F-FDG-PET and PET/CT as a diagnostic method for Ewing sarcoma: a systematic review and meta-analysis.

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**Abbreviations Table**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>$^{18}$F</td>
<td>18 Fluorine</td>
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<tr>
<td>$^{18}$F-FDG</td>
<td>18 fluorine-fluorodeoxyglucose</td>
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<tr>
<td>BMB</td>
<td>bone marrow biopsy</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>CT</td>
<td>computed tomography</td>
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<td>DOR</td>
<td>diagnostic odds ratio</td>
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<td>ES</td>
<td>Ewing Sarcoma</td>
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<td>FDG</td>
<td>fluorodeoxyglucose</td>
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<td>FP</td>
<td>false positive</td>
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<td>HL</td>
<td>Hodgkin Lymphoma</td>
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<td>$I^2$</td>
<td>$I$ square</td>
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<tr>
<td>IV</td>
<td>intravenous</td>
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<tr>
<td>MBq</td>
<td>mega Bequerel</td>
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<td>mCi</td>
<td>milli Curie</td>
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<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
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<tr>
<td>NHL</td>
<td>Non-Hodgkin Lymphoma</td>
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<tr>
<td>NLR</td>
<td>negative likelihood ratio</td>
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<td>NPV</td>
<td>negative predictive value</td>
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<td>PET</td>
<td>positron emission tomography</td>
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<td>PLR</td>
<td>positive likelihood ratio</td>
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Abstract

Purpose: The aim of this study was to evaluate the diagnostic accuracy of $^{18}$-fluorodeoxyglucose-positron emission tomography ($^{18}$F-FDG-PET) and positron emission tomography/computed tomography (PET/CT) in imaging primary and metastatic lesions in Ewing sarcoma (ES).

Methods: PubMed, Cochrane, Scopus, and Web of Science were searched for relevant studies. Data concerning $^{18}$F-FDG-PET/CT diagnostic accuracy were
extracted and then analysed using Open Meta-analyst software. Reported diagnostic accuracy outcomes included sensitivity, specificity, negative likelihood ratio (NLR), positive likelihood ratio (PLR), and diagnostic odds ratio.

Results: 31 studies with a total of 735 patients were included in this meta-analysis. The sensitivity and specificity of $^{18}$F-FDG PET/CT were: 92.6% and 74.1% for total ES lesions, 96.7% and 68.3% for ES primary lesions, 76.1% and 92.4% for lung metastasis, 88.9% and 93.2% for bone metastasis and 89.9% and 92.6% for ES recurrence respectively.

Conclusion: $^{18}$F-FDG PET/CT is sensitive and accurate in diagnosing, staging, and detecting the recurrence of ES compared to non-PET imaging. It has high accuracy for diagnosing recurrence of ES in bone metastases however CT remains a superior diagnostic method for detecting lung metastasis.

Keywords: $^{18}$F-FDG PET; PET/CT; diagnostic accuracy, Ewing sarcoma; meta-analysis; metastasis; recurrence.
Introduction

Ewing sarcoma (ES) is a family of tumours that includes skeletal, extraskeletal, and primitive neuroectodermal tumours of soft tissues [1]. ES and osteosarcoma are the most common primary bone tumours in humans [2]; ES being the second most frequent bone tumour in children and adolescents [3]. The annual incidence of ES is 2.93 per 1,000,000 children [4]. ES is an aggressive cancer with a relatively poor prognosis associated with a high rate of distant metastasis at first presentation. Accurate establishment of initial disease extent is the most crucial factor for determining prognosis and guiding management in ES patients [5-6].

Neoadjuvant chemotherapy is standard treatment for ES, generally followed by surgery, radiotherapy, or a combination of both local treatment modalities, depending on the local, regional, and systemic extent of disease [7]. First line chemotherapy regimens for ES generally include vincristine, doxorubicin, ifosfamide, and etoposide. Protocols also commonly include cyclophosphamide and may contain dactinomycin. [6]. Radiotherapy can be effectively used to attain local disease control. However, ES is only moderately radiosensitive and doses in the range of 45-55.8Gy are required for durable local disease control [8]. Surgery is usually preferred to radiotherapy for younger patients with lesions in “dispensable bones”, including rib, fibula, and smaller lesions of the hands or feet [9]. For smaller tumours, after induction chemotherapy, either radiotherapy or surgery may be sufficient. For more unfavourable tumours, trimodal therapy with chemotherapy, radiation therapy, and surgery may be preferred [10].

At the time of initial evaluation of patients with ES, accurate staging of disease, including detection of distant metastasis is vital for optimum treatment
planning and direction of therapy [11]. Early detection of distant failure and accurate restaging will help plan the most effective salvage therapies. According to the National Comprehensive Cancer Network guidelines, recommended conventional imaging investigations for the staging of ES include chest radiography, bone scan (using technetium-based technique $^{99m}$Tc-MDP), bone marrow biopsy, and conventional imaging techniques including non-contrast computed tomography (NCCT) and magnetic resonance imaging (MRI) [12]. In practice, the most frequently used method for detecting osseous disease is $^{99m}$Tc-MDP bone scanning [13]. Compared to structural imaging tools (such as radiographs, CT, MRI, and bone marrow biopsy), $^{99m}$Tc-MDP can detect skeletal metastases before they become apparent on these less sensitive modalities [14].

$^{18}$F-fluorodeoxyglucose positron emission tomography/ computed tomography ($^{18}$F-FDG PET/CT) is a promising imaging technique for ES diagnosis, staging, and follow-up, through accurate characterisation of local and systemic disease [15]. This modality can accurately image metabolically active cancers because $^{18}$F-FDG shows greater uptake in tumour lesions than in adjacent healthy tissues [16]. PET imaging can provide accurate incremental information to supplement conventional imaging modalities and, in some situations, may replace them. $^{18}$F-FDG PET/CT appears to be both more sensitive and more specific than bone scanning in ES for detecting osseous metastases, because the high FDG uptake in ES lesions compared to normal bone enables visualisation of bone metastases even before the development of the osteoblastic host response that is required for a positive radionuclide bone scan [15].
Several clinical trials have provided useful data on the relative accuracy of $^{18}$F-FDG PET/CT in patients with ES. We conducted a meta-analysis of those trials to evaluate the diagnostic accuracy of $^{18}$F-FDG-PET and PET/CT in imaging primary and metastatic lesions in ES. It is hoped that pooled data on the accuracy of $^{18}$F-FDG PET and PET/CT in the diagnosis, staging, and post-treatment monitoring of ES will prove useful to clinicians in future practice.
Material and Methods

While conducting and drafting this systematic review and meta-analysis we followed the steps described in the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy Studies (PRISMA-DTA)” statement [17]. The protocol of this meta-analysis was published online at the PROSPERO International Prospective Register of Systematic Reviews under registration number (CRD42021242559).

Literature search

We collected data for this review by searching four electronic databases: PubMed, Cochrane, Scopus, and Web of Science, up to March 2021. We used the following keywords in our search: "18F-FDG-PET," "18F-FDG," "PET/CT," "PET-CT," "PET," "positron emission tomography," "Ewing sarcoma," AND "Ewing tumour". Following retrieval of the search results, duplicates were removed using Endnote software, and titles and abstracts were screened. The full texts of the remaining studies after the title and abstract screening were retrieved and screened according to our eligibility criteria. We also searched the bibliography of included studies for further relevant studies.

Inclusion and exclusion criteria

We included trials investigating the diagnostic role of $^{18}$F-FDG PET/CT in the staging and diagnosis of ES in comparison with conventional imaging studies. The study selection had no restrictions regarding language, date of publication, age, sex, or location. Both prospective and retrospective trials were included. When more than one study reported results of the same population, we included the most complete
dataset of results. Studies investigating PET-MRI, reviews, books, chapters, letters, editorials, abstracts, conference papers, non-English articles, animal studies, and studies not reporting sensitivity and specificity of outcomes were excluded.

**Data extraction**

Related data that were extracted from the included studies involved the following domains: 1) summary of the included studies, 2) demographic and pathological characteristics of the studies’ population, and 3) outcomes for the diagnostic accuracy, including true positive, false positive, true negative and false negative data. All review authors contributed to the data extraction.

**Quality assessment**

We used a revised tool for the quality assessment of diagnostic accuracy studies (QUADAS-2), to assess the quality of included studies [18]. The QUADAS-2 tool includes the risk of bias and applicability concerns of the following items: 1) patient selection, including three risk of bias domains: random or consecutive sampling, case-control design avoidance, and inappropriate exclusions avoidance; 2) index test, including two risk of bias domains: blinding of the reference standard results during index test results interpretation, and pre-specification of the used threshold if present; 3) reference standard, including two risk of bias domains: the correct classification of the target condition by the reference standard, and blinding of the index test results during reference standard results interpretation 4) flow and timing, including three risk of bias domains: the appropriate interval between index test and reference standard, including all patients in the analysis, and all patients receiving the same reference standard. Each risk of bias item was judged as low,
high, or unclear risk of bias, and each applicability concern item was judged as low, high, or unclear concern.

**Statistical analysis**

We conducted all analyses using Open Meta-Analyst software. For $^{18}$F-FDG PET/CT diagnostic accuracy assessment, we calculated its sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) with 95% confidence intervals (CIs). In a Summary Receiver Operating Characteristic (SROC) curve, the sensitivity was plotted on the Y-axis and 1-specificity plotted on the X-axis. We pooled the results of included studies using the DerSimonian-Laird method under the random-effects model. For assessment of heterogeneity across pooled studies, we used Chi-square and I-square tests. Significant heterogeneity was considered whenever the Chi-square $P$-value was less than 0.1 and $I^2$ was more than 50%. We conducted the analyses for these outcomes on the total sample. We analysed the diagnostic accuracy outcomes for primary ES lesion, lung metastasis, bone metastasis, lymph node metastasis, ES recurrence, and total ES lesions.
Results

Literature search results

Electronic database searching retrieved a total of 759 unique records. After the screening of titles and abstracts, then of the full texts of these records, 31 studies eligible for our meta-analysis were included in the final analysis. Fig. 1 summarises the flow of the study inclusion and exclusion process.

Characteristics of included studies and their population

Included studies comprised a total of 735 patients. The median patients' age in included studies ranged from 10.5 to 28.4 years. Most studies used PET/CT imaging rather than PET alone. Only three of the included studies had a prospective rather than retrospective design [21-23], and four studies included patients with ES family of tumours rather than ES of the bone [23-26]. Supporting Information Table S1 summarises the characters of the included studies, and Supporting Information Table S2 shows the diagnostic accuracy data of each study.

Quality assessment

Overall, the included studies were of a low risk of bias and applicability concerns. When assessing risk for bias domains, patient selection and reference standard achieved a low risk of bias in most studies. The index test risk of bias was unclear, and the flow and timing domain achieved a high risk of bias across most studies. After evaluation of applicability concerns, patient selection and reference standard achieved a low risk, however, the index test was unclear in about half of the studies. Fig. 2 shows the judgment of quality assessment domains in each study.
Diagnostic accuracy outcomes

Sensitivity

The overall sensitivity of $^{18}$F-FDG PET/CT for the diagnosis of ES was 92.6%; 95% CI [83.6, 96.9], $P < 0.001$ (Fig. 3). Pooled results were heterogeneous ($P < 0.001$, $I^2 = 66.9\%$). Sensitivity for the diagnosis of the primary lesion was 96.7%; 95% CI [92.2, 98.6], $P < 0.001$ (Fig. 4). Pooled results for the primary lesion were homogenous ($P = 0.995$, $I^2 = 0\%$). Sensitivity for diagnosing lymph node metastasis was 79.3%; 95% CI [58.7, 91.2], $P = 0.008$ (Fig. 5). Pooled results for nodal involvement were homogenous ($P = 0.989$, $I^2 = 0\%$). Sensitivity for diagnosis of lung metastasis was 76.1%; 95% CI [61.4, 86.5], $P = 0.001$ (Supporting Information Figure 1). Pooled results for lung metastasis were homogenous ($P = 0.85$, $I^2 = 0\%$). Sensitivity for the diagnosis of bone metastasis was 83.9%; 95% CI [70.5, 91.9], $P < 0.001$ (Supporting Information Figure 2). Pooled results were heterogeneous for lung metastases ($P = 0.01$, $I^2 = 55.7\%$). Sensitivity for diagnosis of ES recurrence was 89.9%; 95% CI [79.9, 95.3], $P < 0.001$ (Supporting Information Figure 3) and pooled results were again homogenous ($P = 0.999$, $I^2 = 0\%$).

Specificity

The overall specificity of $^{18}$F-FDG PET/CT for the diagnosis of ES was 74.1%; 95% CI [43.7, 91.4], $P = 0.115$ (Fig. 3). Pooled results were heterogeneous ($P < 0.001$, $I^2 = 85.3\%$). Specificity for diagnosis of the primary lesion was 68.3%; 95% CI [44.0, 85.6], $P = 0.136$ (Fig. 4) and pooled results were homogenous ($P = 0.726$, $I^2 = 0\%$). Specificity for diagnosing lymph node metastasis was 97.9%; 95% CI [93.5, 99.3], $P < 0.001$ (Fig. 5) and pooled results were homogenous ($P = 0.891$, $I^2 = 0\%$).
Specificity for the diagnosis of lung metastasis was 92.4%; 95% CI [86.3, 95.9], \( P < 0.001 \) (Supporting Information Figure 1) and pooled results were homogenous (\( P = 0.85, \hat{I}^2 = 0% \)). Specificity for the diagnosis of bone metastasis was 93.2%; 95% CI [86.9, 96.6], \( P < 0.001 \) (Supporting Information Figure 2) and pooled results were homogenous (\( P = 0.172, \hat{I}^2 = 27.8\% \)). Sensitivity for the diagnosis of ES recurrence was 92.6%; 95% CI [82.6, 97.0], \( P < 0.001 \) (Supporting Information Figure 3) and pooled results were again homogenous (\( P = 0.962, \hat{I}^2 = 0\% \)). The SROC curves for total, primary lesion, lymph node metastasis, lung metastasis, bone metastasis, and ES recurrence are shown in Fig. 6.

**Positive likelihood ratio**

The pooled PLR of \(^{18}\)F-FDG PET/CT for diagnosis of ES was 3.567; 95% CI [1.713, 7.427], \( P < 0.001 \) and pooled results were heterogeneous (\( P < 0.001, \hat{I}^2 = 84.6\% \)). The PLR for diagnosis of primary lesion was 1.955; 95% CI [1.183, 3.229], \( P = 0.009 \) and pooled results were homogenous (\( P = 0.788, \hat{I}^2 = 0\% \)). The PLR for diagnosing lymph node metastasis was 36.438; 95% CI [11.640, 114.058], \( P < 0.001 \) and pooled results were homogenous (\( P = 0.907, \hat{I}^2 = 0\% \)). The PLR for diagnosis of lung metastasis was 9.377; 95% CI [4.866, 18.072], \( P < 0.001 \) and pooled results were homogenous (\( P = 0.293, \hat{I}^2 = 16.8\% \)). The PLR for diagnosis of bone metastasis was 11.495; 95% CI [8.850, 22.587], \( P < 0.001 \) and pooled results were homogenous (\( P = 0.156, \hat{I}^2 = 29.6\% \)). The PLR for diagnosis of ES recurrence was 11.851; 95% CI [4.863, 28.882], \( P < 0.001 \) and pooled results were again homogenous (\( P = 0.964, \hat{I}^2 = 0\% \)). Figures showing the forest plots for the PLRs are included in the Supporting Information Figures 4-9.

**Negative likelihood ratio**

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The pooled NLR of $^{18}$F-FDG PET/CT for diagnosis of ES was 0.136; 95% CI [0.094, 0.198], $P < 0.001$. Pooled results were homogenous ($P < 0.099$, $I^2 = 34.6\%$). The NLR for diagnosis of primary lesion was 0.104; 95% CI [0.063, 0.172], $P < 0.001$. Pooled results were homogenous ($P = 0.437$, $I^2 = 0\%$). The NLR for diagnosing lymph node metastasis was 0.205; 95% CI [0.065, 0.641], $P = 0.006$ and pooled results were homogenous ($P = 0.998$, $I^2 = 0\%$). The NLR for diagnosis of lung metastasis was 0.285; 95% CI [0.167, 0.485], $P < 0.001$ and pooled results were homogenous ($P = 0.897$, $I^2 = 0\%$). The NLRs for diagnosis of bone metastasis was 0.09; 95% CI [0.052, 0.156], $P < 0.001$ and pooled results were homogenous ($P = 0.386$, $I^2 = 6.1\%$). The NLR for diagnosis of ES recurrence was 0.112; 95% CI [0.046, 0.273], $P < 0.001$, and pooled results were homogenous ($P = 0.999$, $I^2 = 0\%$). Figures showing the forest plots for the NLR are included in the Supporting Information Figures 4-9.

**Diagnostic odds ratio**

The overall DOR for the diagnosis of ES by $^{18}$F-FDG PET/CT was 30.007; 95% CI [17.198, 52.357], $P < 0.001$ and pooled results were homogenous ($P = 0.958$, $I^2 = 0\%$). The DOR for diagnosis of the primary tumour was 33.563; 95% CI [7.978, 141.202], $P < 0.001$ and pooled results were homogenous ($P = 0.999$, $I^2 = 0\%$). The DOR for diagnosing lymph node metastasis was 205.286; 95% CI [42.868, 983.082], $P < 0.001$ and pooled results were homogenous ($P = 0.968$, $I^2 = 0\%$). The DOR for diagnosing lung metastasis was 44.473; 95% CI [14.285, 138.451], $P < 0.001$ and pooled results were homogenous ($P = 0.262$, $I^2 = 21.5\%$). The DOR for diagnosing bone metastasis was 105.687; 95% CI [37.930, 294.484], $P < 0.001$ and pooled results were homogenous ($P = 0.268$, $I^2 = 17.9\%$). The DOR for diagnosing
ES recurrence was 109.976; 95% CI [30.655, 394.535], \( P < 0.001 \) and pooled results were homogenous \( (P = 0.992, \hat{I}^2 = 0\%) \). Figures showing the forest plots for the DORs are included in the Supporting Information Figures 10-15.
Discussion

This meta-analysis included 31 studies that evaluated the diagnostic accuracy of $^{18}$F-FDG PET/CT in ES patients. Our results revealed that $^{18}$F-FDG PET/CT has high sensitivity and specificity (92.6% and 74.1%, respectively) for the diagnosis of ES. $^{18}$F-FDG PET/CT also showed a high accuracy in the early detection of recurrence due to its ability to detect metabolic changes even before detection of any morphological changes apparent on x-rays or other conventional imaging modalities [27]. In addition, $^{18}$F-FDG PET/CT showed high sensitivity and specificity regarding ES metastasis to lymph nodes (79.3%, 97.9%, respectively) and bone (83.9%, 93.2%, respectively).

Our results indicated that $^{18}$F-FDG PET/CT was a highly effective method of diagnosing, staging and detecting recurrences in patients with ES. In particular, $^{18}$F-FDG PET/CT proved to be very sensitive and specific in the detection of recurrent bone lesions compared to other imaging techniques. Moreover, the area under the ROC curve demonstrates that $^{18}$F-FDG PET/CT is an accurate method for the detection of Ewing sarcoma family of tumours.

There are multiple available imaging methods for characterising ES, including MRI, chest CT, bone scintigraphy, $^{18}$F-FDG PET, and PET/CT. The optimal combination of imaging techniques for staging and restaging remains controversial. One significant advantage of $^{18}$F-FDG PET and PET/CT is the ability of a single whole-body scan to sensitively detect systematic metastasis in multiple non-CNS organs, thereby replacing several competing and typically less accurate modalities. In the current study, we performed further examination analyses evaluating the value of PET in the accurate diagnosis of metastatic disease in various anatomical sites.
Bone and bone marrow involvement is typically focal in ES and consequently less likely to be detected by routine “blind” biopsy of accessible marrow in the iliac bone. Ağcı-Küpeli et al. compared the diagnostic accuracy of $^{18}$F-FDG PET/CT with bone marrow biopsy (BMB) for bone marrow involvement (BMI) in patients with a range of malignancies. Their final analysis revealed a superiority of $^{18}$F-FDG PET/CT in the detection of marrow involvement in non-Hodgkin Lymphoma (NHL), Hodgkin Lymphoma (HL), ES, and Neuroblastoma (NB) [28]. Similarly, Chen et al. reported a higher sensitivity and specificity of $^{18}$F-FDG PET/CT than BMB in paediatric NHL patients (95%, 98% vs. 56%, 100%) [4]. Another study by Hassan et al. showed a higher accuracy of $^{18}$F-FDG PET/CT for diagnosing patients with HL [16]. This reducing role of BMB in the initial diagnosis of the previous types of childhood tumours suggested replacing it with $^{18}$F-FDG PET/CT in selected patients [28].

Despite recent advances in MRI, differentiating tumours from scar tissue remains a challenge, especially when tumours co-exist with the scar tissue [29, 30]. A previous trial by Franzius et al., compared $^{18}$F-FDG PET with other imaging modalities (bone scan, MRI, and thoracic CT), and showed that $^{18}$F-FDG PET/CT was accurate in the diagnosis of local and distant recurrence of ES [32]. $^{18}$F-FDG PET was especially beneficial because of its frequent ability to differentiate between the metabolically inactive scar tissue and active tumour [33]. $^{18}$F-FDG PET may also specify the best regions for biopsy in cases of suspected recurrence, avoiding metabolically inactive regions that would be uninformative [33]. Despite the relatively low sensitivity of MRI in detecting tumour in areas of scarring, it had a high contrast resolution; therefore, a hybrid PET/MRI could be of high diagnostic value in ES patients [34].
Another recent study by Saranovic et al. evaluated $^{18}$F-FDG PET/CT as a diagnostic and prognostic tool in ES and neuroectodermal tumours due to its high sensitivity (93.7 %), specificity (87.5 %), and accuracy (91.7 %) [35]. However, they reported two false-positive cases in patients diagnosed with $^{18}$F-FDG PET/CT. These cases were due to misinterpretation of accumulations of $^{18}$F-FDG in muscles six months after surgery [36]. Two false-negative cases were undetected due to the presence of micro-nodular lung changes < 7mm without sufficient tracer accumulation to give an interpretable signal [37]. Other studies by Cistaro et al. and Franzius et al. showed low sensitivity of $^{18}$F-FDG PET/CT in detecting pulmonary metastases due to their small size, the effects of movement, and partial volume effects [35, 39]. A recent study by Elhennawy et al. demonstrated that 12 out of 84 metastatic lung lesions were accurately detected by $^{18}$F-FDG PET/CT whilst 56 out of 84 were accurately detected by CT and MRI [40]. Therefore, a high-resolution CT remains a more sensitive modality for detecting early lung metastases currently and should continue to be used as an initial workup for suspected pulmonary metastases or used in tandem with $^{18}$F-FDG PET/CT.

A previous meta-analysis by Huang et al. stated that the DOR of $^{18}$F-FDG PET/CT reached 60.55 and 347.37 for the diagnosis of ES lung and bone metastasis, respectively [41]. Another meta-analysis by Treglia et al. included 13 studies with 342 patients with ES. The results showed that the sensitivity of FDG-PET and PET/CT was 96%, specificity was 92%, and area under the ROC curve was 0.97 [19]. In our own study, the DOR was 44.473 and 105.687 for lung and bone metastasis, respectively. Franzius et al. reported that $^{18}$F-FDG PET/CT was better in diagnosing bone metastasis relative to bone scintigraphy. $^{18}$F-FDG PET/CT had a sensitivity, specificity, and accuracy of 100%, 96%, and 97% versus 68%, 87%, and
82% for bone scintigraphy [42], suggesting that $^{18}$F-FDG PET/CT, when available, should replace bone scintigraphy.

In contrast, a previous trial found no difference in the sensitivity, specificity, PPV, and NPV between $^{18}$F-FDG PET/CT, technetium-based bone scintigraphy, and whole-body MRI in the diagnosis of ES and osteosarcoma skeletal metastases [20]. Follow-up imaging was constrained in that study for all patients due to the high cost of these imaging modalities [20]. Similar findings were corroborated by an earlier trial [43].

**Strengths and limitations**

The current meta-analysis included new studies up to 2021, including trials unavailable to previous meta-analyses, some with large study populations. We performed a comprehensive search using multiple electronic databases and used the QUADAS-2 to assess the quality of included studies. We pooled $^{18}$F-FDG PET/CT diagnostic parameters in ES for total ES, ES primary lesion, ES lung metastasis, ES bone metastasis, ES lymph node metastasis, and ES recurrence separately. Despite this fastidious approach, we acknowledge that the differing designs of the included studies could sometimes make comparisons difficult. Heterogeneity was detected between the included studies, reflecting different age groups (paediatric and adult populations) and therapeutic regimens. These data, while promising, require confirmation and future research in this area is very likely to be of benefit to patients.

**Conclusion**
In conclusion, our results showed that $^{18}$F-FDG PET/CT has high sensitivity for the diagnosis of ES, especially for initial assessment of the primary lesion and for detecting recurrence. Our findings were consistent with current literature in showing that $^{18}$F-FDG PET/CT has a high specificity in diagnosing ES recurrence and a high accuracy in staging lymph node and bone metastases. Thus, $^{18}$F-FDG PET/CT should be considered a vital component of diagnostic workup when developing future treatment protocols for ES. For lung metastasis our $^{18}$F-FDG PET/CT results were in contention with some research, indicating that $^{18}$F-FDG PET would best be utilised alongside diagnostic CT rather than in isolation. Inclusion of PET is very likely to improve accuracy of staging, detection of early treatment unresponsiveness, and early diagnosis of relapse in patients with ED, thereby improving overall management and patient outcomes.
Declaration

None.

Acknowledgment

None

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.
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**Figure legends**

Fig. 1: The PRISMA flow chart showing the flow of the study selection process.
Fig. 2: The risk of bias summary showing the judgment of each quality assessment domain in included studies.

Records identified through database searching (n = 759)

Records after exclusion of duplicates (n = 738)

Records screened (n = 738)

Records excluded (n = 694)

Full-text articles assessed for eligibility (n = 44)

Full-text articles excluded, with reasons (n = 13)
  Overlapped datasets (2)
  Different population (8)
  Lack of study outcomes (3)

Studies included in quantitative synthesis (meta-analysis) (n = 31)

Fig. 3: Forest plot of the total sensitivity and specificity results of $^{18}$F-fluorodeoxyglucose positron emission tomography/CT ($^{18}$F-FDG PET/CT) in diagnosing Ewing sarcoma.
Fig. 4: Forest plot of the sensitivity and specificity of $^{18}$F-FDG PET/CT in diagnosing Ewing sarcoma primary lesion.

Fig. 5: Forest plot of the sensitivity and specificity of $^{18}$F-FDG PET/CT in diagnosing Ewing sarcoma lymph node spread.
Fig. 6: SROC curve for the overall accuracy of $^{18}$F-FDG PET/CT in diagnosing A) Ewing sarcoma, B) Ewing sarcoma lymph node spread, C) Ewing sarcoma primary lesions, D) Ewing sarcoma lung metastasis, E) Ewing sarcoma bone metastasis, F) Ewing sarcoma recurrence.