



AJCC American Joint Committee on Cancer





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

# **Financial Disclosures**

- Supported by:
  - The Myrna and John Daniels Charitable Trust Canada
  - The Eye Cancer Foundation, Inc. USA
  - The Paul T Finger Fund at Princess Margaret Cancer Center, Canada
- The sponsoring organizations had no role in the design or conduct of this research
- The authors had no conflicts of interest.
- Dr. Gaurav Garg received a Fellowship Grant from The Eye Cancer Foundation, Inc. to study with Dr. Paul T. Finger at The New York Eye Cancer Center.

# Authors – American Joint Committee on Cancer Ophthalmic Oncology Task Force (AJCC-OOTF)

- 1. Gaurav Garg MD\* India
- 2. Paul T. Finger MD USA
- 3. Tero T. Kivelä MD Finland
- 4. E. Rand Simpson, MD Canada
- 5. Brenda L. Gallie, MD Canada
- 6. Svetlana Saakyan, MD Russia
- 7. Anush Amiryan, MD Russia
- 8. Vladimir Valskiy, MD, PhD Russia
- 9. Kimberly J. Chin, OD USA
- 10. Ekaterina Semenova, MD USA
- 11. Stefan Seregard, MD Sweden
- 12. Maria Fili, MD Sweden

- 13. Matthew Wilson, MD USA
- 14. Barrett Haik, MD USA
- 15. Jose M. Caminal, MD Spain
- 16. Jaume Català Mora, MD Spain
- 17. Cristina Gutierrez, MD Spain
- 18. David E. Pelayes, MD, PhD Argentina
- 19. Anibal M. Folgar, MD Argentina
- 20. Martine J. Jager, MD, PhD The Netherlands
- 21. Mehmet Doğrusöz, MD, PhD The Netherlands
- 22. Gregorius P.M. Luyten, MD The Netherlands
- 23. Arun D. Singh, MD USA
- 24. Shigenobu Suzuki, MD Japan

#### 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



© GeoNames, Microsoft, Navinfo, TomTom, Wikiped

#### 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 G 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.





**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

| Variables                          | Statistical Tests                                |
|------------------------------------|--|
| Continuous Variables               | Mean, Standard Deviation, Median, and Range      |
| Categorical Variables              | Frequencies and Percentages                      |
| Risk Factors                       | Univariable Logistics Regression                 |
| Contingency Tables                 | Pearson Chi-Square Test & Fisher's Exact<br>Test |
| Goodness of Fit                    | Hosmer-Lemeshow Test                             |
| Odds Ratios (OR) and p -<br>values | Wald Chi-Square Test                             |

Method -Statistical Analysis

#### Results

- 3610 patients
- Group M 69 (1.9%; 95% Cl, 1.5-2.4)
- **Group N** 3541 (98.1%; 95% Cl, 97.6-98.5)
- **Group M** Intraocular Tumor Location
  - Ciliary body tumor origin OR 2.34; p=0.011 (S)
  - Choroidal tumors with Ciliary Body involvement OR 2.87; p-0.02 (S)
  - Choroidal tumors without Ciliary Body involvement p=0.62 (NS)

**GROUP M** 





## 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)





74-year-old African American female with T4e, posterior ESE stage IV at diagnosis

| Characteristics |           | Group M, n=69             |                           |         | Group N, n = 3541 |                |          |
|-----------------|-----------|---------------------------|---------------------------|---------|-------------------|----------------|----------|
|                 |           | Choroidal                 | Ciliary Body              | Iris    | Choroidal         | Ciliary Body   | Iris     |
| Sample          |           | EE (80%)                  | 11 (16%)                  | 3 (5%)  | 3097 (87%)        | 266 (8%)       | 178 (5%) |
| Tumor           | Mean (SD) | 8.3 (4.8)                 | 9.6 (3.4)                 | -       | 5.7 (3.0)         | 6.0 (3.0)      | -        |
| Thickness       | Median    | 7.7 (2-0-24.5;            | 11.0 (2.7-                | -       | 5.0 (2.0-23.0)    | 5.6 (2.0-16.0) | -        |
| (mm)            | (Range)   | p<0.001) <mark>(S)</mark> | 14.7;                     |         |                   |                |          |
|                 |           |                           | n=0 001) <mark>(S)</mark> |         |                   |                |          |
| Here            | ein, M    | etastati                  | c group                   | was n   | nore lik          | ely fou        | ind to   |
| Diameter        | "tum      | or size                   | with h                    | gher fr | requen            | cy Of E        | SE an    |
| ESE             |           | 6 (11%;                   | 5 (45%;                   | 1 (33%) | 48 (2%)           | 16 (6%)        | 2 (1%)   |
|                 |           | p<0.001) <mark>(S)</mark> | p=0.001) <mark>(S)</mark> |         |                   |                |          |
| CBI             |           | 11 (20%;                  | 11(100%)                  | 1 (33%) | 248 (8%)          | 266 (100%)     | 88 (49%) |
|                 |           | p=0.02) <mark>(S)</mark>  |                           |         |                   |                |          |
| ESE and         |           | 4 (7%;                    | 5 (45%)                   | 1 (33%) | 20 (1%)           | 16 (6%)        | 2 (1%)   |
| CBI             |           | p<0.001) <mark>(S)</mark> |                           |         |                   |                |          |

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 extrahepatic metastsis, 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



- Group M 37 (54%)
- Groun N 303 (9%)

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



**Group M:** 55-year-old female with a highrisk T4e ciliary body melanoma, NVG and hyphema, liver metastasis at diagnosis

**methods.**<sup>.0).</sup> **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).

#### Discussion - Sites of Tumor Origin & CB Involvement

| JOURNAL OF CLINICAL ON   |                                       | Original Investigation   |  |              |               |   |                        |  |  |
|--|---------------------------------------|--|--|--------------|---------------|---|------------------------|--|--|
|  |                                       | International Validation of the American Joint Committee<br>on Cancer's 7th Edition Classification of Uveal Melanoma<br>The ACE Optimates Oncology Task Force  |  |              |               | tic Death in Patients<br>fect on Survival |                        |  |  |
| Sta  | atomic                                | creased 3-fold for stage IIA ( $P < .001$ ), 2-fold for stages IIB<br>( $P < .001$ ) and IIIA ( $P < .001$ ), and 1.6-fold for stage IIIB<br>( $P = .047$ ). In stage IIIC (which only had 21 patients), the HR is | *EXE grouping (log-rank test for trend P < .001). Metastasis-<br>free point estimates as shown in Kaplan-Meier curves were gen-<br>erally worst among patients with both CBI and EXE, followed | 48.8<br>52.2 | 96.5<br>40.5  | 61.5<br>38.5                              | .001 (Mana Ministry)   |  |  |
| Enro<br>Jone   | u Kujala, Be<br>Daniel Gran           | 1.3 (compared with stage IIIB); however, this result was not statistically significant $Q^{2}$ = .57).   | thy EXE only, then those with CBI only, and best among those with neither CBI not EXE. The 5- and 20-year metasitasis-free point estimates sever one room (CL 88%, one) and 8m over            | 23.8<br>44.3 | 9.8<br>29.3   | 4.5<br>17.8                               |                        |  |  |
| ated by seaan's grats from the OT  | elts<br>the 7,369 l                   | Metastasis-Free Point Extimates According to Tumor Size<br>Categories and Subcategories  | CL 82%-80%) for no CBI or EXE, 72%-195% CL 66%-77%) and<br>67% 055% CL 60%-72%) for CBI only, 54% 055% CL 29%-74%]   | 22.0         | 16.8<br>10.3  | 27.1<br>90.7                              |                        |  |  |
| of Tenue Bark Houndarion, Eser<br>pice, Research Foundation of<br>on Corporation, metrumentation<br>Of 1 | 14 Ten-ye<br>139%, resp<br>absence of | Patients with primary citiary body and chorosidal metationia<br>classified according to tornor size category some as follows: TL,<br>1146 patients; T2, 1151 patients; T3, 776 patients; and T4, 124               | *(55% CL, E2% 54%) for both CN and EXE, respectively (Table 3<br>and Figure 28).   | 72.9<br>27.1 | 49.0<br>\$1.5 | 28.5<br>71.5                              | + 001 (Mares Whiteay)  |  |  |
| P < Participation and P < P <  | .001 for T                            | patients (eTable 3 in the Supplement and Table 3). The num-<br>bers of patients with metastasis were as follows: T1, 30 (2.7%),<br>T2, 117 (10.2%), T3, 135 (17.4%), and T4, 43 (24.7%).                           | Patients with ciliary body and choroidal melanoma were<br>also subclassified according to size of the EXE as follows: no<br>EXE, 3163 (98,3%); EXE of 5.0 mm or less, 44 (1.4%); and EXE       | 90.1<br>8.9  | 84.2<br>15.6  | 00.5<br>38.5                              | < 001 (Mare-Whitery)   |  |  |
| 206, Fetarot, and Reamon 279<br>Notes for Sampladada, Sampler,   | 6, 10%, re                            | Univariate analysis was used to determine Kaplan Meier<br>metastasis-free point estimates at 1, 5, and 20 years accord-<br>ing to turnor size foTable 3 in the Supplement. Table 3, and                            | greater than 5.0 mm, 12 (0.4%). The 5- and 10 year Kaplan-<br>Moirr metastasis free point estimates were 87% (55% CL 86%-<br>89%) and 81% (55% CL 79% 84%) for no EXE, 41% (55% CL             | 0            |               | 0   |                        |  |  |
| depositives of polymetric com-<br>mission and author contribution multi-                                 | clusion<br>s evidence-<br>lanomas in  | Figure 2A). Increasing tumor size was associated with an increased risk of metastasis (log-rank test for trend   | 25%-66%) and 43% (95% CL, 25%-66%) for EXE 5.0 mm or<br>smaller, and 42% (95% CL, 7%-7%)(5-year only/for EXE greater<br>than 6 and 2% (95% CL, 7%-7%)(5-year only/for EXE greater              | 21.7         | 60.5          | 100.3                                     | <.001 (Knaskut Hoding) |  |  |
| a found at the end of this   | Cancer.                               | 5 and 10 years were as follows: 97% (95% CL 95%-98%) and   | Kaplan-Meier plot suggests that metastasis is related to the size  | 39.5         | 29.2          | 28.3                                      | <.001 Dfum-Whitneyl    |  |  |

#### Discussion – Tumor Size



to study a heterogenous patient population in ophthalmic oncology. Our results support the continued use of the 7th edition of the AUCC Concer Stoping Manual for useal melanoma.

of this article.

#### Discussion – ESE

#### Research

#### **Original Investigation**

#### International Validation of the American Joint Committee on Cancer's 7th Edition Classification of Uveal Melanoma

The AXE Ophthalmic Oncollogy Task Force

creased 3-fold for stage IIA (P < .001), 2-fold for stages IBB (P = .001) and IIIA (P = .000), and 1.6-fold for stage IIIB (P = .047). In stage IIIC (which only had 2) patients), the HR is 1.3 (compared with stage IIIII); however, this result was not statistically significant (P = .57).

#### Metastasis-Free Point Extimates According to Tumor Size Categories and Subcategories

Patients with primary ciliary body and choroidal melanoma classified according to tomor size category some as follows: Th, 1116 patients; T2, 1151 patients; T3, 776 patients; and T4, 154 and Fjorge 2B). Patients with ciliary body and choroidal melanoma were bers of patients with metastasis were as follows: T1, 30 (2.7%); T2, 117 (10.2%); T3, 135 (17,4%); and T4, 43 (24,7%).

Univariate analysis was used to determine Kaplan Meier metastasis-free point estimates at 1, 5, and 10 years according to tumor size (eTable 3 in the Supplement, Table 3, and Figure 2A). Increasing tumor size was associated with an increased risk of metastasis (log-rank test for trend. P < .001). Metastasis-free point estimates decreased at both 5 and 10 years were as follows: 97% (95% CI, 95%-98%) and 94% (95% CL 92%-96%3 for T1, \$5% (95% CL 82%-88%3 and tons apps, CL 1994, Rend for To. 1996, Josef, CL 1996, Rend and

\*EXE grouping flog-rank test for trend P < .001). Metastasis-1 free point estimates as shown in Kaplan-Meier curves were genserally worst among patients with both CBI and EXE, followed, thy EXE only, then those with CBI only, and best among those with neither CHI nor EXE. The 5- and 10-year metastasis-free point estimates were 90% (95% CL 88%-91%) and 84% (95% CL 82%-80%) for no CBI or EXE, 72%-195% CL 66%-77%) and\* 67% (95% CL 60%-73%) for CBI only, 54% (95% CL 29%-54%) (5-year only) for EXE only, and 33% (95% Cl. 13%-54%) and 33%. \*(95% CL 13% 54%) for both CBI and EXE, respectively (Table 3)

also subclassified according to size of the EXE as follows: no EXE, 3161 (98.3%); EXE of 5.0 mm or lens, 44 (1.4%); and EXE greater than 5.0 mm, 12 (0.4%). The 5- and 10 year Kaplan-Moire motastasis-free point estimates were 87% (55% CL 86%-89%) and 81% (92% CI, 79%-84%) for no EXE, 43% (95% CL, 25%-60%) and 43% (95% CL 25%-60%) for EXE 5.0 mm or smaller, and 42% (95% Cl. 7%-75%) (5-year only) for EXE greater than 5.0 mm, respectively (eTable 4 in the Supplement). The Kaplan-Meier plot suggests that metastasis is related to the size of the EXE (log-rank test for trend P < .0010 (eFigure in the Eventure of

< 001 4.82 (0.18-4.47)

Epicantiar clock head possilla < 001 4.14 (2.88-6.97) Diffuse vs 1<sup>2</sup> Diffuse yo 2<sup>th</sup> <.001 4.35 (5.29-6.89) Diffuse yn 3<sup>m</sup> < 001 4.00 (2.92-5.56)

Diffuse ye 47

#### 033 Consecutive

ID: Sava Nagovi, MD. Danielle S. Rudich, MD; Lauren Forte, BS: rry A. Shields, MD

CES

able 8. Univariate and Multivariate Analysi edictive of Malanema Metastanis in 2023 Clinical Features at Presentation (continu

**Nacard Ratio** (987). Cantidance Value Interval3 Multivieriate Analysis 1.13 (1.08-1.18) wall mailuturea location Poderior was with 2014 2.10(1.104.80) witter register 2008 1.45(1.15-1.94) a in equator materiana? 1.88(1.38-2.06) Hary body in equator melanomal < 001 KM (CH-LSE din 1 ~ 001 ours? 1.05(1.05-1.09) <.001 hises us yellow? 1.01(1.15-1.22) insteal thuid South Street 120 120 151 white-cular automator Project vs about? 1.41(1.00-1.90) Rettings Strated 043 1.02 (5.01-1.47) Present vs. abuser®

American Joint Committee on Cancer Classification of Posterior Uveal Melanoma (Tumor Size Category) Predicts Prognosis in 7731 Patients

Carol L. Shields. MD.<sup>1</sup> Swashi Kaliki, MD.<sup>1</sup> Missons Furnar, MD.<sup>1</sup> Enzo Fulco, MD.<sup>1</sup> Carolina Alarcon, MD.<sup>1</sup> Jerry A. Shields, MD<sup>1</sup>

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 1599 (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, 8.9, and 11.4 mm; P<0.001), mushroom configuration (8%, 20%, 38%, and 39%; P<0.001), associated</p> ustratinal Buid (64%, 80%, 82%, and 83%, P. 0.001), introductor betriantege, 6%, 12%, 17%, and 18%; P<0.001), rupture of Bruch's membrane (9%, 24%, 40%, and 40%; P<0.001), and extraocular extension (1%).</li> 1%, 4%, and 12%; P=0.001). After therapy, Kaplan-Meier estimates of metastasis at 5, 10, and 20 years were 5%, 15%, and 25% for category 11, 14%, 25%, and 40% for category 12, 31%, 49%, and 62% for category 13, and 51%, 63%, and 69% 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, 8%, 13%, and 24% for category T2, 19%, 27%, and 36% for category T3, and 30%, 43%, and 51% 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.

Conclusions: Based on the AJCC classification, increasing tumor category was associated with older age. larger tumor, and greater incidence of subretinal fluid, hemorrhage, and extraocular extension. Compared with uveal melanoma classified as 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.

| Metastasis   | Rajpal | COMS                                    | Kath  | Rietschel                              | Jochems  | <mark>Mean</mark>  | Our Study   |
|--|--------|---|---|--|--|--------------------|---|
| Metastasis   | F/U    | F/U                                     | F/U   | F/U                                    | F/U  | F/U                | Presentation  |
| Sample Size  | 35     | 739                                     | 24  | 119                                    | 175  | <mark>218.4</mark> | 69  |
| Liver  | 71.4%  | 89.0%                                   | 87.0%   | 60.5%                                  | 88.0%  | <mark>79.2%</mark> | 91.3%   |
| Lungs  | 40.0%  | 29.0%                                   | 46.0%   | 24.4%                                  | 25.1%  | <mark>32.9%</mark> | 15.9%   |
| Lymph Nodes  | 14.3%  | 11.0%                                   | 4.2%  | 1.7%                                   | 16.0%  | <mark>9.4%</mark>  | 13.0%   |
| Bones  | 17.1%  | 17.0%                                   | 29.0%   | 8.4%                                   | 15.4%  | <mark>17.4%</mark> | 8.7%  |
| Brain  | 5.7%   | 6.1%                                    | 8.0%  | 4.2%                                   | 1.7%   | <mark>5.1%</mark>  | 5.8%  |
| Subcutaneous tissue  | 34.3%  | 12.0%                                   | 17.0%   | 10.9%                                  | 10.3%  | <mark>16.9%</mark> | 4.3%  |
| Others   | 34.3%  | 11.0%                                   | 51.570  | -                                      | 23.4% 26   |                    |   |
| Multiple Sites   | -      | 43.0%                                   | 54.2%   | 10.9%                                  | 5.7%   | <mark>28.4%</mark> | 31.9%   |
| Tests  | -      | LFTs, CXR,<br>and<br>autopsy<br>studies | LFTs, CXR, abdominal<br>USG, CT, MRI, and<br>autopsy<br>studies | Radiographic<br>imaging,<br>blood test | Lactose dehydrogenase<br>enzyme (LDH),<br>Radiographic imaging |                    | Abdominal USG, CT,<br>MRI, and whole-body-<br>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  |

Discussion – Literature on Metastasis of UM

#### Discussion - Screening

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

Aurélien Freton<sup>1,4,1</sup>, Kimberly J. Chin<sup>1</sup>, Robert Raut<sup>1</sup>, Lawrence B. Tena<sup>2</sup>, Tero Kivelä<sup>1</sup>, Paul T. Finger<sup>1,2,4,8</sup>

 Although hepatic metastases can be discovered in up to 90% of cases with

#### The challenge lies in detecting extrahepatic spread.

and physical examination. Abnormal findings prompted further biopsies, blood tests, imaging, or clinical evaluations for confirmation. The presence of metastatic disease and second cancers were evaluated.

Results. Using the American Joint Committee on Cancer (AJCC) tumor, node, metastasis (TNM) 7th edition criteria, 104 tumors were classified T1 (31%), 162 T2 (49%), 37 T3 (11%), and 30 T4 (9%). Seven of 333 (2.1%; 95% confidence interval [CI] 0.8-4.3) patients had metastatic melanoma. One tumor was a T3 and 6 were T4. Thus, 3% of T3 and 20% of T4 melanomas were found to have metastases at the time of initial diagnosis. Ten patients (3.3%; 95% CI 0.9-5.5) had synchronous second cancers and 28 (8.4%) concurrent benign lesions. The most common metastatic sites were liver (7/7) and bone (2/7). Discussion. This study suggests that PETICT improves the yield of detecting both extrahepatic metastases, especially from tumors defined as AJCC-T4, and synchronous primary cancers, irrespective of the size of the uveal melanoma. With respect to liver metastases, PETICT demonstrated high sensitivity and positive predictive values, indicating an overall better performance than conventional spreanips, propedurps.

abdominal CT or MRI.

# 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



# 53rd Annual Scientific Meeting Retina Society 2020 VR

# The AJCC-OOTF Thanks You!