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ORIGINAL ARTICLE

Initial PET/CT staging for choroidal melanoma: AJCC correlation and second nonocular primaries in 333 patients

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Purpose. *To report on whole body positron emission tomography/computed tomography (PET/CT) screening for metastasis at diagnosis of primary uveal melanoma.*
Methods. *Since August 2003, 333 consecutive patients were diagnosed with uveal melanoma and underwent whole body screening for metastatic disease with PET/CT along with liver function tests and physical examination. Abnormal findings prompted further biopsies, blood tests, imaging, or clinical evaluations for confirmation. The presence of metastatic disease and second cancers were evaluated.*
Results. *Using the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) 7th edition criteria, 104 tumors were classified T1 (31%), 162 T2 (49%), 37 T3 (11%), and 30 T4 (9%). Seven of 333 (2.1%; 95% confidence interval [CI] 0.8-4.3) patients had metastatic melanoma. One tumor was a T3 and 6 were T4. Thus, 3% of T3 and 20% of T4 melanomas were found to have metastases at the time of initial diagnosis. Ten patients (3.3%; 95% CI 0.9-5.5) had synchronous second cancers and 28 (8.4%) concurrent benign lesions. The most common metastatic sites were liver (7/7) and bone (2/7).*
Discussion. *This study suggests that PET/CT improves the yield of detecting both extrahepatic metastases, especially from tumors defined as AJCC-T4, and synchronous primary cancers, irrespective of the size of the uveal melanoma. With respect to liver metastases, PET/CT demonstrated high sensitivity and positive predictive values, indicating an overall better performance than conventional screening procedures.*

Key Words. *Choroidal, Melanoma, Metastasis, Positron emission tomography/computed tomography, Staging, Uveal*

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INTRODUCTION

Positron emission tomography (PET) provides a map of functional glucose usage utilizing a positron-emitting glucose analog, ^{18}F-fluoro-2-deoxyglucose (FDG). This physiologic image is then coupled with an overlay of anatomic computed tomographic (CT) imaging (1). Combined PET/CT offers a 3-dimensional assessment of the FDG uptake as well as anatomic colocalization (form and function on the same diagnostic page) with improved diagnostic accuracy (2).

Cancer cells are characterized by relatively high glycolytic activity, visualized as increased FDG absorption or increased specific uptake values (SUV) and “bright”

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images on PET. However, false-negative findings occur, which have been attributed to less voracious tumors and small tumor size (e.g., micrometastases). Though PET/CT is the most sensitive whole-body screening tool, a negative PET/CT does not exclude metastasis (3).

In the world of general oncology, PET/CT is currently widely used for characterization, localizing, staging, metastases screening, treatment monitoring, and recurrence detection of cancer. Worldwide acceptance has been based on its efficacy, availability, and cost. For example, in the United States and Europe, PET/CT is commonly used for the diagnosis, staging, and restaging of cutaneous melanoma (1-4).

Ophthalmic oncology saw its first clinical use in 2004 when Finger et al and Freudenberg et al reported on detection of metastatic choroidal melanoma (5, 6). Further studies have focused on the primary tumor establishing correlations with size, genetic status, histopathology, prognostic value, and response to radiation therapy (7-11).

Since the Collaborative Ocular Melanoma Study (COMS) group suggested that physical examination, liver function tests, and a chest x-ray were inadequate procedures for metastases screening, there has been renewed interest in alternative diagnostic methods (12). Further, therapeutic options (e.g., hepatic perfusion or resection) are potentially most effective when systemic disease is caught early (e.g., when limited to the liver) (13). In addition, clinical trials for the treatment of metastatic melanoma typically exclude patients with end-stage or intracranial disease (13-15). Hence, though liver imaging (e.g. ultrasound [US], CT, magnetic resonance imaging [MRI]) has gained popularity over the past decade, PET/CT provides increased sensitivity, specificity, and multiorgan evaluation.

In this study, we report a relatively large series of 333 consecutive uveal melanoma patients evaluated by whole body PET/CT imaging for initial staging. In addition, we compare our results to data previously reported from the COMS and relate them to the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) 7th edition staging system (16).

METHODS

A retrospective, noncomparative, observational case series study was performed. This involved a review of the medical records of all patients who underwent a whole body PET/CT examination as a staging procedure to detect metastasis at the time of diagnosis of primary uveal melanoma. This study adhered to the tenets of the Declaration of Helsinki, the Health Insurance Portability and Accountability Act of 1996, and was approved by the Institutional Review Board of The New York Eye Cancer Center.

Entry criteria

Since August 2003, PET/CT has been offered for initial metastatic screening to all patients diagnosed with uveal melanoma. Imaging was performed in addition to a physical examination and liver function tests (γ-glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin).

Abnormalities found on PET/CT imaging were correlated with the known history of infectious or inflammatory disease, their anatomic location and shape. Suspicious findings prompted further action. This included referral to other specialists, blood tests, additional radiologic examinations such as US, mammography, MRI, and/or CT with contrast agents, and biopsy.

Patients were staged according to the 7th edition of the AJCC TNM classification (Tab. I) (16). In addition to being staged by tumor size (T), they were assigned a subgroup of a-e. The “a” signifies that there was no ciliary body involvement or extraocular extension (EOE), “b” signifies that there was ciliary body involvement, “c” signifies no ciliary body involvement but with EOE ≤5 mm in diameter, and “d” signifies ciliary body involvement and EOE ≤5 mm in diameter. Finally, only T4 can denote the letter “e”, which signifies it is a tumor of any size category with EOE more than 5 mm in diameter. For distant metastasis (M), in addition to the presence (“1”) or absence (“0”) of metastasis, the patients were subgrouped as a-c. The “a” signifies largest diameter of the largest metastasis of 3 cm or less, “b” signifies the largest metastasis of 3.1-8.0 cm, and “c” signifies the largest metastasis is 8 cm or greater.

PET/CT imaging

We have described our methods of PET/CT imaging (5, 7, 10). In summary, to increase the signal-to-noise ratio and to standardize the FDG uptake, patients were asked

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TABLE I - AJCC TNM-BASED CLASSIFICATION SYSTEM T (TUMOR) FOR UVEAL MELANOMA STAGING

Thickness (mm)							
>15.0					4	4	4
12.1-15.0				3	3	4	4
9.1-12.0		3	3	3	3	3	4
6.1-9.0	2	2	2	2	3	3	4
3.1-6.0	1	1	1	2	2	3	4
≤3.0	1	1	1	1	2	2	4
	≤3.0	3.1-6.0	6.1-9.0	9.1-12.0	12.1-15.0	15.1-18.0	>18.0
	Largest basal diameter (mm)						

AJCC = American Joint Committee on Cancer; TNM = tumor, node, metastasis.
This chart is a quick guide to determine T stage using tumor size as the criteria. The left vertical column (representing tumor thickness) can be matched to the horizontal column (representing largest tumor basal dimension) to yield the T staging (1-4). Reprinted with permission from: AJCC-UICC Ophthalmic Oncology Task Force: Malignant Melanoma of the Uvea Ophthalmic Sites: Part X. In: Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual, 7th ed. New York, NY: Springer 2009 (16).

to refrain from eating a carbohydrate-based dinner the previous night and to fast 4–6 hours before the beginning of the examination. An intravenous dose of 14.4 to 19 mCi of FDG (depending on the patient's weight) was followed by 10 mL saline flush.

Almost all procedures were performed utilizing a bismuth germinate crystal-based multidetector helical CT scanner (General Electric Discovery ST, Piscataway, NJ, USA). The stated resolution of the PET scan was 4 mm. The PET scan reconstructed the images utilizing the CT scanner information to correct for attenuation. Then Xeleris workstation (General Electric Software, Piscataway, NJ, USA) was used to fuse, produce, and display the PET/CT images. The resultant images were evaluated for areas of focally increased glucose uptake. Measured in standardized uptake value (SUV), those values above 2.5 suggested malignancy.

RESULTS

A total of 333 patients (163 male and 170 female) with a mean age of 64 years (range, 25-98) were included in the study. There were 51 anterior (involving the iris and/or ciliary body) and 282 posterior tumors (confined to the

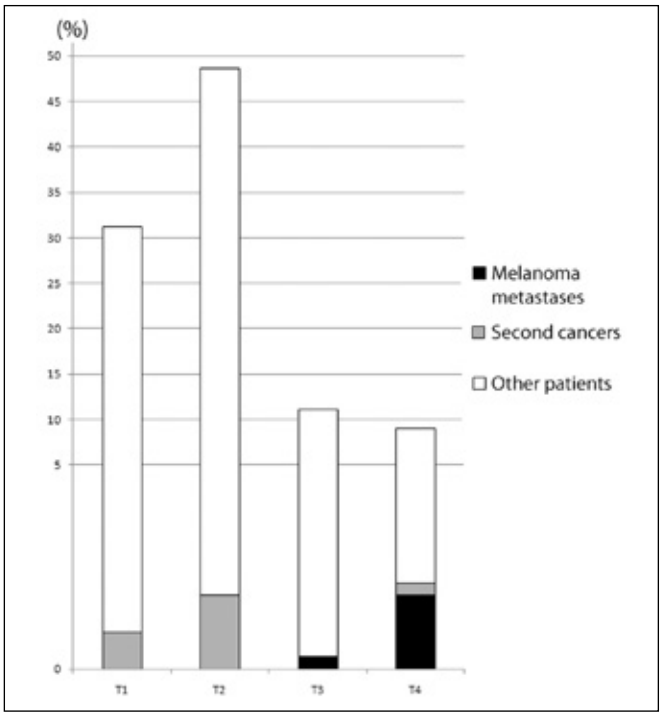

Fig. 1 - *Tumor characteristics within the tumor, node, metastasis–American Joint Committee on Cancer classification, along with metastases and second cancer rates. Note that for visualization purposes, a nonlinear scale was used. The frequency of metastatic disease was significantly higher in the T4 group than in the T3 group (Fisher exact test, p<0.001) (3).*

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choroid). By the 7th edition AJCC TNM classification (Tab. I), there were 104 T1 (31%), 162 T2 (49%), 37 T3 (11%), and 30 T4 (9%) tumors (Fig. 1). According to the COMS criteria, there were 66 small (20%), 213 medium (64%), and 54 large (16%) melanomas.

Metastatic disease findings

Of 333 patients screened by PET/CT, 7 (2.1%; 95% confidence interval [CI] 0.8-4.3) were diagnosed with metastatic melanoma (mean age, 70 years). Six tumors were T4 and one was T3a (Fig. 1). Among the 6 T4 tumors, there were 2 T4a, 1 T4b, and 3 had extrascleral tumor extension, and were graded as 1 T4c and 2 T4e. The range of largest diameter of extrascleral extension was 1.8-26.0 mm. With regards to the COMS criteria, 6 patients had a large tumor and one was medium-sized.

Liver involvement was present in all 7 patients (range of largest metastasis, 0.9-4.1 cm) and it was the only site of detectable metastasis in 5 patients. In 2 patients, metastases were also detected in bone, lungs, lymph nodes, brain, and spleen. Six patients were AJCC M1a and 1 was M1b. Histopathologic confirmation was obtained by liver biopsy in 6 patients. The seventh died of metastatic spread before a biopsy could be performed. Of interest, liver function tests were within normal range in all 7 patients. According to the working formulation for staging metastatic uveal melanoma defined by Eskelin et al, 6 patients were stage IVa and 1 was stage IVb (17).

The probability of having metastases diagnosed during initial screening was significantly higher in patients with T4 tumors (20%; 95% CI 8-39) as compared to T3 tumors (3%; 95% CI 0-14; Fisher exact test, $p=0.04$) or T2 tumors (0%; 95% CI 0-2; Fisher exact test, $p<0.001$). The metastasis rate in patients with tumors considered as large according to the COMS criteria (11%; 95% CI 4-23) was also significantly higher as compared to those judged to have medium-sized tumors (0.5%; 95% CI 0-3; Fisher exact test, $p<0.001$).

Synchronous second cancers

In 10 patients (3.3%; 95% CI 0.9-5.5), PET/CT findings led to the diagnosis of second synchronous cancers (mean age, 71 years). These neoplasms were located in the lungs (n=4), colon (n=3), thyroid (n=1), breast (n=1), and 1 was a lymphoma. Diagnoses of synchronous cancers were confirmed by consecutive subspecialty consultation and subsequent histopathologic analysis. Patients with T1 and T2 melanomas had a comparable chance (1%-2%) of having a second cancer diagnosed as those with T4 tumors.

Benign lesions

In 28 patients (8.4%; 95% CI 5.7-12), PET/CT findings prompted further investigations leading to the diagnosis of benign lesions. These were most often located in lymph nodes (n=9), lung (n=6), and thyroid (n=6). Four patients eventually required biopsies (for breast, thyroid, and pelvic lesions). In all other patients for whom avid lesions were discovered on PET/CT, medical history of patients was contributive enough and strongly supported the benign nature of the lesions (e.g., old healed fractures or reactive cervical lymph nodes).

DISCUSSION

PET/CT as a screening tool

This study shows that PET/CT can be used as a screening tool for initial staging to detect metastasis for patients with uveal melanoma. Specifically, scalp-to-toes PET/CT imaging uncovered extrahepatic metastases that would have been missed with blood tests and abdominal imaging.

Though all patients with metastases in this series had liver involvement, liver imaging alone might not have identified them (Fig. 2). Clearly, our results support the value of PET/CT also in staging patients who have been found to have lesions suspicious of metastasis by any other screening method.

PET/CT for screening of large uveal melanomas

In patients with large tumors, the yield of PET/CT was high. This finding probably reflects increased risk for metastasis in this subpopulation (Tab. II). In this comparison, the COMS size categories were chosen because the COMS study provided the most recent and detailed data suitable for the purpose of comparison. However, even a stronger association was found to exist between AJCC/TNM categories and PET/CT yield (Fig. 1). In fact, within the T4 category the yield was 20% as compared to 11% for COMS large tumors. The latter rate was significantly

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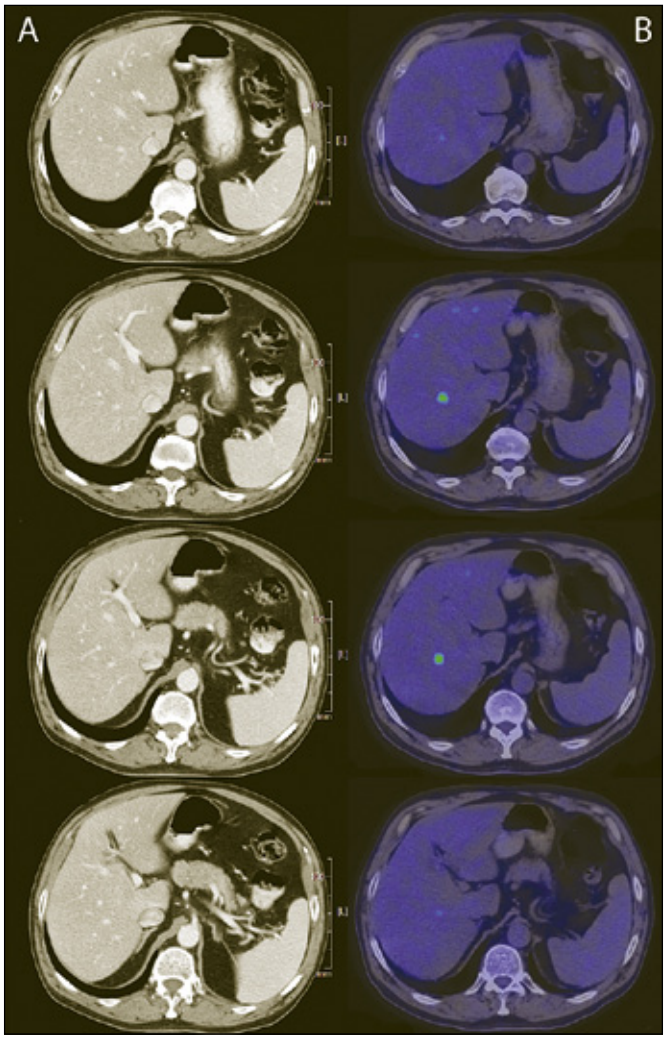

Fig. 2 - *Comparison of computed tomography (CT) with contrast and positron emission tomography (PET)/CT imaging. The liver aspect is unremarkable on consecutive CT sections* **(A)**. *Sections performed at the same level highlighted a suspicious focus of FDG uptake (mean specific uptake value = 2.9) on PET/CT* **(B)**. *The liver biopsy eventually confirmed the diagnosis of metastatic melanoma.*

higher than the 2.4% rate reported in the COMS large tumor study in which liver function tests and chest x-ray were used to scan for metastases (18) (Fisher exact test, p=0.003). However, patients who had extrascleral tumor extension of 2.0 mm or more detected during echography or clinical examination were excluded from the COMS large melanoma study (18), and 2 out of our 3 patients with an extrascleral growth had an extension that was of that size, so that the comparable percentages are 7.4% vs 2.4% (Fisher exact test, p=0.05) (Tab. II).

Specific organ involvement

In our study, every patient with metastasis had liver involvement. When PET/CT demonstrated liver metastasis, all subsequent biopsies were positive. This is not surprising in that the liver is consistently reported as the most common initial metastatic site, accounting for 50% to 90% of cases (17, 19-21). Care should be taken in order to maximize sensitivity, specificity, and accuracy of metastases detection within this organ. Our study found a positive predictive value of 100% when PET/CT revealed abnormal FDG uptake in the liver. This ratio might not be as high in a larger population of patients, but still reflects the low false-positive findings of PET/CT for screening of liver metastases, thus avoiding a major drawback of conventional screening procedures such as US or CT (22, 23).

In one case in our series, PET/CT demonstrated a relatively small and solitary metastasis just 9 mm in largest diameter. Subsequent percutaneous liver biopsy had to be repeated (on 3 separate occasions) and was only successful when the tumor enlarged to 20 mm (Fig. 2). A limit of 9 mm is also reported for detection of metastatic uveal melanoma by liver US (24). These findings suggest that PET/CT is at least as sensitive as US for liver metastases screening, and

TABLE II - COMPARISON OF METASTATIC RATES AT DIAGNOSIS ACCORDING TO THE COMS SUBGROUPS

	COMS				Present study			
	Small	**Medium**	**Large**	**Total**	**Small**	**Medium**	**Large**	**Total**
Population	300	2164	1860	4324	66	213	54	333
Metastases cases	0	21	45	66	0	1	4	7
Ratio	0%	1.0%	2.4%	1.5%	0%	0.5%	7.4%	2.1%

In patients with large tumors, excluding those with an extraocular extension of 2.0 or more, the frequency of metastatic disease was significantly higher in the present study as compared to the Collaborative Ocular Melanoma Study (COMS) (Fisher exact test, p=0.05).

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that its resolution may be ahead of the capability of US-guided fine-needle aspiration liver biopsy (25).

Extrahepatic findings

Two out of 7 patients with metastatic melanoma were found to have multiorgan disease. These findings highlight PET/CT's capability for whole body metastasis screening (26). Significantly, approximately 8% of patients with newly diagnosed metastatic uveal melanoma are reported to have only extrahepatic disease, and 11% have both hepatic and extrahepatic lesions (24).

Synchronous cancers

Whole body screening uncovered synchronous primary cancers as well as hypermetabolic benign processes (27). Approximately as many patients were diagnosed with synchronous, previously undetected nonocular cancers than with metastatic melanoma. All of these tumors would likely have been missed with hepatic screening protocols (28). The high number of patients found to have synchronous cancer suggests (but does not prove) an increased risk for cancer among patients with uveal melanoma.

Of interest, the COMS reported that patients who underwent plaque brachytherapy for choroidal melanoma did not develop more cancers after treatment than a naive population of patients of the same age (28). However, patients with a history of cancer and those found to have second cancers at diagnosis were excluded from participating in the COMS.

In general, multiple primary neoplasms account for 13-16% of all malignancies and are considered to be the sixth most common presentation of cancer (29, 30). More specifically, of 530 patients with uveal melanoma audited for the presence of second cancers, 10% had 2 and 1% had 3 malignant tumors diagnosed in their lifetime (31).

Notably, a long-term follow-up study suggested that 6% of patients with uveal melanoma die of a second malignancy whereas 49% die of metastatic melanoma (31). Although uveal melanoma remains the leading cause of death of patients diagnosed with this cancer, the potential benefit of detecting second cancers early with PET/CT should not be downplayed. According to our results, this benefit extends to all patients diagnosed with uveal melanoma.

Cost effectiveness

Several authors have tried to assess the cost-effectiveness of widespread use of PET/CT in miscellaneous clinical settings (32, 33). In review of this subject many variables must be considered (33). For example, a wide range of prices are charged for PET/CT imaging. Positron emission tomography/CT is likely to be more expensive than abdominal CT or MRI. However, the cost of total body "segmental" MRIs or CTs (plus a PET scan) exceeds that of PET/CT alone.

There is also a human cost. Patients express relief at having a "total body scan" to rule out metastasis. Also consider the human cost of hepatic surgery or targeted hepatic chemotherapy in cases with extrahepatic disease or the cost of missed synchronous primary cancer.

A typical overall approach to analyzing cost-effectiveness consists of quantifying the consequences for clinical practice by calculating the percentage of patients in whom PET/CT induces a change in diagnostic strategy or treatment plan. In that respect, PET/CT screening at diagnosis is more appropriate than during follow-up, because discovery of metastatic disease can alter a patient's treatment plan (e.g., from local to systemic). However, in cases of patients with large tumors and painful eyes, palliative local treatment may be offered despite the presence of even advanced metastasis.

Risk of PET/CT and other imaging modalities

There exists risk in every radiologic test. There is risk of nephrogenic systemic fibrosis with gadolinium-enhanced MRI, second cancer risk associated with radiographic computed tomography, and the risk of a missed tumor with abdominal ultrasound (34, 35). One report indicates that a PET/CT scan results in a 0.2%-0.5% per year risk of developing a second cancer (36). However, the average effective dose received from a PET/CT examination has been reported to range from 18 to 25 mSv, whereas a dose of 30 mSv is reported for a multiphasic abdominal and pelvis scan (37, 38). Though this is a controversial issue, it is commonly accepted that the risk of missing a cancer diagnosis should be weighed against the risk of radiation exposure. Although this topic is beyond the scope of this study, a direct comparison of the risk of radiation-induced cancer from PET/CT versus other imaging techniques (CT, MRI) should be assessed.

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PET/CT applications in practice

Although the data presented herein suggest the use of PET/CT for metastatic screening in the larger T3 and T4 tumors, more studies are clearly needed. For example, continued broad study of PET/CT may be needed to monitor genetically screened high-risk tumors (Class 2 RNA profiles). It may be found helpful in screening select patients for synchronous nonocular primary cancers. Perhaps PET/CT may be found most helpful within specified time windows when previously occult metastases are likely to become radiographically visible. The findings of this study support the continued investigation of PET/CT for initial screening of patients with iris, ciliary body, and choroidal melanoma.

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