Analysis of Thyroid Gland Invasion & Indication of Thyroidectomy in Hypopharyngeal Cancer

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Analysis of Thyroid Gland Invasion & Indication of Thyroidectomy in Hypopharyngeal Cancer

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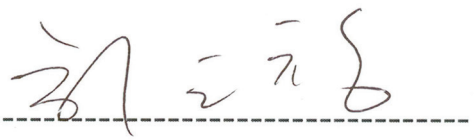
This certifies that the Master's Thesis of Jae Won Chang is approved.



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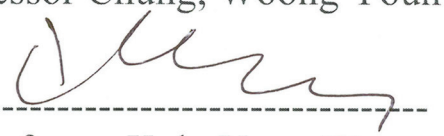

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ABSTRACT

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In order to resect clinically occult metastasis of laryngeal carcinoma to the ipsilateral thyroid lobe and isthmus, routine ipsilateral hemithyroidectomy and isthmusectomy are commonly performed as part of the total laryngectomy procedure. However, when we reviewed surgical specimens after thyroidectomy with concomitant laryngo-pharyngectomy, the incidence of thyroid gland involvement in laryngo-pharyngeal cancer ranged from 0 to 23%. The question remains as to whether thyroid resection should be performed in the setting of no definite thyroid gland invasion on pre-operative evaluation. Thyroid gland is an important endocrine organ that regulates metabolism and maintain homeostasis. Hypothyroidism is a well known postoperative complication that occurs after laryngopharyngectomy regardless of performing thyroidectomy. Because hypothyroidism causes delayed wound healing, resulting in pharyngeal fistula, mood depression, and

cardiac morbidity, thyroidectomy should be avoided if oncologically possible. In the meantime, studies conducted have focused mainly on the laryngeal cancer. However, making a decision to perform concurrent thyroidectomy on patients with hypopharyngeal cancer is important because hypopharyngeal cancer is more highly correlated with other comorbidities than laryngeal cancer.

A retrospective review was conducted on the medical records from the Department of Otolaryngology at Yonsei Universitiy College of Medicine between January 1994 and December 2009. A total of 108 patients received laryngopharyngectomy as a primary treatment of primary hypopharyngeal cancer.

In our study, the incidence of thyroid gland involvement was 4.6% (5 of 108 patients). The most common mechanism of invasion was direct extension through the thyroid cartilage. Thyroid cartilage invasion ($p=0.034$) was a statistically most significant factor in thyroid invasion. Additionally, when pyriform sinus (PS) apex invasion was noted, thyroid gland invasion should be suspected and thus consider thyroidectomy. Although the difference was not statistically significant, the prognosis of the patients with thyroid gland invasion was worse than that of the patients with no invasion.

Key words: Hypopharyngeal cancer, Thyroid invasion, Predictors

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I. INTRODUCTION

The first laryngectomy was done on 31 December 1873 by Theodore Billroth in Vienna.[1] During the same period, surgeons were exploring more conservative partial laryngectomy (Sands, 1863) and hemilaryngectomy (Billroth, 1878) procedures with the goal of avoiding total organ resection.[2] In recent years, there has been an evolving trend toward the use of organ-sparing modalities for the treatment of selected patients with head and neck cancer. This strategy seeks to preserve anatomical structures in the hope that these anatomical structures will continue to provide form and function to laryngeal cancer patients after treatment. During several decades, so much progress was achieved in laryngeal surgery that high local control became available and several conservative resection of larynx has been developed to maintain the

functionality of the larynx.[3]

Extralaryngeal spread of laryngeal cancer to the thyroid gland can theoretically occur by three pathways: direct extension, lymphatic spread, and hematogenous spread. Among these three mechanisms, direct extension is the main mechanism due to the close anatomical relationship of the thyroid gland to the laryngo-pharynx region.[1,4,5]

In order to resect clinically occult metastasis of laryngeal cancer to the ipsilateral thyroid lobe and isthmus, routine ipsilateral hemithyroidectomy and isthmectomy are commonly performed as part of the total laryngectomy procedure.

In 1955, Ogura[6] noted that 10 % (6/59) of his total laryngectomy specimens demonstrated thyroid gland invasion. He recommended routine ipsilateral hemithyroidectomy and isthmectomy for all total laryngectomy cases to ensure adequate local control of the disease. In 1973, Harrison[7] reiterated that total laryngectomy should always include at least isthmectomy and ipsilateral lobectomy plus frozen sectioning of the contralateral lobe of the thyroid. As more studies examined total laryngectomy specimens for thyroid gland invasion, it became apparent that involvement of the gland was, in fact, not a general feature of squamous cell carcinoma of the larynx. In 1976, Sessions[8] noted that less than 1 % of specimens demonstrated cancer invasion of the gland. In their own series of laryngectomy specimens, Biel[4], Brennan[1], Fagan[9], and Ceylan[10] demonstrated rates of invasion of 1 % (10/187), 8 % (8/107), 3 % (2/73), and 0 %

(0/129), respectively. On the basis of these prevalence figures, total thyroidectomy or lobectomy and isthmectomy are therefore performed unnecessarily during total laryngectomy or total laryngopharyngectomy in many cases.

If thyroid gland invasion is definite on the pre-operative evaluation, there is no controversy in performing thyroidectomy during laryngectomy. However, whether performing thyroidectomy and the extent of thyroidectomy (total, hemi-, or no thyroidectomy) in the setting of advanced laryngeal and hypopharyngeal carcinomas without definite thyroid gland invasion remain controversial.[3,11-14]

Hypothyroidism is a well recognized complication of radiotherapy and surgery in the treatment of head and neck cancer, especially laryngo-hypopharyngeal cancer. With hemithyroidectomy, 65% of patients develop hypothyroidism after laryngectomy. Also, when hemithyroidectomy is combined with radiotherapy, the incidence of hypothyroidism is as high as 70–90%. However, the incidence of hypothyroidism decreases significantly when the whole thyroid gland is preserved.[11,14] Hypothyroidism was attributed to the dissection of the preserved hemithyroid, which damages the vasculature of the hemithyroid and consequently impairs its ability to compensate for the loss of the opposite lobe.[15] Hypothyroidism causes delayed wound healing, resulting in pharyngeal fistula, mood depression, and cardiac morbidity. Hypothyroidism develops after treatment for hypopharyngeal cancer more frequently than

laryngeal cancer even when thyroid resection has not been performed.[14] This is accentuated because patients with hypopharyngeal cancer usually receive adjuvant radiotherapy.

In the past 20 years, several studies have been conducted on the prevalence of thyroid gland invasion in laryngopharyngeal cancer to find predictive values of thyroid gland invasion. These studies demonstrated that laryngopharyngeal cancer with thyroid gland invasion is correlated with an anatomic subsite of primary tumors and cellular behavior. However, preoperative factors of performing thyroidectomy during laryngo-pharyngectomy in each tumor subsite are not yet established. Hypopharyngeal cancer is similar to laryngeal cancer in anatomical location, common clinical symptoms, and surgical treatment. However, symptom manifestation can be delayed and multiple invasions are much easier in hypopharyngeal cancer because of no structural barriers such as laryngeal framework. Also, abundant circulating lymphatics result in poor prognosis.[16] Moreover, the characteristics of hypopharyngeal cancer patients are old age, malnutrition, history of smoking and alcohol abuse, and comorbidities such as diabetes and cardiovascular, pulmonary, or liver disease. Hypopharyngeal cancer patients tend to be more adversely affected than laryngeal cancer patients. [17]

The primary objective of this study was to determine the prevalence of histological thyroid gland invasion on total laryngectomy or total laryngo-pharyngectomy operative specimens of hypopharyngeal cancer. The secondary

objective was to identify preoperative predictive factors of this invasion to refine the indications for thyroidectomy and to limit the associated endocrine complications.

This study was different in that previous studies focused mainly on laryngeal cancer with relatively high incidence and better prognosis than hypopharyngeal cancer. Post-operative hypothyroidism is more frequent in patients with hypopharyngeal cancer. Moreover, patients with hypopharyngeal cancer are more strongly related with other morbidities than the patients with laryngeal cancer. Therefore, the decision to perform thyroidectomy, which accentuates post-operative hypothyroidism, is more significant than the decision to perform laryngeal cancer.

This study contributes to improving recovery and quality of life of the patients with hypopharyngeal cancer by providing grounds to prevent unnecessary thyroidectomy during laryngopharyngectomy.

II. SUBJECTS AND METHODS

A retrospective review was conducted on the medical records of Department of Otolaryngology at Yonsei Universitiy College of Medicinethe between January 1994 and December 2009.

Inclusion criteria were patients with squamous cell carcinoma of the

hypopharynx regardless of the lymph node status treated by total or partial laryngopharyngectomy associated with total thyroidectomy or lobectomy and isthmectomy and available medical records of at least two years of follow-up period. Exclusion criteria were patients with different pathological diagnosis between primary hypopharyngeal cancer and thyroid cancer with post-chemoradiation salvage surgery, patients with secondary hypopharyngeal cancer, non-squamous hypopharyngeal cancer, or metastatic disease, and incomplete medical chart review or follow-up loss.

A total of 108 patients received laryngopharyngectomy as a primary treatment of primary hypopharynx cancer. Only six patients were female, and they ranged in age from 37 to 83 years (mean 61.5 years). The minimum follow-up period was two years. Among 108 patients, 49 patients received thyroidectomy (2 patients received total thyroidectomy, 47 received hemi-thyroidectomy with isthemctomy). Patients' clinical characteristics are summarized in Table 1. This study included 102 males and 6 females with a mean age of 61.5 years. Eighty-two patients had pyriform sinus cancer, 22 patients had posterior pharyngeal wall cancer, and 6 patients had postcricoid cancer. Many patients (82 cases) had total laryngopharyngectomy, 3 patients had partial laryngectomy (1 patient had extended supraglottic partial laryngectomy (SPL) and 2 patients had SPL), 23 patients had partial pharyngectomy, and 49 patients had thyroidectomy. All patients had total laryngopharyngectomy.

Table 1. Clinical characteristics of patients with thyroidectomy and without thyroidectomy

		Thyroidectomy (n=49)	No thyroidectomy (n=59)
Mean age		60.7(37-83)	62.1(39-81)
Sex	Male	47	55
	Female	2	4
Primary lesion			
	PS medial wall	28(57.1%)	25(42.4%)
	PS lateral wall	13(26.5%)	16(25.1%)
	Post cricoid	3(6.1%)	1(1.7%)
	P.W.	5(10.2%)	17(28.8%)
cT	T1	4(8.2%)	12(20.3%)
	T2	11(22.4%)	19(32.2%)
	T3	15(30.6%)	11(18.6%)
	T4	19(38.8%)	17(28.8%)
	all patient were T4a		
cN	N0	7(14.3%)	21(35.6%)
	N1	8(16.3%)	7(11.9%)
	N2a	0(0%)	2(3.4%)
	N2b	20(40.8%)	23(39.0%)
	N2c	12(26.5%)	6(10.2%)
	N3	1(2.0%)	0(0%)
Operation	T/L/P/E	13(26.5%)	6(10.2%)
	T/L/P	36(73.5%)	27(45.7%)
	P/L	0(0%)	3(5.1%)
	P/P	0(0%)	23(39%)
Recurrence	+	20(40.8%)	23(39.0%)
	-	29(59.2%)	36(61.0%)

Recurrence Time(M)	25.6(5-114)	18.9(2-60)

*Staging from AJCC 7th edition in 2010

T/L/P/E, Total laryngopharyngoesophagectomy; T/L/P, Total laryngo pharynx-gectomy; P/L, Partial laryngectomy; P/P, Partial pharyngectomy

The indication for laryngopharyngectomy concomitant with total thyroidectomy or lobectomy and isthmectomy was determined preoperatively by the surgeon. Before surgery, all patients were assessed by upper aerodigestive endoscopy with biopsies and contrast-enhanced head and neck computed tomography (CT) and chest CT. TNM staging of the lesion was performed according to the 7th edition of the AJCC Cancer Staging Manual. Endoscopy and surgery were performed by two experienced head and neck surgeons.

The following parameters were studied: patient demographic data, preoperative clinical endoscopic findings (including anatomic lesion of primary cancer, true vocal cord mobility, and larynx invasion), preoperative imaging findings (including of thyroid cartilage, cricoid cartilage, thyroid gland, esophagus, and larynx invasion), the surgical procedure (total laryngectomy /total laryngopharyngectomy with total thyroidectomy/lobectomy and isthmectomy) and histological examination, pathological features of thyroid gland invasion (direct/ lymphatic/hematogenous), recurrence, 2-year and 5-year

overall survival rates, and disease specific survival rate. Operative specimens were examined by one experienced pathologists. CT /MRI images were examined by one experienced neuroradiologist. Statistical analysis was performed by Chi^2 test or Fisher's test with a limit of significance of $P < 0.05$ by SPSS v.18.0 for Windows.

III. RESULTS

Five (4.6%) of 108 patients presented signs of histological thyroid gland invasion. Clinical characteristics of five patients are listed in Table 2.

All patients except the last patient had T4a lesion and preoperative thyroid gland invasion on imaging was identified in two patients, although the difference was not statistically significant. All patients except the last patient showed thyroid invasion by direct course. The last patient had a T2N2bM0 postcricoid carcinoma with aryepiglottic fold invasion without thyroid cartilage invasion on preoperative imaging. This patient's invasion of the thyroid gland was seen on preoperative imaging but there was no evidence of direct invasion on both imaging and pathology. Nodal disease was present in ipsilateral level IV and paratrachea. He had total laryngectomy, partial pharyngectomy, ipsilateral SND (IV,V), and bilateral total thyroidectomy. Then the patient received adjuvant radiotherapy of 5400cGy. He had regional failure in the level

V neck lymph node and distant metastasis in the lungs 13 months after surgery.

We divided the possible predictive factors into two groups: endoscopic sign (Table 3-1) and CT/MRI findings (Table 3-2).

Table 2. Clinical characteristics of five hypopharyngeal cancer patients with thyroid gland invasion.

No.	Sex/Age	Primary site	Stage	Operation	Treatment modality	Recur	Recur gap(M)	Outcome	F/U(M)
1	M/64	PS(l)	T4aN2b	T/L+P/P +ND +hemiT	S+ R.	-		DIOD	20
2	M/58	PS(m)	T4aN2c	T/L+P/P +P/E+ND +hemiT	S+R.	-		NED	193
3	M/63	PS(m)	T4aN2c	T/L+P/P +ND +hemiT	S+R	Lung	11	DOD	38
4	M/56	PS(m)	T4aN2c	T/L+P/P +ND +hemiT	S+R	Lung	19	DOD	49
5	M/56	Post-Cricoid	T2N2b	T/L+P/P +ND +totalT	S+R	Neck, Lung	13	AWD	32

PS(m), Pyriform sinus medial wall; PS(l), Pyriform sinus lateral wall
ND, neck dissection; T/L, Total laryngectomy; P/P, Partial pharyngectomy; P/E, Partial esophagectomy;
hemiT, Hemi-thyroidectomy; totalT, Total-thyroidectomy;
S, Surgery; R, Radiotherapy
AWD, alive with disease; DOD, dead of disease; DIOD, dead irrelevant of disease

Table 3-1. Independent endoscopic correlates of thyroid gland invasion

Endoscopy			Thyroid gland invasion	No Thyroid gland invasion	*P-value*	Se(%)	Sp(%)
Larynx invasion	+		4	29	0.82		
		supraglottic	3	22			
		transglottic	1	7			
	-		1	15			
Invasion of PS apex	+		4	16	**0.06**	80.0%	60.0%
	-		1	28			
Ipsilateral VC fixation	+		3	23	0.56		
	-		2	21			
AEF	+		2	7	0.4		
	-		3	36			

Se, Sensitivity; Sp, Specificity

PS, Pyriform sinus; VC, Vocal cord; AEF, Aryepiglottic fold

Table 3-2. Independent preoperative CT/MRI correlates of thyroid gland invasion

Preoperative CT/MRI		Thyroid gland invasion	No thyroid gland invasion	*P - value*	Se(%)	Sp(%)
cT	T1/T2	1	14	0.511		
	T3/T4	4	30			
cN	N0/N1	0	15	0.15		
	N2/N3	5	29			
Thyroid gland invasion	+	3	2	**0.005**	60.0%	95.5%
	-	2	42			
Thyroid cartilage invasion	+	4	12	**0.034**	80.0%	72.1%
	-	1	32			
Midline Cross	+	0	14	0.17		
	-	5	30			
Esophagus	+	0	4	0.64		
	-	5	40			

Se, Sensitivity; Sp, Specificity

Endoscopic signs predictive of thyroid gland invasion are presented in Table 3-1. Larynx invasion, invasion of the pyriform sinus (PS) apex, ipsilateral vocal cord palsy, and aryepiglottic fold extension were included. Tumors invading the thyroid gland also invaded the PS apex (80%), thyroid cartilage (80%), larynx (80%), ipsilateral true vocal cord (60%), and aryepiglottic fold (40%). None of the cases with hypopharyngeal cancer invading the thyroid gland crossed the midline or extended to esophagus. There were no definite, statistically significant factors at the 95% confidence level. However, we found the factor for invasion of PS apex can predict thyroid gland invasion preoperatively (p=0.06). Sensitivity and specificity as predictive factors for thyroid gland invasion were 80.0% and 60.0%, respectively. We analyzed possible factors such as clinical T and N stages (p=0.511, 0.15), thyroid invasion on CT/MRI findings (p=0.005), thyroid cartilage (p=0.034), and midline cross (p=0.17). From our data, histological thyroid gland invasion was statistically correlated with CT signs of thyroid cartilage invasion (p=0.034) and thyroid gland invasion (p=0.005) in independent correlation. Sensitivity and specificity of thyroid cartilage invasion on CT/MRI as predictive factors of thyroid gland invasion were 80.0% and 72.1%, respectively, whereas those of thyroid gland invasion on CT/MRI were 60.0% and 95.5%, respectively

Although the relationships between patterns of spread and thyroid gland invasion were not statistically significant (Table 4), the most common mechanism of invasion to the thyroid gland was direct extension through the

thyroid cartilage and the anterior commissure (Fig. 1,2).

Table 4. Patterns of spread of thyroid invasion

Patient	Primary site	Direct invasion	Lymphatic spread	Vascular channel spread	Multifocal invasion
1	PS lateral wall	+	-	-	-
2	PS medial wall	+	-	-	-
3	PS medial wall	+	-	-	-
4	PS medial wall	+	-	-	-
5	Post cricoid	-	+	-	+

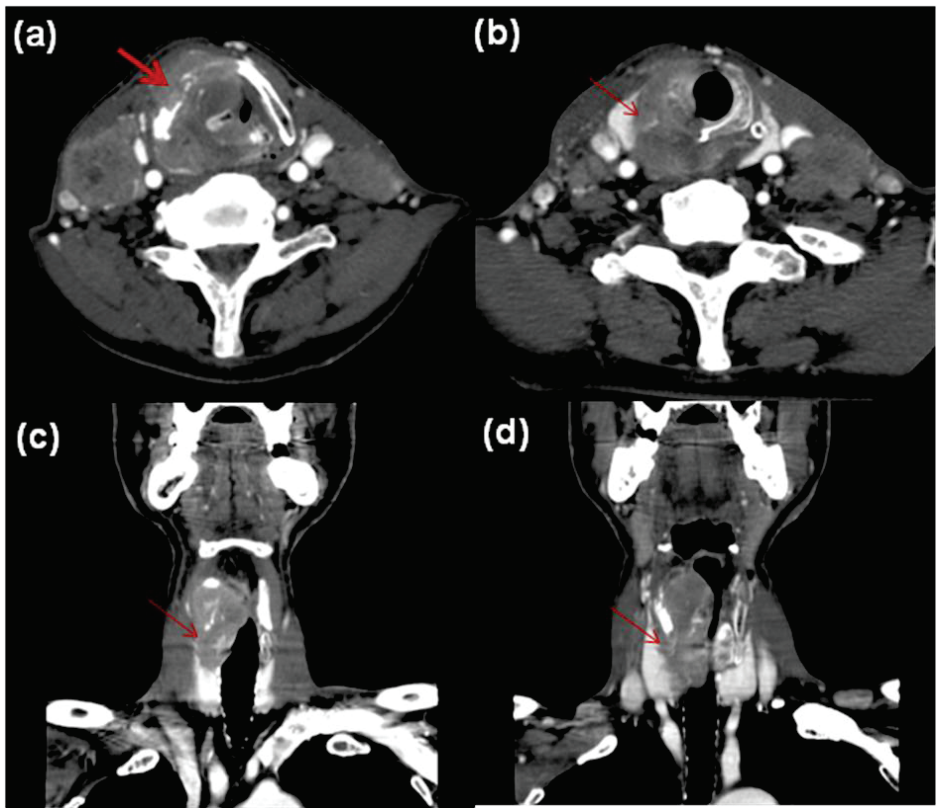


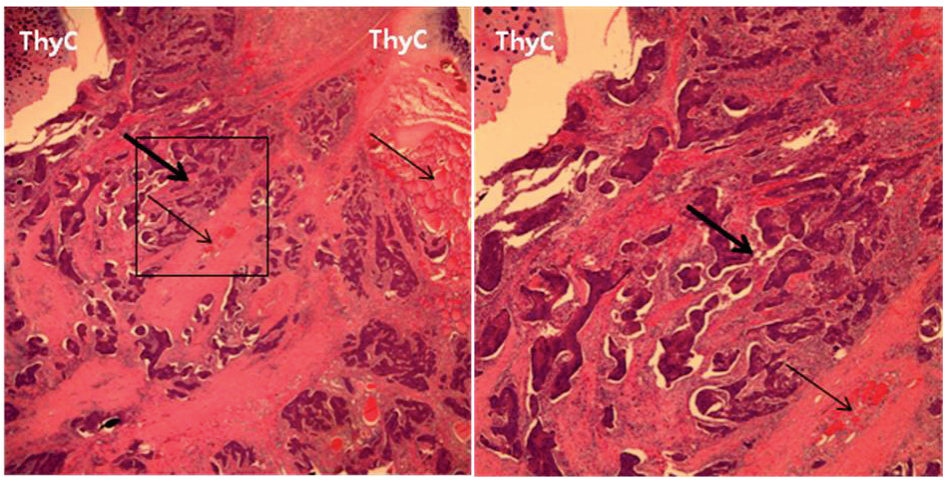
Fig. 1 Direct thyroid gland invasion.

(a) Neck CT enhanced the axial view: Thyroid cartilage destruction

(b) Neck CT enhanced the axial view: Thyroid tissue invasion

(c), (d) Neck CT coronal view: Thyroid tissue invasion

Thick arrow: thyroid cartilage destruction; Thin arrow: direct invasion of tumor of the thyroid gland



(a) H&E stain (x12) (b) H&E stain (x40)

ThyC : Thyroid cartilage

Fig. 2 Histological section showing direct thyroid gland invasion through thyroid cartilage: squamous cell carcinoma (thick arrow), thyroid gland (thin arrow).

One patient with thyroid gland invasion had lymphatic and multifocal spread showing tumor emboli within the perithyroidal lymphatics situated in areas that were not approximate to the site of primary cancer (Fig.3,4).

Distant metastasis or local recurrence developed in three cases with thyroid invasion. All of the distant metastasis occurred in the lungs and one patient had distant metastasis in the lung and nodal recurrence at level V simultaneously.

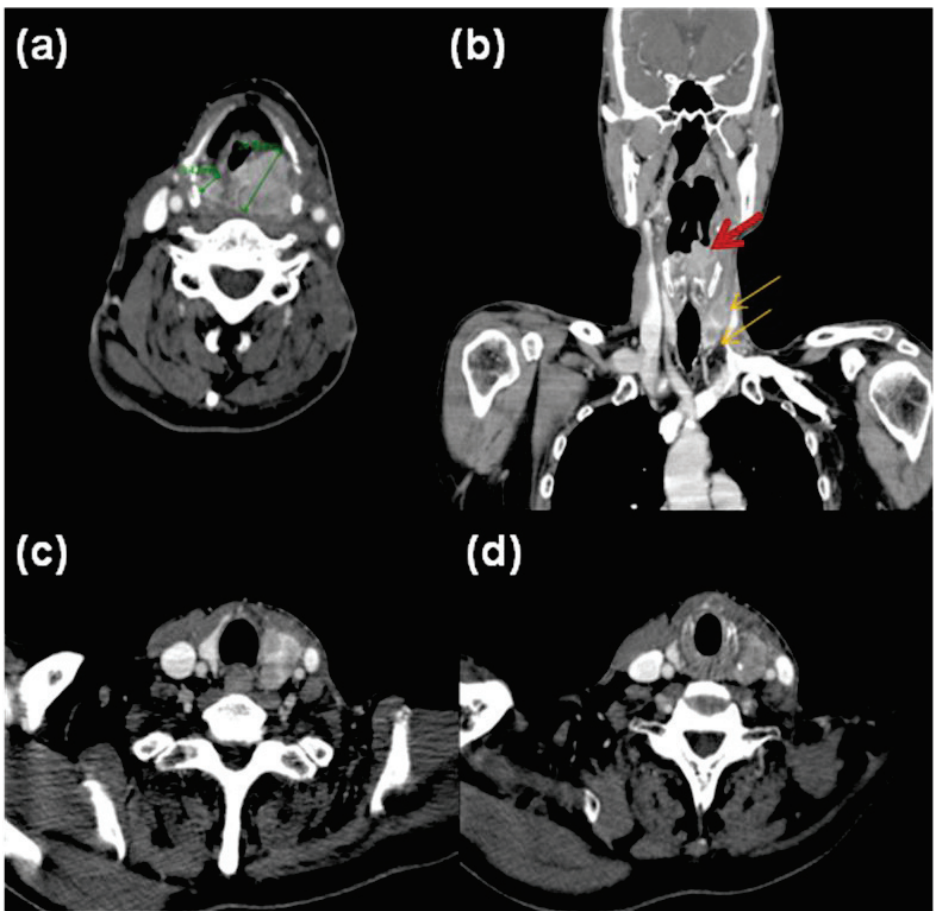
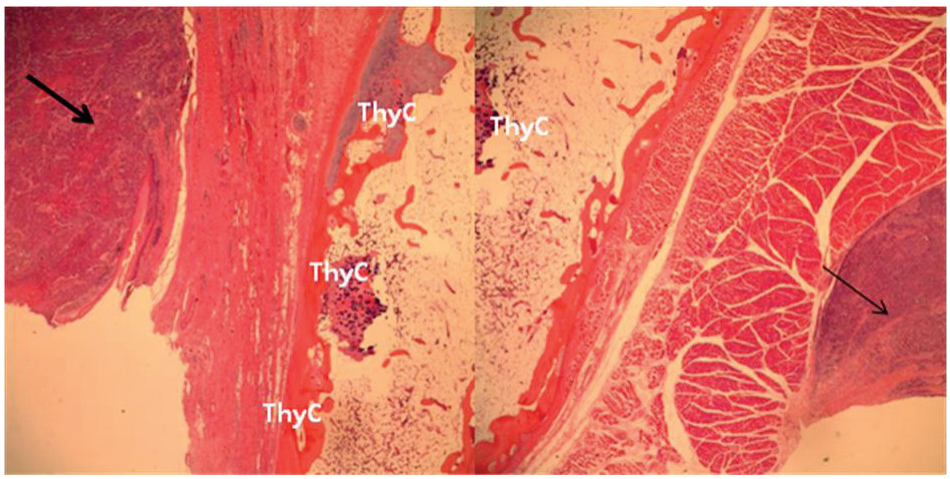


Fig. 3 Multifocal thyroid gland invasion by ipsilateral metastasis without direct extension through thyroid cartilage.

(a) primary mass, (b) coronal image, (c) mid pole thyroid invasion, (d) upper pole thyroid invasion

Thick arrow: primary lesion; Thin arrow: metastasis of the thyroid gland



(a) H&E stain (x12) (b) H&E stain (x12)

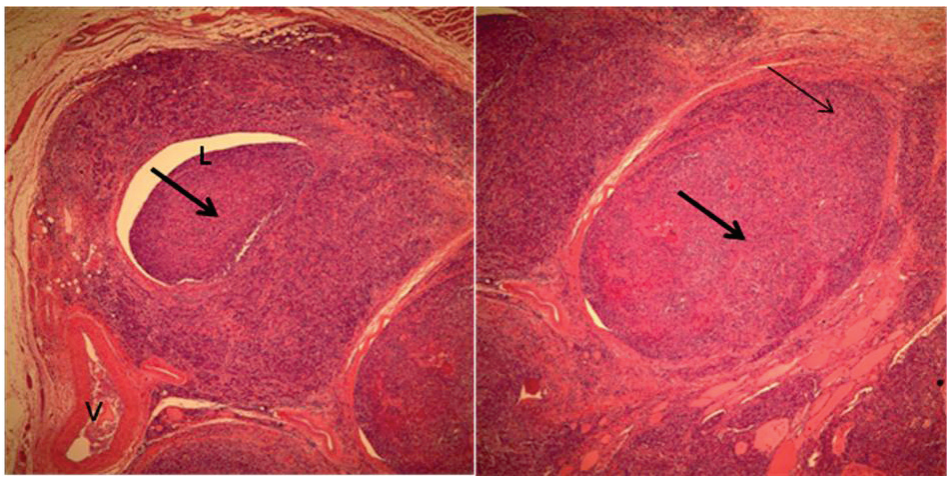
ThyC : Thyroid cartilage

Fig. 4-1 Histological section showing no direct thyroid gland invasion.

(a) Squamous cell carcinoma fully invaded the hypopharynx but the fibroadipose tissue and the thyroid cartilage were well preserved without cancer invasion.

(b) Outside of the thyroid cartilage. Metastasis of the upper pole of the thyroid (thin arrow) is irrelative with primary tumors.

: primary squamous cell carcinoma (thick arrow), thyroid gland metastasis(thin arrow)



(c) H&E stain (x40) (d) H&E stain (x40)

V : Vessle, L : Lymphatic channel

Fig. 4-2 Histological section showing thyroid gland metastasis via lymphatics.

(c) A histological section showing tumor emboli in the lymphatic channel.

(d) Tumor emboli infiltrated with many small lymphocytes, which implies that invasion occurred via lymphatic channels.

: tumor emboli(thick arrow), lymphocyte (thin arrow)

Examination of thyroid function in the patients who had laryngectomy with thyroidectomy demonstrated the rate of incidence of hypothyroidism was 70% (28 of 40 patients) in the group with radiotherapy and 33.3 % incidence (8 of 21 patients) in the group without radiotherapy. The rate of incidence of hypothyroidism was 11.1% (2 of 18 patients) in the group that had only laryngectomy without thyroidectomy and the incidence increased up to 31.7% (13 of 41 patients) when the patients in this group underwent radiotherapy. All the patients were well managed with a proper medical treatment provided by the endocrine department of our institute. (Table 5) .

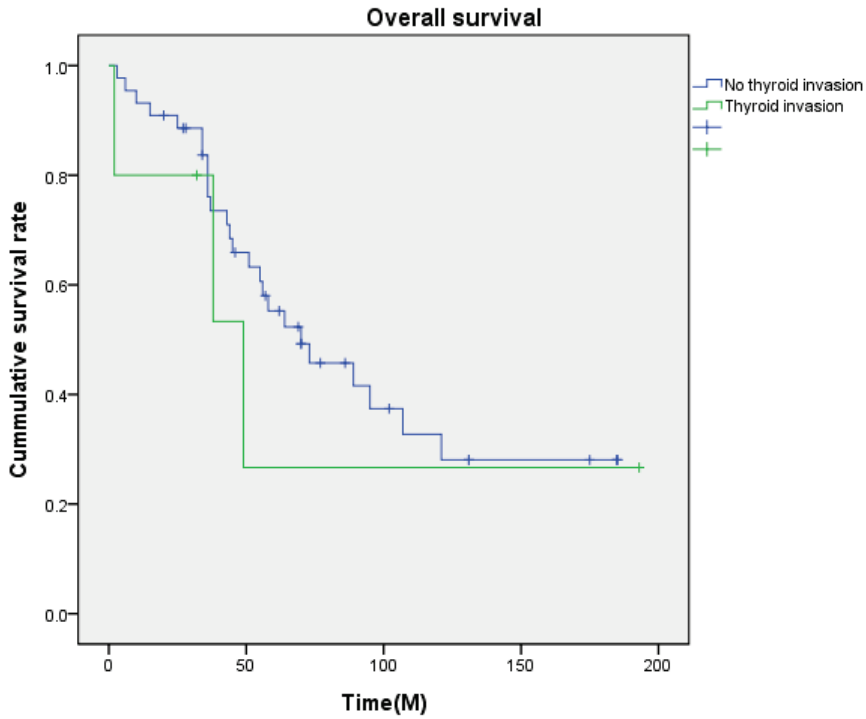
Table 5. Hypothyroidism after surgery

	Thyroidectomy	**No thyroidectomy**
S	33.3%(3/9)	11.1%(2/18)
S + R	70.0%(28/40)	31.7%(13/41)

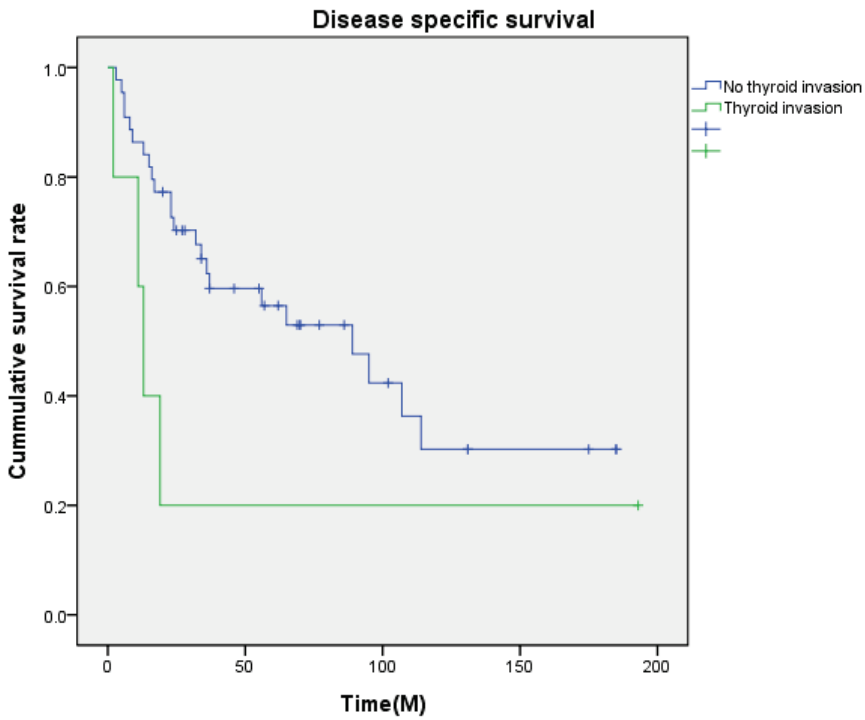
S, Surgery; R, Radiotherap

Prognosis of hypopharyngeal cancer cases with thyroid gland invasion is worse than that of non-invasive tumor cases (5 year OS 26.7%, 55.2%, 5 year DSS 20%, 30%), but the difference is not statistically significant. This result

implies that many patients with thyroid gland invasion die in 2-5 years. Also, frequent relapses occur within 2 years (Fig. 5).



2yrs *OS	inv +	80.0%
	inv -	90.9%
5yrs *OS	inv +	26.7%
	inv -	55.2%



2 yrs **DSS	inv +	20.0%
	inv -	70.2%
5 yrs **DSS	inv +	20.0%
	inv -	30.3%

*OS : Overall Survival, **DSS : Disease specific survival

Fig. 5 Prognosis according to thyroid gland invasion. Prognosis of hypopharyngeal cancer cases with thyroid gland invasion is worse than that of non-invasive tumor cases , but the difference is not statistically significant.

This result shows that many patients with thyroid gland invasion die in 2-5 years. Also, frequent relapses occur within two years.

IV. DISCUSSION

Thyroid gland involvement in laryngopharyngeal cancer is due to the physical proximity of the thyroid gland to the laryngopharynx.[2,10,15] Thyroidectomy is designed to resect any known or occult direct tumor extension or metastasis in order to ensure local control as thyroid gland invasion by squamous cell carcinoma of the pharynx and the larynx constitutes a factor of poor prognosis.[1]

Table 6. Reported incidence for invasion of the thyroid gland with laryngeal and/or hypopharyngeal cancer

Author	Laryngeal carcinoma	Hypopharyngeal carcinoma	Laryngopharyngeal carcinoma	n
Ceylan et al[10]	0%	57%		129
Sparano et al[8]	23%			30
Gallegos et al	12%			92
Dadas et al[12]	1%			182
Fagan et al[14]	2%			102
Yuen et al[18]	19%			16
Brennan et al[1]	3%			247
Croce et al[19]	30%			23
Gilbert et al[20]	14%			173
Biel et al[4]	5%			261
Kim et al[11]			14%	28

A reported incidence of thyroid gland involvement in laryngo-pharyngeal cancer varies from 0 to 23%, which is comparable to the incidence of 4.6% observed in this study.[5,9,17,21](Table 6) Total thyroidectomy or lobectomy and isthmectomy can therefore be considered to be unnecessarily performed in about 95% of cases, an unacceptable figure in view of the potential endocrine complications associated with this procedure, as preservation of both thyroid lobes is associated with a lower long-term prevalence of hypothyroidism.[4]

Many studies have been reported in the literature to provide indications for thyroidectomy associated with laryngopharyngectomy. Biel et al. performed total thyroidectomy or lobectomy and isthmectomy for laryngeal cancers with subglottic extension greater than 10 mm and for stage T4 hypopharyngeal cancers.[4] Dadas et al. performed lobectomy and isthmectomy for laryngeal cancers with subglottic extension greater than 10 mm and in the presence of thyroid cartilage invasion on CT.[21] Sparano et al. performed lobectomy and isthmectomy for laryngeal cancers with subglottic extension greater than 15 mm, fixed vocal folds, extension to the anterior commissure, laryngeal ventricle, cricothyroid mem-brane, and thyroid cartilage.[5]

However, these studies were mainly focused on laryngeal cancer. Laryngeal and hypopharyngeal carcinomas have many similarities, including etiology, clinical presentation, and surgical treatment. At the same time, hypopharyngeal cancer is different from laryngeal cancer such as no anatomic

boundaries of neighboring structures as limiting as those around the larynx. Thus, a disturbance of function is not seen until the disease is advanced and is frequently detected in advanced stages because of the relative paucity of initial symptoms. Because this area also has richer lymphatic drainage than the larynx, a lesional metastasis (such as neck lymph node, thyroid cartilage, and thyroid gland) is not an uncommon finding, especially in the advanced-stage disease. Moreover, patients with hypopharyngeal cancer have a high association with heavy alcohol use and other systemic disorders and thus the morbidity of postoperative period is more frequent in patients with hypopharyngeal cancer than in patients with laryngeal cancer.[11] Therefore, it is more critical for the surgeon to decide whether to resect the thyroid during laryngopharyngectomy.

Laryngopharyngeal cancer can involve the thyroid gland by direct extension or indirectly via lymphatic or vascular structure.[3,5,9,11,20,21] Direct extension is the most common course of invasion in hypopharyngeal cancer.[11] In our cohort, 80% (4 out of 5 patients) of patients with thyroid gland invasion had direct invasion through the thyroid cartilage. Lymphatic drainage from the pyriform sinuses passes through the thyroid membrane primarily to the jugulodigastric lymph node and to the mid-jugular and spinal accessory chains. Lymphatic drainage from the inferior portion of the hypopharynx (e.g. PS apex) and from the postcricoid region also passes to the paratracheal and paraesophageal nodes, which are located near the thyroid gland. In our study, we noted one patient with lymphatic metastasis without direct invasion. His

primary site of cancer was postcricoid and this skipped metastasis to the thyroid gland is highly related with primary anatomic site and lymphatic drainage.

Our study showed that thyroid cartilage invasion on pre-operative imaging was the only statistically significant factor of thyroid gland invasion, in case thyroid gland invasion was not definite in the pre-operative evaluation ($p = 0.034$). When the thyroid cartilage appeared to be intact on preoperative CT/MRI, histological thyroid gland invasion was observed in only 3.03% (1 metastasis). Thyroidectomy therefore does not appear to be indicated in this case (negative predictive value = 97.0%). Although no statistically significant correlation was observed in the 95% confidence interval, the pyriform sinus apex invasion could be a predictive factor of thyroid gland invasion in the 90% confidence interval. ($p = 0.06$)

CT and/or MRI would appear to be essential to define the indications for thyroidectomy. On the basis of our results, ipsilateral lobectomy and isthmectomy appear to be indicated when CT clearly demonstrates thyroid gland invasion and/or thyroid cartilage destruction. In addition, when tumors invade the apex of the pyriform sinus, thyroidectomy must be considered carefully. In contrast, total thyroidectomy does not appear to be indicated in the case of a clearly lateralized tumor, as no invasion of the contralateral thyroid lobe was observed in our study.

Moreover, ipsilateral central lymph node dissection that facilitates thyroidectomy should always be performed in combination with lobectomy and

isthmectomy,. Because the histological results of central lymph node dissection were poorly documented, we were not able to analyze the incidence of central lymph node metastasis despite its intimate anatomical relations.

When no predictive factors were demonstrated on the preoperative work-up, most surgeons carefully based their indications for thyroidectomy on the intraoperative appearance of the thyroid gland[4,9,11,21]

Our data showed relatively high rate of hypothyroidism compared with other study groups for laryngeal and hypopharyngeal cancer even when thyroid resection was not performed. One reason is that the patients in our study were relatively old age at diagnosis. Palmer and colleagues[22] reported that in 37 patients who underwent radiotherapy, total laryngectomy, and thyroid lobectomy, the rate of incidence of hypothyroidism was 44%. Alexander et al.[23] reported that hypothyroidism was observed in 55% of patients who received a hemithyroidectomy and irradiation and in 22% of patients who received hemithyroidectomy alone. The study also demonstrated that these patients with hypothyroidism had significant difficulties with postoperative wound healing and mental depression associated with hypothyroidism. Thus, patients should be evaluated postoperatively and carefully monitored with serial thyroid function tests.

V. CONCLUSION

Although histological thyroid gland invasion is not very rare, routine hemithyroidectomy and isthmectomy may not be required for all hypopharyngeal cancers. Rather, the indications for thyroidectomy in the context of laryngopharyngeal squamous cell carcinoma need to be more clearly defined to decrease the endocrine complications of thyroidectomy that are accentuated by adjuvant radiotherapy.

In our series, thyroid cartilage invasion was the most useful predictive factor in the setting of no definite thyroid gland invasion in pre-operative examinations. When the apex of the PS is invaded by tumors, thyroid gland invasion should be suspected. Except for these two conditions, whether thyroidectomy should be performed depends on the intraoperative appearance of the thyroid gland. These findings need to be confirmed by prospective studies.

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ABSTRACT(IN KOREAN)

하인두편평세포암종에서 갑상선 침범에 대한 분석 및 갑상선 절제술의 적응증

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장 재 원

후두 및 하인두의 편평세포암종으로 인하여 전후두절제술(Total laryngectomy)를 시행받는 환자들에서 동측의 갑상선 절제술(Ipsilateral hemithyroidectomy) 및 협부 절제술(isthmectomy)을 시행하는 경우가 많으나 실제로 수술 후 전후두적출술 및 동측의 갑상선 절제술을 시행 받은 환자에서 병리 검사를 해보면 후두암세포의 갑상선 침범의 빈도는 그리 높지 않음을 알 수 있다. 수술 전 및 수술소견 상 갑상선 침범의 증거가 명확하지 않은 경우 전후두 절제술 시행 시 동시에 갑상선 절제술을 시행하는 것에 대하여는 아직까지 논란의 대상이 되고 있다. 갑상선은 인체의 신진대사 및 항상성을 유지하는데 있어서 중요한 내분비 기관으로 갑상선 절제술을 시행함으로써 수술 후 갑상선 기능 저하 및 저칼슘혈증으로 인하여 수술 후 상처 회복지연 뿐만 아니라, 심혈관계 및 전신적인 영향,

정신적 문제 등이 발생할 수 있기 때문에 불필요한 갑상선 절제술은 피하는 것이 바람직할 것이다. 본 연구자는 비교적 갑상선과 해부학적으로 가까운 곳에 위치하며 두경부 암 중 가장 예후가 좋지 않은 것으로 알려져 있는 하인두의 편평세포암에서 갑상선절제술을 동시에 받은 환자들의 병리조직을 분석하여 갑상선절제술의 적응증 결정하여 수술 전 임상소견 상 갑상선에 명확한 침범 증거가 없는 경우 갑상선 절제술 동시 시행여부를 결정할 수 있는 예측인자를 찾고자 하였다. 아울러 이러한 인자를 통하여 합리적인 의사결정을 하여 수술 집도의가 불필요한 갑상선 절제술을 시행하여 수술 후 환자의 회복 및 삶의 질 향상시키는 데에 이바지하고자 한다.

핵심되는 말 : Hypopharyngeal cancer, Thyroid invasion, Predictors