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Oculoplastic Imaging Update

Value of positron emission tomography/computed tomography in diagnosis and staging of primary ocular and orbital tumors

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Abstract

Accurate and reliable staging methods are crucial for optimal care of patients with ocular and orbital malignancies. Positron emission tomography/computed tomography (PET/CT) has recently emerged as a staging tool in the field of ophthalmic oncology. For detecting primary ocular or orbital lesions, PET/CT does not seem to provide an advantage over clinical ophthalmologic examination or conventional imaging studies such as CT or magnetic resonance imaging of the orbit. However, PET/CT may detect distant metastatic lesions that conventional imaging studies miss. For orbital and ocular adnexal lymphoma, use of PET/CT has been proven to be feasible and is now accepted both as a standard part of the initial staging work-up and for the assessment of response to therapy. For other ophthalmic tumors, PET/CT seems most appropriate for advanced metastatic tumors of the orbit, eyelid, and eye, for which the detection of distant metastasis with 1 comprehensive study may be preferable to performing multiple CT scans with contrast.

Keywords: Positron emission tomography/computed tomography, Cancer staging, Uveal melanoma, Orbital tumors, Orbital lymphoma, MALT lymphoma

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Introduction

The prognosis of patients with a newly diagnosed primary ocular or orbital malignancy depends on the tumor's stage. Cancer staging characterizes the size, location, and histopathologic features of the primary tumor and the degree of regional and distant metastasis associated with the primary tumor. Accurate and reliable staging methods are crucial because clinicians must tailor treatment options specifically to the tumor stage. Whole body positron emission tomography/computed tomography (PET/CT) has been widely used in the staging of lymphoma, cutaneous melanoma, colorectal cancer, and other gastrointestinal malignancies.[1–3] However, the use of PET/CT in the field of ophthalmic oncology has emerged only recently. PET/CT has shown promise in providing accurate detection, staging, and restaging of ocular and orbital tumors, all of which facilitate selection of the most appropriate treatment options.[4] In this review, we will explore the significance of PET/CT in the diagnosis and staging of primary ocular and orbital tumors. PET/CT may also detect metastases in the globe, orbit, or ocular adnexae from primary tumors at other sites, but this review focuses on the use of PET/CT for the diagnosis and staging of primary ocular and orbital malignancies only.

Methods

We carried out a PubMed search of all articles on the clinical usefulness of PET/CT in primary ocular and orbital tumors published in English using the keyword ''PET/CT'', staging,

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ocular tumors, and orbital tumors. Our search was not limited by a date range. We conducted additional searches for ''PET/CT'' and the following tumors: ''ocular lymphoma'', ''orbital lymphoma'', ''uveal melanoma'', ''choroidal melanoma'', ''conjunctival melanoma'', ''cutaneous eyelid melanoma'', ''sebaceous carcinoma'', ''squamous cell carcinoma'', ''Merkel cell carcinoma'', retinoblastoma, and adenoid cystic carcinoma.

Results

Principles and technique of PET/CT

PET has been widely used in whole body imaging of neoplasms. PET demonstrates areas of high uptake of glucose-labeled radiotracer. PET provides functional data by measuring the distribution of administered tracer, but it has poor spatial resolution and provides little information about anatomic structures. CT provides precise anatomic localization of abnormalities but does not provide information about metabolic abnormalities. Combined PET/CT integrates the metabolic information provided by PET with the anatomic information provided by CT and offers several advantages over the use of separate PET and CT: decreased image acquisition time, increased accuracy of tumor localization, increased likelihood of staging in a single step, and removal of opportunities for human error in visually combining separate images.[5–7]

In FDG PET/CT, 18-fluoro-2-deoxy-D-glucose (FDG), a glucose analogue, is converted into FDG-6-phosphate, which is unable to undergo glycolysis and is dephosphorylated at a reduced rate. Since tumor cells have a higher affinity for glucose than normal cells and use glycolysis as their primary mechanism of metabolism, FDG accumulates in tumor cells and can be detected by the scanner.[8] Patients are required to fast for at least 4–6 h before the injection of FDG to reduce physiologic glucose utilization and insulin levels to baseline. The acceptable fasting glucose level is 80–160 mg/dl.[9] FDG is then injected intravenously at a dose calculated according to the following formula: weight of the patient in kilograms multiplied by the target dose per 70 kg.[10,11] After a 45- to 60-min uptake period, CT is performed using a multidetector helical CT scanner. Typically, the body is imaged from head to toe or head to thigh.

The integration of PET and CT images can be accomplished by software or hardware fusion. Movement of internal organs, scanner bed profiles, and patient position limit the accuracy of software fusion. A combined PET/CT scanner, the ''hardware fusion'', overcomes these limitations.[12] The data are analyzed quantitatively by measuring the standardized uptake value (SUV), which is defined as the ratio of the activity within the tissue (Bq/ml) to the injected dose (Bq) divided by the body weight (kg) (activity/[injected dose/body weight]).[9] The SUV is expressed as its maximum. Currently, no standard exists for the cutoff value of SUV used to differentiate benign (metabolically inactive) from malignant (metabolically active) lesions, but authors have used maximum SUV values of 2.5 and 4 for choroidal melanoma for this purpose.[9,11] In 16 patients with ocular adnexal lymphoma (OAL), the mean SUV was 6.5.[13] The resulting images are also analyzed qualitatively for the presence of local tumors, regional nodal metastases, and distant metastases. False-positive findings can be differentiated from true positive findings on the basis of tumor location, symmetry, and clinical history.

Role of PET/CT in uveal melanoma

Uveal melanoma is the most common primary intraocular malignancy in adults, with a reported incidence of 5–7 cases per million individuals per year in North America.[14] The 5-year survival rate for patients with uveal melanoma confined to the eye is 81.6%, and the 1-year survival rate for patients with uveal melanoma with systemic metastases is 13%.[15,16] Uveal melanoma has a unique metastatic pattern of the liver as the first and predominant site of metastasis in over 70% of patients.[17,18]

The Collaborative Ocular Melanoma Study Group established a protocol for the detection of metastatic choroidal melanoma. Components of the protocol include physical examination, hematologic analyses including complete blood cell count and liver function tests (LFTs), chest radiography, ophthalmic ultrasonography, and fluorescein angiography.[10,19,20] If indicated, fine needle aspiration or core needle liver biopsies can be performed for disease confirmation.[20] Studies have shown that although liver ultrasonography, LFTs, and chest radiography have high specificity in the detection of metastatic uveal melanoma, they have low sensitivity.[21,22] Hematologic tests have been shown to have both low sensitivity and low specificity.[21] Eskelin et al. reported that LFTs and abdominal ultrasonography accurately detected liver metastases in only 59% of asymptomatic patients with liver metastases and that chest radiography detected pulmonary metastases in only 2% of patients with pulmonary metastases.[23]

Given these limitations of routine surveillance methods, PET/CT has the potential to provide a substantial benefit. Reddy et al. found that PET/CT was able to detect the metabolic activity of choroidal melanoma and was most effective in detecting American Joint Committee on Cancer T3 and larger choroidal melanomas.[10] However, these investigators concluded that PET/CT was not superior to standard clinical protocol in diagnosing choroidal melanoma. In addition, PET/CT was unable to differentiate between small melanomas and suspicious choroidal nevi. A positive correlation between SUV and the size of choroidal melanoma was found, but there was no significant correlation between SUV and other factors, such as age, sex, or tumor location.[10] In a different study, PET/CT was reported to be able to detect small uveal melanomas despite the limited spatial resolution due to the small physical size of the detectors and diameter of the PET detector ring.[24]

Whole body PET/CT has been shown to play a significant role in detecting regional and distant metastases from uveal melanoma. Klingenstein et al. reported using PET/CT to correctly show metastases in 12 of 12 patients with primary uveal melanoma.[25] Kurli et al. reported 100% sensitivity and 100% specificity of PET/CT in the identification of hepatic metastasis compared to 12.5% sensitivity of LFTs.[20] PET/CT has identified hepatic metastases in patients with normal LFTs and hepatic metastases that could not be detected by abdominal ultrasonography because of hemorrhage and elaborate tumor mass.[25] PET/CT is also useful in identifying extrahepatic metastases, especially osseous metastases.[20] For osseous le-

sions that CT was unable to characterize as benign or malignant, PET/CT was able to make the distinction.[20]

In addition to being used for staging of uveal melanoma, PET/CT has been explored as a noninvasive method to assess the risk of metastasis from uveal melanoma. Finger et al. found that there was a positive correlation between higher SUV and larger anterior epitheloid-cell uveal melanoma. Since the largest tumor diameter and cell type are among the widely accepted risk factors for metastasis and shown by the Collaborative Ocular Melanoma Study to be statistically significant risk factors, Finger et al. concluded that PET/CT may be an effective biomarker for the metastatic potential of uveal melanoma.[9]

There are studies that call into question the value of PET/CT in detecting primary uveal melanoma and liver metastases. Strobel et al. reported that in 13 patients with uveal melanoma with 27 known liver metastases, 16 of 27 liver metastases were negative on FDG PET/CT, for a false-negative rate of 59%.[26] This is in contrast to similar studies that have shown no false-negative events.[11,20] Furthermore, Strobel et al. reported significantly lower SUVs for liver metastases from uveal melanoma (mean value, 3.5) than for liver metastases from cutaneous melanoma (mean value, 6.6). They concluded that FDG PET/CT lacks sufficient sensitivity for detecting liver metastases from uveal melanoma. Strobel et al. explained the high false-negative rate in their study by stating that other studies with no false-negative events included only patients with positive findings on PET and not patients with negative findings on PET but suspicious findings on magnetic resonance imaging (MRI) or CT scans.[26] Orcurto et al. reported that MRI was superior to PET/CT in detecting small liver metastases from uveal melanoma.[27]

In addition to potentially being useful for identifying metastases from uveal melanoma, PET/CT may be useful for evaluation of the response to therapy. PET/CT was found to be superior to MRI in evaluating treatment response.[27] One study showed that SUVs decreased in the primary tumor site (in the eye) over time following ophthalmic plaque radiotherapy.[28,29]

Role of PET/CT in orbital and ocular adnexal tumors

Lymphoma

Orbital lymphoma is the most common primary orbital malignancy in adults.[30] Ocular adnexal lymphoma is the term used in the literature to describe lymphomas involving the orbit, eyelid, or conjunctiva or a combination of these anatomic structures. In a series of patients with OAL of all subtypes at MD Anderson, regional or distant involvement was present in 25 of 43 patients (58%) on initial presentation, indicated by stage greater than IE according to the Ann Arbor Staging System.[31] Therefore, thorough systemic staging is critical for patients who present with OAL. Whole body PET/CT has become part of standard staging for orbital lymphoma and OAL and is probably used more widely for these diseases than for any other tumors of the eye and orbit (Fig. 1).

OAL most commonly arises from the lacrimal gland and conjunctiva and accounts for approximately 8% of all extranodal lymphomas but only 2% of all non-Hodgkin lymphomas. OAL may present bilaterally in any part of the orbit and can be either localized to the orbit and adnexal area or associated with systemic sites of involvement.[32] Current modalities

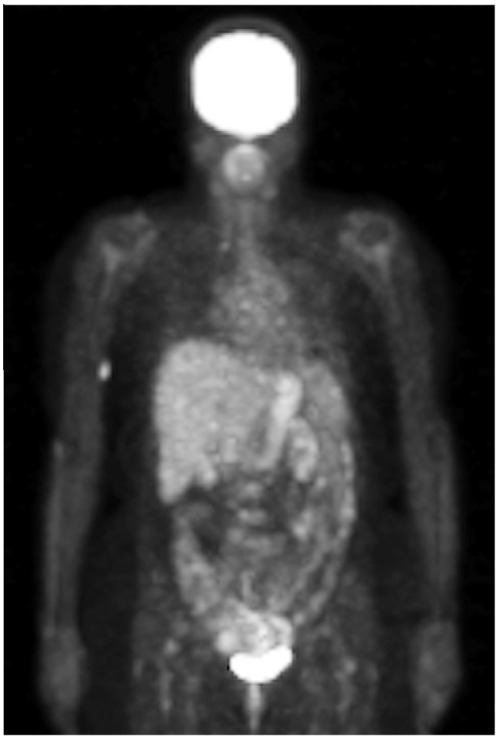

Figure 1. Baseline PET in a patient with lacrimal gland MALT lymphoma shows a focal area of increased FDB uptake in the right arm. An MRI of the upper extremity was subsequently done and confirmed the presence of a lesion in the biceps muscle which upon biopsy proved to be a focus of lymphoma.

for staging of OAL include physical examination, complete blood cell count, contrast-enhanced CT, MRI, and bone marrow biopsy.[33] PET/CT has been shown to have higher sensitivity than CT in detecting systemic sites of involvement from orbital lymphoma and other extranodal lymphomas.[32]

The most common histologic subtype of OAL, accounting for approximately 50% to 70% of OALs, is musosa-associated lymphoid tissue (MALT)-type lymphoma. This is a low-grade type of B-cell non-Hodgkin lymphoma. In 18% of cases, there is bilateral orbital or adnexal involvement.[34] Suga et al. reported that in patients with MALT lymphoma, PET/CT was able to detect contralateral orbital lesions as well as gastric lesions that could not be detected by MRI alone.[35] Roe et al. reported that PET/CT was able to detect OAL in 3 of 4 patients (75%) with biopsy-proven orbital MALT lymphoma and systemic lymphoma in 2 of those 4 patients (50%).[33] PET/CT showed 2 sites of false-negative uptake. The authors concluded that PET/CT has value in diagnosing, staging, and restaging OAL and may help differentiate between atypical lymphoid hyperplasia, low-grade MALT lymphoma, and more aggressive forms.

The conjunctiva is a major site for primary and secondary lymphomas. Matsuo et al. reported the use of PET/CT in detecting relapse of MALT lymphoma in 4 patients.[36] They concluded that PET/CT was able to detect small and thin MALT lymphoma lesions in the conjunctiva.

Low-grade lymphomas such as MALT lymphomas typically have relatively low FDG uptake. Thus, there is an inherent possibility of false-negative findings on PET/CT, and clinical correlation is always necessary. However, in 7 patients with

low-grade MALT lymphoma reported in a series from MD Anderson, all had FDG-avid lesions on pretreatment PET.[13]

Follicular lymphoma is the second most common histologic subtype of OAL after MALT lymphoma. Follicular lymphoma is another form of low-grade B cell lymphoma, characterized by follicles with centrocytes. At initial diagnosis, 42% of patients have systemic involvement outside the orbital area. PET/CT has been shown to be valuable in estimating the size of the lesion and detecting systemic involvement of follicular lymphoma involving the orbit.[37]

Retinoblastoma with invasion of the orbit

Radhakrishnan et al. studied the value of PET/CT in the staging of retinoblastoma with orbital invasion.[38] Typical staging modalities for retinoblastoma are CT or MRI of the orbit and brain. PET/CT findings were found to be falsely negative in 2 of 3 patients with International Retinoblastoma Staging System stage IIIB disease. These investigators reported no significant difference in sensitivity or specificity between PET/CT staging and routine staging. Furthermore, they reported that intraocular retinoblastoma was not FDG avid. However, these investigators also found that PET/CT may be valuable in assessing retinoblastoma spread to the central nervous system via extension through the optic nerve. They found that optic nerve uptake at baseline PET/CT correlated with retinoblastoma extension to the optic nerve. Radhakrishnan et al. concluded that PET/CT may have value in determining the prognosis and assessment of response to treatment in patients with retinoblastoma with invasion of the orbit.

Eyelid sebaceous carcinoma

Metastases from eyelid sebaceous carcinoma can be detected and diagnosed by various methods, including CT, fine needle aspiration, and sentinel lymph node biopsy, depending on the area of metastatic involvement.[39] Krishna et al. reported 2 cases that were successfully staged by PET/CT.[40] In the first case, a sebaceous carcinoma of the lower lid, PET/CT revealed foci of uptake in the submandibular, supraclavicular, mediastinal, and retroperitoneal nodes. PET/CT has also been used to successfully stage an unusual primary sebaceous carcinoma of the parotid gland.[41]

Baek et al. analyzed 15 cases of periocular malignancies, 5 of which were sebaceous carcinomas of the upper eyelid.[42] In follow-up evaluation of these 5 sebaceous carcinomas, PET/CT correctly identified 4 of 4 cases (100%) of regional lymph node involvement. In 1 case, PET/CT detected a clinically palpable ipsilateral parotid lymph node that went undetected by contrast-enhanced CT. Histologic analysis of the node following parotidectomy revealed metastatic sebaceous carcinoma. In 2 more cases in this series, PET/CT more clearly identified regional lymph nodes later found to contain metastasis than did contrast-enhanced CT alone.

Conjunctival melanoma

Kurli et al. reported on the use of PET/CT in 14 patients with locally invasive conjunctival melanoma, 13 with a T3 tumor and 1 with a T4 tumor.[43] Half of the patients in this series were imaged with PET/CT at the time of initial diagnosis of conjunctival melanoma, and half were imaged after treatment with excision with adjuvant cryotherapy and/or chemotherapy. In the patient with the T4 conjunctival melanoma, who had PET/CT performed after treatment and who had no pretreatment PET/CT, PET/CT identified widespread metastases, including intrahepatic metastases, despite normal LFTs, and the patient's disease was appropriately staged as T4N1M4. PET/CT findings were negative in all 13 patients with T3 tumors. The authors concluded that PET/CT has a limited role in staging of conjunctival melanoma during initial screening but may be valuable for restaging and follow-up. In an editorial commenting on Kurli et al's paper, Esmaeli emphasized the importance of performing pretreatment, baseline PET/CT in all patients to evaluate whether the primary tumor is FDG avid,[44] something that Kurli et al. did not do. She furthermore noted that Kurli et al. did not include pathologic details about each conjunctival melanoma, including Breslow thickness, knowledge of which would have helped predict the tumors' metastatic potential. Esmaeli agreed with Kurli et al. that PET/CT has limited efficacy in initial evaluation of conjunctival melanoma but may be useful in the evaluation of response to therapy in patients with known sites of distant metastases.

Baek et al. reported that in follow-up evaluation of 2 patients with conjunctival melanoma, PET/CT successfully identified regional nodal metastases.[42] After parotidectomy, radical neck dissection, and maxillectomy, the first patient had negative findings on PET/CT at 12 months' follow-up. After parotidectomy and nodal dissection, the second patient developed distant metastasis detected by PET/CT at 21 months' follow-up.

Cutaneous eyelid melanoma

In Baek et al's series of PET/CT in patients with periorbital malignancies, 1 patient had melanoma of the upper eyelid.[42] PET/CT at initial evaluation was positive only for the primary lesion, and the patient underwent orbital exenteration with radiotherapy. PET/CT 15 months later successfully identified local recurrence also detected by clinical examination, which indicates that PET/CT did not offer any additional benefit to conventional follow-up methods. In a series of PET/CT for staging in a series of 250 patients with cutaneous melanoma in all anatomic locations, PET/CT identified more metastases than either PET or CT alone.[44] In a series of 78 patients with cutaneous melanoma in all anatomic locations, PET/CT was 95% sensitive and 95% specific in the detection of regional or distant metastases.[45] This series reported 2 false-negative events and 2 false-positive events.

Merkel cell carcinoma

Our literature review returned no articles on the use of PET/CT in eyelid Merkel cell carcinoma. A retrospective review of 6 patients with Merkel cell carcinoma in all anatomic locations showed that PET/CT successfully identified 9 of 10 Merkel cell carcinoma lesions confirmed by physical examination or histopathologic analysis.[46] There was 1 false-positive event and 1 false-negative event. All Merkel cell carcinoma lesions demonstrated relatively intense FDG uptake. Given the typical rapid rate of growth and aggressive metastatic behavior of Merkel cell carcinoma, PET/CT has the potential to rule out or rule in systemic sites of metastasis (Fig. 2).

Squamous cell carcinoma

There is limited literature on PET/CT for eyelid or conjunctival squamous cell carcinoma (SCC). One case report high-

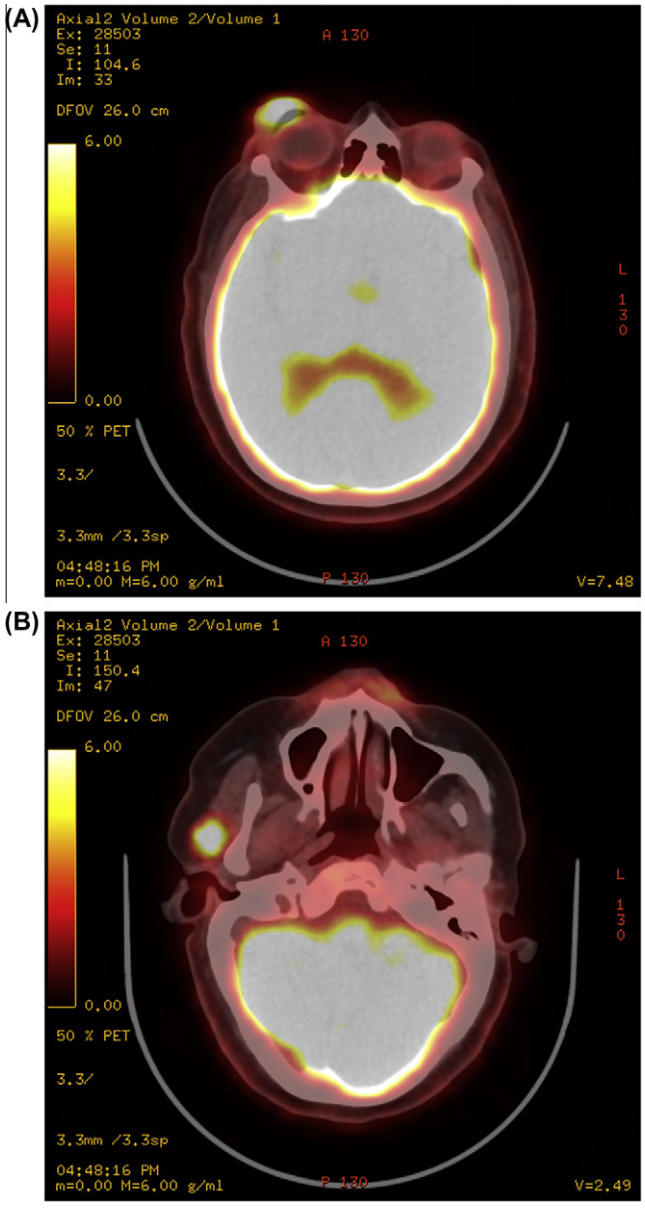

Figure 2. PET/CT findings in a patient with Merkel cell carcinoma of the eyelid. (A) FDG uptake in the upper eyelid. (B) FDG uptake in the parotid nodal basin. The patient also had a palpable mass in the parotid. PET/CT was ordered to rule out other sites of distant metastasis.

lights the detection of SCC of the bulbar conjunctiva and increased FDG uptake in retromandibular, mediastinal, and abdominal lymph nodes.[47] Biopsy of the mediastinal lymph nodes showed inflammation only, and no biopsy was performed of the retromandibular lymph node, which was found to contain metastatic SCC on follow-up PET/CT performed 11 months later, after the node became clinically palpable. This case report illustrates that PET/CT is able to identify both primary conjunctival SCC and regional metastasis, but the report does not show a higher rate of detection of nodal metastasis with PET/CT than with clinical examination or other conventional modalities, such as ultrasonography or conventional CT.

PET/CT, however, may have value in detecting distant metastasis associated with SCC. In a series of 82 patients with recurrent SCC of the head and neck, PET/CT correctly identified distant metastasis in 12 of 14 patients (86%) with distant metastasis, and PET/CT was found to be 86% sensitive and 84% specific for the detection of distant metastasis.[48] In a case-control study of 58 patients with head and neck SCC who underwent both surgery and adjuvant radiotherapy and/or chemotherapy, patients whose disease was initially staged using PET/CT had a significant survival benefit compared to patients for whom PET/CT was not used.[49]

Adenoid cystic carcinoma of the lacrimal gland

Wild et al. reported on the value of PET/CT in restaging of 3 poorly differentiated adenoid cystic carcinomas of the lacrimal gland.[50] In 1 patient, PET/CT successfully identified histologically confirmed local recurrence that was missed on MRI; in a second patient, PET/CT missed a local recurrence that was clearly identified on MRI.

In the initial evaluation of an adenoid cystic carcinoma of the lacrimal gland in Baek et al's series, PET/CT identified both the primary lesion and distant metastasis.[42] In follow-up evaluation of an adenoid cystic carcinoma of the upper eyelid, PET/CT successfully identified both regional and distant metastases.

Challenges in the use of PET/CT

PET/CT is a sensitive method for detecting metabolically active foci, but it may not be as specific for cancer since PET/CT shows uptake in benign infectious and inflammatory lesions and fractures as well as in foci of malignancy. Because PET/CT allows more accurate localization than PET alone, with PET/CT it is possible to detect involvement of the conjunctiva, lacrimal gland, extraocular muscles, and eyelid.[35] However, care must be taken when evaluating orbital lesions with PET/CT because extraocular muscles and lacrimal glands exhibit some background FDG uptake, making it potentially difficult to distinguish normal background uptake from tumor uptake.

The lack of specificity of PET/CT for malignant cells increases the risk for false-positive events. Studies on the specificity of PET/CT in the evaluation of ocular and orbital tumors include a study of uveal melanoma in which PET/CT was used to successfully differentiate benign from malignant lesions by comparing glucose uptake values and SUVs between lesions and the surrounding tissues.[11] In this study, PET/CT was able to increase the number of definite benign or malignant lesions by differentiating physiological variants from true malignancy.

The level of uptake of FDG depends on a variety of factors, including tumor size, metabolic activity, surrounding background activity, and serum glucose level. Different types of tumors demonstrate different FDG uptake ranges; tumors such as low-grade MALT lymphoma and retinoblastoma have been shown to be poorly responsive to FDG, but the degree of uptake of FDG varies by tumor type and individual tumor.[13,51]

Cost and time investment associated with PET/CT

A main concern regarding the routine use of PET/CT is its high cost, which is likely institution dependent but is typically more than the cost of conventional screening methods such as physical examination with palpation of lymph nodes,

hematologic analyses, chest radiography, CT, and MRI. In addition, PET/CT requires more time than conventional CT. Proponents of PET/CT argue that the cost is justified because the early detection of metastatic lesions allows for the formation of more appropriate treatment plans and could prevent futile treatment, thus reducing cost in the long term. Furthermore, PET/CT offers comprehensive imaging of the entire body in a single study, as opposed to separate CT scans with contrast or MRI scans of multiple sites. Accurate characterization of the true cost-benefit ratio of PET/CT versus conventional screening methods is difficult because follow-up regimens, and hence cost, likely vary widely by type, grade, and stage of tumor and by the institution where treatment was delivered.

Currently, Medicare coverage for PET/CT includes the initial treatment, or diagnosis and staging, and subsequent treatment, or restaging and monitoring, for lymphoma, melanoma, and head and neck tumors (not including thyroid or central nervous system tumors) as well as for all other solid tumors, except that Medicare does not cover PET/CT for the initial staging of melanoma for the sole purpose of evaluating regional lymph nodes.[52]

Conclusion

FDG PET/CT is an emerging diagnostic imaging modality for diagnosis, staging, and assessment of response to therapy for ocular and orbital tumors. The use of PET/CT for detecting primary ocular or orbital lesions does not seem to provide an advantage over and above clinical ophthalmologic examination or other conventional imaging studies such as CT or MRI of the orbit. For assessment of regional lymph node metastasis associated with eyelid and adnexal tumors, to date there are no studies suggesting that PET/CT is more sensitive than conventional CT, ultrasonography, or sentinel lymph node biopsy. However, PET/CT can detect distant metastatic lesions that would be missed on conventional imaging. For orbital lymphoma and OAL, use of PET/CT has been proven to be feasible and is now accepted both as a standard part of the initial staging work-up and for the assessment of response to therapy. For other ophthalmic tumors, PET/CT seems most appropriate for advanced cancers of the orbit, eyelid, and eye for which the risk of distant metastasis is high and for which the early detection of distant sites of metastasis with 1 comprehensive study may be preferable to performing multiple CT scans with contrast.

For FDG PET/CT to become an established technique in ophthalmic oncology, larger randomized prospective studies are needed to confirm the sensitivity and specificity of PET/CT for different ocular and orbital tumors as well as to compare PET/CT to other imaging modalities.

Conflicts of interest

The authors have no commercial associations or financial disclosures that might pose a conflict of interest with information presented in this manuscript.

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