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# Patients presenting with metastases: stage IV uveal melanoma, an international study

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This paper was presented as an oral presentation at the 53rd Annual Scientific Virtual Meeting Retina Society 2020 and as a poster presentation for the 35th Annual Meeting of American Academy of Ophthalmology.

Received 11 September 2020
Revised 17 November 2020
Accepted 19 November 2020



**To cite:** Garg G, Finger PT, Kivelä TT, *et al*. *Br J Ophthalmol* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/bjophthalmol-2020-317949

## ABSTRACT

**Objective** To analyse ocular and systemic findings of patients presenting with systemic metastasis.

**Methods and analysis** It is an international, multicentre, internet-enabled, registry-based retrospective data analysis. Patients were diagnosed between 2001 and 2011. Data included: primary tumour dimensions, extrascleral extension, ciliary body involvement, American Joint Committee on Cancer (AJCC)-tumour, node, metastasis staging, characteristics of metastases.

**Results** Of 3610 patients with uveal melanoma, 69 (1.9%; 95% CI 1.5 to 2.4) presented with clinical metastasis (stage IV). These melanomas originated in the iris, ciliary body and choroid in 4%, 16% and 80% of eyes, respectively. Using eighth edition AJCC, 8 (11%), 20 (29%), 24 (35%), and 17 (25%) belonged to AJCC T-categories T1–T4. Risk of synchronous metastases increased from 0.7% (T1) to 1.5% (T2), 2.6% (T3) and 7.9% (T4). Regional lymph node metastases (N1a) were detected in 9 (13%) patients of whom 6 (67%) had extrascleral extension. Stage of systemic metastases (known for 40 (59%) stage IV patients) revealed 14 (35%), 25 (63%) and 1 (2%) had small (M1a), medium-sized (M1b) and large-sized (M1c) metastases, respectively. Location of metastases in stage IV patients were liver (91%), lung (16%), bone (9%), brain (6%), subcutaneous tissue (4%) and others (5%). Multiple sites of metastases were noted in 24%. Compared with the 98.1% of patients who did not present with metastases, those with synchronous metastases had larger intraocular tumours, more frequent extrascleral extension, ciliary body involvement and thus a higher AJCC T-category.

**Conclusions** Though higher AJCC T-stage was associated with risk for metastases at diagnosis, even small T1 tumours were stage IV at initial presentation. The liver was the most common site of metastases; however, frequent multiorgan involvement supports initial whole-body staging.

## INTRODUCTION

Metastasis is the leading cause of death due to uveal melanoma.[1–3] Many reports have described methods of diagnosis, surveillance and treatment of metastases. In 1985, the Collaborative Ocular Melanoma Study (COMS) employed a combination of physical examination for hepatomegaly, enlarged lymph nodes and subcutaneous nodules as well as ancillary chest X-rays and liver function tests.[4 5] Since that time, eye cancer specialists have placed a greater reliance on staging with radiographic imaging especially abdominal ultrasonography (USG), CT, MRI and whole-body positron emission tomography/CT (PET/CT).[1–3 6–10]

The eye does not have significant lymphatic outflow channels.[1 11] Therefore, intraocular melanomas spread through vascular emissaries leading especially to hepatic metastases. However, extrascleral extension allows melanoma cells to access conjunctival lymphatics, leading to rare regional lymph node (RLN) metastases.[12 13] While the liver is the most commonly reported haematogenous site for metastasis, other sites include bone, lungs, skin and brain.[1–8 12–18] Currently, only total-body PET/CT has been widely available to holistically detect both hepatic and extrahepatic sites of metastatic uveal melanoma.[1 2 8]

The time of detection of metastases has an effect on the duration of subsequent survival of patients with uveal melanoma.[1–3] For example, periodic physical examinations, liver function tests and chest X-rays as required by the COMS typically detect late-stage disease leading to less than 6 months of reported survival.[4–6 14] In contrast, centres employing abdominal radiographic imaging detect otherwise subclinical disease, which is associated with longer term overall survival, typically a median of 12 months.[6 19–27] While longer survival has been correlated to early detection or lead-time bias, there exists literature suggesting hepatic metastasectomy, immunotherapy and evolving treatments can sometimes provide cure or prolong life.[2 3 28–30]

Literature review of PubMed and Medline using the keywords: metastasis, melanoma, uvea, ciliary body, iris and choroid revealed no papers describing the clinical characteristics of a series of patients diagnosed with metastatic uveal melanoma at the time of initial presentation as designated stage IV in the eighth edition American Joint Committee on Cancer (AJCC) tumour, node, metastasis (TNM)

classification.[1] This study uses a multicentre, international registry to examine the ocular and systemic findings of patients presenting with systemic uveal melanoma metastasis.

## METHODS

### Definitions

#### Group M

Patients with uveal melanoma with metastasis discovered at initial presentation, that is, stage IV disease in the eighth edition AJCC TNM system.

#### Group N

Patients with uveal melanoma with no evidence of metastasis at initial presentation, corresponding to stage I–III disease in the eighth edition AJCC TNM system.

### The registry

An internet-based retrospective registry was developed by the American Joint Committee on Cancer Ophthalmic Oncology Task Force (AJCC-OOTF). It comprises data on epidemiology, clinical and pathological aspects of patients with uveal melanoma.[15] The present research focused on patients who were diagnosed with uveal melanoma metastasis at initial presentation.

### Internet database, security and patient protection

Data entry, storage, patient privacy and statistical analysis were done in accordance with international standards. Data were secured by omitting any personal patient information, secure socket layer encryption, protection against structured query language injection, locking of records and trail auditing by failed login attempts and web page accessing. Each contributing centre had different unique login issued by the coordinating centre and could only access its own data.

### Eligibility criteria

Ten ocular oncology centres from 8 countries (1178 (30.5%) Canada, 936 (24.3%) USA, 500 (12.9%) Russia, 327 (8.4%) Argentina, 327 (8.4%) Sweden, 275 (7.1%) Spain, 255 (6.6%) The Netherlands and 68 (1.8%) Japan) for a total of 3866 patients from 4 continents (North and South America, Europe and Asia) participated in this registry. Each centre entered consecutive patients with primary melanoma of the iris, ciliary body and choroid who were diagnosed and treated between 1 April 2001 and 1 April 2011. Each centre utilised its standard methods of surveillance for metastasis that always included: abdominal scanning (USG, CT, MRI) and/or whole-body PET/CT. In that 256 patients had incomplete records, 3610 (93.4%) of the 3866 patients were available for this analysis.

### Statistical analysis

Continuous variables were summarised using mean, SD, median and range. Categorical variables were described using frequencies and percentages. For analysis of the significance of intraocular tumour location, we defined tumour origin (iris, ciliary body or choroid) based on the longitudinal centre of the tumour's base. Pearson $\chi^2$ test was used to compare contingency tables if the expected frequency was ≥5; otherwise, we used the Fisher's exact test. Univariable and bivariable logistics regression were employed to analyse tumour characteristics as risk factors for synchronous metastasis. Goodness of fit was verified by Hosmer-Lemeshow test. OR and p values from Wald $\chi^2$ test are revealed. SPSS Statistics V.20 software released 2015 was used for all statistical analyses (IBM).

Main T categories of anatomic extent were defined based on tumour size (largest basal diameter and thickness), whereas ciliary body involvement and extrascleral extension define subcategories.[1] Tumour size including both tumour thickness and largest basal diameter as independent predictors have been strongly associated with metastasis.[1 15 31–33] Ciliary body involvement and extrascleral extension have both been found to be an independent risk factor for metastasis.[1 15 22 31 34] Therefore, all these factors were studied separately for a statistically significant risk of synchronous metastasis. Moreover, this was why the eighth edition AJCC classification separated uveal melanoma into anterior or iris melanoma and posterior or ciliary body/choroidal melanoma anatomical location.[1]

## RESULTS

Of the total cohort of 3610 patients, 69 (1.9%; 95% CI 1.5 to 2.4) presented with synchronous primary uveal melanoma and metastases or stage IV disease (group M). The remainder or

**Table 1** Primary uveal melanoma presenting with metastasis versus with no metastasis

| | | AJCC stage IV uveal melanoma at initial presentation (group M) **n=69** | | | AJCC stage I–III uveal melanoma at initial presentation (group N) **n=3541** | | |
|---|---|---|---|---|---|---|---|
| **Characteristics** | | **Choroidal** | **Ciliary body** | **Iris** | **Choroidal** | **Ciliary body** | **Iris** |
| Sample | | 55 (80%) | 11 (16%) | 3 (4%) | 3097 (87%) | 266 (8%) | 178 (5%) |
| Tumour thickness (mm) | Mean (SD) | 8.3 (4.8) | 9.6 (3.4) | N/A | 5.7 (3.0) | 6.0 (3.0) | N/A |
| | Median (range) | 7.7 (2-0–24.5) | 11.0 (2.7–14.7) | N/A | 5.0 (2.0–23.0) | 5.6 (2.0–16.0) | N/A |
| Largest basal diameter (mm)* | Mean (SD) | 14.4 (4.7) | 10.2 (2.6) | 6.8 (2.0) | 12.1 (3.8) | 10.4 (2.8) | 3.9 (2.7) |
| | Median (range) | 15.0 (2.9–25.0) | 9.1 (6.0–13.8) | 6.4 (5.0–9.0) | 12.0 (2.0–30.0) | 11.0 (2.0–14.0) | 3.0 (0.5–19.0) |
| T-category | T1 | 5 (9%) | 1 (9%) | 2 (67%) | 944 (31%) | 87 (33%) | 92 (52%) |
| | T2 | 18 (33%) | 2 (18%) | 0 (0%) | 1101 (35%) | 107 (40%) | 84 (47%) |
| | T3 | 16 (29%) | 7 (64%) | 0 (0%) | 832 (27%) | 67 (25%) | 0 (0%) |
| | T4 | 16 (29%) | 1 (9%) | 1 (33%) | 220 (7%) | 5 (2%) | 2 (1%) |
| ESE | | 6 (11%) | 5 (45%) | 1 (33%) | 48 (2%) | 16 (6%) | 2 (1%) |
| CBI | | 11 (20%) | 11 (100%) | 1 (33%) | 248 (8%) | 266 (100%) | 88 (49%) |
| ESE and CBI | | 4 (7%) | 5 (45%) | 1 (33%) | 20 (1%) | 16 (100%) | 2 (1%) |

*In the case of iris melanoma, only the largest basal diameter was mentioned.
AJCC, American Joint Committee on Cancer, 8th edition; CBI, ciliary body involvement; ESE, extrascleral extension.

3541 (98.1%; 95% CI 97.6 to 98.5) patients had no evidence of metastasis (stage I–III disease, group N).

### Primary tumour location

In group M, 55 (80%) primary tumours originated in the choroid, 11 (16%) arose in the ciliary body and 3 (4%) were iris melanomas. The corresponding numbers for group N were 3097 (87%), 266 (8%) and 178 (5%), respectively.

Group M analysis for intraocular tumour location revealed that ciliary body tumour origin was a significant risk factor for metastasis at initial presentation (OR 2.34, 95% CI 1.21 to 4.50; p=0.011). Likewise, choroidal tumours with ciliary body involvement were at an equally high risk of synchronous metastasis (OR 2.87, 95% CI 1.46 to 5.63; p=0.02).

### Eighth edition AJCC staging—T category

In group M, choroidal melanomas were classified as 5 (9%) T1, 18 (33%) T2, 16 (29%) T3 and 16 (29%) T4. For ciliary body melanoma, the corresponding values were 1 (9%), 2 (18%), 7 (64%) and 1 (9%). For iris melanomas, which were classified separately, 2 (67%) were T1 and 1 (33%) was T4 (tables 1 and 2). Overall, the percentage of patients with stage IV disease increased by T-category from 0.7% T1, 1.5% T2, 2.6% T3 and 7.9% in T4.

A bivariate logistic regression was performed to ascertain the effects of AJCC T-category and subcategory on the likelihood that patients with uveal melanoma have synchronous metastasis (table 3). The logistic regression model was statistically significant, $\chi2(7)=51.59$, $p<0.001$. The model explained 8.2% (Nagelkerke *R2*) of the variance in synchronous metastasis and correctly classified 98.1% of cases. Here, we see that risk for metastases at diagnosis, even when controlling for intraocular and extraocular invasion, increases logically with increasing T1–T4 (1.0–2.3–3.5–7.6) and the OR of course is somewhat eroded because 'a–e' takes away part of it. The significances, however, are essentially unaltered compared with univariable. For a–d, the logical increase also is maintained (OR 1.00–1.3–3.4–7.2) though 'e' than can be a tumour of any T if extraocular extension is >5 mm does not follow the rule. The significance of 'b' is much eroded, indicating that in the absence of extraocular extension, ciliary body involvement is not contributing much to the added risk given T size (table 3).

On further dividing the group M for eighth edition AJCC T-subcategories table 2, n=69 shows that there were 6% of T1a with no ciliary body involvement or extrascleral extension. A majority of 63% tumours had no ciliary body involvement or extrascleral extension in group M.

### Choroidal melanoma

The median thickness and largest basal diameter of choroidal melanomas in group M (table 1; n=55) were 7.7 mm (range 2.0–24.5) and 15.0 mm (range 2.9–25.0), respectively. The corresponding numbers for group N were 5.0 mm (range 2.0–23.0) and 12.0 mm (range 2.0–30.0), respectively (table 1; n=3097). Both tumour thickness and largest basal diameter were significantly associated with risk of metastasis at presentation (OR

**Table 2** Stage IV uveal melanoma at initial presentation (group M)

| AJCC tumour category | | | Choroidal **n=55** | Ciliary body **n=11** | Iris **n=3** | Total **n=69** |
|---|---|---|---|---|---|---|
| **T-category** | T1a | No CBI/ESE | 4 (7%) | 0 (0%) | 0 (0%) | 4 (6%) |
| | T1b | CBI only | 0 (0%) | 1 (9%) | 2 (67%) | 3 (4%) |
| | T1c | ESE only (≤5 mm) | 1 (2%) | 0 (0%) | 0 (0%) | 1 (1%) |
| | T1d | Both CBI and ESE (≤5 mm) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | T2a | No CBI/ESE | 17 (31%) | 0 (0%) | 0 (0%) | 17 (26%) |
| | T2b | CBI only | 0 (0%) | 2 (18%) | 0 (0%) | 2 (3%) |
| | T2c | ESE only (≤5 mm) | 1 (2%) | 0 (0%) | 0 (0%) | 1 (1%) |
| | T2d | Both CBI and ESE (≤5 mm) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | T3a | No CBI/ESE | 13 (27%) | 0 (0%) | 0 (0%) | 13 (19%) |
| | T3b | CBI only | 2 (4%) | 3 (27%) | 0 (0%) | 5 (7%) |
| | T3c | ESE only (≤5 mm) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | T3d | Both CBI and ESE (≤5 mm) | 1 (2%) | 4 (36%) | 0 (0%) | 5 (7%) |
| | T4a | No CBI/ESE | 8 (14%) | 0 (0%) | 1 (33%) | 9 (13%) |
| | T4b | CBI only | 5 (9%) | 0 (0%) | 0 (0%) | 5 (7%) |
| | T4c | ESE only (≤5 mm) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | T4d | Both CBI and ESE (≤5 mm) | 2 (4%) | 0 (0%) | 0 (0%) | 2 (3%) |
| | T4e | ESE (>5 mm) | 1 (2%) | 1 (9%) | 0 (0%) | 2 (3%) |
| **Metastasis sites** | Regional lymph nodes (N1a) | | 5 (9%) | 4 (36%) | 0 (0%) | 9 (13%) |
| | Liver | | 38 (69%) | 9 (82%) | 3 (100%) | 50 (72%) |
| | Lung | | 3 (5%) | 0 (0%) | 0 (0%) | 3 (4%) |
| | Bone | | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Brain | | 0 (0%) | 0 (0%) | 0 (0%) | (0%) |
| | Subcutaneous tissue | | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Other sites | | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| | Multiple sites | | 14 (26%) | 2 (18%) | 0 (0%) | 16 (24%) |

AJCC, American Joint Committee on Cancer, 8th edition; CBI, ciliary body involvement; ESE, extrascleral extension.

**Table 3** Logistic regression analysis: predictors of stage IV uveal melanoma at presentation

| Logistic regression | Variable | | B (SE) | P value | OR (95% CI) |
|---|---|---|---|---|---|
| **Univariate** | **AJCC T-category** | T1 | | | 1.0 |
| | | T2 | 0.776 (0.420) | 0.065 | 2.2 (0.95 to 4.95) |
| | | T3 | 1.279 (0.413) | 0.002 | 3.6 (1.6 to 8.07) |
| | | T4 | 2.410 (0.431) | <0.001 | 11.1 (4.78 to 25.91) |
| | **AJCC T-subcategory** | a | | | 1.0 |
| | | b | 0.539 (0.303) | 0.075 | 1.7 (0.95 to 3.11) |
| | | c | 1.205 (0.741) | 0.104 | 3.3 (0.78 to 14.26) |
| | | d | 2.621 (0.443) | <0.001 | 13.8 (5.77 to 32.73) |
| | | e | 2.409 (0.779) | 0.002 | 11.1 (2.42 to 51.23) |
| **Bivariate** | **AJCC T-category** | T1 | | | 1.0 |
| | | T2 | 0.818 (0.423) | 0.053 | 2.3 (0.99 to 5.19) |
| | | T3 | 1.252 (0.418) | 0.003 | 3.5 (1.54 to 7.93) |
| | | T4 | 2.022 (0.462) | <0.001 | 7.6 (3.05 to 18.70) |
| | **AJCC T-subcategory** | a | | | 1.0 |
| | | b | 0.244 (0.313) | 0.435 | 1.3 (0.69 to 2.36) |
| | | c | 1.232 (0.764) | 0.107 | 3.4 (0.77 to 15.32) |
| | | d | 1.967 (0.481) | <0.001 | 7.2 (2.78 to 18.36) |
| | | e | 1.240 (0.829) | 0.135 | 3.5 (0.68 to 17.54) |

AJCC, American Joint Committee on Cancer, 8th edition.

1.21, 95% CI 1.14 to 1.29, p<0.001 and OR 1.15, 95% CI 1.08 to 1.22, p<0.001, respectively, for each 1 mm increase).

In group M, 6 (11%) tumours presented with extrascleral extension (mean diameter of 4.8 mm (SD 3.1; median 3.5; range 3.0–11.0)), 11 (20%) had ciliary body involvement and 4 (7%) presented with both (table 1). In group N, 48 (2%) tumours presented with extrascleral extension (mean diameter of 3.7 mm (SD 4.5; median 2.2; range 0.5–27.0)), 248 (8%) had ciliary body involvement and 20 (1%) had both (table 1). All three characteristics predicted metastasis at initial presentation (OR 7.78, 95% CI 3.18 to 19.02, p<0.001; OR 2.87, 95% CI 1.46 to 5.63, p=0.02 and OR 12.07, 95% CI 3.98 to 36.56, p<0.001, respectively).

### Ciliary body melanoma

Ciliary body melanomas in group M (n=11) had a median tumour thickness and largest basal diameter of 11.0 mm (range 2.7–14.7) and 9.1 mm (range 6.0–13.8), respectively. In comparison, group N (n=266) median tumour thickness and largest basal dimensions were 5.6 mm (range 2.0–16.0) and 11.0 mm (range 2.0–14.0), respectively (table 1). In this comparison, tumour thickness was significantly associated with risk of metastasis at presentation (OR 1.37, 95% CI 1.14 to 1.64, p=0.001, for each 1 mm increase) unlike largest basal diameter (p=0.78).

In group M 5 (45%) patients presented with extrascleral extensions with a mean diameter of 4.9 mm (SD 2.0; median 5.0; range 3.0–8.0) as compared with 16 (6%) patients in group N who had extrascleral extensions with a mean diameter of 6.2 mm (SD 11.8; median 3.4; range 1.0–50.0) (table 1). Therefore, the presence of extrascleral extension was a predictor of metastasis at initial presentation (OR 13.02, 95% CI 3.58 to 47.30, p=0.001).

### Iris melanoma

In group M, the three iris melanomas were 5, 6.8 and 9 mm in diameter. These measurements were compared with median 3.0 mm (range 0.5–19.0) from group N (n=178; table 1). In group M, there was 1 patient who presented with both extrascleral extension and ciliary body involvement as compared with 88 (49%) patients who had ciliary body involvement and 2 patients who presented with both extrascleral extension and ciliary body involvement in group N (table 1). In group M, the number of patients with iris melanoma metastases was small, thus risk-based statistical analysis was not possible.

### RLN—N category

The eighth edition AJCC defined N category for RLN metastasis (N1) primarily exists in cases of uveal melanoma with extrascleral extension. As described in the eighth edition AJCC Uveal Melanoma Chapter, anterior extrascleral extension is thought to invade conjunctival lymphatics to reach regional (preauricular and cervical) lymph nodes (N1a).[1] In contrast, tumour deposits in the orbit (associated with extrascleral extension) were considered to be a rare cause of regional nodal spread (N1b).[1] In group M, 9 (13%) patients were staged to N1a (table 2). All had either a ciliary body or a choroidal melanoma (table 2). Of these, 2 (3%) had metastases to preauricular RLN, 3 (4%) to cervical RLN, 3 (4%) had both preauricular and submandibular RLN metastases and the metastases in one patient involved all regional RLN locations. Of the nine patients with RLN metastases (N1a), six (67%) were reported to have extrascleral extension.

### Systemic metastases—M category

Distant metastasis (M1) is graded in the TNM system by the size of the largest diameter of the largest metastasis: ≤3.0 cm (M1a), 3.1–8.0 cm (M1b) and ≥8.1 cm (M1c).[1] This diameter of the largest metastasis was recorded for 40 (59%) patients in group M. Of these, 14 (35%) were M1a, 25 (63%) were M1b and 1 (2%) was M1c. The mean largest diameter was 4.3 cm (SD 3.2; median 4.0; range 1.0–22.0).

Regarding the sites of systemic metastases, hepatic metastases were noted in 63 (91%) patients. Of these, metastases noted as liver-alone were noted in 46 (67%; tables 2 and 4). Of the 69 patients, extrahepatic organs included: 11 (16%) to lung, 6 (9%) bone, 4 (6%) brain, 3 (4%) subcutaneous, 2 (3%) visceral lymph nodal metastases and 1 splenic metastasis. Overall, multiple sites of metastasis were found in 16 (24%) of patients (table 2). Of those 6 (9%) patients who presented with extrahepatic

Table 4 Hepatic metastases based on staging method and AJCC T-category

| T-category | Hepatic metastases only | | Hepatic metastases and involvement of other sites | |
|---|---|---|---|---|
| | Not staged by PET/CT N=23 | Staged by PET/CT N=23 | Not staged by PET/CT N=7 | Staged by PET/CT N=10 |
| T1 | 3 (12%) | 4 (17%) | 0 (0%) | 0 (0%) |
| T2 | 5 (22%) | 4 (17%) | 6 (86%) | 3 (30%) |
| T3 | 5 (22%) | 10 (44%) | 1 (14%) | 5 (50%) |
| T4 | 10 (44%) | 5 (22%) | 0 (0%) | 2 (20%) |

.AJCC, American Joint Committee on Cancer, 8th edition; PET, positron emission tomography; PET/CT, combination PET with synchronous CT analysis.

dissemination, 3 (4.5%) had multiorgan involvement and 3 (4.5%) had lung metastasis.

### Radiographic imaging

PET/CT scan was performed for 340 (9%) of the 3610 patients, including 37 (54%) in group M (table 4) and 303 (9%) in group N. In group M, out of 16 patients with metastases in multiple sites, 8 (50%) were diagnosed by PET/CT scan whereas 8 (50%) were diagnosed by other staging methods at initial presentation. In addition PET/CT also helped in identifying of 5 (56%) RLN. Metastases in multiple sites and RLN were identified by PET/CT more often than without ($p<0.001$). This finding suggests underdiagnosis of multiorgan metastasis when using regional organ-specific staging methods.

### Survival after diagnosis

Median follow-up from initial presentation to last visit of group M was 10.0 months (mean 18.2; SD 19.5; range 1.0–85.0). The corresponding numbers for group N were 38.6 months (mean 47.2; SD 34.9; range 0.9–212.0). The survival time was calculated for 53 (77%) patients in group M. For the rest, survival time was not considered as it exceeded the date of closure of the registry. Group M had a median survival of 12.0 months (mean 20.0; SD 21.3; range 2.0–91.0).

## DISCUSSION

This study uniquely describes the clinical features of stage IV patients identified with metastatic uveal melanoma at the time of initial presentation. These cases were designated patients with stage IV uveal melanoma by the eighth edition AJCC staging system[1] and derived from the AJCC-OOTF international, multicentre, internet-based registry which collected 3866 cases. From that series we analysed a subgroup of 69 stage IV patients for statistically significant differences. Predictive factors for metastasis at initial presentation included: site of origin, tumour thickness, largest basal diameter, extrascleral extension, ciliary body involvement and eighth edition AJCC-TNM category. These characteristics differed in patients with and without synchronous metastases at presentation. Furthermore, we found that whole-body radiographic imaging was more likely to reveal extrahepatic and multiorgan sites of metastasis.

As early as 1979, Zimmerman and McLean [35] published a case series of 29 patients of uveal melanoma with metastasis describing their presenting history and symptoms. Our study is unique as it describes the ocular and systemic, eighth edition AJCC staging of patients with presenting with both uveal melanoma and metastasis.

### Sites of tumour origin

The intraocular location of a uveal melanoma has been shown to influence metastatic risk. Ciliary body location has been associated with a higher mortality rate.[15 19 32 36] We also found that ciliary body origin was associated with metastases at initial presentation. Ciliary body and choroidal location with extrascleral extension were associated with RLN metastases in nine patients.

### Tumour size

Tumour thickness was a significant predictor for stage IV disease at the time of presentation for both choroidal and ciliary body melanomas. However, largest basal diameter was only statistically significant for choroidal melanomas. Lack of an association for ciliary body melanomas possibly was related to the small number of tumours in that location and difficulties related to their measurement. Overall, our findings were consistent with prior studies, suggesting patients with a higher T-category tumour should be more closely monitored for metastatic disease.[1–3 5 15 34 37] Novel finding of this study was that there were 6% of the uveal melanoma with metastasis at initial presentation which belong to subcategory T1a. This emphasises the importance of periodic surveillance even for small tumours perhaps (ie, eighth edition AJCC cT1).

### Extrascleral extension and ciliary body involvement

For choroidal and ciliary body melanoma, presence of extrascleral extension was associated with a significantly higher frequency for synchronous metastasis. However, ciliary body involvement was also associated with synchronous metastases in choroidal melanoma. These findings are consistent with prior studies relating to metastases developing on follow-up.[12 13 17 31 37] It is reasonable to conclude that the presence of ciliary body involvement, extrascleral extension or both on the first visit should raise suspicion for synchronous metastatic melanoma.

### N and M categories

It can be inferred from table 5[5 17 20 38 39] that uveal melanoma metastasises to multiple sites, with the liver being the most frequent. However, the liver is both the most commonly investigated organ and thus selected to be the most common initially reported sites of metastasis. In comparison to other research, our group M study was unique in that whole-body PET/CT imaging was compared for initial staging. In our study, whole-body initial staging enabled early detection of multiple organ metastasis in 50% of 16 stage IV patients in group M. Table 5 shows that uveal melanoma can metastasise to extrahepatic sites and in some cases may involve multiple sites. For example, Kath *et al* detected multiple site metastasis on long-term follow-up in 54% of patients.[38] Failure to detect extrahepatic or multiorgan metastasis can affects treatment decisions and thus patient survival duration.[8 31]

### Survival time

The relatively short 12 months median survival time for group M could be related to relatively high T-categories, one can find

**Table 5** Comparison of metastatic sites of uveal melanoma among various studies

| Study | Rajpal[20] | COMS[5] | Kath[38] | Rietschel[17] | Jochems[39] | Mean | Our study |
|---|---|---|---|---|---|---|---|
| Metastasis | F/U | F/U | F/U | F/U | F/U | F/U | Presentation |
| Sample size | 35 | 739 | 24 | 119 | 175 | 218.4 | 69 |
| Liver | 71.4% | 89.0% | 87.0% | 60.5% | 88.0% | 79.2% | 91.3% |
| Lungs | 40.0% | 29.0% | 46.0% | 24.4% | 25.1% | 32.9% | 15.9% |
| Lymph nodes | 14.3% | 11.0% | 4.2% | 1.7% | 16.0% | 9.4% | 13.0% |
| Bones | 17.1% | 17.0% | 29.0% | 8.4% | 15.4% | 17.4% | 8.7% |
| Brain | 5.7% | 6.1% | 8.0% | 4.2% | 1.7% | 5.1% | 5.8% |
| Subcutaneous tissue | 34.3% | 12.0% | 17.0% | 10.9% | 10.3% | 16.9% | 4.3% |
| Others | 34.3% | 11.0% | 37.5% | N/A | 23.4% | 26.6% | 4.2% |
| Multiple sites | N/A | 43.0% | 54.2% | 10.9% | 5.7% | 28.4% | 23.2% |
| Tests | N/A | LFTs, CXR and autopsy studies | LFTs, CXR, abdominal USG, CT, MRI and autopsy studies | Radiographic imaging, blood test | Lactose dehydrogenase enzyme (LDH), Radiographic imaging | N/A | Abdominal USG, CT, MRI, and whole-body- PET or PET/CT |
| Median survival time in months (time of metastasis to death) | 2.2* | <6 | 13.2 | 12.5 | One-year survival- 47.8% | -† | 12 |

*For Rajpal[20] median survival time of liver metastasis was mentioned as there was no mention of cumulative survival time and hepatic metastasis was most common.
†Mean was not calculated for median survival time.
CXR, chest X-ray; F/U, at follow-up; LFTS, liver function tests; PET, positron emission tomography; PET/CT, combination PET and CT analysis; USG, ultrasonography.

similar survival times in other studies.[6 19–27] Clearly, group M patients had demonstrable late stage, multiorgan disease associated with impending death. Therefore, their relatively short survival was likely related to 'late-stage selection bias'.

## Surveillance

Table 5 emphasises the importance of surveilling the whole body for metastasis. Although hepatic metastases can be discovered in up to 90% of cases with hepatic USG or contrast enhanced abdominal CT or MRI, the challenge lies in detecting extrahepatic spread.[9] In an effort to screen the whole body, Freton *et al* studied initial staging of uveal melanoma in 333 consecutive patients with PET/CT. He found that whole-body imaging improved not only detection of extrahepatic metastases but also revealed that 3.3% of patients had additional non-ocular primary cancers.[8] The complex of concerns regarding the use of each diagnostic method is beyond the scope of this study but has been related to dependence on skilled technicians (USG), radiation dose (PET/CT >CT), side effects of contrast agents (MRI>CT) and relative cost.[3 8 9 40 41]

Various studies have compared different modalities of imaging for detection of metastasis from tumours in other sites (eg, solitary pulmonary nodule and cervical carcinoma). Yi *et al* reported PET/CT is more accurate and sensitive in identifying malignant solitary pulmonary nodules. In contrast, the sensitivity, specificity and accuracy for a malignant solitary pulmonary nodule on high-resolution CT scan were 81%, 93% and 85%, respectively, whereas those on integrated PET/CT were 96%, 88% and 93%, respectively.[40] Similarly, Liu *et al* performed a meta-analysis on 67 studies on cervical carcinoma, concluded that PET/CT has the highest specificity to identify lymph nodes among non-invasive imaging modalities.[41] In our study, PET/CT was significantly more likely to reveal multiorgan metastasis.

## CONCLUSION

We describe patients who initially presented with stage IV uveal melanoma. They were more likely to have tumours with ciliary body origin or involvement, larger tumour thicknesses, greater basal diameters and extrascleral extension. These factors were reflected by their higher eighth edition AJCC TNM categories.[8] We found that stage IV patients were more likely to have multiorgan disease, most often detected by whole-body PET/CT imaging. However, even T1 uveal melanomas may present with synchronous metastasis. Therefore, this study supports initial whole-body staging of all patients with uveal melanoma.

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**Funding** This study was funded by internet technology grants to Princess Margaret Cancer Center's IT program, which has (in turn) participated in the design, construction and maintenance of this uveal melanoma registry. Funders included John and Myrna Daniels Foundation, The Paul T Finger Fund for Ophthalmic Oncology Research and The Eye Cancer Foundation. (http://eyecancercure.com). Dr Garg received an ophthalmic oncology fellowship grant to study with Dr Finger (from The Eye Cancer Foundation). Dr Kivelä reported receiving a governmental grant from the Helsinki University Hospital Research Fund.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** Institutional review board and ethics approvals were written and obtained by each participating centre based on and including required elements from the Princess Margaret Comprehensive Cancer Center of Toronto, Ontario, Canada Internet Technology Protocols. These approvals allowed anonymised patient data to be entered, online into the central database. This study adhered to the Declaration of Helsinki and Health Insurance Portability and Accountability Act of 1986.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as supplementary information. Data are available upon reasonable request.

**Author note** All authors participated in critical review of the manuscript prior to publication (except Drs. Vladimir Valskiy and Barrett Haik who are deceased).



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