaving of tracheal wall; A, End-to-end anastomosis; M, Muscle resection; NA, not available; Res, Resection; Rec, Reconstruction; Pre, Preservation; EBRT, Extra beam radiotherapy

increase of serum thyroglobulin (Tg) levels in two patients. LR was found in the luminal invasion of the trachea in five patients, in the intraluminal or intramuscular invasion of the esophagus in five patients, through trachea and cricoid cartilage involvement in nine patients, through cricoid and thyroid cartilage involvement in two patients, in the intraluminal invasion of the larynx in one patient, and in the soft tissue around the thyroid bed in three patients. The first relapse was observed at the primary site alone in 12 patients, at the primary site and regional lymph node in three patients, at the primary site and distant metastasis in nine patients, and at the primary site, regional lymph node, and distant metastasis in one patient.

The surgical treatments and oncological/functional outcomes of the 25 patients are summarized in Table 4. Recurrences were frequently identified around the cricoid, trachea, and esophagus, and 14 patients required window resection of the trachea. One patient (No. 9) required pharyngeal and esophageal mucosal resection due to wide submucosal invasion in the esophagus (Fig. 1a, b). Two patients (No. 8 and 10) underwent partial or subtotal esophagectomy due to intraluminal invasion (Fig. 1c, d). Total laryngectomy was performed in one patient with severe airway obstruction due to advanced intraluminal laryngeal invasion. Although all structural local diseases were resected with macroscopically

**Table 3** Clinical course and tumor location of 25 patients with locally recurrent PTC

Case	Age/Sex at recurrence	Methods of detection	Months after Initial surgery	Local recurrence Locations	Type	Metastatic recurrence Sites
1	70 F	CT	29	Tra	a	LM
2	82 F	Tg, CT	186	Tra	a	LM
*3	82 F	CT	54	Tra	a	—
4	72 M	CT	78	Tra	a	LM
5	72 M	CT	86	Tra	a	—
6	61 F	US	132	Tra + Eso	b	—
7	71 F	CT	54	Tra + Eso	b	LM
8	75 F	Symptom	168	Eso(m)	b	LNM
9	71 F	CT	86	Eso	b	LM
10	57 F	CT	73	Eso(m), Tra	b	LM
11	67 F	Symptom	36	Cri	c	—
12	67 F	Symptom	87	Tra + Cri	c	—
*13	52 M	CT	51	Tra + Cri	c	—
*14	56 M	CT	32	Tra + Cri	c	—
15	62 F	CT	15	Tra	c	LNM
16	71 M	Symptom	40	Tra	c	—
17	75 M	Tg, PET	54	Tra	c	—
18	69 F	US	72	Cri	c	LNM, LM
19	82 F	Symptom	113	Tra + Cri	c	—
20	77 F	PET-CT	156	Cri + Thy	d	—
21	72 F	CT	34	Cri + Thy	d	—
22	84 M	Symptom	146	Tra	e	LM (BM)
*23	59 M	PET-CT	21	Soft	f	LM (BM)
24	80 F	Symptom	63	Soft	f	LNM
25	72 F	CT	135	Soft	f	LM

\* Initial surgery in our institution

CT, Computed Tomography; US, Ultrasonography; PET, Positron emission tomography; Tg, Thyroglobulin; Tra, Trachea; Cri, Cricoid cartilage; Thy, Thyroid cartilage; Eso, Esophagus; Eso(m), Esophageal muscle; LM, Lung metastasis; LNM, Lymph node metastasis; BM, Bone metastasis; Parentheses, Persistent disease

Type of local recurrence were classified according to the invading structures as follows: (a) intra-tracheal invasion, (b) intraluminal or intramuscular invasion of esophagus (c) trachea and cricoid cartilage involvement, (d) cricoid and thyroid cartilage involvement, (e) intraluminal invasion of larynx, and (f) soft tissue around thyroid.

negative margins, 10 patients were diagnosed with microscopically positive surgical margins. Major surgical complications occurred in six patients, including common carotid artery injury ( $n = 1$ ), unintentional pharyngeal or esophageal injury ( $n = 2$ ), recurrent laryngeal nerve paralysis ( $n = 2$ ), and pharyngeal fistula resulting in common carotid artery rupture ( $n = 1$ ). Fortunately, all these major complications were successfully salvaged by additional surgical procedures without serious permanent damage. Voice function was lost in one patient who underwent a total laryngectomy. Although a trachea-

cutaneous fistula developed in seven patients, their voice function was preserved, and none of the 24 patients experienced difficulties with daily conversation, including these seven patients. All patients had a normal diet and consumed food orally. During the follow-up period after the second surgery, LR occurred again in nine patients who had resected tumors with microscopically positive margins. Distant metastasis was newly identified in seven patients. As a result, six patients were free from disease, 15 patients were alive with disease, and four patients died of the disease. These four patients died

**Table 4** Treatment and Outcome of 25 patients with locally recurrent PTC

Case	Salvage Surgery	Microscopic Surgical margin	Surgical Complications	RAI after Surgery	2nd Relapse	Outcome	Persistent Disease	Follow-up (Months)
1	S	+	—	—	LNM	AWD	Local, DM	106
2	W	—	—	—	DM	AWD	DM	12
*3	CTT + W	+	—	—	Local, DM	DOD	Local, DM	120
4	CTT + W	—	—	—	—	AWD	DM	76
5	CTT + W*	+	VC paralysis	—	—	NED	—	12
6	W	—	—	—	—	NED	—	96
7	CTT + S*	+	Esophageal injury	—	Local	AWD	Local	49
8	E	—	—	—	—	NED	—	67
9	E	—	CCA injury	—	—	AWD	DM	12
10	W, E	—	Pharyngeal fistula CCA rupture	+	—	AWD	DM	12
11	S	—	—	—	LNM	AWD	LNM	42
12	W*	+	—	—	Local, LNM	AWD	Local, DM	82
*13	W	+	—	—	Local, DM	AWD	Local, DM	87
*14	W	+	—	—	Local, DM	DOD	Local, DM	72
15	W	+	—	+	LNM, DM	DOD	Local, DM	63
16	W*	+	—	+	Local, DM	AWD	Local, DM	47
17	W	—	—	—	DM	AWD	DM	33
18	CTT + W*	—	—	—	—	AWD	DM	25
19	CTT + W*	—	—	—	—	NED	—	48
20	S	—	—	—	—	NED	—	9
21	W*	+	Hypopharyngeal injury	—	Local, DM	DOD	DM	79
22	CTT + TL	—	—	—	—	AWD	DM	30
*23	S	—	VC paralysis	+	Local, DM	AWD	DM	6
24	S	—	—	—	MLNM	NED	—	28
25	S	—	—	—	—	AWD	DM	12

\* Initial surgery in our institution

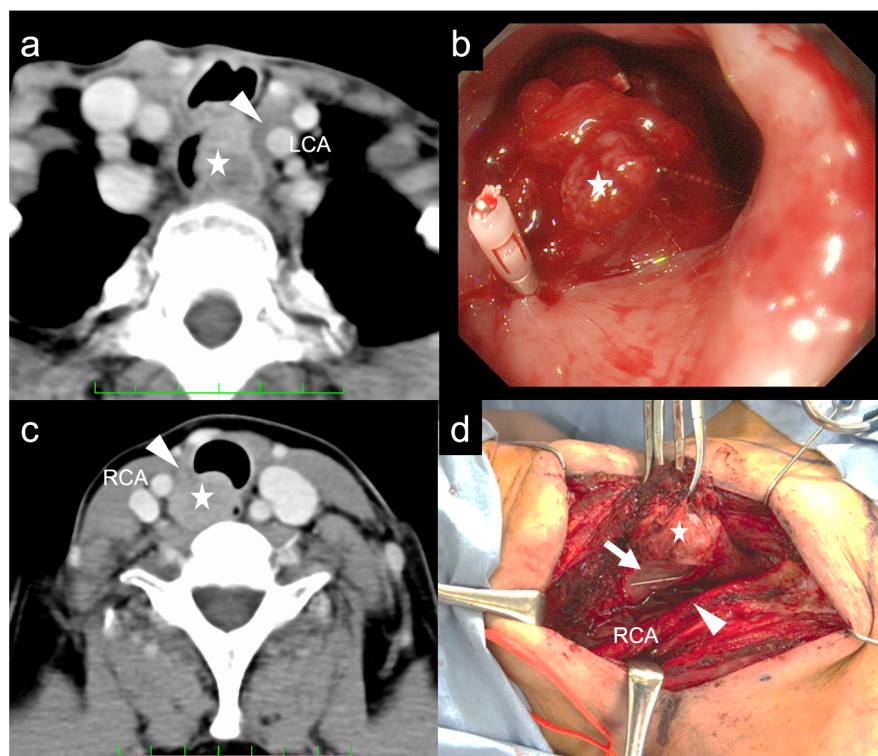
CTT, Complete total thyroidectomy; W, Window resection of trachea; S, shaving of tracheal wall; W\* or S\*, tracheocutaneous fistula remained; E, Esophagectomy; TL, Total Laryngectomy; VC, Vocal cord; RAI, Radioactive iodine; DM, Distant metastasis; LNM, Lymph node metastasis; MLNM, Mediastinum lymph node metastasis; AWD, Alive with disease; DOD, Death of disease; NED, No evidence disease

from lung metastases, and bone metastasis developed in one patient (Table 4). The disease-specific survival (DSS) was 100% at five years and 82% at ten years from the time of the initial surgery (Fig. 2a). The DSS was 100% at five years and 66% at ten years from the time of the salvage surgery for LR (Fig. 2b). Among the four patients who died of disease, LR was detected within five years after the initial surgery.

## Discussion

PTC has an excellent prognosis, as evidenced by the extremely low 10-year disease-specific mortality rate reported in a meta-analysis of 23 studies [7]. Although the recurrence rate is relatively higher, ranging from 1.4% to 35%, the prognosis of recurrent or persistent disease is usually favorable [8-10]. The timing of recurrence varies widely. Mazzaferri and Jhiang reported that 43.3% of recurrences were identified after more than five years of follow-up, and 19.3% were detected more than





**Fig. 1** Representative cases with tracheal and esophageal invasion (Case 9 and 10)

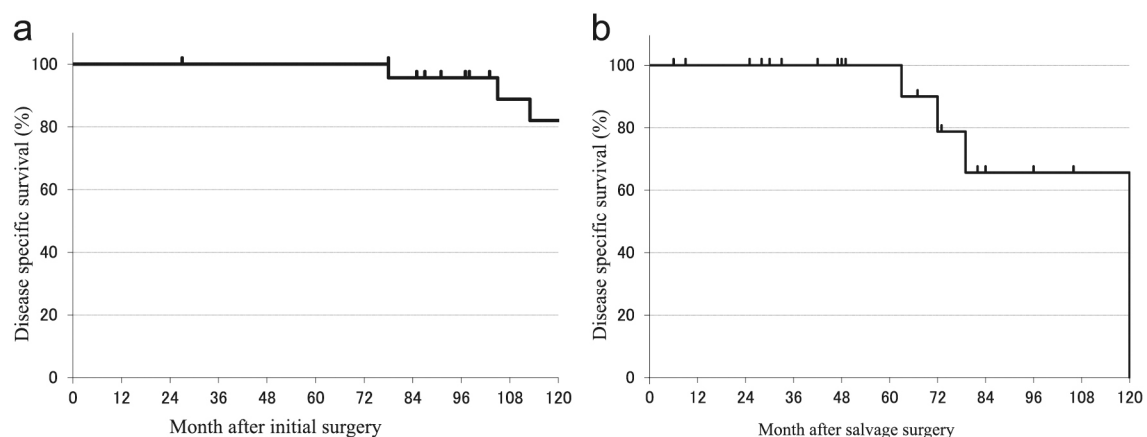
a, b: Contrast enhanced CT (CE-CT) and endoscopic finding of Case 9.

CE-CT revealed intra-esophageal progression of recurrent tumor (white star) (c). Scar tissue area (arrow head) was observed around left common carotid artery (LCA). Endoscopic examination revealed intraluminal tumor (white star) invasion to cervical esophagus (d). A white marking clip indicated oral side end of tumor.

c, d: Contrast enhanced CT (CE-CT) and intraoperative finding of Case 10.

CE-CT revealed trachea involvement of recurrent tumor (a). Recurrent tumor (white star) and scar tissue (arrow head) was observed in left side of right common carotid artery (RCA) and muscular layer of esophageal wall.

In intraoperative finding, defect of esophageal and hypopharyngeal wall were observed (white arrow) (b). Adventitia of right common carotid artery (RCA) was partly removed (arrow head).



**Fig. 2** Kaplan-Meier curves for the cumulative probability of DSS among 25 patients with salvage surgery

Survival time from initial surgery (Fig. 2a) and survival time from salvage surgery for LR (Fig. 2b)

10 years after the initial surgery [11]. In a retrospective study that spanned nearly five decades by Stojadinovic *et al.*, the median time to recurrence after treatment of the

primary tumor was 2.6 years, and 35% of patients had disease recurrence more than five years after resection [12]. In this study, LR was detected a median of 72

months after the initial surgery, and the DSS was excellent five years after the salvage surgery. Additionally, 79% of all patients with LR had high-risk features according to the ATA guidelines [6], and all patients who died of the disease had LR within five years after the initial surgery. Our findings from this retrospective analysis support the practice of life-long surveillance for all high-risk patients and more aggressive treatment for patients who locally relapse within five years after initial surgery.

Recurrence rarely displays subjective symptoms and is often identified *via* follow-up imaging rather than through a patient's complaints. Recently, the widespread use of neck ultrasonography and PET/CT has caused a paradigm shift in the detection of recurrent disease [13]. PET/CT is useful in the assessment of patients who have recurrent tumors that are not demonstrable with other imaging modalities; conversely, <sup>131</sup>I whole body scanning has become less important [14]. In fact, in this study, LR was discovered by subjective symptoms in only 7 of 25 patients. In the remaining 18 patients, LR was discovered by follow-up imaging modalities: neck ultrasonography (US), CT, and PET scans in 2, 13, and 3 patients, respectively. Among them, two patients underwent CT or PET scans triggered by elevated serum Tg levels.

One of the most critical sites of soft tissue extension that must be handled appropriately at the initial surgery is the thyrotracheal suspensory ligament, or recurrent laryngeal nerve insertion point. Involvement in this area can result in residual recurrence not only with recurrent nerve palsy, but also with cricoid and tracheal invasion. In this study, involvement with the trachea and the cricoid cartilage was the most frequent site of recurrence, and the preservation of functional recurrent nerve palsy in this area may result in resection with microscopically positive margins. In salvage surgery, a sharp resection must be made between the scar tissue surrounding the recurrent tumor and the recurrent laryngeal nerve, cricoid, and trachea by skilled hands. Other critical sites of LR are around the trachea and/or esophagus after the shaving procedure of the trachea and esophageal muscle layer resection during the initial surgery. Structural recurrences at these sites are eligible for treatment, even if asymptomatic, because they may cause airway obstruction and/or dysphagia in the near future. In salvage surgery for this situation, creation of a tracheocutaneous fistula or esophageal reconstruction are necessary following a full thickness resection of the trachea or esophagus.

Surgery for recurrent PTC can be high-risk and may lead to a decline in QOL after surgical resection. The surgeon is also presented with the dilemma that preserving function can result in a greater chance of LR.

Because gross residual disease increases the mortality rate and often requires reoperation due to LR, complete extirpation of all gross disease with negative margins or microscopic positive margins should be achieved [15]. In this study, LR occurred again in nine patients who had resected tumors with microscopically positive margins. Of note, four of these patients died of the disease with newly identified distant metastasis. Therefore, functional preservation is also important in excision of locally recurrent lesions, but it may be necessary for the surgeon to perform careful resection with intraoperative rapid diagnosis using frozen section to avoid microscopic residuals.

In surgery for locally recurrent cases, trachea and/or esophageal resection in conjunction with adventitia resection of the carotid artery might be required to secure a surgical margin for adhesion due to scarring, which increases the frequency of postoperative complications [16, 17]. In fact, major surgical complications including common carotid artery injury, unintentional pharyngeal or esophageal injury, recurrent laryngeal nerve paralysis, and pharyngeal fistula occurred in six patients. However, these complications were successfully managed with favorable oncological and functional outcomes in our series. Taken together, we believe that complete surgical resection with macroscopically negative margins for recurrence disease around the trachea, larynx, and esophagus should be considered to prevent possible complications.

Surgical indications for LR should be carefully considered based on the patient's age, performance status, time to recurrence, site of recurrence, etc., and the treatment plan discussion should include watchful waiting, RAI, external beam radiation (EBRT), and the administration of molecular targeted drugs now available for treatments.

This study has several limitations. First, we included a relatively small number of patients with LR of PTC who were treated with surgical resection. Therefore, we could not compare the oncological outcomes with those of patients who received other treatment options including watchful observation, RAI, EBRT, and molecular target therapy. Second, the retrospective nature of this analysis introduces some selection biases. We believe that a future study should include a larger patient population combined with greater uniformity of the treatment approach, which will lead to more robust observations. Lastly, the mean overall follow-up of approximately five years might be considered relatively short in the setting of differentiated thyroid cancer, and thus we believe that long-term observation is necessary.



## Conclusions

Although salvage surgeries for the structural recurrence of PTC have a high risk of complications and may occasionally decrease the patients' QOL, major complications were successfully managed, and favorable oncological and functional outcomes were obtained in our series. Curability, risk of surgical procedure, functional outcome, and life expectancy should all be considered

when making decisions regarding treatment for PTC.

## Statement

**Author Contributions:** All authors had full access to all the data in this study and the accuracy of the data analysis.

**Conflicts of Interest:** All authors have no conflict of interests to be disclosed on this work.

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