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HEAD AND NECK

Prognostic factors of locally invasive well-differentiated thyroid carcinoma involving the trachea

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Abstract To report our experience with tracheal invasive thyroid carcinoma with emphasis on clinical characteristics and treatment modalities, and to identify the prognostic factors for tracheal invasive thyroid carcinoma. Totally 1919 patients underwent surgical extirpation of thyroid cancer from 1990 to 2010. Among them, 65 patients had well-differentiated thyroid cancer with tracheal invasion. The incidence was higher in male and older patients. Patients were treated with tracheal shave excision ($n = 18$), tracheal resection ($n = 37$) and total laryngectomy ($n = 10$). Locoregional recurrence occurred in 39 patients, and metastasis occurred in 25 patients. Simultaneous involvement of the trachea and the esophagus was associated with locoregional recurrence ($p = 0.039$) in univariate analysis, but not confirmed by multivariate analysis. There was significant difference in the disease-specific survival (DSS) according to laryngeal involvement ($p = 0.002$). All the patient in the shave excision group survived until the end of the study period. Although it is categorized in same classification of T4a, simultaneous involvement of the trachea and the esophagus showed higher locoregional recurrence and laryngeal involvement showed lower DSS. Despite the invasion of thyroid cancer into the adjacent aerodigestive tract, many patients showed long survival when they underwent appropriate surgery.

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Introduction

Well-differentiated thyroid carcinoma is well known for its excellent overall prognosis and survival. Despite the close proximity of the thyroid gland to upper aerodigestive tract (ADT) structures, the incidence of laryngotracheal and esophageal invasion by well-differentiated thyroid carcinoma ranges from 1 to 16 % [1–4]. When invasion into the ADT occurs, risk of morbidity and mortality can increase. Extrathyroidal extension has been well recognized as a poor prognostic indicator, with 10-year overall survival rates dropping to 45 % in patients with extrathyroidal extension in contrast to 91 % in those with well-encapsulated tumors [5].

According to the current classification systems of thyroid cancer by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC), invasive thyroid cancer is classified as potentially resectable (T4a, e.g., invasion of the airway, esophagus, or muscles) or usually not resectable (T4b, e.g., invasion of large arteries or the prevertebral fascia) [6–9]. However, a recent study proposed that a further subdivision of the T4a stage based on prognostic consideration is needed [11]. The authors recommended a classification of the stepwise process of ADT invasion based on three-dimensional assessment.

For tumors that invade the upper ADT, current treatment guidelines recommend surgical resection when technically feasible [9, 10]. However, radical resection of a gross tumor is not always feasible, and postoperative morbidity

can be significant in cases of ADT invasion. Furthermore, thyroid cancer has a relatively indolent course in most patients even those with extrathyroidal invasion, and adjuvant therapies such as radioactive iodine or external radiation can be effective. For these reasons, there have been considerable controversies regarding the extent of surgery. In one study, there was no statistically significant difference in survival between patients treated with laryngotracheal resection and those in whom the tumor was only shaved off from the ADT [12]. However, a recent study observed a lower local control rate in patients treated with close or positive microscopic margins versus free margins [13].

We report our experience with tracheal invasive thyroid carcinoma with emphasis on clinical characteristics and treatment modalities. We attempted to identify the prognostic factors for tracheal invasive thyroid carcinoma.

Materials and methods

We performed a retrospective single-center review of patient files from January 1990 through July 2010. This study was approved by our institutional review board. During this period, 1919 patients with thyroid cancer underwent operations at the Department of Otorhinolaryngology-Head and Neck Surgery, Seoul National University Hospital. Among the 1919 patients, 65 patients (3.39 %) underwent operations for well-differentiated thyroid carcinoma with tracheal invasion. Anaplastic and medullary thyroid carcinomas were excluded from this study.

All the patients who were suspected to have local invasion to adjacent organs were preoperatively evaluated with ultrasonography (USG) and or computed tomography (CT). Bronchoscopic examination was performed in some patients with suspicion of having tracheal intralumimal involvement of thyroid cancer. The extent of invasion was also assessed by intraoperative and pathologic findings. The mean follow-up duration was 91.4 months (range, 4–235 months).

The surgical treatments for tracheal invasive thyroid cancer were as follows: shave excision of the trachea, window resection of the trachea, tracheal resection with end-to-end anastomosis (TREE) and laryngectomy. Shave excision was defined as the removal of all gross tumor tissue by a partial thickness resection of the ADT wall. Tracheal window resection was defined as tumor resection and closure of the small defect. The defects were closed primarily with the strap or sternocleidomastoid muscle depending on the site and size; the anterior defect was converted into a tracheostomy in some cases. TREE was indicated for tumors invading the majority of the anterolateral tracheal wall. For these patients, segmental resection for complete removal and primary end-to-end anastomosis were performed. Finally, laryngectomy was indicated for aggressive disease involving the laryngeal lumen or cricothyroid cartilage, or for advanced tumors with a nonfunctional larynx [14]. The type of resection was chosen based on the extent of ADT invasion, tumor type and stage, and patient's general physical condition. The surgical goal was to achieve microscopically clear resection margins based on intraoperative frozen sections, without setting targets for the minimum distance between the tumor and the surgical margin. Of 65 patients, 18 underwent shave excision, 37 underwent tracheal resection including window resection and TREE, and 10 patients underwent laryngectomy. All patients underwent or had already undergone complete therapeutic central and lateral neck dissection if the lymph nodes were present. All received radioactive iodide and/or external radiotherapy.

Locoregional recurrence of thyroid cancer after treatment was the primary end-point used to identify the prognostic significance of each patient or tumor-related variable. Additional end-points were distant metastasis, or disease-specific survival (DSS) rate. Several clinicopathologic factors such as sex, age, tumor size, involved organs, and presence of lateral lymph node metastasis and intraluminal involvement were subjected to univariate analysis using the Mann–Whitney U test, Fischer's exact test and Chi square test. For evaluation of survivals, the Kaplan–Meier method was used and the statistical significance of differences was evaluated using the log-rank test. A binary logistic regression test was used for multivariate analysis of variables that were statistically significant on univariate analysis. We regarded statistical significance as a p value less than 0.05. All statistical analyses were conducted using the SPSS software, version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

General patient characteristics

Table 1 summarizes the demographic and pathologic data of all patients with thyroid cancer included in this study. After dividing the groups according to the presence or absence of clinical tracheal invasion, patients with tracheal invasion were found to be significantly older than those without invasion (60.5 versus 52.4 years, $p < 0.001$). In addition, there were significantly more male patients in the tracheal invasion group ($p = 0.018$). Papillary thyroid carcinoma was the most common pathology in each group, but anaplastic and medullary thyroid carcinoma was frequently seen in the tracheal invasion group.

Among the 65 patients with well-differentiated thyroid cancer with tracheal invasion, the most common chief

Table 1 General characteristics of patients who had aerodigestive tract (ADT) invasion of thyroid carcinoma

	Tracheal invasion		*p* value
	Absent	Present	
Age (years)	52.4 ± 21.5	60.5 ± 10.6	<0.001
Sex (male:female)	470:1379	27:43	0.018
Pathology (%)			
PTC	1762 (95.3)	64 (91.5)	
FTC	65 (3.5)	1 (1.4)	
MTC	11 (0.6)	1 (1.4)	
Anaplastic	11 (0.6)	4 (5.7)	

PTC papillary thyroid carcinoma, *FTC* follicular thyroid carcinoma, *MTC* medullary thyroid carcinoma

complaints requiring a hospital visit were hoarseness (40 %), neck mass (36.9 %), dyspnea (35.4 %), hemoptysis (7.7 %), and dysphagia (4.6 %). Eight patients (12.3 %) were incidentally found to have asymptomatic thyroid cancer. In a comparison of chief complaints according to involved structures such as the esophagus, larynx, and intraluminal mucosa of the trachea, dyspnea was the most common symptom when the tumor involved the larynx. Hemoptysis was the most common symptom in patients with involvement of intraluminal mucosa of the trachea. All patients who showed no symptoms before diagnosis were found to have esophageal involvement intraoperatively.

Extent of invasion vs prognosis

Table 2 lists the demographic findings according to the type of surgical management. We divided the treatments into three groups: shave excision, tracheal resection (wedge tracheal excision and TREE), and laryngectomy. The mean patient ages were similar in all groups, but there were more male patients in the radical resection group than in the shave excision group. The average longest tumor diameter was 2.4 cm in the shave excision group, 3.2 cm in the tracheal resection group, and 4.9 cm in the laryngectomy group. The presence of lateral cervical lymph node metastasis was more frequent in the radical resection group than in the shave excision group. With the exception of one patient, all patients who underwent laryngectomy had a history of previous thyroid cancer surgery.

The extent of invasion was determined according to the involved structures (larynx, trachea, and esophagus), and the depth of wall invasion (extraluminal or intraluminal of the trachea). In addition to the trachea, the tumor was found to involve the larynx in 11 patients, and the esophagus, in 10 patients. Two patients with laryngeal invasion were treated with tracheal/partial laryngeal resection only because their tumors only contacted the larynx; however, most of them (9 of 11 patients) underwent laryngectomy to eradicate the tumor. Among the patients with esophageal invasion, most of them (8 of 10) underwent tracheal resection; one was treated with only shave excision, and the other was treated with laryngectomy. Thirty-four patients had intraluminal involvement of organs (esophagus or trachea), and none of them underwent shave excision of the ADT.

In total, 39 patients (60.0 %) developed local recurrence after treatment, and the average interval between the curative operation and recurrence was 47.6 months. We divided patients into non-recurrence and recurrence groups, and evaluated the effect of the associated factors on the presence of locoregional recurrence (Table 3). None of the subjects variables such as age, sex, and tumor size showed statistically significant differences according to recurrence. The

Table 2 The demographic findings according to types of surgical management

	Shave excision ($N = 18$)	Radical resection	
		Tracheal resection ($N = 37$)	Laryngectomy ($N = 10$)
Age (mean ± SD, years)	59.7 ± 8.5	60.8 ± 9.5	61.0 ± 17.4
Sex (male:female)	6:12	16:21	4:6
Median follow-up(range; months)	70.1(13–192)	97.7(7–235)	106.4(15–219)
Tumor size (mean ± SD, cm)	2.4 ± 1.8	3.2 ± 1.4	4.9 ± 2.4
Lateral cervical node (N1b)	5	14	6
Previous thyroid operation history	7	21	9
Involved organs			
Larynx	0 (0 %)	2 (5.4 %)	9 (90.0 %)
Esophagus	1 (5.6 %)	8 (21.6 %)	1 (10.0 %)
Depth of invasion; Extraluminal/Intraluminal	18/0	10/27	3/7

Table 3 Factors associated with locoregional recurrence in the patients with tracheal invasive thyroid carcinoma

	Recurrence (−) ($N = 26$)	Recurrence (+) ($N = 39$)	p value
Age	62.0 ± 13.0	59.5 ± 8.8	0.347
Sex (male:female)	9:17	17:22	0.606
Tumor size (cm)	2.9 ± 2.0	3.4 ± 1.7	0.344
Lateral cervical node (N1b)	6 (23.1 %)	19 (48.7 %)	0.058
History of previous thyroid operation	10 (38.5 %)	27 (69.2 %)	0.021
Involved organs			
Larynx	3 (11.5 %)	8 (20.5 %)	0.503
Esophagus	1 (3.8 %)	9 (23.1%)	0.039
Intraluminal involvement	11 (42.3 %)	24 (61.5 %)	0.139
Shaving operation vs Radical operation	9:17	9:30	0.399

Table 4 Results of multivariate analysis for prognostic variables of locoregional recurrence in patients with well-differentiated thyroid cancer (based on 39 recurred patients)

	Multivariate Analysis (Cox proportional hazards regression)			
	OR	95 % CI		p value
		Lower	Upper	
Lateral cervical node (N1b) (vs none)	0.393	0.117	1.315	0.130
History of previous thyroid operation (vs none)	0.473	0.147	1.522	0.209
Involved organs				
Esophagus (vs none)	0.252	0.026	2.471	0.237
Intraluminal involvement (vs none)	0.540	0.167	1.743	0.302

OR odds ratio, *CI* confidence interval

presence of lateral cervical lymph node metastasis seemed to be more closely associated with the recurrence group, but with no statistical significance ($p = 0.058$). The treatment modalities (e.g., shave excision or radical excision) also showed no significant differences with respect to recurrence. Interestingly, patients with a history of previous thyroid cancer surgery tended to exhibit recurrence more frequently than did patients who underwent primary treatment ($p = 0.021$). In the evaluation of recurrence according to the involved organs, esophageal invasion showed significantly higher recurrence ($p = 0.039$). The presence of intraluminal involvement and laryngeal involvement showed no significant differences in recurrence.

Subsequent multivariate analysis included presence of previous thyroid operation history, lateral cervical node, esophageal invasion, and intraluminal involvement (Table 4). In multivariate analysis, in contrast to univariate analysis, there was nothing showed statistically significant differences according to presence of locoregional recurrence.

Twenty-five patients (38.5 %) developed distant metastasis. The lung (76.0 %) was the most common site of metastasis, followed by the bone, mediastinal lymph nodes, pelvic area, brain, and liver. Table 5 shows the factors associated with distant metastasis. As the result of local recurrence, a history of thyroid cancer surgery and the presence of lateral cervical lymph node metastasis were also associated with distant metastasis rate in statistically significance ($p = 0.020$, $p = 0.014$). In addition, the radical treatment group showed a significantly higher metastasis rate than did the shave excision group ($p = 0.005$). There were no differences in distant metastasis according to the involved organs or intraluminal involvement. In multivariate analysis, other than local recurrence, the presence of lateral cervical lymph node metastasis and radical operation were associated with significantly higher distant metastasis rates ($p = 0.026$, $p = 0.026$) (Table 6). However, there was no significant differences of distant metastasis according to larynx involvement ($p = 0.534$).

Eleven patients died of the disease, and the most common cause of death was lung metastasis, resulting in respiratory failure and hemoptysis. We analyzed the disease-specific survival rate (DSS) according to the treatment modalities

Table 5 Factors associated with distant metastasis in the patients with tracheal invasive thyroid carcinoma

	Distant metastasis (−) ($N = 40$)	Distant metastasis (+) ($N = 25$)	p value
Age	62.0 ± 13.0	59.5 ± 8.8	0.347
Sex (male:female)	18:22	8:17	0.435
Tumor size (cm)	2.9 ± 2.0	3.4 ± 1.7	0.344
Lateral cervical node (N1b)	10 (25.0 %)	15 (60.0 %)	0.014
History of previous thyroid operation	18 (45.0 %)	19 (76.0 %)	0.020
Involved organ			
Larynx	5 (12.5 %)	6 (24.0 %)	0.311
Esophagus	6 (15.0 %)	4 (16.0%)	1.000
Intraluminal involvement	20 (50.0 %)	15 (60.0%)	0.456
Shaving operation vs Radical operation	16:24	2:23	0.005

Table 6 Results of multivariate analysis for prognostic variables of distant metastasis in patients with well-differentiated thyroid cancer (based on 25 patients with distant metastasis)

	Multivariate Analysis (Cox proportional hazards regression)			
	OR	95 % CI		p value
		Lower	Upper	
Lateral cervical node (N1b) (vs none)	4.380	1.196	16.040	0.026
History of previous thyroid operation (vs none)	3.836	0.883	16.660	0.073
Involved organs				
Larynx (vs none)	0.578	0.103	3.253	0.534
Radical operation (vs shaving operation)	7.607	1.269	45.603	0.026

OR odds ratio, *CI* confidence interval

and the involved organs. There was no significant difference in the DSS according to the treatment modalities (shaving operation vs radical operation). All patients in the shave excision group survived until the end of the study period. The 5-year DSS rate in the tracheal resection group was 90 %, and the 10-year DSS rate was slightly lower at 85 %. However, in cases of total laryngectomy, they showed significant lower DSS than other treat modalities ($p = 0.006$) (Fig. 1). The 5-year and 10-year DSS rates in the laryngectomy group were both 69 %.

Other than esophageal involvement, there was significant difference in the DSS according to laryngeal involvement (Fig. 2). With larynx involvement, the 5-year DSS rate dropped to 68 % compared to 92 % for those without laryngeal involvement.

Discussion

Many studies of thyroid cancer with tracheal invasion have been performed. However, due to the rare incidence of this condition, most studies have been limited in terms of the size of the study group. Of 1919 patients who underwent thyroidectomy over a 20-year period in our institution, only 65 (3.39 %) were well-differentiated thyroid carcinoma with tracheal invasion. Once a thyroid carcinoma has transgressed the glandular capsule, it can invade the airway wall, esophageal wall, or larynx. With respect to the invasion depth, invasion of the ADT is a stepwise process that begins in the outer (superficial) layers and progresses into the deeper layers, and finally entering the lumen. Shin et al. [15] described the stages of tracheal invasion according pathologic findings, and the stages were defined according to the presence of cartilage invasion or intraluminal invasion. Meanwhile, the extent of invasion can be expanded by involvement of adjacent organs. Thyroid carcinomas can involve the larynx by direct invasion through the anterior thyroid cartilage and/or by extension around the posterior cartilaginous rim with invasion of the paraglottic space or pyriform sinus. In addition, thyroid carcinomas can invade the esophagus when they expanded posteriorly.

Tracheal invasion by well-differentiated thyroid carcinoma is a marker of more aggressive tumor behavior, defining a subpopulation of patients at a greater risk of recurrence and death. According to the current

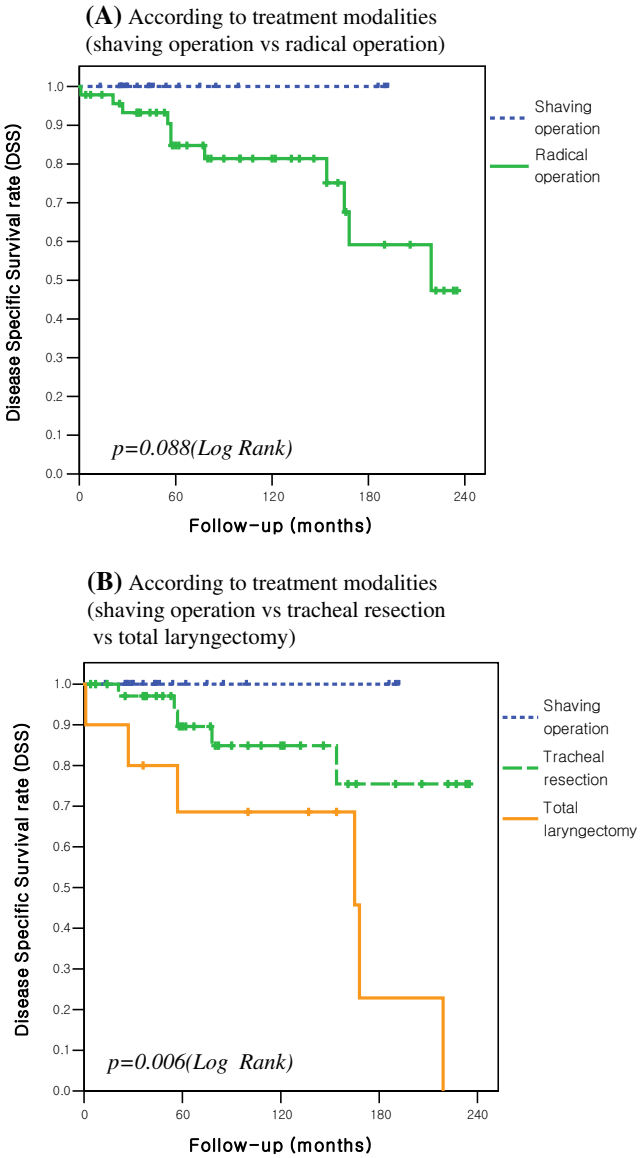

Fig. 1 Disease specific survival rate (DSS) according to treatment modalities. **a** According to treatment modalities (shaving operation vs radical operation). **b** According to treatment modalities (shaving operation vs tracheal resection vs total laryngectomy)

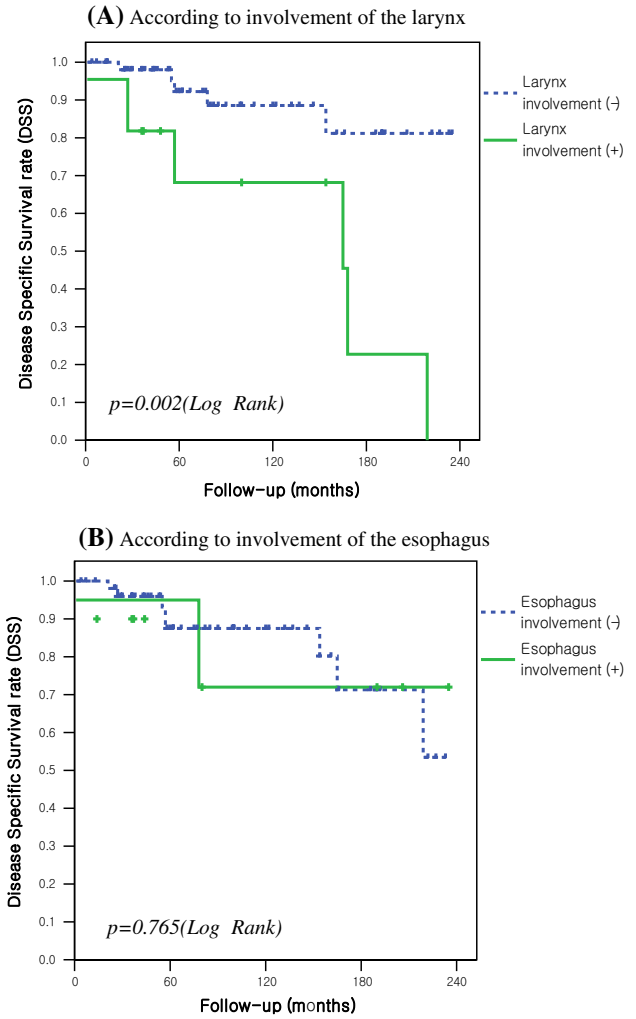

Fig. 2 Disease specific survival rate according to involvement of adjacent organs. **a** According to involvement of the larynx. **b** According to involvement of the esophagus

classification system, advanced thyroid cancer is classified by probable resectability, and the T4a stage includes invasion of the trachea, esophagus, and larynx. According to a previous study, there is no prognostic difference between invasion of the esophagus and trachea. Only invasion of the larynx reflects a more advanced stage of the disease [16]. In respect of recurrence, our results show that simultaneous involvement of the trachea and esophagus is associated with a higher local recurrence rate in univariate analysis, but it is not confirmed by multivariate analysis. Of 10 patients with esophageal involvement, only 2 exhibited esophageal intraluminal extension of thyroid carcinoma, and both were treated with partial esophagectomy. We found that most of the patients with esophageal involvement (8 of 10) had a history of thyroid cancer surgery, and 8 of them also exhibited involvement of the intraluminal tracheal mucosa. Due to anatomical position of the esophagus which located posteriorly of the trachea, it might be easier to invade the tracheal intraluminal mucosa. However, our study group only included 10 patients with esophageal involvement; thus, we cannot come to a definitive conclusion regarding the clinical significance of esophageal involvement with tracheal invasion. Consensus has been reached regarding the association between laryngeal involvement and aggressiveness (lower DSS), and our observations were in agreement with this association. However, any adjacent organ involvement with tracheal invasion was no association with distant metastasis.

A recent study indicated the necessity for reliable subdivision system [11]. The authors stated that the Dralle classification [17] can be helpful regarding both surgical options and oncological outcomes. The Dralle classification is a surgical classification system of complete airway wall resection, such as window resection or circular wall resection. However, the Dralle classification only focuses on deep tracheal wall resection. Which aspect of invasion, depth [intraluminal], surface area [circular involvement], or distance from the primary tumor [adjacent organs like the larynx] has the greatest influence on the aggressiveness remains unclear. Based on our results, aggressiveness appears to be most closely associated with extent of invasion or esophageal involvement. Therefore, a further study involving many institutions is needed to establish a reliable subdivision system of T4a.

The extent of tracheal resection in the management of thyroid carcinoma is controversial [18]. Shave excision is currently defined as removal of gross disease from the surface of the trachea; thus, the surgical margin might be unclear. Some reports have indicated worse survival and higher recurrence in patients treated with shave excision only [19, 20]. In our study, although half of the patients showed positive surgical margin, the local recurrence rate in the shave excision group was not significantly different from that in the other groups with more radical excision. Furthermore, the DSS rate in the shave excision group was 100 %, even at 10 years. Recently, American head and neck society consensus statement for management of invasive well-differentiated thyroid cancer agreed that tracheal shave excision is appropriate when there is minimal cartilage invasion, not involved intraluminal tracheal mucosa [21]. All 11 patients who died of the disease in our study showed distant metastasis, and their cause of death was related to organ failure due to distant metastasis. Despite the invasion of thyroid cancer into the adjacent ADT, many patients showed long survival when they underwent appropriate surgery.

Conclusion

Tracheal invasion by well-differentiated carcinoma has more aggressive tumor behavior, and defines a subpopulation of patients at greater risk of recurrence, distant metastasis and death. Although it is categorized in same classification of T4a, tumor aggressiveness of tracheal invasive thyroid cancer seemed to be closely associated with extent of invasion or esophageal involvement. In our study, simultaneous involvement of the trachea and the esophagus showed higher locoregional recurrence and laryngeal involvement showed lower DSS. However, despite the invasion of thyroid cancer into the adjacent ADT, many patients showed long survival when they underwent appropriate surgery. A further study involving many institutions is needed to establish a reliable subdivision system of T4a.

Compliance with ethical standard

Conflict of interest The authors have no conflict of interest and no financial disclosures.

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