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ORIGINAL ARTICLE – UROLOGIC ONCOLOGY

Surgical Resection Does Not Improve Survival in Patients with Renal Metastases to the Pancreas in the Era of Tyrosine Kinase Inhibitors

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ABSTRACT

Background. The aim of this study was to compare survival of resected and unresected patients in a large cohort of patients with metastases to the pancreas from renal cell carcinoma (PM-RCC).

Methods. Data from 16 Italian centers involved in the treatment of metastatic RCC were retrospectively collected. The Kaplan–Meier and log-rank test methods were used to evaluate overall survival (OS). Clinical variables considered were sex, age, concomitant metastasis to other sites, surgical resection of PM-RCC, and time to PM-RCC occurrence.

Results. Overall, 103 consecutive patients with radically resected primary tumors were enrolled in the analysis. PM-RCCs were synchronous in only three patients (3 %). In 56 patients (54 %), the pancreas was the only metastatic site, whereas in the other 47 patients, lung (57 %), lymph nodes (28 %), and liver (21 %) were the most common concomitant metastatic sites. Median time for PM-RCC occurrence was 9.6 years (range 0–24 years) after nephrectomy. Surgical resection of PM-RCC was performed in 44 patients (median OS 103 months), while 59 patients were treated with tyrosine kinase inhibitors (TKIs; median OS 86 months) ($p = 0.201$). At multivariate analysis, Memorial Sloan Kettering Cancer Center risk group was the only independent prognostic factor. None of the other clinical variables, such as age, sex, pancreatic surgery, or the

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presence of concomitant metastases, were significantly associated with outcome in PM-RCC patients.

Conclusions. The presence of PM-RCC is associated with a long survival, and surgical resection does not improve survival in comparison with TKI therapy. However, surgical resection leads to a percentage of disease-free PM-RCC patients.

Renal cell carcinoma (RCC) is the most common type of kidney cancer in adults. Almost one-third of patients present with metastatic disease at diagnosis and another 20 % develop metastases after nephrectomy.[1,2] Lung and bone metastases represent the most frequent sites of distant metastases, while the percentage of the pancreas (PM-RCCs) is clinically uncommon. These lesions are usually asymptomatic and diagnosed many years after the occurrence of the primary tumor, reflecting a relatively indolent disease. Their ultrasound appearance is generally a hypoechoic mass and may occasionally present with cystic degeneration.[3,4] After contrast media, they usually appear as circumscribed hypervascularized nodules.

Surgical resection of metastases to the pancreas has reported to confer a survival benefit, and total pancreatectomy is often proposed as a valid therapeutic option for both the high rate (50 %) of recurrence after atypical resections[5] and the multifocality of the disease. However, other studies suggest that total pancreatectomy should be avoided, providing adequate resection margins, since maximal tissue preservation can be achieved.[6] Moreover, surgery cannot always be performed due to patient comorbidities and the presence of distant disease.[7] In addition, no robust data demonstrated the advantage of surgical resection on overall survival (OS).

The introduction of biological therapies has changed the outcome of patients with metastatic disease, and tyrosine kinase inhibitors (TKIs) are a good alternative therapeutic option in patients affected by PM-RCCs.[8,9] Grassi et al. investigated the prognostic role of PM-RCCs in a large cohort of 354 patients treated with targeted agents. They showed that the presence of PM-RCCs was associated with a longer survival compared with the 330 patients with metastases to non-pancreatic sites (39 vs. 23 months).[9]

In this scenario, understanding the role of surgery in the era of targeted therapies is of increasing importance. In this study, we report the results from a large Italian multicenter study on the prognosis of patients with PM-RCCs treated with surgery and/or TKIs.

PATIENTS AND METHODS

Study Population

This was a retrospective, observational, multicenter study of medical records from 2005 to 2014 for patients with cytohistological and/or radiological diagnosis of PM-RCCs who were treated at 16 different Italian centers. Data were collected from patients of all ages who received standard treatments (i.e. not on clinical trials or experimental protocols) in accordance with the practice of their treating physician. Patients were collected consecutively to avoid selection bias, and data were collected from medical chart reviews and electronic records. Inclusion criteria were histologic diagnosis of RCC, previous radical nephrectomy, clinical diagnosis of PM-RCCs, and regularly conducted follow-up of the disease. Patients were excluded from the analysis if they had missing information regarding sites of metastasis, and time to either pancreatic or distant metastases.

Patient characteristics and clinicopathological variables considered in this study were sex, age, Memorial Sloan Kettering Cancer Center (MSKCC) prognostic criteria,[10] time from nephrectomy to PM-RCCs, presence of concomitant metastases, and pancreatic surgery. PM-RCCs, as well as other metastatic sites, were defined either with total body contrast-enhanced computed tomography (CT) and/or magnetic resonance imaging (MRI). Patients were further divided and analyzed into groups according to whether they underwent pancreatic surgical resection at any time or therapy with TKIs alone.

Statistical Analysis

Cancer-specific survival was computed from both any site metastasis and PM-RCC to the event (death), and both measurements were considered as outcome measures.

Continuous covariates (age, time from nephrectomy to PM-RCC) were grouped into discrete ordinal categories. Age was divided into two ordinal groups (<65 and ≥ 65 years), while the time from nephrectomy to PM-RCC was divided into three ordinal groups (<1, between 1 and 5, >5 years). Correlation between continuous variables was assessed by means of the Pearson product-limit correlation coefficient.[11] As outcome variables, survival from both the diagnosis of metastatic RCC (mRCC) and the diagnosis of PM-RCC was analyzed.

OS was evaluated from PM-RCC diagnosis via the Kaplan–Meier method, and the Mantel–Haenszel log-rank test was employed to compare survival among groups. Homogeneity of the two groups relating to variable distributions was tested by means of the Chi-square test for difference in proportions. A Cox regression model was applied to the data using a univariate and multivariate approach. The assumption of proportionality of hazards was assessed using the Grambsch and Therneau test of the Schönefeld residuals.[12] Variables not fitting at univariate regression analysis were excluded for the multivariate model. No-multicollinearity of the grouped covariates was

also checked. Significance level in the univariate model for inclusion in the multivariate final model was more liberally set 0.2, according to Hosmer and Lemeshow.[13] All other significance levels were set at a value of 0.05.

The differences of characteristics in patients' eligibility for pancreatic surgery were considered, and the propensity score for each subject was calculated according to the clinical variables driving surgeons' choices (patients' age, Eastern Cooperative Oncology Group Performance Status [ECOG-PS], single vs. multiple metastatic sites) by means of a multivariate logistic regression model. The univariate hazard ratio (HR) for pancreatic surgery was calculated after marginal direct re-weighting for patients' propensity.

Statistical analysis was conducted using R software version 3.0.1 (The R Company, Wien, Austria).

RESULTS

Overall Study Population

Clinical data of 2,283 patients with mRCC treated in 16 Italian centers were retrospectively collected. Of these patients, 103 (5 %) had PM-RCCs and were enrolled in this analysis (Fig. 1); 66 were males (64 %). Median age was 67 years (range 43–85 years), and tumor histology was predominantly clear cell (98 %). Prognostic categories using MSKCC criteria were good in 78 patients (76 %), intermediate in 22 patients (21 %), and poor in 3 patients (3 %). The complete list of patient characteristics is shown in Table 1.

Ninety-eight patients (95 %) had no metastatic RCC at the time of first diagnosis. All 103 patients were treated with radical nephrectomy at first diagnosis of RCC. PM-RCCs were synchronous in only three patients (3 %). In 56 patients (54 %), the pancreas was the only metastatic site, while in the other 47 patients, lung (57 %), lymph nodes (28 %), and liver (21 %) were the most common concomitant metastatic sites. In patients without PM-RCC at primary diagnosis of RCC ($N = 98$), the median time to PM-RCC was 9.6 years (range 0–24 years) after nephrectomy. Of the 98 (73 %) patients without metastases at the time of RCC diagnosis, 72 were asymptomatic at the time of recurrence and were diagnosed during their follow-up;

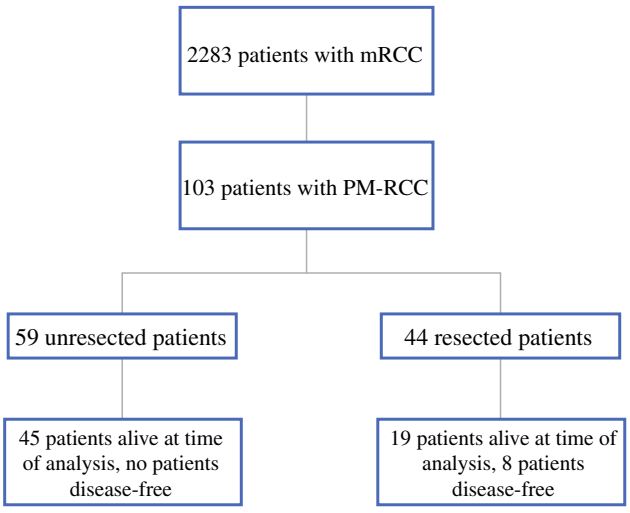

FIG. 1 Selection process for the study population. *mRCC* metastatic renal cell carcinoma, *PM-RCC* pancreatic metastasis from renal cell carcinoma

TABLE 1 Clinicopathological characteristics of the overall population and subgroups (resected/unresected)

	Patients ($N = 103$)	Resected ($N = 44$)	Unresected ($N = 59$)	p value
Age [years; median (range)]	67 (43–85)	66 (46–74)	69 (43–85)	0.37
Sex				
Male	66 (64)	26 (59)	40 (68)	0.63
Female	37 (36)	18 (41)	19 (32)	0.63
Tumor histology				
Clear cell	101 (98)	43 (97)	58 (98)	1
Disease status at RCC diagnosis				
Metastatic	5 (5)	2 (5)	3 (5)	1
Non-metastatic	98 (95)	42 (95)	56 (95)	1
ECOG-PS ≥ 2	4 (4)	0 (0)	4 (1)	0.21
MSKCC risk group				
Good	78 (76)	38 (86)	40 (68)	**0.05**
Intermediate	22 (21)	6 (14)	16 (27)	0.16
Poor	3 (3)	0 (0)	3 (5)	0.35
Synchronous pancreatic metastases	3 (3)	1 (2)	2 (3)	1
Presence of concomitant metastases				
Pancreas as only metastatic site	56 (54)	42 (100)	14 (24)	**<0.01**
Concomitant metastases	47 (46)	2 (0)	45 (76)	**<0.01**
Sites of concomitant metastases				
Lung	27 (57)	2 (5)	25 (42)	**<0.01**
Lymph node	13 (28)	0 (0)	9 (15)	**0.02**
Liver	10 (21)	0 (0)	10 (17)	**0.01**
Bone	7 (15)	0 (0)	7 (12)	**0.05**
Soft tissue	5 (11)	0 (0)	5 (8)	0.13
Brain	2 (4)	0 (0)	2 (3)	0.61

Data are expressed as *n* (%) unless otherwise specified

Significant values are highlighted in bold

ECOG-PS Eastern Cooperative Oncology Group Performance Status, *MSKCC* Memorial Sloan Kettering Cancer Center, *RCC* renal cell carcinoma

26 patients presented with pain (10 %), asthenia (7 %), laboratory abnormalities (6 %), or other symptoms (4 %).

Resected Patients

Among the 56 patients (54 %) with PM-RCCs as the only metastatic site, surgical resection of PM-RCCs was performed in 42 patients (75 %, 41 % of the total study population) at the time of PM-RCC diagnosis. Fourteen patients (25 % of patients with PM-RCCs as the only metastatic site) were not considered fit for surgery due to age or comorbidities. Two patients with concomitant lung metastases underwent pancreatic surgery. The characteristics of resected patients and the differences with the unresected population are shown in Table 1.

PM-RCCs were localized in the head of the pancreas in 11 patients (25 %), in the body in 22 patients (50 %), and in the tail in 3 patients (7 %), while they (or PM-RCCs) were multifocal in 8 patients (18 %).

Surgery consisted of a total pancreatectomy in 9 patients (20 %), distal pancreatectomy in 31 patients (72 %), and middle pancreatectomy in 4 patients (8 %). Six of these patients (14 %) underwent surgery after treatment with TKIs (4 with sunitinib and 2 with pazopanib), including the two patients with concomitant lung metastases, who continued treatment with sunitinib after surgery.

Twenty-eight (67 %) of the 42 patients treated with pancreatic surgery without concomitant metastases relapsed after PM-RCC resection; the median time to relapse was 27 months (range 3–167 months). The incidence and sites of relapses are reported in Fig. 2.

Unresected Patients

Fifty-nine patients (63 %) were not resected and were treated with TKIs at diagnosis of metastatic disease. The list of the characteristics of unresected patients is shown in Table 1. Thirty-nine patients (66 %) were treated with sunitinib, 14 patients (24 %) were treated with sorafenib, and 6 patients (10 %) were treated with pazopanib as first-line therapy. Only two patients (3 %, one with MSKCC intermediate features and one with poor-risk features) were primary refractory to TKIs and experienced progressive disease at 3 months from the start of TKI therapy (one with sorafenib and one with sunitinib).

Forty-one patients (69 %) achieved a partial response, while 16 patients (27 %) had stable disease.

Outcome Analyses in the Overall Population and in Resected/Unresected Patients

The median OS from the diagnosis of PM-RCC was 132 months (95 % CI 86–154). The median OS was not reached in patients with MSKCC good-risk features, 86 months (95 % CI NA (not available)–NA) in the intermediate group, and 42 months (95 % CI 4–NA) in the poor-risk group ($p < 0.001$; Fig. 3). Thirty-five patients (34 %) had died at the time of analysis.

In patients who underwent pancreatic surgery for PM-RCCs, the median OS was 103 months (95 % CI 75–NA). Of these patients, 19 are still alive (43 %), with 8 patients (42 %, 18 % of patients resected at PM-RCC diagnosis) without disease recurrence. The median OS of these 8 patients was 101 months (95 % CI 75–NA). Interestingly, all of them were non-metastatic at diagnosis and presented good MSKCC features, without concomitant sites of metastases. In three of these patients, PM-RCCs were localized in the head of the pancreas and five in the body.

In addition, the median OS was 22 months (95 % CI 10–31) in the 14 patients with PM-RCCs as the only metastatic site but not considered fit for surgery due to age or comorbidities.

In the 59 patients with unresected PM-RCC, the median OS was 86 months (95 % CI 80–NA), reporting 75 months

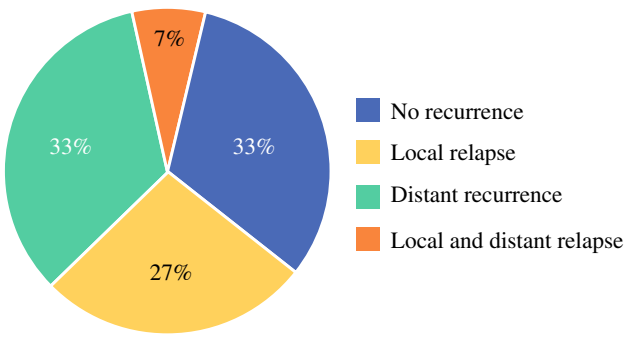

FIG. 2 Incidence/type of relapse in the 42 renal cell carcinoma patients with pancreatic metastases and without concomitant metastases, treated with pancreatic surgery

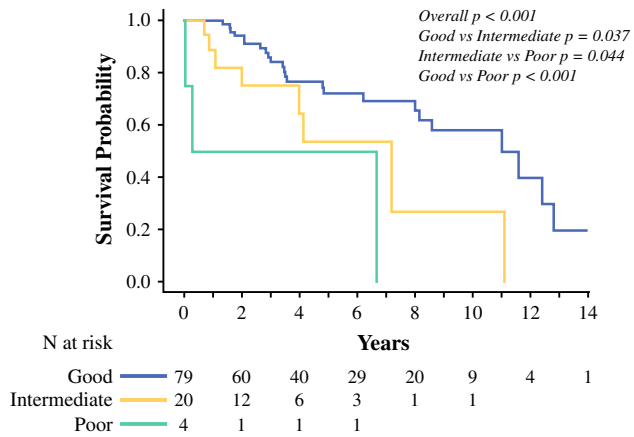

FIG. 3 Overall survival in the entire study population according to Memorial Sloan Kettering Cancer Center prognostic risk score

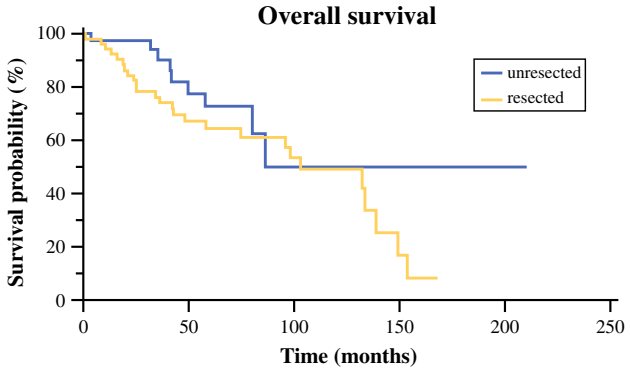

FIG. 4 Overall survival in resected versus unresected patients with pancreatic metastases

(95 % CI 75–NA) in the MSKCC good-risk group, 81 months (95 % CI 47–87) in the intermediate group, and 18 months (95 % CI 0.69–NA) in the poor-risk group ($p < 0.001$). Forty-five patients (76 %) were still alive at the time of analysis.

The difference between resected and unresected patients in terms of OS was not significant (103 vs. 86 months, $p = 0.201$; Fig. 4).

The median disease-free survival (DFS) from surgery was 36.2 months (95 % CI 26.6–76.3).

The median progression-free survival was 41 months (95 % CI 29–NA) in patients treated with TKIs and 41 months (95 % CI 37–NA), 27 months (95 % CI 9–NA), and 16 months (95 % CI 0.7–NA) in patients with good, intermediate, and poor MSKCC risk features, respectively ($p = 0.041$).

Univariate and Multivariate Analyses

At univariate analysis, the MSKCC risk group ($p = 0.02$; HR 1.71; 95 % CI 0.74–3.93) was the only independent prognostic factor. None of the other clinical variables, such as age, sex, pancreatic surgery, or the presence of concomitant metastases, were significantly associated with the outcome of PM-RCC patients. At multivariate analysis, the MSKCC risk group ($p = 0.04$; HR 5.14; 95 % CI 0.98–27.0) confirmed its prognostic role (Table 2).

TABLE 2 Univariate analysis of predictors of overall survival in patients with PM-RCC

	Univariate Cox regression	
	HR (95 % CI)	*p* value
Age, years (<65 vs. >65)	0.70 (0.35–1.38)	0.30
Sex (M vs. F)	1.36 (0.68–2.73)	0.38
ECOG-PS (<2 vs. ≥2)	0.98 (0.88–1.09)	0.72
MSKCC risk group	1.71 (1.14–3.93)	**0.02**
Time to PM-RCC, years (<1 vs. 1–5 vs. >5)	0.99 (0.99–1.00)	0.73
Presence of concomitant metastases (Y vs. N)	1.36 (0.66–2.78)	0.40
Pancreatic surgery (Y vs. N)	0.92 (0.75–1.54)	0.24

Significant value is highlighted in bold

CI confidence interval, *ECOG-PS* Eastern Cooperative Oncology Group Performance Status, *HR* hazard ratio, *MSKCC* Memorial Sloan Kettering Cancer Center, *PM-RCC* pancreatic metastasis from renal cell carcinoma, *M* male, *F* female, *Y* yes, *N* no

DISCUSSION

Pancreatic metastases are rare and represent less than 5 % of pancreatic tumors.[14] Clinical and biological heterogeneity is a major characteristic of RCC.[15,16] RCC can relapse even decades after primary diagnosis, and the pancreas can be a site for late-relapsing disease, showing longer survival than other metastatic sites.[17]

The resection of pancreatic metastases from other than RCC usually portends a poor prognosis and expression of disseminated metastatic disease. On the contrary, the resection of PM-RCCs is reported to be associated with improved outcome.[18,19] However, above all, surgical resection of PM-RCCs remains a controversial therapeutic option in the era of TKIs.[7,20–22]

Recently, Adler et al. performed a systematic review of 18 studies to evaluate the outcome of patients with solid tumors treated with pancreatectomy for metastatic disease. RCC was the most frequent primary tumor (62.6 %), followed by sarcoma (7.2 %) and colorectal carcinoma (6.2 %).[23] Median OS for PM-RCC was 71.7 months, with 70.4 % 5-year survival. The rate of postoperative morbidity (39.85 %) was not negligible, but operative mortality was reassuringly low (mean 2.21 %, range 0–10). Although the evidence supporting this theory is weak and based only on case reports and small retrospective case series, the study suggests that resection of cancers that have metastasized to the pancreas is feasible in selected patients and appears to confer a survival benefit.[23] The lack of prospective clinical trials is partially explained by the rarity and peculiarity of PM-RCCs, which does not allow a standard approach for these patients.

In our study, the median OS from PM-RCC diagnosis was more than 7 years for both resected and unresected patients, thus confirming the indolent biologic behavior of PM-RCCs. These findings were uniformly reported in the 16 centers involved in this analysis.

The median OS was more than 1 year higher in patients who underwent pancreatic surgery compared with unresected patients (103 [95 % CI 75–NA] vs. 86 months [95 % CI 80–NA]), although the difference was not statistically significant ($p = 0.201$) and may be due to the number of patients analyzed in this study. Furthermore, pancreatic surgery was not an independent prognostic

factor at multivariate analysis. In addition, PM-RCC surgical resection was followed by a high rate of recurrence (67 %).

On the other hand, the median DFS was 36.2 months in resected patients, with 18 % still alive and remaining disease-free, and with a median OS of over 8 years. Thus, patients with good MSKCC criteria and without concomitant metastases seemed to be the better candidates to receive pancreatic surgery. On the contrary, no complete responses were observed in patients treated with TKIs. Notably, 76 % had concomitant metastases.

In addition, other factors must be considered. Pancreatogenic diabetes, as a consequence of pancreatic surgery, may compromise the long-term quality of life (QoL) of resected PM-RCC patients. On the other hand, the use of TKIs is associated with a wide range of correlated low- and high-grade adverse events. Validated prognostic factors are dramatically needed to guide the management of these patients and to optimize the cost-effectiveness of these two approaches in this subpopulation.

In our study, the MSKCC risk group was significantly associated with OS, even if the number of patients with poor risk features was very low. Other common clinical and morphological factors do not seem to be of help since age, localization of the metastases in the pancreas, and the presence of concomitant metastatic sites were not associated with the outcome of these patients.

Although the presence of concomitant metastases and ECOG-PS markedly influence the decision process, surgery still shows the highest possibility for DFS in patients in whom the pancreas is the only metastatic site. In the future, the discovery of biological features associated with the indolent behavior and high rate of tumor responses to TKIs in PM-RCC patients may be of help in order to select patients to different therapeutic approaches.

However, there are some limitations to this study. First, this was a retrospective study, which is susceptible to bias in data selection and analysis. Second, resected and unresected patients differ in some of the characteristics reported in Table 1, such as the rate of patients with MSKCC good features and the presence of concomitant metastases. In addition, the number of patients analyzed is relatively small. Furthermore, 14 patients (24 %) were treated with sorafenib (as a function of the data collected from 2005), which has now been replaced by sunitinib and pazopanib as the standard of care. Finally, data on patient QoL would be an important integration for the results of our analysis.

CONCLUSIONS

Despite these limitations, the present data suggest that a surgical approach of PM-RCC should be carefully considered case-by-case, taking into account patient QoL in order to optimize the management of these patients. In this context, the lack of a clear advantage in OS for surgical resection cannot be ignored. Moreover, a careful balance of the benefit/risk ratio must be shared among a multidisciplinary team and with the patient. In addition, the high rate of responses obtained by the use of TKIs in this subpopulation suggest that their use as neoadjuvant or adjuvant therapies should be investigated in prospective studies on PM-RCC patients.

DISCLOSURE Matteo Santoni, Alessandro Conti, Stefano Partelli, Camillo Porta, Cora N. Sternberg, Giuseppe Procopio, Sergio Bracarda, Umberto Basso, Ugo De Giorgi, Lisa Derosa, Mimma Rizzo, Cinzia Ortega, Francesco Massari, Roberto Iacovelli, Michele Milella, Giuseppe Di Lorenzo, Sebastiano Buti, Linda Cerbone, Luciano Burattini, Rodolfo Montironi, Daniele Santini, Massimo Falconi, and Stefano Cascinu have declared no conflicts of interest.

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