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The Evolving Role of FDG-PET/CT in the Management of Cervical Cancer

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Abstract

With the advancement of imaging technologies, the application of ^{18}F-FDG PET/CT in the diagnosis and management of cervical cancer has garnered increasing attention. This article aims to review the clinical progress of PET/CT in the management of patients with cervical cancer. PET/CT has been widely used to assess lymph node status and distant metastases, and it is recommended for comprehensive staging in patients with locally advanced cervical cancer (FIGO stage ≥ IB3), enabling more rational planning and individualized treatment adjustments. Metabolic information from both the primary tumor and lymph nodes can be utilized for treatment response evaluation, prognosis prediction, and recurrence monitoring, ultimately helping to optimize the timing of interventions and improve survival outcomes. Meanwhile, the distribution of ^{18}F-FDG uptake within the tumor can partially reflect tumor heterogeneity and provide complementary information to conventional semi-quantitative parameters. However, the clinical value of PET/CT in the management of patients with cervical cancer remains to be further validated.

Keywords

Cervical Cancer, ^{18}F-FDG PET/CT, Clinical Management

1. Introduction

Cervical cancer (CC) is one of the most common malignancies among women worldwide, with both incidence and mortality rates ranking high, posing a significant public health challenge, particularly in low-income countries [1]. Primary prevention of CC relies mainly on vaccination to prevent high-risk human papillomavirus (HPV) infections, thereby reducing the risk of disease. Meanwhile, secondary prevention strategies have been continuously improving. The implementation of HPV DNA testing has significantly enhanced the efficiency of early screening and intervention, thereby effectively preventing disease progression [2]. Despite ongoing improvements in prevention and screening measures, many patients in low-resource settings are still diagnosed at advanced stages. Therefore, more precise and timely staging is needed to guide subsequent treatment and management strategies [3]. The FIGO staging system is the most widely used standard for CC in clinical practice. Early versions relied mainly on clinical examination. In 2018, the system was updated to include lymph node status as well as imaging and pathological findings, bringing staging closer to clinical practice [4]-[6]. In this context, imaging modalities such as MRI, CT, and ^{18}F-FDG PET/CT have become important complements to staging assessment. Among them, PET/CT, with its ability to provide both metabolic and anatomical information as well as whole-body imaging, has demonstrated superior performance in identifying lymph node involvement (LNI) and distant metastases, providing valuable information for staging [2] [7]-[9]. Accurate staging is essential for treatment planning. Early-stage, localized tumors are usually treated with surgery, whereas locally advanced or large-volume tumors are primarily managed with concurrent chemoradiation (CCRT). Neoadjuvant chemotherapy (NACT) followed by surgery may also be considered a viable alternative [2] [10].

Nevertheless, precise staging is merely the first step in optimizing CC management. PET/CT enables the detection of metabolic alterations prior to anatomical or morphological changes, making it especially useful for the early evaluation of treatment response and identifying suspected recurrence. As imaging research advances, PET/CT is evolving from a purely visual modality into a multifunctional technique capable of quantifying tumor metabolism and characterizing clinically relevant biological behavior. Tumor ^{18}F-FDG uptake frequently demonstrates marked heterogeneity due to metabolic and microenvironmental factors [11]-[13]. While this heterogeneity is visually apparent on PET/CT images, its full extent and clinical implications are still being explored. Notably, tumor metabolic parameters, such as maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG), are closely associated with treatment response and prognosis in patients [14]-[16]. As radiomics has advanced, PET/CT-based radiomic analyses have given rise to a variety of quantitative metrics aimed at more accurately characterizing tumor heterogeneity and underlying biological features [17] [18].

Therefore, this review provides a systematic overview of the evolving roles of ^{18}F-FDG PET/CT in the management of CC, encompassing its applications in initial staging, detection of LNI and distant metastases, evaluation of treatment response and prognosis, recurrence surveillance, and characterization of tumor heterogeneity.

2. Staging

MRI offers excellent soft tissue contrast, enabling precise evaluation of tumor size and the extent of parametrial invasion. It has also been shown to have the highest agreement with pathological measurements, making pelvic MRI the preferred modality for local staging of CC [19] [20]. Evaluation of lymph node status is an essential part of CC staging. Evidence shows that LNI is closely linked to treatment decisions and prognosis, as patients with positive nodes generally show significantly lower 5-year survival than those with negative nodes [21]-[24]. Lymphatic spread in CC typically begins in the parametrial lymph nodes and subsequently involves pelvic lymph nodes, with the obturator nodes most frequently affected and considered the sentinel nodes. Further metastasis may extend to the common iliac and para-aortic lymph nodes [25]. Para-aortic LNI in CC usually arises following pelvic LNI, while isolated para-aortic metastasis is rare [26]-[28]. The risk of pelvic and para-aortic LNI is closely associated with tumor invasion depth, tumor size, and lymphovascular space invasion (LVSI), suggesting that patients with low-risk early-stage CC, especially those without LVSI, have a relatively low likelihood of LNI [26] [28] [29]. In addition, LNI in early-stage CC are often micrometastases with a diameter of less than 5 mm. Given the limited spatial resolution of PET/CT, such nodes are frequently difficult to detect, which reduces the sensitivity of PET/CT [30]. Therefore, PET/CT has a limited role in assessing lymph nodes in early-stage CC. As the disease progresses, the risk and burden of nodal and distant metastases increase, and lymph nodes become larger and more numerous, which enhances PET/CT detection. Hence, whole-body ^{18}F-FDG PET/CT remains recommended for patients with initial FIGO stage ≥ IB3 to evaluate nodal and distant metastases [2] [20] [31] [32].

PET/CT is currently widely regarded as the most effective imaging modality for assessing LNI in CC [20] [33]. Olthof *et al.* reported that ^{18}F-FDG PET/CT demonstrated markedly higher sensitivity for detecting LNI compared with MRI and CT (80% vs. 48% and 40%, respectively). Its specificity was 79%, slightly lower than that of MRI and CT (both 92%), but it achieved the highest positive predictive value (PPV) at 76%, compared with 66% for MRI and 64% for CT. The area under the curve (AUC) for the three modalities was 0.814, 0.706, and 0.667, respectively [8]. In a meta-analysis, Liu *et al.* demonstrated that PET/CT outperformed MRI and CT in sensitivity, specificity, and positive likelihood ratio for detecting LNI, with superior overall diagnostic performance [9]. This superiority is likely related to the imaging mechanism of PET/CT, which detects metabolic activity in tumors to reveal potential metastases, overcoming the limitations of CT and MRI that assess lymph nodes based solely on size or morphology. In CC, more than 80% of metastatic lymph nodes are smaller than 10 mm in diameter [34]. MRI and CT, when using a short-axis diameter of ≥1.0 cm to define lymph node positivity, may fail to detect smaller metastatic lesions [35]. Although lowering the short-axis threshold can improve sensitivity, specificity may consequently be compromised [36]. In contrast, PET/CT can effectively identify LNI with a short-axis diameter greater than 5 mm, demonstrating excellent diagnostic performance, with sensitivity and specificity reaching 100% and 99.6%, respectively [37]. Roh *et al.* reported that the overall sensitivity of PET/CT was 38%, increasing to 52% and 65%

for lymph nodes larger than 5 mm and 10 mm in diameter, respectively [38]. It is currently widely accepted that 5 mm represents the detection threshold for PET/CT examinations.

In locally advanced CC, active management of pelvic and para-aortic metastatic lymph nodes can improve survival, with para-aortic nodes being particularly critical. [2] [10] [39]-[42]. Adam *et al.* reported that PET/CT achieved an overall sensitivity and specificity of 0.88 (95%CI: 0.40 - 0.99) and 0.93 (95%CI: 0.85-0.97) for pelvic lymph nodes, whereas sensitivity declined to 0.40 (95% CI: 0.18-0.66) in the para-aortic region, with specificity remaining 0.93 (95% CI: 0.91-0.95) [43]. This may be due to the relatively low prevalence of para-aortic LNI, which are often micrometastases smaller than 5 mm and may thus limit the sensitivity of PET/CT [44] [45]. Further, Leblanc *et al.* demonstrated that PET/CT had a sensitivity of only 33.3% for detecting small LNI, whereas specificity remained high at 94.2%, indicating that PET/CT still provides an advantage in ruling out false-positive findings [46]. Despite significant improvements in PET/CT image quality with the introduction of technologies such as time-of-flight (TOF), the false-negative rate for detecting para-aortic LNI has remained largely unchanged [47]. While the accuracy of PET/CT for identifying para-aortic LNI remains debated, Gouy *et al.* noted that markedly increased uptake on PET/CT is highly indicative of metastasis and may obviate the need for surgical confirmation [48]. Nonetheless, negative findings should be approached with caution, as PET/CT remains insufficient to fully replace surgical lymph node staging [47] [49] [50].

Multiple international guidelines recommend PET/CT to assess LNI in CC and adjust treatment accordingly [10] [51]. PET/CT-detected positive lesions play an important role in guiding the definition of radiotherapy target volumes and the adjustment of radiation doses [51]-[53]. For patients with PET/CT-positive nodes, Vargo *et al.* reported that extended-field intensity-modulated radiation therapy (IMRT) with additional dose escalation to the involved nodes may improve local control [54]. Meanwhile, PET/CT-guided IMRT can reduce acute hematologic toxicity induced by chemoradiotherapy [55].

Although PET/MRI is more expensive and not yet widely adopted, evidence suggests that it offers higher sensitivity and specificity than PET/CT, MRI, or CT for detecting LNI, potentially enabling more accurate diagnosis. Its clinical potential, therefore, merits further exploration [56].

PET/CT offers simultaneous whole-body anatomical and functional imaging of ^{18}F-FDG uptake, permitting evaluation of disease beyond the local lesion. This provides a clear advantage in evaluating distant metastases, and PET/CT is regarded as the preferred modality [57]. A prospective multicenter study evaluated PET/CT findings in 153 patients with CC. They demonstrated that PET/CT exhibited high specificity (97.7%, 95% CI: 95.1 - 99.1) and a relatively high negative predictive value (NPV) (93.1%, 95% CI: 90.4 - 95.9) for detecting distant metastases, highlighting its important role in initial staging [58].

It should be noted that, in this review, diagnostic performance metrics were reported on either a per-patient or per-node basis across the included studies, contributing to methodological heterogeneity and potentially affecting comparability.

3. Prognosis

Growing evidence suggests that PET/CT is not only critical for staging and treatment planning in CC but also provides important prognostic information. Aggressive tumors generally exhibit higher metabolic activity, and PET/CT can identify metabolic abnormalities before structural changes occur by quantifying tumor ^{18}F-FDG uptake, thereby enabling more accurate prognostic evaluation [59]. With its high reproducibility, SUVmax is recognized as a reliable quantitative indicator of tumor ^{18}F-FDG uptake [60]. Meanwhile, the prognostic value of baseline SUVmax in patients with CC has been increasingly recognized. A study by Voglimacci *et al.* demonstrated that pre-treatment SUVmax is closely associated with overall survival (OS), supporting its use as a noninvasive prognostic biomarker in clinical evaluation [61]. Further studies revealed that patients with higher primary tumor SUVmax had significantly poorer outcomes. In patients with SUVmax <15.6, 4-year OS and disease-free survival (DFS) rates were 85% and 80%, respectively, compared with only 34% and 29% for those with SUVmax ≥15.6 (both $P < 0.001$) [62] [63]. In a large study involving 237 patients, Kidd *et al.* stratified patients into three prognostic groups based on SUVmax. The 5-year OS rates were 95% for those with SUVmax <5.2, approximately 70% for SUVmax 5.2 - 13.3, and just 44% for SUVmax >13.3 [64]. These findings support that higher tumor SUVmax (>13.3) is significantly associated with poorer prognosis, consistent with Voglimacci *et al* [61]. Overall, SUVmax appears to have potential value for clinical risk stratification. However, the proposed cutoffs are cohort- and protocol-dependent and should therefore be interpreted with caution. External validation and imaging protocol harmonization are required before clinical implementation.

In addition to ^{18}F-FDG uptake in the primary tumor, lymph node metabolism also reflects disease progression. A study including 560 patients with CC found that the incidence of LNI increased with advancing clinical stage, and patients with LNI had significantly worse survival outcomes compared with those without nodal involvement [26]. Onal *et al.* found that, in the overall cohort, pelvic lymph node SUVmax was closely associated with both OS and DFS. Patients with SUVmax <7.5 had significantly better OS and DFS than those with SUVmax ≥7.5. However, in the subgroup of patients with only pelvic LNI, SUVmax did not show independent predictive value. Notably, patients with pelvic lymph node SUVmax ≥7.5 were more likely to develop para-aortic LNI [65]. Sarker *et al.* conducted a meta-analysis demonstrating that higher SUVmax in pelvic or para-aortic lymph nodes was associated with a significantly increased risk of adverse events or death. The hazard ratio (HR) for mortality was 2.66 (95% CI: 1.60 - 4.43) for pelvic lymph nodes and 4.41 (95% CI: 2.32 - 8.38) for para-aortic lymph nodes (both $P < 0.001$) [62]. These findings indicate that PET/CT offers value beyond the detection of

LNI by providing metabolic information relevant to disease progression and prognosis.

SUVmax reflects the voxel with the highest metabolic activity but may not adequately represent the overall tumor metabolism due to intratumoral heterogeneity. Primary tumors with higher SUVmax are often larger in diameter or volume, which typically correlates with a worse prognosis [66] [67]. In contrast, volumetric parameters derived from PET/CT, such as MTV and TLG, integrate tumor size and metabolic distribution, enabling a more comprehensive assessment of the tumor's overall metabolic burden. Markus *et al.* reported that baseline MTV and TLG were closely associated with OS and recurrence, whereas SUVmax did not show similar prognostic significance. Notably, post-treatment PET parameters demonstrated stronger predictive value than baseline measurements [68]. A meta-analysis including 660 patients showed that high MTV and TLG were closely linked to an increased risk of adverse events or mortality [69]. Staniewska *et al.* stratified patients according to the median MTV and TLG values, revealing that those below the median had significantly longer OS ($p < 0.001$). Multivariate analysis further demonstrated that TLG was the only independent prognostic factor [70]. Although SUVmax is easy to calculate and observer-independent, volumetric PET parameters, including MTV and TLG, appear to provide superior prognostic value [68].

4. Response Assessment

CCRT remains the standard treatment for locally advanced CC [10]. Multiple studies have shown that abnormal ^{18}F-FDG uptake detected by PET/CT after treatment, whether persistent or newly appearing, reflects tumor response, highlighting its significant value in evaluating treatment efficacy [71] [72]. The NCCN guidelines recommend PET/CT for response assessment approximately 3 - 6 months after treatment completion. However, radiation-related inflammatory changes may lead to abnormal ^{18}F-FDG uptake and false-positive findings, complicating the selection of the optimal imaging time point [10]. According to the European Organization for Research and Treatment of Cancer (EORTC) criteria, post-treatment PET/CT categorizes patient responses as follows: complete metabolic response (CMR), with no ^{18}F-FDG uptake; partial metabolic response (PMR), SUVmax reduction >25%; stable metabolic disease (SMD), SUVmax change within ±25%; and progressive metabolic disease (PMD), SUVmax increase >25%, an increase in tumor uptake along the longest diameter by over 20%, or new lesions with ^{18}F-FDG uptake [73]. The Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) criteria, introduced by Wahl *et al.* in 2009, provide an updated PET/CT metabolic response assessment system based on the EORTC criteria. They further standardize the selection of metrics and the definition of thresholds, enhancing result consistency and cross-center comparability [74]. Solid tumor treatment response is still mainly assessed by anatomical criteria, whereas tumor size changes alone are insufficient to fully reflect therapeutic efficacy [75].

In lymphoma, residual scar tissue can restrict changes in tumor volume, even when treatment is effective [74] [76]. In some novel anticancer therapies, the inhibitory effect on tumor cells may outweigh direct cytotoxicity, such that even when tumor shrinkage is minimal, stable disease may still indicate meaningful clinical benefit [77]-[79]. Wahl *et al.* observed that tumor metabolic changes often precede measurable alterations in tumor size during effective treatment [80]. By overcoming the delays of anatomical imaging, PET functional imaging enables early treatment response assessment, guides therapy adjustments or, when necessary, salvage interventions, ultimately improving patient prognosis and survival.

Evidence indicates that post-treatment metabolic responses are closely linked to prognosis in CC. Notably, findings of metastatic progression or incomplete metabolic response on post-treatment PET/CT provide stronger predictive value for survival than pre-treatment tumor characteristics, including clinical stage and lymph node status [81]. Lima *et al.* evaluated treatment response in 82 patients with CC undergoing CCRT using the EORTC criteria. Their results showed that patients achieving a CMR after treatment had better OS compared with those with PMR, SMD, or PMD [15]. Yoon *et al.* reported that in patients with CC, PET/CT-based response assessment using EORTC criteria provides a more reliable prediction of survival than the Response Evaluation Criteria In Solid Tumours (RECIST) [82]. Evidence suggests that patients achieving a CMR after treatment generally have a favorable prognosis, while those with persistent or progressive disease tend to have poorer clinical outcomes in comparison [15] [71] [81]. However, Michaan *et al.* pointed out that residual ^{18}F-FDG uptake on early post-treatment PET/CT does not necessarily signify a poor prognosis. If subsequent PET/CT scans eventually show a CMR, patients' survival outcomes can be comparable to those who achieve CMR immediately after treatment. This may be because early ^{18}F-FDG uptake does not necessarily reflect residual tumor but may instead arise from prolonged inflammatory responses, suggesting that the tumor has been more effectively eradicated. In such cases, a strategy of follow-up PET/CT may be preferable, potentially sparing patients from unnecessary surgery or other invasive procedures [83].

PET/CT has been widely used to assess treatment response and predict prognosis. Lima *et al.* showed that pretreatment metabolic parameters, including MTV and TLG, allow early prediction of response to CCRT, with MTV providing the strongest predictive value. Patients with baseline positive lymph nodes were more likely to have an incomplete metabolic response after treatment [15]. Gill *et al.* retrospectively analyzed 90 patients with CC and found that baseline MTV and TLG were strong predictors of response to therapy in FIGO stage IB2-IIB disease [84]. Rufini *et al.* conducted a prospective study to evaluate the performance of PET/CT at baseline, during, and after treatment in predicting response to therapy in CC patients receiving NACT, using histopathology as the reference standard. The results showed that at early assessment, metabolic parameters had already declined relative to baseline in patients achieving pathological complete response, with the largest reductions seen in ΔSUVmax, ΔSUVmean, and ΔTLG. Moreover, higher pre-treatment SUV levels in these patients may indicate greater tumor cell sensitivity to CCRT [85]. These findings highlight that the clinical value of baseline and early PET/CT in CC requires further investigation.

5. Recurrence

CC recurrence risk has been shown to increase with FIGO stage, from approximately 11% - 22% in stage IB-IIA patients to 28% - 64% in stage IIB-IVA patients [86]. Recurrence typically indicates poor long-term prognosis, and early detection of recurrence may provide an opportunity for clinical interventions to improve survival [87]-[89]. Occult recurrence may occur in a subset of asymptomatic patients, with lesions usually small and confined to a few sites (oligometastatic) [90] [91]. Palma *et al.* demonstrated that for patients with limited oligometastatic lesions, comprehensive eradication of all recurrent sites may achieve curative outcomes and effectively improve survival [92]. PET/CT enables whole-body imaging in a single session, providing simultaneous metabolic and anatomical information, allowing for early detection of recurrence and distant metastases. Comparison of patients with recurrence and those without showed significant differences in 5-year progression-free survival (PFS) and OS. In PET/CT-negative patients, PFS and OS were 98.62% and 99.31%, respectively, whereas in PET/CT-positive patients, they were 17.83% and 85.38% (PFS: $p < 0.0001$; OS: $p = 0.0015$) [93]. Targeted interventions in patients with recurrence identified by PET/CT extended survival by nearly two years, suggesting the potential role of PET/CT in managing recurrent CC [90].

Mittra *et al.* reported that PET/CT performs well in detecting both local recurrence and distant metastases, with sensitivity, specificity, accuracy, PPV, and NPV of 93%, 93%, 93%, 86%, and 96% for local recurrence, and 96%, 95%, 95%, 96%, and 95% for distant metastases. Moreover, adjusting treatment based on PET/CT results was shown to significantly improve patient outcomes [94]. Multiple studies suggest that PET/CT provides important supplementary imaging in patients with suspected tumor recurrence when MRI or CT findings are equivocal. [10] [95] [96]. In a study of 84 CC patients with suspected post-radiotherapy recurrence, Stojiljkovic *et al.* found that PET/CT outperformed MRI in sensitivity (97.6% vs 80.1%), specificity (61.9% vs 52.4%), and accuracy (79.8% vs 66.7%) [97]. This may be because recurrent lesions after radiotherapy are often difficult to distinguish from treatment-related changes on imaging, and the metabolic information provided by PET/CT can serve as an additional reference, helping to improve diagnostic accuracy. A prospective study by Lai *et al.* showed that PET detected metastatic lesions with 92% (95% CI: 80 - 98) sensitivity, far exceeding the 60% (95% CI: 45 - 74) observed with CT/MRI, demonstrating its superior detection performance [98]. In a study of 126 patients, Yen *et al.* reported that PET/CT led to additional clinical benefit in 73.8% of cases (93/126) compared with CT/MRI, by correcting approximately 74% of false-negative and 26% of false-positive findings.

They emphasized that PET/CT offers clear advantages over CT/MRI in evaluating recurrent CC, not only by detecting extrapelvic metastases but also by demonstrating superior sensitivity and specificity [99]. Evidence increasingly supports incorporating PET/CT into the evaluation of recurrent CC. By providing metabolic information, PET/CT enhances diagnostic accuracy and guides treatment decisions, ultimately optimizing patient management and improving outcomes.

6. Pitfalls and Interpretation

^{18}F-FDG uptake reflects cellular glucose metabolism. Malignant tumors are metabolically active and therefore typically show increased ^{18}F-FDG uptake. However, ^{18}F-FDG uptake is not specific to tumors, as it can also occur in normal tissues and benign lesions. Awareness of common pitfalls in PET/CT interpretation is therefore crucial for enhancing diagnostic accuracy. The most frequent cause of false-positive findings is ^{18}F-FDG accumulation in areas of infection or inflammation [100]. Treatment-related factors, such as postoperative wounds or radiation-induced inflammatory reactions, can also lead to false-positive findings, potentially masking the tumor's ^{18}F-FDG uptake in nearby tissues. Guidelines recommend performing PET/CT approximately 3 - 6 months after treatment completion to minimize the impact of these factors on imaging results [10]. Some tumors with low metabolic activity or weak affinity for ^{18}F-FDG often exhibit minimal uptake, which may result in false-negative findings [101]. The limited spatial resolution of PET can cause underestimation of ^{18}F-FDG uptake in small lesions due to partial volume effects, thereby increasing the likelihood of false-negative findings [102]. CT scans not only serve for attenuation correction but also provide high-resolution anatomical information. Integrating local metabolic activity with the corresponding anatomical structures enables a more comprehensive assessment of lesions, thereby reducing the risk of misdiagnosis and missed lesions [103].

7. Evaluation of Intratumoral Heterogeneity

Tumor heterogeneity is a fundamental feature of cancer, evolving across different stages of tumor progression and coexisting across distinct spatial regions within the tumor, resulting in marked biological differences among cell populations at different locations or time points [104]-[108]. Tumor heterogeneity is closely linked to tumor aggressiveness and resistance to therapy. Inadequate consideration of resistance-related heterogeneity may allow resistant cells to escape treatment, ultimately resulting in treatment failure [104] [109]. Therefore, accurately characterizing heterogeneity is crucial for improving patient outcomes. However, a biopsy typically captures only localized heterogeneity and is usually limited to a single anatomical site [110]. PET/CT enables noninvasive evaluation of global tumor glucose metabolism, making it possible to assess intratumoral heterogeneity across the entire tumor.

Parameters such as SUVmax and TLG are widely used to quantify tumor activity, but they mainly reflect either the peak local uptake or the overall burden, making it difficult to characterize the spatial distribution of metabolism within the malignancy. In recent years, several metrics have been introduced to quantitatively capture the complex spatial characteristics of tumors. By analyzing voxel gray level distribution and spatial arrangement, texture analysis can extract subtle quantitative features from PET/CT images, which may serve as novel imaging biomarkers [111]. Evidence suggests that radiomic features can reflect heterogeneity at the cell level and may hold potential for evaluating LNI, treatment response, and prognosis in cancer [112]-[114]. Li *et al.* reported that the PET/CT texture feature, skewness, can predict LNI in patients with early-stage CC. Predictive accuracy can be further enhanced by combining it with vascular endothelial growth factor expression [17]. Chen *et al.* conducted a retrospective analysis of 142 patients with CC and found that high gray-level run emphasis (HGRE) could reliably predict pelvic residual disease and recurrence risk following CCRT. Lower HGRE values were associated with shorter OS, PFS, and pelvic recurrence-free survival, suggesting that HGRE may serve as an indicator of prognosis [18]. It should be noted that radiomic features are highly influenced by image acquisition parameters, reconstruction methods, and processing approaches; therefore, the quality and robustness of these features directly affect their reproducibility and clinical applicability [115]. Leithner *et al.* demonstrated that ComBat harmonization can reduce inter-scanner variability, thereby improving tissue classification accuracy. They recommended incorporating ComBat harmonization as a preprocessing step in radiomics studies to enhance the generalizability of the results [116].

However, due to the limited interpretability of these features, their clinical application remains restricted, prompting the search for more direct indicators of tumor heterogeneity. Kidd *et al.* explored tumor heterogeneity in terms of overall metabolic distribution by examining how metabolic volume changes across different SUV thresholds, which may overlook the local spatial characteristics of active regions [117]. Study has shown that the spatial positions of metabolically active regions within tumors are not static during growth, but instead undergo a dynamic shift from the core toward the periphery, which is associated with aggressiveness and changes in biological behavior [118]. Against this background, Hovhannisyan-Baghdasarian *et al.* assessed tumor spatial heterogeneity by quantifying the normalized distances from metabolic hotspots to the tumor centroid (NHOC) and to the tumor periphery (NHOP). And their results revealed that, compared with conventional parameters, NHOC and NHOP are more robust, potentially facilitating their clinical application. Moreover, these parameters are closely associated with prognosis: patients with poorer outcomes tend to exhibit higher NHOC and lower NHOP [119]. Hong *et al.* indicated that NHOC and NHOP are linked to tumor aggressiveness and simultaneously provide independent predictive value for breast cancer patients' response to NACT [120].

8. Conclusion

In patients with CC staged ≥ IB3, ^{18}F-FDG PET/CT provides a more comprehensive evaluation of lymph node and distant metastases, supplementing conventional clinical assessment. This additional information can guide treatment planning and individualization, potentially reducing unnecessary therapy-related risks. The metabolic information from PET/CT is essential for evaluating treatment response and prognosis, as well as monitoring recurrence in CC. Identifying patients unlikely to benefit from therapy or at high risk of poor outcomes, it can help inform the optimal timing of clinical interventions to improve survival. The spatial distribution of tumor metabolism on PET/CT partially reflects tumor heterogeneity, allowing deeper insights into tumor biology and offering novel quantitative measures, which complement traditional semi-quantitative parameters. However, the clinical value of PET/CT in the management of CC still requires further investigation and validation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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