Review

Prostate-Specific Membrane Antigen Positron Emission Tomography (PSMA-PET) on Initial Staging of Prostate Cancer Patients. The Beginning of a New Era

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Review

Prostate-Specific Membrane Antigen Positron Emission Tomography (PSMA-PET) on Initial Staging of Prostate Cancer Patients. The Beginning of a New Era

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Abstract: *Background and Objectives:* Prostate cancer (PCa) is a common disease with a significant amount of patients first diagnose with locoregional or distant metastases. This is why it is essential to have imaging tests with sufficient sensitivity and specificity. Having traditional imaging methods with recognized limitations, PET-PSMA is born as a weapon to revolutionize the management of PCa. *Material and Methods:* We made a comprehensive literature review from August to October 2023 using databases and also a review of key clinical guidelines with the topic, focusing on sensitivity and specificity on PSMA-PET, its use in detecting lymph node metastases (LNm), integration into nomograms, comparison with conventional imaging and current guideline recommendations. *Results:* After considering search strategy, inclusion and exclusion criteria; 4 articles and 5 guidelines were particularly taken into account in this review. Most of them conclude with high specificity and limited sensitivity for ^{68}Ga-PSMA-PET, increasing detection rates with respect to conventional imaging modalities, specially in high-risk PCa patients; but it cannot replace an extended pelvic lymph node dissection (ePLND) at this time. *Conclusions:* Although PSMA-PET enhanced sensitivity and specificity over conventional imaging modalities offer a more precise evaluation of disease extent; currently, prospective studies demonstrating a survival benefit are lacking, so caution is advised when making therapeutic decisions.

Keywords: Prostate cancer; Prostate-specific Membrane Antigen Positron Emission Tomography (PSMA-PET); conventional imaging; Initial staging

1. Introduction

Prostate cancer (PCa) is the second most common cancer in men, with an incidence of 1.4 million new diagnoses per year and a global mortality of 350.000 people [1]. While most patients are diagnosed with localized tumors, a significant percentage present with locoregional metastases (15%) or distant metastases (5%) at time of diagnosis, making accurate staging crucial for defining the most appropriate treatment strategy [2,3].

Traditional imaging methods in PCa, such as multiparametric magnetic resonance imaging (mpMRI), contrast-enhanced computed tomography (CT) and technetium-99 m (99mTc)-methylene diphosphonate bone scan (BS), have significant diagnostic limitations [4]. These limitations have

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encouraged the development of advanced molecular imaging techniques like prostate-specific membrane antigen positron emission tomography (PSMA-PET), which offers enhanced sensitivity and specificity in PCa imaging [5].

PSMA-PET is a novel whole-body scanning technique that visualizes PCa with high contrast. PSMA is a cell surface glycoprotein overexpressed on PCa cells. Radiolabelled small molecules that bind with afinity to PSMA facilitate whole-body tumour-specific imaging with PET-CT [6].

Although PSMA-PET has primarly been studied for localizing recurrences [7], emerging data support its use in primary staging, particulary for identifying lymph node (LN) involment, even in subcentimeter nodes [8,9]. This review sysnthesizes current evidence on the diagnostic use of PSMA-PET in localized PCa and analyzes the clinical implications of its implementation in patient management.

2. Material and Methods

A comprehensive literature review was conducted from August to October 2023 using databases such as PubMed/MEDLINE, ScienceDirect, and the Cochrane Library. Keywords included 'prostate cancer', 'positron emission tomography', 'prostate-specific membrane antigen (PSMA-PET)', 'diagnosis', and 'therapy'. Studies related to biochemical recurrence were excluded. Boolean operators "AND"/"OR" were used to combine search terms, and "NOT" was employed to exclude studies focusing on biochemical recurrence. This search strategy was optimized to yield the most relevant studies, particularly from PubMed/MEDLINE.

2.1. Study Selection

The selected studies were filtered according to the following inclusion and exclusion criteria:

2.1.1. Inclusion Criteria

- Original research articles, including clinical trials, systematic reviews, and research studies.
- Studies involving patients aged 18 years or older.
- Publications from 2008 onwards.
- Articles published in English.

2.1.2. Exclusion Criteria

- Descriptive studies, such as case reports or clinical case series.
- Studies involving pediatric patients (under 18 years old).
- Publications prior to 2008.
- Non-English language publications.

Additionally, a review of key clinical guidelines was conducted, including those from the European Association of Urology (EAU) [10], European Society for Medical Oncology (ESMO)[11], American Society of Clinical Oncology (ASCO)[12], American Urological Association (AUA)[13], and the Advanced Prostate Cancer Consensus Conference (APCCC) [14].

2.2. Data Synthesis

Given the limited research on PSMA-PET for primary staging, this review focuses on several key areas: sensitivity and specificity on PSMA-PET, its use in detecting lymph node metastases, integration into established nomograms, comparison with conventional imaging and current guideline recommendations.

The studies analyzed are summarized in Table 1. Current guideline evidence is summarized in Table 2.

3. Results

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After considering search strategy, inclusion and exclusion criteria; 4 articles and 5 guidelines were particularly taken into account in this review. The analysis is organized into the following categories:

3.1. Sensitivity and Specificity of PSMA-PET

Conventional imaging for PCa staging, such as CT or mpMRI, have a low sensitivity to detect ganglionar affection, being less than 40%. CT and MRI imaging rely on morphological features, with LNs larger than 8 to 10 mm considered suspicious. However, more than 80% of PCa LNMs are smaller than 8 mm [15]. Nowadays, bilateral extended pelvic lymph node dissection (ePLND) during radical prostatectomy (RP) is considered the most accurate method for diagnosing LNs involvement [8], while it is is an invasive diagnostic tool associated with complications, like lymphocele (3% to 17% of cases) and lower extremity edema in 3% [16]. On those grounds, PSMA PET has been investigated in the nodal staging evaluation on intermediate and high-risk PCa.

First on 2016, Maurer et al [8] published their results comparing 68Ga-PSMA-PET with CT and mpMRI on 130 patients with intermediate to high-risk PCa scheduled for RP and ePLND. On patient based analysis the sensitivity, specificity and accuracy of 68Ga-PSMA- PET were 65.9%, 98.9% and 88.5%, and those of morphological imaging were 43.9%, 85.4% and 72.3%, respectively. On template based analysis the sensitivity, specificity and accuracy of 68Ga-PSMA-PET were 68.3%, 99.1% and 95.2%, and those of morphological imaging were 27.3%, 97.1% and 87.6%, respectively.

Subsequently, on 2020, Van Kalmthout et al[16] compared ^{68}Ga PetPSMA and bilateral ePLND during RP. They showed 41.5% patient-based sensitivity (95% CI 26.7-57.8) for detecting lymph node metastasis, 90.9% (95% CI 79.3-96.6) patient-based specificity rate, and positive and negative predictive values of 77.3% (95% CI 54.2-91.3) and 67.6% (95% CI 55.6-77.7); resulting the use of PSMA-PET in a change of treatment in 13 patients (12.6%).

3.2. Integration of PSMA-PET into Nomograms

Whether to perform an ePLND is based on well-established preoperative nomograms, such as the Briganti 2017 nomogram [17] and the Memorial Sloan Kettering Cancer Center (MSKCC) nomogram [18]. They are both based on the same clinical, biochemical, and pathological preoperative variables, whereas the Briganti 2019 nomogram [19] also incorporates imaging findings and targeted biopsy histology following mpMRI. The cutoff percent age above which an ePLND is advised, differs between 2% in the National Comprehensive Cancer Network guidelines [20], 5% in the European Association of Urology guidelines [10], and 7% in the Briganti 2019 nomogram [19].

Due to accuracy information of PSMA-PET, it has been considered including it to these nomograms. A multicenter study in 2019 showed the addition of PSMA-PET to previously developed nomograms showed substantially improved performance in predicting the outcome of ePLND correctly. In terms of AUCs, AUCs of the Briganti 2017, MSKCC, and Briganti 2019 nomograms were 0.70 (95% confidence interval [95% CI]: 0.64–0.77), 0.71 (95% CI: 0.65–0.77), and 0.76 (95% CI: 0.71–0.82), respectively; and, after the use of the PET-PSMA, were increased to 0.76 (95% CI:0.70–0.82), 0.77 (95% CI: 0.72–0.83), and 0.82 (95% CI: 0.76–0.87), respectively [21].

3.3. Guideline Recommendations

As it is shown, EAU guidelines [10] reflect PET-PSMA increases detection rates in PCa patients, especially in high risk, when it is compared to conventional imaging. However, it is unclear whether patients with metastases only detectable with PSMA-PET should be managed using systemic therapies only, or whether they should be treated with aggressive local therapies. The latest EAU guidelines 2024 advocate for the use of PSMA-PET in the primary staging of high-risk prostate cancer due to its superior detection rates compared to conventional imaging, with a strong strength rating. However, the guidelines also indicate the need for caution, given that the prognostic implications of detecting metastases solely through PSMA-PET remain uncertain, and further prospective studies

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are needed to clarify its impact on clinical outcomes [22]. It is worth mentioning that they recommend it with a poor strength rating on patients with intermediate risk PCa.

ESMO guidelines [11] describe PET-PSMA has better sensitivity and specificity than CT or BS. Nevertheless, PET-PSMA has not shown to improve clinical outcomes.

ASCO guidelines [12] recommend PET-PSMA when conventional imaging modalities are negative o equivocal in high o very high-risk PCa due to its huge sensitivity. But also this high sensitivity of PET-PSMA to detect low-burden disease may lead to incorrect patient management.

AUA guidelines [13] mention PET-PSMA would be recommended only for high-risk PCa patients, despite the fact that currently PET-PSMA it not indicated in initial stage of PCA.

APCCC14 recommend using PET-PSMA in the stage of high-risk localized PCa, even without having previously used conventional imaging modalities. On other hand, PET-PSMA is not recommend in favourable intermediate-risk disease, and the use of it in unfavourable intermediate-risk PCa is controversial.

Table 1. Most relevant previously published manuscripts on the usefulness of PET-PSMA on localized prostate cancer.

Author	Study Design	Objective	Participants	Results
Hofman MS et al (2020)[6]	Prospective multicentre study	To evaluate accuracy of first-line imaging (CT or BS versus PSMA-PET) for identifying either pelvic nodal or distant-metastatic disease.	302 men (with biopsy-proven prostate cancer and high-risk features at ten hospitals in Australia) were randomly assigned. 152 (50%) men were randomly assigned to conventional imaging and 150 (50%) to PSMA PET-CT.	PSMA-PET had a 27% (95% CI 23–31) greater accuracy than that of conventional imaging (92% [88–95] vs 65% [60–69]; p<0·0001). They found a lower sensitivity (38% [24–52] vs 85% [74–96]) and specificity (91% [85–97] vs 98% [95–100]) for conventional imaging compared with PSMA-PET.
Maurer T et al (2016)[8].	Retrospective analysis	To evaluate the diagnostic value of ^{68}Ga-PSMA-PET in comparison to morphological imaging (CT and mpMRI) for LN staging in patients with intermediate to high risk PCa undergoing RP with ePLND.	130 patients with intermediate to high risk PCa who underwent ^{68}Ga-PSMA-PET and subsequent RP.	^{68}Ga-PSMA ligands have the potential to replace currently used tracers for PET not only for recurrent PCa but also for primary LN staging.
Van Kalmthout et al (2020)[16].	Propective study	Evaluates the diag-nostic accuracy of ^{68}Ga-PSMA-PET/CT to guide its implementation into clinical practice.	Patients newly diagnosed with PCa who have more than 10% risk for LNMs according to the MSKCC criteria and were considered candidates for ePLND	High specificity and moderate sensitivity for ^{68}Ga-PSMA-PET/CT to detect LNM in the initial staging of patients with PCa, negative bone scans and a greater than 10% chance of LNM.
Meijer D et al (2021)[21].	Multicenter study. Retrospective study.	To determine the predictive	All 757 eligible patients who	The addition of PSMA-PET to the

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	performance of the Briganti 2017, MSKCC, and Briganti 2019 nomograms with the addition of PSMA-PET.	underwent a PSMA-PET prior to RARP and ePLND.	previously developed nomograms showed substantially improved predictive performance.

^{68}Ga-PSMA-PET: prostate-specific membrane antigen positron emission tomography with Gallium 68. CT: computed tomography. MpMRI: multiparametic magnetic resonance imaging. RP: radical prostatectomy. EPLND: extended pelvic lymph node dissection. LN: lymph node. LNM: lymph node metastases. MSKCC: Memorial Sloan Kettering Cancer Center . RARP: robotic assisted radical prostatectomy.

Table 2. Worldwide clinical guidelines' evidence about utility of PSMA-PET.

Document led by	Arguments for using PSMA-PET	Arguments against using PSMA-PET
EAU[10]	PSMA-PET increases detection rates with respect to CT and BS, especially in high risk PCa.	It is unclear whether patients with metastases detectable only with PSMA-PET should be managed using systemic therapies only, or whether they should be subjected to aggressive local and metastases-directed therapies. The prognosis and management of patients diagnosed as metastatic by this arm is unknown.
ESMO[11]	PSMA-PET has better sensitivity and specificity than CT or BS	PSMA-PET has not shown to improve clinical outcomes. Patients with localised disease on routine imaging should not be denied radical local treatment solely because metastatic lesions are identified on PSMA-PET. The evidence regarding PSMA-PET is not adequate to make a recommendation concerning their use.
ASCO[12]	PSMA-PET is recommended if conventional imaging modalities are negative or equivocal in high or very high-risk prostate cancer.	PSMA-PET is a costly test. Its huge sensitivity to detect low-burden disease may lead to incorrect patient management.
AUA[13]	Further investigations may establish the value of this test, but it would be recommended only for high-risk PCa patients.	PSMA-PET is an expensive test that is not recommended in initial stage of PCa.
APCCC[14]	PSMA-PET should be used in high-risk localized PCa, nor in favourable intermedaite-risk disease. The use of PSMA-PET in unfavourable intermediate-risk patients is controversial.	There was no consensus on how to treat patients who are M0 on conventional imaging but have positive lesions on PSMA-PET. Therapeutic decisions should be made with caution. Although it is possible that the use of PSMA-PET for staging may improve clinical outcomes by optimising the use of local and/or adjuvant systemic therapy, this has yet to be proved.

PSMA-PET: prostate-specific membrane antigen positron emission tomography. CT: computed tomography. BS: bone scan. PCa: prostate cancer.

4. Discussion

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The role of PSMA-PET in the staging and management of PCa is rapidly evolving. The advent of molecular imaging has reshaped the landscape of its diagnosis, particularly in high-risk patients. The superior sensitivity and specificity of PSMA-PET compared to conventional imaging techniques have prompted its inclusion in primary staging protocols for high-risk PCa, as recommended by the latest EAU guidelines.

An accurate evaluation of the tumor extension at the beginning of the diagnosis is crucial to establish the correct therapeutic strategy. The Tumour, Node, Metastasis (TNM) system of the *American Joint Committee on Cancer and Union Internationale Contre le Cancer* is the most commonly used PCa staging system [23], along with the EAU risk group classification [24].

While CT, MRI, and BS have traditionally been used for staging in patients with local, intermediate to high-risk PCa, these modalities have limited precision in detecting small retroperitoneal lymph node metastases and small-volume bone metastases8.

The individual risk of patients holding positive LNs can be predictable based on validated nomograms. As we have previously reviewed, the most commonly used are Briganti and MSKCC nomograms, which are both based on the same clinical, biochemical, and pathological preoperative variables; whereas the new Briganti 2019 nomogram also includes imaging findings and targeted biopsy histology following mpMRI. Bilateral ePLND during RP is typically performed in case the risk of lymph node metastases exceeds 5%, and ePLND is considered the most accurate method for detecting LN involvement in PCa patients [8,25]. Unfortunately, we know it is an invasive diagnostic intervention associated with substantial complications. For all these reasons, more reliable imaging modalities are needed as an alternative for LN staging, and PSMA-PET has extensively been investigated in the evaluation of nodal staging [16].

PSMA is a cell-surface glycoprotein overexpressed on PCa cells. Radiolabelled small molecules that bind with afinity to PSMA enable whole-body tumour-specific imaging with PET-CT[6]. Two PSMA-targeting PET radiopharmaceuticals, ^{68}Ga-PSMA-11 and 18F-DCFPyL, have gained U.S. Food and Drug Administration approval [26]. In addition, 18F-rhPSMA-7.3, a high-affinity PSMA-PET radiopharmaceutical, is in development as a diagnostic imaging agent for PCa [27].

First of all, Maurer et al [8] published their results comparing ^{68}Ga-PSMA-PET with CT and MRI on 130 patients with intermediate to high-risk PCa scheduled for RP and ePLND. They concluded that preoperative nod staging with ^{68}Ga-PSMA-PET proved to be superior that standard imaging on these patients.

Hofman MS et al published ProPSMA in 2020 [6]. In it, investigators aimed to assess whether PSMA PET-CT had improved accurateness when compared with the combination of CT and BS. The results showed that in patients with high-risk PCa undergoing staging before curative-intent treatment, PET-PSMA should substitute conventional imaging modalities. However, the data provided by PSMA-PET and its subsequent management effects is unclear.

Van Kalmthout et al[16] evaluated the diagnostic accuracy of ^{68}Ga-PSMA-PET in initial staging of PCa assessing patients undergoing lymphadenectomy with ^{68}Ga-PSMA-PET and reevaluating them after the test. They described a 41.5% patient-based sensitivity (95% CI 26.7-57.8) for detecting LN metastasis, a 90.9% (95% CI 79.3-96.6) patient-based specificity rate, and positive and negative predictive values were 77.3% (95% CI 54.2-91.3) and 67.6% (95% CI 55.6-77.7), respectively; resulting the use of PSMA-PET in a change of treatment in 13 patients (12.6%). The clinical utility of PSMA-PET extends beyond mere detection. By integrating PSMA-PET findings into predictive nomograms, clinicians can more accurately assess the risk of LN metastases and tailor treatment strategies accordingly. This is particularly relevant in guiding the decision to perform ePLND, an invasive procedure with significant morbidity.

In a multicenter, international population that underwent robot assisted RP and ePLND, it was evaluated the performance of three well established preoperative nomogram models [17–19] for predicting pN1 disease and assessed whether PSMA-PET imaging was able to improve the performance of these models [21]. They concluded that the addition of PSMA-PET to previously

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developed nomograms showed substantially improved performance in predicting the outcome of ePLND correctly.

Despite these advances, caution is recommended in interpreting PSMA-PET findings, especially when it comes to indicate a change in therapeutic management [4,6,28]. The absence of prospective studies demonstrating a survival benefit from PSMA-PET-driven interventions underscores the need for a measured approach. The EAU guidelines emphasize that while PSMA-PET can enhance diagnostic accuracy, its impact on long-term outcomes remains to be definitively proven.

Recently, there is a study evaluating the usefulness of PSMA-PET to decide whether or not to perform an Eplnd [25], with the consequent increase in unnecessary procedures; and another one designed to select those patients with a higher risk of advance stage of the desease [29]. The first one emphasizes that tools for predicting LN metastases are associated with suboptimal performance for men with N0M0 PCa. The latter conclude that patients with ISUP (International Society of Urological Pathology) grade 2–3, as well as patients with organ-confined disease at mpMRI and a single or two positive nodal findings at PET are those in whom RP may achieve the best oncological outcomes in the context of a multimodal approach.

Summarizing the recommendations of existing clinical guidelines, EAU guidelines [10] expose quite multicentric studies that have demonstrated that PSMA-PET increased detection rates with respect to conventional imaging modalities, due to its sensitivity and specificity, especially in high-risk PCa [6,10,30]. However, in absence of prospective studies demonstrating survival benefit, caution must be used when taking therapeutic decisions [10,31]. ESMO guidelines11 confirm that men with intermediate or high-risk disease should have imaging for nodal or metastatic disease, having PSMA-PET better sensitivity and specificity than CT or BS [10,30], although it have not shown improving clinical outcomes. So that, they defend patients with localized disease on routine imaging should not be denied radical local treatment just because metastatic lesions are identified on novel imaging techniques [11]. ASCO guidelines [12] stands that PSMA-PET shows an excellent sensitivity but also several disadvantages, specially because they are costly and their huge sensitivity to detect low-burden disease may lead to incorrect patient management in some cases. They concluded that PET-PSMA is recommended if conventional imaging modalities are negative or equivocal in high or very high-risk prostate cancer. AUA guidelines [13] expose that PSMA-PET is not recommended in initial stage of PCa. APCCC celebrated in 2022 [14] describes that PSMA-PET should be request in high-risk localized PCa. It should not be used in favourable intermediate-risk disease, being its use controversial in unfavourable intermediate-risk patients. However, APCCC agree with adding the results of PSMA-PET to a new classification of TNM. On the other hand, there was no consensus on how to treat patients who are M0 on conventional imaging but have positive lesions on PSMA PET [15,32].

Why Should We Limit the Use of PSMA in Primary Staging?

PSMA PET/CT is still characterized by limited sensitivity and, at present, cannot replace an ePLND. According to Jansen at al., in their prospective cohort study involving 117 patients, they demonstrated a high specificity (94.4%), but limited sensitivity (41.2%) for the detection of PLN metastases in primary PCa [34]. Similar results were shown in a prospective multicentre phase II/III study with a mean specificity of 97.9% (95% CI 94.5-99.4%) and a mean sensitivity of 40.3% (28.1-52.5%) for pelvic lymph node involvement [35]. This suggests that PSMA-based PET/CT cannot yet replace ePLND.

Regarding other radiotracers, the phase 3 LIGHTHOUSE study [36] investigated 18F-rhPSMA-7.3 in men with newly diagnosed PCa scheduled for RP with ePLND. It is one of the few studies in which all PSMA PET/CT images were analyzed blind by three independent readers using histopathological analysis of LND specimens at RP. Sensitivity of 18F-rhPSMA-7.3 PET/CT for detection of LN metastasis was low at only 23–30% among the three readers, increasing to 38–52% for ISUP 5 cancer, a finding probably explained by higher PSMA expression in higher-grade PCa [37]. This low sensitivity of PSMA PET/CT for detection of LN metastasis is in line with findings from the

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OSPREY [38] and UCLA/UCSF [39] prospective multicenter trials, which reported 18F-DCFPyL and 68Ga-PSMA-11 sensitivity of between 30% and 40% for patients with negative or equivocal stamdard imaging who underwent LND. Despite being lower than initially reported, the PSMA PET sensitivity in these studies is underestimated due to exclusion of patients who did not undergo LND, predominately because of metastatic disease found after on-study PSMA imaging [37]. For this reason, it is predictable that guideline recommendations will migrate towards first-instance PSMA PET/CT staging in high-risk/very high-risk cancers, and therefore clinicians should expect higher PSMA imaging sensitivity than that reported here.

Currently, prospective studies demonstrating a survival benefit are lacking, so caution is advised when making therapeutic decisions [40]. Therefore, it is time to stop using PSMA imaging as standalone binary data and concentrate our research efforts on integration of PSMA imaging findings with other clinico-pathological data to optimize clinical outcomes41.

PSMA-PET is a powerful tool in the diagnostic armamentarium for prostate cancer, particularly in high-risk cases. Its ability to detect metastases with greater accuracy than conventional imaging has the potential to change the course of treatment in a significant subset of patients. However, the integration of PSMA-PET into clinical practice should be accompanied by a thorough understanding of its limitations and the ongoing need for evidence-based decision-making.

5. Conclusion

In the era of new generation imaging, PSMA-PET has emerged as a pivotal technology for the initial staging of high-risk prostate cancer. Its enhanced sensitivity and specificity over conventional imaging modalities offer a more precise evaluation of disease extent, particularly in detecting nodal and distant metastases. Nevertheless, the absence of definitive evidence linking PSMA-PET findings to improved survival outcomes necessitates a cautious approach in clinical decision-making. As the landscape of prostate cancer management continues to evolve, further prospective studies are essential to fully elucidate the role of PSMA-PET in improving patient outcomes.

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