A Comprehensive Comparison of CT, MRI, Positron Emission Tomography or Positron Emission Tomography/CT, and Diffusion Weighted Imaging-MRI for Detecting the Lymph Nodes Metastases in Patients with Cervical Cancer: A Meta-Analysis Based on 67 Studies

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Keywords

CT · Positron emission tomography · MRI · Diffusion-weighted imaging · Cervical cancer · Lymph node · Metastasis

Abstract

Object: In recent times, many published papers reported the diagnostic performance of CT, MRI, positron emission tomography (PET) using 2-[¹⁸F] fluoro-2-deoxy-D-glucose (FDG) and diffusion-weighted magnetic resonance imaging (DW-MRI) for detecting the lymph nodes (LNs) metastases in patients with cervical cancer. This study is aimed at assessing and comparing the diagnostic value of those non-invasive modalities in detecting the LNs metastases in cervical cancer patients. **Methods:** Studies on the non-invasive modalities for the detection of metastatic LNs were searched in PubMed, Medline, Web of Science, Cochrane Library and Embase databases. Pooled positive likelihood ratios and negative likelihood ratios, diagnostic OR, area under curve (AUC), summary receiver operating characteristics were calculated as evaluation indices. **Results:** In region- or node-based analysis, the AUC of DWI-MRI (0.92) and PET or PET/CT (0.90) were

better than CT (0.83), and the difference was significant (DWI-MRI vs. CT: $Z = 4.61, p < 0.001$; PET or PET/CT vs. CT: $Z = 3.61, p = 0.001$). **Conclusion:** Among the 4 non-invasive modalities, the PET or PET/CT has the highest specificity, and DWI-MRI has the highest sensitivity.

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Introduction

Cervical cancer, a malignancy of the cervix, is the fourth-most common cause of cancer and the fourth-most common cause of death from cancer in women in the world. There were an estimated 528,000 new cases, with an estimated 266,000 deaths from cervical cancer worldwide in 2012, accounting for 7.5% of all female cancer deaths [1, 2].

International Federation of Gynecology and Obstetrics (FIGO) is the accepted staging system worldwide for staging and treatment in patients with carcinoma of the cervix. Although not included in the FIGO clinical staging, the pelvic and para-aortic lymph nodes (LNs) status are important prognostic factors in cervical cancer, be-

cause the survival rates of patients with metastases to the nodes are significantly lower than in patients without metastases to the nodes [3, 4]. Therefore, an accurate staging and detection of LNs metastases is essential to ensure appropriate treatment planning and prediction of prognosis for cervical cancer patients [5].

A number of studies has evaluated the diagnostic performance of non-invasive modalities, such as CT, MRI, positron emission tomography (PET)-2-^[18F] fluoro-2-deoxy-D-glucose (FDG) and diffusion-weighted magnetic resonance imaging (DW-MRI), in detecting LN metastasis in cervical cancer patients. MRI and CT have been conventionally and widely used to detect LN metastases, which are based on measurements of node size and/or morphologic information. PET or PET/CT offers combined benefits of anatomic and functional imaging, and has been used to localize areas of increased FDG uptake with improved anatomic specificity [6]. DW-MRI, an MR technique, is a non-invasive functional imaging modality that yields tissue diffusion properties and therefore provides structural information by using the apparent diffusion coefficient (ADC). Recently, many studies have described the usefulness of DW-MRI and ADC values in identifying metastatic LNs from non-metastatic LNs.

Meta-analysis is a powerful method for quantitatively summarizing the results of homogeneous studies. Previous meta-analysis studies have investigated the performance of CT, PET/CT, MRI, and diffusion-weighted imaging (DWI) in detecting the LNs metastases in cervical cancer patients, but as research progressed, an exhaustive and updated meta-analysis is needed [7–9]. Therefore, this meta-analysis is aimed at assessing and comparing the diagnostic values of CT, PET or PET/CT, MRI, and DWI-MRI in detecting the LNs metastases in cervical cancer patients.

Materials and Methods

Literature Search Strategy

This meta-analysis searched databases such as PubMed, Medline, Web of Science, Cochrane Library, and Embase databases by the terms (“cervical cancer,” “lymph node,” “computed tomography” or “CT,” “magnetic resonance imaging” or “MRI,” “positron emission tomography” OR “PET,” “diffusion-weighted imaging” or “DWI”) to retrieve related studies, and the latest retrieval time was July 10, 2016. The flow diagram of the retrieval process is shown in Figure 1.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) human-based study; (2) data available (true-positive [TP], false-positive [FP], true-negative [TN], false-negative [FN]); (3) the diagnostic criteria was clear; (4) sample size

Fig. 1. The flow chart of article screening procedure.

of study more than 10; (5) LNs metastases was confirmed by surgery or biopsy.

Exclusion criteria: (1) animal studies; (2) the reported data was not adaptable; (3) lack of confirmed evidence by pathological examination; (4) review or meta-analysis or comment.

Data Extraction

Two authors independently reviewed the retrieved papers and extracted the key information of each eligible paper (such as study design, FIGO staging, first author’s name, metastatic positions, published year, comparison unit [patient-based, node- or region-based], diagnostic modality, numbers of TP, TN, FN, and FP) based on “inclusion and exclusion criteria” mentioned above.

FIGO Staging

Locally advanced cervical cancer: FIGO stages IIB–IVA; early cervical cancer: FIGO stages I–IIA.

Statistical Analysis

Sensitivity and 95% CI, specificity and 95% CI, positive likelihood ratios (LR+) and 95% CI, negative likelihood ratios (LR–) and 95% CI, diagnostic OR (DOR) and 95% CI, area under curve (AUC) and 95% CI, summary receiver operating characteristics were calculated by hierarchical summary receiver – operating characteristics. I^2 - and Q-statistics were used to represent the statistical heterogeneity. Statistically significant heterogeneity was considered if $p \leq 0.05$, and the random effect model was used. Otherwise, fixed effects model was adopted. Two sample Z-test was conducted to evaluate a significant difference in indices of diagnostic performance between each modality. Quality assessment of diagnostic accuracy studies (QUADAS-2) was used to assess the quality of included studies. A “yes” or “no,” or “unclear” score was given to each item [10]. All the statistical analysis was conducted using Stata 12.0 (StataCorp, College Station, TX, USA).

Table 1. Performance of CT in detecting lymph nodes metastases in cervical cancer patients

Stratification	Subgroups	Studies, <i>n</i>	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)	AUC area (95% CI)
OVER-ALL	–	22	0.57 (0.44–0.69)	0.91 (0.88–0.94)	6.4 (4.4–9.4)	0.47 (0.35–0.63)	14 (8–25)	0.89 (0.86–0.92)
Comparison unit	Patients	18	0.59 (0.44–0.73)	0.91 (0.87–0.94)	6.5 (4.3–9.9)	0.45 (0.31–0.65)	14 (7–29)	0.90 (0.87–0.92) [#]
	Regions or nodes	4	0.50 (0.32–0.68)	0.92 (0.84–0.96)	6.1 (2.7–14.0)	0.54 (0.36–0.80)	11 (4–35)	0.83 (0.79–0.86) [#]
Metastatic positions	Para-aortic	9	0.68 (0.52–0.81)	0.90 (0.84–0.94)	7.1 (4.2–12.0)	0.35 (0.22–0.56)	20 (9–47)	0.91 (0.88–0.93) [*]
	Pelvic	9	0.48 (0.34–0.62)	0.91 (0.86–0.94)	5.1 (2.9–9.1)	0.58 (0.43–0.77)	9 (4–20)	0.84 (0.81–0.87) [*]
	Pelvic and para-aortic	4	0.47 (0.29–0.65)	0.95 (0.89–0.98)	4.9 (1.0–22.6)	0.65 (0.33–1.28)	18 (4–71)	0.88 (0.85–0.91)
FIGO	I–IVA	20	0.59 (0.47–0.71)	0.91 (0.87–0.94)	6.6 (4.4–9.8)	0.45 (0.33–0.60)	15 (8–27)	0.89 (0.86–0.91)

[#] Those results were significantly different by pair-wise Z test ($Z = 2.88, p = 0.005$); ^{*} those results were significantly different by pair-wise Z test ($Z = 3.23, p = 0.001$).

Results

Characteristics of Studies

After a careful review, a total of 67 papers were included in this meta-analysis. Among them, 19 papers had reported the performance of CT, 29 studies had reported the performance of MRI, 28 studies had reported the performance of PET or PET/CT and 7 studies had reported the performance of DWI-MRI, respectively (Appendix 1 and 2). The flow chart of the article screening procedure is shown in Figure 1.

Performance of CT in Detecting the LNs Metastases in Patients with Cervical Cancer

As shown in Table 1 and Figure 2, after pooling 19 studies, the sensitivity, specificity, LR+, LR–, DOR and AUC of CT detecting the LN metastases in cervical cancer patients were 0.57 (0.44–0.69), 0.91 (0.88–0.94), 6.4 (4.4–9.4), 0.47 (0.35–0.63), 14 (8–25), and 0.89 (0.86–0.92), respectively. The results of stratification analysis by comparison unit, metastatic positions, FIGO staging are shown in Table 1. This meta-analysis found that CT was more accurate in patient-based unit (AUC 0.90) than in region- or node-based unit (AUC 0.83), and the difference was significant by pair-wise Z test ($Z = 2.88, p = 0.005$). Compared to pelvic LN metastases (AUC 0.84, 95% CI 0.81–0.87), detecting para-aortic LN metastases (AUC 0.91, 95% CI 0.88–0.93) was more accurate by CT, and the difference was significant by pair-wise Z test ($Z = 2.88, p = 0.005$).

Fig. 2. Summary receiver operating characteristic of the diagnostic performance of CT.

Performance of PET or PET/CT in Detecting the LNs Metastases in Patients with Cervical Cancer

As shown in Table 2 and Figure 3, after pooling 42 studies, the sensitivity, specificity, LR+, LR–, DOR, and AUC of CT in detecting the LNs metastases in cervical cancer patients were 0.66 (0.56–0.75), 0.97 (0.95–0.98), 19.3 (12.3–30.2), 0.35 (0.27–0.47), 55 (30–99), and

Table 2. Performance of PET or PET-CT in detecting lymph nodes metastases in cervical cancer patients

Stratification	Subgroups	Studies, <i>n</i>	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)	AUC area (95% CI)
OVER-ALL	OVER-ALL	46	0.66 (0.56–0.75)	0.97 (0.95–0.98)	19.3 (12.3–30.2)	0.35 (0.27–0.47)	55 (30–99)	0.94 (0.92–0.96)
Comparison unit	Patients	26	0.76 (0.60–0.87)	0.94 (0.91–0.96)	13.2 (8.0–22.0)	0.25 (0.14–0.45)	52 (21–131)	0.95 (0.93–0.97) [#]
	Regions or nodes	20	0.55 (0.44–0.65)	0.98 (0.96–0.99)	26.2 (13.4–51.5)	0.46 (0.37–0.58)	57 (27–120)	0.90 (0.88–0.92) [#]
Metastatic positions	Para-aortic	7	0.81 (0.52–0.95)	0.98 (0.93–0.99)	35.8 (11.3–114.1)	0.19 (0.06–0.60)	186 (30–1,143)	0.98 (0.96–0.99) ^{*, §}
	Pelvic	22	0.55 (0.42–0.67)	0.97 (0.95–0.99)	19.5 (10.5–36.4)	0.46 (0.35–0.61)	42 (20–87)	0.91 (0.88–0.93) [*]
	Pelvic and para-aortic	17	0.72 (0.56–0.84)	0.95 (0.90–0.98)	14.5 (7.0–30.3)	0.29 (0.17–0.49)	50 (17–144)	0.94 (0.91–0.96) [§]
FIGO	Locally advanced	5	0.83 (0.62–0.94) [†]	0.91 (0.85–0.94) ^Δ	8.8 (5.1–15.4)	0.19 (0.08–0.46)	47 (13–169)	0.95 (0.93–0.97) ^{&}
	Early	13	0.41 (0.33–0.50) ^{†, ‡}	0.98 (0.96–0.99) ^Δ	23.3 (10.9–49.9)	0.60 (0.51–0.70)	39 (17–89)	0.76 (0.73–0.80) ^{&, @}
	I–IVA	28	0.73 (0.60–0.83) [‡]	0.96 (0.93–0.98)	18.7 (10.2–34.3)	0.28 (0.18–0.43)	67 (29–157)	0.92 (0.89–0.94) [@]

[#] Those results were significantly different by pair-wise Z test ($Z = 3.80, p < 0.001$); ^{*} those results were significantly different by pair-wise Z test ($Z = 3.81, p < 0.001$); [§] those results were significantly different by pair-wise Z test ($Z = 2.17, p = 0.030$); [&] those results were significantly different by pair-wise Z test ($Z = 7.39, p < 0.001$); [@] those results were significantly different by pair-wise Z test ($Z = 10.32, p < 0.001$); [†] those results were significantly different by pair-wise Z test ($Z = 3.66, p < 0.001$); [‡] those results were significantly different by pair-wise Z test ($Z = 4.11, p < 0.001$); ^Δ those results were significantly different by pair-wise Z test ($Z = 2.06, p = 0.03$).

Fig. 3. Summary receiver operating characteristic of the diagnostic performance of PET or PET/CT.

0.94 (0.92–0.96), respectively. Subgroup analysis found that the performance of PET or PET/CT in detecting the LNs was more accurate in patient-based unit (AUC 0.95, 95% CI 0.93–0.97) than in region- or node-based unit (AUC 0.90, 95% CI 0.88–0.92), and the difference was significant by pair-wise Z test ($Z = 3.80, p < 0.001$); compared to pelvic LNs metastases (AUC 0.91, 95% CI 0.88–0.93), detection of para-aortic LNs metastases (AUC 0.98, 95% CI 0.96–0.99) was more accurate by PET or PET/CT, and the difference was significant by pair-wise Z test ($Z = 3.81, p < 0.001$); PET or PET/CT was more specific in FIGO early staging than advanced staging (advanced: specificity = 0.91, 95% CI 0.85–0.94; specificity = 0.98, 95% CI 0.96–0.99; $Z = 2.06, p = 0.03$), but the sensitivity was lower than advanced staging (advanced: sensitivity = 0.83, 95% CI 0.62–0.94; specificity = 0.41, 95% CI 0.33–0.50; $Z = 3.66, p < 0.001$). So in general, PET or PET/CT performed better in FIGO advanced staging than in early staging (advanced: AUC 0.95, 95% CI 0.93–0.97; early: AUC 0.76, 95% CI 0.73–0.80; $Z = 2.06, p = 0.03$).

Performance of MRI in Detecting the LNs Metastases in Patients with Cervical Cancer

As shown in Table 3 and Figure 4, after pooling 42 studies, the sensitivity, specificity, LR+, LR–, DOR, and AUC of CT in detecting the LNs metastases in cervical

Table 3. Performance of MRI in detecting lymph nodes metastases in cervical cancer patients

Stratification	Subgroups	Studies, <i>n</i>	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)	AUC area (95% CI)
OVER-ALL	–	42	0.54 (0.46–0.61)	0.93 (0.91–0.95)	8.2 (6.0–11.1)	0.50 (0.43–0.58)	16 (11–24)	0.85 (0.81–0.87)
Comparison unit	Patients	24	0.59 (0.51–0.67)	0.90 (0.85–0.93) [#]	5.8 (3.8–8.9)	0.45 (0.37–0.56)	13 (7–22)	0.80 (0.77–0.84)*
	Regions or nodes	19	0.47 (0.36–0.58)	0.96 (0.94–0.97) [#]	12.0 (8.7–16.6)	0.55 (0.45–0.68)	22 (14–33)	0.88 (0.85–0.91)*
Metastatic positions	Para-aortic	3	0.54 (0.09–0.93)	0.94 (0.76–0.99)	8.9 (1.6–50.0)	0.49 (0.14–1.78)	18 (18–263)	–
	Pelvic	17	0.62 (0.51–0.72)	0.93 (0.88–0.96)	8.7 (5.3–14.2)	0.41 (0.31–0.54)	21 (12–39)	0.87 (0.84–0.90) [§]
	Pelvic and para-aortic	22	0.51 (0.42–0.60)	0.93 (0.88–0.95)	7.0 (4.5–11.1)	0.53 (0.44–0.63)	13 (8–23)	0.79 (0.75–0.83) [§]
FIGO	Locally advanced	2	0.88 (0.76–0.96) ^{&}	0.90 (0.86–0.95)	9.1 (5.3–15.7)	0.12 (0.05–0.28)	76 (26–218)	–
	Early	8	0.52 (0.44–0.59) ^{&}	0.94 (0.91–0.96)	8.4 (5.5–12.8)	0.52 (0.44–0.60)	16 (10–26)	0.80 (0.76–0.83)
	I–IVA	32	0.61 (0.47–0.73)	0.89 (0.85–0.92)	5.5 (4.1–7.4)	0.44 (0.32–0.61)	13 (13–21)	0.88 (0.85–0.91)

[#] Those results were significantly different by pair-wise Z test ($Z = 2.18$, $p = 0.029$); * those results were significantly different by pair-wise Z test ($Z = 5.43$, $p < 0.001$); [§] those results were significantly different by pair-wise Z test ($Z = 3.13$, $p = 0.002$); [&] those results were significantly different by pair-wise Z test ($Z = 4.89$, $p < 0.001$).

cancer patients were 0.54 (0.46–0.61), 0.93 (0.91–0.95), 8.2 (6.0–11.1), 0.50 (0.43–0.58), 16 (11–24), 0.85 (0.81–0.87), respectively. Subgroup analysis found that the performance of MRI in detecting the LNs metastases was more accurate in region- or node-based unit (AUC 0.88, 95% CI 0.85–0.91; specificity = 0.96, 95% CI 0.94–0.97) than in patient-based unit (AUC 0.80, 95% CI 0.77–0.84; specificity = 0.90, 95% CI 0.85–0.93), and the difference was significant by pair-wise Z test (AUC $Z = 5.43$, $p < 0.001$; specificity: $Z = 2.18$, $p = 0.029$). Compared to pelvic and para-aortic LNs metastases (AUC 0.79, 95% CI 0.75–0.83), detecting pelvic LNs metastases (AUC 0.87, 95% CI 0.84–0.90) was more accurate by MRI, and the difference was significant by pair-wise Z test ($Z = 3.13$, $p = 0.002$); MRI was more sensitive in advanced FIGO staging than in early staging (advanced: sensitivity = 0.88, 95% CI 0.76–0.96; early: sensitivity = 0.52, 95% CI 0.44–0.59; $Z = 4.89$, $p < 0.001$).

Performance of DWI-MRI in Detecting the LNs Metastases in Patients with Cervical Cancer

This meta-analysis had included 7 papers which focused on the diagnostic performance of DWI-MRI for detecting the LNs metastases in cervical cancer patients, and all of these papers were analyzed on region- or node-based unit. As shown in Table 4, Figures 5 and 6, all diagnostic performance indices indicated that using ADC and relative ADC (rADC) as the diagnostic criteria were better than using short- or long-axis diameter (LD).

Fig. 4. Summary receiver operating characteristic of the diagnostic performance of MRI.

Only when the included papers were more than 3 articles, the AUC could be calculated using Stata software. This meta-analysis found, in general, that using mean ADC criteria was more accurate than short-axis diameter (SD) for detecting the LNs metastases in pa-

Table 4. Performance of diffusion-weighted imaging (DWI)-MRI in detecting lymph nodes metastases in cervical cancer patients

Stratification	Subgroups	Studies, <i>n</i>	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)	AUC area (95% CI)
DWI criteria	Mean ADC	7	0.87 (0.82–0.91)	0.83 (0.78–0.88)	5.2 (3.8–7.1)	0.15 (0.10–0.22)	34 (18–65)	0.92 (0.89–0.94)*
	SD	4	0.73 (0.54–0.86)	0.77 (0.68–0.84)	3.2 (2.4–4.3)	0.35 (0.20–0.61)	9 (5–18)	0.82 (0.78–0.85)*
	LD	3	0.80 (0.74–0.84)	0.56 (0.53–0.59)	1.9 (1.4–2.6)	0.30 (0.14–0.66)	6 (2–19)	–
	rADC	3	0.85 (0.78–0.90)	0.88 (0.86–0.90)	6.2 (2.3–16.4)	0.17 (0.07–0.43)	42 (7–235)	–

ADC, apparent diffusion coefficient; SD, short-axis diameter; LD, long-axis diameter; rADC, relative apparent diffusion coefficient. * Those results were significantly different by pair-wise Z test ($Z = 3.92$, $p < 0.001$).

Fig. 5. Summary receiver operating characteristic of the diagnostic performance of DWI-MRI using SD as criteria.

Fig. 6. Summary receiver operating characteristic of the diagnostic performance of DWI-MRI using mean ADC as criteria.

tients with cervical cancer (mean ADC: AUC 0.92, 95% CI 0.89–0.94; SD: AUC 0.82, 95% CI 0.78–0.85; $Z = 3.92$, $p < 0.001$).

Comprehensive Comparison of CT, PET or PET/CT, MRI and DWI Performed for Detecting the LNs Metastases in Patients with Cervical Cancer

In patient-based analysis, although the point estimates of sensitivity, specificity, LR+, LR–, and DOR of PET or PET/CT were all better than those of CT and MRI, the difference was not significant in terms of statistics. The

AUC values were significantly different in CT, PET or PET/CT, and MRI by pair-wise comparison, and the order of their diagnostic effects was: PET or PET/CT (95%), CT (90%), and MRI (80%).

In region- or node-based analysis, among the 4 non-invasive modalities, the sensitivity of DWI-MRI (0.87) was much better than the other 3 modalities, but the specificity was lower than others, and the difference was significant. In comparison, the LR+ of DWI-MRI (5.2) was worse than PET or PET/CT (26.2) and MRI (12.0), but the LR– of DWI-MRI (0.15) was the best among those

modalities. The AUC of DWI-MRI (0.92) and PET or PET/CT (0.90) were both better than CT (0.83), and the difference was significant (DWI-MRI vs. CT: $Z = 4.61$, $p < 0.001$; PET or PET/CT vs. CT: $Z = 3.61$, $p = 0.001$; Table 5).

Quality Assessment

According to QUADAS-2 guidelines, all the 20 studies included for this meta-analysis were assessed. As shown in Table 6, 5 studies were of low quality, 19 papers were of unclear risk of bias and 43 papers were of low risk of bias.

Publication Bias

Neither the Egger's nor the Begg's test found significant publication bias in this meta-analysis.

Discussion

Cervical cancer is a common malignant cancer in women worldwide. The presence of metastatic LN is one of the most important factors that influence treatment approaches and therapeutic outcomes in cervical cancer patients [3, 4], so the accurate detection of LN metastases has significant importance in clinic. The finding of LN metastases is associated with a reduction in the 5-year survival rate, despite the integration of adjuvant radiotherapy to the surgery [12]. With the progress of medical science and technology, the application of imaging technologies, including CT, MRI, PET, and DWI, may make it possible for pelvic and para-aortic LN metastases to be effectively detected in cervical cancer patients.

A total of 67 original studies have been included in this meta-analysis. Because most individual studies have a limited number of cases, meta-analysis uses more data and provides more reliable results. To the best of our knowledge, this paper is the first and most comprehensive meta-analysis for the diagnostic performance of CT, PET/CT, MRI, and DWI-MRI for detecting LN metastases in cervical cancer patients. From 2010 to now, there are 4 meta-analysis papers focusing on this subject [8, 9, 72, 73], but our meta-analysis is the first one to comprehensively compare and diagnose efficacies of the 4 modalities.

This meta-analysis pooled the data from 19 studies about the diagnostic performance of CT, and the results show that the specificities were more than 90% in all subgroup analyses, indicating that CT had a high specific-

ity in the detection of LN metastases. But the sensitivities did not fare well. The results of most subgroup analyses show that the sensitivities were lower than 60%. The results of this paper were consistent with the findings from the meta-analysis of Choi's team [9].

A total of 42 papers that studied the MRI performance had been included. The overall sensitivity and specificity of MRI were 54 and 93%, respectively. Subgroup analysis found that the sensitivity of MRI was 88% in locally advanced staging of FIGO, and it was significantly higher than early staging (52%). Although MRI had a higher sensitivity in the detection of both para-aortic and pelvic LN metastases, its sensitivity was not as high as its specificity, which was similar to CT.

18F-FDG PET is a functional method based on the increased glucose metabolism of cancer cells, regardless of node size, and PET/CT can often detect tiny metastatic LNs ranging in size from 5 to 9 mm, which cannot be diagnosed by MRI or CT [64]. The results of our meta-analysis also found that the sensitivities of PET or PET/CT in the detection of LN metastases were 76% as patient-based unit and 55% in region- or node-based unit, which were higher than CT and MRI, respectively. Meanwhile, this analysis found that the specificity of PET or PET/CT was the highest among the 4 non-invasive modalities, both in patient-based (94%) and region- or node-based units (98%).

In recent years, DW-MRI has been used as a new diagnostic technique to detect the LN metastases in cervical cancer patients. Diffusion imaging is an MRI method that produces in vivo MRI of biological tissues sensitized with the local characteristics of molecular diffusion, generally water [74]. So it can make subtle abnormality more obvious and can provide better characterization of tissue and their pathological processes at the microscopic level [75]. In addition, quantitative assessment can be performed by measuring ADC [76]. Of late, DWI has been introduced for the differentiation of benign and malignant lesions in extracranial organs, especially for the diagnosis of abdominal and pelvic organs [77]. Although this ADC concept has been extremely successful, especially for clinical applications, it has been challenged recently, as new, more comprehensive models of diffusion in biological tissues have been introduced [78, 79]. After review, this research found that most included papers used ADC, rADC, SD, and LD as a criteria for the detection of LN metastasis in cervical cancer patients. The results of this meta-analysis found that using ADC and rADC had higher sensitivities and specificities than using SD and LD. Because of insufficient papers, only the AUC values of mean ADC

Table 5. Comparison of diagnostic performances of 4 non-invasive modalities in detecting lymph nodes metastases in cervical cancer patients

Stratification	Subgroups	Studies, <i>n</i>	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR- (95% CI)	DOR (95% CI)	AUC area (95% CI)
Patient-based unit	CT	18	0.59 (0.44–0.73)	0.91 (0.87–0.94)	6.5 (4.3–9.9)	0.45 (0.31–0.65)	14 (7–29)	0.90 (0.87–0.92)*, \$
	MRI	24	0.59 (0.51–0.67)	0.90 (0.85–0.93)	5.8 (3.8–8.9)	0.45 (0.37–0.56)	13 (7–22)	0.80 (0.77–0.84)*, *
	PET or PET/CT	26	0.76 (0.60–0.87)	0.94 (0.91–0.96)	13.2 (8.0–22.0)	0.25 (0.14–0.45)	52 (21–131)	0.95 (0.93–0.97)*, \$
Regions or nodes units	CT	4	0.50 (0.32–0.68) [√]	0.92 (0.84–0.96)	6.1 (2.7–14.0)	0.54 (0.36–0.80) ^φ	11 (4–35)	0.83 (0.79–0.86) ^{Ⓜ, ‡}
	MRI	19	0.47 (0.36–0.58) ^Δ	0.96 (0.94–0.97) ^Σ	12.0 (8.7–16.6) ^{&}	0.55 (0.45–0.68) ^ω	22 (14–33)	0.88 (0.85–0.91)
	PET or PET/CT	20	0.55 (0.44–0.65) ^Π	0.98 (0.96–0.99) ^Ω	26.2 (13.4–51.5) [^]	0.46 (0.37–0.58) ^ψ	57 (27–120)	0.90 (0.88–0.92) [Ⓜ]
	DWI-MRI	7	0.87 (0.82–0.91) ^{√, Δ, Π}	0.83 (0.78–0.88) ^{Σ, Ω}	5.2 (3.8–7.1) ^{&, ^}	0.15 (0.10–0.22) ^{ψ, ω, φ}	34 (18–65)	0.92 (0.89–0.94) [‡]

* Those results were significantly different by pair-wise Z test ($Z = 4.61, p < 0.001$); # those results were significantly different by pair-wise Z test ($Z = 8.15, p < 0.001$); \$ those results were significantly different by pair-wise Z test ($Z = 2.71, p = 0.007$); [√] those results were significantly different by pair-wise Z test ($Z = 3.88, p = 0.001$); ^Δ those results were significantly different by pair-wise Z test ($Z = 6.48, p < 0.001$); ^Π those results were significantly different by pair-wise Z test ($Z = 5.19, p < 0.001$); ^Σ those results were significantly different by pair-wise Z test ($Z = 4.73, p < 0.001$); ^Ω those results were significantly different by pair-wise Z test ($Z = 5.46, p < 0.001$); [&] those results were significantly different by pair-wise Z test ($Z = 3.71, p < 0.001$); [^] those results were significantly different by pair-wise Z test ($Z = 3.19, p = 0.001$); ^φ those results were significantly different by pair-wise Z test ($Z = 4.21, p < 0.001$); ^ψ those results were significantly different by pair-wise Z test ($Z = 6.27, p < 0.001$); ^ω those results were significantly different by pair-wise Z test ($Z = 5.24, p < 0.001$); [‡] those results were significantly different by pair-wise Z test ($Z = 4.61, p < 0.001$); [Ⓜ] those results were significantly different by pair-wise Z test ($Z = 3.61, p = 0.001$).

Table 6. Risk of bias of included studies

First author	Year	Patient selection			Index test	Reference standard			Flow and timing		Summary risk of bias	Applicability
		1	2	3	4	5	6	7	8	9		
Bandy	1985	U	Y	Y	U	Y	U	U	Y	Y	B	H
Bellomi	2006	U	Y	Y	U	Y	U	U	Y	N	A	H
Camilien	1988	U	Y	Y	U	Y	U	U	Y	N	A	H
Chu	1996	U	Y	Y	Y	Y	U	U	Y	Y	B	H
Grumbine	1981	U	Y	Y	U	Y	U	U	Y	Y	B	H
Heller	1990	U	Y	Y	Y	Y	U	U	Y	Y	B	H
Hertel	2002	U	Y	Y	U	Y	U	U	Y	Y	B	H
Kim	1990	U	Y	Y	U	Y	U	U	Y	Y	B	H
Kim	1993	U	Y	Y	Y	Y	U	U	Y	Y	B	H
Matsukuma	1987	U	Y	Y	U	Y	U	U	Y	Y	B	H
Subak	1995	U	Y	Y	U	Y	U	U	Y	N	A	H
Engelshoven	1984	U	Y	Y	Y	Y	U	U	Y	N	A	H
Wenzel	1985	U	Y	Y	Y	Y	U	U	Y	Y	B	H
Walsh	1981	U	Y	Y	U	Y	U	U	Y	Y	B	H
Yang	2000	U	Y	Y	U	Y	U	U	Y	Y	B	H
Choi	2004	U	Y	Y	U	Y	U	U	Y	Y	B	H
Chung	2007	U	Y	Y	U	Y	Y	U	Y	Y	B	H
Greco	1989	U	Y	Y	U	Y	U	U	Y	Y	B	H
Hawighorst	1998	U	Y	Y	U	Y	U	U	Y	Y	B	H
Hawnaur	1994	U	Y	Y	Y	Y	U	U	Y	Y	B	H
Hricak	1988	U	Y	Y	U	Y	U	U	Y	Y	B	H
Janus	1989	U	Y	Y	U	Y	U	U	Y	N	A	H
Lv	2014	U	Y	Y	Y	Y	U	U	Y	Y	B	H
Narayan	2001	U	Y	Y	Y	Y	U	U	Y	Y	B	H
Park	2005	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Reinhard	2001	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Sahdev	2007	Y	Y	Y	U	Y	U	U	Y	Y	C	H
Sheu	2001	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Waggenspack	1988	Y	Y	Y	U	Y	U	U	Y	Y	C	H
Yu	1998	Y	Y	Y	U	Y	Y	U	Y	Y	C	H

Table 6. (continued)

First author	Year	Patient selection			Index test	Reference standard			Flow and timing		Summary risk of bias	Applicability
		1	2	3	4	5	6	7	8	9		
Kim	2009	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Belhocine	2002	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Choi	2006	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Crivellaro	2012	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Chung	2010	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Kitajima	2012	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Kitajima	2015	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Lin	2003	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Loft	2007	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Ma	2003	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Signorelli	2011	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Nogami	2014	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Roh	2005	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Sironi	2006	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Wright	2007	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Xu	2016	Y	Y	Y	Y	Y	Y	U	Y	Y	C	H
Stecco	2016	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Walsh	1980	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Brenner	1982	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Villasanta	1983	Y	Y	Y	Y	Y	Y	U	Y	Y	C	H
Vas	1985	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Choi	2006	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Rose	1999	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Kim	1994	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
YEH	2002	Y	Y	Y	Y	Y	Y	U	Y	Y	C	H
Havrilesky	2003	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Yildirim	2008	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Kitajima	2009	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Chung	2009	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Sandvik	2011	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Kim	2011	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Choi	2009	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Chen	2009	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Liu	2011	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Kim	2008	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Lin	2008	Y	Y	Y	Y	Y	U	U	Y	Y	C	H
Xue	2008	Y	Y	Y	Y	Y	U	U	Y	Y	C	H

1: was a consecutive or random sample of patients enrolled? 2: was a case-control design avoided? 3: did the study avoid inappropriate exclusions? 4: were the index test results interpreted without knowledge of the results of the reference standard? 5: is the reference standard likely to correctly classify the target condition? 6: were the reference standard results interpreted without knowledge of the results of the index test? 7: was there an appropriate interval between index test(s) and reference standard? 8: did all patients receive a reference standard? 9: were all patients included in the analysis? Y, yes; U, unclear; N, no; A, high risk of bias; B, unclear risk of bias; C, low risk of bias; H, high applicability.

and SD subgroups were calculated. And study paper found that all the evaluating indicators in mean ADC subgroups were better than SD.

According to this study, MRI and PET/CT performed better in advanced stage cervical cancer patients than in early stage for detecting LN metastases. Two factors

might account for this: 1 higher nodal metastases rate and 2 more frequent occurrences of bulky nodes, with macroscopic deposits of tumor, in advanced stage of the disease than in early stage [42]. Thus, the detection rates of PET/CT and MRI were increased. Meanwhile, these reasons also explained why the sensitivity of MRI or PET/CT was

significantly better in advanced stage than in early stage, but the specificity was not significantly different.

After comprehensively analyzing the diagnostic performance for those 4 non-invasive modalities, this study found that the DWI-MRI was the best one in the context of sensitivity (88% of regions or nodes units), and PET or PET/CT was the best one in the context of specificity (94% of region- or node-based units and 98% of patient-based unit). The AUC of both PET or PET/CT and DWI-MRI were all higher than 90%, indicating that these 2 modalities were highly valuable in detecting the LN metastasis in cervical cancer patients.

Conclusion

Compared to CT and MRI, PET or PET/CT, and DWI-MRI have a high accuracy in detecting LN metastasis in cervical cancer patients. Among the 4 non-invasive modalities, the PET or PET/CT has the highest specificity, and DWI-MRI has the highest sensitivity.

Disclosure Statement

The authors state that there are no conflicts of interest to disclose.

Appendix

Appendix 1. Summary of the information of included studies on CT, PET or PET/CT, and MRI for detecting LNs metastases in patients with cervical cancer

First author	Year	Comparison	Location	PET or PET/CT				CT				MRI			
				TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN
Bandy [11]	1985	P	Para-aortic	–	–	–	–	9	3	3	29	–	–	–	–
Bellomi [12]	2005	R	Pelvic	–	–	–	–	31	30	17	418	35	31	13	417
Camilien [13]	1988	P	Pelvic and para-aortic	–	–	–	–	3	1	9	38	–	–	–	–
Chu [14]	1996	P	Pelvic	–	–	–	–	4	1	6	17	–	–	–	–
Grumbine [15]	1981	P	Pelvic and para-aortic	–	–	–	–	0	1	6	17	–	–	–	–
Heller [16]	1990	P	Para-aortic	–	–	–	–	31	8	30	184	–	–	–	–
Hertel [17]	2002	P	Pelvic	–	–	–	–	3	8	17	47	3	7	9	48
Hertel [17]	2002	P	Para-aortic	–	–	–	–	3	9	13	66	0	1	6	60
Kim [18]	1990	R	Pelvic	–	–	–	–	6	12	6	36	3	1	12	44
Kim [19]	1993	R	Pelvic	–	–	–	–	7	11	22	158	7	2	22	167
Matsukuma [20]	1989	P	Pelvic and para-aortic	–	–	–	–	5	2	2	61	–	–	–	–
Subak [21]	1995	P	Pelvic	–	–	–	–	3	3	2	29	8	5	5	53
Engelshoven [22]	1984	P	Para-aortic	–	–	–	–	3	4	1	12	–	–	–	–
Walsh [23]	1981	P	Para-aortic	–	–	–	–	11	2	2	0	–	–	–	–
Yang [24]	2000	R	Pelvic	–	–	–	–	11	2	6	57	12	6	5	53
Choi [25]	2004	R	Pelvic	–	–	–	–	–	–	–	–	8	14	6	198
Chung [26]	2007	P	Pelvic and para-aortic	–	–	–	–	–	–	–	–	24	10	6	59
Chung [26]	2007	R	Pelvic and para-aortic	–	–	–	–	–	–	–	–	30	44	66	693
Greco [27]	1989	P	Pelvic and para-aortic	–	–	–	–	–	–	–	–	3	6	5	32
Hawighorst [28]	1998	P	Pelvic	–	–	–	–	–	–	–	–	13	3	6	11
Hawnaur [29]	1994	P	Pelvic and para-aortic	–	–	–	–	–	–	–	–	12	4	4	29
Hricak [30]	1988	P	Pelvic and para-aortic	–	–	–	–	–	–	–	–	9	2	2	44
Janus [31]	1989	P	Para-aortic	–	–	–	–	–	–	–	–	3	2	1	16
Lv [32]	2014	P	Pelvic and para-aortic	34	7	0	46	–	–	–	–	15	8	19	45
Lv [32]	2014	R	Pelvic and para-aortic	61	17	6	1,079	–	–	–	–	25	16	42	1,080
Narayan [33]	2001	P	Pelvic and para-aortic	4	1	3	16	–	–	–	–	6	0	6	12
Narayan [33]	2001	R	Pelvic and para-aortic	10	1	2	11	–	–	–	–	6	0	6	12
Park [34]	2005	P	Pelvic	6	0	8	22	–	–	–	–	8	6	6	16
Park [34]	2005	R	Pelvic	9	0	13	50	–	–	–	–	12	10	10	40
Reinhard [3]	2001	P	Pelvic	10	0	1	24	–	–	–	–	8	4	3	20
Reinhard [3]	2001	N	Pelvic	17	2	4	269	–	–	–	–	14	8	7	263
Sahdev [35]	2007	P	Pelvic and para-aortic	–	–	–	–	–	–	–	–	7	11	12	120
Sahdev [35]	2007	N	Pelvic and para-aortic	–	–	–	–	–	–	–	–	12	15	32	1,427

Appendix 1. (continued)

First author	Year	Comparison	Location	PET or PET/CT				CT				MRI			
				TP	FP	FN	TN	TP	FP	FN	TN	TP	FP	FN	TN
Sheu [36]	2001	P	Pelvic and para-aortic	–	–	–	–	–	–	–	–	9	4	2	26
Waggenspack [37]	1988	P	Para-aortic	–	–	–	–	–	–	–	–	3	0	0	17
Yu [38]	1998	P	Pelvic and para-aortic	–	–	–	–	–	–	–	–	9	7	5	73
Kim [39]	2009	P	Pelvic and para-aortic	14	14	16	35	–	–	–	–	17	16	13	33
Kim [39]	2009	N	Pelvic and para-aortic	26	30	33	464	–	–	–	–	32	38	27	456
Belhocine [40]	2002	P	Para-aortic	19	8	3	187	–	–	–	–	–	–	–	–
Choi [41]	2006	P	Pelvic and para-aortic	10	4	3	5	–	–	–	–	4	5	9	4
Choi [41]	2006	R	Pelvic and para-aortic	19	9	14	112	–	–	–	–	10	9	23	112
Crivellaro [42]	2012	P	Pelvic	4	2	11	52	–	–	–	–	–	–	–	–
Chung [43]	2010	P	Pelvic	8	9	20	46	–	–	–	–	18	17	10	38
Kitajima [44]	2012	R	Pelvic and para-aortic	14	6	22	158	–	–	–	–	–	–	–	–
Kitajima [44]	2015	P	Pelvic	12	2	1	17	–	–	–	–	9	0	4	17
Lin [45]	2003	P	Pelvic and para-aortic	12	2	2	34	–	–	–	–	–	–	–	–
Loft [46]	2007	P	Para-aortic	15	1	0	104	–	–	–	–	–	–	–	–
Loft [46]	2007	P	Pelvic	21	7	1	50	–	–	–	–	–	–	–	–
Ma [47]	2003	P	Pelvic and para-aortic	38	0	0	66	–	–	–	–	–	–	–	–
Signorelli [48]	2011	P	Pelvic	9	4	19	127	–	–	–	–	–	–	–	–
Signorelli [48]	2011	R	Pelvic	10	4	30	862	–	–	–	–	–	–	–	–
Nogami [49]	2014	R	Pelvic and para-aortic	5	4	10	51	–	–	–	–	–	–	–	–
Nogami [49]	2014	R	Pelvic and para-aortic	11	9	25	803	–	–	–	–	–	–	–	–
Roh [50]	2005	P	Pelvic	9	0	13	50	–	–	–	–	–	–	–	–
Roh [50]	2005	R	Pelvic	14	12	23	385	–	–	–	–	–	–	–	–
Sironi [51]	2006	P	Pelvic and para-aortic	11	1	4	31	–	–	–	–	–	–	–	–
Sironi [51]	2006	R	Pelvic and para-aortic	13	3	5	1,060	–	–	–	–	–	–	–	–
Wright [52]	2005	R	Pelvic and para-aortic	1	1	3	40	–	–	–	–	–	–	–	–
Wright [52]	2005	R	Pelvic	2	1	3	84	–	–	–	–	–	–	–	–
Wright [52]	2005	R	Pelvic and para-aortic	10	4	9	36	–	–	–	–	–	–	–	–
Wright [52]	2005	R	Pelvic	12	8	14	84	–	–	–	–	–	–	–	–
Xu [53]	2016	R	Pelvic and para-aortic	19	8	4	20	–	–	–	–	–	–	–	–
Stecco [54]	2016	P	Pelvic	7	3	1	16	–	–	–	–	7	3	1	16
Stecco [54]	2016	R	Pelvic	26	17	11	162	–	–	–	–	33	15	4	164
Walsh [55]	1980	P	Pelvic and para-aortic	–	–	–	–	12	3	3	7	–	–	–	–
Brenner [56]	1982	P	Para-aortic	–	–	–	–	4	0	2	6	–	–	–	–
Brenner [56]	1982	P	Pelvic	–	–	–	–	4	1	2	13	–	–	–	–
Villasanta [57]	1983	P	Para-aortic	–	–	–	–	10	4	3	25	–	–	–	–
Wenzel [58]	1985	P	Para-aortic	–	–	–	–	10	1	2	20	–	–	–	–
Wenzel [58]	1985	P	Pelvic	–	–	–	–	10	3	6	11	–	–	–	–
Choi [59]	2006	R	Pelvic and para-aortic	–	–	–	–	–	–	–	–	12	24	3	346
Choi [59]	2006	N	Pelvic and para-aortic	–	–	–	–	–	–	–	–	15	47	17	1,830
Rose [60]	1999	P	Para-aortic	11	0	0	5	–	–	–	–	–	–	–	–
Kim [61]	1994	P	Pelvic	–	–	–	–	–	–	–	–	23	2	14	223
Yeh [6]	2002	P	Pelvic	10	2	1	29	–	–	–	–	–	–	–	–
Havrilesky [62]	2003	P	Para-aortic	12	2	2	13	–	–	–	–	–	–	–	–
Yildirim [63]	2008	R	Pelvic	2	2	2	10	–	–	–	–	–	–	–	–
Kitajima [64]	2009	P	Pelvic and para-aortic	6	3	6	30	–	–	–	–	–	–	–	–
Kitajima [64]	2009	R	Para-aortic	11	2	11	729	–	–	–	–	–	–	–	–
Kitajima [64]	2009	R	Pelvic	12	2	11	1,198	–	–	–	–	–	–	–	–
Chung [4]	2009	P	Pelvic	7	1	10	16	–	–	–	–	–	–	–	–
Chung [4]	2009	R	Pelvic	12	2	21	169	–	–	–	–	–	–	–	–
Sandvik [65]	2011	P	Pelvic	1	3	4	28	–	–	–	–	–	–	–	–
Lin [66]	2008	N	Pelvic	–	–	–	–	–	–	–	–	4	22	22	990
Lin [66]	2008	R	Pelvic	–	–	–	–	–	–	–	–	3	4	9	284
Lin [66]	2008	P	Pelvic	–	–	–	–	–	–	–	–	2	2	5	41

Appendix 2. Summary of the information of included studies on DWI for detecting LNs metastases in cervical cancer patients

First author	Year	Location	Parameters	TP	FP	FN	TN
Kim [67]	2011	N	LD	57	264	13	346
Kim [67]	2011	N	Mean ADC	58	143	12	467
Kim [67]	2011	N	SD	64	216	6	394
Choi [68]	2009	N	LD	86	110	32	111
Choi [68]	2009	N	Mean ADC	101	45	17	176
Choi [68]	2009	N	SD	65	36	53	185
Chen [69]	2009	N	Mean ADC	55	22	11	65
Chen [69]	2009	N	Mean RADC	53	24	13	63
Chen [69]	2009	N	SD	39	25	27	62
Liu [70]	2011	N	LD	43	48	3	94
Liu [70]	2011	N	Mean ADC	41	13	5	129
Liu [70]	2011	N	Mean RADC	39	13	7	129
Liu [70]	2011	N	SD	35	21	11	121
Kim [70]	2008	N	Mean ADC	26	48	4	176
Lin [66]	2008	N	Mean ADC	23	126	3	886
Lin [66]	2008	N	Mean RADC	26	109	0	903
Xue [71]	2008	N	Mean ADC	16	6	0	60

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