RESEARCH ARTICLE

Clinicopathologic Findings and Treatment Outcome of Laryngectomized Patients with Laryngeal Cancer and Hypopharyngeal Cancer: An Experience in Thailand

Noppadol Larbcharoensub[1]*, Duangkamon Wattanatranon[1], Juvady Leopairut[1], Suwimon Suntisuktana[2], Boonsam Roongpupaht[3], Chalermchai Chintrakarn[3], Jumroon Tungkeeratichai[3], Phurich Praneetvatakul[3], Thongchai Bhongmakapat[3], Wichit Cheewaruangroj[3], Supawadee Prakunhungsit[3]

Abstract

Objective: To evaluate the clinicopathologic findings and treatment outcome in laryngectomized patients with laryngeal cancer and hypopharyngeal cancer. **Materials and Methods:** The authors retrospectively reviewed the medical records of 212 patients who had been newly diagnosed and treated with laryngectomy between January 2000 and December 2010. The age, gender, clinical manifestations, associated predisposing condition, tumor WHO grade, AJCC tumor stage, maximum tumor size, anatomical involvement, type of surgery, postoperative sequelae, treatment and therapeutic outcome were analyzed. **Results:** The present study included laryngeal cancer (n = 155) and hypopharyngeal cancer (n = 57). The patients' age ranged from 38 to 84 years, with the mean age of 62.08±9.67 years. The common clinical presentations were hoarseness (73.6%), cervical lymphadenopathy (35.8%), sorethroat (22.2%), and odynophagia (14.6%). The laryngeal cancer commonly involves true vocal cord (86.5%), anterior commissure (65.8%), false vocal cord (56.8%), laryngeal ventricle (53.5%), subglottis (47.1%), and paraglotic space (35.5%), respectively. Fifty-three percent of cases had stage IV cancer. The most common postoperative surgical sequela was hypothyroidism (77.8%). The overall 5-year survivals for laryngeal cancer and hypopharyngeal cancer were 55% and 9%, respectively. The 5-year survival for node-negative cases was 61.8% versus 17% for node-positive cases ($p< 0.001$). AJCC stage of laryngeal cancer and hypopharyngeal cancer was a significant predictor of 5-year survival ($p< 0.001$ and $p = 0.004$, respectively). **Conclusions:** The advanced AJCC stage, advanced T stage, advanced N stage, extracapsular tumor spread, and tumor invasion of false vocal cord, epiglottis, preepiglottic space, paraglottic space, thyroid cartilage, cricothyroid membrane were found to significantly augment the decrease of 5-year survival in laryngeal cancer. Only advanced AJCC stage was significantly associated with 5-year survival rate in hypopharyngeal cancer.

Keywords: Laryngeal cancer- hypopharyngeal cancer- head and neck cancer- clinicopathologic findings- Thailand

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Introduction

Laryngeal cancer and hypopharyngeal cancer are two common malignancies of the head and neck. The incidence is increasing over time in much of the world. The diseases commonly occur in elderly patients. Most of laryngeal cancer and hypopharyngeal cancer are squamous cell carcinoma (SCC) followed by adenocarcinoma. The treatment modalities include surgery, radiotherapy and chemotherapy. Laryngectomy is the treatment of choice for locally intermediate to advanced laryngeal cancer and hypopharyngeal cancer.

Little published information is available concerning the clinicopathologic finding and treatment outcome of laryngeal cancer and hypopharyngeal cancer, particularly in Thailand. Most studies have been epidemiological in nature and only a few studies have been conducts with laryngectomy. Moreover, all of the published data are reported in the clinical aspect (Boonyaphiphat et al., 1994; Chitapanarux et al., 2014; Dechaphumkul et al., 2011; Jantharapattana, 2013; Ratanaanekchai and Reechaipichitkul, 2006). The clinicopathologic analysis of laryngeal cancer and hypopharyngeal cancer has not been well elucidated. The objectives of the present study were to evaluate the clinicopathologic findings and treatment outcome in laryngectomized patients with laryngeal cancer and hypopharyngeal cancer in Thailand.

At present, there are limited clinicopathologic data

*[1]Department of Pathology, [2]Department of Nursing, [3]Department of Otolaryngology, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. *For Correspondence: Noppadol.lar@mahidol.ac.th*

regarding the laryngeal cancer and hypopharyngeal cancer in Thailand (Boonyaphiphat et al., 1994;Chitapanarux et al., 2014; Dechaphumkul et al., 2011; Jantharapattana 2013; Ratanaanekchai and Reechaipichitkul, 2006). The objectives of the present study were to evaluate the clinicopathologic findings and treatment outcome in laryngectomized patients with laryngeal cancer and hypopharyngeal cancer in Thailand.

Materials and Methods

A total of 217 consecutive patients with laryngeal cancer and hypopharyngeal cancer, who were newly diagnosed and treated with laryngectomy at department of Otolaryngology, Faculty of Medicine Ramathibodi Hospital, Mahidol University, between January 2000 and December 2010, were recruited in this study. However, complete clinical and pathologic records were available only in 212 patients. The authors reviewed the medical records and extracted information including age, gender, clinical manifestations, associated predisposing condition, histopathology and tumor grade according to World Health Organization (WHO) grade, tumor stage, maximum tumor size, anatomical involvement, type of surgery, postoperative sequelae, treatment and therapeutic outcome. Pathologic specimens of larynx and cervical lymph node were examined by pathologists (NL, DW, JL). The histopathologic diagnoses and anatomical involvement of laryngeal cancer and hypopharyngeal cancer were reviewed. Stages were defined according to the American Joint Committee on Cancer (AJCC) staging system. Further treatment depended on the malignant involvement of the cervical lymph node or the surgical margin not being free after attempted surgical resection. If they were involved then radiotherapy would be given. Chemotherapy was provided in addition to irradiation in patients who had advanced stage cancers with advance features including extracapsular tumor spread and/or positive surgical margin for tumor. Most of the patients were scheduled for post-treatment follow up every 1-3 months for 2 years and every 6 months afterward. All living patients who did not show up at the scheduled check up or loss to follow up were reminded by phone.

Patients were grouped based on primary lesion. Statistical analysis was performed using SPSS version 18.0. Categorical variables were compared using Chi-Square tests for association. A two-tailed Fisher's exact test was used to evaluate statistical significance between groups. The data of the patients between 2000 and 2006 were used to analyze for survival time and disease-free survival. Survival time was calculated from the date of beginning of laryngectomy until the date of death. Disease-free survival was calculated from the date of laryngectomy to the date of appearance of the new lesion. Survival profiles of the entire group and subgroup were examining using Kaplan-Meier method. The significance of differences in survival was evaluated using the log-rank test. Multivariate survival analysis was performed with the Cox proportional-hazards model. The present study was approved by the Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects of Faculty of Medicine Ramathibodi Hospital, Mahidol University (ID 11-54-34).

Results

Patient characteristics

Two hundred and twelve cases were found to meet the inclusion criteria. There were 155 cases of laryngeal cancer and 57 cases of hypopharyngeal cancer, affecting patients between 38 and 84 years with the mean age of 62.08 ± 9.67 years. The majority of patients were males (94.8%). One hundred and ninety patients (89.6%) were smokers. Demographic data of the patients presented in Table 1 and 2.

Clinical characteristics

The clinical presentations were hoarseness (156 cases, 73.6%), cervical lymphadenopathy (76 cases, 35.8%), sorethroat (47 cases, 22.2%), odynophagia (31 cases, 14.6%), as shown in Table 1. The underlying diseases were hypertension (52 cases, 24.5%), chronic obstructive pulmonary disease (COPD) (36 cases, 17%), pulmonary tuberculosis (23 cases, 10.8%), benign prostatic hyperplasia (BPH) (13 cases, 6.1%), as shown in Table 1. Only one case was seropositive for human immunodeficiency viral (HIV) infection.

Anatomical involvements by tumor

The extent of organ involvement included true vocal cord (147 cases, 69.3%), false vocal cord (105 cases, 49.5%), pyriform sinus (77 cases, 36.3%), and others, as shown in detail in Table 3. In laryngeal cancer and hypopharyngeal cancer, the greatest dimension of tumor size ranged between 0.2 to 8 and 1.3 to 8 cm, with the mean size of 2.6 ± 1.4 and 3.4 ± 1.3 cm, respectively. Lymph node metastasis was found in 40 and 45 patients (25.8% and 78.9%) of laryngeal cancer and hypopharyngeal cancer, respectively. Extracapsular tumor spread in metastatic laryngeal cancer and hypopharyngeal cancer was seen in 15 and 21 patients (9.7% and 36.8%), respectively. The distribution by AJCC surgical stage I, II, III and IV of laryngeal cancer was 4.5%, 22.6%, 27.1%, and 45.8%, respectively. The distribution by AJCC surgical stage II, III and IV of hypopharyngeal cancer was 10.5%, 17.6%, and 71.9%, respectively.

Histopathology

The histopathology of laryngeal cancer revealed well-differentiated SCC (79.4%), moderately-differentiated SCC (13.5%), poorly-differentiated SCC (3.2%), and basaloid SCC (1.9%). The histopathologic grade of hypopharyngeal cancer revealed well-differentiated SCC (57.9%), moderately-differentiated SCC (22.8%), and poorly-differentiated SCC (15.8%). The spindle cell carcinoma, adenosquamous carcinoma, atypical carcinoid tumor, and polymorphous adenocarcinoma had a small proportion. The details of histopathologic characteristics are displayed in Table 1.

Treatment and therapeutic outcome

All patients underwent surgical laryngectomy. The

Table 1. Patients' Characteristics with Laryngeal Cancer and Hypopharyngeal Cancer

Detail	Laryngeal cancer (n = 155)		Hypopharyngeal cancer (n = 57)	
	No. of patients	Percent	No. of patients	Percent
Gender				
Male	147	94.8	54	94.7
Female	8	5.2	3	5.3
Clinical presentation				
Hoarseness	139	89.7	17	29.8
Cervical lymphadenopathy	35	22.6	41	71.9
Sorethroat	14	9	33	57.9
Odynophagia	11	7.1	20	35.1
Dyspnea	9	5.8	1	1.8
Cough	7	4.5	2	3.5
Weight loss	6	3.9	4	7
Dysphagia	4	2.6	6	10.5
Hemoptysis	3	1.9	2	3.5
Smoking	142	91.6	48	84.2
Underlying diseases				
Hypertension	36	23.2	16	28.1
Chronic obstructive pulmonary disease	25	16.1	11	19.3
Pulmonary tuberculosis	18	11.6	5	8.8
Benign prostate hyperplasia	7	4.5	6	10.5
Associated malignancy				
Pulmonary carcinoma	5	3.2	0	0
Thyroid carcinoma	0	0	1	1.8
Histopathology				
SCC, well-differentiated	123	79.4	33	57.9
SCC, moderately-differentiated	21	13.5	13	22.8
SCC, poorly-differentiated	5	3.2	9	15.7
Basaloid SCC	3	1.9	0	0
Spindle cell carcinoma	0	0	1	1.8
Adenosquamous carcinoma	1	0.6	1	1.8
Atypical carcinoid tumor	1	0.6	0	0
Polymorphous adenocarcinoma	1	0.6	0	0
AJCC Stage				
Stage I	7	4.5	0	0
Stage II	35	22.6	6	10.5
Stage III	42	27.1	10	17.6
Stage IV	71	45.8	41	71.9
T stage				
T1	11	7.1	3	5.3
T2	38	24.5	24	42.1
T3	47	30.3	18	31.6
T4	59	38.1	12	21.1
N stage				
N0	116	74.8	13	22.8
N1	12	7.7	7	12.3
N2	27	17.4	32	56.1
N3	0	0	5	8.8
Extracapsular tumor spread	15	9.7	21	36.8
5-year survival rate	55*	53.9*	9**	22.5**

* Total 106 diagnosed cases before 2006, loss follow-up 4 cases; ** Total 41 diagnosed cases before 2006, loss follow-up 1 case

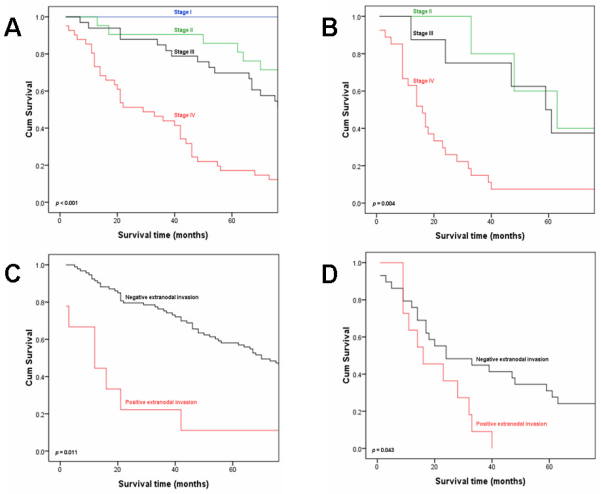

Figure 1. Disease-Specific 5-Year Survival Rates According to The Kaplan-Meier Method by Disease Stage (A, laryngeal cancer; B, hypopharyngeal cancer), and disease-specific 5-year survival rates according to the Kaplan-Meier method by extracapsular tumor spread; (C, laryngeal cancer; D, hypopharyngeal cancer).

surgical procedure varied from total laryngectomy (86.8%), supracricoid laryngectomy (8%), hemilaryngectomy (3.3%), frontolateral partial laryngectomy (0.9%) and extended epiglottectomy (0.9%). The average length of total hospitalization and postoperative stay was 26.7 and 20.9 days, respectively. The overall 5-year survival of laryngeal cancer and hypopharyngeal cancer was 53.9% and 22.5%, respectively. Radiotherapy and chemotherapy were given in 143 (67.5%) and 45 (21.2%) laryngectomized patients, respectively.

Table 2. Patients' Characteristics with Laryngeal Cancer and Hypopharyngeal Cancer

Detail	Laryngeal cancer (n = 155)	Hypopharyngeal cancer (n = 57)
Mean age (years) ± SD	61.5±9.4	63.8±10.2
Preoperative hematocrit (%) ± SD	39.3±5.3	39.9±5.5
Maximum tumor size (cm.) ± SD	2.6±1.4	3.4±1.3
Nearest surgical margin (cm.) ± SD	0.7±0.5	0.5±0.3
Total admission day (days) ± SD	25.8±22.1	29.1±23.5
Total postoperative admission day (days) ± SD	19.6±13.9	24.2±22.7
Disease-free survival time with 95% CI (months)	61 (45.3-76.7)*	18 (6.9-29.1)**
Stage I	99 (83.6-114.4)	-
Stage II	88 (68.6-107.4)	63 (30.8-95.2)
Stage III	70 (52.2-87.8)	59 (39.6-78.4)
Stage IV	18 (9.6-26.4)	11 (8.5-13.5)
Median survival time with 95% CI (months)	67 (49.7-84.3)*	23 (13.7-32.3)**
Stage I	118 (84.6-151.4)	-
Stage II	108 (78.1-137.9)	63 (30.8-95.2)
Stage III	78 (60-96)	59 (39.6-78.4)
Stage IV	29 (14.7-43.3)	16 (10.9-21.1)

* Total 106 diagnosed cases before 2006, loss follow-up 4 cases; ** Total 41 diagnosed cases before 2006, loss follow-up 1 case

Table 3. Anatomical Location of Lesions in The 212 Patients with Laryngeal Cancer and Hypopharyngeal Cancer

Location	Laryngeal cancer* (n = 155)		Hypopharyngeal cancer* (n = 57)	
	No. of patients	Percent	No. of patients	Percent
True vocal cord				
Right	32	20.6	5	8.8
Left	33	21.3	4	7
Bilateral	69	44.5	4	7
False vocal cord				
Right	24	15.5	6	10.5
Left	26	16.8	6	10.5
Bilateral	38	24.5	4	7
Laryngeal ventricle				
Right	22	14.2	7	12.3
Left	25	16.1	4	7
Bilateral	36	23.2	3	5.3
Pyriform sinus				
Right	12	7.7	22	38.6
Left	9	5.8	23	40.4
Bilateral	2	1.3	9	15.8
Subglottis				
Right	26	16.8	3	5.3
Left	15	9.7	1	1.8
Bilateral	32	20.6	1	1.8
Anterior commissure	102	65.8	1	1.8
Posterior commissure	27	17.4	7	12.3
Preepiglottic space	41	26.5	4	7
Paraglottic space				
Right	21	13.5	14	24.6
Left	14	9	11	49.3
Bilateral	20	12.9	1	1.8
Epiglottis	21	13.5	10	17.6
Aryepiglottic fold				
Right	18	11.6	17	29.8
Left	12	7.7	15	26.3
Bilateral	7	4.5	1	1.8
Vallecula	2	1.3	1	1.8
Thyroid cartilage				
Right	16	10.3	3	5.3
Left	11	7.1	3	5.3
Bilateral	10	6.5	0	0
Cricoid cartilage				
Right	8	5.2	0	0
Left	3	1.9	1	1.8
Bilateral	6	3.9	0	0
Cricothyroid membrane				
Right	16	10.3	2	3.5
Left	11	7.1	3	5.3
Bilateral	10	6.5	0	0
Arytenoid cartilage				
Right	11	7.1	5	8.8
Left	11	7.1	4	7
Bilateral	11	7.1	2	3.5
Trachea				
Right	2	1.3	0	0
Left	0	0	0	0
Bilateral	2	1.3	0	0
Thyroid gland				
Right	5	3.2	0	0
Left	0	0	1	1.8
Bilateral	2	1.3	0	0

* the patients may have one or more than one lesions

Table 4. Five-Year Survival Rate in The 142 Patients with Laryngeal Cancer and Hypopharyngeal Cancer Correlated with Clinicopathologic Findings

Clinicopathologic findings	Laryngeal cancer (n = 102)		Hypopharyngeal cancer (n = 40)	
	No. of patients	*p*	No. of patients	*p*
Histopathology		0.036		0.863
SCC, well-differentiated	49/82 (59.8%)		6/25 (24%)	
SCC, moderately-differentiated	5/13 (38.5%)		1/7 (14.3%)	
SCC, poorly-differentiated	0/5 (0%)		2/7 (28.6%)	
Adenosquamous carcinoma	0/1 (0%)		0/1 (0%)	
Atypical carcinoid tumor	1/1 (100%)		-	
AJCC Stage		<0.001		0.004
Stage I	7/7 (100%)		-	
Stage II	18/21 (85.7%)		3/5 (60%)	
Stage III	23/33 (69.7%)		4/8 (50%)	
Stage IV	7/41 (17.1%)		2/27 (7.4%)	
T stage		<0.001		0.098
T1	7/8 (87.5%)		0/2 (0%)	
T2	19/25 (76%)		7/18 (38.9%)	
T3	23/34 (67.6%)		2/10 (20%)	
T4	6/35 (17.1%)		0/10 (0%)	
N stage		<0.001		0.055
N0	51/80 (63.8%)		5/10 (50%)	
N1	3/8 (37.5%)		2/6 (33.3%)	
N2	1/14 (7.1%)		2/22 (9.1%)	
N3	-		0/2 (0%)	
Extracapsular tumor spread	1/9 (11.1%)	0.011	0/11 (0%)	0.043
Smoking (%)	51/94 (54.3%)	1	8/36 (22.2%)	1
Median survival time in smoking patients with 95% CI (months)	67.0 (48.0-86.0)		20.0 (11.8-28.2)	

The postoperative sequelae related to laryngectomy were evaluated for all patients. The common postoperative sequelae was hypothyroidism (165 cases, 77.8%), followed by hypocalcemia (128 cases, 60.4%), and

Table 5. Five-Year Survival Rate in Patients with Laryngeal Cancer and Hypopharyngeal Cancer Correlated with Anatomical Location of Cancer

Location	Laryngeal cancer* (n = 102)		Hypopharyngeal cancer* (n = 40)	
	No. of patients	*p*	No. of patients	*p*
True vocal cord		0.083		0.654
Positive	51/89 (57.3%)		1/9 (11.1%)	
Negative	4/13 (30.8%)		8/31 (25.8%)	
False vocal cord		0.003		1
Positive	22/55 (40%)		2/11 (18.2%)	
Negative	33/47 (70.2%)		7/29 (24.1%)	
Laryngeal ventricle		0.073		1
Positive	22/50 (44%)		2/10 (20%)	
Negative	33/52 (63.5%)		7/30 (23.3%)	
Subglottis		0.072		0.557
Positive	19/44 (43.2%)		0/4 (0%)	
Negative	36/58 (62.1%)		9/36 (25%)	
Pyriform sinus		0.401		1
Positive	6/14 (42.9%)		9/39 (23.1%)	
Negative	49/88 (55.7%)		0/1 (0%)	
Anterior commissure		0.674		1
Positive	30/68 (44.1%)		0/1 (0%)	
Negative	17/34 (50%)		9/39 (23.1%)	
Posterior commissure		0.113		1
Positive	6/17 (35.3%)		0/3 (0%)	
Negative	49/85 (57.7%)		9/37 (24.3%)	
Preepiglottic space		0.001		1
Positive	5/22 (22.7%)		1/4 (25%)	
Negative	50/80 (62.5%)		8/36 (22.2%)	
Paraglottic space		0.003		0.707
Positive	10/32 (31.3%)		3/17 (17.7%)	
Negative	45/70 (64.3%)		6/23 (26.1%)	
Epiglottis		0.041		0.175
Positive	2/10 (20%)		0/7 (0%)	
Negative	53/92 (57.6%)		9/33 (27.3%)	
Aryepiglottic fold		0.327		0.134
Positive	9/21 (42.9%)		3/23 (13%)	
Negative	46/81 (56.8%)		6/17 (35.3%)	
Vallecula		0.461		-
Positive	0/1 (0%)		-	
Negative	55/101 (54.5%)		9/40 (22.5%)	
Thyroid cartilage		<0.001		0.306
Positive	3/21 (14.3%)		0/6 (0%)	
Negative	52/81 (64.2%)		9/34 (26.5%)	
Cricoid cartilage		0.295		1
Positive	3/9 (33.3%)		0/1 (0%)	
Negative	52/93 (55.9%)		9/39 (23.1%)	
Cricothyroid membrane		0.008		0.545
Positive	4/17 (23.5%)		1/3 (33.3%)	
Negative	51/85 (60%)		8/37 (21.6%)	
Arytenoid cartilage		0.056		0.09
Positive	8/23 (34.8%)		0/9 (0%)	
Negative	47/79 (59.5%)		9/31 (29%)	
Trachea		0.21		-
Positive	0/2 (0%)		-	
Negative	55/100 (55%)		9/40 (22.5%)	
Thyroid gland		0.094		1
Positive	0/3 (0%)		0/1 (0%)	
Negative	55/99 (55.6%)		9/39 (23.1%)	

* the patients may have one or more than one lesions

Table 6. Multivariate Analysis of Predictors of 5-Year Survival In Laryngeal Cancer and Hypopharyngeal Cancer

Variables	Laryngeal cancer* (n = 102)					Hypopharyngeal cancer* (n = 40)				
	SE	*P*	OR	95% CI for OR		SE	*P*	OR	95% CI for OR	
				Lower	Upper				Lower	Upper
Histopathology	0.12	0.041	1.277	1.01	1.615	0.195	0.407	1.175	0.802	1.721
T stage	0.126	<0.001	1.692	1.323	2.164	0.229	0.007	1.856	1.185	2.908
N stage	0.225	0.008	1.823	1.173	2.834	0.229	0.047	1.576	1.006	2.469
Extracapsular tumor spread	0.539	0.778	0.859	0.299	2.469	0.427	0.534	1.305	0.565	3.013

pharyngocutaneous fistula (12 cases, 5.7%).

The median follow-up time for the remaining 142 patients (2000-2006) was 48 months (range 1 to 142 months). Five patients had no complete follow-up data and therefore were excluded from the survival analysis. At the time of analysis, 64 patients (45.1%) were alive, 77 patients (54.2%) died of cancers and 1 patient (0.7%) died by accident. Of 147 patients, 51 (34.7%) developed recurrence. Distribution of recurrence and metastasis by site were as follows: lung in 30 patients (20.4%),

tracheostoma in 16 patients (10.9%), cervical lymph node in 12 patients (9.4%), bone in 9 patients (6.1%), skin in 7 patients (4.8%), and liver in 3 patients (2%). The details of disease free survival and median survival time are shown in Table 2. The 5-year survival rate for node-negative cases was 61.8% versus 17% for node-positive cases ($p< 0.001$), as shown in Figure 1. The univariate analysis of 5-year survival was found to correlate with various clinicopathologic findings of 142 patients with laryngeal cancer and hypopharyngeal cancer, as shown in Table 4 and 5. The multivariate analysis of 5-year survival was correlated with various clinicopathologic findings of 142 patients with laryngeal cancer and hypopharyngeal cancer, as shown in Table 6.

Discussion

Laryngeal cancer and hypopharyngeal cancer are two common malignant cancers of the upper respiratory tract. The prevalence of laryngeal cancer and hypopharyngeal cancer is increasing. The authors have described our experience in managing 155 and 57 laryngectomized patients with laryngeal cancer and hypopharyngeal cancer, respectively. The mean age of these patients was 62.08 ± 9.67 years although the age range extended from 38 to 84 years; about 95% of the patients were more than 45 years. This age range is consistent with the previously reported age-group in which the age range of patients with laryngeal cancer was 29 to 90 years (Boonyaphiphat et al., 1994; Chitapanarux et al., 2014; Dechaphumkul et al., 2011; Jantharapattana 2013; Ratanaanekchai and Reechaipichitkul, 2006). The prevalence for laryngeal cancer and hypopharyngeal cancer seems to increase with age. Laryngeal cancer and hypopharyngeal cancer are nineteen times more common in men than in women (Boonyaphiphat et al., 1994; Chitapanarux et al., 2014; Dechaphumkul et al., 2011; Jantharapattana 2013; Ratanaanekchai and Reechaipichitkul, 2006). Smoking is the most important risk factor for laryngeal cancer and hypopharyngeal cancer. Ninety percent of our patients were smokers, in which there is more prevalence in laryngeal cancer than hypopharyngeal cancer. SCC is the most common malignant cell type in laryngectomized patients.

Laryngeal cancer is often detected at an early stage because complaints of hoarseness and change in voice occur relatively early in the nature of disease. Hypopharyngeal cancer provokes complaints in an advanced stage and the cervical lymphadenopathy is the most common presentation. The average maximum tumor size of hypopharyngeal cancer (3.4 ± 1.3 cm) was larger than that of laryngeal cancer (2.6 ± 1.4 cm). Therefore the overall prognosis in hypopharyngeal cancer was poorer than laryngeal cancer.

In accordance with many studies, the present data confirmed that the common postoperative sequelae was hypothyroidism (77.8%), followed by hypocalcemia (60.4%) and pharyngocutaneous fistula (5.7%) (Hall et al., 2003; Ratanaanekchai et al., 2004; Sparano et al., 2005). Moreover, in this study, there were five patients who developed hypercalcemia after laryngectomy with total thyroidectomy and parathyroidectomy. Hypothyroidism has been reported in up to one fourth of patients without adjunctive radiotherapy and in up to 70% with radiotherapy (Ho et al., 2008). Hypocalcemia caused by surgically induced hypoparathyroidism may occur with advertent removal of parathyroid glands during thyroidectomy. Hypercalcemia is an uncommon complication encountered, frequently associated with subsequent recurrence and systemic metastasis. The pathogeneses of hypercalcemic paraneoplastic syndrome include 1) bony osteolytic metastasis, which was found in only one case of this study; 2) the production of calcemic tumoral substance such as parathyroid hormone-related peptide, interleukin-1, transforming growth factor-alpha, tumor necrotic factor, and 1, 25-dihydroxyvitamin D, which could not be confirmed in the authors' study. It is important for the laryngologist to inform the patient that a relative frequency of postoperative sequelae could be encountered.

The prevalence of distant metastasis in laryngeal cancer was 7.2% and lung was the most common site (Yucel et al., 1999). In the present study, lung is also the most common metastasized site, followed by bone, skin, and liver. Stomal recurrence occurs in 1.7% to 14.7% of all patients who have undergone laryngectomies (Rubin et al., 1990; Esteban et al., 1993). In the authors' report, stomal invasion occurred in 10.9%. The precise pathogenesis of stomal recurrence remains unknown. The possible pathogeneses include: 1) unrecognized tumor at the surgical resected margin; 2) development of a second primary malignancy; 3) tumor implantation at the time of tracheostomy or primary surgery; and 4) recurrence secondary to metastases in the paratracheal or pretracheal lymph nodes (Barnes, 2009).

In previous studies, the prognostic value of other clinicopathologic variables (i.e., patient age, lesion size, histopathologic grade, margin status, surgical status of the cervical nodes, AJCC stage) has been demonstrated (Barnes et al., 2005; Barnes, 2009; Ramroth et al., 2011). The present study was able to show that advanced AJCC stage, advanced tumor status, advanced nodal status and tumor invasion of the false vocal cord, epiglottis, preepiglottic space, paraglottic space, thyroid cartilage, cricothyroid membrane were significantly associated with 5-year survival rate ($p< 0.001$) in laryngeal cancer by univariate analysis, but the advanced nodal status did not affect the disease-free survival. These results are similar to previous reports (Barnes et al., 2005; Barnes, 2009; Ramroth et al., 2011) and additional demonstrate that the poor prognostic parameter of tumor-invasion of cricothyroid membrane, which is not describe in the recent WHO T-stage (Barnes et al., 2005).

Invasion of the laryngeal cartilages, T4, is an adverse prognostic indicator associated with an increased incidence of nodal metastasis. Cricothyroid membrane involvement is a sign of aggression of laryngeal cancer. This cricothyroid membrane is the soft tissue between cricoid and thyroid cartilages, which is easily tumor invasion more than the cartilaginous part of cricoid and thyroid cartilages. Normal laryngeal cartilage is resistant to tumor invasion because of its ability to release proteins

that inhibit substances known to facilitate invasion such as collagenase, other proteinase and tumor angiogenetic factors (Kuettner et al., 1977). This cricothyroid involvement is a more common finding in T4 stage tumor. Moreover, there were 15 cases in laryngectomized patients with tumor invading cricothyroid membrane without laryngeal cartilaginous involvement in the present study. These patients had overall survival and disease free survival resembling T4 tumor status. The cricothyroid membrane invasion was significantly associated with decreased 5-year survival in laryngectomized patients with laryngeal cancer ($p = 0.008$). All laryngectomized specimens must be serially cut for searching tumor involvement of cricothyroid membrane.

The supraglottis including false vocal cord, preepiglottis, and epiglottis is richly supplied with lymphatic system whereas the glottis has little to no lymphatic drainage, which makes the cancer invading supraglottis more prone to have lymphatic metastasis. Moreover, the preepiglottic space is poorly vascularized (Fletcher and Hamberger, 1974). The anoxic concept of tumor invading preepiglottic space must be significant, possibly explaining the relative radioresistant, which also affects the survival. In the authors' series, laryngeal cancer involving false vocal cord, epiglottis and preepiglottic space was significantly associated with decreased 5-year survival rate. However there was no association in the case of hypopharyngeal cancer. Only advanced AJCC stage was significantly associated with 5-year survival in hypopharyngeal cancer ($p = 0.004$). This result is similar to previous data (Barnes et al., 2005; Barnes, 2009). Prognostic factors in laryngeal cancer are not significant in hypopharyngeal cancer because tumor invasion of the false vocal cord, epiglottis, preepiglottic space, paraglottic space, thyroid cartilage, cricothyroid membrane are uncommon site of invasion in hypopharyngeal cancer. Therefore, the result shows a statistically insignificant relationship between tumor invasion and 5-year survival. The other parameters including postcricoid and upper esophageal involvements are not included in our study, because there are only three case of postcricoid invasion and one case of esophageal invasion. Small sample sizes do not yield statistical significance.

The presence of extracapsular tumor spread should be determined by histopathologic examination of the lymphadenectomy specimen. The presence of extracapsular tumor spread in metastatic lymph nodes augments the risk of distant metastasis by nine times in laryngeal cancer and correlates with the 5-year survival (Oosterkamp et al., 2006). Extracapsular tumor spread may represent a biologic staging parameter that should be viewed as an aid in the selection of more-intensive or less-intensive radiotherapy. The occurrence of extracapsular tumor spread should be given in the pathologic report as TNEM (tumor, node, extracapsular tumor spread and metastasis) staging system. However, multivariate 5-year survival analysis of extracapsular tumor spread in both laryngeal cancer and hypopharyngeal cancer are not statistically significant ($p = 0.778$ and $p = 0.534$, respectively). The TNEM category might be helpful in better prognostic determination of laryngectomized patients. Prospective study of TNEM staging system of laryngeal cancer should be studied in more detail.

Since the present report was a retrospective study, some information was missing and incomplete. The limitation in the present study was varying technique of the surgical procedure including total laryngectomy, supracricoid laryngectomy, hemilaryngectomy, frontolateral partial laryngectomy, and extended epiglottectomy. However, most common surgical procedure was total laryngectomy (86.8%). Another limitation was the patients who were treated by various physicians over a long period of time. In addition, because the study period spans more than 10 years, the data may not represent current practice patterns, which tend to be minimally invasive and organ preservation surgery.

In conclusion, most patients with laryngeal cancer manifest with hoarseness. Cervical lymphadenopathy and odynophagia are commonly present in hypopharyngeal cancer. The advanced AJCC stage, advanced T stage, advanced N stage, extracapsular tumor spread, and tumor invasion of false vocal cord, epiglottis, preepiglottic space, paraglottic space, thyroid cartilage, and cricothyroid membrane significantly augment the decrease of 5-year survival in laryngeal cancer. Only advanced stage was significantly associated with 5-year survival rate in hypopharyngeal cancer. Accurate diagnosis of the pathological stage is essential for patient counseling and informed decision making. The authors believed that this report had provided clinicopathologic data for Thai laryngectomized patients with laryngeal cancer and hypopharyngeal cancer.

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References

Barnes L (2009). Disease of the larynx, hypopharynx and trachea. In: Surgical pathology of the head and neck, Barnes L, ed., 3rd ed. Informa healthcare USA, New York, pp 109-200.

Barnes L, Tse LLY, Hunt JL, et al (2005). Tumours of the hypopharynx, larynx and trachea: Introduction. In: Barnes L, Eveson JW, Reichart P, Sidransky D (Editors). World health organization classification of tumours. Pathology and genetics of head and neck tumours. Lyon: IARC Press, pp 111-7.

Boonyaphiphat P, Mitarnun W, Boonyaphiphat P (1994). Precancerous lesion and early carcinoma of the pyriform sinus. *J Med Assoc Thai*, **77**, 187-94.

Chitapanarux I, Tharavichitkul E, Chakrabandhu S, et al (2014). The treatment outcome of radical radiotherapy in laryngeal cancer. *J Med Assoc Thai*, **97**, 101-6.

Dechaphunkul T (2011). Epidemiology, risk factors, and overall survival rate of laryngeal cancer in Songklanagarind Hospital. *J Med Assoc Thai*, **94**, 355-60.

Esteban F, Moreno JA, Delgado-Rodriguez M, Mochon A (1993). Risk factors involved in stomal recurrence following

laryngectomy. *J Laryngol Otol*, **107**, 527-31.
Fletcher GH, Hamberger AD (1974). Causes of failure in irradiation of squamous-cell carcinoma of the supraglottic larynx. *Radiology*, **111**, 697-700.
Hall FT, O'Brien CJ, Clifford AR, et al (2003). Clinical outcome following total laryngectomy for cancer. *ANZ J Surg*, **73**, 300-5.
Ho AC, Ho WK, Lam PK, Yuen AP, Wei WI (2008). Thyroid dysfunction in laryngectomees-10 years after treatment. *Head Neck*, **30**, 336-40.
Jantharapattana K (2013). Oncologic and functional outcomes in advanced laryngeal and hypopharyngeal cancer treated with concurrent chemoradiation versus primary surgery followed by adjuvant treatment. *J Med Assoc Thai*, **96**, 1164-8.
Kuettner KE, Soble L, Croxen RL, et al (1977). Tumor cell collagenase and its inhibition by a cartilage-derived protease inhibitor. *Science*, **196**, 653-4.
Oosterkamp S, de Jong JM, Van den Ende Pl, et al (2006). Predictive value of lymph node metastases and extracapsular extension for the risk of distant metastases in laryngeal carcinoma. *Laryngoscope*, **116**, 2067-70.
Ramroth H, Schoeps A, Rudolph E, et al (2011). Factors predicting survival after diagnosis of laryngeal cancer. *Oral Oncol*, **47**, 1154-8.
Ratanaanekchai T, Art-smart T, Vatanasapt P (2004). Dysphagia after total laryngectomy resulting from hypocalcemia: case report. *J Med Assoc Thai*, **87**, 722-4.
Ratanaanekchai T, Reechaipichitkul W (2006). Recurrent laryngeal cancer after surgical treatment. *J Med Assoc Thai*, **89**, 350-3.
Rubin J, Johnson JT, Myers EN (1990). Stomal recurrence after laryngectomy: interrelated risk factor study. *Otolaryngol Head Neck Surg*, **103**, 805-12.
Sparano A, Chernock R, Laccourreye O, Weinstein G, Feldman M (2005). Predictors of thyroid gland invasion in glottic squamous cell carcinoma. *Laryngoscope*, **115**, 1247-50.
Yucel OT, Yilmaz T, Unal OF, Turan E (1999). Distant metastases in laryngeal squamous cell carcinoma. *J Exp Clin Cancer Res*, **18**, 285-8.