

The clinical impact of ^{18}F -FDG PET/CT in extracranial pediatric germ cell tumors

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Abstract

Background Extracranial germ cell tumors are an uncommon pediatric malignancy with limited information on the clinical impact of ^{18}F -fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in the literature. **Objective** The purpose of this study was to evaluate and compare the clinical impact on management of ^{18}F -FDG PET/CT with diagnostic computed tomography (CT) in pediatric extracranial germ cell tumor.

Materials and methods The list of ^{18}F -FDG PET/CT performed for extracranial germ cell tumor between May 2007 and November 2015 was obtained from the nuclear medicine database. ^{18}F -FDG PET/CT and concurrent diagnostic CT were obtained and independently reviewed. Additionally, the patients' charts were reviewed for duration of follow-up and biopsy when available. The impact of ^{18}F -FDG PET/CT compared with diagnostic CT on staging and patient management was demonstrated by chart review, imaging findings and follow-up studies.

Results During the study period, 9 children (5 males and 4 females; age range: 1.6–17 years, mode age: 14 years) had 11 ^{18}F -FDG PET/CT studies for the evaluation of germ cell tumor. Diagnostic CTs were available for comparison in 8 patients (10 ^{18}F -FDG PET/CT studies). The average interval between diagnostic CT and PET/CT was 7.2 days (range: 0–37 days). In total, five lesions concerning for active malignancy were identified on

diagnostic CT while seven were identified on PET/CT. Overall, ^{18}F -FDG PET/CT resulted in a change in management in 3 of the 9 patients (33%).

Conclusion ^{18}F -FDG PET/CT had a significant impact on the management of pediatric germ cell tumors in this retrospective study. Continued multicenter studies are required secondary to the rarity of this tumor to demonstrate the benefit of ^{18}F -FDG PET/CT in particular clinical scenarios.

Keywords Children · Computed tomography · Germ cell tumors · Outcome · Positron emission tomography · ^{18}F -fluorodeoxyglucose

Introduction

Extracranial germ cell tumors are an uncommon pediatric malignancy. They account for approximately 3% of childhood cancers in children younger than 15 and 14% of cancers in adolescents ages 15–19 [1, 2]. Extracranial germ cell tumors can be classified as gonadal or extragonadal with most extragonadal germ cell tumors occurring at midline sites (i.e. sacrococcygeal, mediastinal or retroperitoneal) [3, 4]. As a group, these lesions demonstrate a heterogeneous clinical course. While most mature teratomas have a relatively benign course (except in cases of malignant transformation of the mature cystic types), the prognosis of immature teratomas and malignant germ cell tumors significantly varies depending on patient age, clinical stage and dominant histology [1–6].

In the evaluation of pediatric germ cell tumors, diagnostic computed tomography (CT) and magnetic resonance imaging (MRI) are frequently used at different time points in patient management. The regions imaged frequently include CT scan of the primary site and chest and MRI of the primary site [3]. Previous studies in children have shown a possible role of ^{18}F -

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fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) in the staging, documenting treatment response and restaging of germ cell tumors, among a larger cohort of pediatric tumors [7, 8]. However, these previous studies included only two [7] and three children [8] with germ cell tumors, respectively. Previous studies in germ cell tumors in adults have demonstrated mixed findings at different time points of the disease process and still have a questionable role [9].

The purpose of this study was to retrospectively evaluate the clinical impact of ^{18}F -FDG PET/CT in the management of pediatric germ cell tumors and to compare it with diagnostic CT in our pediatric patient population.

Materials and methods

Patients

The study was approved by our Institutional Research Ethics Board and waiver for individual consent was granted. We retrospectively reviewed ^{18}F -FDG PET/CT performed from May 1, 2007, to Nov. 30, 2015, in pediatric patients with biopsy-proven germ cell tumor at a tertiary care pediatric institution and identified the clinical indication.

Imaging

As in a previous study at our institution [10], all PET/CT examinations were performed according to the standard clinical protocol of our institution using a (16-multidetector CT) PET/CT hybrid scanner (Gemini GXL; Philips Healthcare, Cleveland, OH, USA). Weight, height and blood glucose concentrations were recorded for all patients. All patients had blood glucose levels <11 mMol/L before radiotracer administration. Image acquisition for the whole-body PET scan started approximately 60 min after injection of 5.18 MBq/kg (0.14 mCi/kg) ^{18}F -FDG, at doses ranging from 37 MBq (1 mCi) to 370 MBq (10 mCi). Patients were imaged from skull base to mid thighs (3 min per bed position, with an average of 7–10 bed positions per scan). Patients who had recently undergone diagnostic CT scans were imaged using a reduced dose helical CT scan (5 mm/slice, 90 kVP; 20 and 30 mAS for patients weighing <30 and ≥ 30 kg, respectively) prior to the PET scan for attenuation correction and anatomical localization. Diagnostic CT scans were obtained when clinically indicated and when patients had not undergone a recent CT scan. In those cases, the attenuation correction was calculated based on the correlative diagnostic CT images (5-mm slice, 120 kV, and a weight-based range for the mA, with a maximum of 200 mA with dose modulation). The PET images were reconstructed using the iterative method of line of response (line of response row action maximum-likelihood algorithm or 3-D row action maximum-likelihood algorithm).

The spatial resolution of the system was 5.1 mm in the transverse direction and 6.0 mm in the axial direction.

Imaging evaluation

CT scans were reviewed by two radiologists (E.M. with 5 years and A.H. with 2 years of post fellowship experience) on a local PACS workstation (Centricity; GE Healthcare, Barrington, IL, USA), and PET images were reviewed by two nuclear medicine physicians (A.S. with 9 years and R.V. with 3 years of post pediatric nuclear medicine fellowship experience) independently on a nuclear medicine workstation (Extended Brilliance TM workspace, Philips). The radiologists and nuclear medicine physicians were aware of the clinical concern of germ cell tumor but were blinded to the results of other imaging and laboratory investigations. Discordant interpretations were resolved by consensus between the two readers. Attenuated-corrected images were used for visual and semiquantitative analyses. The maximum standardized uptake value SUV_{max} of the foci of increased activity were measured by drawing a region of interest over the lesions in the axial view using the standard software supplied by the vendor.

Lesions concerning for germ cell tumor or metastases were identified on diagnostic CT and ^{18}F -FDG PET/CT. Morphological criteria identified CT-positive lesions. Abnormal focal increased uptake not related to a normal variant or known benign pathology with activity greater than background liver activity in a morphological lesion was identified as a PET/CT positive lesion. The abnormalities on ^{18}F -FDG PET/CT and CT scans were recorded separately and compared on a patient basis. The patients were staged or restaged according to the most frequently described postsurgical system [11]. The patients were considered upstaged with ^{18}F -FDG PET/CT when by adding the ^{18}F -FDG PET/CT results to the conventional CT the disease staging or restaging was increased [11].

Patient chart review

The impact of ^{18}F -FDG PET/CT on staging and patient management was determined by reviewing diagnostic CT and ^{18}F -FDG PET/CT lesions, associated clinic notes, subsequent treatment and follow-up with biopsy results when available.

Results

From May 2007 to November 2015, nine patients had 11 ^{18}F -FDG PET/CT. There were 5 males and 4 females with a mode age of 14 years (range: 1.6–17 years). Eight patients had a single study while one patient had three studies. Four studies were performed to assess for recurrence, five to assess metabolic activity of a residual mass, one for staging and one for identifying a biopsy target.

In eight patients (10 ^{18}F -FDG PET/CT studies), there were diagnostic CTs available for comparison. The average interval between diagnostic CT and PET/CT was 7.2 days (range: 0–37 days). In these patients, all except 1 had at least 2 years of clinical follow-up. In total, 13 lesions concerning for active malignancy were identified on diagnostic CT while 15 lesions were identified on PET/CT. Nine lesions were positive on both CT and PET. Four lesions were positive only on CT, while six lesions were positive only on PET.

CT and PET were concordant in nine lesions. The results of CT and PET were non-concordant in 10 lesions. Four CT-positive and PET-negative lesions showed no progression after at least 2 years of clinical and radiologic follow-up without treatment. Six CT-negative and PET-positive lesions showed more heterogeneous outcomes. One lesion was biopsy proven to represent metastasis, another lesion showed no progression on limited follow-up (5 months), and four lesions demonstrated no progression after 2 years of follow-up.

Overall, ^{18}F -FDG PET/CT resulted in a change in management in three of the nine patients (33%). These included two patients in whom PET/CT demonstrated no significant FDG uptake within residual mediastinal masses and who subsequently were stable clinically/radiologically after no additional treatment (Fig. 1). In another case, ^{18}F -FDG PET/CT identified recurrent disease in a lymph node not morphologically considered pathological on CT in a patient without biochemical evidence of recurrence. This node was subsequently surgically resected and proven to represent recurrent disease (Fig. 2). It should be noted that in one patient, PET showed two thoracic lesions not demonstrated on CT. The findings on PET/CT resulted in further investigation. As these lesions showed faint uptake and subsequent tumor markers were negative, they were considered likely false-positive by the clinicians and had no significant impact on subsequent patient care. These patients and findings are described in more detail in Table 1.

Fig. 1 A 15-year-old boy with mediastinal germ cell tumor. CT (a), fused positron emission tomography (PET)/CT (b), maximum intensity projection (c) and attenuation corrected PET (d) images from a study demonstrate a large residual anterior mediastinal mass with no significant ^{18}F -fluorodeoxyglucose (FDG) uptake (arrows). The peripheral parts of the mass show mild increased FDG uptake with maximum standardized uptake value (SUV_{max}) = 1.4. The center of the mass is hypometabolic due to possible central necrosis. The patient was followed up for 2 years with no evidence of recurrence

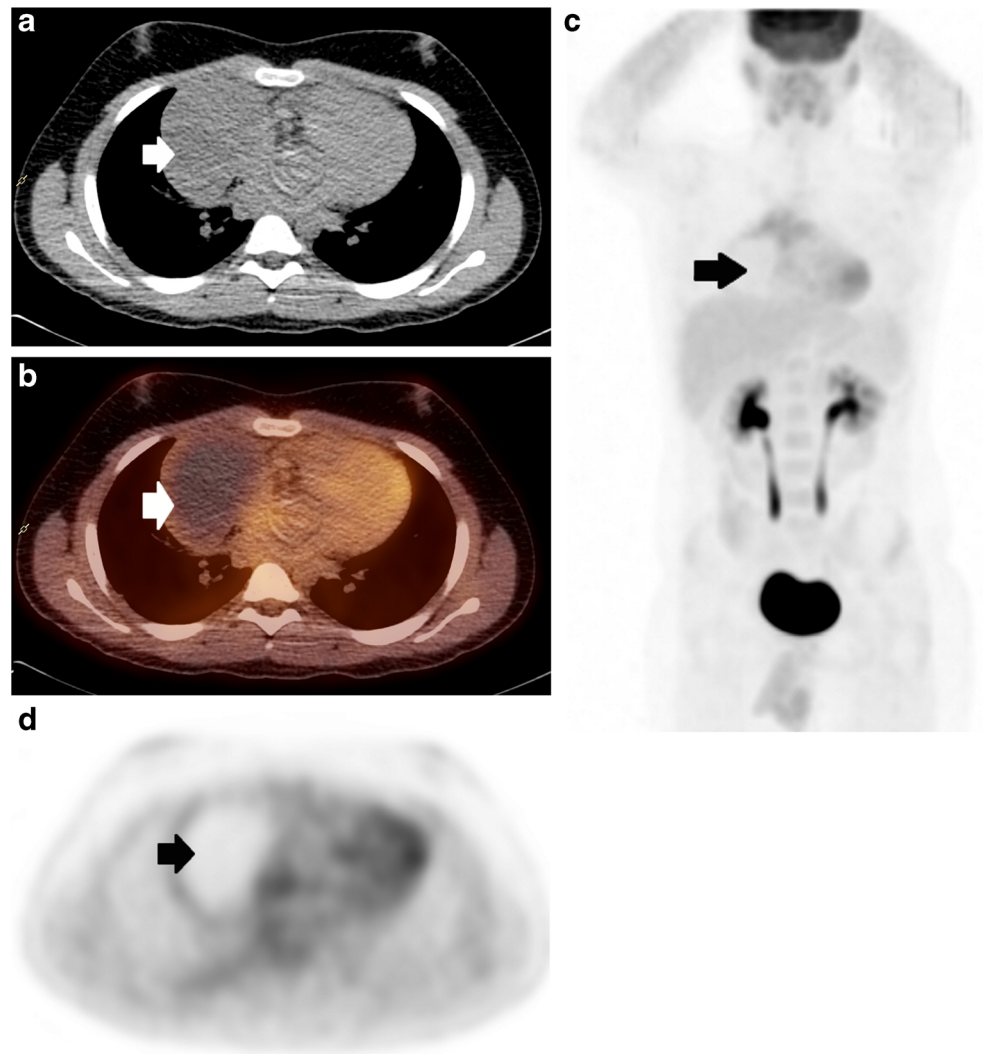
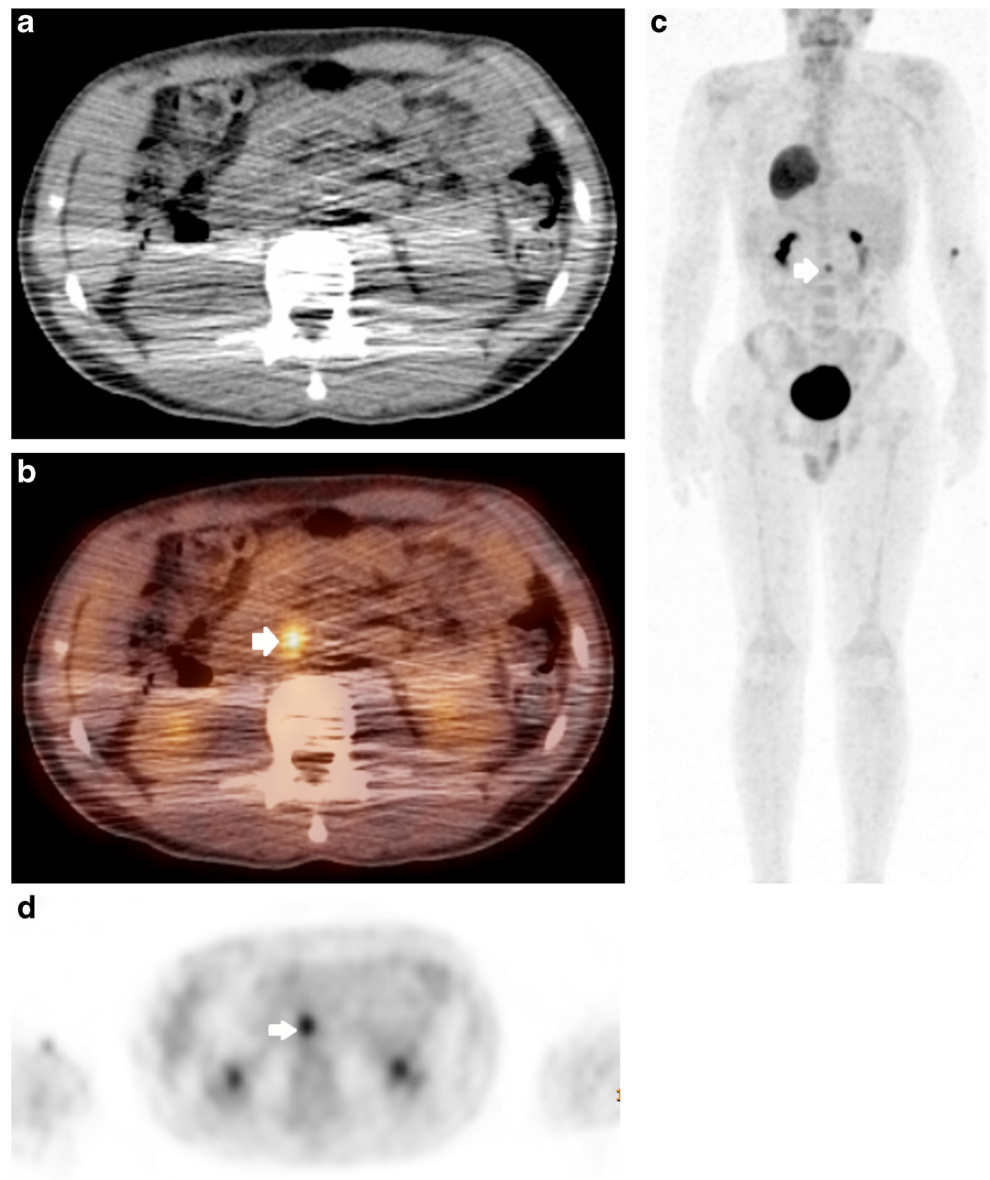


Fig. 2 A 15-year-old boy with testicular cancer. CT (a), fused positron emission tomography (PET)/CT (b), maximum intensity projection (c) and attenuation corrected PET (d) images demonstrate ^{18}F -fluorodeoxyglucose (FDG) uptake within a retroperitoneal lymph node (arrows) visible on the latter three images. The measured maximum standardized uptake value =5.1. Based on our result, the patient underwent open biopsy and the pathological results confirmed recurrent tumor. Subsequently, the patient received additional three cycles of chemotherapy



Discussion

Pediatric germ cell tumor is a rare clinical entity and an uncommon pediatric malignancy. Previous studies describing the benefit of ^{18}F -FDG PET/CT have described a limited number of cases [7, 8]. On summary review of the literature, no articles considering the value of ^{18}F -FDG PET/CT described a sample size in children as large as the one described here. ^{18}F -FDG PET/CT's diagnostic value for rapidly dividing metabolically active malignancies such as osseous and soft-tissue sarcomas and Hodgkin and non-Hodgkin lymphoma, while somewhat controversial, has been well described [12]. Given the heterogeneity of the biological behavior of extracranial germ cell tumors, as well as previous review in adults, ^{18}F -FDG PET/CT's diagnostic value is less immediately intuitive [9].

Additionally, as indicated above, identifying the value of ^{18}F -FDG PET/CT in adult germ cell tumors is neither straightforward nor confirmed. An extensive review indicated that ^{18}F -FDG PET/CT is helpful in assessing pure seminomatous residual lesions, not helpful in staging or in assessing mature teratoma or residual non-seminomatous lesions, and is of uncertain benefit in assessing patients with biochemical evidence of recurrence with negative anatomical imaging (i.e. CT, MRI and US) [9]. This uncertainty, as well as potential differences in biological behavior between adult and pediatric germ cell tumors, emphasizes the importance of further study of the role of ^{18}F -FDG PET/CT in pediatric germ cell tumors.

As indicated by a recent review, significant advances in managing this heterogeneous group of malignancies have required the formation of international registries such as the Malignant Germ Cell Tumours International Collaborative to formulate risk

Table 1 PET/CT findings

| Patients | Age in years | Gender | Pathological diagnosis | Location | CT findings | | PET/CT findings | | | Did PET/CT change management? |
|----------|--------------|--------|------------------------|-----------------------|--|----------------------|---|----------------------|-------------------------------|-----------------------------------|
| | | | | | Sites of CT lesions (No. of lesions) | Total No. of lesions | Sites of PET lesions (No. of lesions) | Total No. of lesions | SUV _{max} | |
| Case 1 | 15 | Male | Mixed germ cell tumour | Testicle | Pulmonary lesions (2) Aortocaval LN (1)** | 3 | Spermatic cord (1) Right groin (1) Supraclavicular (1) Left paratracheal (1) Aortocaval (1) | 5 | 3.8 2.6 2.2 2 1.8 | No |
| Case 2 | 14 | Female | Gonadal dysgerminoma | Ovary | None | 0 | None | 0 | 0 | No |
| Case 3* | 15 | Male | Seminoma | Mediastinum | Mediastinum (1)** Mediastinum (1)** Pulmonary (1)** Mediastinum (1)** | 1 2 1 | Mediastinum (1) Mediastinum (1) Pulmonary (1) Mediastinum (1) | 1 2 1 | 8.6 1.4 3.1 1.4 | No Yes: No chemo or Bx No |
| Case 4 | 15 | Male | Seminoma | Mediastinum | Mediastinum (1)** Manubrium (1) | 2 | Mediastinum (1) | 1 | 1.6 | Yes: No chemo or Bx |
| Case 5 | 17 | Male | Seminoma | Mediastinum | Mediastinum (1)** | 1 | Mediastinum (1) | 1 | 3.8 | No: 5 months follow-up |
| Case 6 | 13 | Female | Mature teratoma | Ovary | Left adnexa (2)** Pre-sacral(1)** | 3 | Left adnexa (1) Pre-sacral (1) | 2 | 2.8 6.7 | No |
| Case 7 | 16 | Female | Yolk sac tumor | Ovary | None | 0 | None | 0 | 0 | No: MRI showed peritoneal disease |
| Case 8 | 15 | Male | Mixed germ cell tumor | Testicle | None | 0 | Aortocaval (1) | 1 | 5.1 | Yes |
| Case 9 | 2 | Female | Yolk sac tumor | Sacrococcygeal region | N/A | N/A | Liver (1) | 1 | 2.2 | No |

LN lymph node, SUV_{max} maximum standardized uptake value, *chemo* chemotherapy, *Bx* biopsy, *N/A* not available

*Case 3 had 3 CTs and PET/CTs displayed in the table in three subsequent rows (at diagnosis, during treatment and during follow-up)

**CT and PET/CT findings were anatomically concordant

Bx biopsy, *chemo* chemotherapy, *LN* lymph node, *N/A* not available, *No.* number, *PET* positron emission tomography, SUV_{max} maximum standardized uptake value

stratification systems [4]. Previous studies have included larger cohorts of children with germ cell tumors when assessing the role of ¹⁸F-FDG PET/CT in pediatric malignancies. One of these studies that included three children with germ cell tumors (one with metastatic germ cell tumor and two with ovarian dysgerminoma) indicated that ¹⁸F-FDG PET/CT may be a promising tool [8]. Another, which included two children with germ cell tumors in a cohort of 43 children and adolescents, showed a significantly increased specificity of PET/CT for the characterization of pulmonary metastases with a diameter greater than 0.5 cm and lymph node metastases with a diameter of less than 1 cm was significantly increased over that of CT alone [7].

¹⁸F-FDG PET/CT effectively altered management in three patients as described before. The clinical impact of ¹⁸F-FDG PET/CT in these scenarios relates to one of this modality's primary benefits – its ability to characterize metabolic activity. In the two patients with residual morphological mediastinal masses, subsequent to chemotherapy and prior to morphological resolution, ¹⁸F-FDG PET/CT demonstrates metabolic inactivity. In the patient with undiagnosed malignant lymph node disease, subsequent to morphological declaration, ¹⁸F-FDG PET/CT demonstrated metabolic evidence of disease.

Not surprisingly, ¹⁸F-FDG PET/CT identified focal increased FDG uptake that was subsequently demonstrated to be false-positive and likely benign reactive or inflammatory in origin. This occurred in two patients' lymph nodes that were not considered pathological on CT and were also not clinically suspected to be malignant. These nodes remained stable on follow-up. Clearly, recognizing the possibility of false-positives remains very important for this sensitive but sometimes not specific modality.

On the other hand, we did not have false-negative findings in our series. All negative ¹⁸F-FDG PET/CT positive CT lesions (four CT positive and PET negative lesions in two patients) showed no progression after 24 months of follow-up. The results may suggest a high negative predictive value of an ¹⁸F-FDG PET/CT in pediatric germ cell tumors. Clearly, this observation should be verified with a larger sample.

In this series, there was a spectrum of clinical stages present in the pediatric patients undergoing ¹⁸F-FDG PET/CT assessment of germ cell tumors. The clinical indications for the PET/CT in this patient series were solely based on the clinician's discretion. PET/CT was not routinely performed for pediatric patients with germ cell tumors in our center. The patients were

referred when there was unusual imaging findings, a suspicious residual mass or evidence of disease recurrence and sometimes for selection of the optimal site for biopsy. Moreover, the study is limited as it is both retrospective and small in sample size. Given the rarity of this entity, this is currently unavoidable. Considering the burgeoning role of ^{18}F -FDG PET/CT in pediatric oncology, and encouraging current results, further work in this area with a larger sample size is needed to definitively establish the role of ^{18}F -FDG PET/CT in extracranial pediatric germ cell tumor. Additionally, it would be ideal if discrete standardized uptake value cutoffs for differentiation of benign reactive findings from malignancy in a variety of pediatric germ cell tumors could be ascertained from further larger cohort studies.

Conclusion

^{18}F -FDG PET/CT may have a substantial impact on the management of suspected recurrent or residual germ cell tumors in children. Continued multicenter study is required secondary to the rarity of this tumor to demonstrate the benefit of ^{18}F -FDG PET/CT in particular clinical scenarios including staging, residual disease post therapy, recurrence and identifying the most metabolically active site for biopsy.

Compliance with ethical standards

Conflicts of interest None

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