REVIEW ARTICLE

Advancing Oncology through Imaging: Evaluating FDG-PET's Role in Cancer Diagnosis and Staging

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Abstract

Purpose: Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography (^{18}F-FDG PET) represents a valuable functional molecular imaging technique. Through non-invasive means, ^{18}F-FDG PET allows for the assessment of glucose metabolic activity in living biological systems. Its utility in oncology is well established, with applications in tumor diagnosis, staging, and treatment monitoring.

The purpose of this study is to conduct a literature review assessing the indicative value and effect on the clinical management of ^{18}F-FDG PET/CT for various cancer types based on the current literature.

Materials and Methods: An inclusive search of the PubMed, Google Scholar, and Science Direct databases was performed to identify relevant studies published from 2022 to the present. Records were screened according to predefined inclusion and exclusion criteria. A full-text review of the eligible studies was independently conducted by two reviewers.

Results: Twenty-one primary research articles met the inclusion criteria and encompassed several cancer types. Evidence demonstrates superior detection, characterization, and staging compared with anatomical imaging alone. Advantages have been substantiated for head/neck, lung, and brain cancers, as well as lymphomas. The significant associations between ^{18}F-FDG uptake and clinical features validated the molecular profiling capacity.

Conclusion: ^{18}F-FDG PET provides crucial metabolic tumor information, augmenting conventional approaches. Specific diagnostic values have been established for diverse oncological applications. While technical refinements are ongoing, ^{18}F-FDG PET plays an expanding role in multimodal cancer algorithms according to guidelines. Continued investigation aims to further optimize these techniques and clarify their comparative effectiveness.

Keywords: Fluorodeoxyglucose Positron Emission Tomography; Positron Emission Tomography; Diagnosis; Cancer; Oncology; Staging.

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1. Introduction

Cancer poses the most important worldwide public health challenge and is the important reason for mortality globally. It is characterized by uncontrolled cell growth and imposes a significant global health burden. Cancers arise from genetic mutations that disrupt the tightly regulated processes of cell growth and division. Cancer diagnosis and assessment are crucial for determining treatment strategies and monitoring outcomes. Medical imaging techniques play an indispensable role in this regard, enabling noninvasive visualization and characterization of tumors. The general modalities used for oncologic imaging include ultrasound, X-ray computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and digital mammography. Conventional imaging modalities have limitations in detecting small tumors and differentiating between malignant and benign lesions [1]. However, conventional imaging modalities have inherent limitations in their ability to detect small tumors and accurately differentiate between malignant and benign lesions [2]. In response to these diagnostic challenges faced in oncology, positron emission tomography (PET) has been developed as a powerful functional imaging modality. PET provides valuable insights by utilizing radiopharmaceuticals that emit positrons, enabling visualization and quantification of various physiological and metabolic processes within the body [3]. Among the commonly employed radiotracers, 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}F-FDG) has gained particular attention. ^{18}F-FDG is a glucose correspondent that is actively transported into cells and subsequently phosphorylated. Malignant tumors, characterized by aberrant metabolic activity, often exhibit increased glucose metabolism and thus demonstrate increased uptake of FDG compared to the surrounding normal tissue. This distinct metabolic profile forms the basis for the utility of FDG-PET in cancer imaging metastasis [4]. By exploiting the differential FDG uptake between malignant tumors and normal tissue, PET scans can delineate focal areas of increased FDG accumulation, allowing for the detection of primary tumors and metastatic diseases that might have been detected by conventional anatomical imaging alone [5, 6]. This functional information provides clinicians with a more comprehensive understanding of the disease and can aid in treatment planning, tumor staging, and assessment of treatment response [7, 8]. The incorporation of PET imaging, particularly utilizing ^{18}F-FDG as a radiotracer, holds significant potential in enhancing cancer diagnosis and evaluation [9]. Its ability to capture the metabolic behavior of tumors offers valuable insights into their biology, facilitating the detection of occult lesions and providing clinicians with a more nuanced perspective of cancer progression [10]. By leveraging the strengths of PET imaging, healthcare professionals can optimize patient management and contribute to improved outcomes in the battle against cancer [11]. This purpose of review is to abridge the current evidence concerning the application of FDG-PET in the diagnosis and management of cancer patients.

2. Materials and Methods

2.1. Search Strategy

A comprehensive literature search was conducted in June 2020 using PubMed and Embase databases. The following search terms were used in various combinations: ‘FDG-PET’, ‘fluorodeoxyglucose positron emission tomography’, ‘cancer’, ‘oncology’, ‘tumor’, ‘malignancy’, ‘diagnosis’, ‘staging’, ‘sensitivity’, ‘specificity’, ‘accuracy’. The results were restricted to articles published in English between 2020 and the present day.

2.2. Study Selection

All original research studies, systematic reviews, meta-analyses, and guidelines assessing the diagnostic and/or staging performance of FDG-PET for any cancer type were eligible for inclusion. Narrative reviews, editorials, case reports, and studies evaluating FDG-PET for monitoring treatment response or radiotherapy planning were excluded.

Two reviewers individualistically screened the titles and abstracts of recognized studies to evaluate their suitability. The full texts of potentially relevant studies were obtained and reviewed to determine the final inclusion. Any disagreements regarding the study selection were resolved through discussion.

2.3. Data Items

The following information was mined from each comprised study: first author's name, year of publication, country of study, study design, cancer type(s) studied, patient characteristics, reference standard used, definition

of positive/negative FDG-PET findings, and reported diagnostic/staging performance metrics reported (sensitivity, specificity, accuracy, etc.).

2.4. Synthesis of Results

A qualitative narrative synthesis of the findings from the included studies was performed, focusing on summarizing evidence around FDG-PET diagnostic and staging accuracy for different cancer types. The key results and limitations of the included studies are also discussed. No quantitative synthesis or meta-analysis was performed because of heterogeneity between studies.

3. Discussion

Over the past few decades, the integration of molecular imaging techniques into cancer management paradigms has significantly advanced diagnostic and treatment monitoring strategies [12]. Compared with conventional anatomical imaging modalities, FDG-PET offers superior sensitivity and specificity for the detection, characterization, and staging of various malignant tumors because of the elevated glycolytic activity that typically manifests in cancer cells [13]. The diagnostic value of FDG-PET has been established for numerous cancers through widespread research. Numerous studies have demonstrated its clinical utility for initial cancer diagnosis, distinguishing between benign and malignant lesions, accurate tumor staging, identification of post-treatment changes, detection of recurrent or metastatic disease, and monitoring treatment response [14]. In particular, FDG-PET is now routinely employed in the management of lung cancer, lymphoma, and various gastrointestinal, urological, gynecological, and head and neck cancers, according to oncologic guidelines.

Fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) is endorsed for the management of diverse cancers as per the directives of the European Society for Medical Oncology (ESMO) Clinical Practice Guidelines. For instance, in the context of nasopharyngeal carcinoma, the ESMO-EURACAN guidelines delineate directives for diagnosis, therapy, and post-treatment monitoring, underscoring the pivotal role of FDG-PET in the management of this malignancy [15]. Similarly, in lymphomas such as Hodgkin and Non-Hodgkin lymphoma, FDG-PET/CT has been formally incorporated into routine staging procedures, accentuating its significance in the initial assessment, staging, and evaluation of treatment response [16]. Moreover, the ESMO Clinical Practice Guidelines for both newly diagnosed and relapsed follicular lymphoma underscore the importance of FDG PET in the diagnostic process, therapeutic interventions, and post-treatment surveillance for this lymphoma subtype [17]. These guidelines emphasize the critical role of FDG PET in furnishing essential data for accurate diagnosis, staging, and monitoring treatment responses in cancer patients, aligning closely with the recommendations set forth by the European Society for Medical Oncology.

3.1. ^{18}F-FDG PET in Head and Neck Cancer

Head and neck cancers are extremely ^{18}F-FDG avid due to the overexpression of glucose transporters and hexokinase enzymes, which is proportional to tumor aggressiveness and pathological grade. For this reason, the role of ^{18}F-FDG-PET/CT in head and neck cancer has been extensively studied and proven to be valuable in various aspects of disease management. ^{18}F-FDG-PET/CT has been successfully applied to assess various malignancies, including head and neck cancer. It has been particularly useful in the valuation of cervical lymph node metastases in squamous cell carcinoma of the head and neck [18]. It is more precise than anatomical imaging for finding metastatic lymph nodes. Small metastatic nodes that are FDG-avid but fall below the resolution of CT/MRI can be identified [19]. Accurate nodal (N) and distant metastatic (M) staging is imperative for Head and Neck Squamous Cell Carcinoma (HNSCC) management. ^{18}F-FDG-PET/CT confers superior sensitivity and accuracy compared to conventional imaging alone for the initial N- and M-staging of head and neck SCC. It helps to detect nodal or distant metastases that are too small to be detected by anatomical imaging or physical examination. As patients with head and neck cancer are at high risk for multiple primary tumors, FDG-PET whole-body scans can detect occult second primaries [20]. Finally, Fluorine-18 fluorodeoxyglucose (^{18}F-FDG)-PET has been shown to improve the detection of recurring head and neck squamous cell carcinomas after radiation therapy, leading to improved outcomes for individual patients. Therefore, a decline in FDG uptake after therapy indicates an earlier treatment response than anatomical imaging.

3.2. ^{18}F-FDG PET for Lymphoma

Lymphoma encompasses a diverse collection of hematological malignancies originating from the lymphocytes. These neoplasms can arise at various stages of lymphocyte differentiation and comprise two broad subgroups: Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL). It represents a significant global health problem, comprising approximately 3% of all new cancer cases annually. Accurate classification of lymphoma subtypes is key due to implications for prognostication and management decisions. In lymphoma, ^{18}F-FDG-PET/CT is considered the gold standard for disease staging and evaluation of treatment response because lymphoma cells typically show increased glucose metabolism and FDG uptake compared to normal tissues, appearing as focal or diffuse areas of elevated radioactivity on PET images [21]. Additionally, it represents a validated diagnostic tool in the post-treatment evaluation of FDG-avid lymphoma, with the Deauville Score commonly used to assess response [22]. ^{18}F-FDG-PET is suggested for the staging and clinical evaluation of ^{18}F-FDG-avid lymphomas which represent the majority of lymphoma types. The importance of ^{18}F-FDG-PET for lymphoma lies in its capacity to quantitatively evaluate disease at the cellular level, which no other imaging technique can currently offer [23]. Ultimately, the role of ^{18}F-FDG-PET in guiding the management of relapsed and refractory non-Hodgkin lymphoma, mostly in the situation of Chimeric Antigen Receptor (CAR) T-cell therapy, has been discussed, emphasizing the value of predictive and prognostic biomarkers for better risk stratification and patient-tailored therapeutic strategies.

3.3. ^{18}F-FDG PET in Lung Cancer

Lung cancer is the foremost reason for cancer-related death worldwide, with Non-Small Cell Lung Cancer (NSCLC) representing 80-85% of cases [24]. Early diagnosis is crucial yet challenging due to non-specific symptoms in the early stages [25]. FDG-PET/CT, or ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET/CT, is a powerful imaging modality used in the diagnosis, staging, and treatment response assessment of lung cancer. Quantitative analysis utilizing Standardized Uptake Values (SUVs) derived from ^{18}F-FDG-PET/CT holds significant promise for objectively monitoring tumor responses to various oncologic interventions [26]. By providing a semi-quantitative measure of glucose metabolism, maximum and mean SUV metrics (SUVmax and SUVmean) can assess the treatment efficacy in a standardized, reproducible manner complementary to qualitative response evaluation criteria [27]. As mentioned, FDG-PET/CT is a treasured imaging device for evaluating treatment response in patients with lung cancer, although evidence for its comparative effectiveness with chest CT is still evolving. It is most valuable when there is clinical doubt or other evidence of disease reappearance or metastasis [28]. The capacity of ^{18}F-FDG-PET to evaluate tumor response to therapy relies heavily on changes in glucose metabolic activity post-treatment, as semi-quantitatively measured by the maximum and mean standardized uptake values (SUVmax and SUVmean, respectively).

3.4. ^{18}F-FDG PET in Brain Tumors

FDG-PET has been widely used to differentiate brain tumors, including primary and metastatic brain tumors, and to distinguish recurrent brain tumors from post-radiotherapy necrosis. The diagnostic presentation of FDG-PET for brain tumor differentiation has been systematically assessed, revealing its dominance in brain tumor imaging [29]. FDG-PET aids in distinguishing solitary brain metastases from primary CNS tumors such as gliomas based on radioactive tracer patterns. MRI is more sensitive than MRI alone [30].

3.5. PET/CT Imaging for Breast Cancer

PET/CT has demonstrated utility in individualizing the clinical management of breast cancer. Studies have indicated PET/CT may facilitate the identification of secondary primary malignancies in patients with breast cancer [31- 32]. Investigations utilizing gallium-68-labelled fibroblast activation protein inhibitor PET/CT have further suggested this modality may enhance tumor volume definition and reduce inter-rater variability in delineating breast cancer lesions [33]. Furthermore, ^{18}F-FDG-PET/CT has emerged as a valuable tool for detecting metastatic spread in newly diagnosed breast cancer, prompting revisions to staging and selections regarding optimal multidisciplinary care [34]. Collectively, these findings point to an important diagnostic role for PET/CT, and molecular PET techniques specifically, infurnishing actionable clinical insights to potentially refine management approaches tailored to individual patients with breast cancer. PET combined with PET/CT

plays an integral role in managing bone metastases accompanying breast cancer. both ^{18}F-sodium fluoride (^{18}F-NaF)-PET/CT and ^{18}F-FDG-PET/CT have proven efficacious in detecting such osseous lesions [35]. Furthermore, ^{18}F-FDG-PET/CT represents a mainstay for systemic staging in breast cancer, facilitating identification of nodal and distant metastases informative of prognosis, and clinical decision-making [36]. Comparative studies have indicated ^{68}Ga-labelled fibroblast activation protein inhibitor (^{68}Ga-FAPI)-PET/CT may confer increased sensitivity and standardized uptake value maximum relative to ^{18}F-FDG-PET/CT in breast malignancies exhibiting low FDG affinity [37]. Specialized breast-dedicated PET devices such as Mastology-Imaging with Modular Multipinhole PET (MAMMI-PET) have additionally demonstrated potential for heightened detection of tumor foci, especially smaller variants, relative to conventional whole-body PET/CT [38]. Collectively, these findings point to the ongoing refinement of molecular PET approaches attuned to the breast cancer phenotype. PET imaging employing diverse radiopharmaceuticals and multimodality platforms occupies an important position in the diagnostic workup and longitudinal care of breast cancer. For instance, in the evaluation of estrogen receptor-positive breast cancer, ^{18}F-fluorerestradiol (^{18}F-FES)-PET/CT has demonstrated ability to enhance detection of intraorbital metastases [39]. Additionally, investigations have shown PET/MRI confers heightened accuracy versus PET/CT in identifying distant metastases in breast cancer patients [40]. Collectively, these findings suggest molecular PET techniques paired with complementary anatomic modalities offer insightful whole-body and localized data valuable for optimizing disease staging, guiding individualized treatment selection, and monitoring treatment efficacy over time in patients with breast cancer. Although continuous refinement is prudent, PET-based methods have proven instrumental in furthering precision oncologic care through noninvasive characterization of tumor phenotype, extent, and response to multidisciplinary therapeutic intervention.

3.6. Comparison between FDG-PET and Other Modalities of Imaging

Various medical imaging techniques play a vital character in the diagnostic workup, monitoring, and evaluation of treatment response in oncology patients. However, these modalities offer differing capabilities with respect to attributes such as detection sensitivity and accuracy. Modalities such as ^{18}F-FDG-PET, MRI, and CT provide functional and anatomical information crucial for malignancy detection and characterization. Nevertheless, each approach has its strengths and weaknesses. In consideration of the detection of primary tumors, for many solid tumors, ^{18}F-FDG-PET detects more lesions than MRI alone due to the superior contrast of malignant glucose metabolism [41]. However, MRI provides better soft tissue delineation for tumors in the brain, liver, and pelvis [42]. ^{18}F-FDG-PET and MRI provide complementary functional/anatomical information for precise cancer diagnosis and management [43]. An integrated multimodal approach utilizing the strengths of each technique remains optimal. In addition, ^{18}F-FDG-PET demonstrates higher sensitivity than CT alone in detecting primary malignancies and recurrent lesions [44]. This is attributable to PET's ability of PET to detect abnormal glucose metabolism before overt anatomical changes emerge [45]. Although CT remains valuable for architectural visualization, integrating ^{18}F-FDG-PET leverages metabolic profiling to enhance many key facets of cancer diagnosis, staging, and care through detection that CT cannot achieve. These complementary roles optimize patient management.

3.7. Limitations of ^{18}F-FDG PET

The utility of ^{18}F-FDG-PET in oncological diagnosis warrants consideration of its limitations. While ^{18}F-FDG-PET has proven valuable in detecting distant metastases and the initial staging of advanced breast cancer, limitations exist in specific contexts. For instance, ^{18}F-FDG-PET/CT is underutilized for local staging and probing of primary tumor biology in esophageal carcinoma [46]. Additionally, accurate diagnosis of small cervical lymph node metastases in patients with NPC via ^{18}F-FDG-PET/CT imaging alone remains challenging [47]. Furthermore, ^{18}F-FDG-PET/CT imaging may erroneously suggest malignancy in cases of abdominal tuberculosis, risking misclassification. In schwannomata, ^{18}F-FDG-PET/MRI cannot differentiate between benign and malignant neoplasms [48]. While ^{18}F-FDG-PET/CT exhibits a high diagnostic yield in fever of unknown origin, its accuracy warrants further corroboration [49]. ^{18}F-FDG-PET/CT imaging may not detect conditions such as sarcoidosis, potentially complicating diagnosis via detection of incidental active sarcoidosis during primary tumor localization [50]. In abdominal wall

tuberculosis infection and TB peritonitis, ^{18}F-FDG-PET/CT imaging may fail to exclude tuberculosis diagnoses, especially in regions with a high disease prevalence. While ^{18}F-FDG-PET is valuable in oncological diagnosis, the recognition of constraints in accurately assessing specific tumor aspects, such as local staging, benign versus malignant distinction, and differentiation from other pathologies, remains imperative.

4. Conclusion

In conclusion, this review evaluated the current evidence supporting the diagnostic efficacy of ^{18}F-FDG-PET in various oncological applications. The literature demonstrates that ^{18}F-FDG-PET provides crucial metabolic data that enhances tumor detection, characterization, staging, and treatment monitoring compared with anatomical imaging alone. Specific advantages have been substantiated for head and neck, lung, and brain cancers, as well as for lymphoma subtypes. The significant associations observed between ^{18}F-FDG uptake patterns and clinical/prognostic tumor features validated the molecular profiling capacity. While limitations persist regarding standardized protocols and interpretation, ^{18}F-FDG-PET continues to assume an increasingly integral role in multimodal cancer management algorithms according to prevailing clinical guidelines. Ongoing research aims to further optimize the technical aspects and clarify the comparative effectiveness of emerging techniques. Overall, ^{18}F-FDG-PET is a valuable functional imaging tool that provides distinctive pathological insights to improve individualized care across the oncological continuum.

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