

Clinicopathologic Characteristics and Prognosis of Breast Cancer Patients Associated with Pregnancy and Lactation: Analysis of Case-Control Study in Japan

Tsunehiro Ishida,¹ Takao Yokoe,¹ Fujio Kasumi,² Goi Sakamoto,³ Masujiro Makita,³ Takeshi Tominaga,⁴ Kohjiro Simozuma,⁴ Kohji Enomoto,⁵ Kiyoshi Fujiwara,⁵ Takeshi Nanasawa,⁶ Takashi Fukutomi,⁶ Teruyuki Hirota,⁷ Mamoru Fukuda,⁸ Shigeto Miura,⁹ Hiroki Koyama,¹⁰ Hideo Inaji¹⁰ and Hiroshi Sonoo¹¹

¹Second Department of Surgery, Gunma University School of Medicine, 3-39-15 Showa-machi, Maebashi 371, ²Department of Surgery, ³Department of Pathology, Cancer Institute Hospital, 1-37-1 Kamiikebukuro, Toshima-ku, Tokyo 170, ⁴Department of Surgery, Tokyo Metropolitan Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113, ⁵Department of Surgery, Keio University School of Medicine, 35 Shinano-machi, Shinjuku-ku, Tokyo 160, ⁶Department of Surgery, ⁷Department of Pathology, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, ⁸First Department of Surgery, St. Marianna University School of Medicine, 2-16-1 Sugou, Miyamae-ku, Kawasaki 213, ⁹Department of Surgery, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-ku, Nagoya 464, ¹⁰Department of Surgery, Center for Adult Diseases, Osaka, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537 and ¹¹Division of Endocrine Surgery, Kawasaki Medical School, 577 Matsushima, Kurashiki 701-01

Clinicopathologic characteristics and prognosis of breast cancer patients associated with pregnancy and lactation were clarified by means of a case-control study of matched non-pregnant and non-lactating patients with breast cancer. From 18 institutions in Japan, a total of 192 subjects with breast cancer diagnosed during pregnancy (72 cases) and lactation (120 cases) were collected between 1970 and 1988, accounting for 0.76% of all breast cancer patients. The duration of symptoms was longer and tumor size was larger in the study subjects. Although the disease-free interval was longer than that in the control patients, the survival time was shorter. There was no characteristic difference in histologic type. Vascular invasion and lymph node metastasis were found more frequently in the subjects. The positive rates of estrogen receptor and progesterone receptor were lower in the subjects. The 5- and 10-year survival rates of the study patients were 65% and 55%, respectively, and these survivals were significantly lower than those of the control ($P < 0.001$). The survival rates were poorer in the subjects, in accordance with stage and lymph node metastasis. The results suggest that most of the patients with breast cancer diagnosed during pregnancy and lactation are in a more advanced stage because of a delay in detection and diagnosis, and hence have unfavorable prognosis. Therefore, it is important to diagnose and treat early for improvement of prognosis in patients with breast cancer during pregnancy and lactation.

Key words: Breast cancer — Pregnancy — Lactation — Prognostic factor

The prognosis of breast cancer diagnosed and treated during pregnancy and lactation has been thought to be worse than that of common breast cancers. Among the patients with breast cancer associated with pregnancy and lactation, however, those without axillary lymph node metastasis show as favorable a prognosis as the non-pregnant and non-lactating patients. Most patients with breast cancer associated with pregnancy and lactation are younger, and it is therefore necessary to investigate whether the prognosis actually is poor in comparison with age-matched patients with non-pregnant or non-lactating breast cancer. If the prognosis is worse than that of patients with breast cancer diagnosed during non-pregnant or non-lactating periods, it is important to clarify whether the poor prognosis is merely related to

stage of the disease, or whether a breast cancer which occurs during pregnancy and lactation has an essentially more malignant biological nature.

There have been no reports on large numbers of patients in Japan as to the incidence and prognosis of breast cancer associated with pregnancy and lactation, partly because it is relatively uncommon. The Japanese Breast Cancer Society started a study group on "Breast Cancer Associated with Pregnancy and Lactation" in July 1988. The study group has performed a case-control study using control patients with breast cancer matched for age, period of treatment and institution, in order to clarify the clinicopathologic characteristics and prognosis. The present report describes the results of a collaborative study centering on prognostic factors of breast cancer associated with pregnancy and lactation in Japanese patients.

¹ To whom correspondence should be addressed.

SUBJECTS AND METHODS

A pregnant or lactating case of breast cancer was defined as breast cancer definitely diagnosed during pregnancy or lactation (within 2 years after delivery). The study group consisted of 11 institutions (9 institutions of surgery and 2 of pathology) in the Japanese Breast Cancer Society, and 9 other institutions of surgery were asked to cooperate by filling out a questionnaire. The pregnant and lactating cases of breast cancer between January 1970 and December 1988 were thus collected from 18 clinical institutions throughout Japan and analysis was performed. They were analyzed by a case-control study using matched patients with breast cancer during non-pregnant or non-lactating periods as controls, who were matched with the subjects as to age (± 3 years), period of treatment (± 1 year) and same institution at each hospital.

Of 192 pregnant and lactating cases of breast cancer (0.76% of all 25,317 breast cancer cases during the same period), 72 (0.28%) and 120 (0.47%) were diagnosed during pregnancy and lactation, respectively. There were 191 non-pregnant and non-lactating cases of breast cancer, serving as the control group.

Statistical analysis was performed by the *t* test and chi-square test. Survival curves were calculated according to the Kaplan-Meier method and compared by the generalized Wilcoxon test and Cox-Mantel test. A difference was considered to be statistically significant at $P < 0.05$.

RESULTS

Comparison of study subjects and controls The average age of the subjects was 32.3 years, which was the same as that of the controls (Table I). The frequency of a family history of breast cancer in the subjects' relatives, within the third degree of relationship by blood, was three times

higher than that in the controls (12.4% of subjects versus 4.2% of controls, $P < 0.05$).

The period between the time when symptoms were first noticed and the time of diagnosis averaged 6.3 months in the subjects, being longer by about 1 month than in the controls. The tumor size was significantly larger on palpation and on cross-section in the subjects ($P < 0.05$). This indicated delayed diagnosis and a large tumor diameter in the subjects. The mean disease-free interval was significantly longer, but the survival period was shorter in the subjects (Table I).

Characteristics of study subjects and control group The subjects showed the same age distribution as did the controls. The duration of symptoms was significantly longer in the subjects than that in the controls ($P < 0.05$,

Table II. Distribution of Study Subjects (Pregnancy and Lactation) and Control Group by Duration of Symptoms and Stage

Characteristics	No. of patients (%)		Chi-square test
	Study subjects	Control group	
Duration of symptoms (mo)			
-1	54 (29.8)	77 (43.3)	$\chi^2 = 11.76$ $P < 0.05$
2-3	36 (19.9)	39 (22.2)	
4-6	38 (21.0)	20 (11.4)	
7-12	32 (17.7)	22 (15.5)	
13-	21 (11.6)	18 (10.2)	
Stage (TNM)			
0	2 (1.1)	5 (2.7)	$\chi^2 = 28.64$ $P < 0.01$
Tis	2 (1.1)	6 (3.2)	
I	26 (13.9)	49 (26.2)	
II	87 (46.5)	91 (48.7)	
IIIa	39 (20.9)	30 (16.0)	
IIIb	19 (10.9)	3 (1.6)	
IV	12 (6.4)	3 (1.6)	

Table I. Comparative Data in Breast Cancer Patients Associated with Pregnancy and Lactation, and Control Group

Category (mean values)	Study subjects			Control group (n=191)
	Pregnancy (n=72)	Lactation (n=120)	Total (n=192)	
Age (yr)	32.6	32.1	32.3	32.8
Duration of symptom (mo)	6.2	6.3	6.3	5.4
Tumor size on palpation (cm)	4.4	4.7	4.6*	3.0*
Tumor size on cut surface (cm)	2.8	4.3*	3.9*	2.6*
Disease-free interval (mo)	22.6	19.3	20.7*	13.6*
Survival time (mo)	53.6	60.5	57.9	73.6

* Significantly different from the control group level at $P < 0.05$, by *t* test

Table II). According to the TNM classification established by the Japanese Breast Cancer Society,¹⁾ the number of subject patients with early stage (T0, Tis or Stage I) was small, and a larger number of patients showed Stage III or IV ($P < 0.01$). This tendency was more marked in the breast cancer diagnosed during lactation than that during pregnancy.

Diagnosis and treatment The number of subjects who had undergone mammography was only 50, and the rate of correct diagnosis, 68%, was worse than the 74% of the control group. On the other hand, the accuracy of diagnosis by ultrasonography was 93% (39/42 cases),

suggesting that this method is more useful for diagnosis of breast cancer associated with pregnancy and lactation. Preoperative biopsy had been performed in 51% of the subjects, indicating some difficulty in making the diagnosis.

As for surgical procedure, extended radical mastectomy, standard mastectomy and modified mastectomy were carried out in 48%, 33% and 17%, respectively, of the subjects. The frequency of extended surgery was thus higher in the subjects than in the controls ($P < 0.05$). Oophorectomy was performed in 30 pregnant and lactating cases (16%), while it was done in only one control (0.5%).

With regard to treatment of the fetus in pregnant patients, artificial abortion was conducted in 93% (25/27 cases) when the disease was diagnosed in the first trimester. In 18 patients during the second trimester, artificial abortion was performed in 56% and spontaneous delivery in 33%. Spontaneous delivery and cesarean section were employed in 57% (12/21 cases) and 33%, respectively, when diagnosed in the third trimester.

Histopathologic findings The histologic observation revealed that the incidence of noninvasive carcinoma was somewhat low, but there were no characteristic distributions of the histologic types in the breast cancer diagnosed during pregnancy and lactation (Table III). The number of patients with lymphatic invasion of carcinoma cells tended to be large in the subjects, and the number of patients with vascular invasion was significantly higher ($P < 0.05$). Lymph node metastases were found in 58% of the subjects and the metastases of n2 or more were large. There was a significant difference between the subjects and controls.

Hormone receptors Both estrogen receptor (ER) and progesterone receptor (PgR) were examined individually at the institutions using the dextran-coated charcoal method (DCC). The cutoff level of positive receptors was more than 5 fmol/mg of protein. Table IV shows the positive rate of hormone receptors. The ER positivity in pregnant and lactating cases was 44%, showing a ten-

Table III. Distribution of Study Subjects (Pregnancy and Lactation) and Control Group by Histologic Factors

Characteristics	No. of patients (%)		Chi-square test
	Study subjects	Control group	
Histologic type			
Noninvasive ca.	3 (1.6)	9 (4.8)	
Invasive ductal ca.	174 (92.1)	165 (87.8)	$\chi^2 = 5.25$
Mucinous ca.	3 (1.6)	7 (3.7)	NS
Medullary ca.	7 (3.7)	6 (3.2)	
Others	2 (1.1)	1 (0.5)	
Lymphatic invasion			
ly0	51 (68.0)	67 (83.8)	$\chi^2 = 5.31$
ly1	16 (21.3)	9 (11.3)	NS
ly2, 3	8 (10.6)	4 (5.0)	
Vascular invasion			
v0	22 (29.3)	44 (55.0)	$\chi^2 = 11.08$
v1	26 (34.7)	22 (27.5)	$P < 0.05$
v2, 3	35 (46.7)	21 (26.3)	
Lymph node status			
n0	76 (41.8)	99 (54.4)	$\chi^2 = 8.18$
n1 α	36 (20.3)	38 (20.9)	$P < 0.05$
n1 β	24 (13.6)	20 (11.0)	
n2 \leq	43 (24.3)	25 (13.7)	

NS: not significant.

Table IV. Positivity of Hormone Receptors in Study Subjects and Control Group

	ER (+)	Chi-square test	PgR (+)	Chi-square test
	No. positive (%)		No. positive (%)	
Pregnancy and lactation	36 (44)	$\chi^2 = 2.17$	16 (29)	$\chi^2 = 18.60$
Control group	39 (57)	NS	40 (69)	$P < 0.01$
Pregnancy group	7 (30)	$\chi^2 = 4.65$	6 (29)	$\chi^2 = 7.95$
Control group	17 (61)	$P < 0.05$	23 (68)	$P < 0.01$
Lactation group	29 (50)	$\chi^2 = 0.13$	10 (29)	$\chi^2 = 10.25$
Control group	22 (54)	NS	17 (71)	$P < 0.01$

ER: estrogen receptor, PgR: progesterone receptor, NS: not significant.

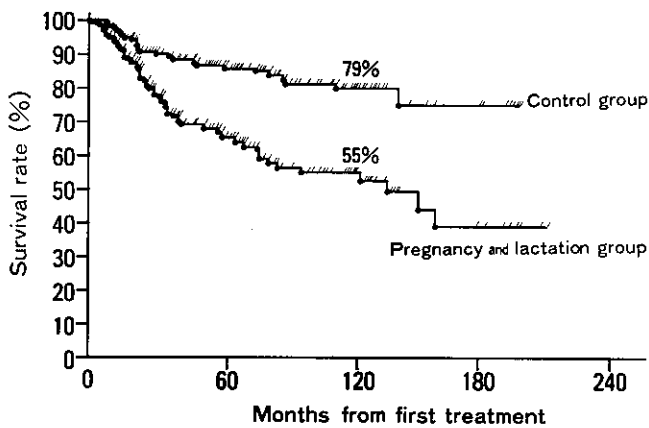


Fig. 1. Cumulative survival rate (Kaplan-Meier) of patients with breast cancer associated with pregnancy and lactation (n=192), and control group (n=191). The difference between the two groups was statistically significant at $P < 0.001$ (generalized Wilcoxon test; $P = 0.0003$, Cox-Mantel test; $P = 0.00003$).

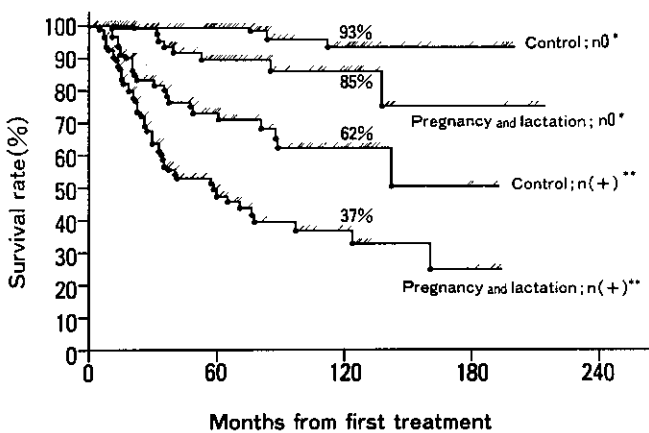


Fig. 2. Cumulative survival rate (Kaplan-Meier) by lymph node status: pregnancy and lactation group (n0: 71 cases, n(+): 101 cases) versus control group (n0: 99 cases, n(+): 77 cases). * Significantly different from the control group value at $P < 0.05$ (generalized Wilcoxon test; $P = 0.014$, Cox-Mantel test; $P = 0.019$). ** Significantly different at $P < 0.01$ (generalized Wilcoxon test; $P = 0.0015$, Cox-Mantel test; $P = 0.0007$).

dency to be lower than in the control group. In particular, the positivity of ER (30%) in the pregnant patients was significantly lower than in controls ($P < 0.05$). The PgR positivity was also low, 29%, in both pregnant and lactating cases ($P < 0.01$).

Table V. Cumulative Survival Rate of Patients with Pregnant Breast Cancer Related to Phase of Pregnancy at Diagnosis

Phase	No. of patients	Survival rate (%)	
		5 years	10 years
1st trimester	34	83	74*
2nd trimester	16	72	59
3rd trimester	19	51	25*

* Significantly different between the 1st trimester and 3rd trimester at $P < 0.01$ (generalized Wilcoxon test; $P = 0.0044$, Cox-Mantel test; $P = 0.0091$).

Survival Breast cancer recurred postoperatively in 72 (37.5%) of the pregnant and lactating cases. Eighty-eight patients (45.8%) survived with relapse-free status, and 71 (37.0%) died of the tumor. Thus, the outcomes of the pregnant and lactating cases were significantly poor ($P < 0.01$). The cumulative 5- and 10-year survival rates (Kaplan-Meier method) were 65% and 55%, respectively, in all patients with breast cancer during pregnancy and lactation, showing significantly poorer prognosis than in the control group ($P < 0.001$, Fig. 1). The 5- and 10-year survival rates in 171 patients with Stage I, II or III were 67% and 58%, which were significantly worse than those of 84% and 77%, respectively, in the control group ($P < 0.001$). According to stage, the survival rate was significantly poor in Stage II and IIIa cases. As Figure 2 shows, depending on the presence or absence of lymph node metastasis, the 10-year survival rate in cases with metastasis was 37%, which was significantly worse than that (62%) in the control group ($P < 0.01$). There was also a statistically significant difference between the two groups of node-negative patients ($P < 0.05$).

In the t 2 (2.1 cm or larger with no invasion to skin or pectoral muscle)¹⁾ lactating cases, the survival rate was worse than that in the control group. With regard to the correlation with cross-sectional tumor size, cases with large tumors were dominant in the lactating cases at the same stage.

As for the relationship between the period of pregnancy and operative results, the patients diagnosed during the first trimester of pregnancy showed the best results, while those diagnosed during the third trimester showed the worst survival (Table V). However, when examined as to the background factors, many patients diagnosed in the third trimester were in a more advanced stage of the disease. The 5-year survival rate in the patients with breast cancer diagnosed during pregnancy, who received oophorectomy, was 42%, which was significantly worse than the 77% in those without oophorectomy ($P < 0.01$). The 5- and 10-year survival rates in the 39 ER-negative cases of pregnant and lactating breast cancer were 60%

and 35%, respectively, showing significantly poorer results than in ER-negative controls ($P < 0.05$). Many ER-negative cases associated with pregnancy and lactation were also found to have more advanced disease.

DISCUSSION

Clinicopathologic features of breast cancer associated with pregnancy and lactation remain unknown in many respects, partly because the incidence is relatively low. This disease also has many clinical problems such as selection of treatment method and estimation of prognosis, in relation to fetal and neonatal care. Therefore, this study group of the Japanese Breast Cancer Society analyzed the clinicopathologic characteristics and prognosis of the disease by utilizing a case-control study which compared the results of subject patients and control patients.

The incidence of breast cancer associated with pregnancy and lactation accounts for 1–2.5% of all breast cancers in the Western literature.^{2–6)} By combining all data collected in Japan, the incidence was calculated to be 1.32% (113/8,567 cases) at the 7th Meeting of the Japanese Breast Cancer Society (1967), 1.06% (233/22,066) in the registration survey for breast cancer patients throughout Japan (1976–1982), and 0.76% (192/25,317) in the present study. Thus, the breast cancer associated with pregnancy and lactation continues to be relatively rare in Japan.

In general, pregnancy and lactation are believed to decrease the risk of occurrence of breast cancer. The present survey revealed that the frequency of family history of breast cancer in the subjects was three times higher than in the controls. This result suggests that some hereditary factors are involved in the occurrence of this malignancy. Some reports have also shown that the frequency of family history of breast cancer is higher in breast cancer patients 35 years of age or younger.^{7,8)}

Breast cancer associated with pregnancy and lactation tends to have definitive diagnosis made long after the symptoms are first noticed.^{9,10)} In other words, delay in visiting the hospital and in making the definitive diagnosis by the physician often leads to late-stage disease.^{4,5)} The present study also revealed that the average duration of symptoms in the subject patients was longer than in the control.

Since pregnancy and lactation induce marked growth of mammary parenchymal tissues and increase lymph and blood flow,¹¹⁾ the validity of the diagnosis by palpation and mammography is generally poor. Considering the influence of radiological exposure on the fetus, X-ray diagnosis is limited to some extent. On the other hand, ultrasonography and aspiration cytology are more useful for the diagnosis of pregnant and lactating breast cancer.

It is important to make a definitive diagnosis for a suspected tumor, by biopsy under local anesthesia.^{2,10)}

The number of study subjects showing a clinically early stage was smaller than in the control group, and 37% of subjects had advanced disease (stage III or IV).¹¹⁾ The tumor size was also significantly larger in the subjects, suggesting that large tumor size is one of the factors contributing to the poor prognosis.

There was no difference in the distribution of histologic types between the subject and control groups, but the incidence of scirrhous carcinoma tended to be higher in the lactating cases. King *et al.*¹²⁾ reported that scirrhous carcinoma accounted for 70% of pregnant cases. Some reports have shown that there are many patients with a high histological grade among pregnant cases.^{12–14)} The present study revealed a high incidence of vascular invasion by cancer cells. While a high proportion of lymph node metastasis, up to 70–89%, has been reported,^{2,15)} it was 58% in the present study. The number of metastatic lymph nodes was larger and the degree of the metastasis was more advanced in the subjects than in the control.

There have been a few reports on hormone receptors in breast cancer associated with pregnancy and lactation.^{6,16,17)} The present study revealed that the ER-positive rate (44%) tended to be lower than in the control group and that the PgR-positive rate (29%) was significantly lower. A low incidence of ER-positive cancers was found in the pregnant patients. Nugent and O'Connell⁶⁾ reported that 71% (10/14) of pregnant cases were ER-negative, and ER negativity was regarded as a prognostic factor indicating poor outcome.¹⁶⁾ The positive rate of ER is believed to be low in young patients with breast cancer as well,^{7,8,17)} but the low positive rate for hormone receptors in pregnant patients may be attributable to the possibility of false-negative results in DCC assays. This point should be studied by an enzyme immunoassay, that is not affected by any endogenous hormone.

Most breast cancers associated with pregnancy and lactation should be surgically treated. In general, a similar surgical procedure to that used for non-pregnant or non-lactating breast cancer has been performed.^{7,18)} Modified radical mastectomy must be regarded as the standard procedure at present for breast cancer during pregnancy and lactation in Western countries,^{2,18)} while standard or extended radical mastectomy has frequently been performed in Japan. Since the incidence of lymph node metastasis is high, mastectomy with thorough axillary dissection should be selected. Advanced stage cases must be treated with multimodality therapy including preoperative and postoperative intensive chemotherapy, radiation and endocrine therapy.^{2,18)} Therapeutic abortion and oophorectomy in pregnant patients are not recognized to improve survival.^{2,6,9,10,12,19)} Therefore,

artificial abortion may be performed only in patients in their first trimester and in patients with advanced stage disease, upon their request.²⁰⁾

The prognosis of breast cancer diagnosed during pregnancy and lactation has been poor in the past, probably because there is a high incidence of axillary lymph node metastasis.²⁾ However, node-negative patients in pregnancy and lactation have had no worse prognosis than general breast cancer.^{6, 12, 20)} In the present study, the 10-year survival rate for pregnant and lactating cases was 55%, which is significantly lower than that of the control group. The survival rates in study cases with lymph node metastasis (5-year survival: 48%; 10-year survival: 37%) were also significantly worse than in the control group. Breast cancer patients during pregnancy and lactation in more advanced stage (II or IIIa) and n-number ($n2 \leq$) had the poorer prognosis, even if they were matched for stage and included in the same category. Tretli *et al.*¹³⁾ conducted a case-control study in which the risk of death for breast cancer patients diagnosed during pregnancy was found to be 3.1 times higher than for the control group. They concluded that pregnancy itself is a poor prognostic factor. Several investigators^{6, 14)} also considered the following to be factors indicative of a poor prognosis: younger women; high rate of ER negativity; high rate of lymph node metastasis; high histological grade; rapid growth.

In conclusion, breast cancer associated with pregnancy or lactation showed essentially no distinct difference in histologic features, compared with non-pregnant and non-lactating breast cancer. Influential factors leading to

delay in detection and diagnosis of cancer and eventually to delay in commencement of treatment include age under 35 years, the low incidence, the patient's tremendous concern about delivery and neonatal care, and the marked hypertrophy of mammary gland tissues during pregnancy and lactation. Therefore, many patients have more advanced stage disease, when they first attend hospitals. The special hormonal environments during pregnancy and lactation may accelerate cancer growth and progression, leading to the poor therapeutic results. A high ER-negative rate, and a high percentage of nodal involvement and vascular invasion must be associated with the poor prognosis. In fact, this study shows poor survival despite the longer disease-free interval. There is no marked difference in the prognosis among early stage cases, but once lymph node metastasis occurs, the surgical results may become worse in correlation with the extent of rapid metastatic spread.¹¹⁾ Therefore, early detection and treatment are important for improvement of therapeutic results of breast cancer associated with pregnancy and lactation.

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