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# Metabolic activity of primary uveal melanoma on PET/CT scan and its relationship with monosomy 3 and other prognostic factors

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## ABSTRACT

**Purpose** To correlate the metabolic activity of primary uveal melanoma on positron emission tomography (PET)/CT scan with known clinical and pathological prognostic factors.

**Methods** A retrospective cohort analysis of eyes enucleated for uveal melanoma that underwent preoperative imaging with a PET/CT scan was performed. Tumour dimensions were recorded and classified using Collaborative Ocular Melanoma Study (COMS) and American Joint Committee on Cancer (AJCC) Tumour - Nodes - Metastases (TNM) criteria. Metabolic activity was determined by measurement of the maximal standardised uptake value (SUVmax) on PET/CT scans. SUVmax of >2.5 and >4 was also used as cut-off value for metabolic positivity. Chromosome 3 and 8 status was determined using fluorescence in situ hybridisation analysis. Pearson correlation,  $\chi^2$  test and non-parametric tests were used.  $p < 0.05$  was considered statistically significant.

**Results** Seventy-six uveal melanomas were imaged preoperatively with a PET/CT scan. Overall 92% of tumours had a SUVmax >2.5 and 67% had a SUVmax >4. Monosomy 3 was found in 35 melanomas, of which 94% had an SUVmax >2.5 and 80% had an SUVmax >4. Only 57% of disomy 3 melanomas had an SUVmax >4. SUVmax was significantly increased in tumours with monosomy 3 ( $p = 0.043$ ) but not in tumours with chromosome 8 gain ( $p = 0.49$ ). SUVmax and increasing tumour size were positively correlated ( $p < 0.05$ ). Using the AJCC criteria, there was a significant difference in SUVmax among prognostic groups ( $p = 0.024$ ). There was no correlation with histopathological cell type ( $p = 0.923$ ).

**Conclusions** Metabolic activity of uveal melanoma on PET/CT scan is positively correlated with monosomy 3, increasing tumour size and TNM prognostic groups. No association with chromosome 8 gain or histopathology cell type was noted. SUVmax >4 is a relative but not an absolute indicator of monosomy 3 status.

## INTRODUCTION

Uveal melanoma is the commonest primary intraocular malignancy. Despite the availability of treatment modalities, the survival rates have not changed in 30 years. Cumulative rates of metastases in the Collaborative Ocular Melanoma Study at 5 and 10 years after treatment were 25% and 34%, respectively. Common sites of metastases include the liver (90%), lung (24%) and bone (16%). Median survival for a hepatic metastasis is 6 months with an estimated survival of 15–20% at 1 year and 10% at 2 years, irrespective of treatment.<sup>1</sup>

Loss of one copy of chromosome 3 is associated with a 5-year survival of approximately 50%,

whereas disomy 3 has been reported to predict 100% survival<sup>2–3</sup> or less.<sup>4</sup> These chromosomal abnormalities, together with large tumour size and epithelioid cell type, are established poor prognostic risk factors.<sup>5</sup>

In recent years, dual-modality positron emission tomography/CT (PET/CT) imaging has emerged as an important staging modality for systemic malignancies.<sup>6</sup> Its advantage is the depiction of metabolic activity as obtained by 18-fluoro-2-deoxyglucose PET in combination with detailed morphologic characteristics from CT. Individual case series have demonstrated that whole-body 18-fluoro-2-deoxyglucose tomography (18-FDG PET/CT) imaging is sensitive in detecting hepatic and extrahepatic metastases in uveal melanoma patients.<sup>7–9</sup> However, detection of primary choroidal melanoma has been reported to be dependent on tumour size,<sup>10–11</sup> status of chromosome 3<sup>12</sup> and histopathology cell type.<sup>13</sup>

The aim of this study was to record the degree of ocular metabolic activity seen on PET/CT scanning in patients undergoing primary enucleation for uveal melanoma. The level of metabolic activity (maximal standardised uptake value (SUVmax)) was correlated with the individual clinical, pathological and cytogenetic features of each tumour.

## MATERIALS AND METHODS

This work was approved by the Institutional Review Board of Moorfields Eye Hospital. The clinical records of all patients that underwent primary enucleation for uveal melanoma between 2009 and 2012 were reviewed. Tumour dimensions (thickness, maximal and minimal base diameter) and anatomic location were recorded with fundus examination and B-scan ocular ultrasound (Acuson Sequoia 512—Siemens AG, Munich, Germany) (figure 1). Uveal melanoma size was classified according to the American Joint Committee on Cancer (AJCC) 7th edition system and the Collaborative Ocular Melanoma Study (COMS) criteria. Tumour area and volume were calculated as previously described.<sup>9</sup>

All patients were staged with a PET/CT scan (Philips Gemini TF LSO64) (figure 1). Images used in visual and region of interest (ROI) analysis were acquired in three-dimensional and reconstructed using OSEM (ordered subset expectation maximisation; 33 subsets, three iterations, no filters). All patients fasted for 6 h and the uptake time was 60 min. Half-body imaging was acquired in 10 or 11 bed positions from skull base to thighs. The CT



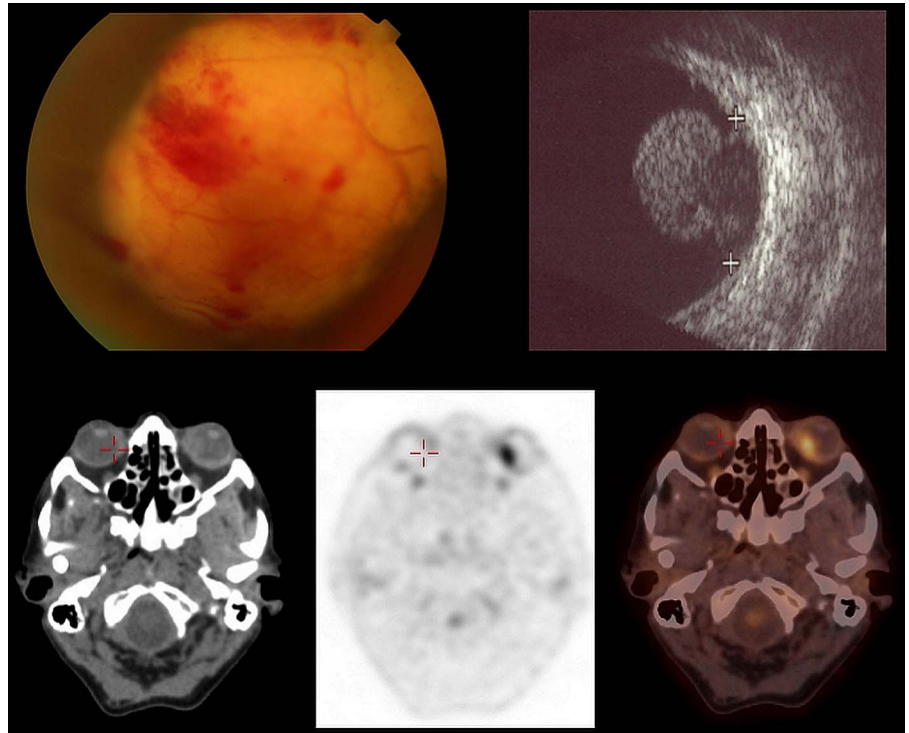
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**Figure 1** Top row: fundus photograph of a large left amelanotic choroidal melanoma. Choroidal vessels are discernible with an associated superficial haemorrhage and retinal detachment. Ultrasound scan indicated a mushroom shaped lesion measuring 7.5 mm. Bottom row: the composite of CT scan and positron emission tomography (PET) scan demonstrates the anatomic location and metabolic fluoro-2-deoxyglucose uptake of the melanoma.



scan for attenuation correction and anatomical localisation was performed at 120 Kvp and 60 mAs. Additional views of the head and neck were acquired at the end to minimise effects of patient movement. All PET/CT images were evaluated for areas of increased fluorodeoxyglucose uptake (SI and TS). If fluorodeoxyglucose uptake was identified at the site of the melanoma, the SUVs were derived from ROI drawn on contiguous axial slices encompassing the entire lesion and by SUVmax that was localised to the area of tumour seen clinically. SUV provides an index of tracer uptake that can be compared between scans. It provides a semiquantitative measure of tracer uptake and is based on the approximation that the tracer is uniformly distributed throughout the body, hence normal tissue SUV is approximately=1

$$\text{SUV} = \frac{\text{tracer uptake (in MBq/mL)} \times 1000}{\text{Administered activity (MBq)/Patient weight (kg)}}$$

Following enucleation, a fresh tumour tissue sample was obtained with a punch biopsy with a 6 mm trephine. Biopsy samples were manually disaggregated and aspirate samples centrifuged at 1200 rpm to remove transport medium prior to preparation of slides. The samples were incubated in 0.075 M KCl for 15 min and then fixed with methanol to acetic acid (3:1). Interphase fluorescence in situ hybridisation (FISH) was performed using three DNA probes (CEP3 SpectrumOrange to CEN 3, Vysis, Des Plaines, Illinois, USA), specific for the centromere region of chromosome 3 (3p11.1-q11.1) and (LSI IGH/MYC, CEP8 triple colour, dual fusion probe, Vysis, Des Plaines, Illinois, USA), for the centromere region of chromosome 8 (8p11.1-8q11.1), MYC (8q24) and IGH@ (14q32, used as a control) according to the manufacturer's protocol (Abbott Laboratories, Downers Grove, Illinois, USA). Slides were counterstained with 4',6'-Diamidino-2-phenylindole dihydrochloride (DAPI) (Invitrogen). For each probe set, a total of 100 non-overlapping nuclei were analysed by two independent analysts

using a fluorescence microscope (Zeiss Axio Imager M1) equipped with dual and triple filters. Representative images were captured and stored using the Isis colour fluorescence and FISH imaging system (Metasystems, Germany). A cut-off limit for the detection of monosomy of chromosome 3 was 10%, and the cut-off limit for the detection of amplification of chromosome 8 was 5%. All karyotypes were described according to the International System for Human Cytogenetic Nomenclature.<sup>14</sup>

The removed globe was sent for histopathology reporting. Melanoma was classified as spindle A or B, mixed or epithelioid. The presence of retinal detachment, haemorrhage, necrosis and inflammatory infiltration was recorded.

### Statistical analysis

Statistical analysis was performed using statistical software (SPSS V.13.0). Descriptive statistics were used to evaluate tumour features. The relationship between tumour metabolic activity (SUVmax) and tumour dimension was determined with Pearson's correlation coefficient. Previously published cut-off indices (>2.5 and >4) for SUVmax were also used in the evaluation of data.<sup>10</sup>  $\chi^2$  test was used to determine any statistically significant difference between the groups according to the published SUVmax cut-off values. Correlation with tumour location, histopathology and cytogenetic status was determined with the Mann-Whitney and Kruskal-Wallis tests. A p value of >0.05 was considered to be statistically significant.

### RESULTS

Seventy-six eyes were included in the study (table 1). All tumours were detectable and measurable on PET/CT scan. SUVmax values had a significantly positive correlation with tumour thickness ( $r=0.368$ ,  $p=0.001$ , Pearson's correlation coefficient) (figure 2A), area ( $r=0.241$ ,  $p=0.036$ ) (figure 2B) and volume ( $r=0.36$ ,  $p=0.001$ ) (figure 2C). No correlation was noted with maximal base diameter ( $r=0.181$ ,  $p=0.117$ ) or tumour location ( $p=0.2$ , Kruskal-Wallis test). Using the AJCC

**Table 1** Patient demographics, tumour data and corresponding SUVmax values

		SUVmax median (mean±SD) (range)	p Value (test)*
Total number of patients	76	5.45 (6.35±3.5) (2–15.9)	
Male	46/76 (60.5%)		
Female	30/76 (39.5%)		
Tumour dimensions			
Median (mean±SD) (range)			
Tumour thickness (mm)	10 (10.1±2.5) (4.7–15.9)		
Maximal base diameter (mm)	15 (14.7±3.2) (4.5–20.3)		
Area (mm <sup>2</sup> )	143 (147.4±58.08) (23.7–287.7)		
Volume (mm <sup>3</sup> )	942 (1040.9±570) (87–2546)		
COMS classification†			
Medium melanomas	12/76 (15.8%)		
Large melanomas	64/76 (84.2%)		
AJCC classification			
IIA (T1b-d and T2a N0 M0)	4/76 (5.3%)	3 (2.9±0.6) (2.2–3.6)	0.024 (Kruskal–Wallis test)
IIB (T2b and T3a N0 M0)	30/76 (39.5%)	4.9 (5.3±2.79) (2.1–13.2)	
IIIA (T2c-d and T3b-c and T4a N0 M0)	27/76 (35.5%)	6.5 (7.1±3.8) (2–14.7)	
IIIB (T3d and T4b-c N0 M0)	13/76 (17.1%)	7.1 (7.9±3.7) (3.4–15.9)	
IIIC (T4d-e N0 M0)	2/76 (2.6%)	7.4 (7.4±5.09) (3.8–11)	
Tumour location			
Ciliary body	11/76 (18%)	7 (7.4±3.2) (3.6–13.3)	0.2 (Kruskal–Wallis test)
Ciliochoroidal	30/76 (41%)	6 (6.8±3.9) (2–15.9)	
Choroidal	35/76 (48%)	5 (5.4±2.8) (2.1–13.2)	
Histopathology‡			
Epithelioid	13/75 (17.3%)	6.4 (6.7±3.6) (2.3–14.7)	0.923 (Kruskal–Wallis test)
Spindle A	31/75 (41.3%)	5.2 (6.3±3.5) (2.1–14.7)	
Spindle B	4/75 (5.3%)	5.3 (6.3±3.6) (2–15.9)	
Mixed	27/75 (36%)	4.1 (5.1±2.7) (3.2–9.1)	
High risk	35/75 (46.6%)	5.7 (6.4±3.5) (2.1–14.7)	0.687
Low risk	40/75 (53.3%)	4.9 (6.2±3.6) (2–15.9)	
Pathology features			
Necrosis	6/76 (8%)	5.6 (6.9±3.6) (3.1–13.3)	0.61
No necrosis	70/76 (92%)	5.4 (6.3±3.5) (2–15.9)	
Inflammation	13/76 (17%)	6.4 (6.6±4.4) (2.1–14.2)	0.82
No inflammation	63/76 (83%)	5.3 (6.3±3.3) (2–15.9)	
Retinal detachment	46/76 (60.5%)	6.3 (6.8±4.8) (2–15.9)	0.15
No retinal detachment	30/76 (39.5%)	4.7 (5.5±2.9) (2.1–14.2)	
Haemorrhage	10/76 (13%)	4 (5.8±3.8) (2.8–14.7)	0.56
No haemorrhage	66/76 (87%)	5.7 (6.4±3.5) (2–15.9)	
Cytogenetic analysis§			
Chromosome 3			
Monosomy 3	35/73 (47.9%)	6.5 (7±3.3) (2–15.9)	0.043
Disomy 3	35/73 (47.9%)	4.3 (5.6±3) (2.2–14.7)	
Failure	3/73 (4%)		0.49
Chromosome 8			
Gain of 8	52/73 (71.2%)	6.3 (6.1±3) (2–15.9)	
Disomy 8	18/73 (24.7%)	4.1 (6.2±4.2) (2.4–14.7)	
Failure	3/73 (4%)		
Monosomy 3/gain of 8	33/73 (45%)	6.55 (7.2±3.2) (2–15.9)	
Monosomy 3/disomy 8	2/73 (2.7%)	2.45 (2.45±0.5) (2.1–2.8)	0.015¶
Disomy 3/gain of 8	19/73 (26%)	4.3 (5.1±3.1) (2.2–14.2)	
Disomy 3/disomy 8	16/73 (22%)	4.2 (6.3±4) (2.7–14.7)	0.354

\*Mann–Whitney test unless noted.

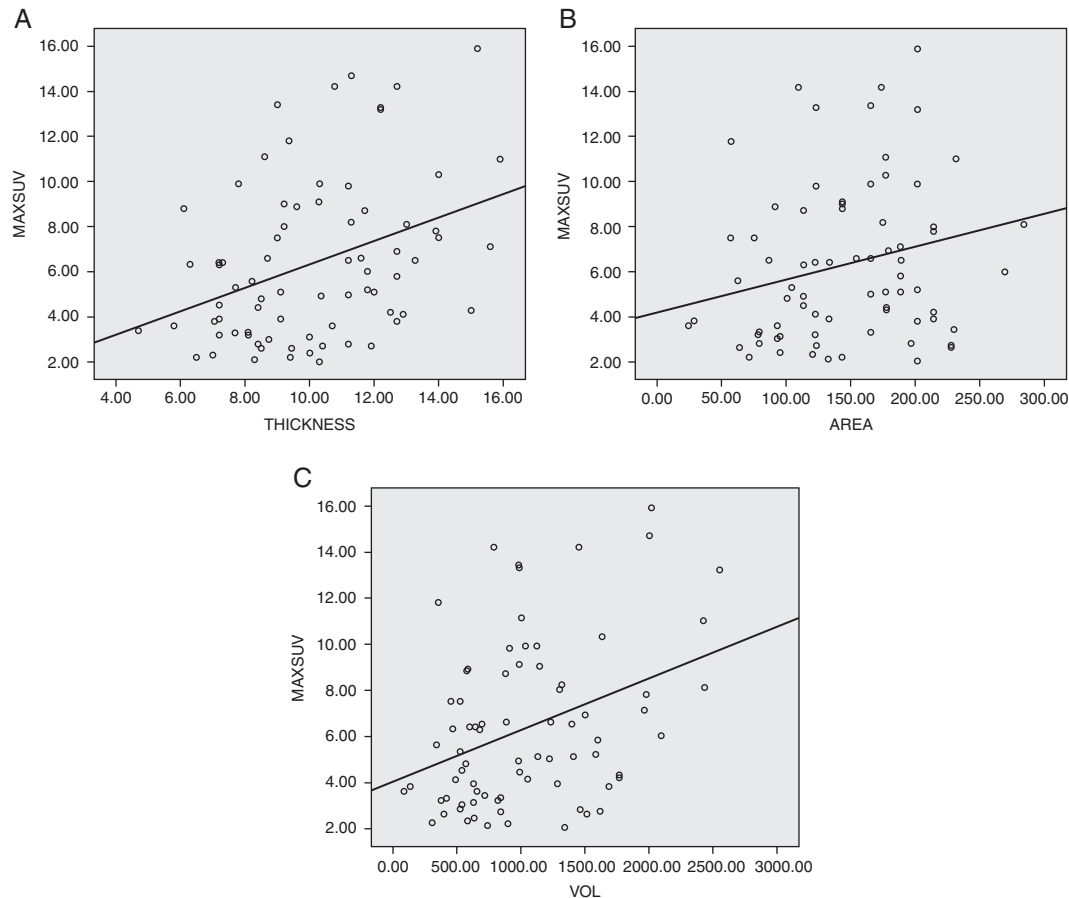
†Small melanoma (1.5–2.4 mm in thickness and 5–16 mm in diameter), medium melanoma (2.5–10 mm in thickness and ≤16 mm in diameter) and large melanoma (&gt;10 mm in thickness and &gt;16 mm in diameter).

‡Available in 75 tumours.

§Available in 73 tumours.

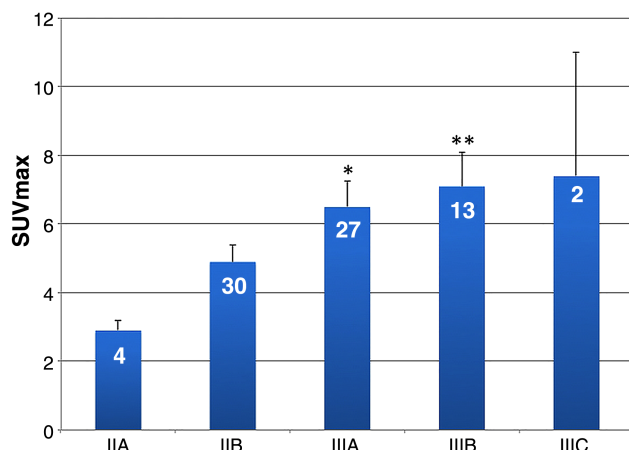
¶Versus disomy 3/gain 8.

AJCC, American Joint Committee on Cancer; COMS, Collaborative Ocular Melanoma Study; SUVmax, maximal standardised uptake value.



**Figure 2** Correlation of maximal standardised uptake value (SUVmax) with tumour dimensions. Significant positive correlation of SUVmax with thickness (A) ( $r=0.368$ ,  $n=75$ ,  $p=0.001$ , Pearson's correlation coefficient), area (B) ( $r=0.241$ ,  $n=76$ ,  $p=0.036$ , Pearson's correlation coefficient) and volume (C) ( $r=0.36$ ,  $n=75$ ,  $p=0.001$ , Pearson's correlation coefficient) are depicted. [Area (a) ( $\text{mm}^2$ )  $\pi (d_1+d_2/4)^2$  and volume ( $\text{mm}^3$ )  $2/3a \times h$ ].

classification (table 1), there was a statistically significant difference among prognostic groups ( $p=0.024$ , Kruskal–Wallis test). Analyses are presented in detail in figure 3. Groups IIIA and IIIB had significantly higher SUVmax in comparison to other groups. Interestingly, in the COMS classification, no significant difference was noted between groups ( $p=0.161$ , Mann–



**Figure 3** Maximal standardised uptake value (SUVmax) (mean $\pm$ SE) in different prognostic groups (numerical values in table 1). (\*) Statistically significant difference of IIIA versus IIA ( $p=0.04$ ). (\*\*) Statistically significant difference of IIIB versus IIA ( $p=0.002$ ), versus IIB ( $p=0.014$ ) (Mann–Whitney test).

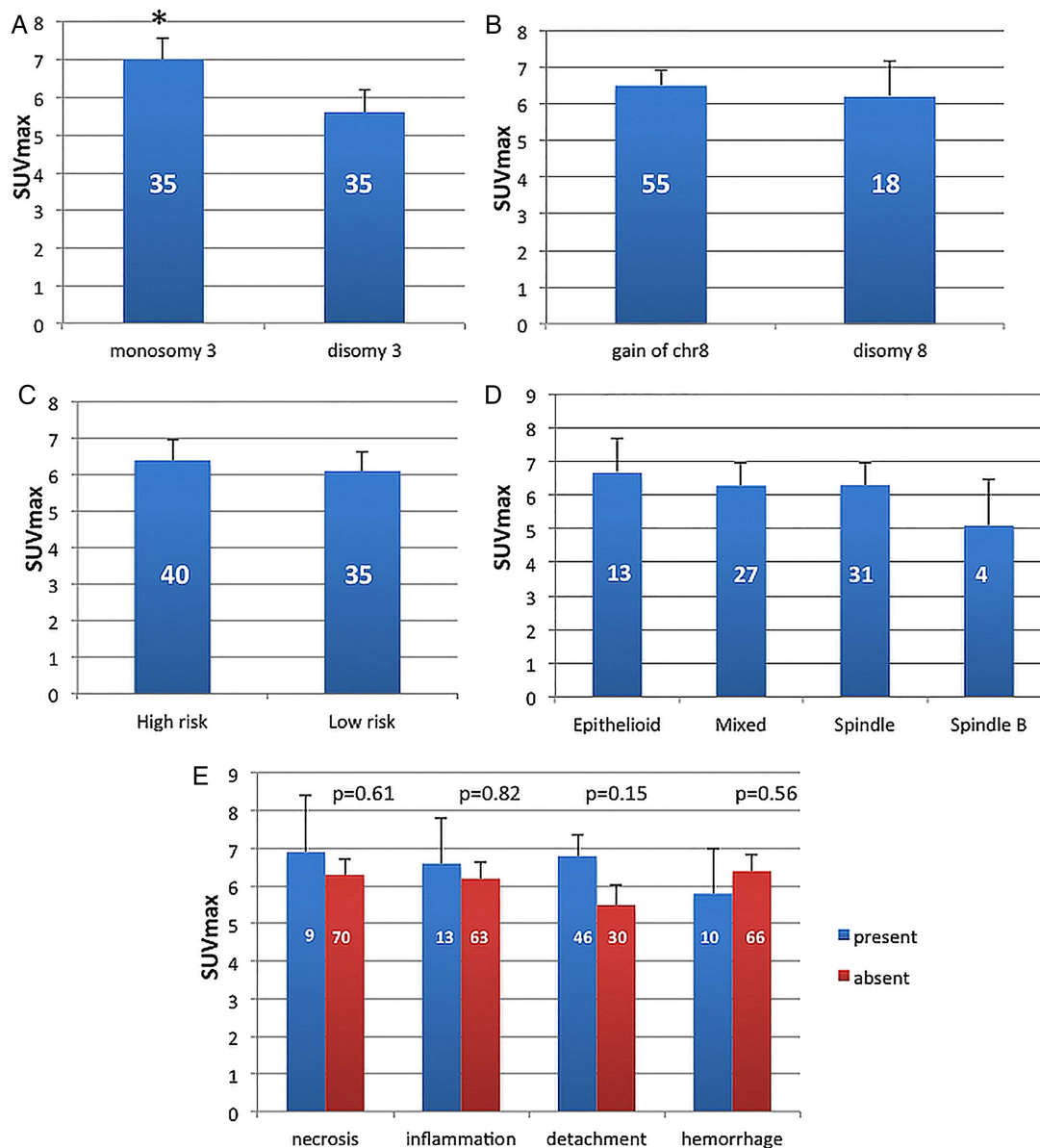
Whitney test). SUVmax  $>2.5$  was noted in 70/76 (92%) and SUVmax  $>4$  was noted in 51/76 (67%) of examined tumours.

Cytogenetic analysis was performed on 73 tumours (table 1). SUVmax values were significantly higher in monosomy 3 compared with disomy 3 tumours ( $p=0.043$ , Mann–Whitney test) (table 1, figure 4A). There was no significant difference in thickness ( $p=0.7$ ), area ( $p=0.95$ ) or volume ( $p=0.88$ , Mann–Whitney test) between groups. A SUVmax of  $>2.5$  was noted in 33/35 (94%) of tumours with monosomy 3 and 32/35 (91.5%) of tumours with disomy 3 ( $\chi^2$ ,  $p=0.8$ ). A SUVmax  $>4$  was noted in 28/35 (80%) monosomy 3 tumours and 20/35 (57%) of disomy 3 tumours ( $\chi^2$ ,  $p=0.06$ ). Based on analysis of the cut-off value, SUVmax  $>4$  is better at predicting a monosomy 3 tumour than a SUVmax  $>2.5$ , but this was not statistically significant.

With regard to status of chromosome 8, no significant difference was noted in SUVmax ( $p=0.49$ , Mann–Whitney test) (table 1, figure 4B). SUVmax  $>2.5$  was noted in 51/55 (92.7%) of tumours with gains in chromosome 8 and 17/18 (94.4%) with the normal diploid component ( $\chi^2$ ,  $p=0.6$ ). SUVmax  $>4$  was noted in 41/55 (74.5%) and 13/18 (72%) in each group ( $\chi^2$ ,  $p=0.06$ ).

When chromosome status was assessed collectively (table 1), the coexistence of monosomy 3 and gains in chromosome 8 was associated with significantly higher SUVmax when compared against tumours with disomy 3 and gains in chromosome 8 ( $p=0.015$ , Mann–Whitney test). SUVmax  $>2.5$  was noted in 33/34 (97%) of tumours with monosomy 3/gain of chromosome 8 and 15/15 (100%) of tumours with normal diploid





**Figure 4** (A–E). Maximal standardised uptake value (SUVmax) correlation with assessed parameters. Number of patients in each group denoted on bar. (A) SUVmax was significantly higher in melanomas with monosomy 3 versus tumours with normal diploid component ( $p=0.04$ , Mann–Whitney test). (B) No significant difference with regards to chromosome 8 status ( $p=0.49$ , Mann–Whitney test). (C, D) SUVmax correlation with histopathology cell type and histopathology features in uveal melanoma. (C) No significant difference noted between high-risk (epithelioid and mixed) and low-risk (spindle A and B) uveal melanomas ( $p=0.687$ , Mann–Whitney test). (D) Similar results noted among specific histopathology cell types ( $p=0.923$ , Kruskal–Wallis test). (E) No significant difference noted in SUVmax in lesions with or without necrosis, inflammation, detachment or haemorrhage (Mann–Whitney test,  $p$  values on chart).

component ( $\chi^2$ ,  $p=0.694$ ). A SUVmax  $>4$  was noted in 29/34 (85.3%) and 9/15 (60%), respectively ( $\chi^2$ ,  $p=0.06$ ). SUVmax  $>4$  was therefore better in this context than SUVmax  $>2.5$  to associate metabolic uptake with high-risk chromosome status though this was again not statistically significant.

Histopathology cell type was available on 75 enucleated eyes (table 1). SUVmax did not correlate with cell type ( $p=0.923$ , Kruskal–Wallis test). In addition, no correlation with SUVmax was noted when cell types were qualified as high risk (epithelioid and mixed, 40/75 (53.3%)) versus low risk (spindle A and B, 35/75 (46.6%)) ( $p=0.687$ , Mann–Whitney test) (table 1, figure 4C, D). There were no dimensional differences among histopathology cell types ( $p=0.78$  for thickness,  $p=0.83$  for volume,  $p=0.55$  for area, Kruskal–Wallis test).

Tumours with necrosis, inflammatory infiltration or haemorrhage did not have a significantly different SUVmax (table 1, figure 4E). Interestingly, melanomas with an associated detachment did present with a considerable although non-significantly higher uptake ( $p=0.15$ , Mann–Whitney test).

## DISCUSSION

PET/CT scan in ophthalmic oncology has demonstrated high sensitivity and a positive predictive value for liver metastases in patients with primary uveal melanoma.<sup>7</sup> In addition, PET/CT has been shown to improve the detection of extrahepatic metastases or synchronous primary cancers.<sup>7–11</sup> In the London Ocular Oncology service, PET/CT scans are routinely used in staging melanoma patients scheduled for enucleation. It is not

recommended as a surveillance investigation because of the significant radiation-related cancer risk.<sup>15</sup> The evaluation of uveal melanoma with PET/CT scan has been implicated as a prognostic tool in individual case series, and the metabolic uptake was recorded qualitatively<sup>13</sup> or semiquantitatively with SUVmax or SUVmean.<sup>10 12 16–18</sup> The aim of this study was to examine the correlation of metabolic activity against clinical, cytogenetic and histopathological factors. In this study, absolute SUVmax values were primarily used. In addition, cut-off values of  $>2.5$  or  $>4$  were also used to categorise a 'positive' SUVmax as previously reported.<sup>10 12 17</sup> The selection of these cut-off values has not been standardised.

Chromosome 3 monosomy in uveal melanoma is a commonly used predictor of mortality.<sup>2 3 5</sup> Disomy of chromosome 3 has a protective effect, but recent data indicate that the presence of the SF3B1 mutation on chromosome 3 might be associated with increased mortality.<sup>4</sup> Additional abnormalities in chromosomes 1, 6 and 8 have also been considered as prognostic factors.<sup>19</sup> Cytogenetic information is usually obtained by fine needle aspiration biopsy. PET/CT is a non-invasive investigation, which may be able to provide important prognostic information without the need for a biopsy.

To date, there is only one other publication supporting the association between SUVmax and loss of chromosome 3. McCannel *et al*<sup>12</sup> analysed 37 uveal melanomas and concluded that cases with SUVmax  $>2.5$  correlated positively with loss of chromosome 3. FISH analysis was used to record loss of chromosome 3; however, the cut-off percentage to determine monosomy 3 was not reported. In this study, 13/37 (35%) patients were found to have loss of chromosome 3 and of these, 7/13 (54%) had a SUVmax  $>2.5$ . All of the disomy 3 tumours had a SUVmax  $<2.5$ . Of note, the seven tumours with positive SUVmax and chromosome 3 loss were significantly larger. We found that SUVmax values increase with tumour dimensions, and this is likely to be a confounding factor in their data.

In our study, 35 of 73 patients were found to have monosomy 3 on FISH analysis using a cut-off of 10% of cells affected to determine chromosome status. The FISH technique was done under optimal conditions using a fresh tissue biopsy from tumour. It should be noted that other techniques have yielded superior results in the detection of monosomy 3.<sup>20</sup> SUVmax was significantly higher in patients with monosomy 3. The two groups were of similar size (35 tumours each) and the tumour thickness, area and volume were comparable. Our results also show that SUVmax cut-off values cannot distinguish between monosomy and disomy 3 melanoma; however, a higher SUVmax of  $>4$  was more helpful in determining monosomy 3 status.

Chromosome 8 status was also examined in order to determine any association with increased SUVmax. Gains in chromosome 8 are known to be associated with a poorer prognosis in uveal melanoma.<sup>21</sup> The presence of gains in chromosome 8 was seen in 55 of 73 uveal melanomas. Gains in chromosome 8 did not correlate with increased SUVmax values. The assessment of combined chromosome expression further reinforces the aforementioned results. Tumours with monosomy 3/gains in chromosome 8 had a significantly higher SUVmax than disomy 3/gains in 8 and a SUVmax  $>4$  would be more helpful in identifying an association with high-risk melanomas for chromosome 3/8 status.

Tumour size is important in the prognostication of choroidal melanoma. Increased melanoma size has been shown to be directly analogous to metastatic potential.<sup>22</sup> In this study, both standard classification systems (AJCC and COMS) were used.

AJCC subgroups IIIA and IIIB were found to have significantly higher SUVmax uptake in comparison to other groups, confirming the importance of tumour dimensions. In prior studies using the COMS classification, the tumour population has been heterogeneous with medium uveal melanoma represented in 7–36% and large uveal melanoma in 16–94%.<sup>8 10 12 16–18</sup> Only a few studies have included small melanomas.<sup>10 16</sup> Our study consisted of 16% medium and 84% large melanomas with no small melanoma. Reddy *et al* measured the metabolic activity on PET/CT in 18/50 (36%) small, 24/50 (48%) medium and 8/50 (16%) large uveal melanomas. Interestingly, none of the small uveal melanomas had an SUVmax  $>2.5$ , but 75% of the large tumours did, accounting for the low overall detection rate of 28%.<sup>10</sup> In our study, 92% of uveal melanomas had an SUVmax  $>2.5$ . This striking difference could be attributed to the larger tumours in our series. The average resolution of a PET/CT scanner is 4 mm, which may limit its ability to detect and measure activity in small choroidal melanoma. Several publications have proven that SUVmax has a positive correlation with tumour size.<sup>12 16 17</sup> Our findings confirmed this correlation with regards to thickness and found an additional positive correlation between SUVmax and increasing tumour volume.

Ciliary body melanoma is associated with poor survival.<sup>9</sup> Tumours in this location tend to be larger and of mixed cell type.<sup>22 23</sup> A trend for an association with higher SUVmax and anterior location has been implied in a case series of 14 patients<sup>17</sup> though no correlation was found in a larger sample size by the same group.<sup>10</sup> In our study, there was no significant difference in SUVmax uptake among ciliary body, ciliochoroidal or choroidal melanomas.

Uveal melanoma prognosis is also associated with tumour pathology. Epithelioid and mixed cell tumours are considered as high risk, and spindle cell melanomas are considered as low risk.<sup>18</sup> Previous studies<sup>23</sup> have reported that 10-year mortality ranged from 11% to 19% in spindle A tumours, 21–36% in spindle B tumours, 63–79% in mixed-cell tumours and 72–100% in epithelioid tumours. In a case series of 14 uveal melanomas, the SUVmean was significantly increased in mixed cell versus spindle cell tumours.<sup>16</sup> Finger *et al*<sup>17</sup> also reported a trend for higher SUVmax in epithelioid tumours in 14 cases, though this series had three epithelioid tumours one of which had no uptake. On the other hand, a recent study of 34 melanomas<sup>18</sup> did not yield a significant difference for SUVmax among different cell types. Our study supports the latter findings as no such correlation was noted.

The presence of necrosis, inflammation or haemorrhage has been reported to affect PET/CT uptake. Tumour necrosis has been reported to be present in melanomas with high metabolic uptake.<sup>13</sup> Faia *et al*<sup>16</sup> reported a significant association of SUVmean with necrosis and focal inflammation in 3/14 cases. In our study, no significant difference in SUVmax was found for subgroups of patients with tumour necrosis (6/75,  $p=0.8$ ) or associated inflammation (13/75,  $p=0.8$ ). This may be because the number of tumours with these findings was small. Retinal detachment at the time of diagnosis has been reported as a risk factor for local recurrence and metastasis.<sup>24</sup> In our study, retinal detachment was present in 60% of melanomas (46/76). The SUVmax was considerably higher in tumours with a retinal detachment, but this was not statistically significant ( $p=0.1$ ).

One practical limitation of our study is that the absolute cut-off value for SUVmax to predict monosomy 3 status could not be determined. This may be due to the known limitations of FISH analysis or the fact that other chromosomes that impact

on metabolic activity were not tested. It would be useful to use gene expression profiling instead, which targets many more chromosomes in uveal melanoma.

In conclusion, SUVmax as a measure of metabolic activity of primary uveal melanoma on PET/CT scan may have prognostic implications. SUVmax was confirmed to have a significant positive correlation with tumour size and monosomy 3 but did not correlate with histological cell type or chromosome 8 status. To our knowledge, this is the largest study that has examined the correlation of SUVmax in primary uveal melanoma with known clinical, histopathological and cytogenetic features. In addition, this is the first study to examine any association with chromosome 8 status. Our results suggest that the cut-off SUVmax value of 2.5 used as an indicator of positive metabolic activity cannot be used to distinguish between monosomy 3 and disomy 3 tumours. SUVmax >4, though not an absolute indicator, might be more helpful in identifying monosomy 3 and gain of chromosome 8 tumours.

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## REFERENCES

- Papastefanou VP, Cohen VM. Uveal melanoma. *J Skin Cancer* 2011;2011:573974.
- Prescher G, Bornfeld N, Hirtche H, et al. Prognostic implications of monosomy 3 in uveal melanoma. *Lancet* 1996;347:1222–5.
- Onken MD, Worley LA, Harbour JW. Association between gene expression profile, proliferation and metastasis in uveal melanoma. *Curr Eye Res* 2010;35:857–63.
- Koopman AE, Yavuziyigitoglu S, Vaarwater J, et al. SF3B1 and EIF1AX mutations in uveal melanoma: a protective factor or not? *OOG Spring Meeting*, Krakow, 2014.
- Damato B, Duke C, Coupland SE, et al. Cytogenetics of uveal melanoma: a 7-year clinical experience. *Ophthalmology* 2007;114:1925–31.
- Patel K, Hadar N, Lee J, et al. The lack of evidence for PET or PET/CT surveillance of patients with treated lymphoma, colorectal cancer, and head and neck cancer: a systematic review. *J Nucl Med* 2013;54:1518–27.
- Freton A, Chin KJ, Raut R, et al. Initial PET/CT staging for choroidal melanoma: AJCC correlation and second nonocular primaries in 333 patients. *Eur J Ophthalmol* 2012;22:236–43.
- Lee CS, Cho A, Lee KS, et al. Association of high metabolic activity measured by positron emission tomography imaging with poor prognosis of choroidal melanoma. *Br J Ophthalmol* 2011;95:1588–91.
- Singh AD, Bhatnagar P, Bybel B. Visualization of primary uveal melanoma with PET/CT scan. *Eye (Lond)* 2006;20:938–40.
- Reddy S, Kurli M, Tena LB, et al. PET/CT imaging: detection of choroidal melanoma. *Br J Ophthalmol* 2005;89:1265–9.
- Finger PT, Kurli M, Reddy S, et al. Whole body PET/CT for initial staging of choroidal melanoma. *Br J Ophthalmol* 2005;89:1270–4.
- McCannel TA, Reddy S, Burgess BL, et al. Association of positive dual-modality positron emission tomography/computed tomography imaging of primary choroidal melanoma with chromosome 3 loss and tumor size. *Retina* 2010;30:146–51.
- Modorati G, Lucignani G, Landoni C, et al. Glucose metabolism and pathological findings in uveal melanoma: preliminary results. *Nucl Med Commun* 1996;17:1052–6.
- Shaffer LG, Slovak ML, Campbell LJ. *An international system for human cytogenetic nomenclature*. Karger Publications, 2009.
- Wen JC, Sai V, Straatsma BR, et al. Radiation-related cancer risk associated with surveillance imaging for metastasis from choroidal melanoma. *JAMA Ophthalmol* 2013;131:56–61.
- Faia LJ, Pulido JS, Donaldson MJ, et al. The relationship between combined positron emission tomography/computed tomography and clinical and light microscopic findings in choroidal melanoma. *Retina* 2008;28:763–9.
- Finger PT, Chin K, Iacob CE. 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. *Br J Ophthalmol* 2006;90:1263–6.
- Calcagni ML, Mattoli MV, Blasi MA, et al. A prospective analysis of <sup>18</sup>F-FDG PET/CT in patients with uveal melanoma: comparison between metabolic rate of glucose (MRglu) and standardized uptake value (SUV) and correlations with histopathological features. *Eur J Nucl Med Mol Imaging* 2013;40:1682–91.
- Ewens KG, Kanetsky PA, Richards-Yutz J, et al. Genomic profile of 320 uveal melanoma cases: chromosome 8p-loss and metastatic outcome. *Invest Ophthalmol Vis Sci* 2013;54:5721–9.
- Aronow M, Sun Y, Sauntharajah Y, et al. Monosomy 3 by FISH in uveal melanoma: variability in techniques and results. *Surv Ophthalmol* 2012;57:463–73.
- Cassoux N, Rodrigues MJ, Plancher C, et al. Genome-wide profiling is a clinically relevant and affordable prognostic test in posterior uveal melanoma. *Br J Ophthalmol* 2014;98:769–74.
- Shields CL, Kaliki S, Furuta M, et al. American Joint Committee on Cancer classification of posterior uveal melanoma (tumor size category) predicts prognosis in 7731 patients. *Ophthalmology* 2013;120:2066–71.
- Zimmerman LE, McLean IW, Foster WD. Does enucleation of the eye containing a malignant melanoma prevent or accelerate the dissemination of tumour cells? *Br J Ophthalmol* 1978;62:420–5.
- Desjardins L, Levy-Gabriel C, Lumbroso-Lerouic L, et al. Prognostic factors for malignant uveal melanoma. Retrospective study on 2,241 patients and recent contribution of monosomy-3 research. *J Fr Ophthalmol* 2006;29:741–9.



# Metabolic activity of primary uveal melanoma on PET/CT scan and its relationship with monosomy 3 and other prognostic factors

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