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PET-CT in children: where is it appropriate?

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Abstract

The use of PET/PET-CT is a rapidly growing area of imaging and research in the care of children. Until recently, diagnostic imaging methods have provided either anatomical or functional assessment. The development of fused imaging modalities, such as PET-CT or PET-MRI, now provides the opportunity for simultaneously providing both anatomical and functional or physiological assessment. This review will discuss current established uses of PET-CT, possible uses and potential research investigations in the use of this modality in the pediatric population. The focus of this paper will be its use in children being treated for non-central nervous system and non-cardiac disorders.

Keywords

PET-CT; Pediatric cancer; Infection; ^{18}F-FDG PET

Introduction

The use of PET and PET-CT in adults has been well established for oncological purposes. However, this is a new and rapidly growing area of imaging and research in the care of children. Until recently, diagnostic imaging methods have provided either anatomical or functional assessment. The development of fused imaging modalities, such as PET-CT and PET-MRI, now provides the opportunity for simultaneously providing both anatomical and functional or physiological assessment.

This review will discuss established uses of PET-CT, possible uses, potential research investigations, and ongoing questions regarding the use of this modality in the pediatric population and will focus on children being treated for non-central nervous system and non-cardiac disorders.

Established uses in pediatric oncology

^{18}F-FDG PET/PET-CT has been shown to provide useful information in evaluating a wide variety of pediatric tumors [1–5]. In a modest cohort of pediatric oncology patients, Wegner

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et al. [3] reported that PET-CT changed the management of malignant diseases in 24% of cases and was reported to be useful in disease assessment in 75%.

Lymphoma

Value similar to that established in adult Hodgkin lymphoma and non-Hodgkin lymphoma is being shown in pediatric cases [6–8]. The use of PET/PET-CT is particularly helpful in the initial staging of and in monitoring response to therapy in pediatric lymphoma.

Sarcoma

As with lymphomas, accurate staging, monitoring of disease response to therapy and detection of recurrent disease are critical components of oncological therapy. ^{18}F-FDG-PET/PET-CT has been shown to contribute to all of these aspects in children diagnosed with soft-tissue and bone sarcomas [4, 9]. Further, there is evidence to suggest that tumor activity shown by ^{18}F-FDG-PET/PET-CT and its change in response to therapy may be predictive of outcomes [10–14].

Other tumors

PET-CT is proving to be useful in the evaluation of neuroblastoma [4, 5, 8, 15, 16] and Wilms tumor [2, 17–21]. At least in the case of Wilms tumor, preliminary experience suggests that the intensity of metabolic activity seems to correlate with the degree of histological differentiation [18, 19].

In each of these malignancies, ^{18}F-FDG-PET/PET-CT may contribute significantly to disease management and even provide opportunity for modification and minimization of treatment effect (such as in radiation treatment planning) when utilized at diagnosis for disease staging, during therapy to assess response to treatment, and off-therapy to serve both as an overall indicator of disease response and provide baseline assessment for future surveillance studies. Certainly in the diagnosis and treatment of active disease, the role of ^{18}F-FDG-PET/PET-CT has been shown to be extremely valuable in the care of children as it is in the care of adults. However, because of children's sensitivity to ionizing radiation exposure—and in children with cancer, repeated exposures are expected—the impact of ionizing radiation as a potential long-term toxicity is paramount in the design of clinical protocols incorporating PET/PET-CT. Thus, the use of surveillance or off-therapy monitoring needs to be considered in the context of the individual disease, likelihood of recurrence, and salvage rates of recurrent disease that may not be detected in its early stages.

Regardless of the treatment phase during which ^{18}F-FDG-PET/PET-CT is utilized, the development of new sites of metabolic activity are a concern for recurrent or progressive disease. This is particularly true with the development of pulmonary nodules that may be benign or malignant. Currently, pulmonary lesions that are hypermetabolic are typically considered to more likely be malignant than benign [17]. In such cases, PET-CT is able to direct lesions for biopsy to determine histopathologically between benignity and malignancy. Problematic, however, is the limited resolution of ^{18}F-FDG-PET/PET-CT compared to standard diagnostic CT. Many pulmonary metastases are millimetric in size and therefore fall below the resolution of PET-CT [14, 20, 22]. Thus, fusion images of PET-CT

provide superior diagnostic information compared to CT alone in predicting benignity versus malignancy in lung lesions [23]. Demonstration of metabolic activity also may direct surgical planning and impact the decision as to whether surgical resection is warranted [3].

^{18}F-FDG-PET/PET-CT provides important information for planning radiation therapy portals [24]. By incorporating metabolic activity demonstrated by ^{18}F-FDG-PET/PET-CT into the radiation therapy planning schema, targeting and selection of radiation dose is based on metabolic activity in addition to tumor size. The use of PET/PET-CT allows improvement of tumor delineation and targeted regions while concurrently providing for treatment modification based on response to preceding chemotherapy. As an example, Hodgkin disease in the pediatric population is approached with multi-modality management that involves oncological therapy, radiology for imaging, and radiation oncology for determination of sites and volume of radiation therapy. ^{18}F-FDG-PET allows refined treatment planning for radiation therapy, thereby obviating unnecessary exposure of metabolically inactive sites of disease. This approach improves constraints on tissue exposure, minimizing toxicity and allowing for increased targeted dose to persistently metabolically active sites of disease [24].

Benign disease

Determination of metabolic activity indicative of active as opposed to inactive disease is also important in monitoring and treating benign diseases such as Langerhans cell histiocytosis (LCH) [17, 25–27] and neurofibromatosis [17].

Langerhans cell histiocytosis

Langerhans cell histiocytosis (LCH) has historically been evaluated using radiographic skeletal survey and ^{99m}technetium bone scan to determine presence, absence and change in lesions of LCH [25, 28]. With the incorporation of PET-CT into the armamentarium for monitoring pediatric patients with LCH, the degree of metabolic activity has been found to serve as a valuable indicator that is more sensitive than skeletal survey for identifying active lesions [25, 27, 29]. For patients receiving chemotherapy for LCH, protocol-driven response assessments determine the frequency and timing of imaging. The long-term utility of LCH monitoring using ^{18}F-FDG-PET/PET-CT has yet to be fully established.

Neurofibromatosis type 1

Published experience with PET/PET-CT in cases of neurofibromatosis type 1 (NF1) lesions indicates that this modality provides information regarding metabolic activity within these lesions. An effective method for determining malignant degeneration of such lesions into malignant peripheral nerve sheath tumors (MPNST) is needed. Clinically, lesions that may be painful or increase in size are worrisome for malignant degeneration [30]. Assessment of metabolic activity in these lesions using ^{18}F-FDG-PET/PET-CT provides important information regarding the potential for malignant degeneration and further, may direct the site warranting biopsy or surgical resection [30, 31]. Bredella et al. [30] reported FDG-PET to have high sensitivity, specificity, positive and negative predictive values, and accuracy in detecting malignant degeneration of NF1 lesions (95%, 72%, 71%, 95%, and 82%,

respectively). The value of standard uptake value (SUV) in predicting outcome is inconsistent [31, 32].

Other potential uses for ^{18}F-FDG-PET/PET-CT

Infection and inflammatory conditions

Nonmalignant processes such as infections and other inflammatory processes are associated with hypermetabolic glucose metabolism. Thus, there exists the potential for ^{18}F-FDG-PET/PET-CT to contribute valuable information. Preliminary studies indicate a role for ^{18}F-FDG-PET/PET-CT in the care of patients with chronic diseases and unidentified sources of infection [33–39].

In cystic fibrosis (CF), focal areas of hypermetabolic activity with an SUV in excess of 3.0 were found during exacerbations of CF and infection. These areas of increased metabolic activity resolved with appropriate therapy while corresponding CT abnormalities persisted [40]. Similar utility has been reported in cases of sarcoidosis [41].

^{18}F-FDG-PET may also be useful for diagnosing both acute and chronic musculoskeletal infections. It may be particularly helpful in patients who have undergone limb-sparing procedures and in whom infection or disease recurrence is suspected as the presence of a metallic prosthesis may limit imaging by both MRI and CT [33, 42, 43].

Inflammatory diseases, such as Takayasu arteritis, have also been shown in rare reports to be metabolically active when assessed by ^{18}F-FDG-PET/PET-CT [44, 45]. Similarly, inflammatory changes associated with Crohn's disease has prompted investigation into the utility of ^{18}F-FDG-PET/PET-CT enterography [46, 47], but the results are thus far inconsistent. Groshar et al. [46] reported a significantly increased maximum SUV in abnormal bowel segments (5.0 +/− 2.5 [95% confidence interval, 4.5–5.5] compared with normal segments 2.1 +/− 0.69 [95% confidence interval, 1.9–2.2; P<0.0001]). They also found that the maximum SUV differed significantly by degree of disease involvement depicted by CT enterography (P<0.00001) [46]. In contrast, Ahmadi et al. [47] found that though CT enterography scores correlated with SUV values, not all abnormal small bowel segments were identified. Those segments that failed to accumulate ^{18}F-FDG were associated with failure of medical therapy [47].

ALARA considerations in pediatric PET/PET-CT imaging

As with all imaging studies that expose a patient to ionizing radiation, ALARA principles should be followed. As PET-CT represents a form of hybrid imaging, parameters reflecting both the nuclear medicine and the CT aspects of this modality need to be considered as exposures are cumulative [48]. Factors that can be adjusted to control patient exposures include the dose of radiopharmaceutical administered, the frequency of PET/PET-CT imaging, use of diagnostic CT techniques versus attenuation CT techniques, anatomic areas of imaging coverage.

Recommendations for administered radiopharmaceutical activity in children and adolescents take into account patient size and sensitivity of pediatric tissues to ionizing radiation [49,

50]. One report indicates that, based upon 0.14 mCi/kg administered dose, the effective dose from 18F-FDG may range from 50 mSv in a 1-year-old patient to 8.6 mSv in a 15-year-old [51]. Further reduction of dose compared with adult dosing may be considered; in some cases, lengthening of imaging time may be required to obtain a diagnostic quality study [51]. Certainly, the frequency of scanning with PET/PET-CT contributes to the overall cumulative exposure to ionizing radiation. Imaging should coincide with the phase of treatment that best demonstrates disease response to therapy and/or the need for restaging.

CT-related exposure parameters also contribute to the overall patient exposure to ionizing radiation and vary considerably depending upon the techniques used [51–54]. A CT of the neck, chest, abdomen and pelvis using standard diagnostic techniques has been reported to range from 10 to 16 mSV for a single study [51]. Guidelines for optimization of CT techniques for pediatric patients are beyond the scope of this paper but are readily available through the Image Gently™ website [55]. Use of CT for localization and co-registration of PET images may allow reduction of CT technique by 50 to 65% [51]. Further reduction of CT-related exposures to as low as 3% of diagnostic scans, can be achieved in cases where CT is used for attenuation correction only [51, 54]. With the ongoing technologic evolution of PET-CT scanners, CT parameters may be adjusted to optimize the quality and type of information needed for a given anatomic area within the PET-CT study.

Conclusion

Certainly, ^{18}F-FDG-PET/PET-CT has a growing role in the evaluation of pediatric oncology patients. Its value in predicting long-term outcomes is not completely understood. Its sensitivity for detecting metabolically active sites is not limited to malignant diseases. The role of ^{18}F-FDG-PET/PET-CT in identifying nonmalignant processes and monitoring response to therapy has yet to be fully investigated.

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