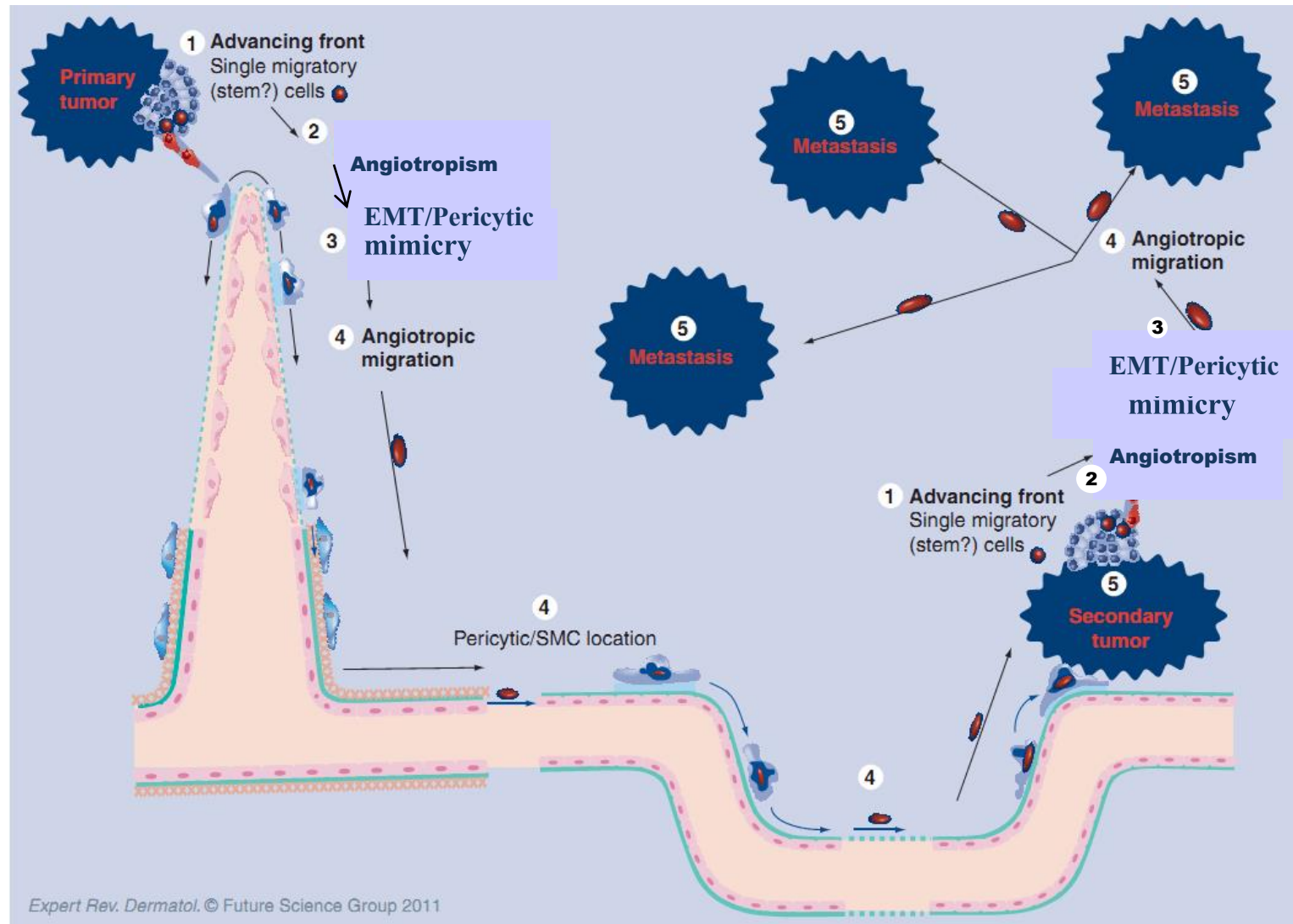


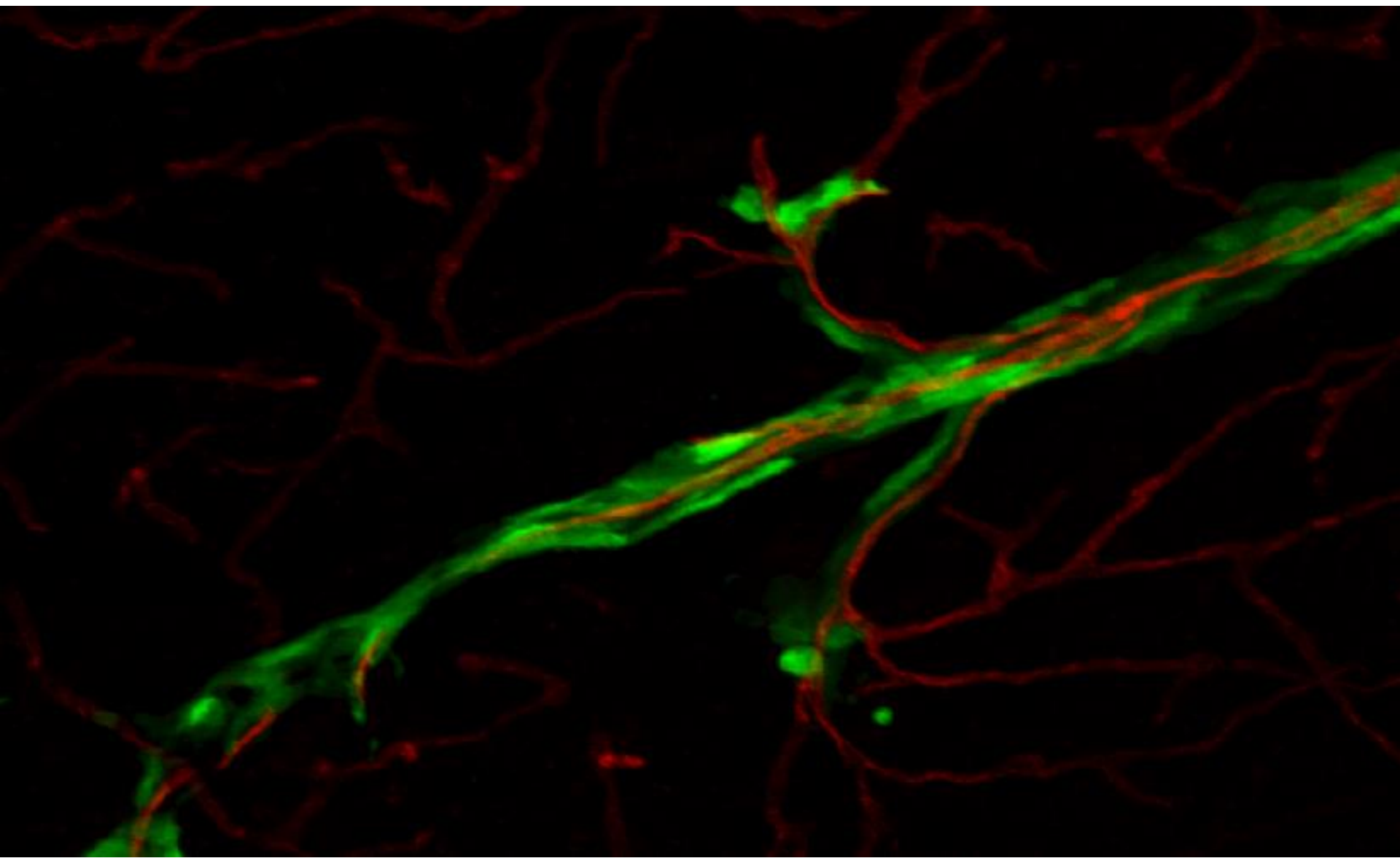
Uveal Melanoma: Pathological Aspects

Raymond Barnhill
Institut Curie
Paris, France

Melanoma Ex Blue Nevus	Uveal Melanoma
Mesenchymal melanocytes	Mesenchymal melanocytes
Blue nevus	Uveal Melanocytosis
Cellular Blue Nevus (CBN) (Melanocytoma)	Cellular Uveal Nevus Melanocytoma
Atypical CBN	Atypical UN
Melanoma ex Blue Nevus	Uveal Melanoma
Angiotropism	Angiotropism
GNAQ, GNA11, CYSLTR2, BAP1, EIF1AX, SF3B1 Monosomy 3, gain 8q	GNAQ, GNA11, CYSLTR2, BAP1, EIF1AX, SF3B1 Monosomy 3, gain 8q

Extravascular Migratory Metastasis (EVMM) Angiotropic Tumor Cells





Blue Nevus-like Melanoma

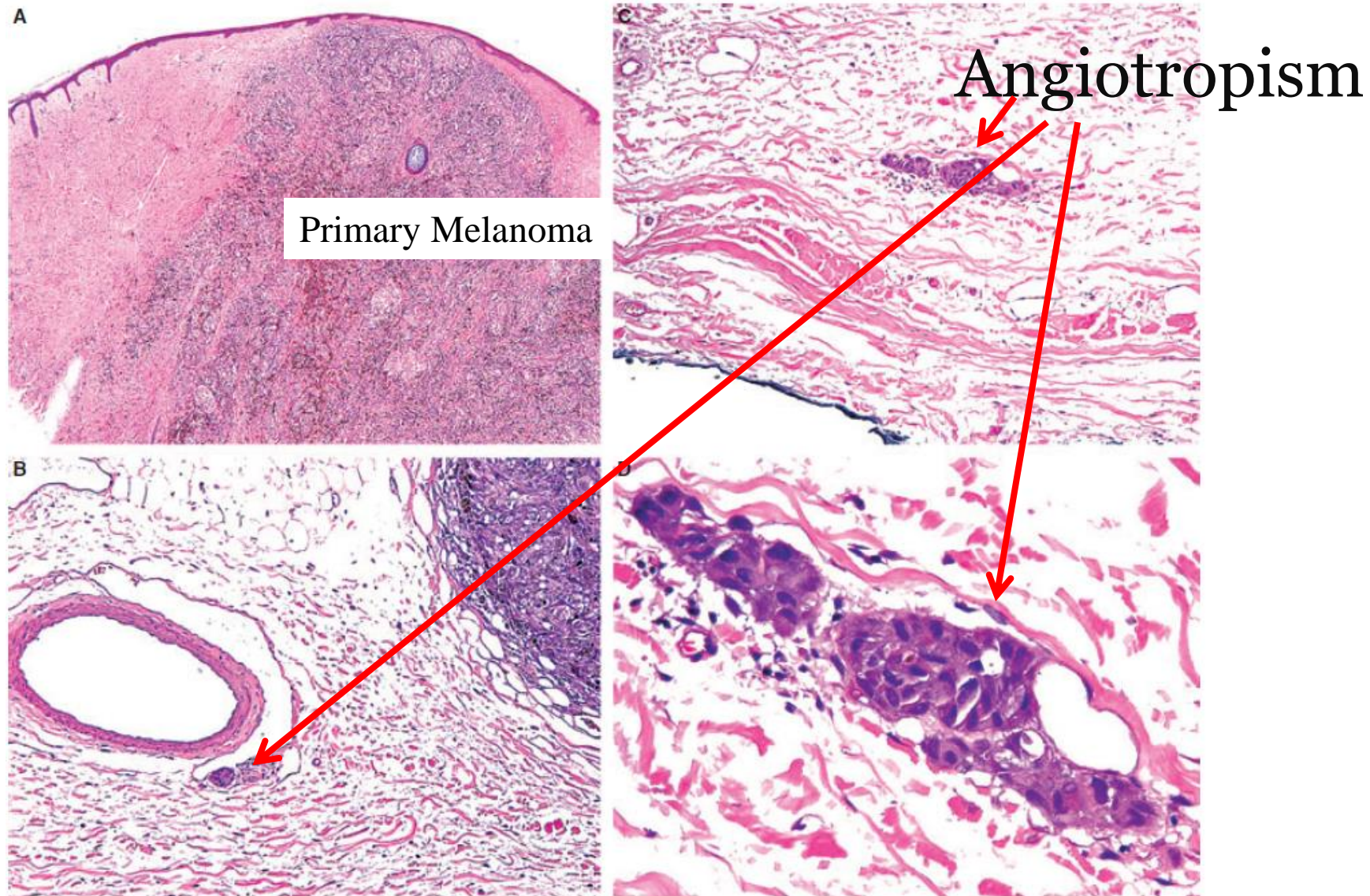
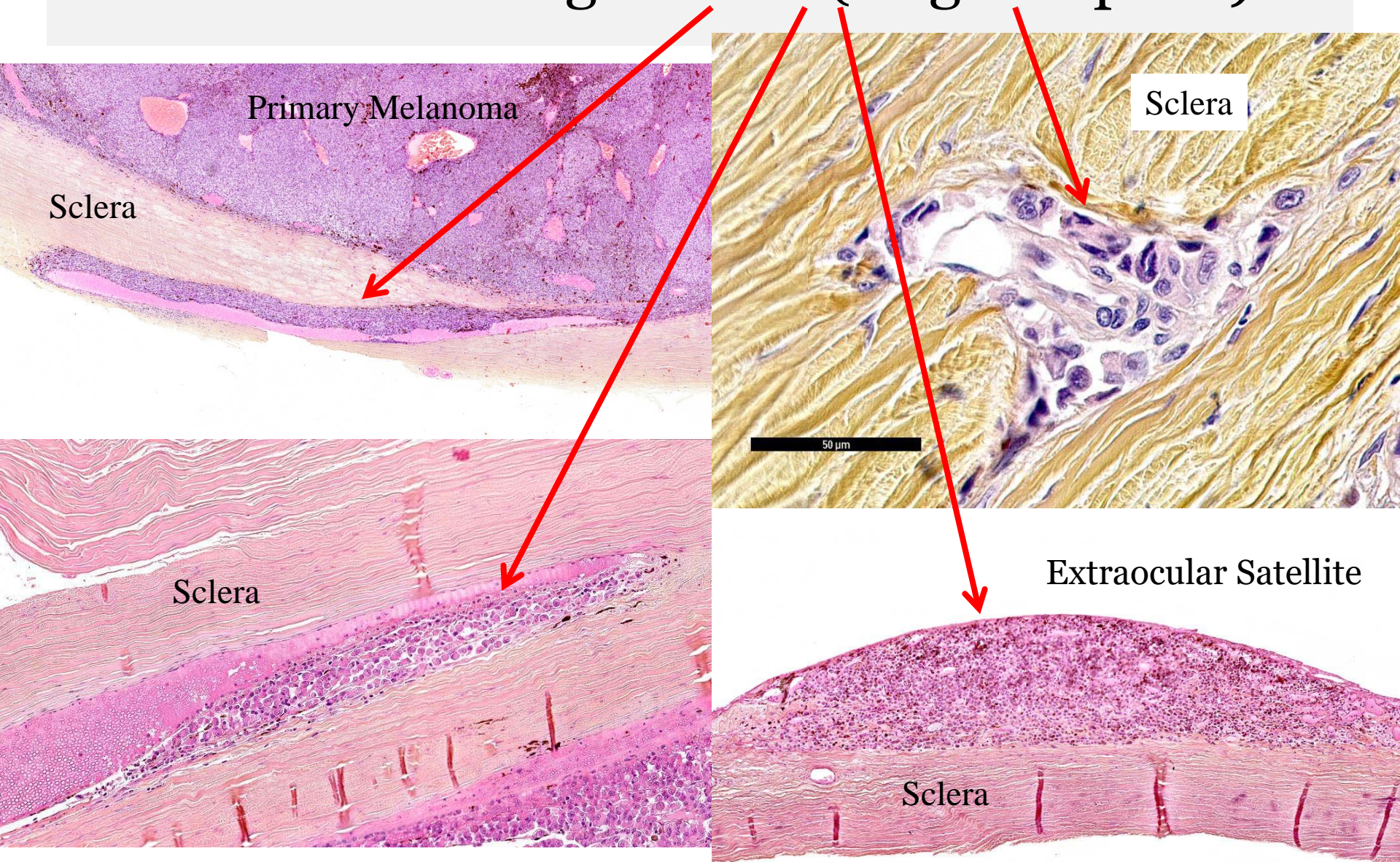
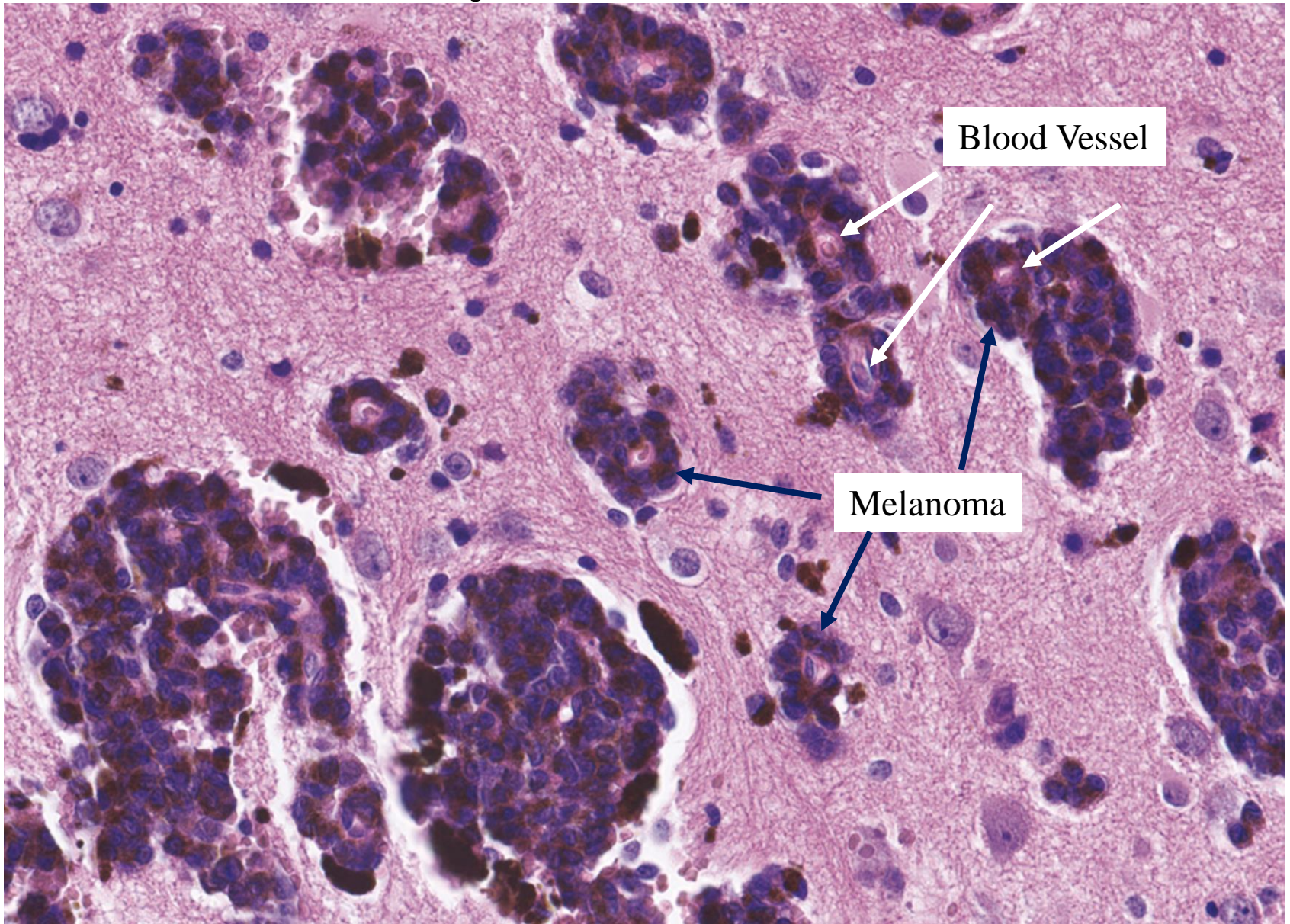


Figure 1. Invasive melanoma with microscopic satellites (MS). A, Primary invasive melanoma at scanning magnification. B, MS some distance from the primary melanoma. The MS exhibits angiotropism. C, Another MS in the nearby dermis demonstrating angiotropism. D, At high magnification of (C), melanoma cells comprising the MS are aligned along the external surface of the microvascular channel.

Uveal Melanoma: Intra-Scleral/Extraocular Extension Along Vessels (Angiotropism)



Angiotropism in Primary CNS Melanoma



EXTRASCLERAL EXTENSION AND ORBITAL RECURRENCE OF MALIGNANT MELANOMAS OF THE CHOROID AND CILIARY BODY

Henry J. Starr and Lorenz E. Zimmerman

Int Ophthalmol Clin 1962

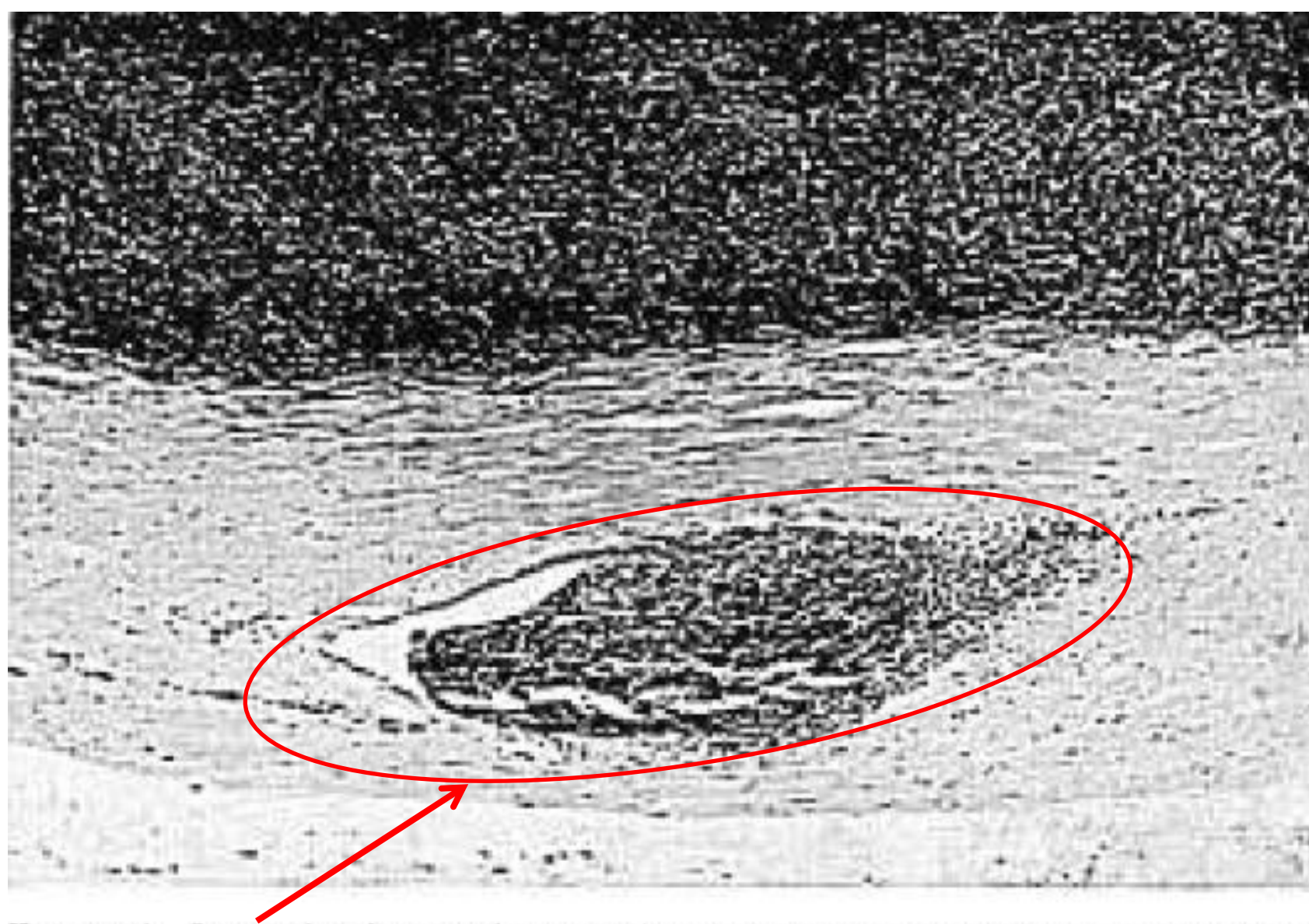


FIGURE 4. Intrascleral extension of spindle B melanoma cells; no extraocular extension observed. Melanoma recurred in socket ten months after enucleation, treated with x-ray, then excised two years and five months after enucleation. Patient died fifteen months later. $\times 50$. AFIP Neg. 61-6369.

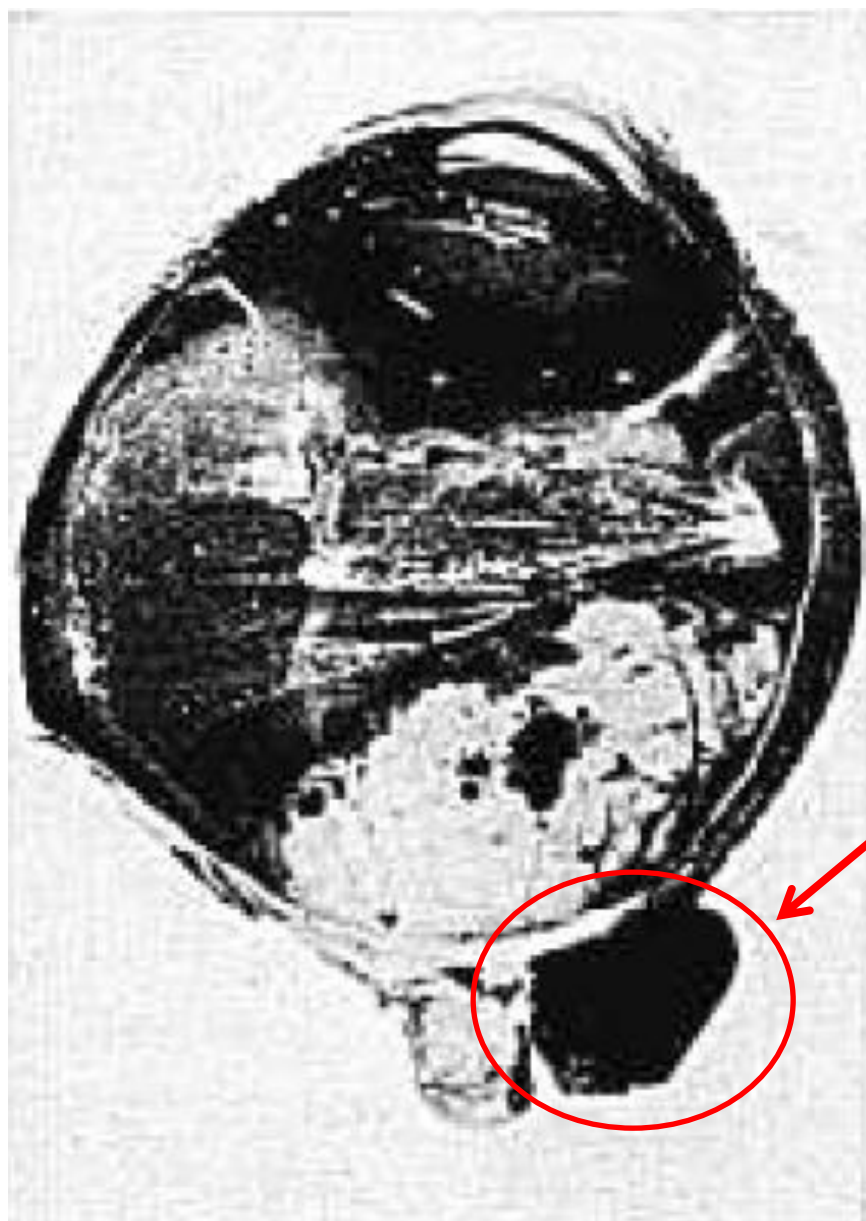


FIGURE 1. Malignant melanoma of choroid, mixed cell type, with extraocular extension. The epibulbar nodule adjacent to the optic nerve measured 6.5 mm. in diameter and was not encapsulated. Exenteration was not performed; the patient died with generalized metastasis one year and eight months after enucleation. AFIP Neg. 506871-01251.

The biological and prognostic significance of angiotropism in uveal melanoma

Raymond L Barnhill^{1,2}, Mengliang Ye³, Aude Batistella⁴, Marc-Henri Stern⁴, Sergio Roman-Roman³, Rémi Dendale⁵, Olivier Lantz⁶, Sophie Piperno-Neumann⁷, Laurence Desjardins⁸, Nathalie Cassoux^{2,8} and Claire Lugassy³

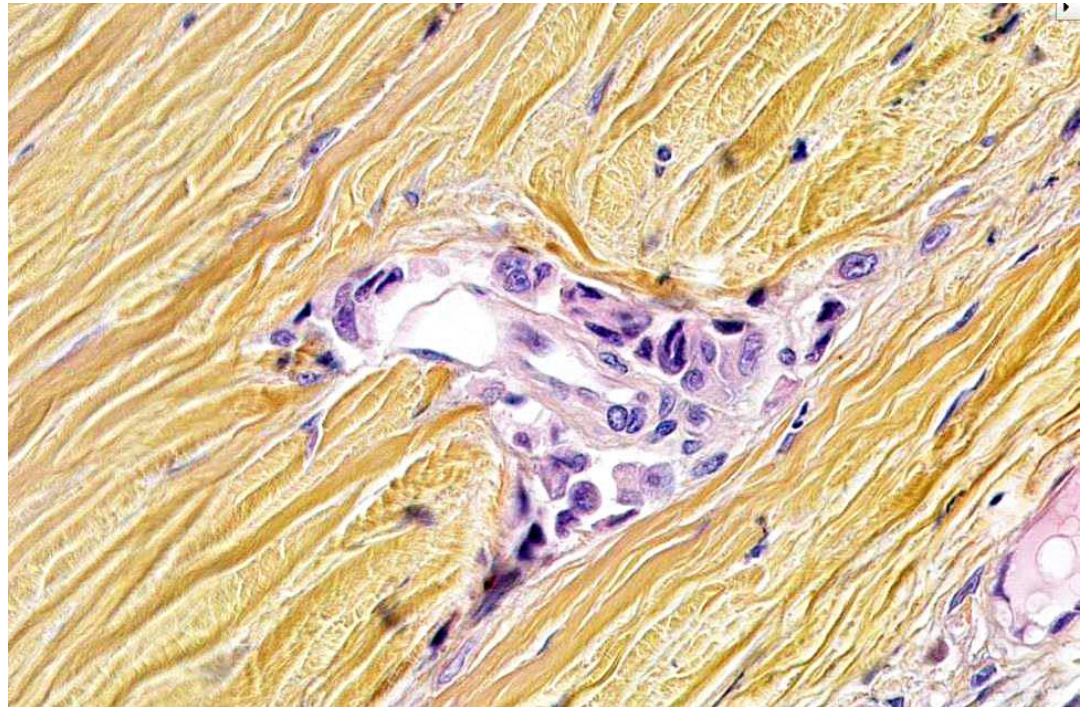
Angiotropism is a marker of extravascular migration of melanoma cells along vascular and other structures and a prognostic factor in cutaneous melanoma. Because of this biological and prognostic importance in cutaneous melanoma, angiotropism was studied in uveal melanoma (UM). This retrospective study performed at a single ocular oncology referral

Methods

- 89 primary uveal melanomas enucleated from 2006 – 2008
- Clinical, histological, and molecular data recorded
- HES stained slides examined for angiotropism
- Number of glass slides recorded per case

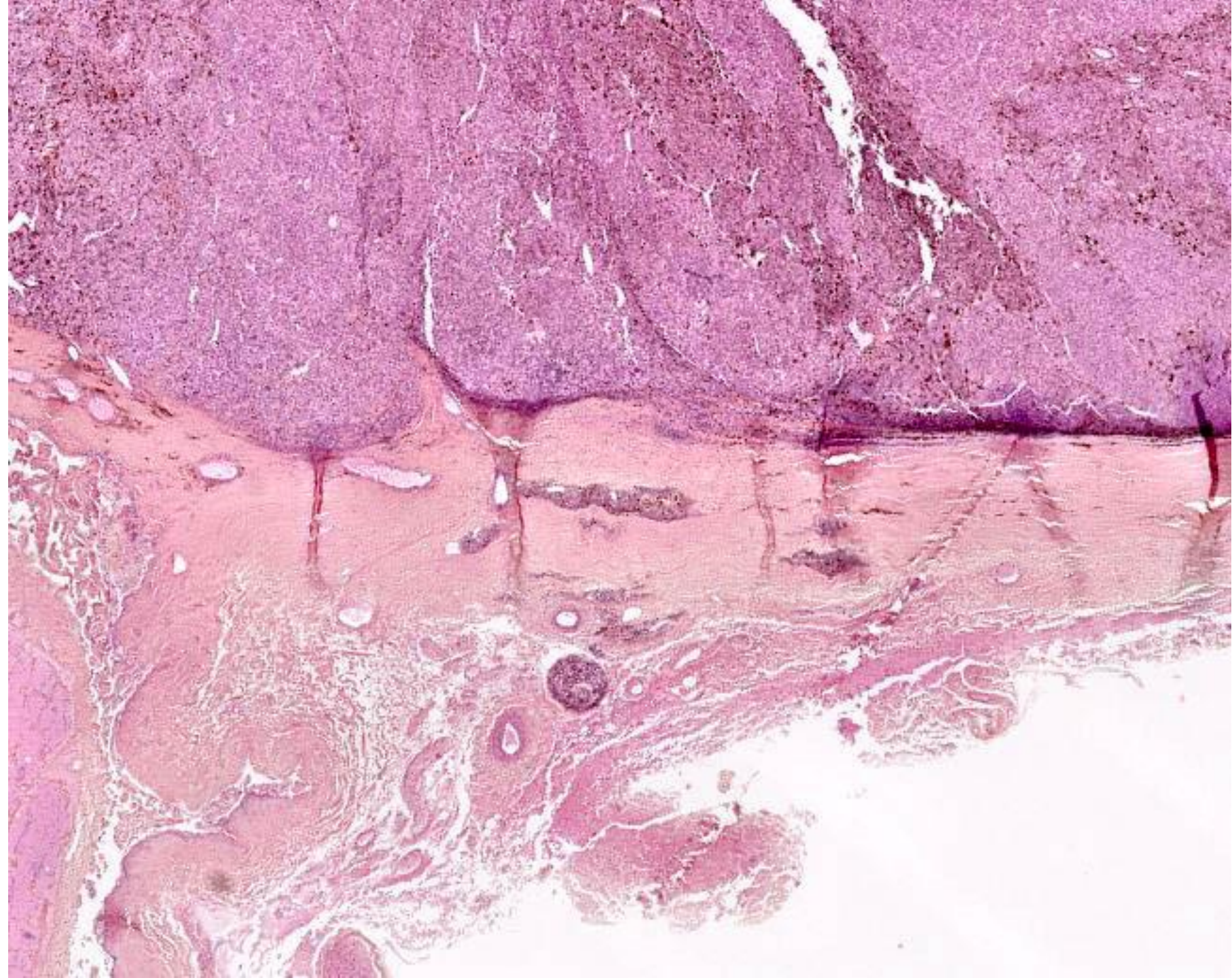
Angiotropism: Definition

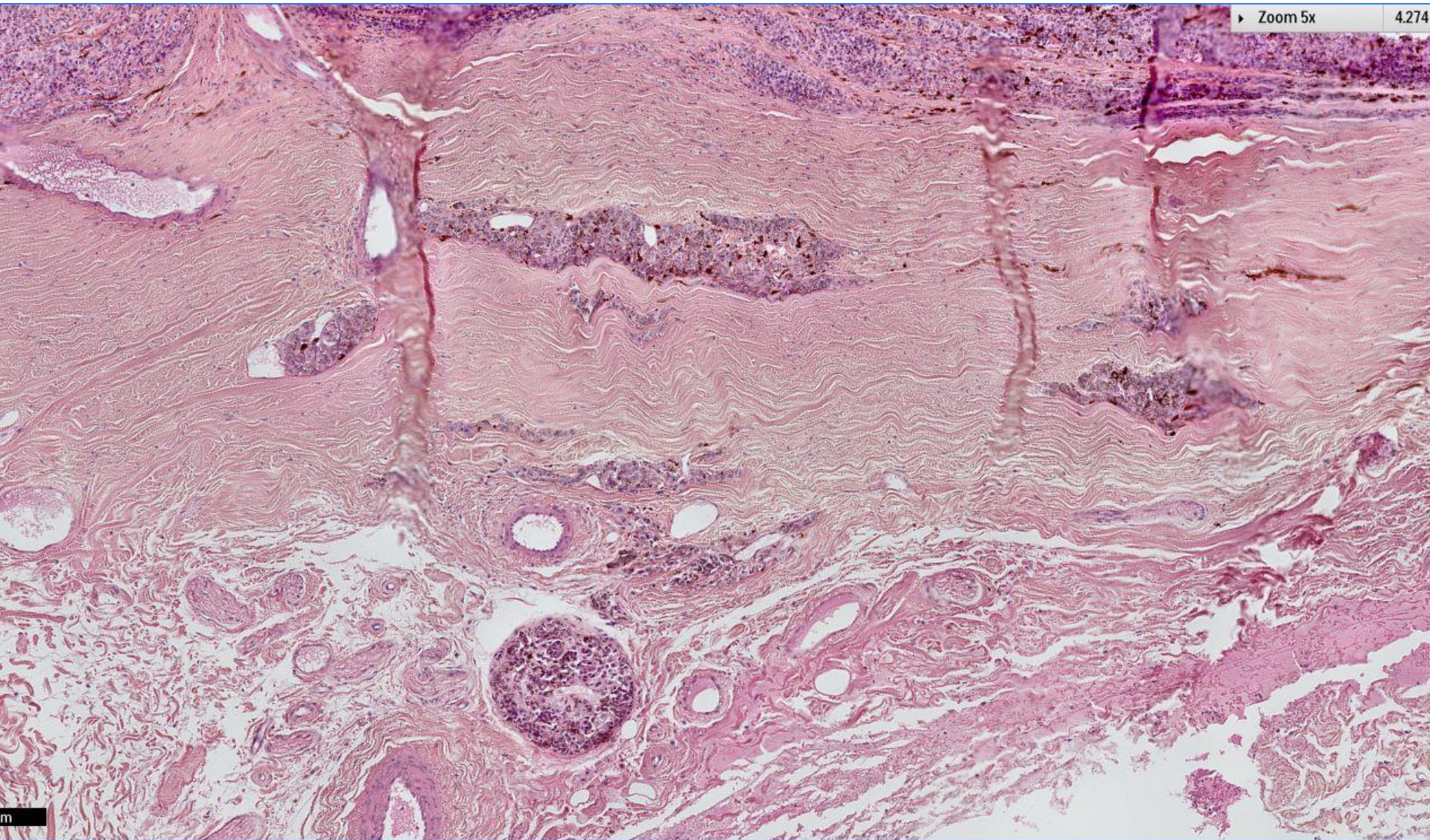
- Melanoma cells on the abluminal surfaces of microvascular channels
- Sclera or episcleral tissue
- One of more foci beyond the principal melanoma uveal mass
- Absence of intravascular invasion

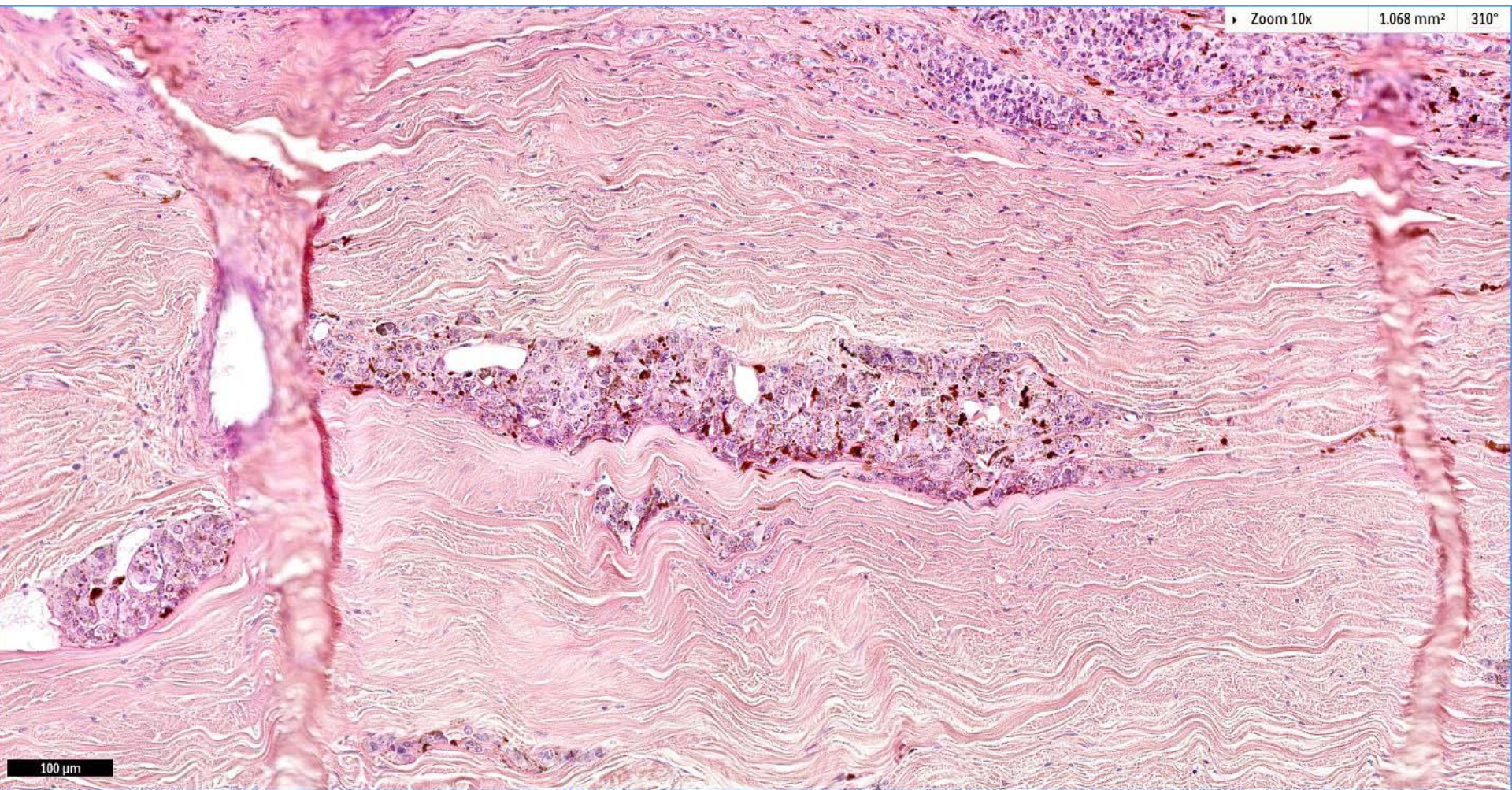


Vascular Channels

- Ciliary arteries, anterior and posterior
- Vortex veins
- Canals of Schlemm







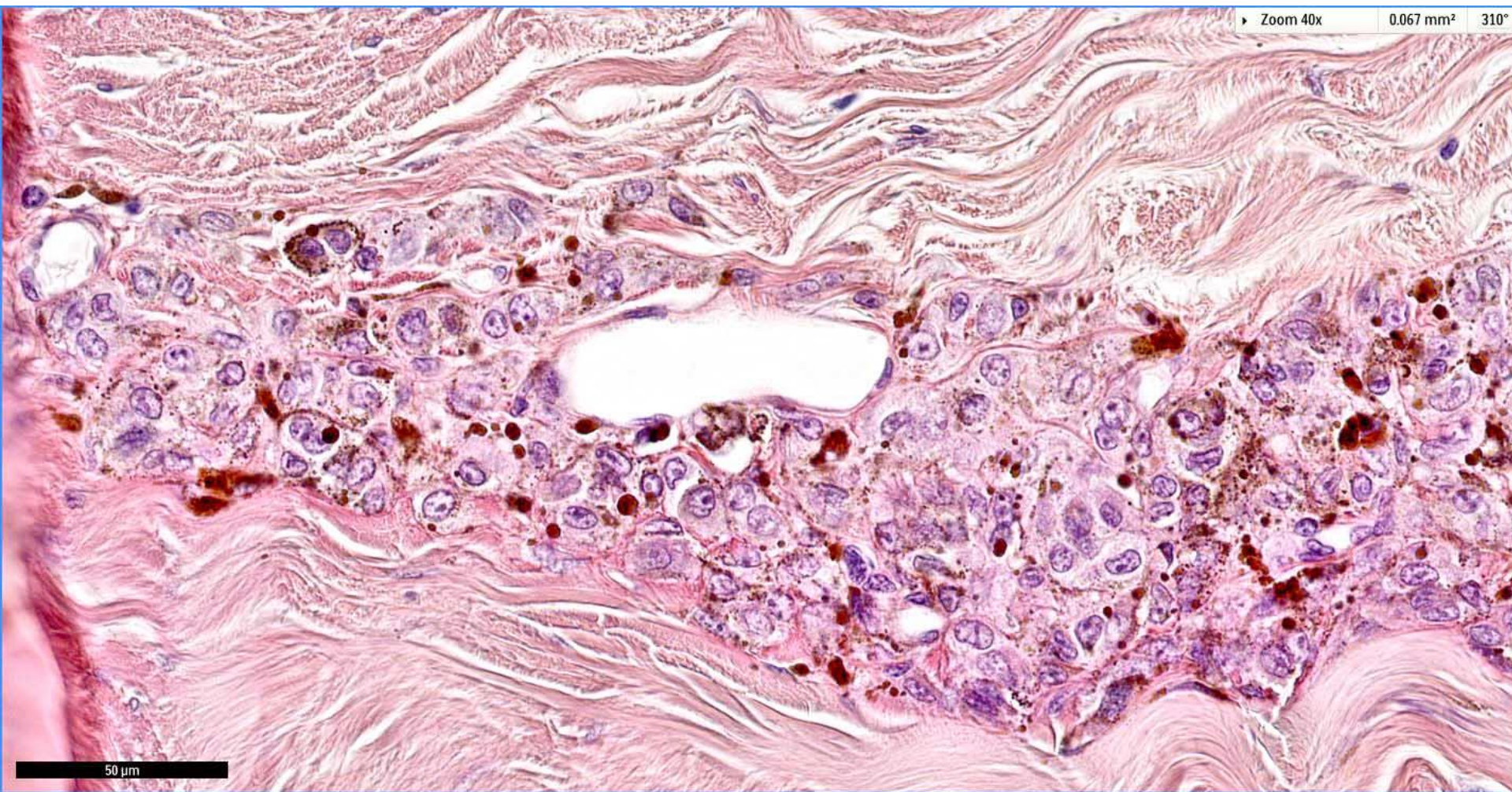
Zoom 10x 1.068 mm² 310°

100 μm

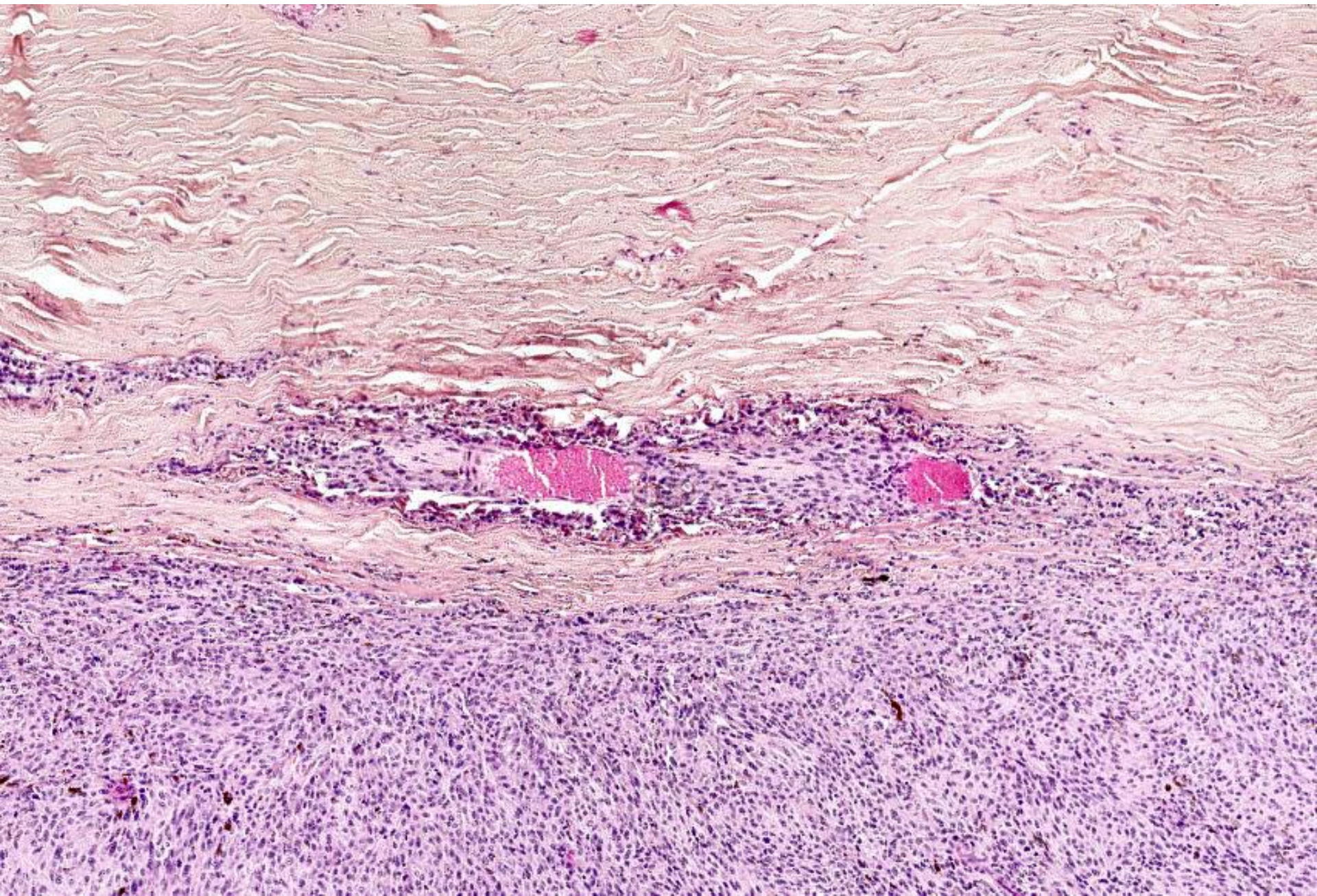
► Zoom 40x

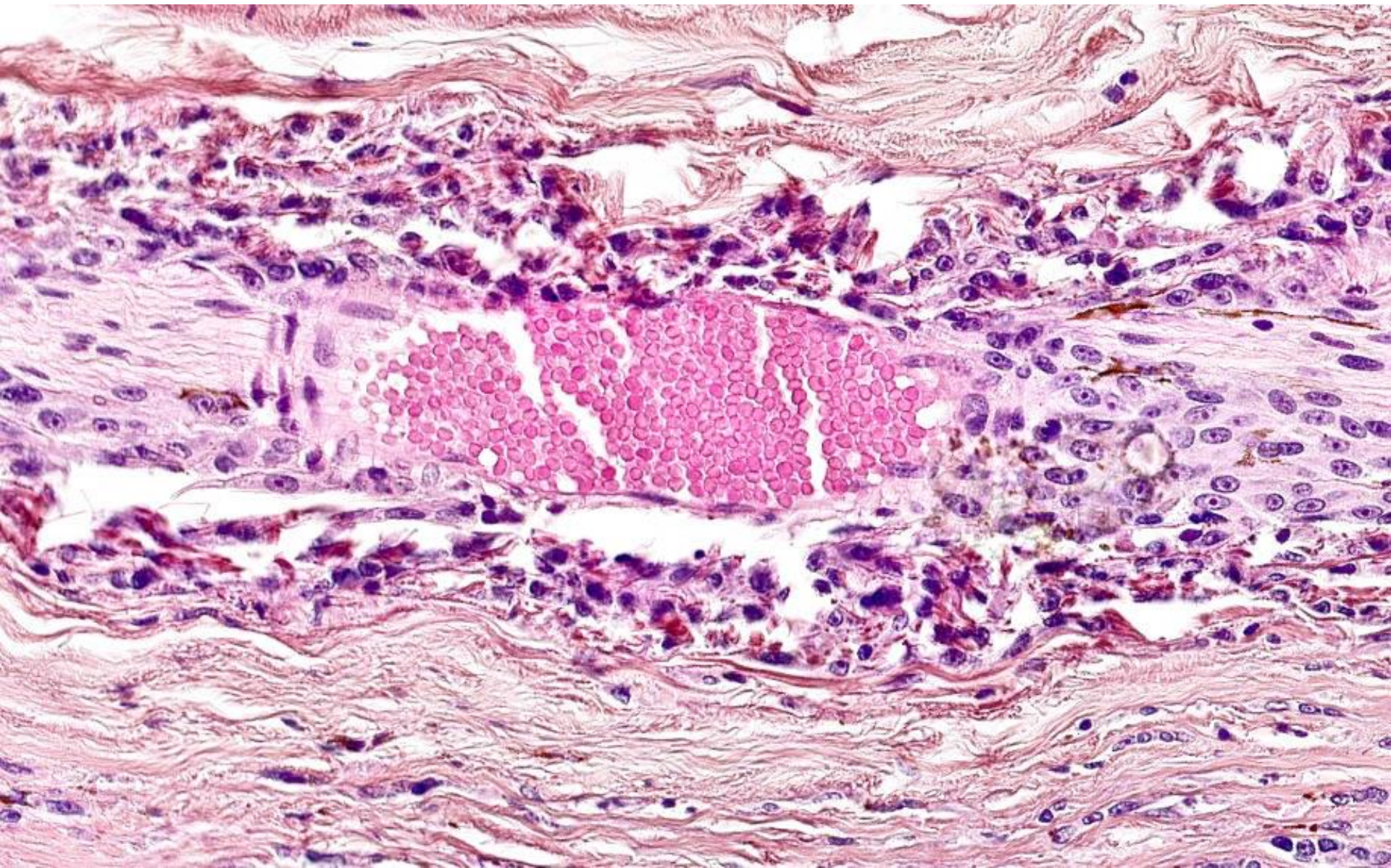
0.067 mm²

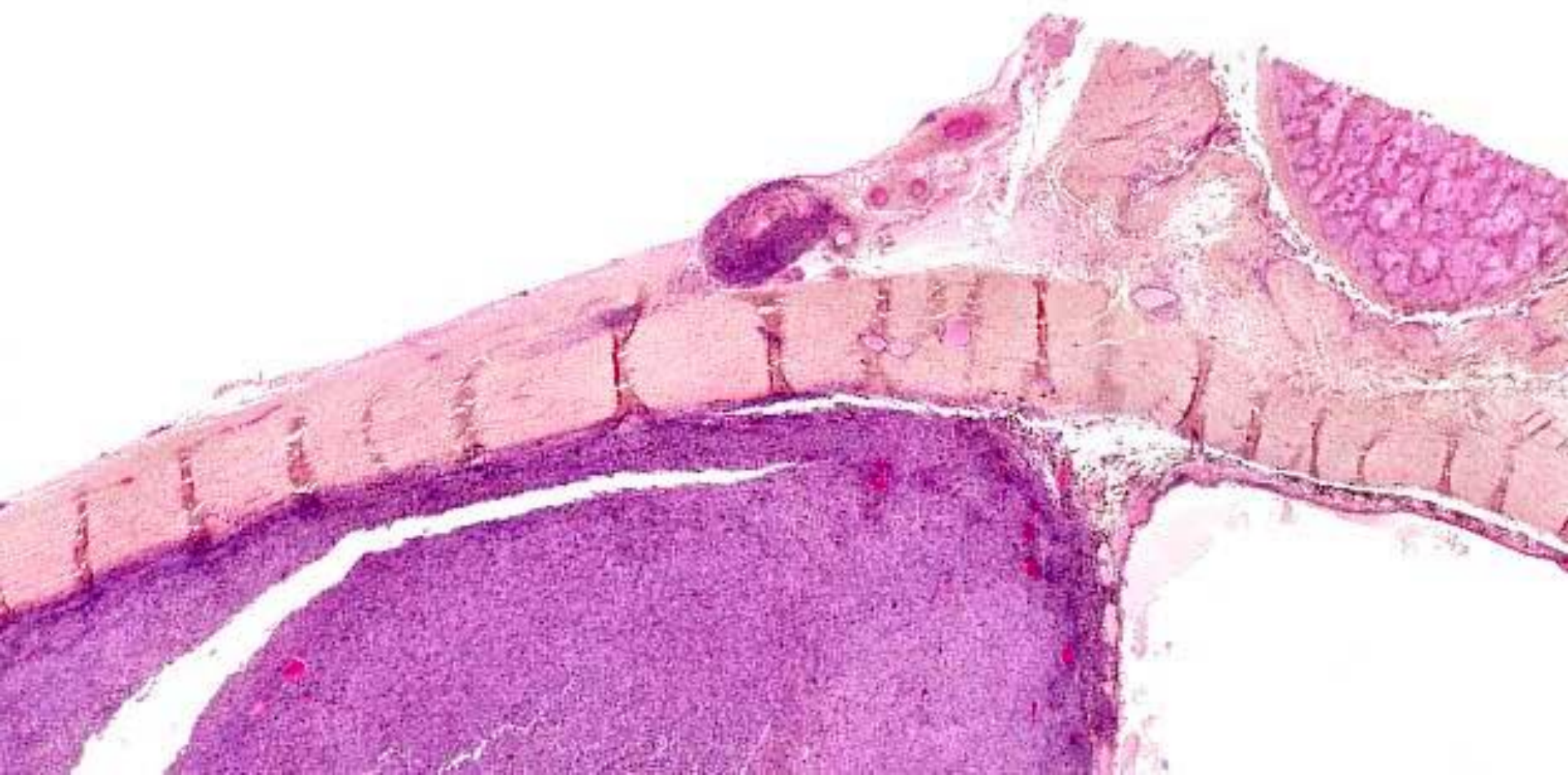
310°

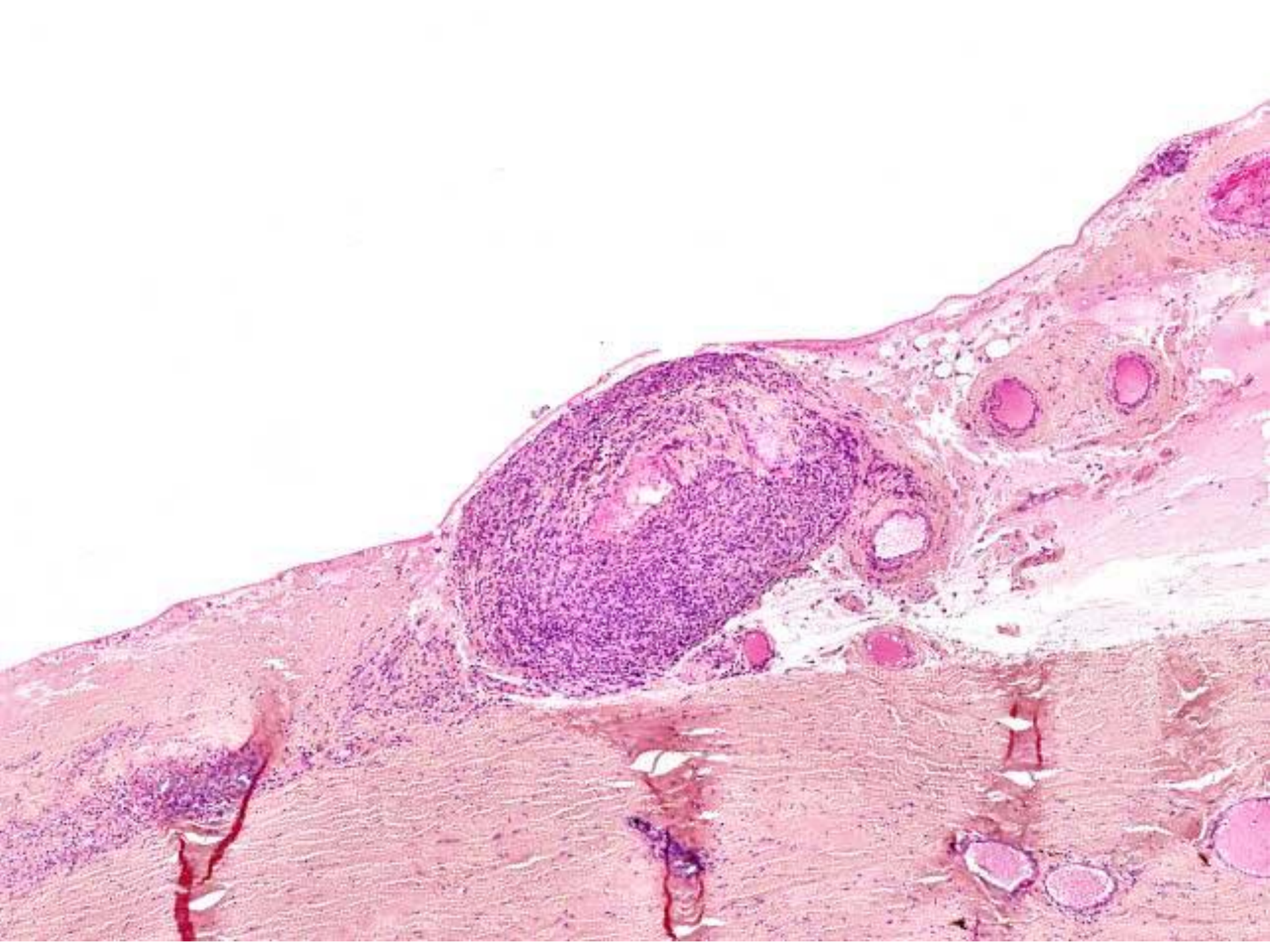


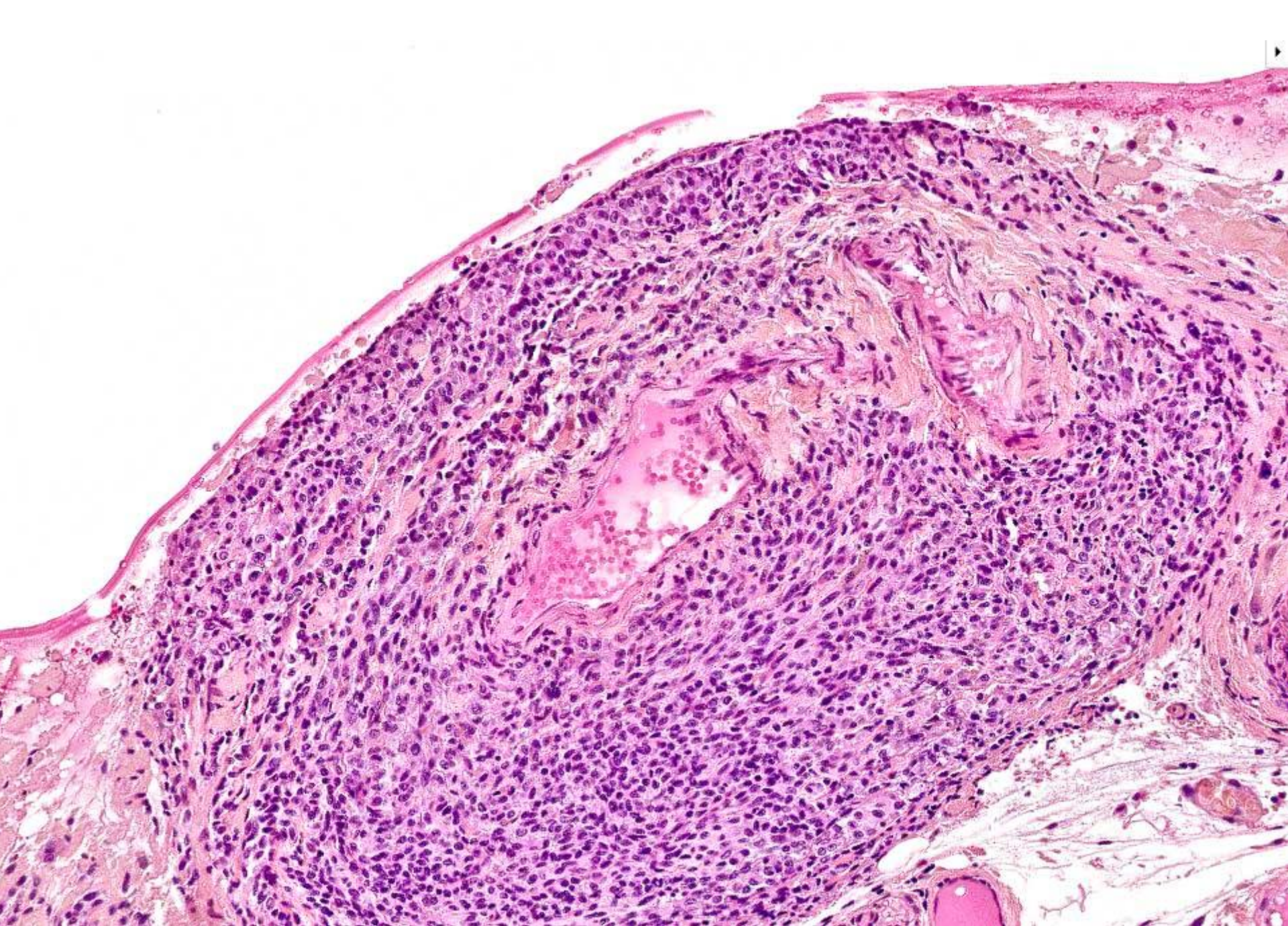
50 µm











Results

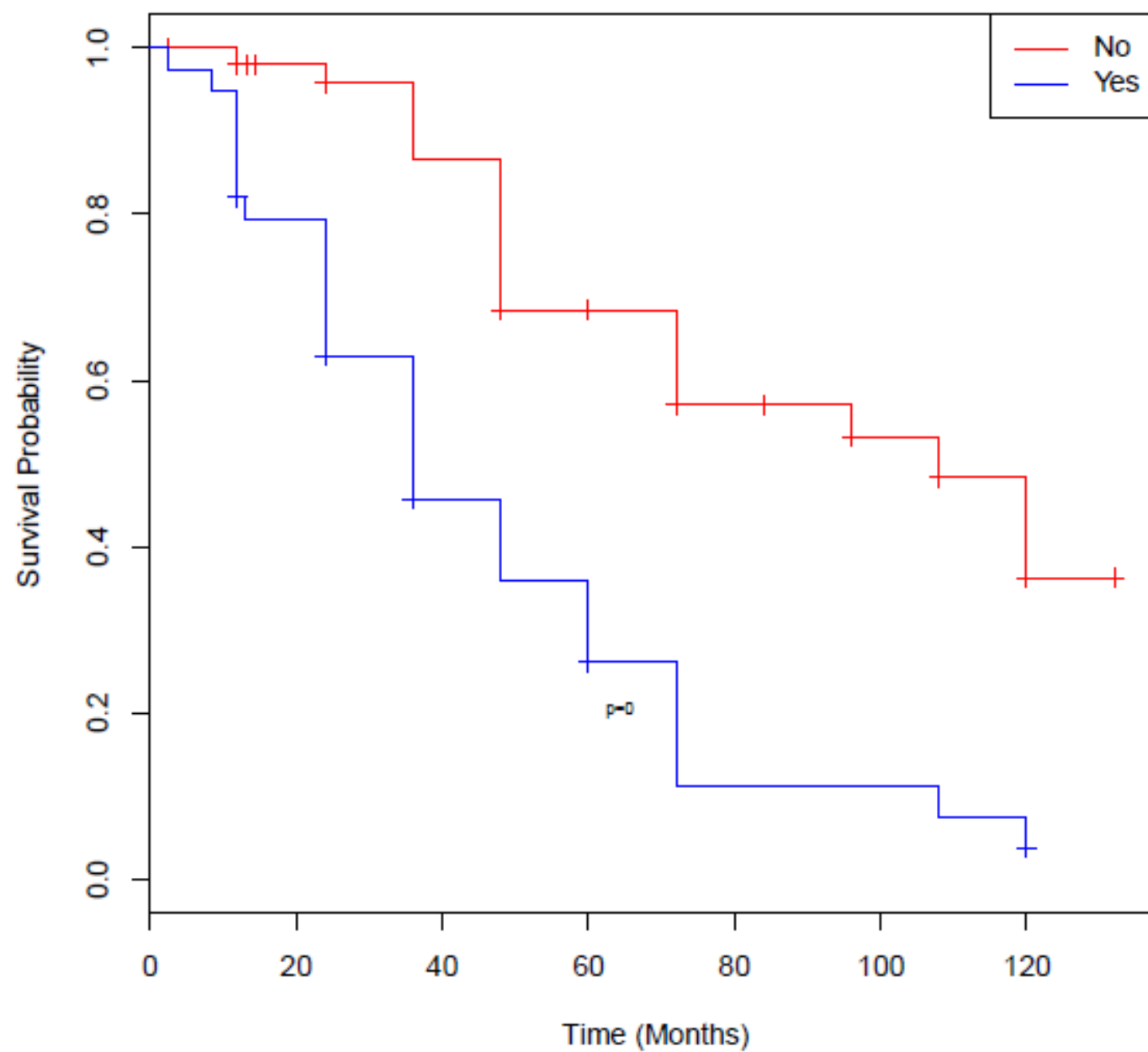
- Frequency of angiotropism:
 - 39/89 cases — 43.8%
- Frequency of neurotropism:
 - 16/89 — 18%

Results

Chi-square Statistic

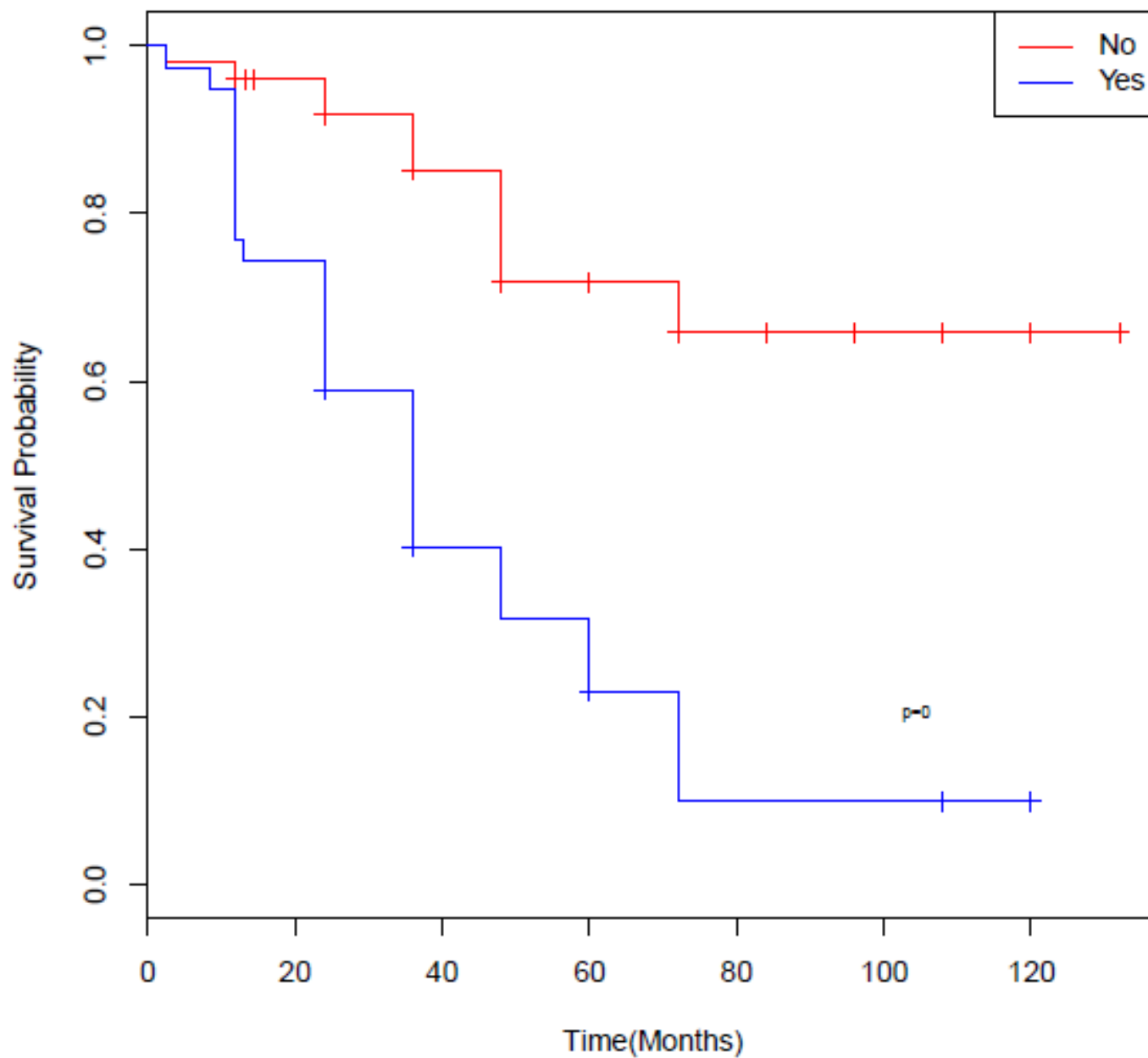
- Association with Angiotropism:
 - Metastatic disease - $p=0.000186^*$
 - Death $p<0.00001^*$
 - BAP1 mutation $p=0.077017$ NS
 - Loss of 3p $p=0.087157$ NS
 - Gain of 8q $p=0.218809$ NS

Metastasis-free Survival
Angiotropism with log-rank test



Overall Survival

Angiotropism with log-rank test






Uveal Melanoma Metastasis Liver



Replacement and desmoplastic histopathological growth patterns: A pilot study of prediction of outcome in patients with uveal melanoma liver metastases

Raymond Barnhill^{1,2*} , Peter Vermeulen^{3,4}, Sofie Daelemans^{3,4}, Pieter-Jan van Dam^{3,4}, Sergio Roman-Roman⁵, Vincent Servois⁶, Ilse Hurbain^{7,8,9}, Sophie Gardrat¹, Graça Raposa^{7,8,9}, André Nicolas¹, Rémi Dendale¹⁰, Gaëlle Pierron¹¹, Laurence Desjardins¹², Nathalie Cassoux^{2,12}, Sophie Pipemo-Neumann^{13†}, Pascale Mariani^{14†} and Claire Lugassy⁵

¹Department of Pathology, Institut Curie, Paris, France

²University of Paris René Descartes Faculty of Medicine, Paris, France

³HistoGeneX, Antwerpen, Belgium

⁴Faculty of Medicine and Health Sciences, University of Antwerp – MIPRO Center for Oncological Research (CORE) - TCRU, GZA Sint-Augustinus, Antwerpen, Belgium

⁵Department of Translational Research, Institut Curie, Paris, France

⁶Department of Radiology, Institut Curie, Paris, France

⁷Institut Curie, PSL Research University, CNRS, Paris, France

⁸Sorbonne Universités, UPMC Univ Paris 06, CNRS, Paris, France

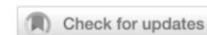
⁹Cell and Tissue Imaging Core Facility PICT-IBISA, Institut Curie, Paris, France

¹⁰Department of Radiotherapy, Institut Curie Orsay, Paris, France

Methods

- 41 excisional specimens with metastatic uveal melanoma from living patients
- Evaluation for Histopathologic Growth Patterns (HGP) analogous to results obtained from other solid tumors:
 - Colorectal carcinoma
 - Breast carcinoma

REVIEW ARTICLE



Cellular and Molecular Biology

Histopathological growth patterns of liver metastasis: updated consensus guidelines for pattern scoring, perspectives and recent mechanistic insights

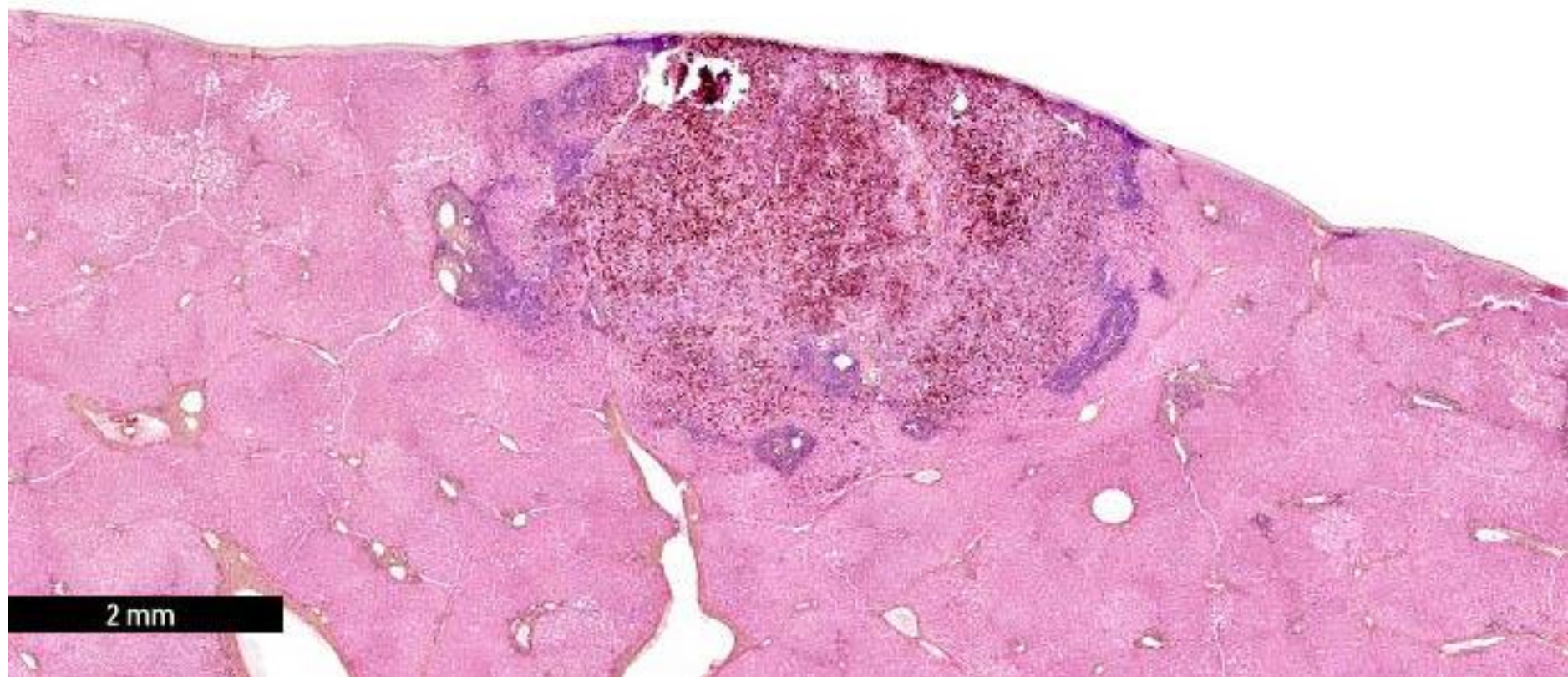
Emily Latacz^{1,37}, Diederik Höppener^{2,37}, Ali Bohlok^{3,37}, Sophia Leduc⁴, Sébastien Tabariès⁵, Carlos Fernández Moro^{6,7}, Claire Lugassy⁸, Hanna Nyström^{9,10}, Béla Bozóky⁷, Giuseppe Floris^{11,12}, Natalie Geyer¹³, Pnina Brodt¹⁴, Laura Llado¹⁵, Laura Van Mileghem¹, Maxim De Schepper⁴, Ali W. Majeed¹⁶, Anthoula Lazaris¹⁷, Piet Dirix¹, Qianni Zhang¹⁸, Stéphanie K. Petrillo¹⁷, Sophie Vankerckhove³, Ines Joye¹, Yannick Meyer², Alexander Gregorieff^{17,19,20}, Nuria Ruiz Roig^{21,22,23}, Fernando Vidal-Vanaclocha²⁴, Larsimont Denis²⁵, Rui Caetano Oliveira^{26,27,28}, Peter Metrakos¹⁷, Dirk J. Grünhagen², Iris D. Nagtegaal²⁹, David G. Mollevi^{22,30}, William R. Jarnagin³¹, Michael I D'Angelica³¹, Andrew R. Reynolds³², Michail Doukas³³, Christine Desmedt⁴, Luc Dirix¹, Vincent Donckier^{3,37}, Peter M. Siegel^{5,34,37}, Raymond Barnhill^{8,35,37}, Marco Gerling^{13,36,37}, Cornelis Verhoef^{2,37} and Peter B. Vermeulen^{1,37}✉

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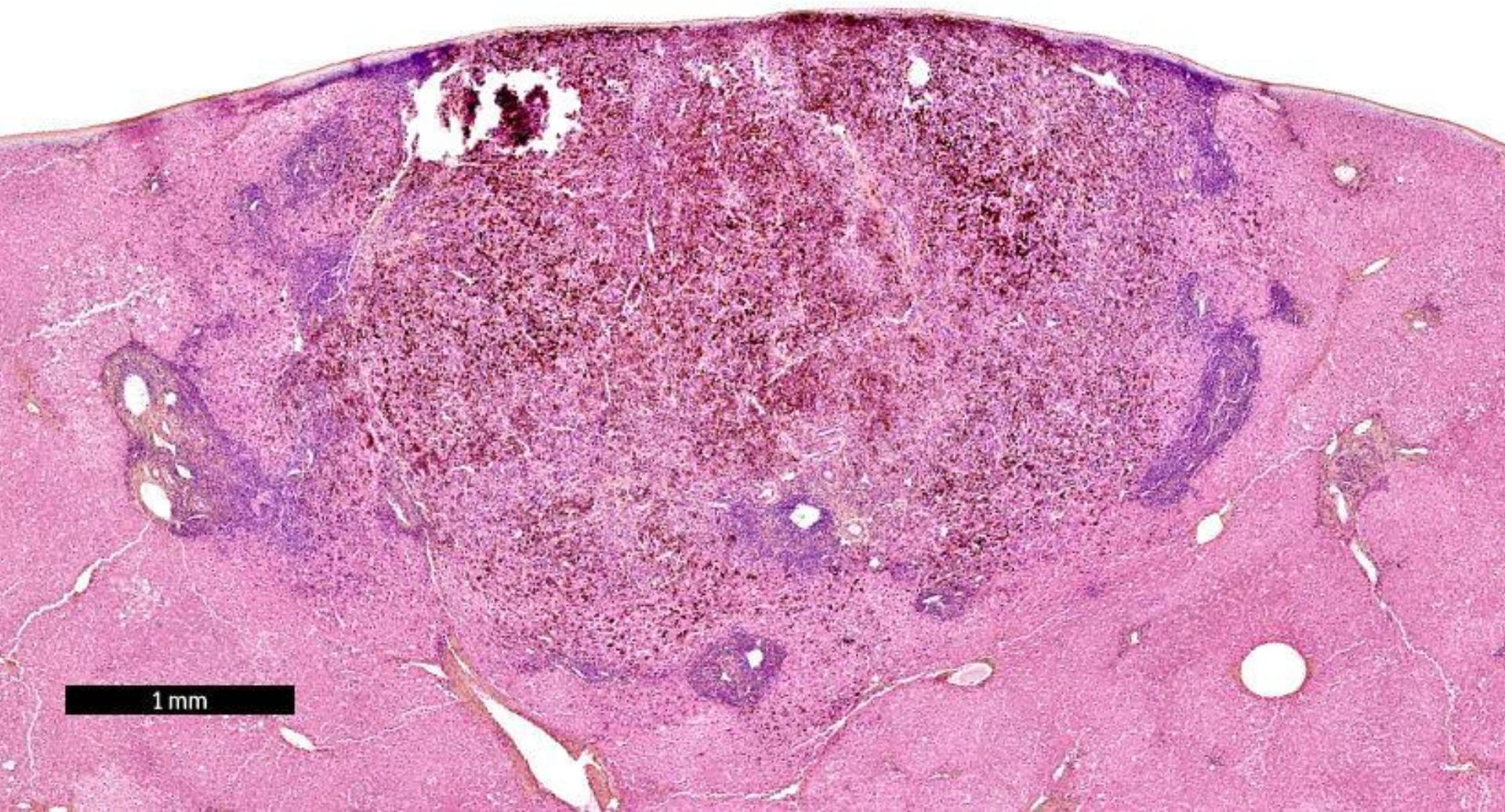
The first consensus guidelines for scoring the histopathological growth patterns (HGP) of liver metastases were established in 2017. Since then, numerous studies have applied these guidelines, have further substantiated the potential clinical value of the HGP in patients with liver metastases from various tumour types and are starting to shed light on the biology of the distinct HGP. In the present guidelines, we give an overview of these studies, discuss novel strategies for predicting the HGP of liver metastases, such as deep-learning algorithms for whole-slide histopathology images and medical imaging, and highlight liver metastasis animal models that exhibit features of the different HGP. Based on a pooled analysis of large cohorts of patients with liver-metastatic colorectal cancer, we propose a new cut-off to categorise patients according to the HGP. An up-to-date standard method for HGP assessment within liver metastases is also presented with the aim of incorporating HGP into the decision-making processes surrounding the treatment of patients with liver-metastatic cancer. Finally, we propose hypotheses on the cellular and molecular mechanisms that drive the biology of the different HGP, opening some exciting preclinical and clinical research perspectives.

Histopathologic Growth Pattern	Metastasis-Liver Interface	Liver Architecture	Tumor vascular reaction
Replacement	Infiltration and replacement of hepatic plates. No desmoplasia	Preservation	Vascular co-option/ Angiotropism
Desmoplastic	Separation of metastasis from liver parenchyma by rim of desmoplasia	Obliteration	Angiogenesis
Pushing	Hepatic plates compressed, pushed away without invasion by cancer cells No desmoplasia	Obliteration	Angiogenesis

Replacement

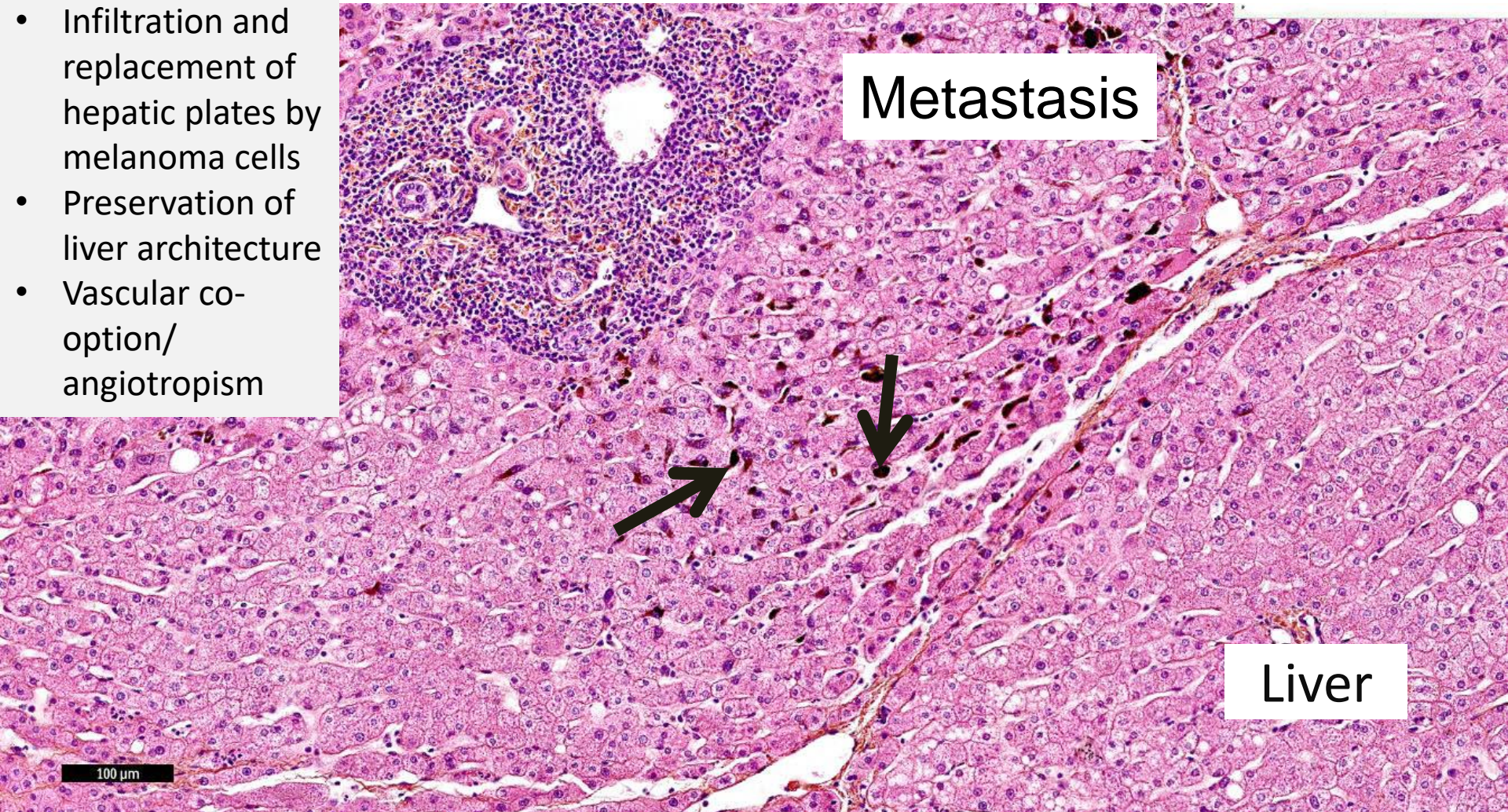


Replacement

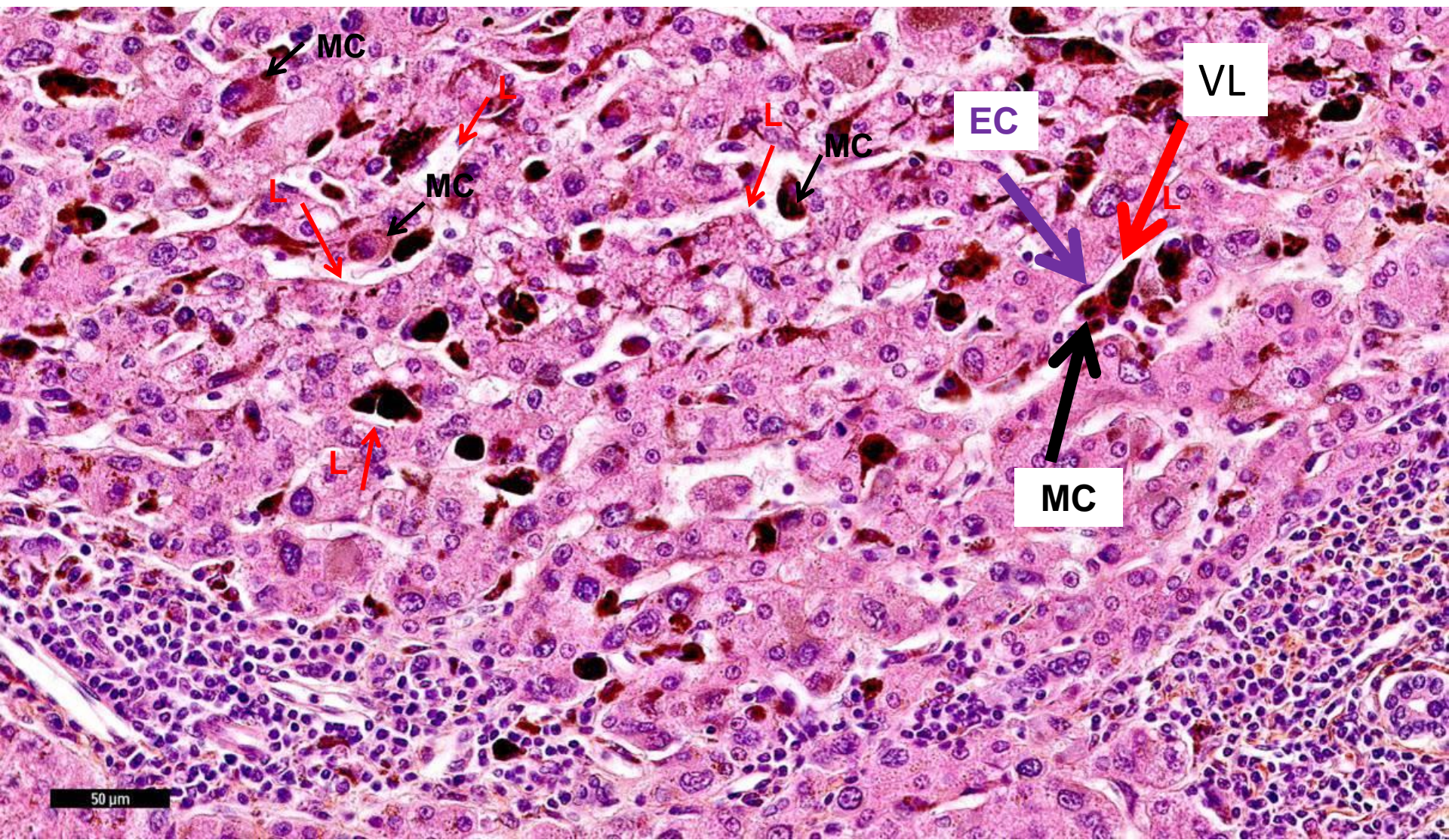


Replacement Pattern

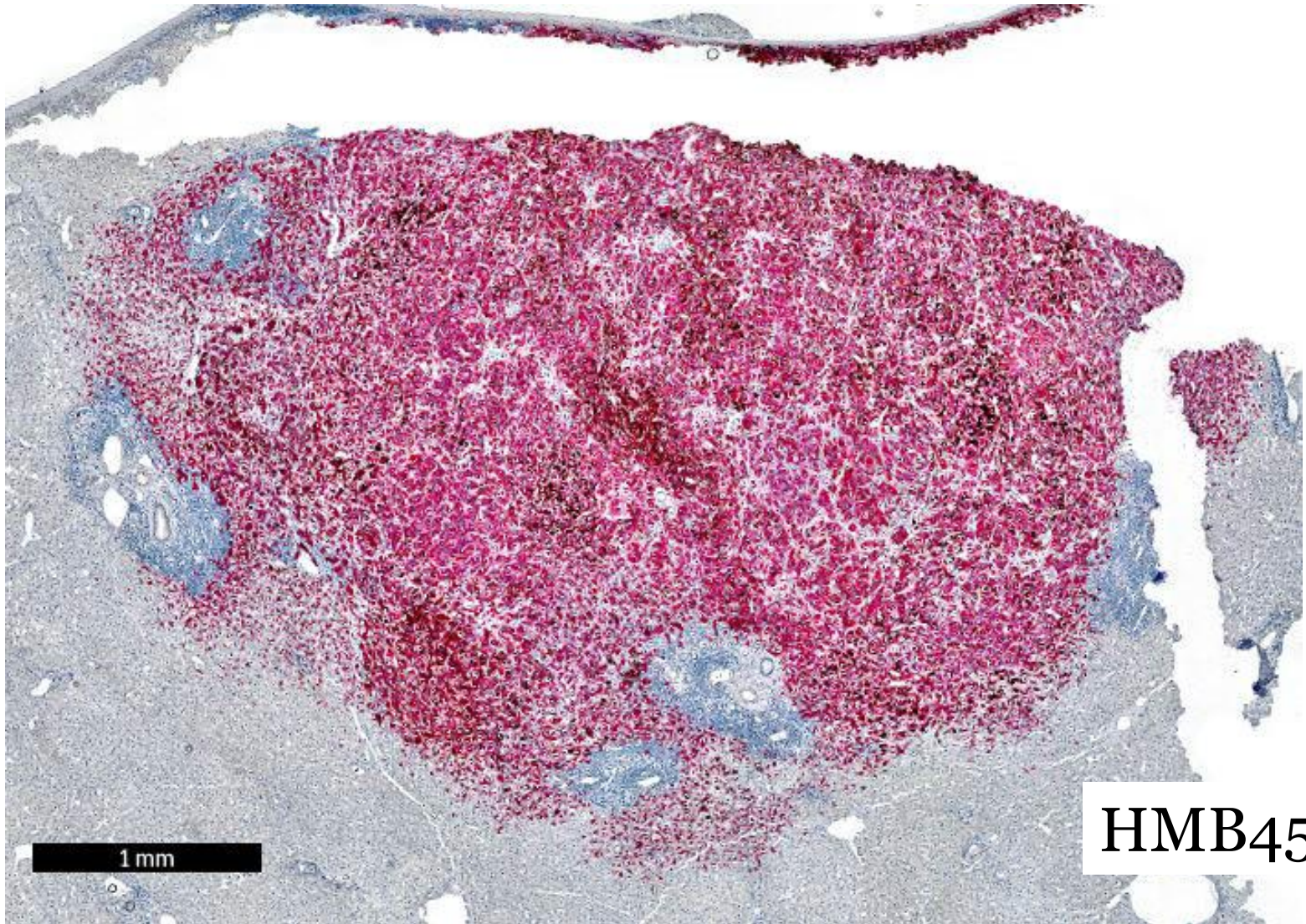
- Infiltration and replacement of hepatic plates by melanoma cells
- Preservation of liver architecture
- Vascular co-option/ angiotropism



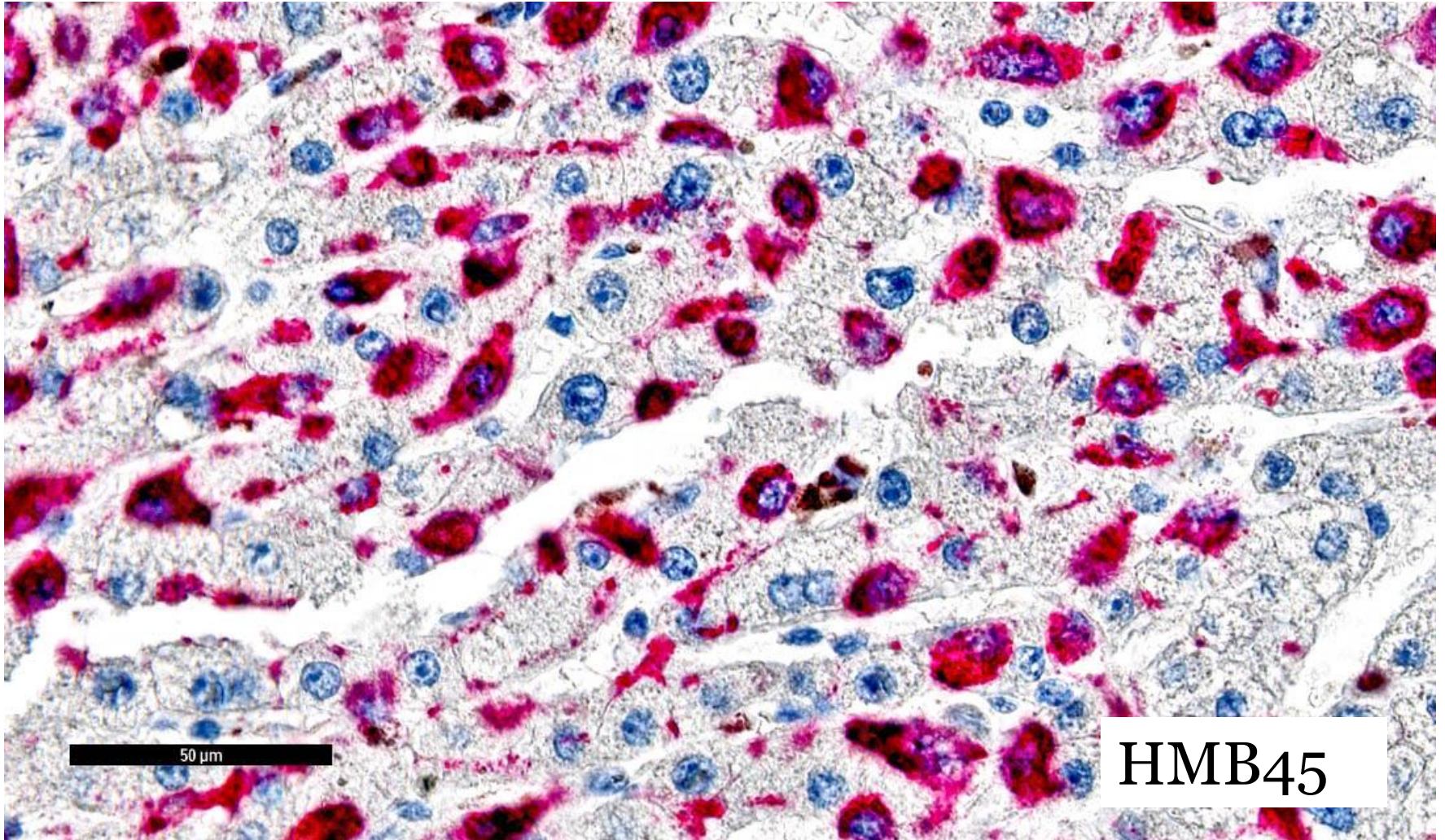
Replacement



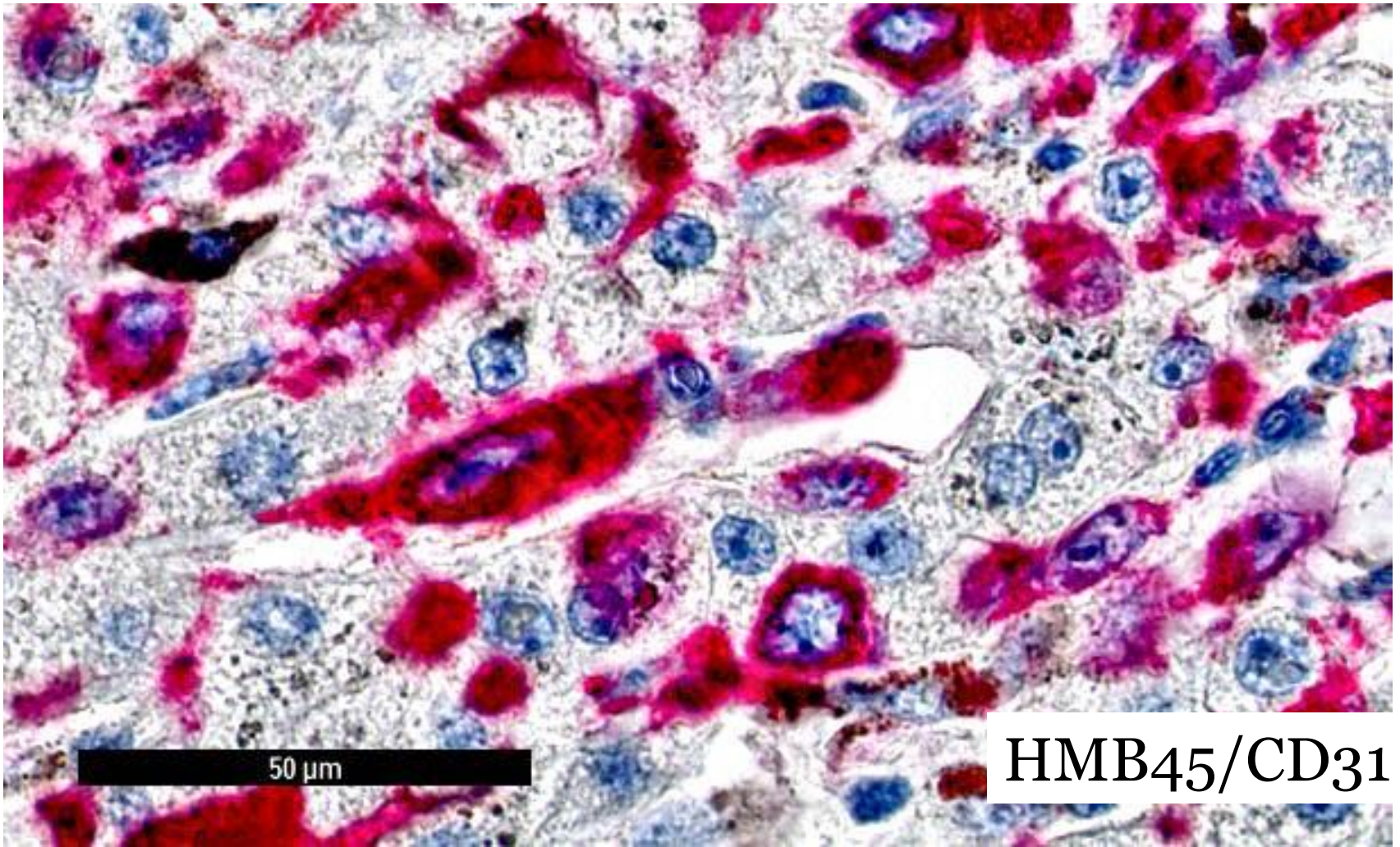
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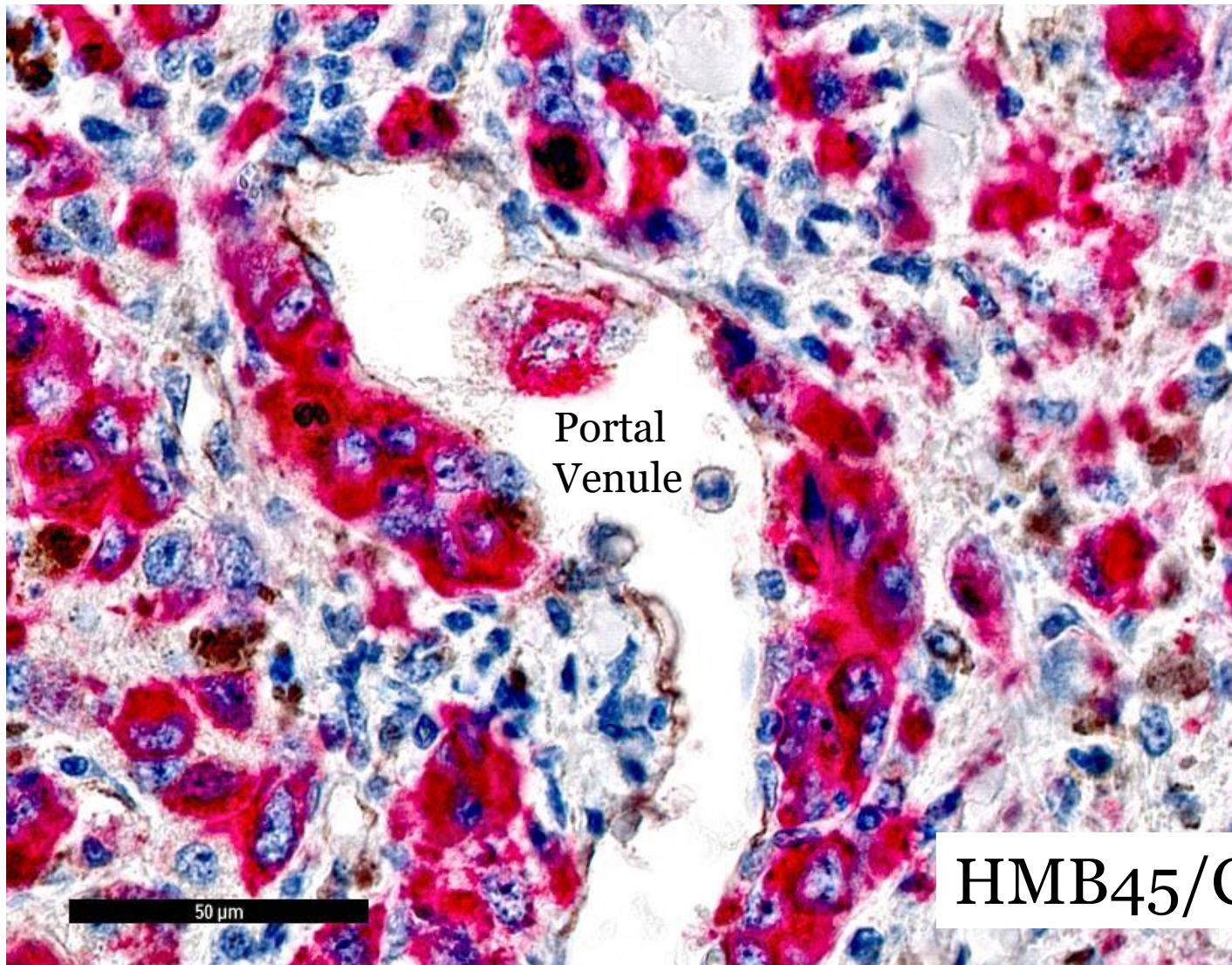
Replacement



Replacement

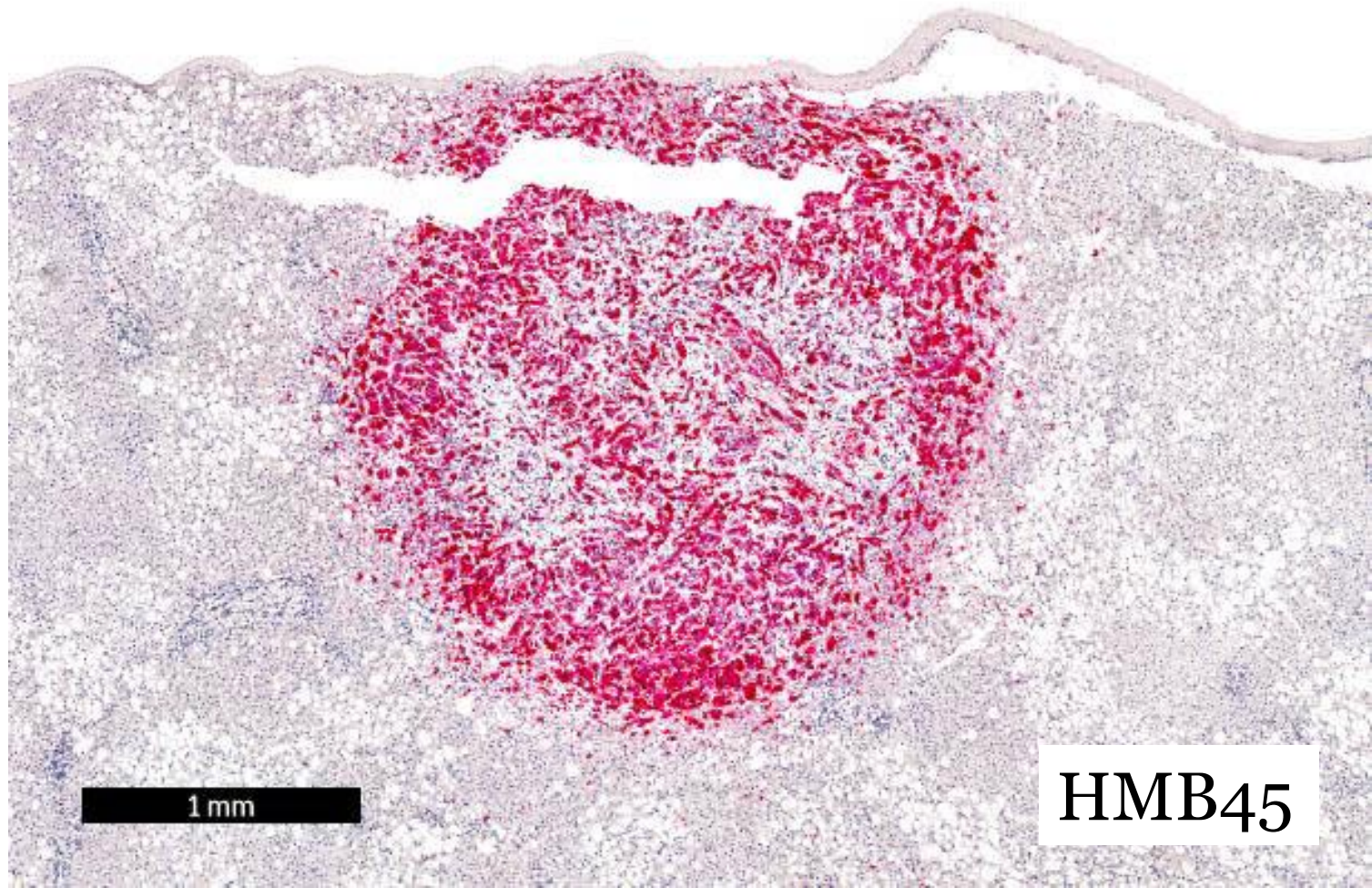


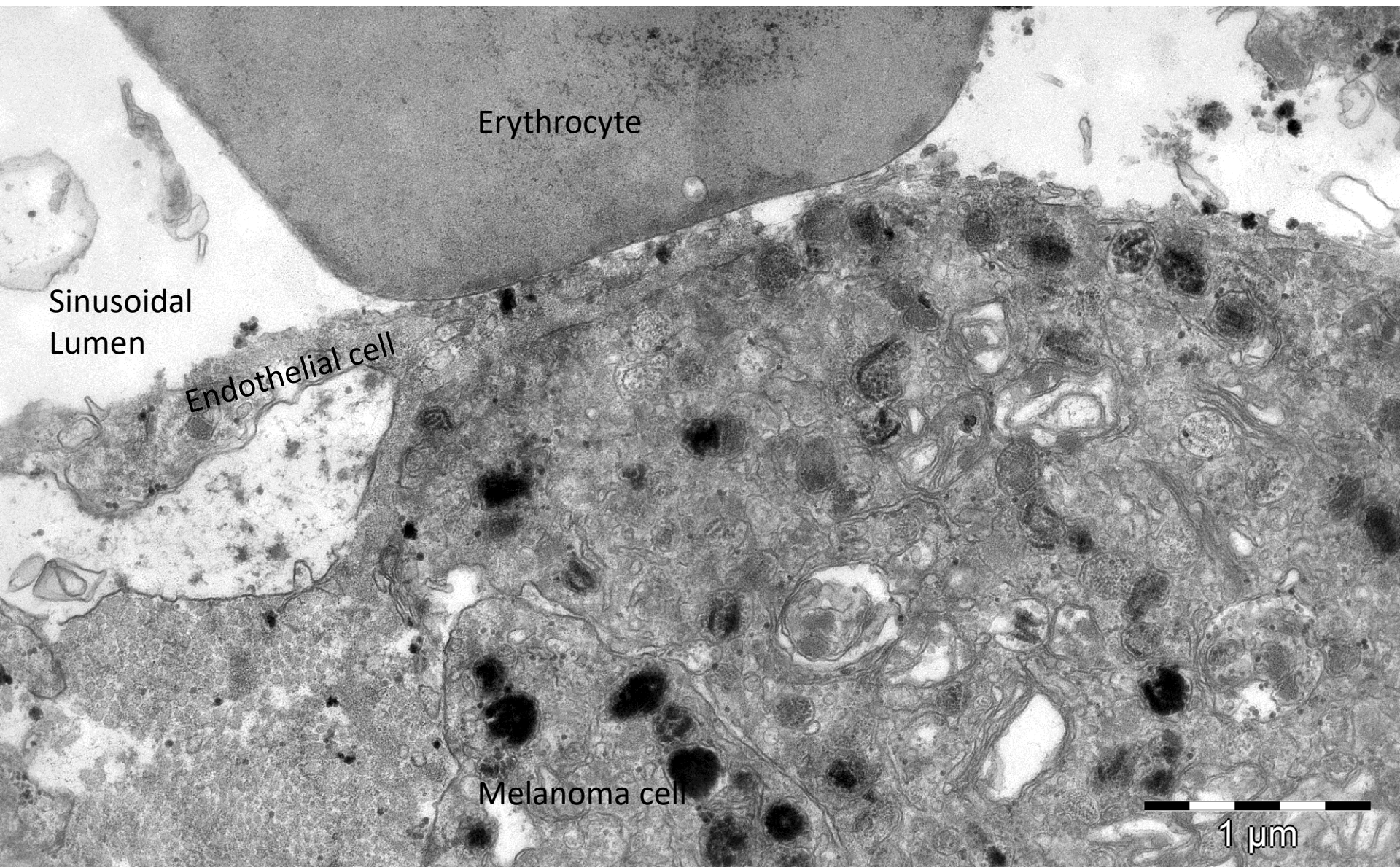
Replacement



Ultrastructural Analysis of Hepatic Metastases of Uveal Melanoma

Micrometastasis with Replacement Pattern





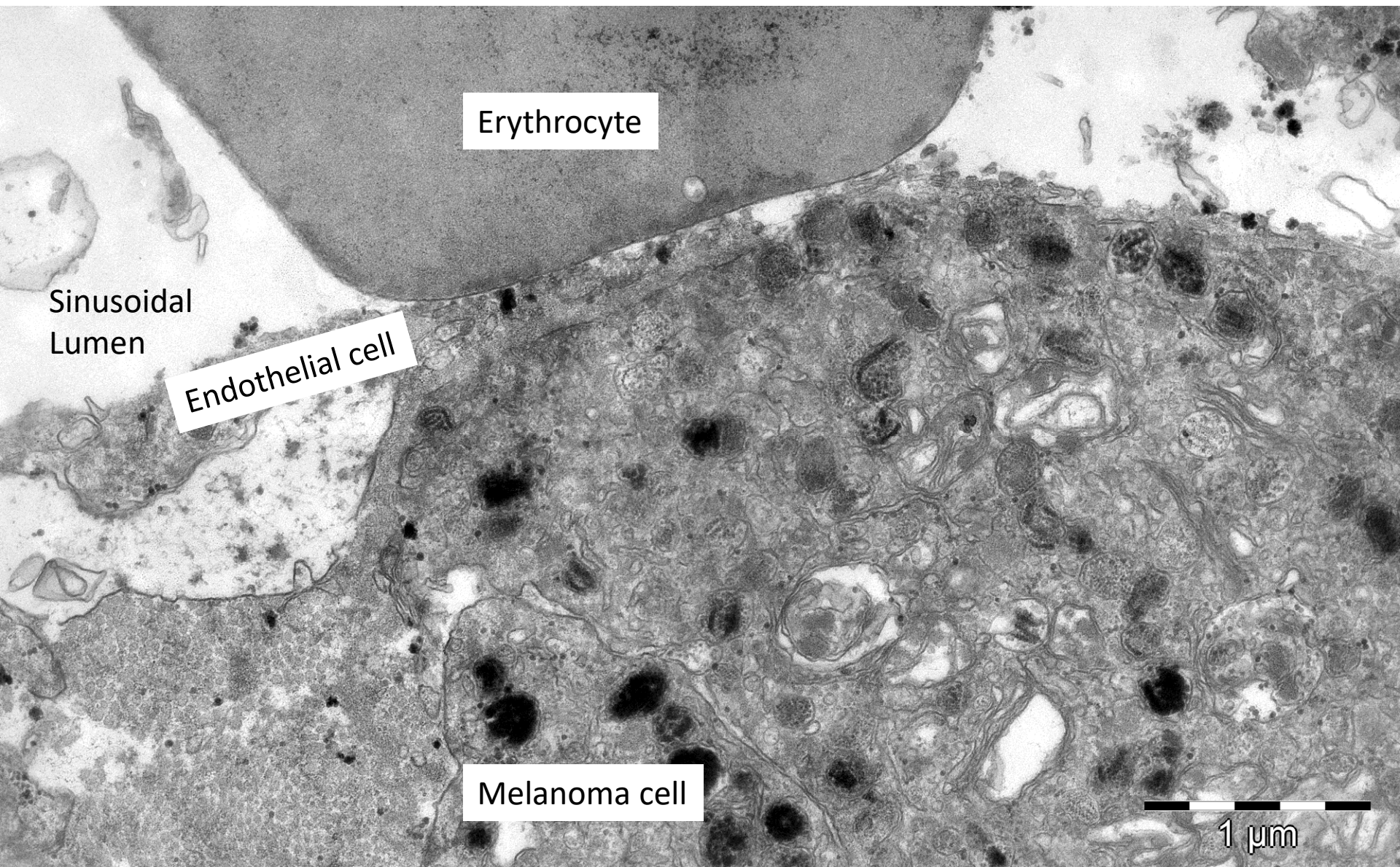
Erythrocyte

Sinusoidal
Lumen

Endothelial cell

Melanoma cell

1 μ m



Erythrocyte

Sinusoidal
Lumen

Endothelial cell

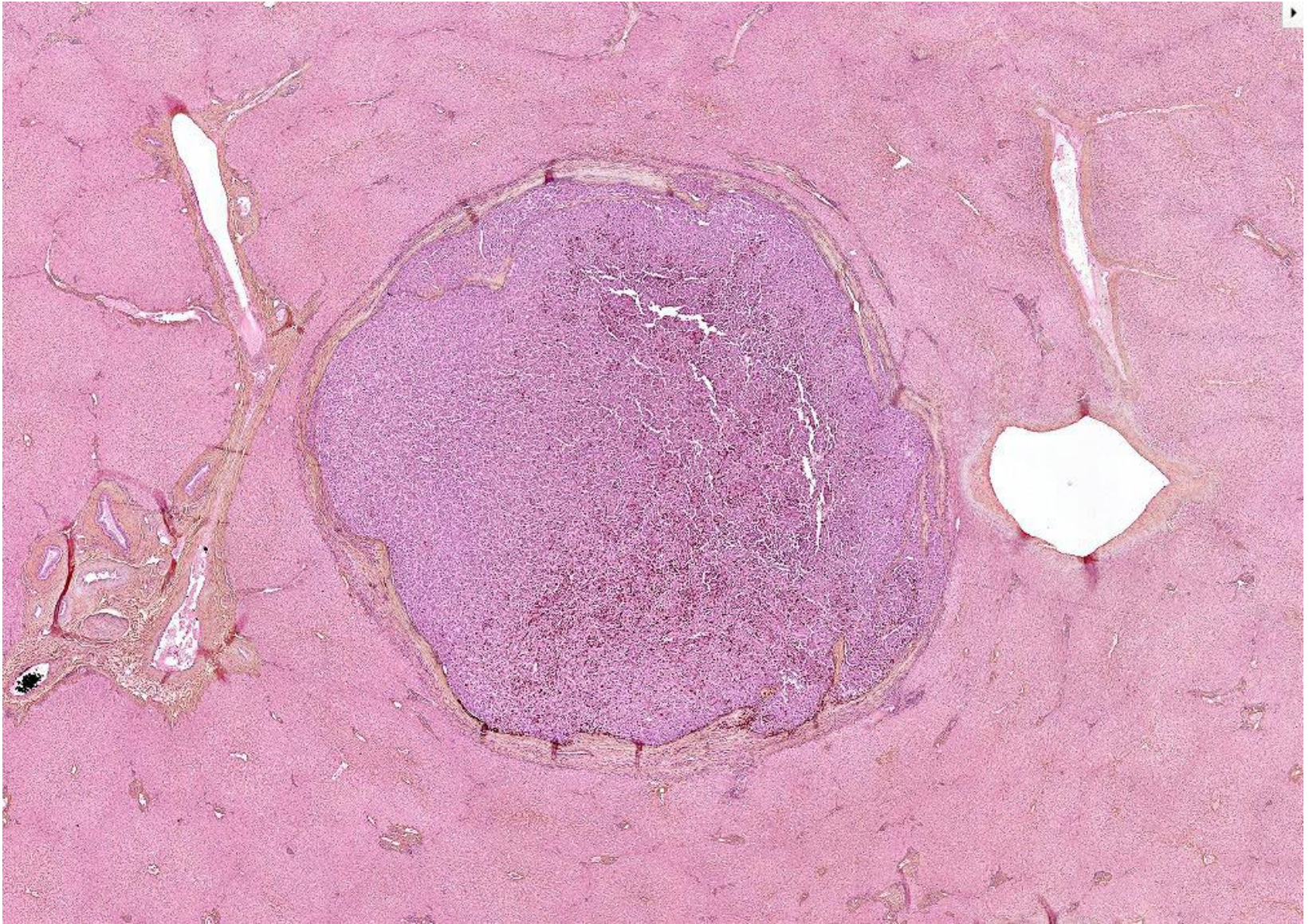
Melanoma cell

1 μ m

Metastasis with Replacement Pattern

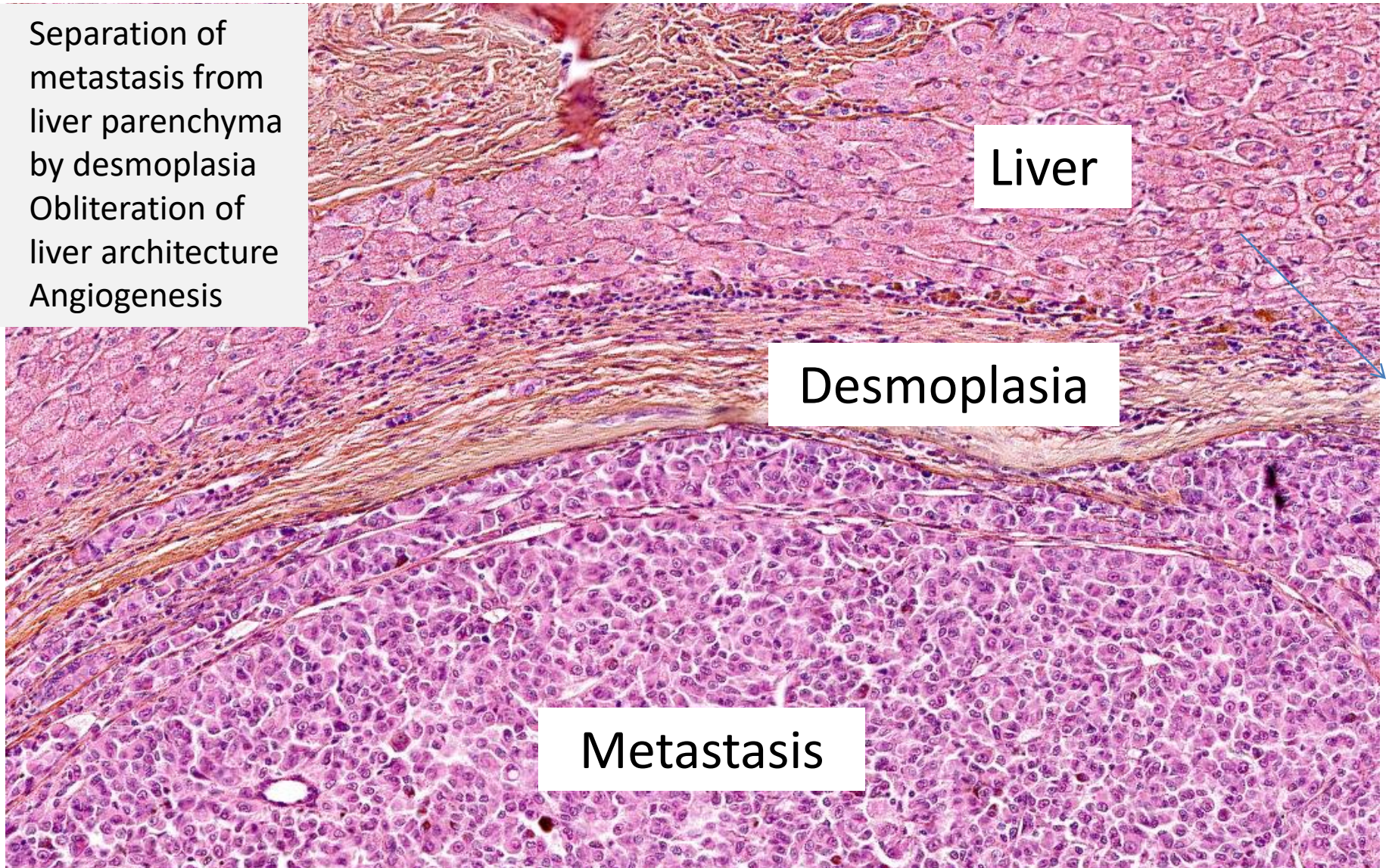
- Electron microscopy demonstrates uveal melanoma cells disposed along the abluminal (external) surfaces of sinusoidal endothelial cells in the space of Disse
- This corresponds to a pericytic location in angiotropism or vascular co-option

Desmoplastic Pattern

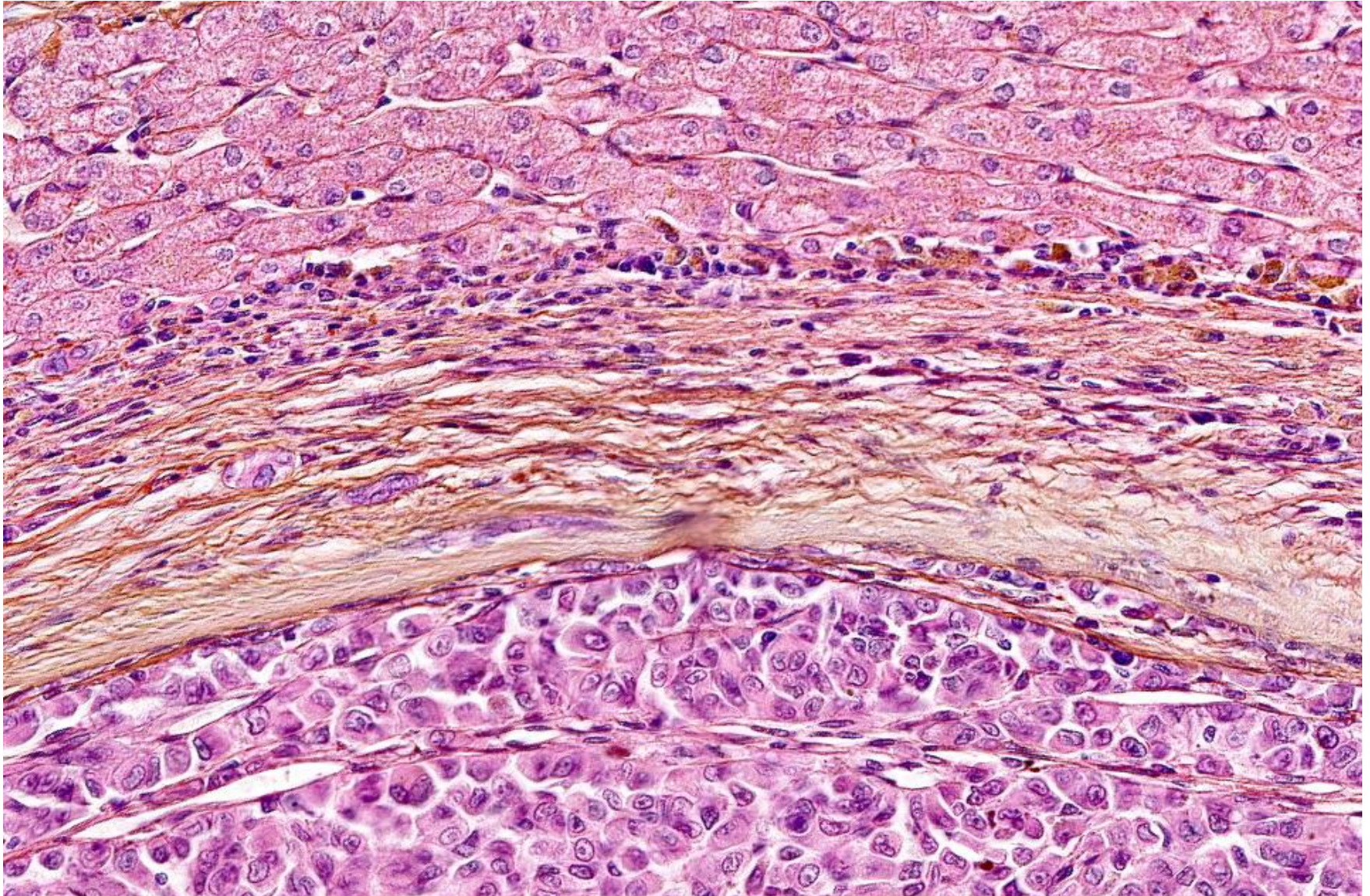


Desmoplastic Pattern

- Separation of metastasis from liver parenchyma by desmoplasia
- Obliteration of liver architecture
- Angiogenesis



Desmoplastic Pattern



Histopathological Growth Patterns

UM Liver Metastases n=41

- PURE

100% Replacement	63%
100% Desmoplastic	10%
- MIXED

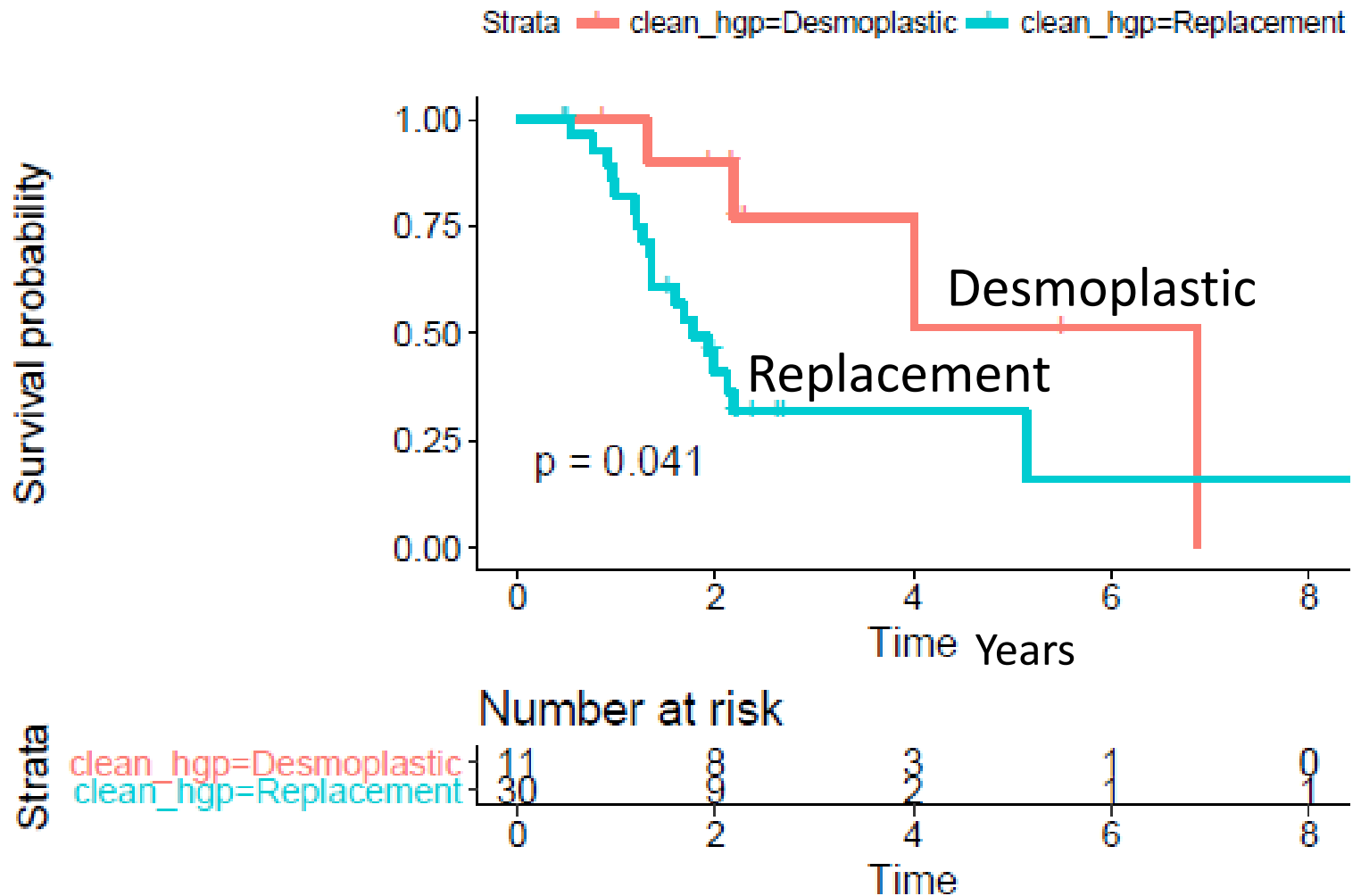
Replacement, Desmoplastic	27%
---------------------------	-----
- ANY REPLACEMENT 90%

Histopathological Growth Patterns

UM Liver Metastases n=41

- > 50% Replacement 73%
- > 50% Desmoplastic 27%

HGP and Overall Survival



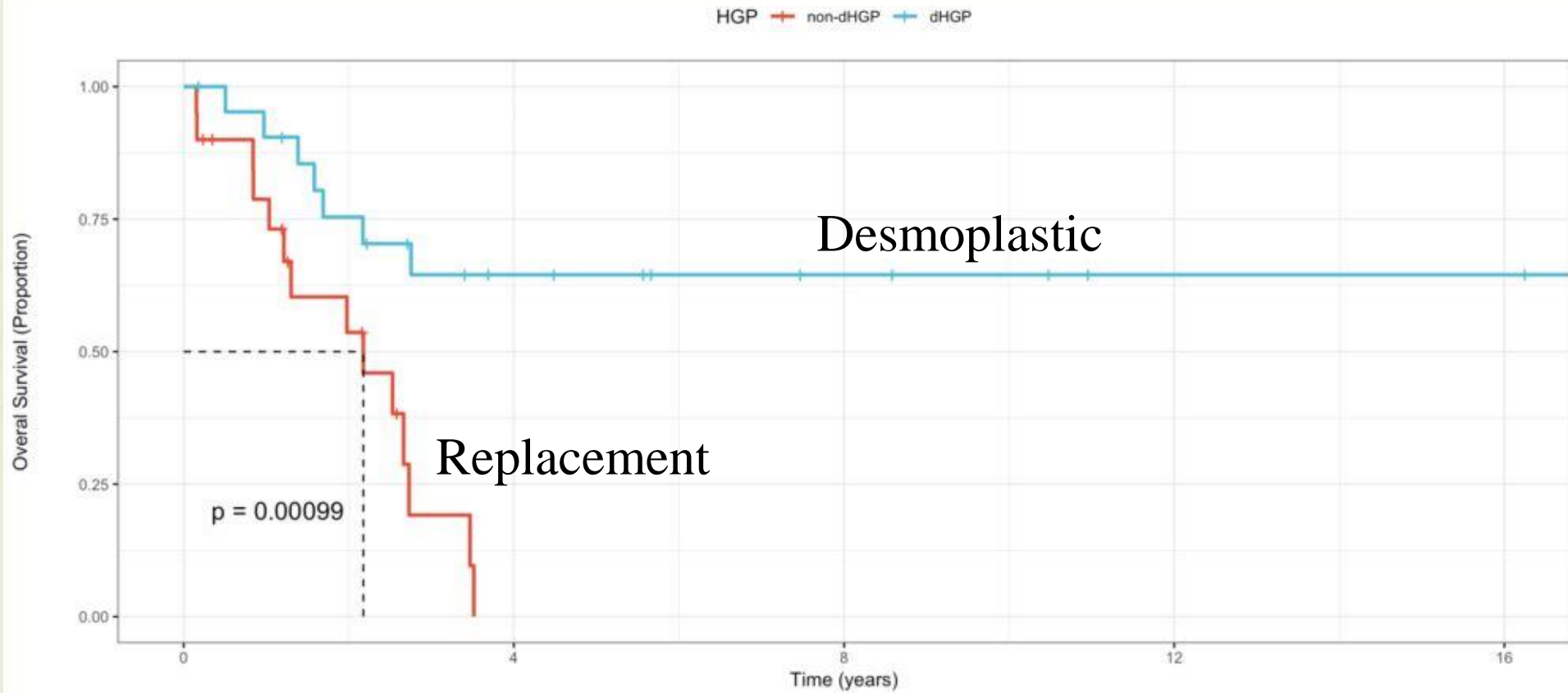
Multivariate Analysis

Hazard Ratio

• <u>Factor</u>	<u>HR</u>	<u>p value:</u>
- HGP	6.71	p=0.019*
- Mono 3	1.88	p=0.342
- Chrom 8g	2.10	p=0.266
- LTD	0.37	p=0.07

HGP and Overall Survival

Cutaneous Melanoma



Number at risk

non-dHGP	20	0	0	0	0
dHGP	22	9	5	2	2

Conclusions

- Angiotropism is an adverse prognostic factor in primary uveal melanoma
- Replacement pattern:
 - adverse prognostic factor for patients with UM liver metastasis
 - biomarker of angiotropism/vascular co-option, and a migratory phenotype

Conclusions

- Desmoplastic pattern:
 - more favorable prognostic factor
patients with UM liver metastases

Conclusions

- The detection of angiotropism in both primary UM and in UM liver metastases with the Replacement HGP suggests a role for Extravascular Migratory Metastasis in this malignancy, as will be developed by Dr. Lugassy.