SCIENTIFIC REPORT

18-Fluorine-labelled 2-deoxy-2-fluoro-D-glucose positron emission tomography/computed tomography standardised uptake values: a non-invasive biomarker for the risk of metastasis from choroidal melanoma

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Aims: To correlate the clinical, ultrasound and pathological features of the eyes first evaluated by 18-fluorine-labelled 2-deoxy-2-fluoro-D-glucose (FDG) positron emission tomography (PET)/computed tomography and then enucleated for choroidal melanoma.

Methods: 14 consecutive patients enucleated for choroidal melanoma were examined. At presentation, clinical, ultrasound and PET/computed tomography imaging were carried out. Ultrasound was used to measure the tumour size and evaluate the tumour shape and intrinsic vascularity (blood flow). Histopathological and immunohistochemical evaluations included tumour cell type, necrosis, glycogen content, vascularity and extrascleral extension.

Results: 13 tumours were T3 and one T2 (American Joint Committee on Cancer – International Union against Cancer). The mean tumour height was 10.6 (range 3.5–17.7) mm with a largest basal dimension of 19.3 (range 14.5–30) mm. Patients having melanoma with the highest six standardised uptake values (SUV) ≥ 4.0 were (on average) >10 years older, their melanomas had larger basal dimensions and were epithelioid-cell type; three melanomas were centred anterior to the equator; three contained enlarged blood vessels ($>150 \mu\text{m}$ in diameter); and three formed extrascleral extension. Patients with the two highest SUV tumours died due to metastatic melanoma.

Conclusion: PET/computed tomography imaging offers a physiological assessment of glucose metabolism in primary choroidal melanomas. Increased FDG PET/computed tomography SUV was positively correlated with known clinical, pathological and ultrasound features linked to metastatic potential of choroidal melanoma.

The Collaborative Ocular Melanoma Study (COMS) and The American Joint Committee on Cancer (AJCC) – International Union against Cancer have established size-based classifications of primary choroidal melanomas.^{1–3} In clinical practice, each choroidal melanoma is also characterised by its ophthalmoscopic appearance, associated retinal detachment and orange pigmentation.⁴ Diagnostic ultrasound helps define the tumour's shape, dimensions, retinal detachment, extrascleral tumour extension and vascularity.^{5,6} Photographic imaging (with angiography) offers unique views of the tumour borders, vascular patterns and leakage.⁷ Using all these criteria, the accuracy of clinical diagnosis has been reported to be 99.6% (among

COMS-eligible patients).⁸ Commonly and widely used risk factors for metastasis include patient's age, largest tumour diameter, intraocular tumour location, cell type, vascular patterns and the presence of extrascleral tumour extension.^{9–11} Among these, the COMS found that the patient's age and largest tumour diameter were statistically significant risk factors. Recently, interest is seen in incorporating molecular and genetic-based prognostic factors.¹²

The advent and evolution of positron emission tomography (PET) heralded renewed interest in physiological tumour imaging.¹³ Refinements in PET imaging and fusion with computed radiographic tomography have placed form and function on the same diagnostic page. PET/computed tomography has offered a non-invasive method to determine the standardised uptake value (SUV) of 18-fluorine-labelled 2-deoxy-2-fluoro-D-glucose (FDG) in choroidal melanoma.^{14,15} Specifically, PET SUV detects uptake of radiolabelled glucose by transporter-1 receptors typically increased in tumour cells undergoing glycolysis. The greater the metabolic activity, the higher the SUV. PET/computed tomography-derived FDG SUV intensity has been used to determine malignancy and response to treatment, and to assess the risk of metastasis.^{16–18}

Here, we study 14 choroidal melanomas evaluated by PET/computed tomography and subsequently treated by enucleation. Patient and tumour characteristics were correlated with ultrasound, pathological and PET/computed tomography findings. SUV was correlated with known clinical, pathological and ultrasound features associated with risk for metastatic choroidal melanoma.

PATIENTS AND METHODS

Since 2004, out of 147 consecutive patients diagnosed with choroidal melanoma within the framework of The New York Eye Cancer Centre (New York City, New York, USA), 133 (90.5%) could be initially treated by observation or plaque irradiation, whereas 14 (9.5%) required primary enucleation (table 1).

Pre-operative metastatic surveys included but were not limited to a whole-body FDG PET/computed tomography with fusion (fig 1). The entire body was scanned so as to reassure the patient that no portion of the body was excluded and also owing to the 50% incidence of osseous foci (in patients found to have metastatic choroidal melanoma).¹⁹ Of

Abbreviations: AJCC, American Joint Committee on Cancer; COMS, Collaborative Ocular Melanoma Study; FDG, 18-fluorine-labelled 2-deoxy 2-fluoro-D-glucose; PET, positron emission tomography; SUV, standardised uptake values

Table 1 Patient characteristics compared with positron emission tomography/computed tomography 18-fluorine-labelled 2-deoxy-2-fluoro-D-glucose standardised uptake values

Patient no	Age (years)	Total F/U (months)	Metastatic disease	Deceased	PET—SUV maximum
1	95	1	Yes	Yes	9.0
2	65	11	Yes	Yes	7.1
3	45	4	No	No	6.9
4	88	6	No	No	6.2
5	57	20	No	No	4.1
6	49	1	No	No	4.0
Mean	67	7.2			6.2
7	54	21	No	No	3.5
8	67	24	No	No	3.5
9	62	6	No	No	3.0
10	41	12	No	No	2.8
11	69	11	No	No	2.5
12	54	2	No	No	1.7
13	48	24	No	No	0.0
14	62	12	Yes	No	0.0
Mean	57	14			2.1

PET, positron emission tomography; SUV, standardised uptake value.

our 14 patients, 13 were negative for metastatic disease. The one with metastatic choroidal melanoma required enucleation for pain control and died (table 1). All patients were informed of the potential risks and benefits of observation, plaque brachytherapy and enucleation. The study adhered to the tenets of the Declaration of Helsinki and the US Health Insurance Portability and Privacy Act of 1996.

PET/COMPUTED TOMOGRAPHY IMAGING

We have previously described our technique of PET/computed tomography imaging.¹⁴ In brief, patients were instructed to refrain from intake of carbohydrates and to fast for 4–6 h before injection of FDG. Serum glucose levels were acceptable in the range of 80–160 mg/dl. Full-body PET/computed tomography imaging began at the top of the head and ended at the bottom of the feet. The computed tomography consisted of a multidetector helical scanner; oral contrast was used but breath-hold technique was not. Imaging parameters were 80–140 kV, 40–80 mA, 0.8 s per computed tomogram rotation, and a table speed of 33.75 mm/rotation. Slice thickness (computed tomogram) was 3.75 mm (image interval 3.27 mm). Then PET acquisition involved FDG injection (target dose of 185 mBq (range 370–740 mBq)) calculated as patient weight multiplied by the target dose in mBq/70 kg. FDG injection was followed by 10 cm³ normal

saline. PET imaging began within 45 min and ended no later than 1.5 h after injection. Scans were acquired in two-dimensional mode with real-time subtraction. Reconstruction was an ordered subset expectation maximisation with 30 subsets and two iterations. A post-filter of 6.14 mm full-width at half-maximum and a loop filter of 4.69 mm full-width at half-maximum were used, as well as a z axis filter. Images were reconstructed in a 128×128 matrix and displayed in a field of diameter 60 cm. PET scan resolution was 4 mm. Transmission times of 2–3 min were required at each of the nine bed positions.

After each position, the 512×512 cm computed tomography matrix was fed into the PET scan. The PET scan reconstructed the images on the fly and used the computed tomography scan to correct for attenuation. Xeleris Software (General Electric, Piscataway, New Jersey, USA) was used to fuse and display the PET/computed tomography images (fig 1). Glucose uptake and a maximum SUV (max) were calculated for each site using the conventional formula:

$$\text{SUV} = \frac{\text{Tissue activity (mBq/ml)}}{\text{Injected dose (mBq) / Body weight (kg)}}$$

Figure 1 Three images of the right eye of patient no 1 with the high (9.0) standardised uptake value (SUV) ring melanoma. Left, the computed tomogram (CT) shows the anatomical density best seen at the nasal ciliary body. Middle, fusion of the CT and positron emission tomogram (PET) shows the blend of form and function (on the same diagnostic image), where the high SUV ring melanoma is localised to the anterior uvea. Right, the PET shows avid 18-fluorine-labelled 2-deoxy-2-fluoro-D-glucose uptake by the ring melanoma (with little reference to its anatomical location).

PET/computed tomography images were studied for the presence and luminescence of the intraocular melanomas (fig 1).

RESULTS

Standardised uptake values

We chose an SUV of 4.0 to distinguish metabolically active versus metabolically inactive tumours (table 1). This threshold is not a clinical standard (none exists), but appeared to be a natural divide in our dataset and may be relevant in itself. In this study, high SUV was ≥ 4.0 (mean 6.2, range 4.0–9.0) in 6 (43%) of the 14 tumours. The melanomas with high SUV occurred in patients who were (on an average) 10 years older, and patients with the highest two SUV values died of metastatic melanoma (fig 1).

Ultrasound findings

Ultrasonographic tumour characteristics were examined (table 2). The mean tumour height and largest basal diameter of all 14 melanomas were 10.6 (range 3.5–17.7) mm and 19.3 (range 14.5–30) mm, respectively. The higher SUV tumours were noted to have a mean largest dimension of 21 compared with 18.1 in the lower SUV group. They were also taller. We noted a predominance of mushroom-shaped tumours, a high incidence of observable tumour blood flow and secondary retinal detachments. These findings were (in general) consistent with the size of tumours studied. Five of six of the highest SUV tumours detected by PET/computed tomography were mushroom shaped. These were only exceeded by the largest uveal melanoma, the ring melanoma with an SUV of 9.0. The three highest SUV tumours were centred anterior to the equator (table 2).

Pathology

Histopathological analysis for tumour cell type, vascularity, necrosis and extrascleral extension was carried out (table 3). The ophthalmic pathologist was blinded to the patient's history, clinical evaluations and SUV findings by PET/computed tomography. Epithelioid-cell tumours constituted 50% of the six high SUV tumours (≥ 4.0). Immunohistochemical studies (factor 8 stain for vascular endothelial cells) also showed a mean of 2.5 blood vessels per five $\times 20$ fields versus 3.1 in the lower SUV group. However, all of the large blood vessels (>150 μ m in diameter) were observed in patients with high SUV. Additional analysis for

tumour necrosis as well as diastase-digested preparations (for glycogen) was unremarkable. Finally, it is important to note that three of the top six SUV melanomas had formed extrascleral extension (table 3). However, extrascleral extension was also noted in the one SUV 0, epithelioid-cell tumour that had metastasised.

DISCUSSION

PET/computed tomography fusion scanners have brought molecular imaging to the forefront of malignant melanoma diagnosis and staging.²⁰ The combination of PET with computed tomography has increased the confidence and accuracy of diagnosis compared with PET/computed tomography alone.²⁰ PET/computed tomography imaging of intraocular melanoma has found that increasing tumour size is related to SUV positivity.¹⁵ Specifically, (0%) of AJCC-T1/small, 33% of T2/medium and 75% of T3/large choroidal melanomas exhibited SUV values ≥ 2.5 .¹⁵ Similarly, we found that the sole T2 tumour and (10/13) 77% of the T3 tumours exhibited SUV values ≥ 2.5 . The highest SUV (9.0) was in the melanoma with the largest tumour dimension (fig 1). Though size was a factor, many tumours did not accumulate FDG, indicating that size was not the only factor governing SUV positivity. In all studies, a considerable number of choroidal melanomas (T2 and T3) could be prospectively analysed for the prognostic value of their SUV intensity.

In interpretation of the value of SUV, it is important to note that no predictor of metastasis (eg, vascularity, cell type, largest tumour dimension or intraocular location) can be expected to be invariably correct. This is understandable, in that no single medical test is 100% accurate in clinical practice. However, as noted with other malignancies, a high SUV was associated with known risk factors for metastasis, metastatic disease and poor survival. Our data uncovered trends towards a higher SUV among larger, anterior and epithelioid-cell melanomas. Higher SUV tumours were seen in older patients with larger tumour diameters (the statistically significant risk factors determined by the COMS study). These findings suggest that high SUV tumours are more likely to metastasise and that SUV information may be useful in evaluation of the metastatic potential of a choroidal melanoma.

It is striking that PET/computed tomography SUV may offer a non-invasive physiological measure of choroidal melanoma metabolism, correlated with known risk factors

Table 2 Ultrasound findings compared with positron emission tomography/computed tomography 18-fluorine-labelled 2-deoxy-2-fluoro-D-glucose standardised uptake values

Patient no	Apical Ht (mm)	LTD (mm)	Tumour location	Tumour size		Tumour shape	Retinal detachment	Vascularity ultrasound	PET—SUV maximum
				AJCC - UICC	COMS				
1	5.5	30	cb	T3	Large	Ring	No	NA	9
2	12.3	19.1	7:30 ea	T3	Large	Mushroom	Yes	Yes	7.1
3	12.9	18	7:30 cb	T3	Large	Mushroom	Yes	Yes	6.9
4	17.7	17.9	7:00 pe	T3	Large	Mushroom	Yes	Yes	6.2
5	11.5	16.1	6:00 ep	T3	Large	Mushroom	Yes	NA	4.1
6	12	25	4:30 e	T3	Large	Mushroom	Yes	Yes	4
Mean	12.0	21.0							6.2
7	6	15.8	6:00 pe	T2	Medium	Dome	Yes	NA	3.5
8	14	17.2	9:00 e	T3	Large	Mushroom	Yes	Yes	3.5
9	12	20.5	9:00 e	T3	Large	Mushroom	Yes	No	3
10	13.7	17.8	8:00 pe	T3	Large	Dome	No	Yes	2.8
11	5.9	20.8	6:00 cb	T3	Large	Dome	Yes	Yes	2.5
12	3.5	19	12:00 ea	T3	Large	Dome	No	Yes	1.7
13	13.7	14.5	11:00 e	T3	Large	Mushroom	Yes	Yes	0
14	8.3	18.9	3:00 pe	T3	Large	Dome	Yes	NA	0
Mean	9.6	18.1							2.1

a, anterior; AJCC, American Joint Committee on Cancer; cb, ciliary body; COMS, Collaborative Ocular Melanoma Study; e, equator; Ht, height; LTD, largest tumour dimension; NA, not available; p, posterior; PET, positron emission tomography; SUV, standardised uptake value; UICC, International Union against Cancer.

Table 3 Pathological findings compared with positron emission tomography/computed tomography 18-fluorine-labelled 2-deoxy-2-fluoro-D-glucose standardised uptake values

Patient no	Pathology cell type	Pathology extrascleral extension	Tumour necrosis	Cytoplasmic glycogen	Tumour blood vessels, Mean/five ×20 fields	Tumour large vessels, >150 µm	PET—SUV maximum
1	Mixed	Yes	Yes	Yes	2.1	No	9.0
2	Mixed	Yes	No	No	0.9	No	7.1
3	Epithelioid	No	No	No	2.7	Yes	6.9
4	Epithelioid	No	No	No	2.4	No	6.2
5	Mixed	Yes	No	No	1.5	Yes	4.1
6	Epithelioid	No	No	No	5.6	Yes	4.0
Mean	50%	50%	17%	17%	2.5	50%	6.2
7	Spindle B	No	No	No	0.7	No	3.5
8	Spindle B	No	No	No	3.7	No	3.5
9	Spindle B	No	No	No	6.7	No	3.0
10	Mixed	No	No	Yes	0.9	No	2.8
11	Mixed	No	No	No	0.9	No	2.5
12	Mixed	No	No	No	2.1	No	1.7
13	Spindle B	No	No	Yes	8.5	No	0.0
14	Epithelioid	Yes	No	No	1.5	No	0.0
Mean	12.5%	12.5%	0%	25%	3.1	0%	2.1

Mixed, both epithelioid and spindle melanoma cells; PET, positron emission tomography; SUV, standardised uptake value.

for metastasis. This compelling evidence is enough to warrant a more large-scale, prospective statistical analysis of the prognostic value of PET/computed tomography SUV for choroidal melanoma.

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