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Cognitive function, mood, and sleep quality in patients treated with intensity-modulated radiation therapy for nasopharyngeal cancer: a prospective study

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Abstract

***Objective*: The aim of this study was to prospectively evaluate the cognitive function, depression, anxiety, and sleep quality in patients with nasopharyngeal cancer (NPC) before and after intensity-modulated radiotherapy (IMRT).**

***Methods*: Eligible patients with newly diagnosed NPC treated with primary IMRT were recruited. A series of neuropsychological tests were performed within 1 week before and after IMRT. Cognitive function was measured with the Das–Naglieri cognitive assessment system. The Self-rating Anxiety Scale and Self-rating Depression Scale were used to assess mood states. Sleep quality was evaluated by means of the Pittsburgh Sleep Quality Index.**

***Results*: A total of 51 patients were enrolled. The overall prevalence of depression, anxiety, and poor sleep quality showed a significant increase after RT, compared with their pre-RT levels (39.2% vs. 3.9%, $p = 0.000$; 19.6% vs. 3.9%, $p = 0.039$; 64.7% vs. 37.3%, $p = 0.003$, respectively). Multiple linear regression analysis revealed that pre-RT depression and younger age and pre-RT anxiety and younger age were significant predictors of post-RT depression and anxiety, respectively ($p < 0.05$). Poor sleep quality before treatment was also associated with poor sleep after RT ($p = 0.032$). However, the cognitive function evaluated by the cognitive assessment system from pre-RT was similar to the post-RT results.**

***Conclusions*: Exposure to ionizing radiation for the treatment of NPC decreased mood and sleep quality following IMRT, especially for patients with depression, anxiety, younger age, or poor sleep before treatment. No acute cognitive deficits were found resulting from IMRT, but the long-term effects of RT might still warrant concern.**

Introduction

Radiotherapy (RT) is the primary treatment for nasopharyngeal cancer (NPC), which is endemic in Southeast Asia, especially in China [1]. Most patients achieve long-term survival after definitive RT with concurrent platinum-based chemotherapy for locoregionally advanced NPC. The 5-year and 10-year overall survival rates are 67–79.6% and 66.5% respectively [2,3]. As the survival rate and favorable outcomes of NPC increase, the side effects of RT have received extensive attention, such as RT-induced cognitive impairment. The cognitive decline induced by RT is well recognized in brain tumors, as well as head and neck cancers (HNCs) [4,5]. Many areas of cognition can be affected, and deficits in attention, memory, and executive function [6], leading to a seriously compromised quality of life [7]. Because of the specific anatomical location and the biological characteristics of NPC, although the tumor receives a sufficiently large dosage of radiation, normal brain tissues, especially the temporal lobes, are often within the target volume and receive unnecessary radiation. Radiation-induced temporal lobe injury is associated with cognitive deficits and results in memory or learning dysfunction [8]. Patients with NPC treated with RT may be at a great risk for the development of cognitive impairments.

The diagnosis and subsequent treatment of cancer can have a potentially devastating effect on psychosocial functioning [9]. Sleep disturbance and psychological distress are the most common symptoms observed in these patients. Depression, anxiety, and sleep disorders have a profound impact on the quality of life [10] but are also adversely related to cardiac morbidity, inhibited healing, and interference with clinical outcomes [11,12]. However, relatively few studies have assessed psychological functioning and sleep among NPC patients treated with intensity-modulated RT (IMRT).

Although there have been some investigations into the relationships between cognitive dysfunction and irradiation in NPC patients [13,14], most of these studies focused on the cognitive decline of patients with radiation-induced brain injury or radionecrosis, which manifested with

characteristic signs on follow-up computed tomography (CT) or magnetic resonance imaging (MRI). Additionally, the majority of studies examined patients treated with conventional two-dimensional (2D) RT [7,13,14]. However, there is evidence that patients could develop cognitive impairment before signal abnormalities of CT or MRI [15]. Moreover, with the wide use of 3D conformal RT (3D-CRT) and IMRT, sparing large volumes of the temporal lobes of NPC patients from receiving a high dose can be possible, which may mitigate cognitive decline induced by RT. Finally, most studies were limited by retrospective design or small patient numbers. Fewer reports have concentrated on acute cognitive impairment following RT or IMRT.

Therefore, the objective of this prospective study was to explore cognitive function among NPC patients within a week after IMRT, compared with pretreatment measures. We also evaluated the prevalence of depression, anxiety, and sleep changes in these patients and identified factors (patient and treatment-related characteristics) associated with posttreatment depression, anxiety, and poor sleep quality.

Methods

Patients

Patients with NPC were recruited to participate in this prospective assessment from December 2012 to July 2013, through the Department of Radiation Oncology at the Cancer Hospital of Guangxi Medical University. Eligibility criteria were the following: (a) primary diagnosis of NPC, seventh edition Union for International Cancer Control stage I to IVb, treated with IMRT, (b) aged from 18 to 60 years, (c) mastered 26 letters of the English alphabet, (d) no evidence of cranial CT or MRI abnormality, and (e) no prior RT or chemotherapy. Patients with a history of psychiatric disorder, intellectual disability or dementia, those with previous/current use of antidepressants or anxiolytics, and those diagnosed with a second tumor or treated with conventional RT were excluded. All enrolled participants provided written informed consent. This study was approved by the Ethics Committee of Guangxi Medical University.

Intensity-modulated radiotherapy and concurrent chemotherapy

All patients were treated with 6 MV photons by use of an IMRT technique with nine portals. The patients were immobilized with thermoplastic cast. A planning CT scan was obtained for the localization of targets and organs at risk. The left and right temporal lobes were each contoured on the CT image. All patients were treated with 1.8–2 · 26 Gy per fraction, with five daily fractions per week for 6–7 weeks. The prescribed dose was 70–72.32 Gy to the primary tumor and 60–70 Gy to positive nodes. All potential sites of local infiltration and bilateral cervical lymphatics were irradiated with 60–62 and 54–55.8 Gy, respectively. Patients with stages III–IVb and some with stage II disease were given concurrent chemotherapy, consisting of 100 mg/m^2 of cisplatin every 3 weeks on days 1, 22, and 43 during RT for each cycle.

Cognitive function assessment

The Chinese version of the Das–Naglieri cognitive assessment system (CAS) was used to evaluate cognitive processes. The CAS has now been used in neuropsychological assessments for both children and adults [16] and is modeled on the planning–attention–simultaneous–successive theory of cognitive processes [17]. These four cognitive processes were derived from three functional units of human cognitive processes described by Luria's qualitative theory. The CAS consisted of 12 subtests, with 3 subtests for each planning–attention–simultaneous–successive factor. McCrea using CAS to assess functions in patients with stroke lesions and traumatic brain injury found that the executive function, verbal information, and attention were impaired [18,19]. CAS is also used to evaluate attention and executive function in a normal person [20,21]. Its sensitivity has been empirically confirmed, as well as its reliability and construct validity. Additionally, the Chinese version of CAS was shown to have the same features [22]. Although CAS was standardized on 2200 persons aged between 5.0 and 17.92 years, tests of mental ability that provided adult norms extending into the late teens found that the population of 18 year olds did not perform much differently than the adult population at large [23]. Moreover, across most of the CAS subtests, there were near asymptotic levels of performance, cresting near the age of 18 years [16]. Further evidence proved this finding, when the subtests of the CAS examined college students and were able to objectively measure changes in cognitive functioning across subgroups, without any floor or ceiling effects [24]. The subtest scales and full-scale scores were expressed as standard scores with a mean of 100 and a standard deviation of 15. The score for each subtest was computed according to the CAS manual [16].

Self-rating Depression Scale

The Self-rating Depression Scale (SDS) is a 20-item questionnaire designed to assess depression over the preceding week. Each item is scored from 1 to 4. The raw score is converted into a standardized score. In accordance with the Chinese norm, a score higher than 50 was used to define the presence of depression. The Cronbach's alpha coefficient and test–retest reliability were 0.862 and 0.820, respectively [25].

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Self-rating Anxiety Scale

Self-rating Anxiety Scale (SAS) is a 20-item scale to evaluate subjective feelings of anxiety. Each question is scored from 1 to 4. After being standardized, a score of 50 or more on SAS categorized individuals as having anxiety, according to the Chinese version. The split-half reliability and test–retest reliability were 0.696 and 0.777, respectively [25].

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) is a self-administered questionnaire to evaluate subjective sleep quality during the previous month. It contains 19 self-rated questions, including 7 subscore components (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication, and daytime dysfunction). Each subscore component is scored from 0 to 3, and the total score range is 0–21. The cutoff score of the Chinese version of the PSQI is 5. A total score >5 indicates poor sleep, and the higher the score, the poorer the sleep quality. The Cronbach's alpha coefficient and test–retest reliability were 0.82–0.83 and 0.85, respectively [26].

Procedures

All patients received a cranial MRI exam before and after treatment. The participants took the additional tests individually in a quiet room. A trained postgraduate student administered the tests. The interviewer was blind to the disease and treatment mode of the patients. The total assessment lasted approximately 1.5–2 h, with several minutes of rest between the tests, in order to minimize fatigue and to ensure optimal subject performance. The administration order was fixed. Measures were performed at two time points: after diagnosis and before the treatment of RT (pre-RT) and within a week after 6–7 weeks of RT (post-RT).

Statistical analyses

All data were subjected to descriptive analyses. We used the paired-sample *t*-test to determine the exact significance of the differences in cognitive function, SDS, SAS, and PSQI scores, before and after RT. McNemar's test was performed to compare the prevalence of depression, anxiety, and poor sleep quality over time. To explore potential predictors of post-RT depression and anxiety, stepwise multiple linear regression was used. Because the global PSQI dependent continuous variable scores were not normally distributed, we divided them into two groups, according to the cutoff point: with poor sleep quality scores >5 and good sleep quality scores ≤5. Logistic regression models were used to analyze the relationships between poor sleep quality post-RT and other variables. All tests were two-sided, and a p-value of <0.05 was considered statistically significant. SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

A total of 61 eligible NPC patients were approached for enrollment, 4 refused to participate and 6 did not complete the survey, owing to severely adverse reactions to treatment. The mean age of the final 51 enrolled participants (32 men and 19 women) was 40.1 ± 8.7 years (range, 24–60 years). All participants had completed the IMRT treatment, and the majority had received two or three cycles (94.1%) of concurrent cisplatin chemotherapy. The baseline characteristics of patients are listed in Table 1. No radionecrosis was found in any of the 51 participants during the follow-up MRI. The mean doses to the left and right temporal lobes were 18.9 ± 2.8 and 19.3 ± 4.3 Gy, respectively.

Cognitive performance

The standard scores of all CAS subtests and full scores from pre-RT were similar to those after IMRT (Figure 1). There were nearly no changes in attention subtests and full scores before and after treatment (75.7 ± 11.3 vs. 75.5 ± 11.5, $p = 0.818$; 68.5 ± 15.8 vs. 68.6 ± 15.2, $p = 0.979$). The mean scores of the simultaneous subtests after RT tended to be lower than baseline scores (90.3 ± 14.9 vs. 91.8 ± 14.6, $p = 0.237$), whereas the scores of the planning and successive subtests were a little higher post-RT than those before treatment (65.1 ± 13.0 vs. 63.9 ± 13.9, $p = 0.213$; 75.3 ± 14.9 vs. 74.2 ± 16.2, $p = 0.256$). However, no statistically significant differences were found.

Table 1. Patient characteristics ($N = 51$)

Characteristic	No. of patients	Years	%
Age			
Mean ± SD		40.1 ± 8.7	
Range		24–60	
Gender			
Male	32		62.7
Female	19		37.3
Education level			
Primary	4		7.8
Middle	19		37.3
High	13		25.5
University	15		29.4
Stage (7th UICC)			
Stage II	8		15.6
Stage III	29		56.9
Stage IV	14		27.5
Concurrent chemotherapy			
One cycle	3		5.9
Two cycles	13		25.5
Three cycles	35		68.6

SD, standard deviation; UICC, Union for International Cancer Control.

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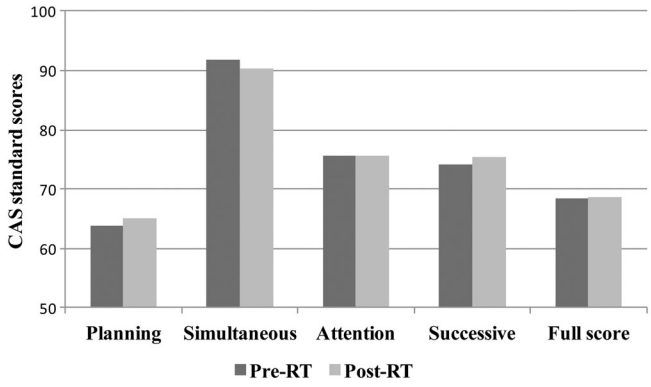

Figure 1. The mean standard scores of planning, simultaneous, attention, successive, and full scores (evaluated by cognitive assessment system (CAS)) before and after intensity-modulated radiotherapy

Psychological characteristics and sleep quality

Before RT, the percentages of participants who presented with mild to severe depression on SDS and anxiety on SAS were both 3.9% (2/51). In the post-RT setting, clinical cutoff scores were exceeded by 39.2% (20/51) of patients on the depression scale and 19.6% (10/51) on the anxiety scale (Table 2). The mean standardized SDS and SAS scores were higher post-RT than those at baseline (50.3 ± 9.9 vs. 40.0 ± 8.5, $p = 0.000$; 43.4 ± 9.1 vs. 37.2 ± 6.7, $p = 0.002$).

Patients with poor sleep quality (global PSQI score >5) before RT comprised 37.3% of the subjects. However, the population subsequently grew to 64.7% post-RT, and the observed increase in mean global PSQI scores was statistically significant, compared with pre-RT scores (8.0 ± 4.3 vs. 5.2 ± 3.6, $p = 0.023$).

Predictors of postradiotherapy depression, anxiety, and sleep

Variables such as age, gender, education, clinical stage, concurrent chemotherapy cycle, pre-RT depression, pre-RT anxiety, and pre-RT poor sleep quality were included to investigate the potential predictors for depression, anxiety, and poor sleep after RT. Multiple linear regression analyses revealed that pre-RT depression and younger age were significantly associated with increased post-RT depression, whereas pre-RT anxiety and younger age were the significant predictors of post-RT anxiety ($p < 0.05$ for all, Tables 3 and 4). None of the other variables predicted an increase in post-RT depression and anxiety according to SDS and SAS.

Results of binary logistic regression analysis showed that poor sleep pre-RT was an independent risk factor for poor sleep quality after treatment; the odds ratio was 4.76 (95% CI = 1.143–19.475, $p = 0.032$). No correlations were found between other covariates (age, gender, education, clinical stage, concurrent chemotherapy cycle, pre-RT depression, and pre-RT anxiety) and global PSQI scores >5, post-RT.

Table 2. Depression, anxiety, and sleep before and after radiotherapy (RT)

	Pre-RT (*N* = 51)	Post-RT (*N* = 51)	*p*-value
Morbidity of depression			
Depression (%)	2 (3.9)	20 (39.2)	0.000
No depression (%)	49 (96.1)	31 (60.1)	
SDS score (Mean ± SD)	40.0 ± 8.5	50.3 ± 9.9	0.000
Morbidity of anxiety			
Anxiety (%)	2 (3.9)	10 (19.6)	0.039
No anxiety (%)	49 (96.1)	41 (80.4)	
SAS score (Mean ± SD)	37.2 ± 6.7	43.4 ± 9.1	0.002
Sleep quality			
Poor sleep quality (%)	19 (37.3)	33 (64.7)	0.003
Good sleep quality (%)	32 (62.7)	18 (35.3)	
Global PSQI score (Mean ± SD)	5.2 ± 3.6	8.0 ± 4.3	0.023

SDS, Self-rating Depression Scale; SD, standard deviation; SAS, Self-rating Anxiety Scale; PSQI, Pittsburgh Sleep Quality Index.

Discussion

This longitudinal study is an investigation of cognitive function, emotional status, and sleep changes in NPC patients within a week before and after IMRT. To our knowledge, the present study is the first to prospectively assess acute changes of cognitive functioning and sleep in NPC patients treated with IMRT. Results showed that there was no acute change in cognitive function after IMRT, as evaluated by CAS. However, depression and anxiety increased. Nearly two thirds of patients had poor sleep quality after RT. Those with depression, anxiety, and poor sleep pre-RT were more likely to develop negative mood and bad quality of sleep post-RT, and younger patients were at increased risk of depression and anxiety at the end of treatment.

With the increased use of IMRT and the effectiveness of concurrent chemotherapy, patients with NPC have presented excellent long-term results. Therefore, the substantial risks of acquiring late or delayed radiation injuries

Table 3. Multiple linear regression analysis of potential predictors for postradiotherapy (RT) depression

Model	B-coefficient	S. E.	*p*-value	Adj. R2
1 (constant)	20.345	6.833	0.005	
Pre-RT depression	0.684	0.138	0.000	0.321
2 (constant)	32.455	8.571	0.001	
Pre-RT depression	0.681	0.132	0.000	
Age	−0.299	0.137	0.035	0.379

Table 4. Multiple linear regression analysis of potential predictors for postradiotherapy (RT) anxiety

Model	B-coefficient	S. E.	*p*-value	Adj. R2
1 (constant)	12.995	8.246	0.123	
Pre-RT anxiety	0.677	0.185	0.001	0.191
2 (constant)	28.046	10.123	0.008	
Pre-RT anxiety	0.627	0.177	0.001	
Age	−0.324	0.138	0.024	0.271

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must be taken seriously. Previous studies have demonstrated that patients can develop late cognitive dysfunction, impairments in attention, immediate and delayed verbal recall, immediate visual recall, and memory after years of radiation for NPC [13,27]. Cheung *et al*. [28] also reported that memory, planning, abstract thinking, and executive functions were significantly impaired in NPC patients with temporal lobe necrosis after treatment of RT at least 1 year prior, when compared with patients without radionecrosis and normal control subjects, although their attention and general intelligence were unaffected. This conclusion was consistent with a recent study that investigated the cognitive function of NPC patients with radiation-induced brain injury after years of treatment [7]. All subjects with the late cognitive deficits mentioned earlier were treated with conventional RT and presented with brain injury induced by RT. However, with advances in 3D-CRT and IMRT, it is possible to spare large volumes of normal brain tissue from receiving unnecessary exposure and may thereby decrease the prevalence of cognitive impairment or brain injury. Kam *et al*. [29] revealed that IMRT was able to reduce D_{max} to the temporal lobes in T2N2M0 and T4N2M0 NPC patients by 34 and 20.5 Gy, respectively, compared with conventional RT. Results from a long-term follow-up (median, 50.9 months) also showed that no radiation encephalopathy or cranial nerve injury was observed in 198 patients treated for NPC with IMRT [30]. Our present results showed no acute changes in the cognition of NPC patients after treatment with IMRT. Although a recent prospective study reported that 76.7% of patients treated with IMRT had significantly lower cognitive functioning scores compared with their pre-RT scores [31], and significant deterioration in short-term memory and language abilities were found, the endpoint of this assessment was at 12–26 months (mean, 18 months) after the completion of IMRT. This period is obviously inconsistent with the current study, which evaluated acute effects within a week after treatment with IMRT. These findings indicate that there may be no cognitive damage in the short term in patients with NPC who underwent IMRT. On the contrary, most patients are likely to develop late or delayed cognitive deterioration after years of 3D-CRT or IMRT. A study conducted in patients treated with 3D-CRT for low-grade glioma demonstrated that there was no memory impairment at 6 months after the irradiation. However, a cognitive decline was noted 12 months after treatment [32].

Depression and anxiety are the most common psychological problems observed in oncology patients [33], in addition to sleep disturbance [34]. In this study, depression and anxiety, from mild to severe, were observed in only 3.9% of NPC patients immediately pre-RT, whereas approximately a third of participants reported poor sleep quality before treatment. The reasons for low levels of psychological disorders pre-RT are likely that, among all malignant tumors, NPC is regarded as having a favorable outcome, and some patients can even be cured. Most can obtain long-term survival after treatment. However, our results were inconsistent with a recent study that reported a higher prevalence of depression and anxiety in NPC patients before RT [35]. This was likely because eligible participants included in the latter were all stage III/IV with locally advanced NPC, who might suffer more severe psychological distress, whereas our study included some stage II patients.

After treatment, results showed that the prevalence and mean scores of depression, anxiety, and sleep disturbance were significantly increased compared with pre-RT levels. Given the side effects of radiation, such as dysphagia, chewing, xerostomia, and decreased gustatory sensitivity, which contribute to depression, anxiety, and decreased quality of life [36,37], as well as more severe symptoms associated with greater sleep dysfunction [38], it is not surprising that psychological disorders and poor sleep levels increase dramatically after treatment. The present findings are consistent with a recent prospective study in which the mean symptom scores of depression and anxiety were significantly higher after RT compared with baseline levels [35]. Lee *et al*. [39] also reported that depression reached a peak at the end of RT. In contrast to depression, the anxiety levels did not significantly change. Given that most patients received two or three cycles of concurrent chemotherapy, chemotherapy itself might contribute to bad mood and sleep disturbance [40]. However, evidence revealed that neither concurrent nor nonconcurrent chemotherapy were associated with post-RT depression, anxiety, or sleeplessness [7,38,41], and our results showed that the concurrent chemotherapy cycle was not an independent risk factor for post-RT depression, anxiety, or poor sleep. Therefore, the results should be interpreted with caution.

In regard to the risk factors influencing depression, anxiety, and poor sleep quality after treatment, as would be expected, we found that patients with depression, anxiety, and poor sleep quality pre-RT showed a significant correlation with the same symptoms after IMRT. Similar results were also found in several studies of other HNCs [41,42]. Moreover, evidence has shown that there are some associations between greater sleep dysfunction and depression [38], indicating these factors can influence each other. In this study, the findings also suggested that younger patients with NPC appeared to suffer greater post-RT psychological distress than older patients. The exact factors responsible for depression and anxiety are likely complex, because of the multifactorial nature of the associations. One reason could be that younger patients have fewer social experiences, are more likely to despair over disease, and are more sensitive to pain or the side effects of concurrent chemoradiotherapy than older patients, which could cause increased psychological distress, poor sleep, and decreased quality of life. Data

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similarly reveal that younger age adversely influences depression and quality of life in other HNCs [41,43].

There were some notable limitations of this study. First, this is a self-control study. It may not truly reveal factors that result in the differences before and after treatment. Limited by the design, practice effect might have occurred in our research. However, this type of error is no exception in many other kinds of cognitive tests. Because no test is a perfect measure of its construct and all tests contain error, approaches to minimizing practice effect involve increased familiarity with a task through the use of extended practice items or using alternate forms of the same test [44]. Or parallel control was used in the tests. Second, although the CAS test has been widely used to evaluate the cognitive process, many studies also support its use in adults [16,23,24,45], it was standardized on persons between the ages of 5.0 and 17.92 years. Therefore, caution should be used in the interpretation of our results. Third, the observation end point was within a week of the day after the conclusion of IMRT. Finally, six patients did not complete the posttest because of edema, fatigue, or vomit. We are not sure whether they have poor sleep quality, anxiety, depression, and cognitive impairment. But they were excluded from this study. Even though no differences were found in cognitive function at this point in time, the long-term effects that tend to be permanent should demand more attention.

The present study indicates that exposure to ionizing radiation in NPC patients contributes to decreases in mood and sleep quality following IMRT. Patients with depression, anxiety, younger age, and poor sleep quality pre-RT are inclined to continue to report psychological distress or sleep disturbance post-RT. Supportive care measures to reduce symptom severity might be considered during and after treatment. Although there was no acute change in cognitive function after IMRT, future research with a longer follow-up and a control design should be continued to evaluate the potential effects of RT on cognitive function, mood, and sleep in NPC patients.

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Conflict of interest

The authors have declared no conflicts of interest.

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