INTRODUCTION

Tongue cancer comprises the majority of oral cavity cancer in Asian countries and worldwide.\(^1\)\(^2\) It has the highest incidence rate (3.2:100,000) and mortality rate (0.6:100,000) among all other oral cavity cancers globally.\(^2\)

In Thailand, the tongue is the most common anatomical site for oral cavity cancer, with an incidence rate of 2.2 and 1.0 per 100,000 in men and women, respectively, in 2011. Oral tongue squamous cell carcinoma (OTSCC) is the most frequent type of all tongue cancer.\(^3\)\(^4\) Moreover, the number of patients in Thailand diagnosed with oral cancers increased continuously from 2004 to 2015.\(^5\) As in the United States from 2007 to 2016, the incidence rate for both the base of tongue and anterior tongue cancer increased equally (1.8% per year on average).\(^6\)

The 5-year survival rate in tongue cancer is the second-best of all oral cancers in many countries. The 5-year overall survival (OS) was 62.2% in China,\(^7\) 62.8% in Germany,\(^8\) and 68.1% in the United States.\(^9\) However, in developing
countries, the mortality rate was higher. In India, the 5-year relative survival rate in 2003 was 37.9%,\textsuperscript{10} and the 3-year relative survival rate in Northeastern Thailand from 1985 to 2001 was as low as 29.3%\textsuperscript{11}. Multiple risk factors have been identified as considerably associated with oral cancers. These factors are low socioeconomic status, betel-nut chewing, tobacco use, alcohol consumption, and viral infection (eg, Epstein Bar Virus, Human Simplex Virus-1, and Human papillomavirus type 16).\textsuperscript{1,12-15}

More aggressive diseases, such as those with tumors invading adjacent structures, lymph node metastasis, or distant metastasis, resulted in poorer survival outcomes.\textsuperscript{16} Many studies found a significant association of oral cancer with a low socioeconomic population.\textsuperscript{1} These patients generally presented with regional and distant stages of disease due to late diagnosis and treatment. Multimodality of treatment, including radiation and chemotherapy, has been used to reduce the tumor size before surgery to achieve superior outcomes.\textsuperscript{17-19} Nevertheless, there is a decrease in the quality of life regarding appearance, articulation, deglutition, taste, and sensation.\textsuperscript{20} Numerous poor prognostic factors have been identified in oral squamous cell carcinoma (OSCC), such as tumor size greater than T2 according to TNM staging, nodal metastasis, involvement of pathological margin, histologic grade, perineural invasion (PNI), lymphovascular invasion, and extranodal extension (ENE).\textsuperscript{21-24} The primary goal of this study was to discover the prognostic factors of OTSCC that significantly influenced survival differences in Thailand as, at present, only a few such studies have been reported.

**PATIENTS AND METHODS**

This study was approved by the Khon Kaen University Ethics Committee in Human Research, No. HE611620. A retrospective chart review from January 2012 to December 2016 that included all OTSCC patients with confirmed pathological diagnosis in Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, was analyzed. All patients had a complete investigation and were classified based on the eighth edition of the American Joint Commission on Cancer TNM system before starting any modality of treatment. This study included a total of 183 cases.

General information, such as age, sex, occupation, education, underlying disease, weight, height, body mass index (BMI), and ASA classification, was recorded. Treatment details consisting of radiotherapy, chemotherapy, and surgical procedures were documented. In addition, tumor characteristics regarding TNM staging, histologic grade, the status of resected margin, ENE, and vertical dimension of tumor were collected.

The data were analyzed using STATA, version 10.1 (StataCorp LLC, College Station, Tex.). The quantitative data were presented as mean with SD, and a percentage was used to represent the categorical data. The survival time was calculated from the date of diagnosis to the date of death or the last day of this study (December 31, 2020), by the Kaplan-Meier method with a 95% confidence interval (95% CI). The significant difference in survival was calculated with the log-rank test. The univariate and multivariate Cox proportional hazards models were used to represent the crude and adjusted hazard ratio (HR), and a P value less than 0.05 was considered significant.

**RESULTS**

Patient demographic data are shown in Table 1. There were more female patients than male patients with OTSCC [113 (61.75%) female cases and 70 (38.25%) male cases]. Mean age and BMI were 55.77 ± 14.16 years and 20.89 ± 3.89 kg per m², respectively. Notably, the majority of patients had comorbidities (77, 42.08%). Most patients were farmers (130 cases, 71.04%), and most patients had education below a bachelor’s degree (179 cases, 97.81%). Approximately one-third of all cases used tobacco (62 cases, 33.88%) and consumed alcohol (55 cases, 30.05%). The ASA classification in the population was shown greater in classes I and II (95.3%).

| Characteristics            | n (%)          |
|----------------------------|----------------|
| Total cases                | 183 (100%)     |
| Gender                     |                |
| Women                      | 113 (61.75%)   |
| Men                        | 70 (38.25%)    |
| Age at diagnosis (y, mean ± SD) | 55.77 ± 14.16 |
| Weight (kg, mean ± SD)     | 53.60 ± 11.13  |
| BMI (kg/m², mean ± SD)     | 20.89 ± 3.89   |
| Occupation                 |                |
| Farmer                     | 130 (71.04%)   |
| Worker                     | 18 (9.84%)     |
| Businessman                | 14 (7.65%)     |
| Officer                    | 12 (6.55)      |
| Monk                       | 5 (2.73%)      |
| Others                     | 4 (2.19)       |
| Education                  |                |
| High school and below      | 179 (97.81%)   |
| Bachelor and higher        | 4 (2.19%)      |
| Smoking                    |                |
| Smoking                    | 62 (33.88%)    |
| Betel-nut chewing          | 15 (8.2%)      |
| Alcohol drinking           | 55 (30.05%)    |
| Comorbidity                | 77 (42.08%)    |
| ASA classification         |                |
| 1                          | 86 (47.00%)    |
| 2                          | 89 (48.03%)    |
| 3                          | 8 (4.37%)      |
The patients received adjuvant or definite radiation treatment in 115 cases (62.84%) and chemotherapy in 53 cases (28.96%).

The median OS of 1-, 3-, and 5-year patient survival after diagnosis with OTSCC are displayed in Table 3.

The median OS time are such deleterious variables affecting the long-term outcome as late TNM staging, including stage 3 (42.73%, 95%CI 30.2–55.27) and stage 4 (27.09%, 95%CI 20.2–33.98); moderate, poor or undifferentiated tumor (11.33%, 95%CI 9.56–13.10); involved surgical margin (15.7%, 95%CI 12.58–18.82); radical neck dissection (12.47%, 95%CI 11.30–13.64); and nonsurgery group (7.6%, 95%CI 5.41–9.79).

Supplemental Digital Content 1 shows the Kaplan-Meier curves of survival in OTSCC and describes the significant differences in survival relevant to TNM stage (P < 0.001), histologic grade (P < 0.001), surgical intervention (P < 0.001), and type of neck dissection (P = 0.001). (See figure, Supplemental Digital Content 1, which displays Kaplan-Meier curves 5-year overall survival of OTSCC by TNM staging, histopathological differentiation, surgery, type of neck dissection, and pathological margin. [http://links.lww.com/PRSGO/B816].) In the surgery group, there was no statistically significant difference of survival in either the positive or negative pathological margin group (P = 0.061).

Unadjusted HR calculated with the univariate Cox proportional hazards model is shown in Table 4. The analysis revealed that women (HR 1.58, 95%CI 1.07–2.32; P = 0.021), age 70.5 years or older (HR 2.06, 95%CI 1.33–3.19; P = 0.001), and BMI less than 18.5 kg per m² (HR 2.37, 95%CI 1.62–3.47; P < 0.001) significantly worsened the prognosis. The RND surgery group (HR 3.08, 95%CI (1.65–5.74; P < 0.001), the vertical dimension of tumor 20 mm or more (HR 4.61, 95%CI 2.45–8.67; P < 0.001), the presenting of ENE (HR 4.12, 95%CI 2.33–7.29; P < 0.001), and non-well-differentiated histologic grading group (HR 2.01, 95%CI 1.39–2.90; P < 0.001) decreased survival of OTSCC as well.

On the other hand, surgical treatment had the benefit of improving survival outcome substantially (HR 0.21, 95%CI 0.15–0.31; P < 0.001).

Table 5 shows the results of applying the multivariate Cox proportional hazards model to identify the important prognostic factors. The adjusted HR disclosed that a BMI less than 18.5 kg per m² (adjusted HR 3.03, 95%CI 1.11–8.25), a vertical dimension of tumor 20 mm or more (adjusted HR 5.84, 95%CI 2.58–13.3), age 70.5 years or older (adjusted HR 2.03, 95%CI 1.33–3.17; P < 0.001), and BMI less than 18.5 kg per m² (adjusted HR 2.37, 95%CI 1.62–3.47; P < 0.001) significantly worsened the prognosis.

Table 2. Perioperative Data

| Characteristics       | n (%)       |
|-----------------------|-------------|
| Tumor staging         |             |
| T1                    | 25 (13.66%) |
| T2                    | 54 (29.51%) |
| T3                    | 44 (24.04%) |
| T4a                   | 53 (28.96%) |
| T4b                   | 7 (3.83%)   |
| Nodal staging         |             |
| N0                    | 64 (34.97%) |
| N1                    | 45 (24.59%) |
| N2a                   | 3 (1.64%)   |
| N2b                   | 40 (21.86%) |
| N2c                   | 23 (12.57%) |
| N3                    | 8 (4.37%)   |
| Metastasis            |             |
| M0                    | 175 (95.63%)|
| M1                    | 8 (4.37%)   |
| TNM Staging           |             |
| 1                     | 21 (11.48%) |
| 2                     | 28 (15.30%) |
| 3                     | 39 (21.31%) |
| 4                     | 95 (51.91%) |
| Surgical treatment    |             |
| Yes                   | 125 (68.31%)|
| No                    | 58 (31.69%) |
| Margin status         |             |
| Clear                 | 111 (88.8%) |
| Involved              | 14 (11.2%)  |
| Neck dissection       |             |
| SOHND                 | 72 (60.50%) |
| MRND                  | 92 (76.89%) |
| RND                   | 15 (12.61%) |
| Extranodal extension  |             |
| Yes                   | 15 (8.2%)   |
| No                    | 168 (91.8%) |
| Perineural invasion   |             |
| Yes                   | 12 (6.56%)  |
| No                    | 171 (93.44%)|
| Radiation treatment   |             |
| Yes                   | 115 (62.84%)|
| No                    | 68 (37.16%) |
| Chemotherapy          |             |
| Yes                   | 53 (28.96%) |
| No                    | 130 (71.04%)|

(6.56%), respectively. The patients received adjuvant or definite radiation treatment in 115 cases (62.84%) and chemotherapy in 53 cases (28.96%).

The median OS of 1-, 3-, and 5-year patient survival after diagnosis with OTSCC are displayed in Table 3.
have been found predominantly in northeastern Thailand.\(^{11,15}\) A higher ratio of female-to-male patients (1.6:1) was observed. Since 1985, a high percentage of women with oral cancer have been found predominantly in northeastern Thailand.\(^{11,15}\)

For oral cancer, the average ages of non-Asian and Asian patients with neck cancer, most patients were men older than 50 years.\(^{25}\) In our current study, however, we found that the mean age of the 183 patients in our study was 55 years. Out of the 183 cases in our study, 125 patients (68.31%) underwent surgery. According to the data categorized by surgery, presented by 15.9% of the total subjects and the important factor in the upper aerodigestive tract cancer. Our study, however, contained an inadequate population and failed to recognize betel-nut chewing as a significant risk factor. Similarly, alcohol drinking and tobacco smoking were less favorable in women and thus considered insignificant.\(^{15}\)

Most patients who presented to the hospital in the late stage expressed difficulty chewing and swallowing, which consequently caused weight loss associated with low BMI and malnutrition. The average BMI in our study was 20.89 kg/m\(^2\), which can adversely influence disease prognosis. Correspondingly, low pretreatment BMI (＜25.0 kg/m\(^2\)) was found to have a detrimental effect on OSCC survival in a cross-sectional study that included 320 patients.\(^{28}\)

DISCUSSION

Tongue cancer is the most frequent diagnosis of all oral cancers, and OTSCC is the primary pathological type.\(^{4}\) Several studies in Thailand reported prognostic factors that affect survival outcome. In the United States during 2006–2015, according to the SEER database of head and neck cancer, most patients were men older than 50 years.\(^{35}\)

For oral cancer, the average ages of non-Asian and Asian patients in a multicenter study between 2005 and 2014 were 69.99 years and 56.37 years, respectively.\(^{4}\) Similarly, the mean age of the 183 patients in our study was 55 years. In our current study, however, we found a higher ratio of female-to-male patients (1.6:1). Since 1985, a high percentage of women with oral cancer have been found predominantly in northeastern Thailand.\(^{11,15}\)

95%CI 1.75–19.54), a histologic grade with moderate or poor differentiated tumor (adjusted HR 3.09, 95%CI 1.16–8.24), and the group of operated cases with RND (adjusted HR 4.29, 95%CI 1.3–14.17) had detrimental effects on survival, with a \(P\) value less than 0.05. Lastly, radiotherapy was the only factor that had the advantage of increasing overall survival (adjusted HR 0.25, 95%CI 0.07–0.82; \(P = 0.022\)).

The higher ratio of female patients can be explained by a previous study by Kampangsi et al, which showed that, in the past, betel-nut chewing was a habit common among Thai people, especially among women, who chewed betel nuts daily starting at an early age.\(^{15}\) Betal nuts have been reported to contain carcinogens, such as polycyclic aromatic hydrocarbons, polonium 210, and nitrosamine, all of which subsequently cause precancerous lesions, including oral leukoplakia and oral submucous fibrosis.\(^{27}\)

Most patients who presented to the hospital in the late stage expressed difficulty chewing and swallowing, which consequently caused weight loss associated with low BMI and malnutrition. The average BMI in our study was 20.89 kg/m\(^2\), which can adversely influence disease prognosis. Correspondingly, low pretreatment BMI (＜25.0 kg/m\(^2\)) was found to have a detrimental effect on OSCC survival in a cross-sectional study that included 320 patients.\(^{28}\)

In this current study, most of the population (71.04%) worked in agriculture, a manifestation of low socioeconomic status in Thailand. A previous study also found low socioeconomic status to be a risk factor for oral cancer.\(^{1}\) It has long been accepted that smoking and alcohol consumption are oral cancer risk factors.\(^{12–14}\) However, we discovered that only 33.88% of the patients smoked, and 30.05% consumed alcohol in our study. Additionally, 15 cases (8.2%) in our study had a history of betel-nut chewing. This result differed from the Kampangsi et al study, which reviewed 17,388 patients and concluded that betel-nut chewing was presented by 15.9% of the total subjects and the important factor in the upper aerodigestive tract cancer. Our study, however, contained an inadequate population and failed to recognize betel-nut chewing as a significant risk factor. Similarly, alcohol drinking and tobacco smoking were less favorable in women and thus considered insignificant.\(^{15}\)

Out of the 183 cases in our study, 125 patients (68.31%) underwent surgery. According to the data categorized by tumor staging and TNM staging in Table 2, most cases presented with T3 and T4 (56.83%); hence the diagnoses were primarily in TNM stages 3 and 4 (75.22%). In a study published by Rogers et al, 144 OTSCC patients of 489 OSCC patients who underwent surgery had a 5-year

### Table 4. Unadjusted HR by the Univariate Cox Proportional Hazards Model Predicting Overall Survival

| Factors | HR | 95% CI | \(P\) |
|---------|----|--------|------|
| Gender  | Men | 1.58   | (1.07–2.32) | 0.021 |
| Age (y) | ≥70.5 | 2.06   | (1.35–3.19) | 0.001 |
| BMI (kg/m\(^2\)) | ≥18.5 | 1.76   | (0.95–3.29) | 0.075 |
| ASA classification  | 1  | 1  | 1  |
| Vertical dimension of tumor | <20 mm | 1.76   | (0.95–3.29) | 0.075 |
| Surgery | No | 0.21   | (0.15–0.31) | <0.001 |
| Extranodal extension | No | 1  | 1  |
| Perineural invasion | No | 1  | 1  |
| Resected margin | Negative | 1.32   | (0.67–2.60) | 0.428 |
| Positive | 1.89 | (0.96–3.73) | 0.065 |
| Length of free margin | >3 mm | 2.37   | (1.27–4.44) | 0.007 |
| Differentiation | Well | 1  | 1  |
| Moderate + poor | 2.01 | (1.39–2.90) | <0.001 |
| Type of neck surgery | SOHND + MRND | 3.08 | (1.65–5.74) | <0.001 |
| RND | 1  | 1  | 1  |
| Radiation | No | 1  | 1  |
| Yes | 0.83 | (0.57–1.21) | 0.341 |

### Table 5. Adjusted HR by Multivariate Cox Proportional Hazards Model Predicting Overall Survival

| Factors | Crude HR (95% CI) | \(P\) | Adjusted HR (95% CI) | \(P\) |
|---------|------------------|------|----------------------|------|
| BMI ≥18.5 | 1  | <0.001 | 1  | 0.030 |
| <18.5 | 2.37 | (1.62–3.47) | 0.001 | 3.03 | (1.11–8.25) |
| Vertical dimension | of tumor | <0.001 | 0.004 |
| <20 mm | 1  | 1  | 1  |
| ≥20 mm | 4.61 | (2.45–8.67) | 1  | 5.84 | (1.75–19.54) |
| Differentiation  | Well | 1  | 1  |
| Moderate + poor | 2.01 | (1.39–2.90) | <0.001 | 1  | 1  |
| Type of neck surgery | SOHND + MRND | 3.08 | (1.65–5.74) | <0.001 | 1  | 1  |
| RND | 1  | 1  | 1  |
| Postoperative radiotherapy | No | 1  | 1  |
| Yes | 0.83 | (0.57–1.21) | 0.25 | (0.07–0.82) |
OS equal to 64%. The tumors were primarily in the T1–T2 status. In contrast, the 5-year OS in our study was only 49.4% in the surgery group due to the patients presenting late with high-risk tumor stages T3–T4. Although patients presented with cancer in most cases, a clear surgical margin as high as 88% was obtained in our study. In the nonoperated group, most cases had at least a locally invasive tumor and advanced disease stage. Instead of surgery, this patient group chose as their primary treatment complementary and alternative medicine or other nonoperative modalities, typical to the deep-seated paranormal beliefs of the low socioeconomic population in northeastern Thailand. The bad prognosis of these patients aggravated the decline of their overall survival outcome.

The pathological result in this study reported that ENE and PNI were present in small percentages (8.2% and 6.56%, respectively). However, the univariate Cox proportional hazard analysis revealed that ENE markedly altered the OTSCC prognosis outcome (HR 4.12, \(P < 0.001\)). Thus, multiple ENE studies confirmed its importance as a prognostic factor for OSCC. Comparing ENE-negative and ENE-positive groups in the lymph node metastasis group, the ENE-positive group had a lower survival outcome. On the contrary, our study found PNI an insignificant prognostic factor. Unlike in our result, a case-control study of PNI in OSCC by Laske et al demonstrated that PNI had a critical impact on survival outcome. As mentioned earlier, the insignificant result probably came from the small number of PNI presented in our patients.

The Kaplan-Meier graph displayed in Supplemental Digital Content 1 indicates that early TNM stages and well-differentiated tumors can predict a good survival outcome in OTSCC. The survival was significantly higher in patients who underwent surgery (median survival 57.63 months versus 7.6 months; \(P < 0.001\)). In the operated group, there were 119 patients with neck dissection surgery. Comparing the groups revealed that patients who underwent SOHND had the greatest survival. The modified radical neck dissection and RND groups had inferior survival outcomes successively (\(P = 0.001\)). These outcomes corresponded precisely with the nature of the disease in malignancy. In patients with bulky cervical lymph node metastasis or extensive soft tissue involved in an extracapsular spread, RND was performed. Therefore, patients who underwent multiple nodal metastases usually had a detrimental prognosis. According to the surgical margin, surgery that can gain a clear margin had a superior survival outcome over the involved margin group (5-year OS 52.1% versus 28.57%; \(P = 0.061\)). The lack of statistically significant difference in survival was most likely due to the small number of positive margin group cases in our study. Dissimilarly, Rogers et al reported, via a large retrospective study of 489 oral cancer patients, a remarkable difference in survival between clear and involved margins (5-year OS 66% versus 35%).

A small study conducted by Geum et al in Korea consisted of 37 patients with 11 cases of tongue cancer. It revealed that TNM stage, cervical lymph node metastasis, and recurrence after surgery had critically impacted the 5-year survival of oral cancer. Montoro published a similar prognostic factors report consisting of 45 oral squamous cell carcinoma cases in Brazil, which indicated that neck node metastasis had a notable effect on survival. The pathological study revealed that an early tongue cancer stage (T1 and T2 with N0M0 stage) with a depth of invasion greater than 4 mm, a high worst pattern of invasion, and high tumor budding were the critical indicators for predicting prognosis in OTSCC. In an additional study of histologic grade, a poor or undifferentiated tumor was also strongly associated with lowering the survival of oral squamous carcinoma. An extensive database that included a total of 2082 OSCC patients with the tongue as the prominent anatomical location revealed several independent prognostic factors (ie, age < 60 years, presence of severe comorbidities, positive margin status, presence of vascular invasion, presence of PNI, T3-4 stage, and pN2-3 stage).

In our study, the univariate Cox proportional hazards model disclosed that surgery was the only good prognostic factor (HR 0.21; 95% CI 0.15–0.31; \(P < 0.001\)). This calculation may have been reflected in finding that survival improved for patients who presented with a late disease stage but had surgery. Many meaningful poor prognostic factors include women (HR 1.58; 95% CI 1.07–2.32; \(P = 0.021\)), age 70.5 years or older (HR 2.06; 95% CI 1.33–3.19; \(P = 0.001\)), BMI less than 18.5 kg per m\(^2\) (HR 2.37; 95% CI 1.62–3.47; \(P < 0.001\)), vertical dimension of tumor 20 mm or more (HR 4.61; 95% CI 2.45–8.67; \(P < 0.001\)), presence of ENE (HR 4.12; 95% CI 2.33–7.29; \(P < 0.001\)), surgical margin 5 mm or less (HR 2.37; 95% CI 1.27–4.4; \(P = 0.007\)), histologic grade with moderate, poor, or undifferentiated tumor (HR 2.01; 95% CI 1.39–2.90; \(P < 0.001\)), and RND in operated patients (HR 3.08, 95% CI 1.65–5.74; \(P < 0.001\)). Older age tends to lower the survival of any disease, and low BMI is relevant to oral cavity cancer in general. Our study recognizes that these factors are confounding. The high ratio of women in our study population resulted in a bias in our analysis. Therefore, our study did not conclude female gender a true poor prognostic factor. Vertical tumor size had been shown beneficial for computer tomography-based preoperative measurements for predicting survival. Nevertheless, identifying its implication on clinical significance requires further investigation. The extent of nodal extension, a surgical margin 3 mm or less, and a moderate or poor histologic grade are deleterious factors for oral cavity cancers. Meanwhile, the univariate Cox proportional hazards model analysis revealed that ASA classification, PNI, involved surgical margin group, and radiotherapy were insignificant. Finally, after adjusting the evaluation from the multivariate Cox proportional hazards model, adjuvant radiotherapy was a remarkably good prognostic factor in OTSCC (adjusted HR 0.25; 95% CI 0.07–0.82, \(P = 0.022\)). As a standard practice, operated patients with extranodal extensions, positive surgical margin or presenting other adverse risk factors (eg, multiple positive lymph nodes, perineural invasion, lymphovascular invasion, pathological T3 or T4 primary, and positive level IV or V lymph nodes), and who received radiotherapy were shown to have a better survival outcome.

**Strength and Limitation of the Study**

Our study, consisting mainly of the advanced stage of OTSCC across a large population, disclosed an advantage of

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surgery on survival even in advanced stages compared with the nonoperated group, neither clear nor involved surgical margin achievement. In addition, our results showed a predominantly higher ratio of female patients compared with other studies, which may have consequently presented a population biased toward fewer tobacco smoking and alcohol consumption incidences. However, some parameters, such as the positive margin group and PNI, were presented in a few cases, and thus, this might consequently affect the insignificant difference of survival outcomes.

CONCLUSIONS

In this study, we comprehensively analyzed factors for predicting the survival of OTSCC. We found that surgery and radiotherapy were good prognostic factors, whereas presenting a vertical dimension of tumor 20 mm or more, the presence of ENE, a surgical margin 3 mm or less, a histologic grade with a moderate or poor differentiated tumor, and an RND in an operated group were poor prognostic factors.

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