Clinical Characteristics of Patients Presenting with Uveal Melanoma and Metastases (Stage IV): A Multicenter, International Study
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Purpose of this Study

To analyze ocular and systemic findings of patients presenting with both uveal and metastatic melanoma at first presentation.

[AJCC *Stage IV* Disease]
Method – AJCC-OOTF World-Wide Centers

10 oncology centers from 8 countries for a total of 3866 patients from 4 continents between April 1, 2001 to 2011
Method – Registry Study

Internet-based retrospective registry.

Institutional review board and Ethics approvals were obtained by

All Centers obtained IRB and Ethics approval by Princess Margaret Cancer Center, Toronto, Ontario, Canada

This study adhered to the Declaration of Helsinki and Health Insurance Portability and Accountability Act (HIPAA) of 1986.
Methods – Patients Divided into 2 Groups

**Group M:** Stage IV metastatic disease at initial presentation

**Group N:** Stage I-III no metastatic disease at initial presentation

PET/CT Multifocal Metastases
Stage IV: Metastatic Uveal Melanoma

Time of detection – affects survival.

No Prior Literature

**Group M:** 50-year-old male, neovascular glaucoma, T3-sized mushroom-shaped tumor with total RD. Immediate enucleation for choroidal melanoma for pain control. Post-operative PET/CT shows multi organ metastasis
Background: Systemic Evaluations

• Metastasis - leading cause of death
• Greater reliance on staging with
  • Radiographic Imaging (USG/CT/MRI)
  • Whole-body PET/CT.
• Liver - most common site
  • other sites - bone, lungs, skin, and brain.

Group N: 60-year-old male with T1b iris melanoma tumor underwent local resection. PET/CT revealed liver metastasis
<table>
<thead>
<tr>
<th>Variables</th>
<th>Statistical Tests</th>
</tr>
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<td>Continuous Variables</td>
<td>Mean, Standard Deviation, Median, and Range</td>
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<td>Categorical Variables</td>
<td>Frequencies and Percentages</td>
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<tr>
<td>Goodness of Fit</td>
<td>Hosmer-Lemeshow Test</td>
</tr>
<tr>
<td>Odds Ratios (OR) and p-values</td>
<td>Wald Chi-Square Test</td>
</tr>
</tbody>
</table>
Results

• 3610 patients
• **Group M** - 69 (1.9%; 95% CI, 1.5-2.4)
• **Group N** - 3541 (98.1%; 95% CI, 97.6-98.5)

**Group M - Intraocular Tumor Location**

• Ciliary body tumor origin - OR 2.34; p=0.011
• Choroidal tumors with Ciliary Body involvement - OR 2.87; p=0.02
• Choroidal tumors without Ciliary Body involvement - p=0.62

**GROUP M**

- Argentina: 30
- United States: 29
- Sweden: 7
- Spain: 2
- The Netherlands: 1

**GROUP N**

- Argentina: 29
- United States: 30
- Sweden: 7
- Spain: 2
- The Netherlands: 1

**Percentages of Melanoma in Each Group**

**Group M**
- Choroidal Melanoma: 80% (55)
- Ciliary Body Melanoma: 8% (266)
- Iris Melanoma: 4% (11)

**Group N**
- Choroidal Melanoma: 87% (3097)
- Ciliary Body Melanoma: 5% (178)
- Iris Melanoma: 5% (178)
Results – Higher AJCC T – Category was Significant

- 0.7% T1, 1.5% T2, 2.6% T3 and 7.9% in T4 ($\chi^2 (3) = 50.1; p<0.001$) (Significant)

<table>
<thead>
<tr>
<th>T – CATEGORY – GROUP M</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Choroidal Melanoma</td>
<td>2</td>
<td>18</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Ciliary Body Melanoma</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Iris Melanoma</td>
<td>2</td>
<td>18</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

74-year-old African American female with T4e, posterior ESE stage IV at diagnosis
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Group M, n=69</th>
<th>Group N, n = 3541</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Choroidal</td>
<td>Ciliary Body</td>
</tr>
<tr>
<td>Sample</td>
<td>55 (80%)</td>
<td>11 (16%)</td>
</tr>
<tr>
<td>Tumor Thickness (mm)</td>
<td>Mean (SD)</td>
<td>8.3 (4.8)</td>
</tr>
<tr>
<td></td>
<td>Median (Range)</td>
<td>7.7 (2-0-24.5; p&lt;0.001)</td>
</tr>
<tr>
<td>Diameter (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ESE</td>
<td>6 (11%; p&lt;0.001)</td>
<td>5 (45%; p=0.001)</td>
</tr>
<tr>
<td>CBI</td>
<td>11 (20%; p=0.02)</td>
<td>11 (100%)</td>
</tr>
<tr>
<td>ESE and CBI</td>
<td>4 (7%; p&lt;0.001)</td>
<td>5 (45%)</td>
</tr>
</tbody>
</table>

Herein, Metastatic group was more likely found to have larger tumor size with higher frequency Of ESE and CBI.

Results – Choroidal vs Ciliary Body vs Iris Melanoma
Results – Stage IV Metastasis and Nodal Involvement

• **Metastatic Sites**
  
  • *Multiple Sites - 22 (32%)*
    
    • All iris melanoma had liver-only metastasis.
    • 6 (9%) patients presented with only extra-hepatic metastasis, 4 (6%) of these had multiorgan involvement and 2 (3%) had lung metastasis.
  
  • **Lymph Node Positive:** - 9 (13%) patients (either had a ciliary body or a choroidal melanoma).
    • Of these 6 (67%) had extrascleral extension.
Results – PET-CT & Survival

- PET-CT was used in
  - Group M - 37 (54%)
  - Group N - 303 (9%)

- Multiple Sites - 13 (59%) (p<0.001)

- Median Follow-up
  - Group M - 10.0 months (mean 18.2; SD 19.5; range 1.0-85.0).
  - Group N - 38.6 months (mean 47.2; SD 34.9; range 0.9-212.0).

- Median Survival
  - Group M - 12.0 months (mean 20.0; SD 21.3; range 2.0-91.0).

This finding suggests underdiagnosis of multiorgan metastasis when utilizing regional organ-specific staging methods.

**Group M**: 55-year-old female with a high-risk T4e ciliary body melanoma, NVG and hyphema, liver metastasis at diagnosis.
Discussion - Sites of Tumor Origin & CB Involvement
Discussion – Tumor Size

Main Outcome Measures: Melanoma-related metastasis and death.

Results: Of 7731 patients with posterior uveal melanoma, the AJCC classification based on T was category T1 in 3557 (46%), T2 in 2082 (27%), T3 in 1399 (21%), and T4 in 493 (6%). Based on tumor categories T1, T2, T3, and T4, respectively, features that showed significant increase with tumor category included patient age at presentation (57, 58, 58, and 61 years; \( P = 0.001 \)), tumor base (8, 12, 15, and 20 mm; \( P = 0.001 \)), tumor thickness (3.5, 5.2, 8.5, and 11.4 mm; \( P = 0.001 \)), mushroom configuration (8%, 20%, 38%, and 39%; \( P = 0.001 \)), associated subretinal fluid (64%, 80%, 82%, and 83%; \( P = 0.001 \)), intracocular hemorrhage (6%, 12%, 17%, and 18%; \( P = 0.001 \)), rupture of Bruch's membrane (9%, 24%, 43%, and 56%; \( P = 0.001 \)), and extracocular extension (1%, 9%, 17%, and 22%; \( P = 0.001 \)). After therapy, Kaplan-Meier estimates of mortality at 5, 10, and 20 years were 8%, 15%, and 25% for category T1, 14%, 25%, and 40% for category T2, 31%, 49%, and 69% for category T3, and 51%, 63%, and 89% for category T4, respectively (\( P = 0.001 \)). Kaplan-Meier estimates of death at 5, 10, and 20 years were 4%, 8%, and 11% for category T1, 6%, 13%, and 24% for category T2, 19%, 27%, and 36% for category T3, and 30%, 43%, and 55% for category T4, respectively (\( P = 0.001 \)). Compared with category T1, the hazard ratio for metastasis and death for T2 was 1.8 and 1.9, respectively; that for T3 was 4.5 and 4.7, respectively; and that for T4 was 8.2 and 8.8, respectively.
Discussion – ESE

American Joint Committee on Cancer’s 7th Edition Classification of Uveal Melanoma (Tumor Size Category) Predicts Prognosis in 7731 Patients

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Conclusions: Based on the AJCC classification, increasing tumor category was associated with older age, larger tumor, and greater incidence of subretinal fluid, hemorrhage, and extraciliary extension. Compared with category T1, the rate of metastasis and death was 2 times greater for T2, 4 times greater for T3, and 8 times greater for T4. The risk for metastasis and death increased 2-fold with each increasing melanoma category.
<table>
<thead>
<tr>
<th>Metastasis</th>
<th>Rajpal</th>
<th>COMS</th>
<th>Kath</th>
<th>Rietschel</th>
<th>Jochems</th>
<th>Mean</th>
<th>Our Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample Size</td>
<td>F/U</td>
<td>F/U</td>
<td>F/U</td>
<td>F/U</td>
<td>F/U</td>
<td>F/U</td>
<td>Presentation</td>
</tr>
<tr>
<td>Metastasis</td>
<td>35</td>
<td>739</td>
<td>24</td>
<td>119</td>
<td>175</td>
<td>218.4</td>
<td>69</td>
</tr>
<tr>
<td>Liver</td>
<td>71.4%</td>
<td>89.0%</td>
<td>87.0%</td>
<td>60.5%</td>
<td>88.0%</td>
<td>79.2%</td>
<td>91.3%</td>
</tr>
<tr>
<td>Lungs</td>
<td>40.0%</td>
<td>29.0%</td>
<td>46.0%</td>
<td>24.4%</td>
<td>25.1%</td>
<td>32.9%</td>
<td>15.9%</td>
</tr>
<tr>
<td>Lymph Nodes</td>
<td>14.3%</td>
<td>11.0%</td>
<td>4.2%</td>
<td>1.7%</td>
<td>16.0%</td>
<td>9.4%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Bones</td>
<td>17.1%</td>
<td>17.0%</td>
<td>29.0%</td>
<td>8.4%</td>
<td>15.4%</td>
<td>17.4%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Brain</td>
<td>5.7%</td>
<td>6.1%</td>
<td>8.0%</td>
<td>4.2%</td>
<td>1.7%</td>
<td>5.1%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td>34.3%</td>
<td>12.0%</td>
<td>17.0%</td>
<td>10.9%</td>
<td>10.3%</td>
<td>16.9%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Others</td>
<td>34.3%</td>
<td>11.0%</td>
<td>37.5%</td>
<td>-</td>
<td>23.4%</td>
<td>26.6%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Multiple Sites</td>
<td>-</td>
<td>43.0%</td>
<td>54.2%</td>
<td>10.9%</td>
<td>5.7%</td>
<td>28.4%</td>
<td>31.9%</td>
</tr>
<tr>
<td>Tests</td>
<td>LFTs, CXR, and autopsy studies</td>
<td>LFTs, CXR, abdominal USG, CT, MRI, and autopsy studies</td>
<td>Radiographic imaging, blood test</td>
<td>Lactose dehydrogenase enzyme (LDH), Radiographic imaging</td>
<td>Abdominal USG, CT, MRI, and whole-body PET or PET/CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Survival Time in months (time of metastasis to death)</td>
<td>2.2</td>
<td>&lt;6</td>
<td>13.2</td>
<td>12.5</td>
<td>One-year survival- 47.8%</td>
<td>12</td>
<td></td>
</tr>
</tbody>
</table>
Discussion - Screening

- Although hepatic metastases can be discovered in up to 90% of cases with hepatic USG, abdominal CT or MRI.

The challenge lies in detecting extrahepatic spread.
Summary: Patients who Present with Metastasis

- More likely to have
  - Ciliary Body Origin or Involvement
  - Larger Tumor Thickness
  - Greater Basal Diameter
  - Extrascleral Extension
- Even T1 uveal melanomas presented with synchronous metastasis.
- Multi-organ disease best detected by whole body PET/CT imaging.
- **This study supports initial choroidal melanoma staging with total body FDG -PET/CT**
The AJCC-OOTF

Thanks You!