RESEARCH COMMUNICATION

Survival and Prognostic Factors of Different Sites of Head and Neck Cancer: An Analysis from Thailand

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Abstract

Background: Head and neck cancers are prevalent in Thailand, in particular in the southern region of the country. However, survival with a large data set has not been reported. The purpose of the present study was to evaluate the survival figures and the prognostic factors in a cohort of patients treated in a university hospital located in the south of Thailand. Patients and Methods: Consecutive new cases of primary carcinoma of the oral cavity, oropharyx, hypopharynx and larynx, treated at Songklanagarind Hospital during 2002 to 2004, were analyzed. The 5-year overall survival rates were obtained by the Kaplan-Meier method. Prognostic factors were identified through multivariate Cox regression analysis. Results: A total 1,186 cases were analyzed. Two-thirds (66.6%) of the cases were at advanced stage (stage III & IV) at presentation. The five-year overall survivals for the whole cohort, oral cavity, oropharynx, hypopharynx and larynx were 24.1%, 25.91%, 19.2%, 13.4%, 38.0% respectively. Stage and treatment type were strong prognostic factors for all sites. An age ≥ 80 years was associated with poor survival in oral cavity and larynx cancer. Conclusions: The results revealed remarkably poor outcomes of the patients in the series, indicating a strong need to increase the proportion of early stage presentations and maximize the treatment efficacy to improving outcomes. Very old patients are of particular concern for treatment care of oral cavity and larynx cancer.

Keywords: Head and neck cancer - upper aerodigestive tract - cancer - survival - prognosis - Thailand

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Introduction

Head and neck cancer (HNCA) is among the major public health problem worldwide, especially in developing countries (Jemal et al., 2011). Oral cavity cancer is the most common among the various anatomical subsites. In Thailand, HNCA is common in the southern region et al., 2010). The age-standardized incidence rate (ASR) of oral cavity cancer in males in Songkhla province, southern Thailand, is among the highest incidences (8.3 per 100,000), slightly lower than the eastern region of the country but it is considerably higher than the average global incidence in both developed (6.9 per 100,000) and less developed areas (4.6 per 100,000) (Jemal et al., 2011). Head and neck cancer is known to be associated with high morbidity and mortality. Mortality from oral cancer averages less than half the incidence (Jemal et al., 2011). The 5-year survival rate of HNCA has subtly increased during the past two decades, in contrast with the advances in treatment modality (Carvalho et al., 2005). This figure is largely a result of the advanced stage of the disease at diagnosis which, in turn, limits or causes suffering from treatment. In addition, the survival and prognostic factors of different anatomical sites are reported to differ. The 5-year survival rates fall between 40 to 60%, based on the site (Woolgar et al., 1999; Pericot et al., 2000). These rates are likely the result of multiple factors, including the stage of disease at the time of diagnosis, treatment modalities, and the site-specific morbidity associated with each treatment.

Although the survival rate of HNCA has been frequently cited as subtly changing during the past years, an analysis of survival based on the Surveillance, Epidemiology and End Results (SEER) database in the United States form 1973 to1997 revealed a significant improvement of the 5-year survival rates of some specific sites, including the nasopharynx, oropharynx and hypopharynx (Carvalho et al., 2005). Even though HNCA is among the five leading cancers in Thailand, the survival figure of the disease has been rarely reported in the literature. Therefore, we have analyzed the overall survival rates and clinicopathological prognostic factors of a cohort of HNCA patients treated at a university hospital located in the south of Thailand. A special focus of this study is a site-specific analysis, including the oral cavity, oropharyx, hypopharynx and larynx. Our study has provided the current situation for

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survival figures and treatment results of HNCA in our institution, which approximately represents the survival figure in the population.

Materials and Methods

Patients and clinical information

The study included all new patients with primary carcinoma of the four anatomical sites in the head and neck region, including the oral cavity (ICD10, C00-C06), oropharyx (C09-C10), hypopharynx (C12-C13) and larynx (C32), who sought treatment at Songklanagarind Hospital from January 2002 to December 2004.

Case finding and clinicopathological data as well as follow-up information were prospectively collected from hospital and pathological records by a trained nurse of the Department of Otorhinolaryngology, Faculty of Medicine, Prince of Songkla University. For patients who were treated by the Department of Surgery, the data was retrieved from the Cancer Registry Unit of Songklanagarind Hospital which is responsible for registering all cancer cases in the hospital. Patients diagnosed in either our hospital or at other hospitals and referred for treatment were included. Data on stages was missing in patients who did not come for further investigation or treatment after diagnosis.

Primary tumors, lymph node involvement and stage determination were classified according to the International Union Against Cancer (UICC) classification, Fifth Edition, 1997. Pretreatment staging and evaluation included complete history taking, physical examinations and investigations. Physical examinations included a complete otolaryngologic endoscopic examination under local or general anesthesia. Plain film of the chest and a CT scan of the head and neck were done in most cases for primary, nodal and distant metastasis evaluation. Complete blood count, blood urea nitrogen, serum creatinine and liver function tests were basic laboratory workups.

Treatment protocol

All new cancer patients were subject to treatment planning based on a multidisciplinary tumor conference. Performance status based on the Eastern Cooperative Oncology Group (ECOG) (Oken et al., 1982) was assessed for a treatment decision. Either surgery or radiotherapy was the only modalities in stage I and early stage II cancer. Combined surgery and radiotherapy was chosen for patients with late stage II, stage III and stage IV cancer. Radiochemotherapy was the treatment of choice for advanced stage cancer with an unacceptable outcome of surgical morbidity and for patients who had an ECOG scale of 0-2. Radiotherapy alone was considered for palliative treatment in patients with advanced stage disease and who were not physically fit for combined therapy.

Radiation protocol

Patients were treated with a 6 MV linear accelerator or Cobalt-60 machine. The position and treatment fields were determined by conventional simulation. The daily conventional fractionation of 2 Gy per fraction was used to deliver a radiation dosage of 66-70 Gy in 33-35 fractions over 45-47 days for the primary tumors and macroscopic lymph node. The adjacent non-tumor area or the negative surgical margin was treated with 50-54 Gy in 25-27 fractions. The spinal cord was shielded after 40-44 Gy, then the electron beams were used for the remaining optimal radiation dosage.

Death information

Death information was retrieved from the Department of Provincial Administration, Ministry of Interior. In Thailand, death has to be reported to the local registration office within 24 hours. Census registration data is linked nationwide and can be assessed with authorized permission. The Cancer Registry Unit of the hospital updates the death information from the census registration data twice yearly. Patients not found dead in this database up to December 2008 were designated as alive in this study cohort. The cause of death was classified as related or unrelated to cancer.

Statistical analysis

Statistical analysis was carried out using the statistical package STATA version 6.0. Two-year and 5-year overall survival of the whole cohort and of each anatomical site were obtained by the Kaplan-Meier method and the significance of differences between curves as classified by variable category was evaluated by the log-rank test as univariate analysis. The starting date of the analysis was set at the date of definite clinical diagnosis usually confirmed by pathological reports. The endpoint was the date of death updated most recently, during October to December 2008. Patients who were still alive at this time were considered as censored cases. Multivariate Cox proportional hazards regression was performed to investigate the relationship between clinicopathological characteristics and survival. A p value less than or equal to 0.05 was considered statistically significant.

Results

During 2002 to 2004, there was a total of 1,186 cases of HNCA, including 410 oral cavity cases (34.6%), 357 oropharynx cases (30.1%), 198 hypopharynx cases (16.7%) and 221 larynx cases (18.6%). The histological type of the tumors was mostly squamous cell carcinoma (94.8%).

Patient characteristics for all cases and each site are shown in Table 1. The mean age of the patients was 65.43 years and equal for all sites. Approximately 90% of patients were males, except in oral cavity where males constituted 58% of the cases. Two-third (66.61%) of the cases presented with advanced stage (stages III & IV) cancer. Hypopharynx cancer had the highest proportion of patients with advanced stage (84.85 %), while larynx cancer had the smallest proportion (58.37%). Radiation alone was the most common treatment for all sites (32.7-51.8%) while a minority of patients receiving surgery alone (1.4-8.78%). Nearly one-third of the patients (337 cases, 28.41%) received no treatment. These untreated patients were slightly older than the treated group (68.19 versus 64.33 years) and the stages of disease at diagnosis were stage I-II, 20.18%; stage III-IV, 64.99% and

unknown stage, 14.84% compared to 30.86%, 67.26% and 1.88%, respectively, in the treated patients (data not shown).

For the whole series, 889 patients (74.96%) were dead at the end of 2008. The overall median survival time was 24.08 months with 2-year and 5-year overall survival (OS) rates of 37.76% and 24.08% respectively. The 5-year OS among the four sites was significantly different (p value of log-rank test 0.000). Larynx cancer had the highest 2-year and 5-year OS (57.36% and 38.00%), followed by oral cancer (36.36% and 25.91%), oropharynx (32.96% and 19.24%) and hypopharynx (27.41% and 13.43%) (Figure 1). The survival curves orderly declined from higher to lower stages. The survival curve of each stage is clearly separated in oral cavity cancer with some overlapping in other cancer sites. Five-year OS according to clinicopathological variables are present in Table 2. Univariate analysis using log-rank test revealed that stage and treatment were consistently significantly

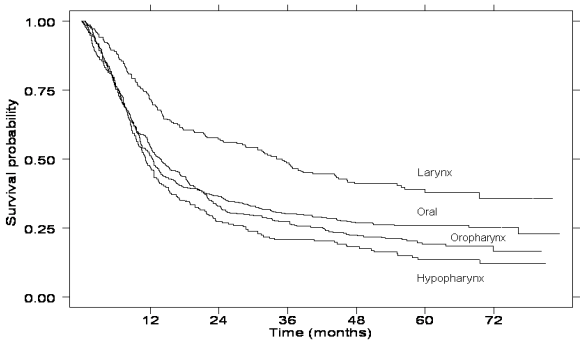

Figure 1. The Overall Survival According to the Four Anatomical Sites

Table 1. Patient Characteristics of All Cases and by the Four Anatomical Sites

Variables	Number of cases (%)				
	All cases	Oral cavity	Oropharynx	Hypo-pharynx	Larynx
Age (mean, SD)	65 (12)	65 (13)	65 (11)	66 (11)	66 (11)
Gender:					
Male	55 (81)	238 (58)	328 (92)	184 (92)	205 (93)
Female	31 (20)	172 (42)	29 (8)	4 (7)	6 (7)
Stage:					
I	3 (13)	61 (15)	33 (9)	(4)	1 (23)
II	7 (15)	75 (18)	63 (18)	9 (5)	0 (14)
III	6 (22)	82 (20)	89 (25)	46 (23)	49 (22)
IV	4 (44)	163 (40)	159 (45)	122 (62)	80 (36)
Unknown	6 (6)	9 (7)	3 (4)	3 (7)	1 (5)
Treatment:					
Surgery	9 (4)	36 (9)	5 (1)	2 (1)	6 (3)
RT a	14 (43)	134 (33)	185 (52)	97 (49)	98 (44)
Surgery	286 (24)	114 (28)	65 (18)	48 (24)	59 (27)
No	37 (28)	126 (31)	102 (29)	51 (26)	58 (26)
Differentiation:					
Well	416 (35)	214 (52)	94 (26)	39 (20)	69 (31)
Moderate	303 (26)	77 (19)	120 (34)	59 (30)	47 (21)
Poor	136 (12)	19 (5)	60 (17)	34 (17)	23 (10)
Unknown	331 (28)	100 (24)	83 (23)	66 (33)	81 (37)

* 'Abbreviations: RT, radiotherapy

Table 2. Five-Year Overall Survival Rates, According to Clinicopathological Variables

Variables	All cases	Oral cavity	Oro-pharynx	Hypo-pharynx	Larynx
Age:					
< 60	26.8	29.6	20.3	11.1	45.6
60-69	29.3	29.3	25.3	20.9	42.7
70-80	20.4	24.2	13.7	11.3	33.3
> 80	12.0	14.9	8.1	5.9	10.5
p	0.000[a]	0.134	0.056	0.383	0.000
Gender					
Male	23.1	24.2	18.9	13.4	49.1
Female	28.2	28.3	22.6	14.3	37.4
p	0.437	0.635	0.811	0.542	0.133
Stage					
I	53.7	45.7	47.7	0	69.8
II	34.5	37.5	26.2	44.4	38.7
III	24.1	20.1	19.7	23.8	37.9
IV	12.8	14.8	10.5	7.2	21.5
Unknown	17.5	32.2	15.4	0	0
p	0.000	0.000	0.000	0.000	0.000
Treatment					
Surgery	59.8	61.7	80.0	0	50.0
RT	20.8	18.6	17.8	11.8	38.6
Surgery	38.5	32.7	38.7	29.7	56.4
Untreated	11.4	17.1	6.0	0	16.8
p	0.000	0.000	0.000	0.000	0.000
Differentiation					
Well	27.8	27.3	21.2	12.8	46.2
Moderate	20.3	25.1	16.8	14.5	27.2
Poor	22.9	0	20.4	29.8	33.5
Unknown	23.2	27.2	19.0	5.1	37.7
p	0.635	0.055	0.751	0.024	0.242

* '[a]p value, log-rank test

Table 3. Multivariate Cox Regression Analysis of Oral Cavity and Oropharynx Cancer

Variables	Oral cavity		Oropharynx	
	HR (95% CI)	p	HR (95% CI)	p
Age:				
<60	1		1	
60-69	1.01 (0.73-1.39)	0.94	1.00 (0.73-1.38)	0.96
70-79	1.06 (0.78-1.44)	0.70	1.41 (1.04-1.93)	0.03
> 80	1.57 (1.09- 2.27)	0.02	1.04 (0.67-1.64)	0.84
Gender:				
Male	1		1	
Female	1.14 (0.88- 1.47)	0.29	0.96 (0.61-1.51)	0.87
Stage:				
I	1		1	
II	1.23 (0.77-1.95)	0.38	2.02 (1.14-3.55)	0.02
III	1.93 (1.24-3.00)	0.00	2.15 (1.24-3.74)	0.01
IV	2.70 (1.80-4.06)	0.00	3.53 (2.09-5.94)	0.00
Unknown	1.15 (0.63-2.13)	0.64	2.16 (0.95-4.89)	0.07
Treatment:				
RT	1		1	
Surgery	0.33 (0.18-0.61)	0.00	0.17 (0.02-1.27)	0.09
Surgery+RT	0.62 (0.45-0.84)	0.00	0.57 (0.40-0.82)	0.00
No	1.29 (0.97-1.71)	0.08	2.37 (1.79-3.13)	0.00
Differentiation:				
Well	1		1	
Moderate	0.96 (0.71-1.32)	0.84	0.89 (0.65-1.22)	0.49
Poor	1.68 (1.02-2.79)	0.04	0.75 (0.51-1.09)	0.14
Unknown	0.72 (0.53-0.97)	0.04	0.84 (0.56-1.10)	0.16

* 'HR, hazard ratio; CI, confidence interval

Table 4. Multivariate Cox Regression Analysis of Hypopharynx and Larynx Cancer

Variables	Hypopharynx		Larynx	
	HR (95% CI)	p	HR (95% CI)	p
Age:				
<60	1		1	
60-69	0.83 (0.52-1.22)	0.31	1.27 (0.79-2.05)	0.32
70-79	0.98 (0.65-1.48)	0.94	1.55 (0.94-2.56)	0.08
> 80	1.22 (0.67-2.22	0.51	5.31 (2.63-10.7)	0.00
Gender				
Male	1			
Female	0.96 (0.52-1.73)	0.87	0.65 (0.29-1.45)	0.30
Stage				
I	1			
II	1.14 (0.34-3.81)	0.84	2.74 (1.31-5.74))	0.01
III	1.55 (0.59-4.12)	0.38	5.15 (2.68--9.90)	0
IV	3.23 (1.29-8.12)	0.01	8.47 (4.53-15.8)	0
Unknown	3.90 (1.29-11.8)	0.02	5.29 (2.14-13.1)	0
Treatment				
RT	1			
Surgery	2.46 (0.57-10.6)	0.23	1.07 (0.32-3.59)	0.90
Surgery+RT	0.68 (0.43-1.07)	0.10	0.49 (0.31-0.81)	0.01
No	1.93 (1.28-2.91)	0.00	1.98 (1.27-3.10)	0.00
Differentiation				
Well	1			
Moderate	1.01 (0.64-1.59)	0.96	1.60 (0.98-2.62)	0.06
Poor	0.82 (0.45-1.49)	0.51	0.78 (0.40-1.49)	0.45
Unknown	1.23 (0.79-1.96)	0.34	0.95 (0.59-1.51)	0.82

associated with survival for all the four sites, while age was significant in the larynx and grade was only significant in hypopharyx cancer.

In multivariable analysis (Table 3 & 4), the results were consistent with the univariate analysis. Stage and treatment were strong prognostic factors for 5-year OS in all sites. An age > 80 years are significantly associated with poor survival in oral cavity and larynx cancer. For the oropharynx, hypopharynx and larynx, an unknown stage was associated with poor survival which is similar to stage III/IV; whereas, in oral cavity cancer, it did not differ from stage I/II. Regarding treatment type, surgery was associated with the best 5-year OS in oral cavity and oropharyx cancer, but with very poor survival in hypopharynx and larynx cancer. The two patients with hypopharyx cancer who received surgical treatment (total laryngectomy) had stage III and IV diseases and one of them died from postoperative sepsis. For the larynx, three of the six patients treated with surgery had stage I and the other three had advanced stages or unknown stage.

Discussion

Head and neck cancers are diseases associated with high morbidity and mortality. They are prevalent in developing countries including Thailand. In the present study, consecutive new cases of oral cavity, oropharynx, hypopharynx and larynx cancers diagnosed during 2002 to 2004 were analyzed for their 5-year overall survival and associated clinicopathological variables. The results reveal very low 5-year overall survival rates which are significantly related to the advanced stages at presentation and the treatment modality used.

The present study revealed considerably low 5-year survival rates in all the four anatomical sites of HNCA. Cancer of the larynx had the best survival rate (38%) followed by oral cavity (25.91%), oropharynx (19.24%) and hypopharynx (13.24%). This trend of ordering is similar to other reports (Le Tourneau et al., 2005). The 5-year survival rates in the present study are notably lower than other reports, especially those from Western countries (Carvalho et al., 2005; Barzan et al., 2002; MacKenzie et al, 2009). The analyses of the SEER database in the US during 1992 to 1997 revealed 5-year overall survival rates for oral cavity/pharynx cancer of 56.3% and for larynx of 63.5%, which are nearly double our figures.3 In addition, the authors analyzed the time trends over twenty years and found a notably increased survival rate in oropharynx cancer (36.3% to 49.1%, p = 0.001) and hypopharyx cancer (28.3% to 33.3%; p = 0.015). The increase in survival rates during the years for these cancers is thought to be due to the increased combined surgery and radiation modality (21% to 34%). The vast improvement in the survival rate of oropharynx cancer patients from the increase in combined surgery and radiation rather than radiation alone is also reported in European countries (Mäkitie et al., 2009; Lybak et al., 2011). The smaller proportion of patients receiving this combined treatment could be one of the reasons contributing the poor survival in our series.

In the present study, clinical stage was found to be the strongest prognostic factor for survival which is consistent with most other studies (Pericot et al., 2000; Yeole et al., 2003; Rusthoven et al., 2008; De Paula et al., 2009). The advanced stages accounted for 66% of the whole series. This frequency would reach 70%, since most of the patients with an unknown stage (5.7%) were those with advanced diseases who refused treatment or who were absent for treatment after planning were included. However, the proportion of advanced stage at presentation should be lower in the general population because this study was done in a referral university hospital. A considerable high proportion of advanced disease (up to 80%) is also reported in India (Mohanti et al., 2007) and Brazil (De Paula et al., 2009), in contrast with lower stage at presentation in Western countries (Rusthoven et al., 2008; MacKenzie et al., 2009). For example, the SEER data from the Unites States reported advanced stage of oral cavity accounts for 46.7% compared to 59.9% in our series (Carvalho et al., 2005).

Comparing the survival among the four anatomical sites, the larynx and oral cavity have a higher proportion of early disease (36% and 33%, respectively), while hypopharynx had the highest proportion of advanced disease at the time of diagnosis (84.34%). This accounts for the superior survival rates for oral and larynx cancer and the worst survival rate for hypopharynx cancer. Multiple factors may also contribute to advanced stage at presentation, including personal factors, health education, health care access, or others. The previous study from our hospital has revealed that having herbal medicine before seeking professional health care provider is significantly associated with advanced stage at presentation in oral cancer patients (Kerdpon and Sriplung, 2001). Delayed

seeking of care by physicians allows cancer to progress, resulting in advanced disease at presentation.

In HNCA, extent of disease determine the treatment options. Single modality (surgery or radiotherapy) is used for stage I and early stage II cancer and combined surgery and radiotherapy is treatment option for locally advanced tumor. Our results revealed that treatment type strongly influences the survival. In our cohort, the proportion of surgery alone (1.01-8.8%) is remarkably low compared to other series like the series of SEER of the US (10.2-48.9%). This can be expected given the small proportion of localized stage at presentation in our patients. In a report from Northeastern Italy, even with a similar stage distribution to us, a very high proportion of oral cancer (45.6%) and oropharynx cancer (21.5%) received surgery alone compared to 8.78% and 1.40%, respectively, in our series (Barzan et al., 2002). Also, the proportion of patients treated with surgery plus radiation is lower than the aforementioned series stated (Carvalho et al., 2005; Barzan et al., 2002). This combined treatment has been shown to improve locoregional control and overall survival for locally advanced HNCA (Mäkitie et al., 2006; Lybak et al., 2011). This indicates that our patients did not receive the treatment option that should be received according to their stage of disease.

For HNCA, the selection of treatment for each individual depends on various factors, primarily based on the extension of the tumor and the patient's surgical risk. For our patients, their input or decision is also an important determining factor for treatment selection. This is demonstrated by the large number of patients, nearly one-third of the them (330 from a total 1186 cases), who did not proceed for treatment as planned. These patients were slightly older than those who received treatment (68.1 versus 64.4 years). Even though a large proportion of them had stage IV disease (42%), the rest were stage I-III, treatable and would have fully benefitted from treatment. However, the reasons for refusing or their absence for treatment are not known. Determining these reasons would be worthwhile for improving the management of a patient's decision process.

Our results show that older patients were significantly associated with poor survival. This is consistent with other reports (Singh et al., 2000; Warnakulasuriya et al., 2007). However, a few authors have not found the independent effect of age on survival (De Paula et al., 2009). Different cutoff values of age used in these analyses likely effects the results. When we used a cutoff value of younger or older than sixty-five years of age, a significant effect for age on survival was seen only in larynx cancer, not other sites. When we used seventy years as a cutoff value, the significance of age was evident in oropharynx and larynx cancer. Finally, when classifying old age into more than one group (less than 60, 60 to 70; 70 to 80, and greater than 80 years), the distinctive effect of older age on increasing trends was seen. In the study of De Paula et al. (2009), the authors focused on a very young age group (less than 45 years). By using young age as a cut point, the effect of very old age - the sixth, seventh or more decades - may not be seen. The poor outcome in very old patients is known to be related to co-morbidity and treatment related morbidity (Chen et al., 2001; Clark et al., 2006).

In summary, the present data reveals the unfavorable outcomes of head and neck cancer patients in our population. Patients came at an advanced stage of disease which critically effects treatment results and prognosis. Therefore, efforts to increase the proportion of patients with early stage cancer is a major concern. Also, treatment efficiency should be improved, in particular, combined treatment modality. Finally, effective patient education and communication are serious concerns for maximizing the number of patients achieving treatment as planned.

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