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Patterns of pathological response to neoadjuvant chemotherapy and its clinical implications in patients undergoing interval cytoreductive surgery for advanced serous epithelial ovarian cancer- A study by the Indian Network for Development of Peritoneal Surface Oncology (INDEPSO)

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ABSTRACT

Objectives: The goals were to study
- The pattern of pathological response to neoadjuvant chemotherapy (NACT) and its clinical implications
- The impact of chemotherapy response grade (CRG) on survival

Methods: A retrospective analysis of patients undergoing interval cytoreductive surgery (CRS) between January 2013 to December 2017 was performed. The surgical and pathological reports were analyzed and surgical and pathological PCI compared. The pathological response to chemotherapy was assessed using the score developed by Bohm. et al.

Results: In 79 patients, it was observed that sites involved by disease first like ovaries and pelvic peritoneum (lower region) were the last to respond preceded by the omentum, right upper quadrant (RUQ) peritoneum (upper region) and parietal peritoneum (middle region). Microscopic residual disease was seen in 20.2% in normal looking areas of peritoneum and in 20% with no gross residual disease in the RUQ. Visual inspection during surgery overestimated the disease extent in 40.5% and underestimated it in 15.1%.

There was no difference in the progression free ($p = 0.587$) and overall survival ($p = 0.157$) between patients with CRG 1, 2 and 3 (poor, moderate, and complete/near complete response, respectively). Retroperitoneal nodes were positive in 0% with CRG 3, 27.5% with CRG 2 and 72.7% with CRG 1 ($p < 0.0001$).

Conclusions: The pathological response to NACT follows a specific pattern. Visual inspection is of limited value in assessing disease extent following NACT. Surgery following NACT should target sites involved before NACT and not just residual disease. The response in regional nodes should be included in chemotherapy response scores.

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Introduction

Neoadjuvant chemotherapy is used to downstage the disease in patients with advanced ovarian cancer presenting with unresectable disease upfront [1]. The response evaluation criteria in solid tumors (RECIST) version 1.1 are used to evaluate response to chemotherapy in clinical trials and in clinical practice [2]. These criteria rely on the reduction in size of the maximum tumor diameter. Unlike breast and rectal cancers in which there is one primary site and a predefined regional nodal basin, advanced ovarian cancer comprises of multiple tumor nodules scattered over part or whole of the peritoneum. Many tumor nodules are too small to be picked up on imaging, thus, making it difficult to determine the exact extent and response to therapy preoperatively. Peritoneal spread occurs through the transmesothelial and translymphatic pathways [3]. The commonest sites of tumor deposits are pelvic peritoneum, omentum, right subphrenic peritoneum (undersurface of the diaphragm) and right paracolic gutter. This distribution follows the flow of peritoneal fluid and gravitational forces and is also due to a greater concentration of lymphatics in these regions [3]. Involvement of small bowel and its mesentery occurs in later stages. However, it is uncertain whether the response to chemotherapy also occurs in a sequential manner. This may be of significance because surgeons rely on intraoperative visualization of residual tumor nodules to determine the extent of surgery and visual inspection can underestimate or overestimate the extent of disease. In patients who have gross residual disease, the decision making is simple, however, certain regions are difficult to evaluate without a thorough exploration-like the lesser sac and the domes of the diaphragm. Secondly, there are areas of complete or near complete response where it is impossible to accurately determine the presence or absence of residual disease on visual examination [4]. In malignant peritoneal mesothelioma, microscopic residual disease has been observed in normal looking areas of peritoneum [5]. The same is not known for ovarian cancer. A knowledge of patterns of response to NACT could help define the extent of surgery that needs to be performed in patients undergoing interval CRS. We performed this analysis to study the pattern of distribution of residual disease following NACT and its potential clinical implications. Our second goal was to determine the impact of pathological response to chemotherapy on survival.

Methods

Prospective and retrospective data was collected from members of the Indian network for development of peritoneal surface oncology (INDEPSO). Institutional permission was obtained by each surgeon. Ethical approval was not required for this study. Patients undergoing interval CRS with or without intraperitoneal chemotherapy (IPC) for advanced (new FIGO stages III-C and IV-A) serous epithelial ovarian, fallopian tube and primary peritoneal cancer were included [6]. All other histologies were excluded. Patients who had gross ascites with peritoneal disease in the upper abdomen for which NACT was administered were included. Patients in whom there was no unresectable peritoneal disease and were administered NACT for other reasons like distant organ metastases or unresectable pelvic disease were excluded.

Surgical procedures and systemic chemotherapy

A thorough exploration of the entire abdominal cavity from the xiphoid to the pubis was performed for all patients and the surgical goal was to obtain a complete cytoreduction (no macroscopic residual disease). The extent of peritonectomy was classified as total parietal peritonectomy (TPP) comprising of all 5 parietal peritonectomies (pelvic, bilateral anteroparietal peritoneum, right upper quadrant (RUQ) and left upper quadrant peritoneum (LUQ)) and resection of the greater and lesser omenta or selective parietal peritonectomy (SPP) that comprises of one or more of these procedures. Systematic retroperitoneal lymphadenectomy was performed in all patients. Even when there was a single nodule in any region, a formal peritonectomy was performed for that region. Standard prognostic indicators like the peritoneal cancer index (PCI) and completeness of cytoreduction score (CC-score) used in peritoneal surface oncology were used to report the disease extent and completeness of surgery respectively [7]. Patients received either no intraperitoneal (IP) chemotherapy or early post-operative intraperitoneal chemotherapy (EPIC) with paclitaxel or hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin [8,9].

All patients received 6 cycles of standard doublet chemotherapy comprising of a platinum compound and taxane (as neoadjuvant and adjuvant therapy).

Pathological evaluation

A detailed evaluation of surgical notes and pathology reports was performed. A pathological PCI (similar to surgical PCI) was calculated based on the size and distribution of tumor nodules on histopathological examination and a comparison made with the surgical PCI. The PeRitOneal MalIgnancy Stage Evaluation online application (e-PROMISE) was used to define the anatomical structures in each region of the PCI (Supplementary material 1) [10].

The peritoneal cavity was divided into 3 regions-the upper region comprising of regions 1, 2 and 3 of Sugarbaker's PCI, middle region comprising of regions 0, 4, 8 and the lower region comprising of regions 5, 6 and 7. The omentum was evaluated separately from the structures in region 0 and each small bowel region (9–12) too. The areas bearing tumors were listed for each patient and the pattern of response studied. Histological confirmation of disease was taken as presence of tumor in that region.

The pathological response to chemotherapy was graded based on the chemotherapy response score developed by Bohm et al. (Supplementary material 2) that has been validated [11,12]. The term 'chemotherapy response grade' (CRG) is used here. CRG 1 stands for minimal or no tumor response; CRG 2 for appreciable tumor response amid viable tumor that is easily identifiable and CRG 3 for complete or near-complete response with no residual tumor or minimal irregularly scattered tumor foci up to 2 mm in size [11]. The response was assessed not just in the ovaries and the omentum (as in Bohm's study) but also at the peritoneal sites. In addition, the resected lymph nodes were examined for presence or absence of tumor and the response in the nodes was not stratified according to this scoring system since lymph node response is not included in it.

Follow up and diagnosis of recurrence

Disease progression was defined based on the recommendations by the Gynecologic Cancer Inter Group (GCIG) and was either radiological evidence of progression or an increase in tumor marker level [13].

Statistical analysis

Categorical data were described as number (%). Abnormally distributed continuous data were expressed as median and range. Categorical data were compared with the x^2 test. Multivariate Cox proportional hazard regression was used to describe association between individual risk factors and progression free survival (PFS)

and overall survival (OS) both, in terms of hazard ratio and its 95% confidence interval (CI). Survival curves were calculated using the Kaplan–Meier method and compared using the two-tailed log-rank test. SPSS Version 20 (SPSS Inc., Chicago, IL) and MedCalc Version 12.2 were used for analysis. A p-value of <0.05 was considered statistically significant. Time to disease progression and survival were both calculated from the date of surgery.

Results

From January 2013 to December 2017, 79 patients were treated at 5 Indian centers (Table 1). 74 patients had stage IIIC and 5 IVA. The median PCI was 10 [range 2–36]. A TPP was performed for 30 (37.9%) and SPP for 49 (62.1%). A CC-0 resection was obtained in 62 (78.4%), CC-1 in 16 (20.2%) and CC-2/3 in 1 patient. Grade 3–4 morbidity was observed in 10 (14.4%) patients at 30 days and 14 (20.2%) at 90 days. 4 (5.06%) patients died within 90 days of surgery. 75 (94.9%) had high grade serous carcinoma and 4 (5.1%) low grade tumors.

Chemotherapy response grade

The pathological response grade was CRG 3 in 17 (17.7%) including 2 (2.5%) with a complete response, CRG 2 in 40 (51.8%) and CRG 1 in 22 (27.8%) (Table 2).

Pattern of response to chemotherapy

A complete response at the primary site was seen in 2 patients. In 4 others, there was residual disease in the ovaries with a complete response at all other sites. The next most common site of residual disease was the lower region with 89.8% patients having residual disease in this region, followed by the omentum (residual disease in 77.2%), the upper region in 56.9% and the middle region in 29.1%. In the upper region, region 1 was dissected in 61 (77.2%) and positive in 44 (55.6%) and region 3 was dissected in 40 (50.6%) and positive in 21 (26.5%). Disease on the small bowel was not seen in absence of disease in both the lower and upper regions and disease in the upper region was not seen in absence of disease in the lower region. This pattern was not different in patients undergoing TPP or SPP ($p = 0.06$) (Table 3) or in 3 different pathological response groups ($p = 0.224$) (Table 4). Of the 61 patients with omental involvement, 54 had gross disease and 7 had only microscopic disease. In 54 patients with gross disease, the RUQ showed disease in 41 (75.1%) patients and 4/7 patients with microscopic disease had RUQ involvement on pathology.

Table 1
Patient and disease characteristics, surgical details and perioperative outcomes in patients undergoing interval CRS.

Characteristic		All patients n = 79 (%)
Mean age in years (range)		53.5 (28–71)
Histological subtype	ESOC	76 (96.2)
	PPSC	3 (3.8)
No of neoadjuvant chemotherapy cycles	≤3	75 (94.9)
	>3	4 (5.1)
IP chemotherapy	none	21 (26.5)
	HIPEC	36 (45.5)
	EPIC	22 (27.8)
PCI	0–10	42 (53.1)
	>10	37 (46.9)
CC-score	CC-0	62 (78.4)
	CC-1	16 (20.2)
	CC-2/3	1 (1.3)
30- day grade 3–4 Morbidity	Yes	10 (75.9)
	No	69 (24.1)
90-day grade 3–4 morbidity	Yes	4 (5.0)
	No	75 (95.0)
90-day mortality	Yes	4 (5.0)
	No	75 (95.0)
Median progression free survival (months)		33
Median overall survival (months)		NR

Abbreviations: NR-not reached; ESOC- epithelial serous ovarian carcinoma; PPSC-primary peritoneal serous carcinoma.

Comparison of the surgical and the pathological findings

In 16 (20.2%) patients, there was microscopic residual disease when the peritoneum had no visible tumor deposits. Looking at the RUQ, of 10 patients who had no visible disease, microscopic residual disease was found in 2 (20%) patients.

The pathological PCI was the same as the surgical PCI in 35 (44.3%), more in 12 (15.1%) and less in 32 (40.5%). More patients in the CRG 2 group had a higher pathological PCI than the surgical PCI compared to the other two groups ($p = 0.003$). The surgical PCI was higher than the pathological PCI in CRG 3 compared to other groups.

Response in the lymph nodes

Retroperitoneal nodes were positive in 0% with CRG 3, 27.5% with CRG 2 and 72.7% with CRG 1 ($p < 0.0001$).

Survival outcomes

At the median follow up of 18 months, the median PFS was 33 months [95% CI, 22.5 months- 43.4 months] and the 5 year PFS was 21.2%. The median PFS was 33 months for CRG 1, 33 months for CRG 2 and 19 months for CRG 3 ($p = 0.587$). The PFS was inferior in patients with major morbidity ($p = 0.01$) but was not vary significantly among the three pathological response groups (Table 5). The median OS was not reached for the whole cohort as well as in the three groups and the Kaplan Meier analysis did not show a significant difference in OS ($p = 0.157$) (Fig. 1). The projected 5-year OS 69.6%. The only independent predictor of a longer overall survival was grade 3–4 morbidity ($p = 0.01$).

Discussion

This study points out lacunae in scientific literature regarding the pathological response to chemotherapy in ovarian cancer that have important clinical implications. Our results showed that response to NACT follows a specific pattern. Regions that were first involved by tumor were the last to have a complete response. The last site to respond were the ovaries, preceded by lower region, the omentum, upper region, then middle region and then the small bowel. This sequential response was seen in each patient. An explanation for this may be the high concentration of disease in these regions with multiple clones of tumors cells and a higher probability of harboring drug resistant clones [3]. None of the patients in the CRG 3 group had residual disease on the small bowel. Though the study is retrospective and the exact extent of disease before NACT in each patient has not been mapped, a thorough exploration from the xiphoid to the pubis was performed for all patients and an upper quadrant peritonectomy performed in 61 (77.2%) of the patients. Thus, it is unlikely that a potential site of residual disease was not explored. Moreover, the selection criteria were similar and only patients with gross ascites and extensive upper abdominal disease that was unresectable were included in the study leading to a homogenous patient population in terms of initial disease extent.

Only 2.5% of the patients had a complete response at all resected

Table 2
Comparison of disease characteristics in patients with CRG 1, 2 and 3.

Characteristic		All patients (%)	CRG 3 (n = 17)	CRG 2 (n = 40)	CRG 1 (n = 22)	P-Value
Mean age in years (range)		53.5 (28–71)	58.8 (31–71)	52.6 (28–70)	54.6 (33–69)	
Histological subtype	ESOC	76 (96.2)	15	40	21	0.34
	PPSC	3 (3.8)	2	0	1	
No of chemotherapy cycles	≤3	74 (93.6)	15	37	22	0.70
	>3	5 (6.4)	2	3	0	
IP chemotherapy	none	21 (26.5)	7	6	8	0.034
	HIPEC	36 (45.5)	4	20	12	
	EPIC	22 (27.8)	6	14	2	
PCI	0–10	41 (51.8)	15	24	2	<0.0001
	>10	38 (48.2)	2	16	20	
Extent of peritonectomy	TPP	30 (37.9)	6	11	13	0.047
	SPP	49 (62.1)	11	29	9	
CC- score	CC-0	62 (78.4)	16	35	11	<0.001
	CC-1	16 (20.2)	1	4	11	
	CC-2/3	1 (1.3)	0	1	0	
Median progression free survival (months)		37	19	33	33	0.157
Median overall survival (months)		NR	NR	NR	NR	0.587

Abbreviations: NR-not reached. ESOC- epithelial serous ovarian carcinoma; PPSC-primary peritoneal serous carcinoma.

Table 3
Pathological findings in patients with total and selective parietal peritonectomy.

Characteristic		All patients n = 79 (%)	TPP n = 30	SPP n = 49	p-value
Pathological response	CRG 3	17 (21.5)	7	10	0.96
	CRG 2	40 (50.6)	10	30	
	CRG 1	22 (27.8)	13	9	
Surgical versus Pathological PCI	More	13 (15.1)	4	9	0.20
	Less	31 (40.5)	10	21	
	Same	35 (44.3)	16	19	
Regional nodes Involved	Involved	27 (34.1)	12	15	0.25
	Not involved	49 (62.0)	15	34	
	Not dissected	3 (3.9)	3	0	
Site of residual disease	Ovaries/tubes	75 (94.9)	27	48	0.065
	Lower region	72 (91.1)	26	46	
	Omentum	61 (77.2)	25	36	
	Middle region	36 (45.5)	21	15	
	Upper region	44 (51.8)	24	20	
Disease in 'normal looking' peritoneum (Surgical PCI 0 for the region)	Present	16 (20.2)	9	7	0.09
	Absent	63 (79.8)	21	42	

Table 4
Pathological findings in patients with CRG 1,2 and 3.

Characteristic		All patients (%)	CRG 3 (n = 17)	CRG 2 (n = 40)	CRG 1 (n = 22)	P-Value
Site of residual disease	Ovaries	75 (94.9)	15	40	20	0.224
	Lower region	72 (91.1)	11	39	22	
	Omentum	61 (77.2)	4	36	21	
	Middle region	36 (45.5)	2	15	19	
	Upper region	44 (55.6)	3	23	18	
Disease in 'normal looking' peritoneum (Surgical PCI 0 for the region)	Present	14 (17.7)	2	6	6	0.43
	Absent	65 (82.3)	15	34	16	
Surgical versus pathological PCI	Same	26 (32.9)	1	18	7	0.003
	Less	13 (16.4)	3	9	1	
	More	40 (50.6)	13	13	14	
Regional nodes	Positive	27 (55.1)	0	11	16	<0.0001
	Negative	49 (62.0)	16	29	4	
	Not dissected	3 (3.7)	1	0	2	

sites. Studies have shown a superior PFS and OS in patients who have a complete or near complete response to chemotherapy [12,14]. This was not observed in our study; the median OS was not reached in CRG 1, 2 and 3 (p = 0.157). One of the reasons for this could be the high rate of CC-0 resection (78.4%) and performing systematic peritonectomies in all involved regions. The follow-up is short and a difference may be seen on a longer follow-up but the early results are encouraging (projected 5-year survival of nearly 70%).

The next important finding in this study was the limitation of visual inspection in evaluating the response to chemotherapy. The disease was overestimated in 40.5% (surgical PCI > pathological PCI) and underestimated in 15.1% (surgical PCI < pathological PCI). It is not possible to say what difference between the surgical and pathological PCI is significant, but in most cases the difference was due to disease being absent on pathology when residual disease was suspected by the surgeon and vice-versa. There was residual disease in normal peritoneal regions in 20.2%.

Table 5
Factors affecting progression free and overall survival.

Variable	PFS		OS	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Age <50 versus >50	0.39		0.31	
ECOG performance status (0/1 versus 2/3)	0.56		0.67	
3 versus > 3 cycles of NACT	0.37		0.55	
PCI (<10 versus 10–20 versus>20)	0.73		0.42	
TPP versus SPP	0.47		0.06	0.09
CRS alone versus HIPEC versus EPIC	0.54		0.55	
CC- score 0–1 versus CC-2/3	0.90		0.84	
CRG 3 versus CRG 2/1	0.58		0.15	
Positive retroperitoneal nodes	0.95		0.64	
30-day grade 3–4 morbidity	0.06		0.001	0.10
90-Day grade 3–4 morbidity	0.20		0.003	0.01

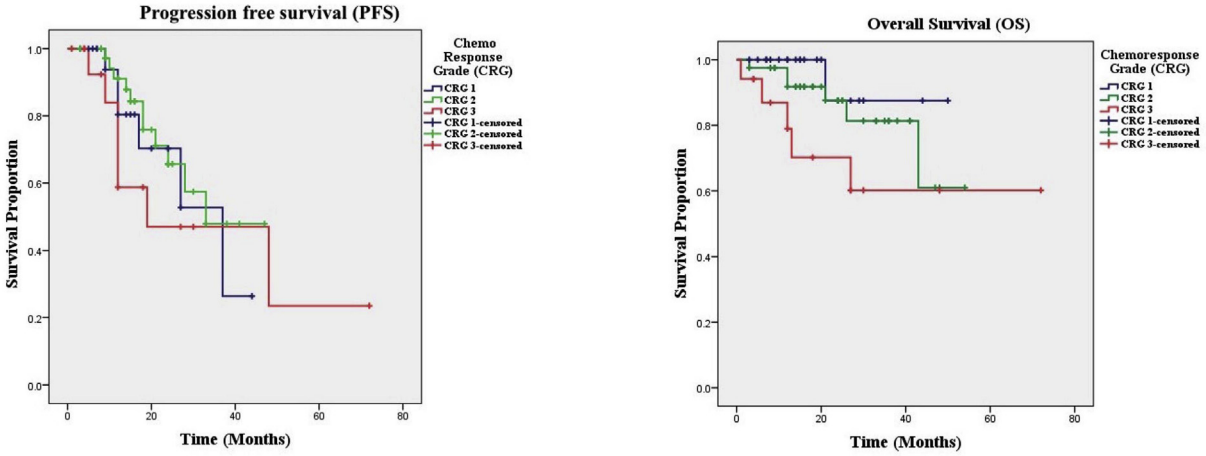

Fig. 1. Comparison of PFS and OS in patients with CRG 1, 2 and 3.

Though the survival benefit of complete removal of macroscopic disease has been demonstrated in ovarian cancer, many surgeons still consider residual disease <1 cm as optimal cytoreduction following NACT [15,16]. There should be no controversy regarding optimal cytoreduction following chemotherapy since any residual disease represents chemoresistant disease and will lead to recurrence if not resected [17,18]. Hence, the goal of surgery should be CC-0 resection. In case there is a complete response in a particular region or only scar tissue, our results favour performing a peritonectomy in that regions since one-fifth of the patients with normal looking peritoneum will have microscopic residual disease. A complete response is sustained only in 8–10% and even fluorescence guided tumor localization cannot predict recurrence [19]. Surgery following NACT should target previous disease sites and not just the sites of residual disease. NACT should be used to downstage the disease and reduce the morbidity and not to reduce the extent of the surgery.

Our recommendation is further supported by the fact that the median PFS was similar in the CRG 3 group (complete/near complete responders) compared to CRG 1 (poor response) and 2 (moderate response) (19 months versus 33 months, $p = 0.58$) though it is expected to be longer [12]. There were fewer number of TPP performed in this group (Table 3). And it further highlights the limitation of detecting residual disease on visual examination, especially in patients having a complete/near complete response, thus, subjecting them to less extensive surgery leading to increased recurrence.

The incidence of retroperitoneal lymph node involvement in advanced ovarian cancer ranges 50–80% [20]. Systematic retroperitoneal lymphadenectomy has a survival benefit in patients who have had a complete/optimal cytoreduction [21,22]. A randomized trial showed no benefit of a systematic lymphadenctomy in patients with negative nodes on imaging in stages II-IV though 56% had microscopic disease in lymph nodes in absence of disease on imaging [23]. There was a high proportion of positive retroperitoneal nodes in patients with CRG 2 and 1. Though there was no difference in survival between patients with positive and negative nodes, this was perhaps because a systematic lymphadenectomy was performed in all patients. We do not have details of preoperative imaging for all patients to determine what percentage of patients with negative nodes on imaging had residual disease in lymph nodes. Further prospective evaluation is needed to determine which patients benefit from this procedure. Secondly, the response in lymph nodes should be incorporated into the chemotherapy response scoring systems for ovarian cancer.

This study is retrospective with a relatively small number of patients especially in different subgroups which are major limitations. The response to chemotherapy is evaluated at a single timepoint, though majority of the patients received only 3 cycles of chemotherapy. The surgical approach was different between surgeons-two surgeons performed TPP for all patients while the others performed a TPP to only obtain a complete cytoreduction. However, this gives an opportunity to determine the presence of absence of microscopic disease in normal looking areas of peritoneum. The follow-up is short and use of IP chemotherapy heterogeneous which may have had an impact on survival. Despite these

limitations, it shows that the response to chemotherapy in ovarian cancer follows a specific pattern which needs to be studied prospectively. It also identifies the need to establish by consensus, guidelines for surgery after NACT in ovarian cancer. The key points that need to be addressed are whether to resect previous disease sites or not and how to categorize the morphological response on visual inspection during surgery-e.g. areas of scarring. Our findings strongly support resecting previous disease sites and areas of scarring and these findings should be confirmed in prospective studies.

Conclusions

The response of peritoneal metastases in ovarian cancer to NACT follows a specific pattern which should be evaluated prospectively. Visual inspection is inaccurate in determining the response to chemotherapy. Microscopic residual disease is seen in 'normal looking' areas of the peritoneum following NACT and the overall all incidence of complete responders is low. Therefore, surgery following NACT should target sites involved before NACT and not just the residual disease. The response in regional nodes should be included in chemotherapy response scores.

Conflicts of interest

The authors have no other disclosures or conflicts of interest.

Disclosures

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2019.01.009.

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