Survival Time and Prognostic Factors of Oral Cancer in Ubon Ratchathani Cancer Center

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Objective: *To characterize the survival time and prognostic factors of oral cancer in Ubon Ratchathani, Thailand.*
Material and Method: *A total of 519 patients with oral cancer in the Ubon Ratchathani Cancer Center were recruited retrospectively over 5 years, from January 1, 2002 to December 31, 2006. The survival status of the patients was followed until December 31, 2007. Survival times were estimated and compared using the product-limit (Kaplan-Meier) method. Cox Proportional Hazards models were used to examine prognostic factors.*
Results: *At the end of the study, 384 patients (74.0%) had died. The mean age of the patients at diagnosis was 64.15 years, with a male to female ratio of 1:1.56. Location of cancer were found at tongue (25.2%), buccal mucosa (22.4%), gum (21.1%), lip (17.5%) and others (13.7%). Squamous cell carcinoma was the most common cell type (92.7%). The median survival time was 337 days and the survival probability at 1, 3 and 5-years were 46.7%, 26.4% and 18.2%, respectively. In multivariable analysis, patients at the greatest risk of death were those having cancer of the tongue (HR 1.93, 1.20, 3.11) compared to cancer of the lip and being in stage IV at diagnosis (HR 3.57, 95% CI = 1.79, 7.13) as compared to stage I.*
Conclusion: *Patients with advanced tumors had the worst prognosis, underscoring the importance of improved early detection for early treatment.*

Keywords: *Oral cancer, Survival time, Prognostic factors*

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Oral cancer is the eighth most common cancer worldwide and has one of the highest mortality rates among all malignancies. Incidence rates for oral cancer vary in men from 1 to 10 cases per 100,000 population in many countries. The prevalence of oral cancer is particularly high among men. It is more common in developing countries than developed countries[1,2]. In Thailand, cancer of the oral cavity is common and ranked fourth among men[3,4]. It was behind only liver cancer, lung cancer and colon & rectal cancer, respectively. For women, the morbidity rate of oral cancer ranked seventh. The incidence rate was higher among men (Age-standardized rate, ASR 6.8 per 100,000) than women (ASR 4.8 per 100,000), it was highest in Songkhla (ASR 12.9 per 100,000) followed by Bangkok (ASR 7.9 per 100,000) and Chiang Mai (ASR 7.7 per 100,000). For women, the incidence of oral cancer was highest in Khon Kaen.

The Ubon Ratchathani Cancer Center serves the lower north-east region (9 province: Ubon Ratchathani, Amnat Charoen, Yasothon, Si Sa Ket, Surin, Buri Ram, Nakhonpranom, Mukdahan and Roi Et). The center provides a wide range of treatment modalities including surgery, radiotherapy, chemotherapy and combined treatment. The number of all type of cancer patients treated since the establishment of the center in 1998 was 975 cases. The number dramatically increased from 1,204 in 2001 to 2,211 in 2005. For oral cancer, the number increased from 75

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cases in 2001 to 159 cases in 2005[5]. Despite the increasing number of oral cancer cases, survival and associated factors in this setting have never been evaluated to the best of the authors' knowledge. The aim of the present study was to characterize survival times and prognostic factors of oral cancer treated in the Ubon Ratchathani Cancer Center.

Material and Method

The present study included all patients with oral cancer who were diagnosed by pathologic examination who had been treated at the Ubon Ratchathani Cancer Center. The data were collected from medical records of the patients diagnosed over the 5-year period January 1, 2002, to December 31, 2006. A total of 758 patients were diagnosed with oral cancer during the period; however only the 519 cases with complete data of all variables were included in the present study. The 239 cases excluded were not significantly different from those included with respect to age, sex and stage of disease. Follow-up was conducted through December 31, 2007, Data on survival were ascertained from medical records, telephone interviews with the patients or close relatives and the Population Registration Database, Ministry of Interior. Other information included demographic data *i.e.* age, sex, occupation, smoking, histological type, treatment method (radiotherapy, surgery, chemotherapy, combined treatments), first date of diagnostics, date of death, stage of disease by the TNM classification as diagnosed and recorded in the patient's chart or hospital record. The time of survival was calculated as the number of days between the dates of diagnosis and death or end of follow-up.

Statistical analysis

The product-limit (Kaplan-Meier) method was used to estimate and compare survival times for the potential prognostic factors (independent variables). The log-rank test was used to test differences between subgroups of these variables. One-year, 3-year and 5-year survival rates were calculated by the product-limit method. Univariate Cox proportional hazards models were used to compare mortality risk between subgroups. Independent variables which yielded p-values < 0.25 in univariate analysis were included in multivariable Cox Proportional Hazard regression with a variable selection strategy of backward elimination. Hazard ratios (HRs), 95% confidence intervals (95% CIs) and p-values were obtained for the best-fit model. Modeled associations with p-values < 0.05 were considered statistically significant. In all Cox models, the time variable was elapsed time since diagnosis and the event of mortality.

Results

Of the 519 total patients, 384 had died (74.0%) and 135 were alive (26.0%) at the end of follow-up. Most of the oral cancer patients (69.7%) were $\geq$ 60 years of age. The mean age at diagnosis was 64.15 years (SD = 11.95). There were 317 females and 202 males. Locations of the primary tumor were as follows; 91 at lip, 116 at buccal mucosa, 132 at anterior two-thirds of tongue, 110 at gum/retromolar ridge and 70 at other sites (hard palate, floor of mouth and minor salivary gland). At diagnosis, 247 cases in stage IV, 107 cases in stage III, 109 cases in stage II and 34 cases were in stage I. Two hundred and seventy-six oral cancer patients (52.6%) were treated with a single treatment such as surgery (5.6%), radiotherapy (46.4%) and chemotherapy (0.6%); 210 patients (40.5%) were treated by a combination of two or more treatments such as surgery and radiotherapy (22%), radiotherapy and chemotherapy (17.3%) and surgery with radiotherapy with chemotherapy (1.2%). Thirty-six patients (6.9%) were treated by best supportive care (Table 1).

Table 2 shows median survival time and probability of survival at 1, 3 and 5 years of the patients by occupation, BMI, treatment type, location of the primary tumor and staging of cancer. The overall survival probability at 1, 3 and 5-years were 46.7%, 26.4% and 18.2%, ($p < 0.01$) respectively (Fig. 1). The survival curves of patients in different stages is shown in Fig. 2. The 5-year survival rates of patients in stage I, II, III and IV were 55.0, 25.7, 16.6 and 10.1 respectively (p-value < 0.0001). The 5-year survival rates of patients with primary tumors of the lip, buccal mucosa, gum, tongue and other sites were 35.6%, 9.2%, 14.3%, 14.5% and 26.8% (p-value < 0.001), respectively (Fig. 3). Table 3 shows crude and adjusted hazard ratio of independent factors in the best fit model associated with survival of the patients. In univariate analysis, factors that were statistically associated survival at p-value < 0.25 included, location of the primary tumor, stage of tumor at diagnosis and treatment type. Other independent variables including sex, age and marital status were not associated with survival (p-value > 0.25), therefore they were not included in the final multivariable model.

In the multivariable Cox model, modeled hazard of death in housewives was significantly higher than those in the merchant and civil servant group.

Table 1. Characteristics of oral cancer patients (n = 519)

Variables	Number (%)
Sex	
Male	202 (38.9)
Female	317 (61.1)
Age	
< 60	157 (30.3)
≥ 60	362 (69.7)
Mean (SD) = 64.15 (11.95)	
Occupation	
Farmer	416 (81.9)
Housewife	40 (7.9)
Employee	18 (3.5)
Government officer	11 (2.2)
Merchant	8 (1.6)
Others	15 (3.0)
Location of the primary tumor	
Anterior two-thirds of tongue & others	132 (25.4)
Buccal mucosa	116 (22.4)
Gum, Retromolar ridge, Alveolar ridge	110 (21.2)
Lip	91 (17.5)
Hard palate	38 (7.3)
Floor of mouth	32 (6.2)
Histological grading	
Well differentiated	263 (50.7)
Moderately differentiated	138 (26.6)
Poorly differentiated	35 (6.7)
Undifferentiated	3 (0.6)
Unknown	80 (15.4)
Stage of disease at diagnosis	
Stage 1	34 (6.6)
Stage 2	109 (21.0)
Stage 3	107 (20.6)
Stage 4	247 (47.6)
Unknown	22 (4.2)
Treatment type	
Single treatment	
Radiotherapy	241 (46.4)
Surgery	29 (5.6)
Chemotherapy	3 (0.6)
Combination treatment	
Surgery+Radiotherapy	114 (22.0)
Radiotherapy+Chemotherapy	90 (17.3)
Surgery+Radiotherapy+Chemotherapy	6 (1.2)
Best supportive care	36 (6.9)

(HR 2.97, 95% CI 2.74, 3.19), for location of the primary tumor, the risk of death of patients with tongue cancer was the highest (HR 1.93, 95% CI 1.20, 3.11) compared to cancer of the lip. The patients with stage IV had higher risk of death (HR 3.57, 95% CI 1.79, 7.13) compared to those in stage I. Patients who received

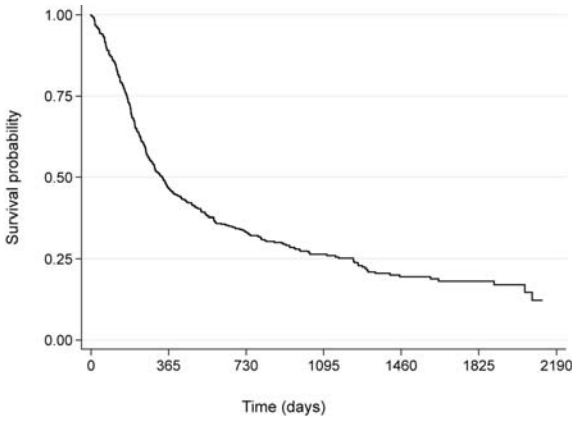

Fig. 1 Kaplan-Meier survival curve of all 519 oral cancer patients

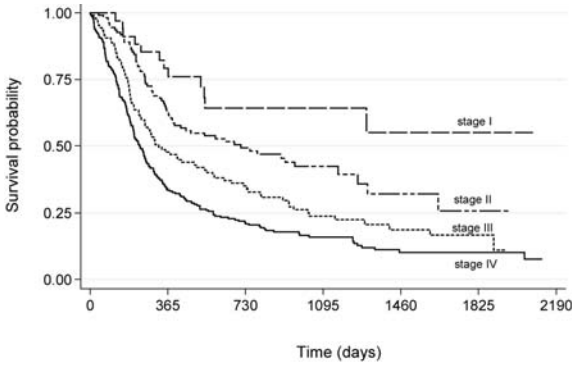

Fig. 2 Kaplan-Meier survival curves by stage of tumor at diagnosis

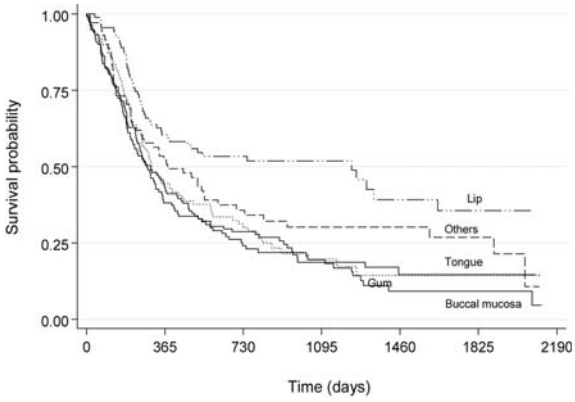

Fig. 3 Kaplan-Meier survival curves by anatomic site of the primary tumor

Table 2. Median survival and probability of survival at 1, 3 and 5 years by potential prognostic factors

Variables	n	Median survival time (day)	1-year survival (%)	3-year survival (%)	5-year survival (%)
Occupation					
Farmer & Employee	434	312	45.0	23.5	14.9
Housewife	40	359	50.0	37.5	26.7
Merchant, Governent officer and others	34	785	58.8	37.1	37.1
Body mass index					
< 18.5	226	262	41.1	21.1	16.7
≥ 18.5	199	474	58.0	32.3	19.3
Treatment type					
Single Rx	273	327	46.7	28.8	20.6
Combined Rx	210	387	51.8	26.2	16.4
Best supportive	36	127	16.6	8.3	0
Location of the primary tumor					
Lip	91	1,234	60.4	51.8	35.6
Buccal	116	281	38.1	19.4	9.2
Gum	110	303	44.5	19.7	14.3
Tongue	132	298	43.4	18.7	14.5
Others	70	377	52.1	30.1	26.8
Squamous cell carcinoma					
No	27	825	62.9	43.3	36.0
Yes	481	328	46.4	25.5	17.4
Stage of disease					
Stage 1	34	>2,190	79.2	64.2	55.0
Stage 2	109	709	62.3	42.3	25.7
Stage 3	107	323	47.6	23.8	16.6
Stage 4	247	233	33.6	15.8	10.1

combined treatment had a significantly lower risk of death than did patients treated by other types. (HR 0.68, 95% CI 0.53, 0.87) (Table 3).

Discussion

Most of the patients had primary school educational attainment and they worked in agriculture and the labor force. These subjects had relatively low socioeconomic status, and their modeled hazard of death was 2.63 times higher than that of merchants and government officers. This might be related to limited accessibility to care; indeed, these patients were diagnosed at a later stage than others[5]. The poor prognosis among farmers and laborers was consistent with other studies[6-10].

The longest survival time was found for cancer of the lip (five-year survival 35.6%) and shorter survival times were found in buccal mucosa, gum and tongue cancers (five-year survival 9.2%, 14.3% and 14.5%, respectively). This finding was also consistent with several other studies[11-13]. Lip cancer is more visible than the other types, and thus could be less likely to spread to lymph nodes before diagnosis and treatment[14]. Stage of disease was an important predictor of survival. The survival time was longest in patients with stage I or II and shorter in the later stages. This finding, too, was consistent with numerous other studies[13, 15-19]. The present study found that the five-year survival rate was 16.6% in stage III and 10.1% in stage IV, which were similar to those observed in other developing countries[20-22]. However, better survival rates of about 30% to 70% in stages III and IV have been reported from western countries[16,18,23]. This difference could be due to greater accessibility to medical services and availability of adequate treatment, in western countries.

In general, patients in stage I or II were treated by surgery or radiation while those in stage III and IV were treated by concurrent chemoradiation or other combined treatment. According to the clinical guideline of the National Comprehensive Cancer Network (NCCN), patients in early stages of oral

Table 3. The association of survival hazard and prognostic factors by Cox proportional hazards models

Variables	Crude hazard ratio	Adjusted hazard ratio	95% CI
Occupation			
Farmer+Employee	1.67	2.63	1.49, 4.76
Housewife	1.47	2.97	2.74, 3.19
Merchant+Government officer+Others	1	1	
Location of the primary tumor			
Lip	1	1	
Buccal mucosa	2.25	1.47	0.90, 2.40
Gum	1.92	1.43	0.86, 2.36
Tongue	2.05	1.93	1.20, 3.11
Others	1.59	1.27	0.75, 2.14
Squamous cell carcinoma			
No	1	1	
Yes	1.72	1.51	0.82, 2.76
Stage of disease			
Stage 1	1	1	
Stage 2	1.89	1.71	0.83, 3.49
Stage 3	3.01	2.62	1.28, 5.37
Stage 4	4.22	3.57	1.79, 7.13
Treatment type			
Single treatment	1	1	
Combination treatment	0.92	0.68	0.53, 0.87
Best supportive care	2.48	1.99	1.17, 3.38
Body mass index	0.92	0.94	0.91, 0.98

cancer would usually be treated by surgery or radiation and patients in advanced stages would usually receive combination therapy. However, in practice, those criteria were not applied to all patients at the Ubon Ratchathani center; specific treatment selection also depended on the patients' and relatives' preferences. For example, there were patients who refused surgery and accepted only supportive care. This could result in a shorter survival time in this series of patients, even for those in the early stages of disease. The authors observed that those who had received supportive care had the worst outcome. This could be due to the fact that they were in the late stage of the disease, whereas the better survival in those treated with single therapy was probably due to their being in an early stage when diagnosed. In the present study, survival was similar in patients receiving single treatment and combined treatment. This could reflect that the combined therapy for some patients in the 3rd state could help prolong their lives comparably to those in the earlier stages Further research is needed to quantify and compare effectiveness of different treatment modalities.

In the present study, survival was not associated with sex, marital status, occupation, smoking, drinking alcohol, chewing betel areca nuts, family history of cancer or comorbidity. This was consistent with some studies[17-19]. In contrast, some other studies reported significant associations of these factors with survival time[19]. Failure to observe associations might be partly attributable to reporting bias. For example, if smokers with late-stage cancer underreported their smoking relative to those with early-stage disease, underestimation of the hazard ratio for smoking could result.

There were some limitations in the present study. Information in the medical records was not complete. For instance, histological grading was missing in 79 cases; therefore, histological grading was not considered in the analysis. Also, it was not possible to compare effects of different treatment modalities in detail. Causes of death of the patients were also not described in details in the medical records, however it might be due to the progression of diseases and/or complication of treatments. Further studies might look into this issue.

Even so, the authors believe that the present study is useful. To the best of our knowledge, this is the first report of survival rates and risk factors in oral cancer patients at the Ubon Ratchathani Cancer Center. The present findings should be valuable in future management of these patients. It will be very important to improve early detection of oral cancers, especially those that are not readily visible.

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การรอดชีพและปัจจัยพยากรณ์ผู้ป่วยโรคมะเร็งช่องปาก ศูนย์มะเร็ง จังหวัดอุบลราชธานี

วัชรินทร์ กรวยสวัสดิ์, วิชัย เอกพลากร, Robert S Chapman

การศึกษาการรอดชีพ และปัจจัยพยากรณ์โรคของผู้ป่วยมะเร็งช่องปากที่รับการรักษาที่ศูนย์มะเร็ง จังหวัดอุบลราชธานี ตั้งแต่ 1 มกราคม พ.ศ. 2545 ถึง 31 ธันวาคม พ.ศ. 2549 จำนวน 519 ราย ข้อมูลผู้ป่วยได้จากเวชระเบียน การสำรวจทางโทรศัพท์จากผู้ป่วย และญาติ และข้อมูลทะเบียนราษฎร์ กระทรวงมหาดไทย

ผลการศึกษาพบว่าผู้ป่วยเสียชีวิต 384 ราย ผู้ป่วยมีอายุเฉลี่ย 64.15 ปี อัตราส่วนหญิงต่อชาย เท่ากับ 1.56:1 ผู้ป่วย ร้อยละ 81.9 มีอาชีพทำนา ตำแหน่งมะเร็งปฐมภูมิพบที่ลิ้นร้อยละ 25.2, กระพุ้งแก้มร้อยละ 22.4, เหงือกร้อยละ 21.2, ริมฝีปากร้อยละ 17.5 และอื่น ๆ ร้อยละ 13.7 (เพดานแข็ง, พื้นช่องปากและต่อมน้ำลาย) ชนิดของเซลล์ที่พบมากที่สุดคือ squamous cell carcinoma ร้อยละ 92.7 ผู้ป่วยส่วนใหญ่อยู่ในระยะที่ 4 ร้อยละ 47.6, ระยะที่ 3 ร้อยละ 20.6, ระยะที่ 2 ร้อยละ 21 และระยะที่ 1 ร้อยละ 6.6 ค่ามัธยฐานของการรอดชีพของผู้ป่วยคือ 337 วัน อัตราการรอดชีพ 1 ปี 3 ปี และ 5 ปี เท่ากับร้อยละ 46.7, ร้อยละ 26.4 และร้อยละ 18.2 ตามลำดับ เมื่อวิเคราะห์ความสัมพันธ์เชิงซ้อนโดยใช้ Cox Proportional Hazards Model พบว่าตำแหน่งมะเร็งที่ลิ้นมีความเสี่ยงต่อการเสียชีวิตสูงที่สุด (hazard ratio = 1.93, 95% CI = 1.20-3.11) ผู้ป่วยในระยะที่ 4 มีความเสี่ยงต่อการเสียชีวิตสูงที่สุด (hazard ratio = 3.57, 95% CI = 1.79-7.13) ผู้ป่วยที่ได้รับการรักษาแบบผสมผสานมีความเสี่ยงต่อการเสียชีวิตน้อยที่สุด (hazard ratio = 0.68, 95%CI = 0.53-0.87)

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