

RESEARCH ARTICLE

Ten-Year Outcome of Different Treatment Modalities for Squamous Cell Carcinoma of Oral Cavity

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Abstract

Objective: This study reports outcomes of squamous cell carcinoma of oral cavity (SCCOC) patients with different treatment modalities. **Materials and Methods:** We evaluated the treatment outcomes of 775 newly diagnosed SCCOC patients treated in our hospital between 2001 and 2010. Outcome data were obtained from the medical records. Survival rates were estimated by the Kaplan-Meier method. Cox-proportional-hazard regression models were used to compare the risk of death among all risk factors. **Results:** The patients were divided into group 1) surgery ± adjuvant radiotherapy (RT) (n = 323) or group 2) RT ± chemotherapy (CT) for curative intent (n = 315) or group 3) RT/CT for palliative intent (n = 137). The overall 10-year survival rate was 17%. Statistically significant difference was noted in 10-year overall survival when SCCOC was managed surgically as compared to curative RT and palliative RT/CT with 25.3 %, 12.9%, 4.7%, respectively. The hazard ratio of cancer death in group 1 was 2.0 (95% CI 1.7-2.4) as compared to group 2. **Conclusion:** This study suggested that surgery must be the mainstay of treatment in locally advanced stage SCCOC. Palliative RT/CT still offered long term survival in some SCCOC patients.

Keywords: Oral cavity- squamous cell carcinoma- treatment- modalities

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Introduction

Cancer of the oral cavity accounts for approximately 3% of the cancer burden worldwide and squamous cell carcinoma of oral cavity (SCCOC) is the most common type (de Camargo Cancela et al., 2010), representing more than 90% of all tumors in the oral cavity. An estimated 300,400 new cases and 145,400 deaths from oral cavity cancer occurred in 2012 worldwide (Torre et al., 2015). In Thailand, according to GLOBOCAN 2012 report, it is in the eight rank of most common cancer accounting for 3,689 new cases (Ferlay et al., 2013). The age-standardized rates by world population (ASR;W) for incidence and mortality were 4.0/100,000 and 2.1/100,000, respectively (Ferlay et al., 2013). Regarding oral cancer in northern Thailand, our previous study (Komolmalai et al., 2015) reviewed 874 medical records of patients with SCCOC between 2001 and 2010 at Maharaj Nakorn Chiang Mai Hospital, which is considered to be the largest cancer treatment center in northern Thailand and focused on young age patients. This study was performed to evaluate the same cohort patient, focused on the outcome of different treatment modalities on the 10-year survival

rates and identify the factors affecting the prognosis of SCCOC patients.

Materials and Methods

This study is an audit of outcome of the same patient cohort in our previous study (Komolmalai et al., 2015), 874 SCCOC patients diagnosed at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai, Thailand in 2001-2010. Data were extracted using ICD-10, oral cavity cancer includes cancer of the lip (ICD-10: C00), cancer of the tongue (ICD-10: C01-02), and cancer within other regions of the oral cavity (ICD-10: C03-06). Among those SCCOC patients, treatment information and medical records of 775 patients could be found and obtained from Chiang Mai Cancer Registry, Maharaj Nakorn Chiang Mai Hospital, which is a tertiary care center in northern Thailand. The status of the patients and the date of death were obtained by the mortality data from the National Registration Department.

The aim and modality of treatment was judged by the multidisciplinary team based on the performance status and stage of the disease. Patients who had early

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stage and good performance status were treated either surgery or radiotherapy (RT). Adjuvant radiotherapy was added in the case with high risk features such as; positive or close margin, positive nodes, and soft tissue/skin invasion. Patients with locally advanced stage with good performance status and no medical inoperable conditions were considered for surgery and postoperative RT. Other locally advanced stage with medical inoperable condition or patients who refuse surgery were considered for curative RT with or without chemotherapy (CT). Patients who had poor performance status and locally advanced stage were planned for palliative RT/CT. In this study, we divided our patients according to the treatment into 3 modalities; group 1) Surgery ± adjuvant RT, group 2) Curative RT± CT, and group 3) Palliative RT/CT.

Details of each modality are as followed;

1) *Surgery ± adjuvant RT*

Surgical resection for the primary tumor was done with a surgical margin of 1-1.5 cm. In clinical N+ neck, a comprehensive neck dissection was performed in every patient. Before 2009, early-stage oral cavity cancer patients with clinical N0 neck were treated with either elective neck dissection or observation but since then selective neck dissection was done in almost all cases. In our clinical practice, elective neck dissection was performed in T3 lesion or T1-T2 N0 lesion with depth of invasion more than or equal to 6 millimeters. Postoperative RT would be assigned for a pathologic report of closed or positive surgical margin, pathological T3-4, extracapsular spreading of lymph node, multiple lymph node metastasis and multiple level of lymph node metastasis with 60-66Gy in 30-33 fractions. After the year 2007, postoperative chemoradiotherapy has been applied when there were closed or positive surgical margin and/or extracapsular invasion.

2) *Curative RT ± CT*

External beam RT 60-70 Gy in 30-35 fractions with 6 MV linear accelerator was used for curative intent. Most of the patients received 2-dimension and 3- dimension conformal RT. A small portion of patients were treated with intensity modulated radiotherapy (IMRT) or brachytherapy alone. RT alone was used for early stage cancer, but concurrent or induction chemotherapy with platinum-based regimen (weekly or tri-weekly scheduled) was used in every locally advanced stage patients.

3) *Palliative RT/CT*

Patients with poor performance status and had local symptoms received either external beam RT 30-45 Gy in 10-15 fractions with 6 MV linear accelerator with palliative intent or palliative CT depend on physician preference.

Statistical Analysis

For all patients, population characteristics were presented as medians and interquartile ranges (IQRs) for continuous variables and as counts and percentages for categorical variables. In the final study population for treatment outcome analysis, only patients who received

different treatment modalities were analyzed. Patients with unknown treatment status in the medical records were excluded. The time to death was measured from the time of diagnosis to the death date. Survival times were censored at the dates of last contact for patients who were lost to follow-up.

The survival rate was calculated using the Kaplan Meier method, and the log rank test was performed for significance test of the predicted factors that affect the prognosis. The association between baseline characteristics and death were assessed using univariable and multivariable Cox proportional hazards models: gender, age, occupation, site of cancer, grade, stage of cancer, alcohol status, smoking status, betel status and type of treatment. Continuous variables were dichotomized according to the median values. Any variable having a significant univariate test at p-value cut-off point of 0.25 was selected as a candidate for the multivariate analysis. All reported P values are 2 sided and P-values <0.05 were considered statistically significant. All analyses were performed using STATA software version 10.1 (Stata Corp, College Station, TX).

Results

Eight hundred and seventy-four SCCOC patients were treated at Maharaj Nakorn Chiang Mai Hospital between 2001 and 2010. The patients were divided into group 1)surgery ± adjuvant RT (n = 323) or group 2) RT ± CT for curative intent (n= 315) or group 3] RT/CT for palliative intent (n = 137) and unknown group (n = 99). This study was focused on the outcome of different treatment modalities, 99 patients were then excluded from the treatment outcome analysis because of unknown treatment status in the medical records. All of them received the treatment in other hospitals. The final study population for treatment outcome analysis consisted of 775 patients. Baseline characteristics are detailed in Table 1. Most of our patients were oral tongue cancer (39%). Three hundred and ninety five patients (51%) were locally advanced stage (III-IVC). Median age was 64 years (IQR: 54-74 years). Fifty-four patients and 147 patients were lost to follow-up at 5-year and 10-year follow-up time, respectively. Median follow-up duration was 13.0 months (IQR: 6.4-46.3 months). The 5 and 10-year OS for

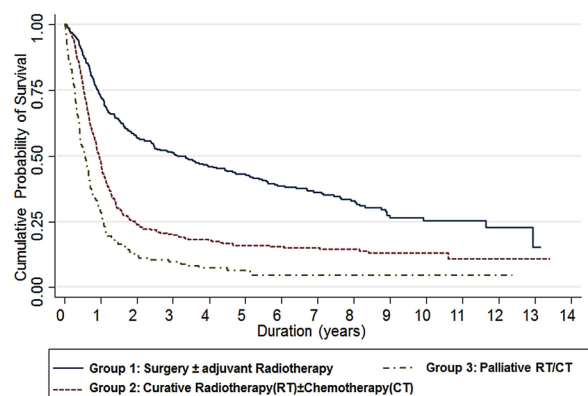


Figure 1. Kaplan-Meier Estimates of Overall Survival by Treatment Groups

Table 1. Baseline Characteristics

Covariates	Overall (N=775) n (%)	Alive (N=171) n (%)	Death (N=604) n (%)	P- value
Gender (n=775)				0.217
Female	316 (41)	77 (24)	239 (76)	
Male	459 (59)	94 (20)	365 (80)	
Age (years) (n=775)				<0.001
Median age (IQR)	64 (54-74)	57 (49-67)	66 (55 -76)	
< 65	394 (51)	121 (31)	273 (69)	
≥ 65	381 (49)	50 (13)	331 (87)	
Site (n=775)				0.005
Tongue	305 (39)	63 (21)	242 (79)	
Gum	140 (18)	30 (21)	110 (79)	
Buccal mucosa	107 (14)	23 (22)	84 (78)	
Palate	87 (11)	17 (20)	70 (80)	
FOM	77 (10)	12 (16)	65 (84)	
Lip	59 (8)	26 (44)	33 (56)	
Grade (n=775)				0.01
Well	457 (59)	110 (24)	347 (76)	
Moderately	213 (28)	36 (17)	177 (83)	
Poorly	57 (7)	8 (14)	49 (86)	
Undifferentiated/ Unknown	48 (6)	17 (35)	31 (65)	
Stage (n=775)				<0.001
Early Stage (I,II)	255 (33)	87 (34)	168 (66)	
Locally Stage (III-IVC)	395 (51)	66 (17)	329 (83)	
Unknown	125 (16)	18 (14)	107 (86)	
Alcohol Status (n=608)				0.061
Never used	192 (32)	53 (28)	139 (72)	
Ever	416 (68)	85 (20)	331 (80)	
Smoking Status (n=616)				<0.001
Never used	120 (19)	46 (38)	74 (62)	
Ever	496 (81)	94 (19)	402 (81)	
Betel Status (n=512)				0.244
Never used	368 (72)	91 (25)	277 (75)	
Ever	144 (28)	28 (19)	116 (81)	
Treatment (n=775)				<0.001
Surgery ± Adjuvant RT	323 (42)	110 (34)	213 (66)	
Curative RT ± CT	315 (40)	51 (16)	264 (84)	
Palliative RT/CT	137 (18)	10 (7)	127 (93)	

P-value from Fisher exact test; Abbreviation, RT, Radiotherapy; CT, chemotherapy

all patients was 26 % and 17%, respectively. For group 1; 323 patients received surgery ± adjuvant RT, the median follow-up time was 31.7 months; IQR:10.4-76.9), 11.0 months (IQR: 6.2-21.6) for 315 patients in group 2 who received curative RT± CT, and 6.5 months (IQR: 3.2-12.7) for 137 patients received only palliative RT/CT. The 5 year OS was 43.1% VS 15.9% VS 6.6%, in group 1, 2, and 3, respectively; and 10 year OS was 25.3% VS 12.9% VS 4.7%, in group 1, 2, and 3, respectively. Figure 1 presents the Kaplan-Meier curve of overall survival (OS)

Table 2. Univariable and Multivariable Cox Proportional Hazard Regression Analysis

Covariates	Univariable analysis		Multivariable analysis	
	Hazard Ratio (HR)	95% CI	Adjusted Hazard Ratio (aHR)	95% CI
Gender				
Female	1			
Male	1.2	(1.0-1.4)		
Age (years)				
< 65	1		1	
≥ 65	1.7	1.4-2.0	1.4	(1.2 – 1.7)
Site (n=775)				
Lip	1			
Tongue	2.1	1.4 – 3.0		
Gum	2.1	1.4 – 3.1		
Buccal mucosa	2.5	1.6 - 3.8		
Palate	2.4	1.6 - 3.7		
FOM	2.2	1.4 – 3.2		
Grade				
Well	1			
Moderately	1.2	(1.0 - 1.5)		
Poorly	1.6	(1.2 – 2.2)		
Undifferentiated/ Unknown	0.7	(0.5 – 1.1)		
Stage				
Early Stage (I,II)	1		1	
Locally Stage (III-IVC)	1.9	(1.6 – 2.3)	1.7	(1.4 – 2.1)
Unknown	1.9	(1.5 – 2.5)	1.4	(1.0 – 1.9)
Alcohol Status				
Never used	1			
Ever	1.2	(1.0 – 1.5)		
Smoking Status				
Never used	1		1	
Ever	1.7	(1.3 – 2.2)	1.4	(1.1 – 1.8)
Betel Status				
Never used	1			
Ever	1.2	(1.0 – 1.5)		
Treatment				
Surgery ± Adjuvant RT	1		1	
Curative RT ± CT	2	(1.7 – 2.4)	1.7	(1.4 – 2.1)
Palliative RT/CT	3.5	(2.8 – 4.4)	2.9	(2.3 – 3.8)

Abbreviation: RT, Radiotherapy; CT, chemotherapy

in relation to the primary treatment group. The prognosis was found to differ significantly between the three groups. When focused to the site of SCCOC, Figure 2 shows that lip had statistically significant better survival than other sites in oral cavity, p <0.001. A specific Kaplan-Meier curve of tumor sites by different treatment modalities present in Figure 3(a) for group 1 patients and Figure 3(b) for group 2 patients. Ten year OS was no statistically different between each tumor sites following surgery ± RT (p= 0.045) or curative RT ± CT (p=0.102).

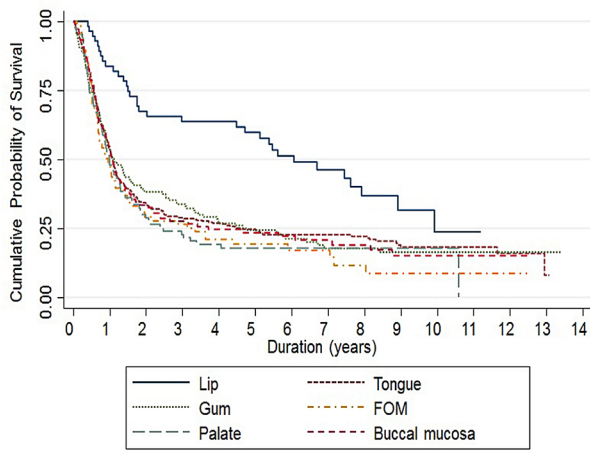


Figure 2. Kaplan-Meier Estimates of Overall Survival by Tumor Sites

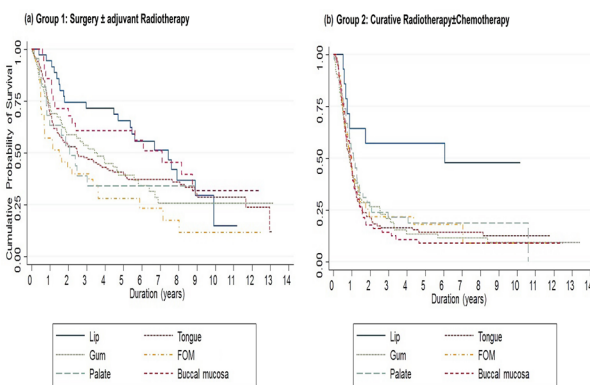


Figure 3. Kaplan-Meier Estimates of Overall Survival of Each Tumor Sites by the Treatment Modalities. (a) Group 1, Surgery ± adjuvant RT; (b) Group 2, Curative RT ± chemotherapy

Survival differences depending on tumor stage was shown in Figure 4 (a) with p -value < 0.001 favor in stage I disease, and still seen the statistically difference when we group the patients into early stage (I-II) and locally advanced stage (III-IVC) as shown in Figure 4 (b) ($p < 0.001$). Table 2 shows the results of univariable and multivariable cox proportional hazard regression analysis of nine potential prognostic factors. Univariate analysis did not reveal any significant differences in survival according to alcohol drinking and betel chewing. Multivariable analysis of appropriate variables was then performed. Age, stage, smoking status, and modalities of treatment proved to be a statistically significant independent predictor of reduced 10 year OS (aHR = 1.4 (95% CI: 1.2 -1.7) for age ≥ 65 years, aHR = 1.7 (95% CI: 1.4 -2.1) for locally advanced stage compared with early stage; $p < 0.001$, aHR = 1.4 (95% CI: 1.1 -1.8) for smoking status, aHR = 1.7 (95% CI: 1.4 -2.1) for curative RT \pm CT and aHR = 2.9 (95% CI: 2.3 -3.8) for palliative RT/CT compared with surgery treatment.

Discussion

The survival rate of oral cancer have been increased approximately 15 percent from 1960s until 2004 (National Institute of Dental and Craniofacial Research, 2014).

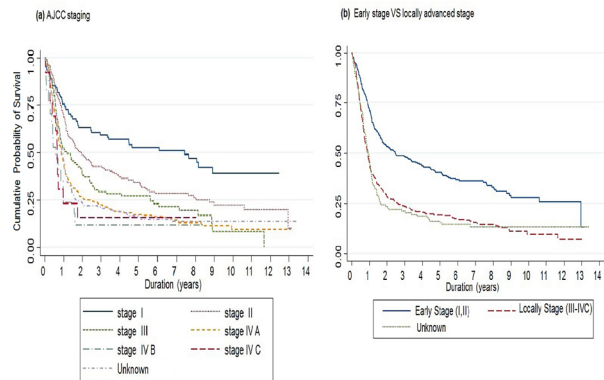


Figure 4. Kaplan-Meier Estimates of Overall Survival by Tumor Stages. (a), overall survival curves by AJCC staging; (b), overall survival curves by early stage VS locally advanced stage.

Rosebush et al., (2011) reported a good outcome of 5 year OS at 60%. Camisasca et al., (2011) reported even better 5 year survival as high as 92% but only 30% in patients with recurrence. Wang et al. (Wang et al., 2013) have demonstrated the 5 year OS of 31.8% in patients with recurrence and as high as 79.9% in patients without recurrence. Our study reports only overall survival for all SCCOC and did not report the recurrence status due to the high rate of loss to follow up. The only accurate data is overall survival since we got all from the Office of Central Civil Registration, Ministry of the Interior. We found that the outcome of our SCCOC patients were poorer than others, with 5 year OS of only 26%, and 10 year OS rate of 17% for all treatment modalities. This would be the high percentage of locally advanced stage in our series.

Surgery or radiotherapy alone is a modality of choice for early stage SCCOC. For locally advanced stage, combined modalities such as surgery and postoperative radiotherapy with or without chemotherapy or non-surgical treatment such as induction chemotherapy or concurrent chemo-radiotherapy (CCRT) are the popular treatment decision (Amdur et al., 1989; Dinshaw et al., 2005; Patel and Shah, 2005) and the treatment policy in our center is the same as others (Amdur et al., 1989; Dinshaw et al., 2005; Patel and Shah, 2005). Our study should not be considered as a direct comparison between surgery and radiotherapy because of the retrospective nature and selective bias in the treatment modalities. The data show a significant better 10 year OS for the primary surgically treated patients. This study presents evidence that primary surgery might have a clear role in advanced SCCOC patients.

At the randomized analysis of Robertson et al. found the statistically significant outcome with a mark difference in overall survival in favor surgery plus postoperative RT than RT alone in the management of intraoral cancers (Robertson et al., 1998). When focused to the specific site of tumor, we did not find that group 1 treatment had the effect on survival in each tumor sites, but it seems like that curative RT (group 2) had the good survival only in the lip site. The hazard ratio of death from cancer in both RT groups (group 2, 3) was 2.0 (95% CI 1.7-2.4) as compared to group 1. Statistically significant difference was noted

in 10-year overall survival when SCCOC was managed surgically as compared to curative RT and palliative RT/CT with 25.3% VS 12.9% VS 4.7%, respectively. Most of the patients (54.6%) who receive curative RT were locally advanced stage (III-IVC) which was slightly more than in surgical treatment (46.7%), suggested that surgery must be the mainstay of treatment in this group of patient and postoperative RT had an additive benefit.

There was limited data on long term OS of surgery with or without RT and focused in all sites and all stages of SCCOC. In our study, 10-year OS rate was 25.3 % through surgical treatment with or without adjuvant RT for the SCCOC patients. This is similar when compared to the result of Grau et al. (2002), which reported 10 year OS of 30%, and 20% in stage III, and IV SCCOC, respectively. However, our data had lower outcome comparing to other literatures (Ruggeri et al., 2005; Listl et al., 2013). Study of Ruggeri et al., (2005) demonstrated 10 year OS of 39.5% in SCCOC patients treated by surgery and neoadjuvant chemotherapy whereas the German group (Listl et al., 2013) provided only 5-year OS of 54.6% with non-specific treatment. Our surgical colleagues (Sittitrai et al., 2013) studied the result of surgery with or without postoperative radiotherapy in selected good prognosis group SCCOC (early stage T1-2, N0-1 oral tongue site) in the same period of our study. They found the very good outcome with 2 year OS of 85.7%. Another German study (Udeabor et al., 2012) also showed an excellent result in 10-year survival rate of oral cavity and oropharyngeal cancer as high as 46.9%, their study had the average age of the patients younger than ours (57.6 VS 64), and also had higher numbers of early stage cancer than ours; 58.7% of patients were T1-2, whereas 30% in our study. Shrimpe et al., (2010) obtained a 41.4 and 54.2% 5-year OS in a group of 1539 patients with T1-2N1 SCCOC treated with surgery alone and surgery plus postoperative RT. As we mentioned that our clinical practice in elective neck dissection has been changed since 2009, and our analysis was performed in the cohort patients treated between 2001 and 2010. This would be another cause of poor outcome in our group 1 patients comparing to others. The results from many studies (Fakih et al., 1989a; Fakih et al., 1989b; Kligerman et al., 1994) suggest that elective neck dissection offers benefits in overall survival, disease free survival, and cancer specific survival.

When focused to the patients who received only palliative RT/CT due to their poor performance stage and/or too advanced disease, we found that palliative RT/CT still offered long term survival in some SCCOC patients with 10-year OS of 4.7%. Das et al., (2013) found the 2 year cumulative survival probability was 17% in palliative RT schedule for inoperable head and neck cancer.

It has been studied about the correlation of many independent factors with prognosis of patients with SCCOC, but none of the factor can alone influence the prognosis of this disease. Our study found 4 factors that influence the risk of death for SCCOC; age more than 65 years, locally advanced stage (stage III-IVC), smoking history, and non-surgical treatments. The tumor site has been proposed to be an independent prognostic factor in SCCOC. In this analysis for overall cohort, tumor site

was not a significant factor for OS both on univariate and multivariate analysis. This is difference from the study of prognostic factors from India (Murthy et al., 2010) that site of tumor retained its significance for loco-regional control and disease free survival. For overall staging, significant difference was observed especially between early and advanced stage on both univariate and multivariate analysis. Focused in the treatment modality, surgical treatment with or without RT had superior outcomes than curative RT with or without chemotherapy. Our experience parallels to that of other studies (Ruggeri et al., 2005; Murthy et al., 2010; Listl et al., 2013). Better outcome than our study, Spencer et al., (2002) reported the excellent 5 year cumulative survival rate; 92% for the patients who undergone surgery, 69% for patients who received RT, and 71% for the patients who treated with combination therapy. Their study also found the decreased outcome when the patients are in advanced stage with 74% for surgery group, 37% for RT alone, and 51% for combination therapy, but it still concluded surgical treatment had the better outcome than radiotherapy in SCCOC patients.

In conclusion, the result of retrospective cohort of SCCOC patients treated at a single center showed that surgical treatment with or without adjuvant RT showed superior outcomes as compared to curative radiotherapy with or without chemotherapy especially in locally advanced stage. We should not disregard the difference in outcome between two modalities in potentially resectable locally advanced stage SCCOC. Moreover, even in the patients with poor performance status or too advanced disease, palliative RT/CT still has the role and offered long term survival in some SCCOC.

Statement conflict of Interest

No potential conflicts of interest were disclosed.

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