Original Article

Which Treatment Modality is the Best for Advanced Buccal Mucosa Cancer?

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Objective: The present study aimed to evaluate the efficacy of various treatment modalities for advanced buccal mucosa cancer.

Materials and Methods: This was a retrospective study conducted at the Division of Plastic and Reconstructive Surgery in the Department of Surgery at Khon Kaen University's Faculty of Medicine (Khon Kaen, Thailand). The study period was between 2006 and 2010. The inclusion criterion was diagnosis with buccal mucosa cancer at any stage.

Results: There were 101 patients with buccal mucosa cancer who met the study criteria. A majority of the patients were elderly, with 40.6% being 70 to 79 years old and 35.64% being 60 to 69 years old. Eighty-one (80.2%) patients were female and 20 were male. The overall median survival time for all stages was 12.5 months, with a range of 0.6 to 146.6 months. The survival outcomes of combination therapy consisting of surgical resection and chemoradiation did not differ from those of surgery plus radiotherapy.

Conclusion: A combination therapy for advanced buccal mucosa cancer consisting of surgical resection and chemoradiation did not differ from surgery plus radiotherapy in terms of survival.

Keywords: Survival rate, Oral cancer, Surgical resection, Radiotherapy, Chemoradiation, Buccal carcinoma

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Buccal mucosa cancer, a cancer of the oral cavity, is prevalent in India and Southeast Asia, but not in the United States[1]. Betel nut chewing is a common cause of this cancer in India and Thailand[2,3]. The most common pathology is squamous cell carcinoma, which is also a major cause of morbidity and mortality in patients with head and neck cancer. Buccal mucosa cancer is also considered to be more aggressive than lip cancers, with a five-year survival rate of 58.3% compared to 70 to 90% in cases of lip cancer[4]. There are several factors that may affect the survival/recurrence rate of buccal mucosa cancer including size, margin, stage, and treatment modalities[5-7]. Even in T1 tumors, the local recurrence rate has been shown to be 40% after primary resection[5]. Cases in which the cell type is poorly differentiated and of buccal mucosa grade IV have been found to have adjusted odds ratios for death of 2.35 and 6.56, respectively[7].

Treatment modality is one of the most important factors associated with survival in the buccal mucosa cancer. The treatment plan for patients with squamous cell buccal carcinoma depends on the stage of the disease and on the overall health status of the patient. For stage I and II cancers, a single modality therapy consisting of surgery or radiotherapy is the treatment of choice. In cases of advanced cancer, surgical resection is the primary treatment modality, but adjuvant therapy (either radiotherapy or chemotherapy) is also recommended. Other optional treatments are also available. Patients with T1-2N0 disease may benefit from adjuvant radiotherapy[4]. Neck dissection has also been suggested to prevent locoregional control of buccal mucosa cancer[8]. For advance stage head and neck cancer, the treatment outcomes vary depending on the extent of tumor invasion and treatment modalities[9]. Some studies have suggested surgical salvage with pre or post-operative chemoradiation[10,11], but the treatment outcomes (including complications) are still a matter of controversy[12-15]. Some studies have also suggested that post-operative radiation may lead to better surgical outcomes[16]. In the authors' institution (a university hospital located in an endemic area of buccal mucosa cancer) there are various treatments provided for patients with this disease. For stages 1 and 2, the main treatment is surgery, but for cases of advanced cancer, a combination of treatments is used. This study aimed to compare the results of various treatment modalities to determine which is the most effective for advanced buccal cancer.

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Materials and Methods

This was a retrospective study conducted at the Division of Plastic and Reconstructive Surgery in the Department of Surgery at Khon Kaen University's Faculty of Medicine (Khon Kaen, Thailand). The study period was between 2006 and 2010. The inclusion criterion was diagnosis with buccal mucosa cancer at any stage. Mortality was the primary outcome of interest. Most patients underwent follow-up examinations to confirm that they remained disease free for at least 5 years, but some were lost to follow-up. Patients with secondary buccal mucosa cancer or those who were treated prior to study participation were excluded.

Baseline clinical features, treatment, and survival rates were recorded. The treatment protocol depended on the stage of the disease. For stages 1 and 2, the main treatment was surgery. Treatment modalities using a combination of tumor-eradication methods were chosen for advanced patients (stages 3 and 4). The possible treatment modalities were cisplatin-based chemotherapy either before or after surgery with post-operative radiation or post-operative radiation alone. The choice of modality depended on the preferences of the surgeon and contraindications for chemotherapy. The neoadjuvant chemotherapy regimen consisted of 100 mg/m^2 of cisplatin for one day plus 1,000 mg/m^2 of 5-fluorouracil for four days. The radiotherapy dose was between 50 to 70 centigray (cGy), usually 66 cGy. Palliative cases were often treated with radiation alone.

The treatment approaches for patients with advanced stage buccal mucosa cancer fell into four categories:

1) Incomplete treatment due to loss to follow-up (patients who suffered from side effects or complications of previous treatment and refused undergo further tumor eradication).

2) Surgery with postoperative radiation.

3) Neoadjuvant or adjuvant chemotherapy, surgery, and postoperative radiation.

4) Palliative radiation and supportive symptomatic treatment only (in cases that were beyond standard treatment) Response to treatment was evaluated based on medical records, the telephone interview, or the national civil registration database. The sequence of treatment was also recorded if a combination of treatments was given.

Statistical analyses

Patients were divided into two groups according to mortality status: (survival or death). Data were compared between the two groups. Input variables were factors with a *p*-value of less than 0.20 according to univariate analysis. Analytical results were presented as hazard ratios and 95% confidence intervals (CIs). All analyses were performed using SPSS software (Chicago, Illinois, USA).

The Kaplan-Meir and The Wilcoxon (Breslow–Gehan) test were used to determine survival data in variable groups. The results of survival analysis performed using the Cox proportion hazards regression model are presented as *p*-values and median survival times for each group being compared with hazard ratios and confidence intervals. All analyses were performed using STATA.

Ethical approval

All procedures involving human participants in this study were performed in accordance with the ethical standards of the Center for Ethics in Human Research, Khon Kaen University (HE 611060) and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Results

During the study period, there were 101 patients with buccal mucosa cancer who met the study criteria. Clinical and variables for all patients are listed in Tables 1 to 4. A majority of the patients were elderly, with 40.6% in the 70 to 79 years age group and 35.64% in the 60 to 69 years age group. Eighty-one (80.2%) of the 101 patents were female, and 20 were male. Betel nut chewing was predominant among the female participants. The overall median survival time for all stages of disease was 12.5 months, a range of 0.6 to 146.6 months.

Multiple modalities of treatment were used in patients with advanced cancer (stages 3 and 4; Table 3). However, some patients who did not meet the criteria for palliation were unfortunately lost to follow-up and only received a single therapy. 27.06 percent of the patients received neoadjuvant chemotherapy combined with surgery and radiation (iii),. 15.29 percent received surgery with post-operative radiation (ii), and 57.65 percent were treated with a single therapy (i), which represented either an incomplete protocol caused by loss to follow-up (44.71%) or the administration of palliative radiation alone (iv, 12.94%).

Table 1. Patient demographics

Stage	Total	Male	Female
1	7 (6.93%)	1	6
2	9 (8.91%)	4	5
3	16 (15.84%)	3	13
4	69 (68.32%)	12	57
Median age, years	70 (35 to 91)	66.5 (35 to 82)	70 (43 to 91)

Table 2. Age distribution

Age	No. of patient	Percent
30 to 39	1	0.99
40 to 49	4	3.96
50 to 59	9	8.91
60 to 69	36	35.64
70 to 79	41	40.60
80 to 89	8	7.92
90 to 99	2	1.98

Table 3. Treatment modality for advanced stage disease (stage 3 and 4)

Treatment modality	No. of patient	Percent
(i) Incomplete treatment	38	44.71
(ii) Surgery with postoperative radiation	13	15.29
(iii) Chemotherapy, surgery, and postoperative radiation	23	27.06
(iv) Palliative radiation	11	12.94
Total	85	100

Table 4. Cox proportional hazards regression model with advanced tumor stage

	Median survival time	Hazard ratio	95% CI	*p*-value
Female	9.3	1.92	0.91 to 4.05	0.08
Age >60	9.3	2.32	0.99 to 5.40	0.05
Stage 4	11	1.13	0.58 to 2.17	0.71
Treatment group				
Group 3	Reference			
Group 1	5.7	3.94	1.05 to 7.57	<0.001
Group 2	37.9	1.02	0.38 to 2.72	0.96
Group 2	Reference			
Group 1	5.7	3.86	1.63 to 9.13	<0.001
Group 3	34.1	0.98	0.37 to 2.61	0.97

Group 1; single therapy: palliative radiation, incomplete treatment (surgery or chemotherapy alone)
Group 2; surgery with postoperative radiation
Group 3; chemotherapy, surgery and postoperative radiation

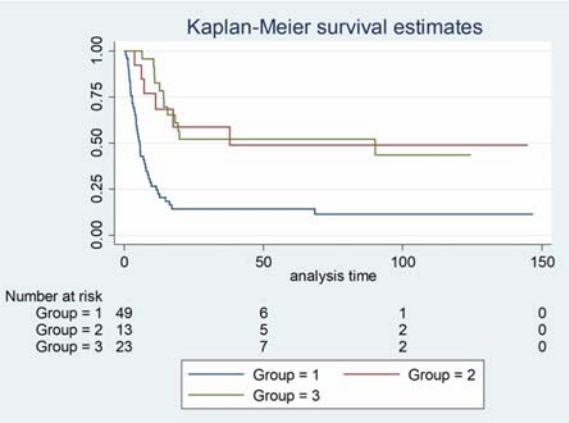

Figure 1. Overall survival differences by treatment modality in advanced buccal cancer stage by Kaplan-Meier analysis.

In patients who received a complete treatment protocol for advanced stage disease, there was no statistically significant difference in terms of disease-specific survival among those who received chemotherapy, surgery, and post-operative radiotherapy (group 3) or surgery with post-operative radiotherapy (group 2). Patients with advanced cancer who only received a single type of therapy (group 1) had significantly poorer survival outcomes when compared with the other groups (Figure 1). Survival in advanced disease did not differ significantly by sex, age, or stage of disease (3 vs. 4).

Discussion

In cases of advanced buccal mucosa cancer, the standard of care for localized disease regardless of cancer staging has been a combination of surgical resection and radiotherapy, which can reduce mortality. The effects and benefits of neoadjuvant chemotherapy are still being debated. In our experience, neoadjuvant chemotherapy decreases tumor size, making the tumors easier to operate on, but the effect on survival is not clear.

This report differed from many studies in terms of the incidence of the disease. Previous studies have reported a male to female ratio of 4: 1 in head and neck cancer, probably caused by smoking[17,18]. Buccal mucosa cancer is an aggressive cancer with a rate of locoregional recurrence that can be high as 66%[4,5]. Due to the high risk of locoregional metastasis, radical resection should be performed with adjuvant therapy, particularly local radiotherapy[1,8,19]. The three-year survival rate has been shown to be approximately 55%[1,8]. One study found that out of 32 patients, the most effective treatment was surgery plus radiotherapy, which is consistent with our findings[1].

In the past, advanced stage cancer patients who were classified as being inoperable received only palliative treatment such as radiation. Now, adjuvant chemotherapy and radiation are used concurrently, a treatment regimen that has been associated with a high level of response in cases considered to be "beyond surgical treatment". Many publications have discussed the pros and cons of induction chemotherapy[20-23]. These studies have shown that this type of treatment can both improve survival outcomes and decreased the size of tumor before surgery, which can help ameliorate the effects of the cancer. Many studies have demonstrated the benefits of induction chemotherapy before surgery[24-26] and that chemotherapy (either as induction or adjuvant therapy) may help to significantly reduce distant metastasis[17]. It is important to note that not all of these studies were conducted in patients with buccal mucosa cancer. Some were performed in patients with oral cavity squamous cell carcinoma.

Some studies, however, have shown the induction or neoadjuvant chemotherapy in buccal mucosa cancer to be ineffective in terms of survival[22,27]. Our study also found that although neoadjuvant or adjuvant chemotherapy with cisplatin plus 5-fluorouracil (group 3) successfully reduced mortality, the results did not differ from those of surgery plus radiotherapy (group 2) according to a Cox proportional hazards regression model (Table 4, 0.38 to 2.72 in 95% CI, 0.96 *p*-value with group 3 as a reference and 0.37 to 2.61 in 95% CI, 0.97 *p*-value with group 2 as a reference). However, based on our experience, chemotherapy is beneficial in that it decreases tumor size, allowing for an easier surgical approach. The strength of the present study is that the sample size was quite large compared with those in previous studies. We also controlled for cancer stage. Some limitations, however, exist. First of all, due to the retrospective study design, some data that may affect the treatment outcomes were missing, such as co-morbid diseases and the exact causes of death. Second, based on chart review and follow-up data, many of the patients who underwent chemotherapy as an induction did not receive any other treatments. A large percentage (44.71%) of patients were lost to follow-up after the neoadjuvant chemotherapy. The national population database only shows deaths, but not their specific causes. It was therefore hypothesized that some of these deaths may have been caused by infection or electrolyte imbalance, meaning that poor nutritional support and low socioeconomic status could have led to improper care in these patients. Based on this outcome, a protocol should be developed to implement an intensive home-care program which has helped in decreasing the side effects of chemotherapy. For the advantage of neoadjuvant chemoradiation with the shrinking tumor process before surgery with the supportive care for the management of chemotherapy-induced side effects should be strongly concern.

Conclusion

A combination therapy for advanced buccal mucosa cancer consisting of surgical resection and chemoradiation did not differ from surgery plus radiotherapy in terms of survival.

What is already known on this topic?

In cases of advanced squamous cell buccal carcinoma, surgical resection is the primary treatment modality, but adjuvant therapy (either radiotherapy or chemotherapy) is also recommended.

What this study adds?

Surgical resection with chemoradiation treatment in advanced buccal carcinoma did not differ from surgery plus radiotherapy in terms of survival. But for best supportive care of the infection and electrolyte imbalance will increase the favorable outcome and the effective of neoadjuvant chemoradiation with the shrinking tumor process before surgery.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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