LIFEFEST2026

Nashville

The Role of Pathology in Liposarcoma

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Role of Pathology in Liposarcoma

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Outline

- Classification
- Histology
- Molecular Findings

WHO Classification of Soft Tissue Sarcomas

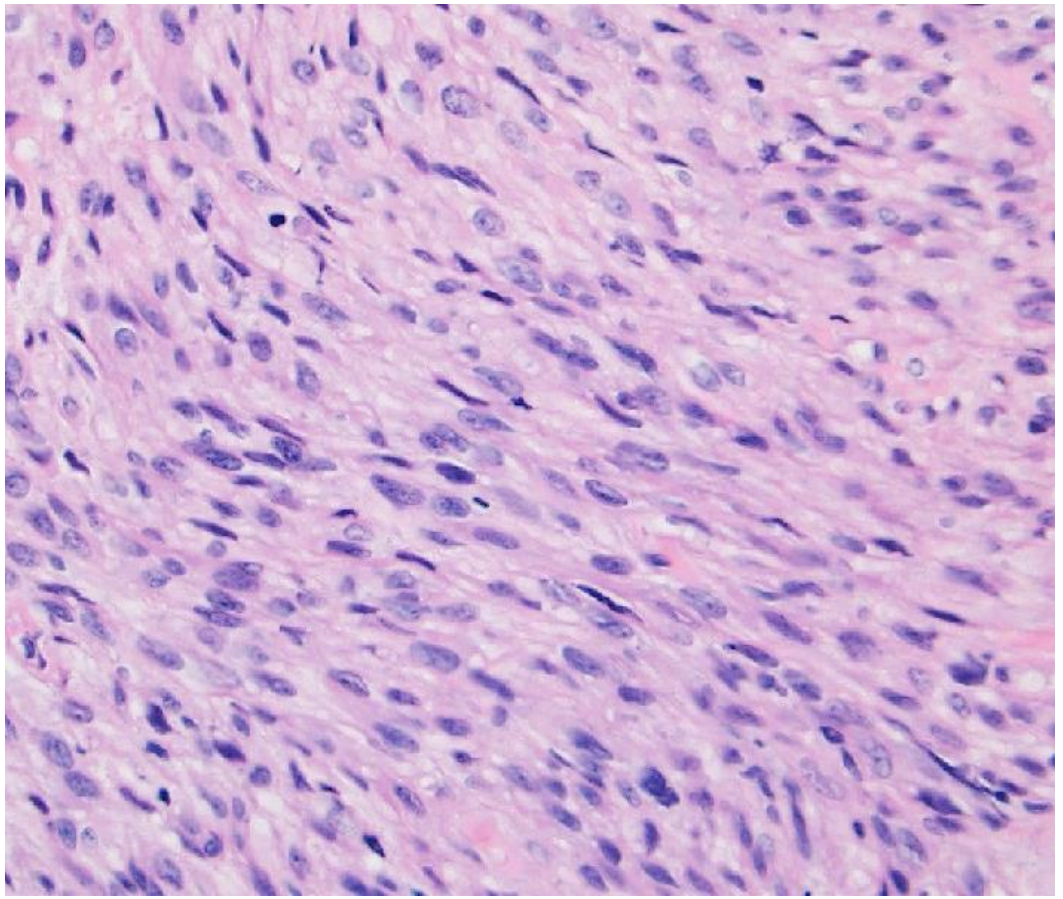
- By behavior:
  - Benign
  - Intermediate
    - Locally aggressive/risk for recurrence
    - Rarely metastasizing
  - Malignant

- By differentiation (resemblance to normal connective/soft tissue):
  - Adipocytic (lipomatous)
  - Fibroblastic/Myofibroblastic
  - Fibrohistiocytic
  - Smooth or skeletal muscle
  - Vascular
  - Pericytic (perivascular)
  - Gastrointestinal stromal tumor
  - Chondro-osseous
  - Peripheral nerve sheath
  - Uncertain differentiation

Classification of Liposarcomas

- Atypical lipomatous tumor (ALT) / well-differentiated liposarcoma (WDLPS)
- Dedifferentiated liposarcoma (DDLPS)
- Myxoid liposarcoma (MLPS)
- Pleomorphic liposarcoma
- Myxoid pleomorphic liposarcoma

From Tissue To Light Microscopy

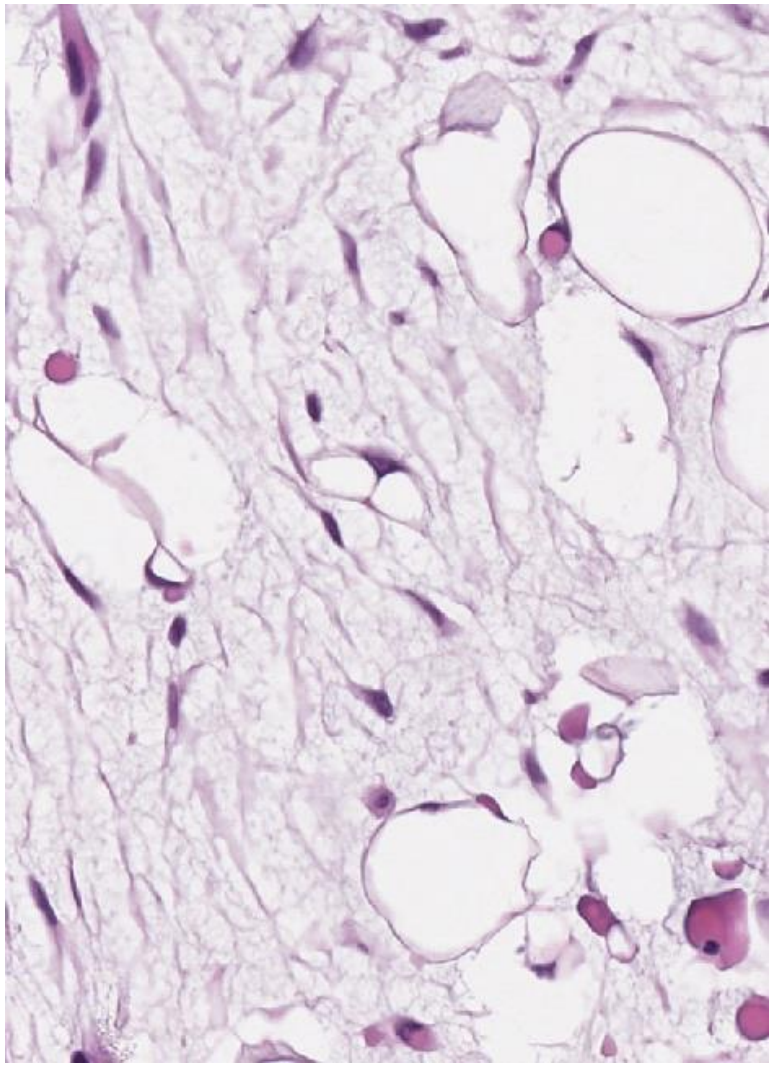


Time from biopsy to H&E slides: 24-48 hours

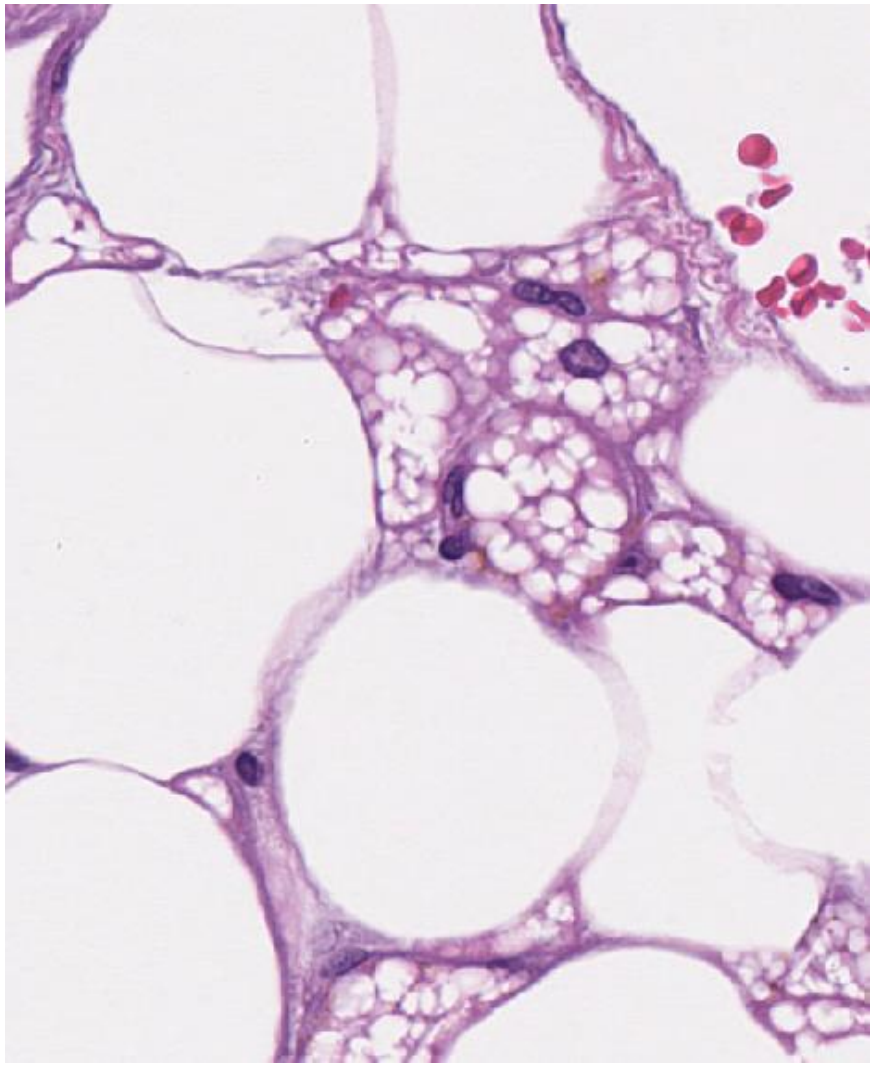
Histology

- Liposarcomas:
  - Malignant tumors with adipocytic differentiation
- Lipoblast:
  - Neoplastic cell recapitulating normal fat differentiation
  - More common and easy to find in certain liposarcoma subtypes
  - Not a requirement for diagnosis for all liposarcomas

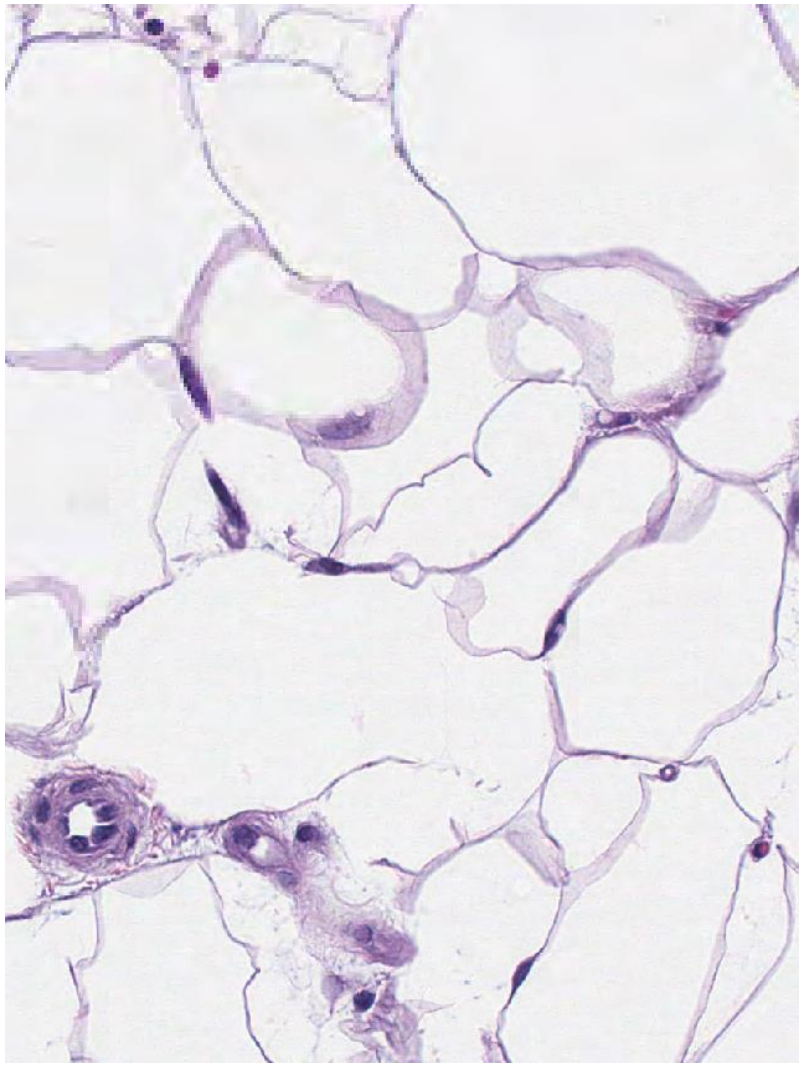
Normal Fat Cells



Immature fat with lipoblasts



Brown/metabolically active fat



White fat

Atypical lipomatous tumors/Well-differentiated liposarcoma (ALT/WDLPS)

- 30-40% all liposarcomas
- Most closely resembles mature fat
  - Lipoblasts are rare
    - Atypical stromal cells much more common
- Most common in late adult life (60-70 years of age)
- Various anatomic locations
  - Rarely in superficial soft tissues
- Symptoms dependent on tumor location and size

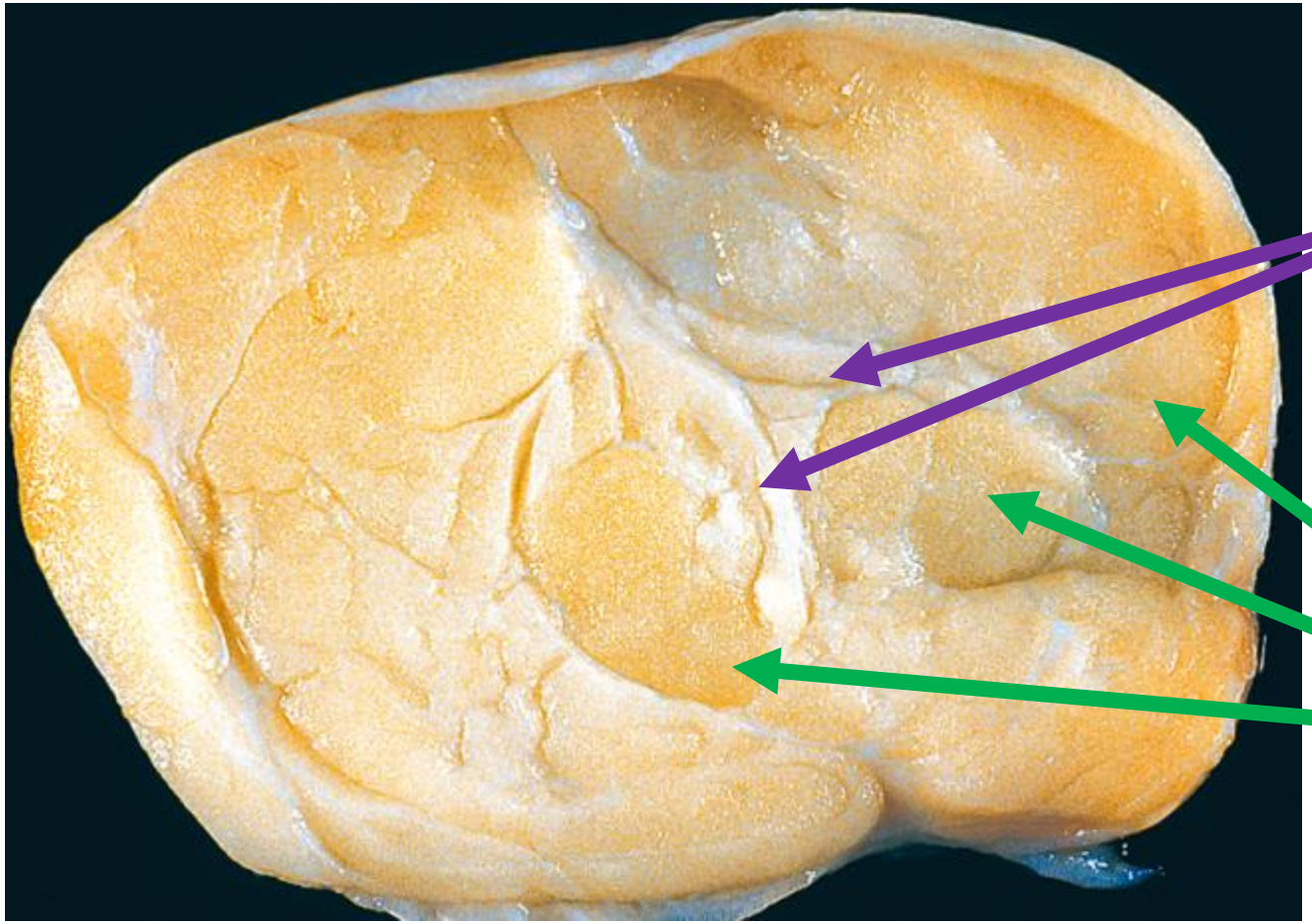
Atypical lipomatous tumors/Well-differentiated liposarcoma (ALT/WDLPS)

- Biologic spectrum of a histologic and molecular entity
  - *MDM2* (12q) amplification
  - ALT: extremities
    - Locally aggressive
    - Usually amenable to resection
  - WDLPS: retroperitoneum, mediastinum, paratesticular, intracranial

Site	Recurrence (%)	Died of Disease (%)	Dedifferentiation (%)	Years Follow-up: Range (Median)
Extremity	43	0	6	2-25 (9)
Retroperitoneum	91	33	17	1-35 (10)
Groin	79	14	28	2-25 (8)
total	63	11	13	

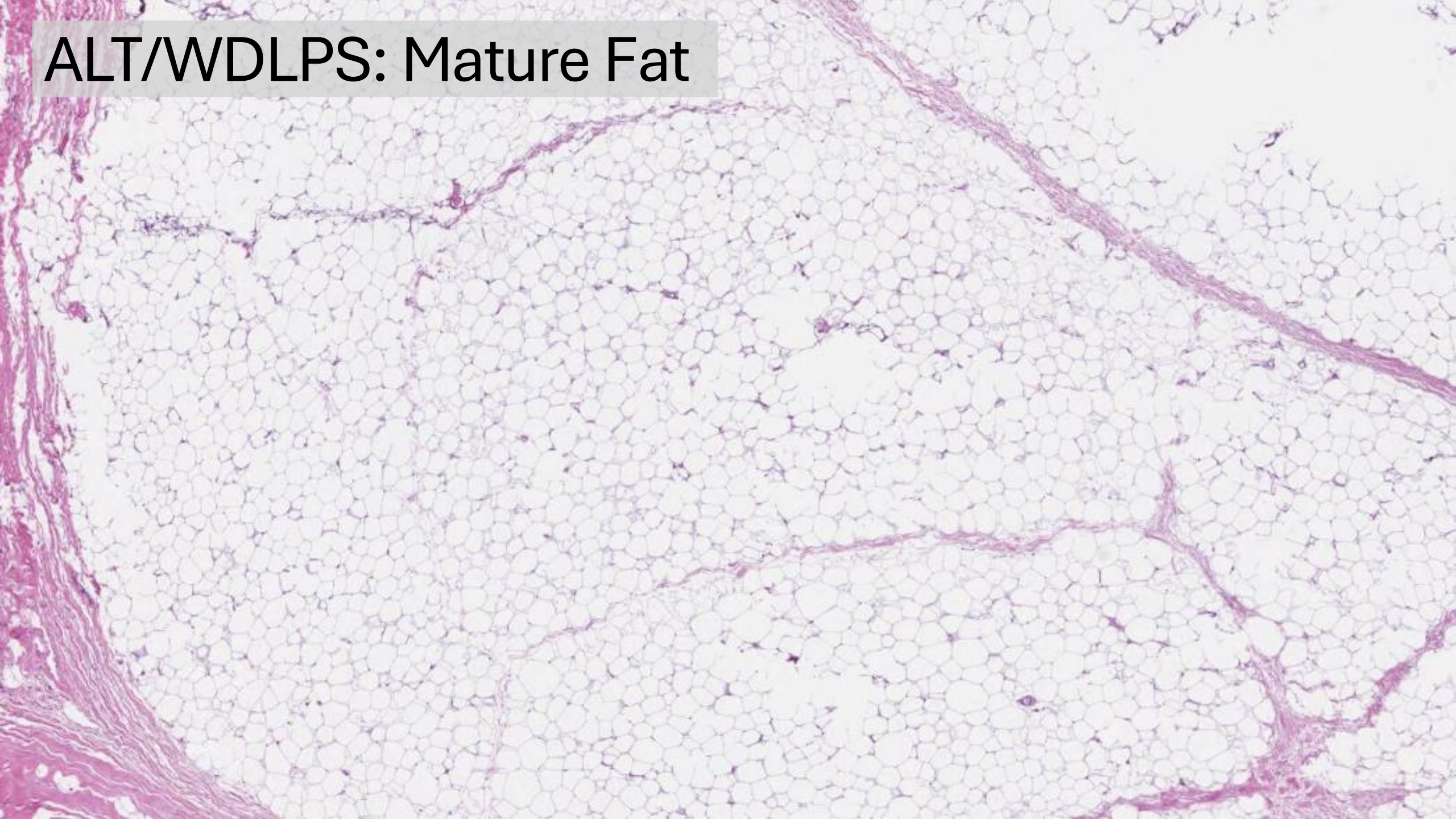
Weiss SW and Rao VK. *Am J Surg Pathol* . 1992;16:1051–1058.

ALT/WDLPS: Gross Features

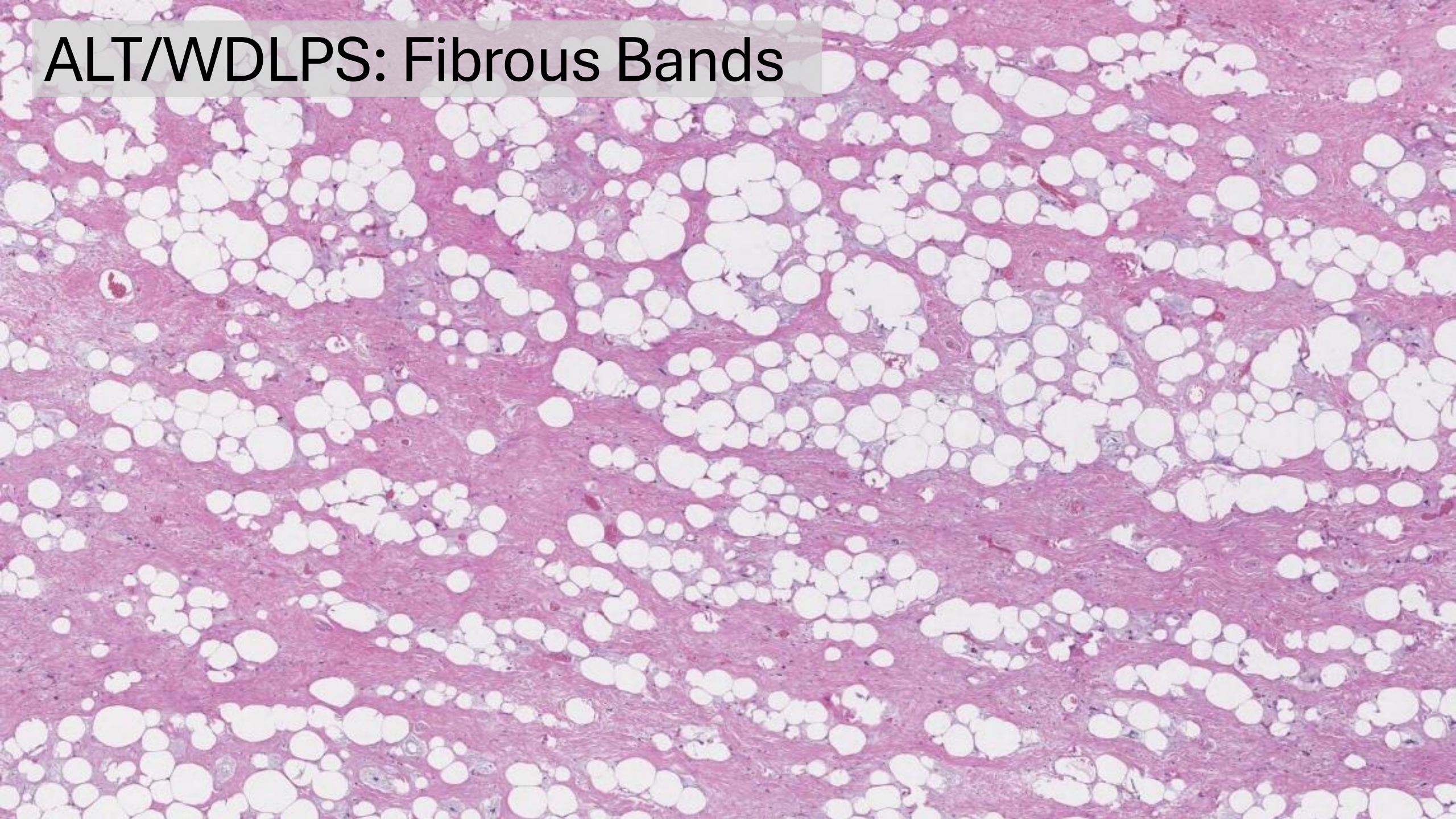


Enzinger and Weiss, 8th ed.

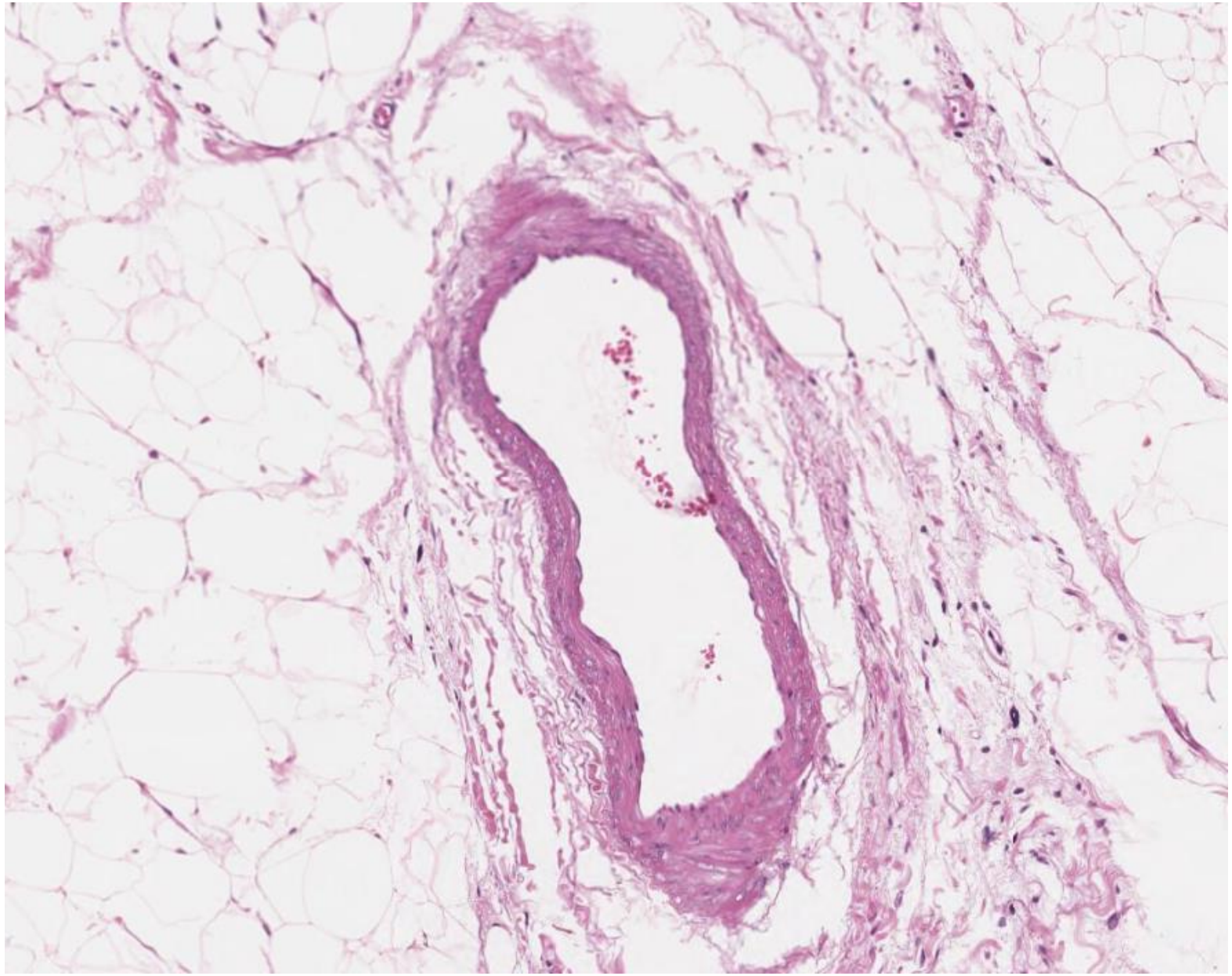
ALT/WDLPS: Mature Fat

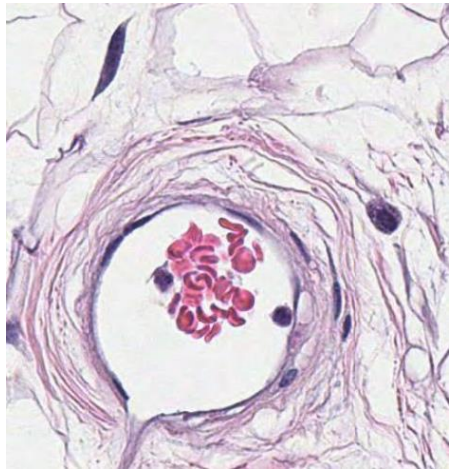


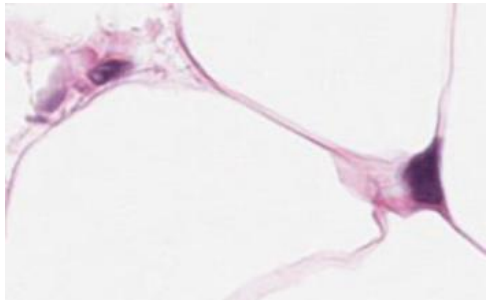
ALT/WDLPS: Fibrous Bands

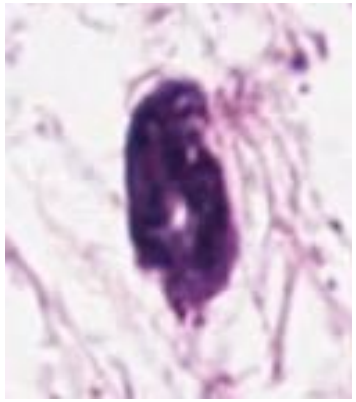


ALT/WDLPS: Atypical Stromal Cells

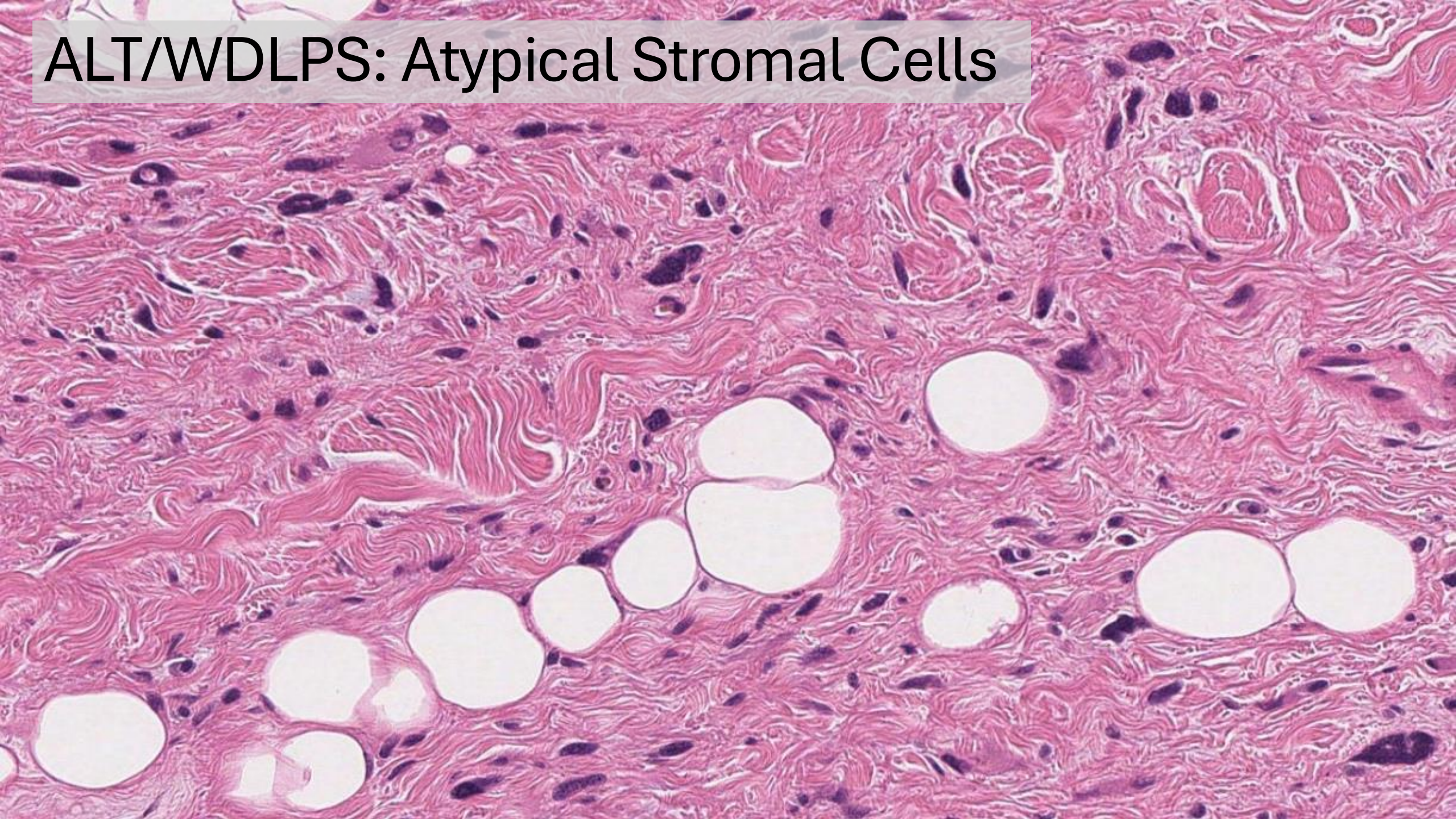




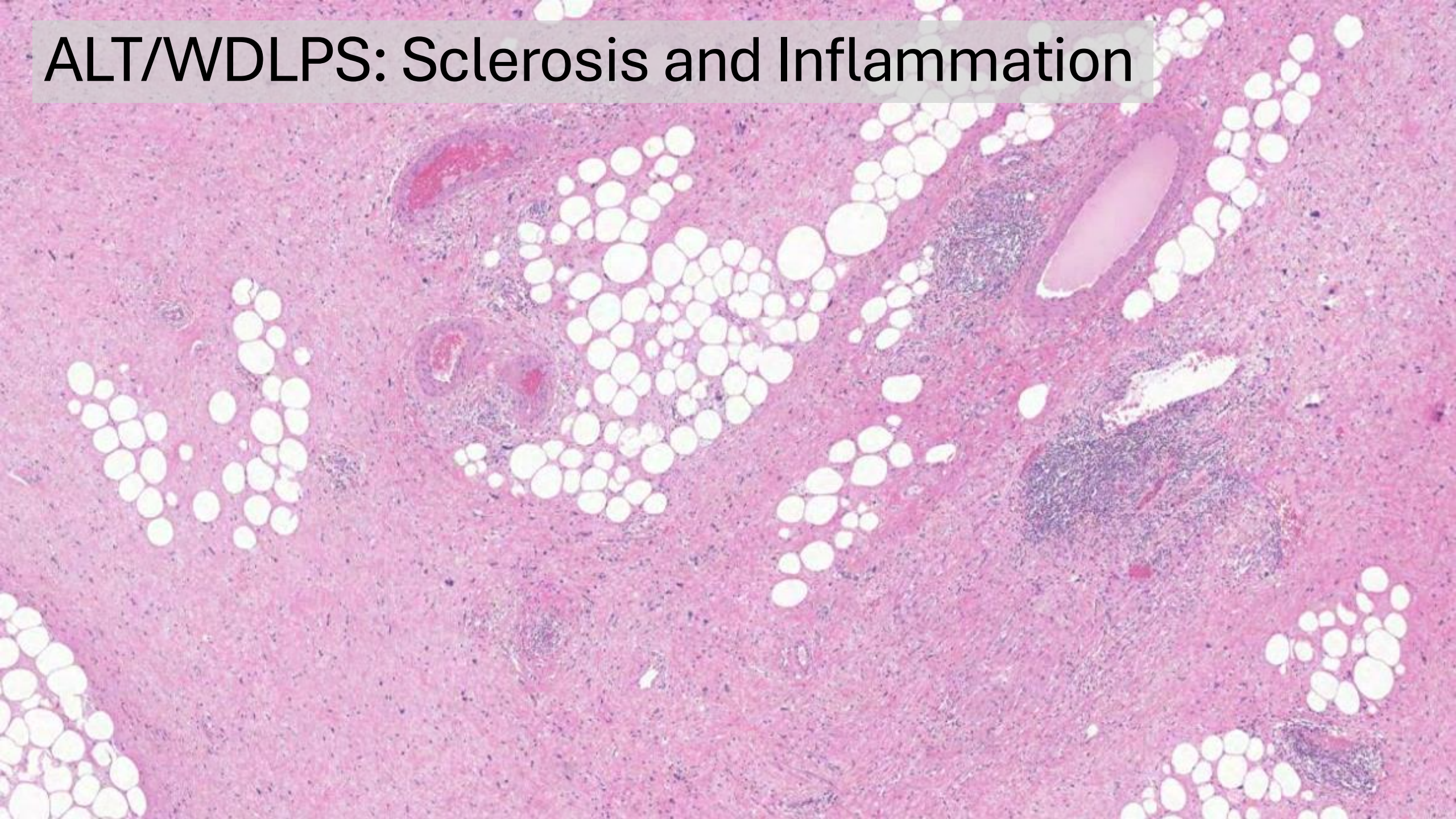




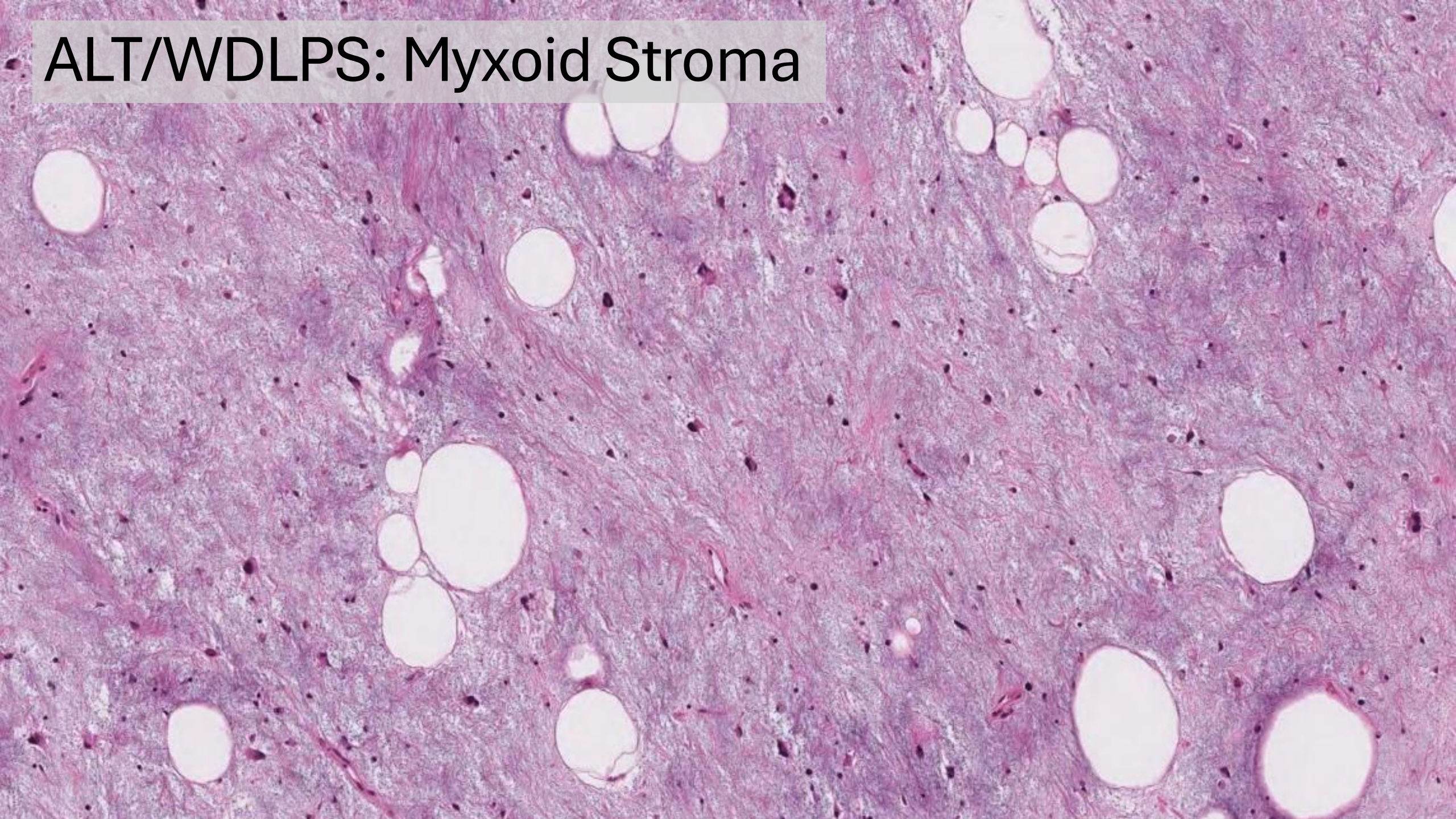
ALT/WDLPS: Atypical Stromal Cells



ALT/WDLPS: Sclerosis and Inflammation



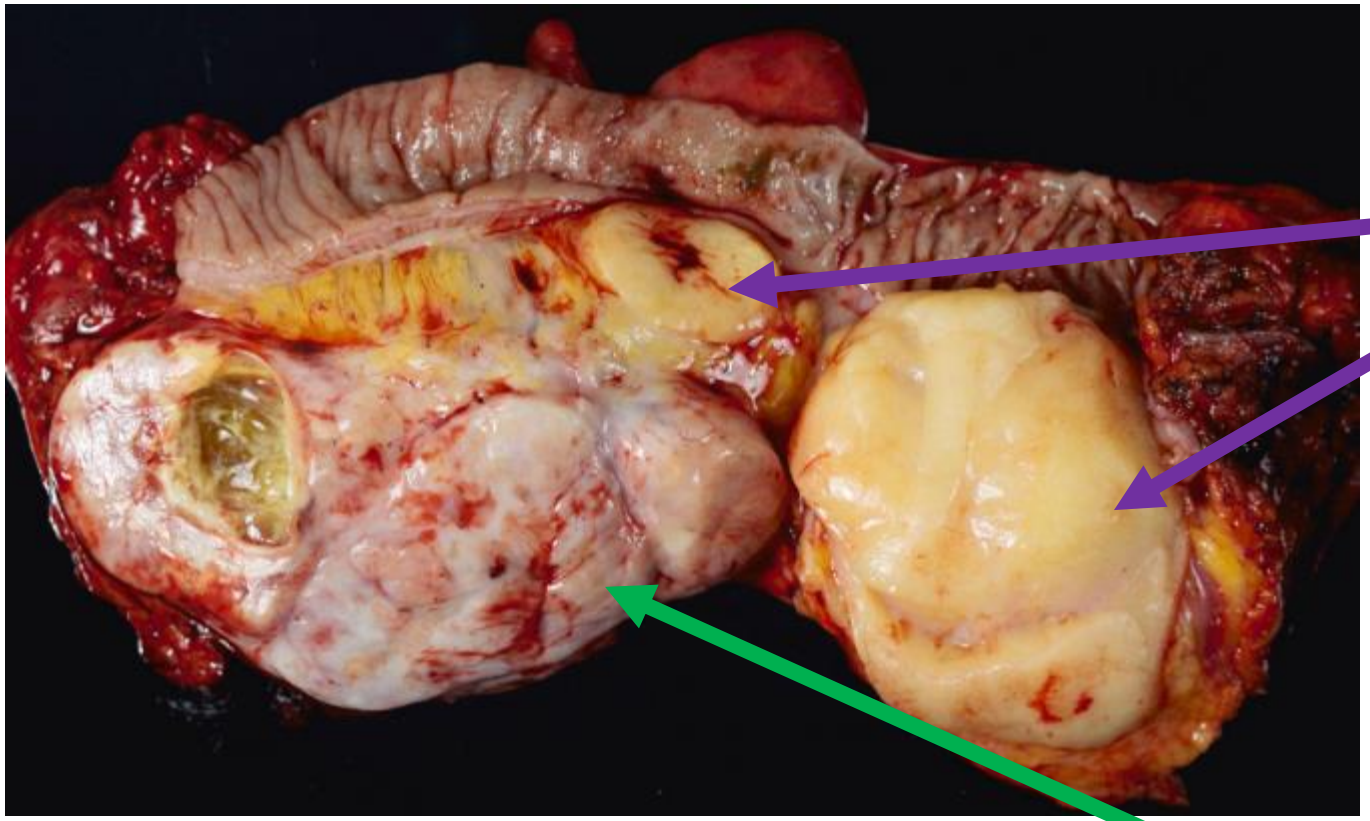
ALT/WDLPS: Myxoid Stroma



Dedifferentiated Liposarcoma (DDLPS)

- 20% liposarcomas
- *MDM2* amplification as in ALT/WDLPS
  - Other, cumulative genetic events lead to dedifferentiation
- Dedifferentiation:
  - Progression to higher-grade tumor
    - Loses adipocytic differentiation
      - Except in homologous dedifferentiation
  - Can be present at initial diagnosis (90% cases)
    - Remainder in recurrences of WDLPS
- Well-differentiated areas demarcated from dedifferentiated areas

DDLPS: Gross Features

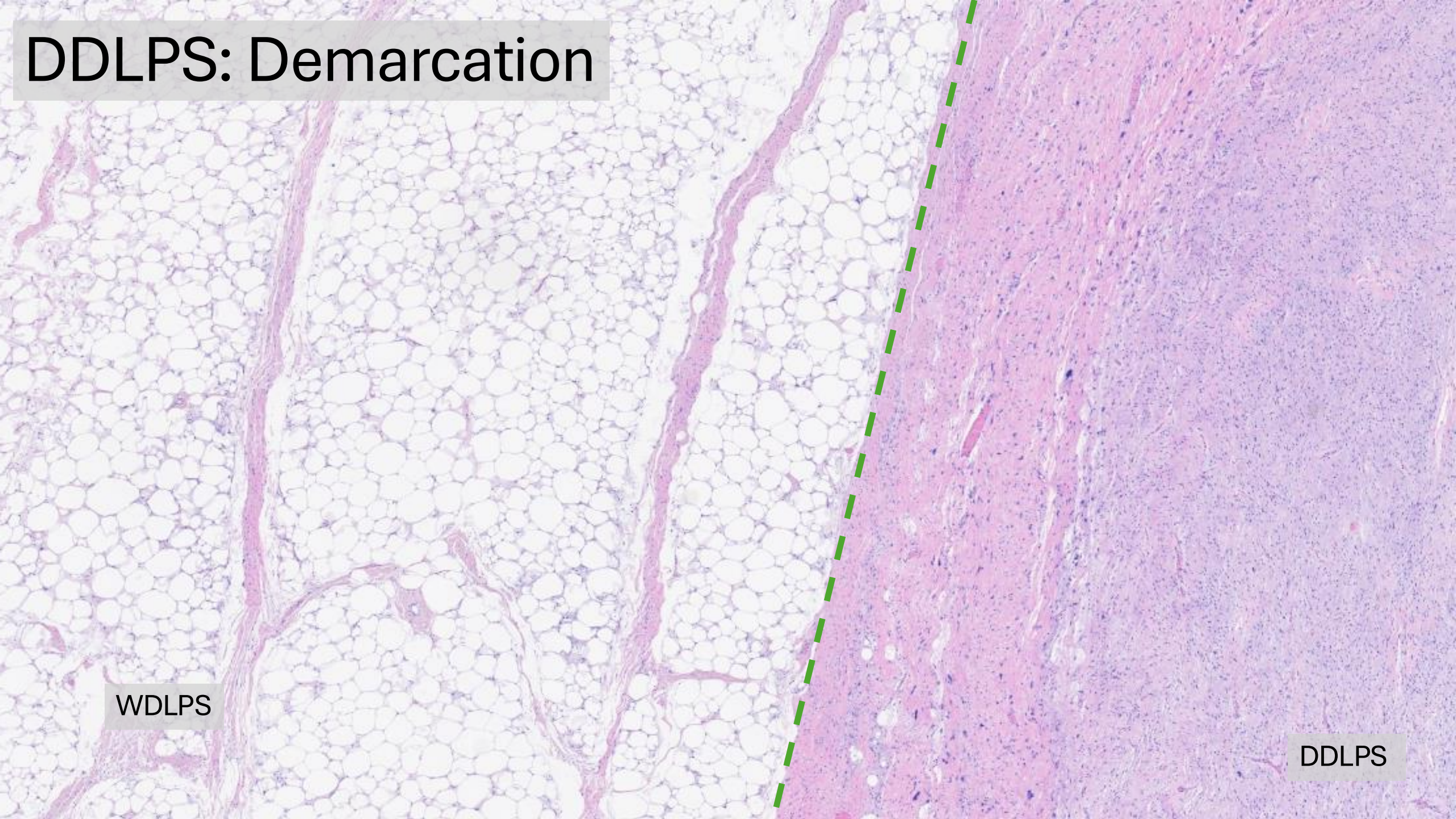


Well-differentiated areas

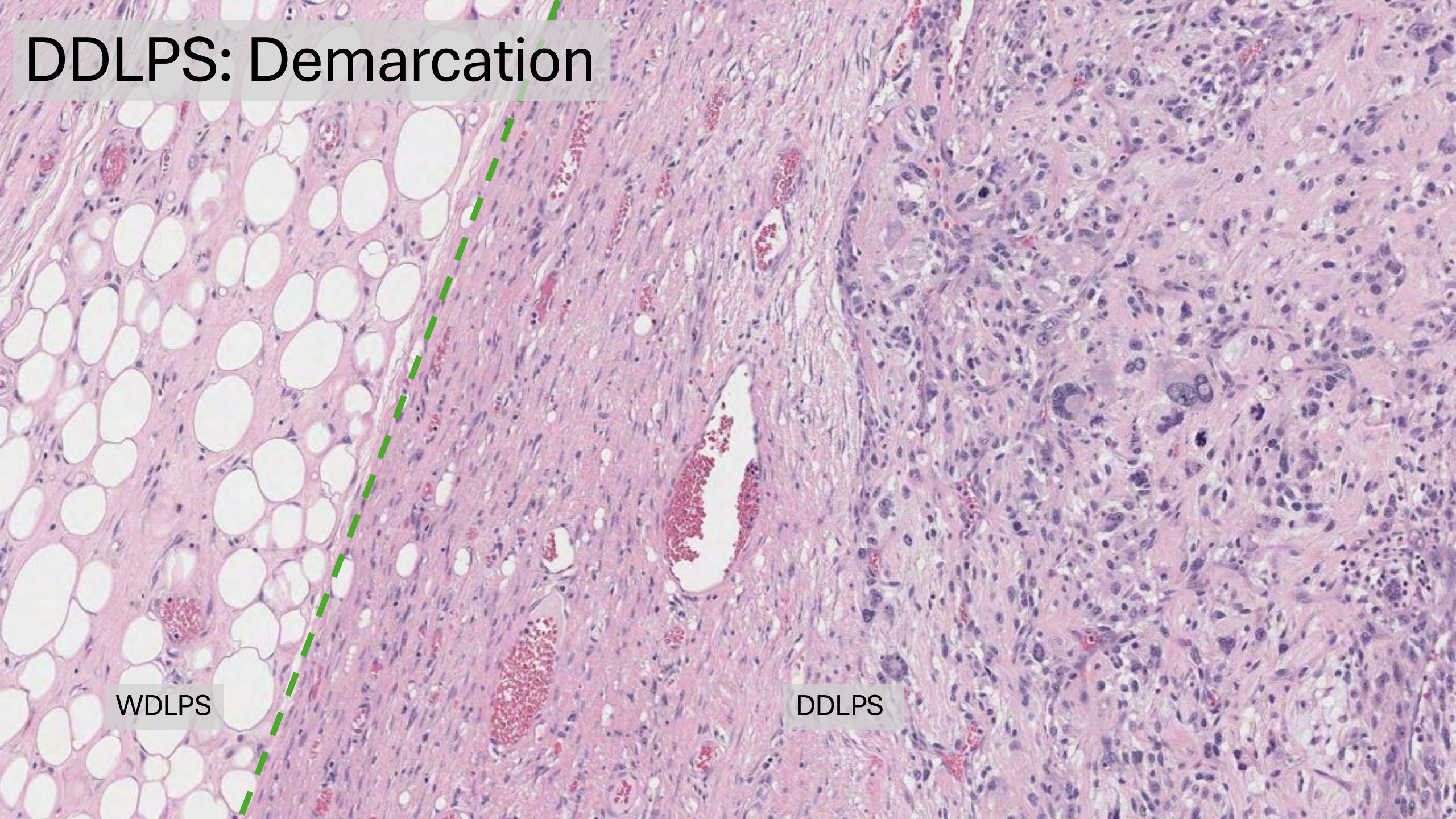
Dedifferentiated focus

Enzinger and Weiss, 8th ed.

DDLPS: Demarcation



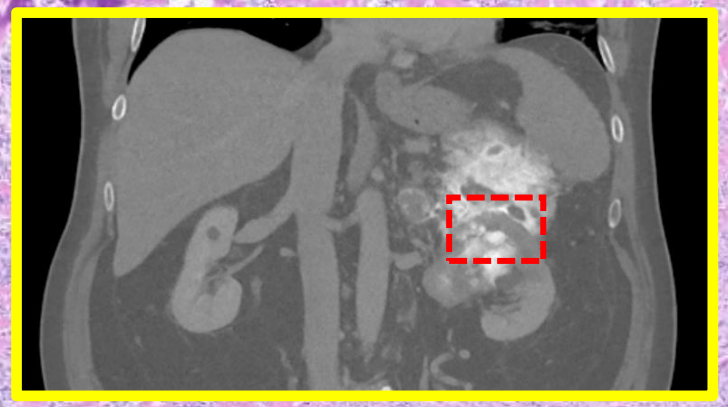
DDLPS: Demarcation



DDLPS

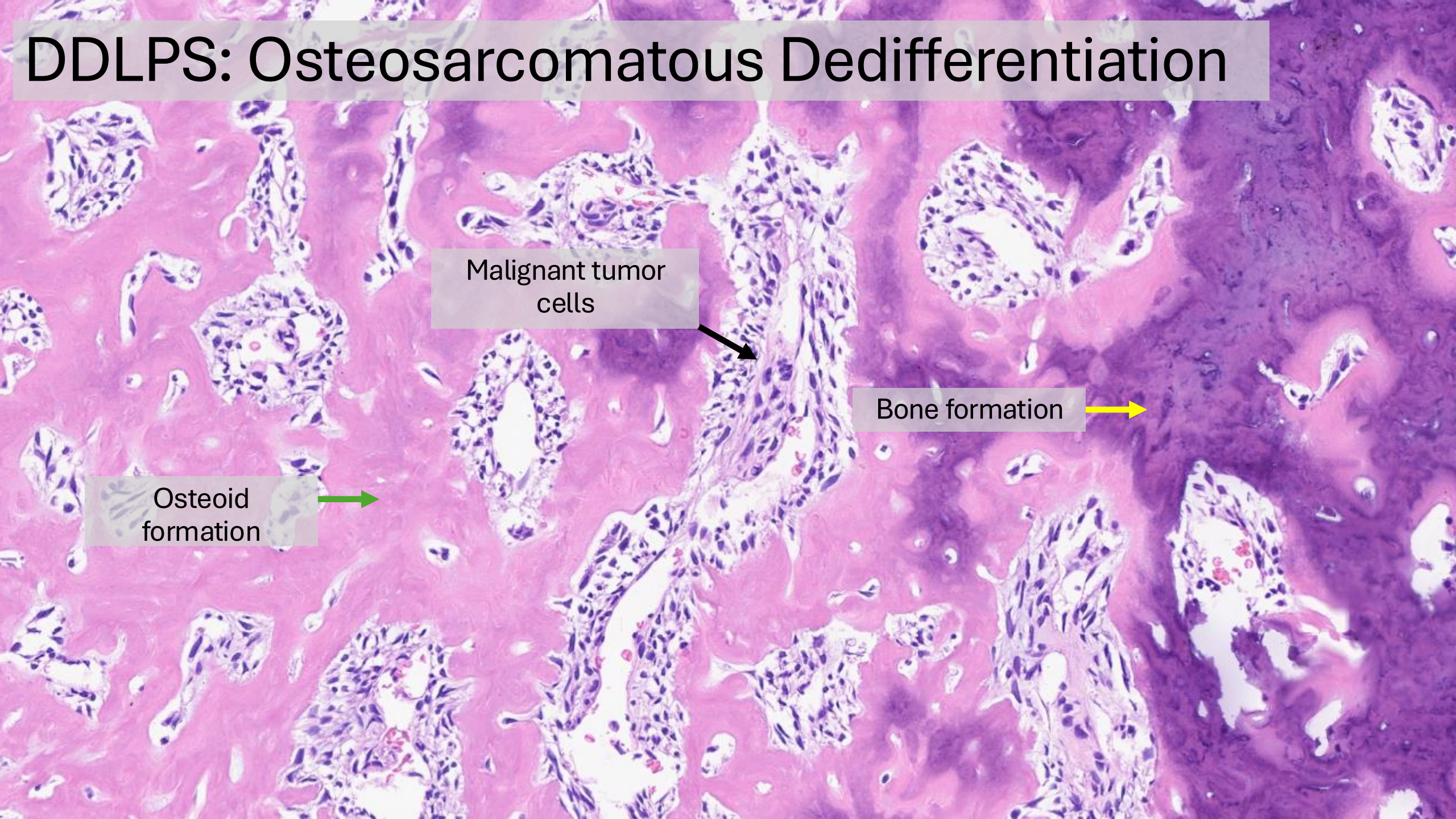
Calcified, malignant tumor

Tumor front invading kidney

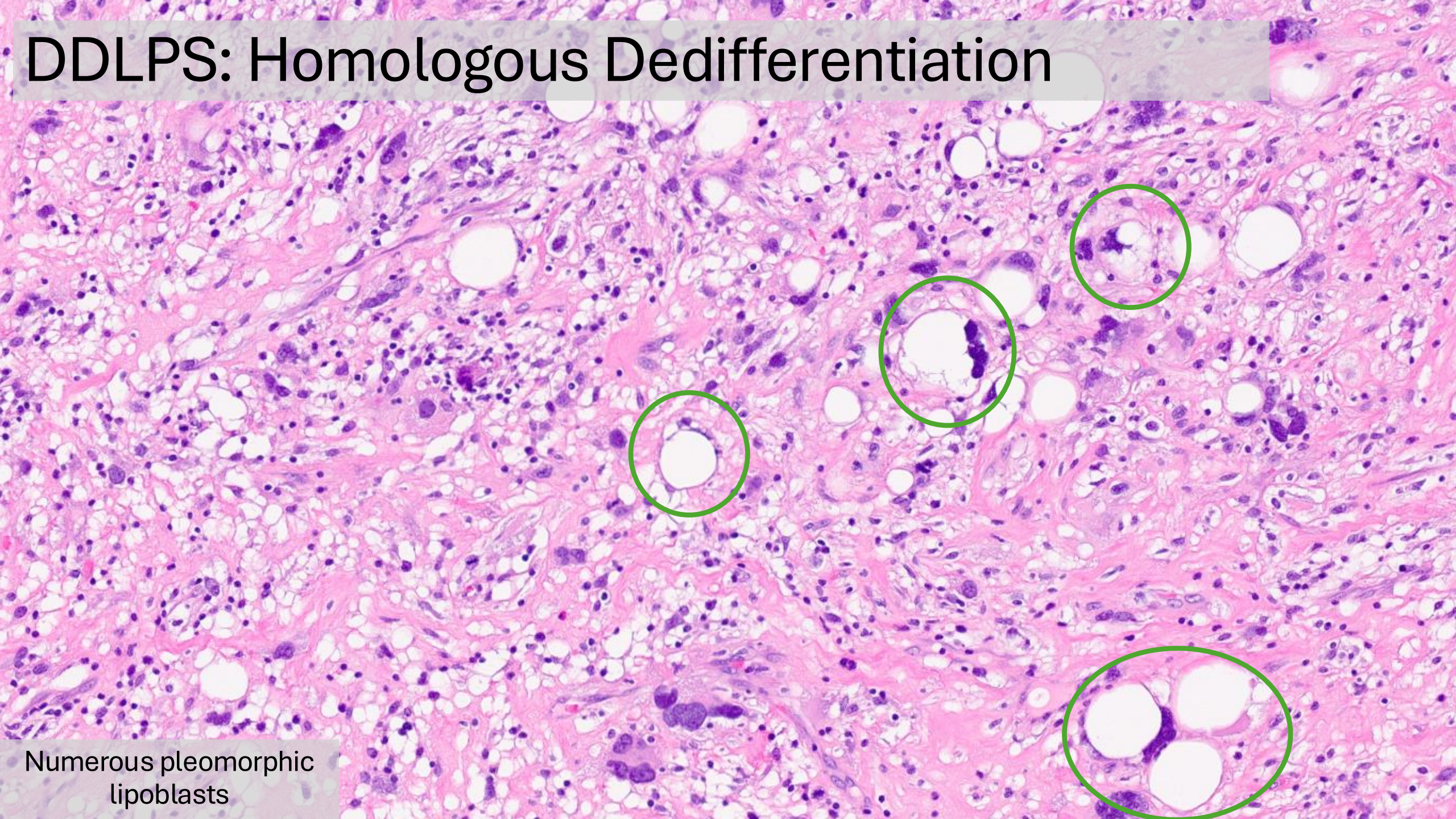


Background kidney

DDLPS: Osteosarcomatous Dedifferentiation



DDLPS: Homologous Dedifferentiation

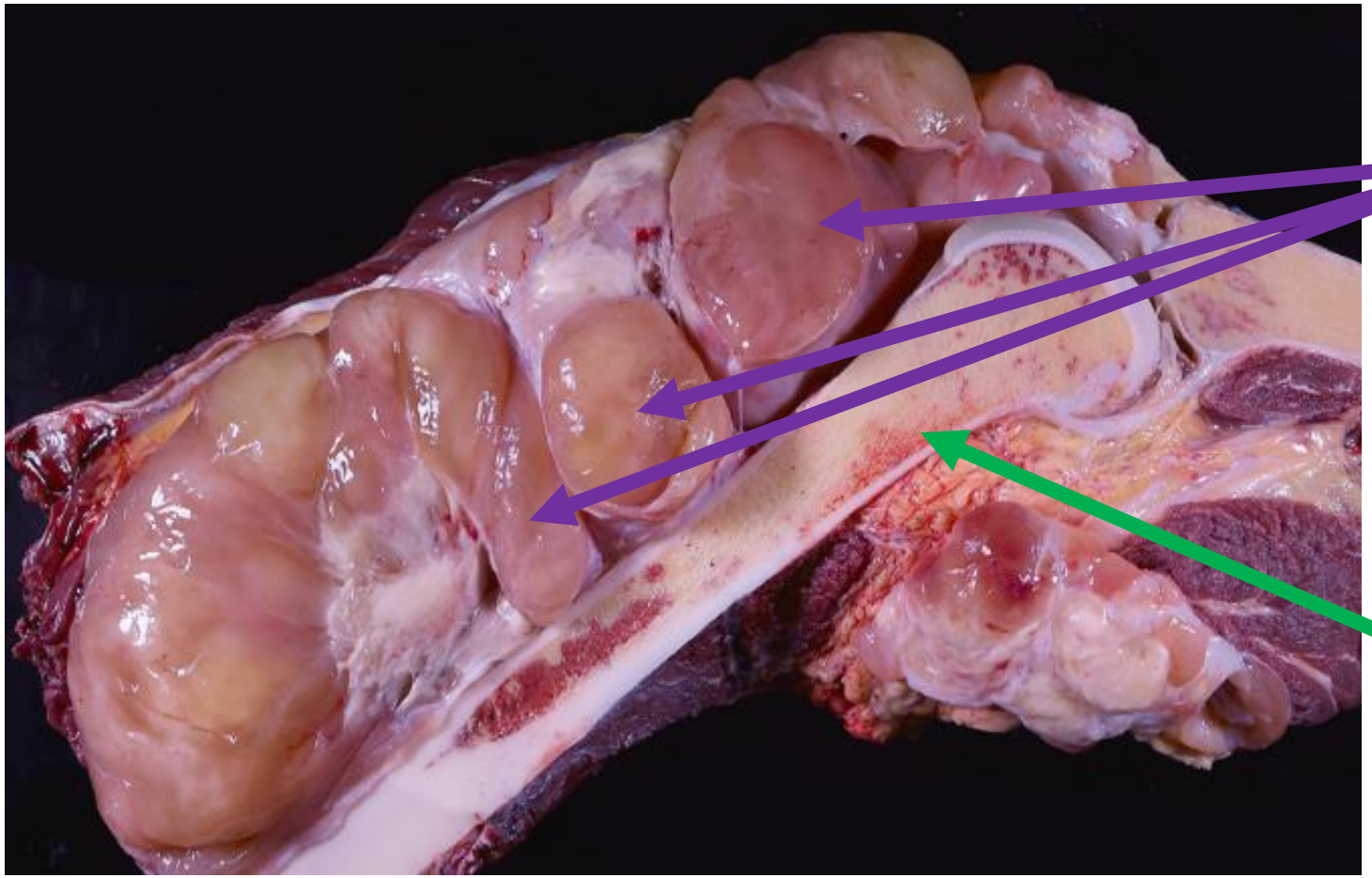


Numerous pleomorphic lipoblasts

Myxoid Liposarcoma (MLPS)

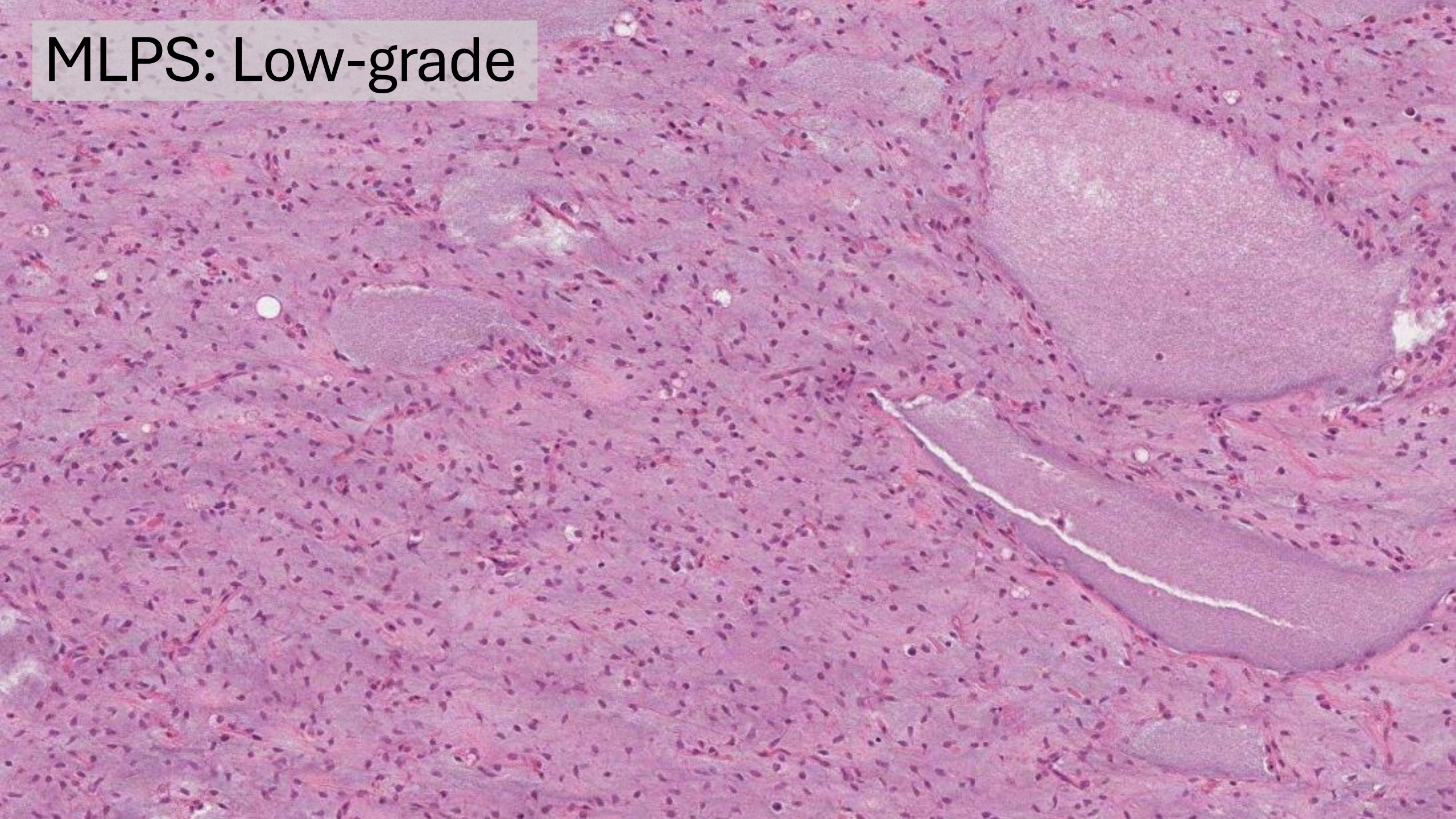
- Young to middle-aged adults
- Deep soft tissue of extremities
- Local recurrence: 30%
- Metastatic risk increases with presence of round cell component (high-grade MLPS)
  - >5% round cell considered high grade
- *FUS-DDIT3* t(12;16)
  - Rarely *EWSR1-DDIT3* t(12;22)

MLPS: Gross Features

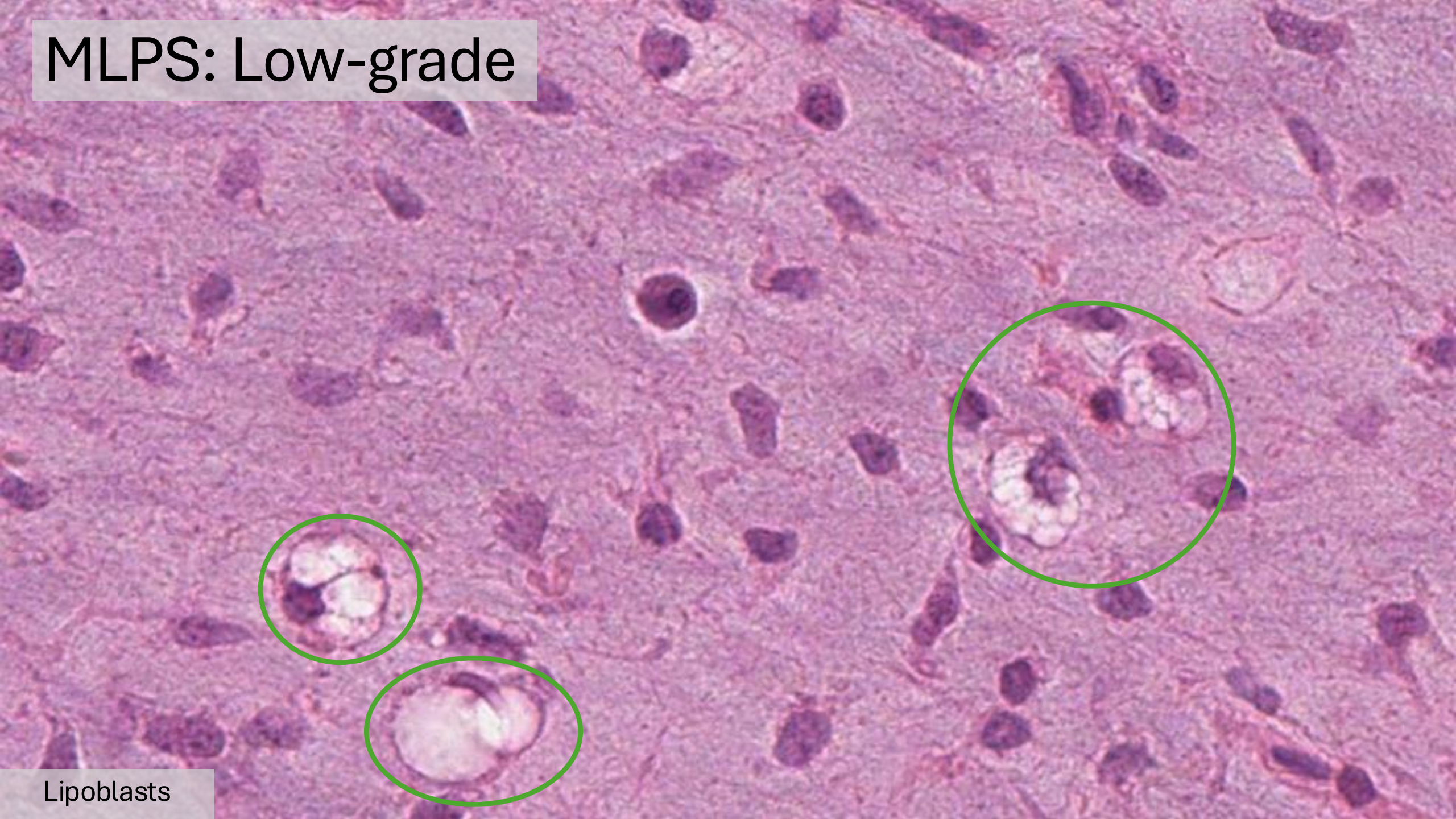


Enzinger and Weiss, 8th ed.

MLPS: Low-grade

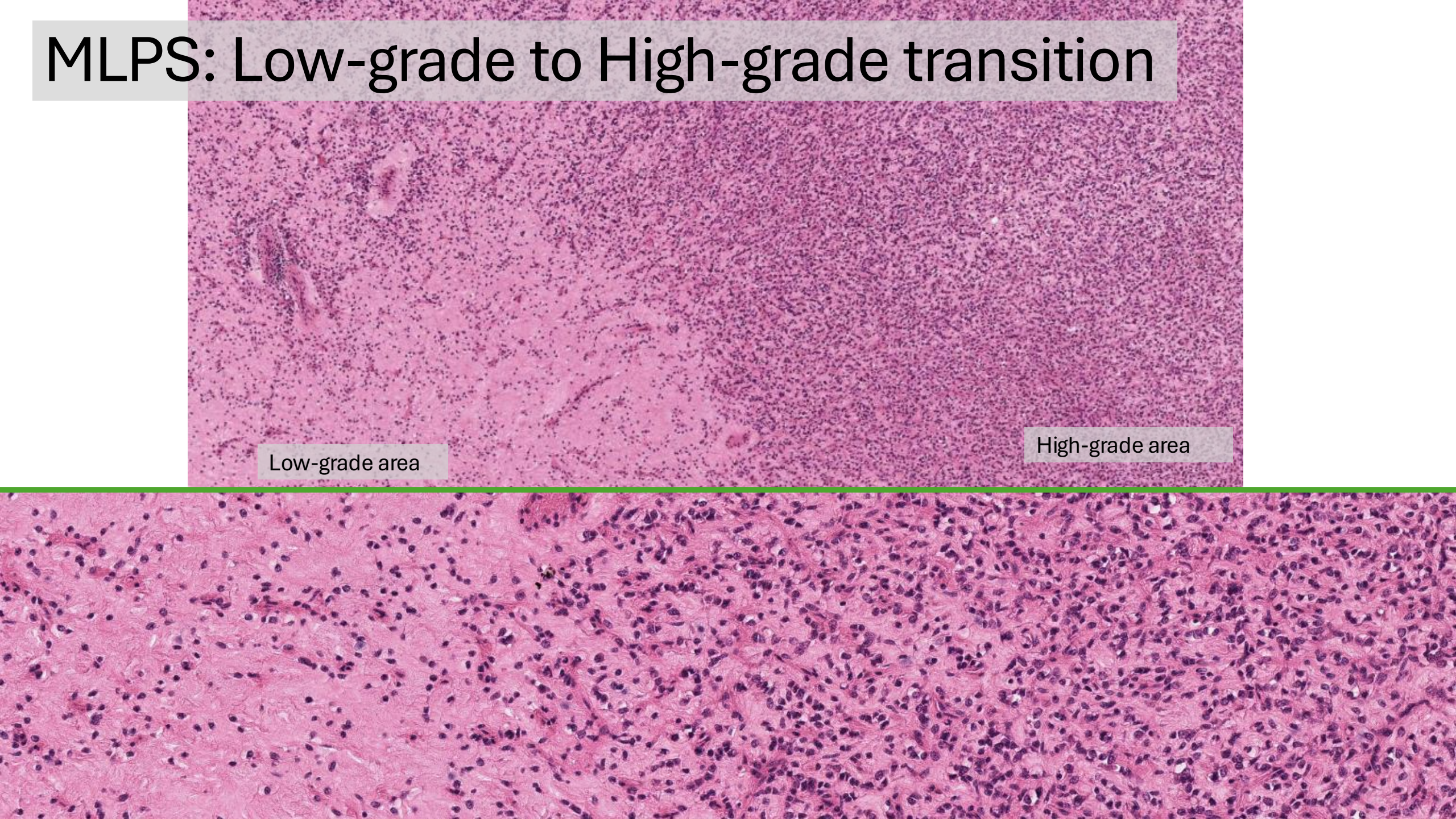


MLPS: Low-grade



Lipoblasts

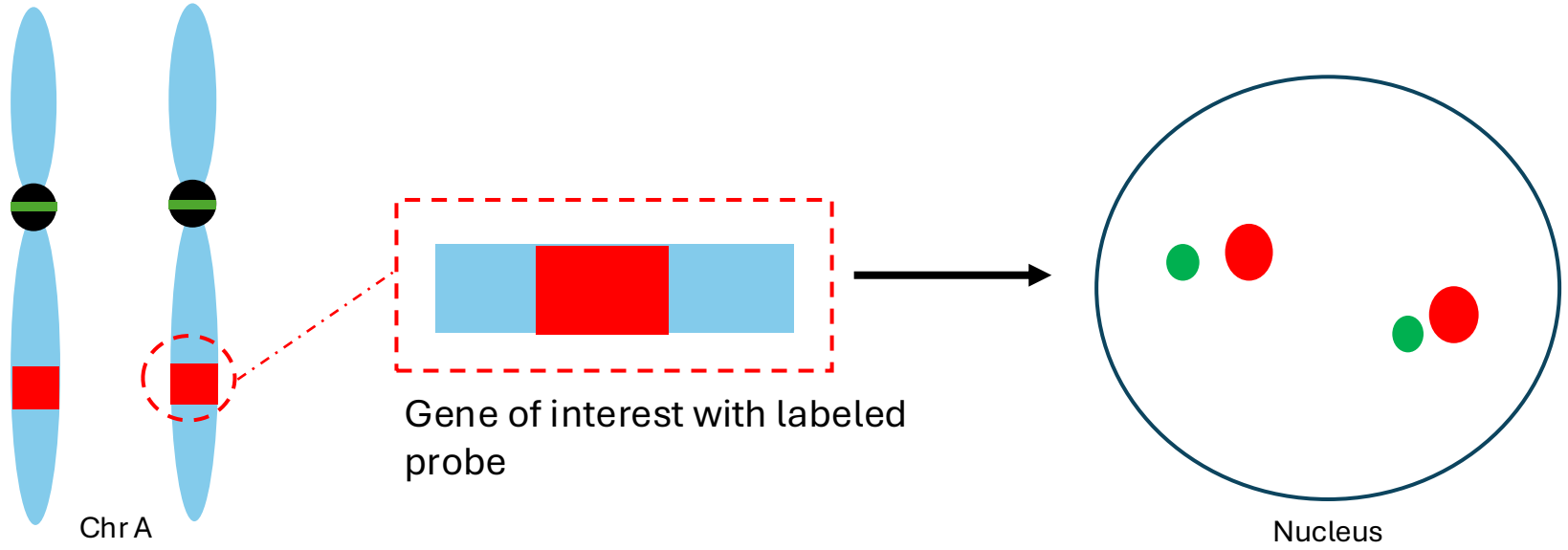
MLPS: Low-grade to High-grade transition



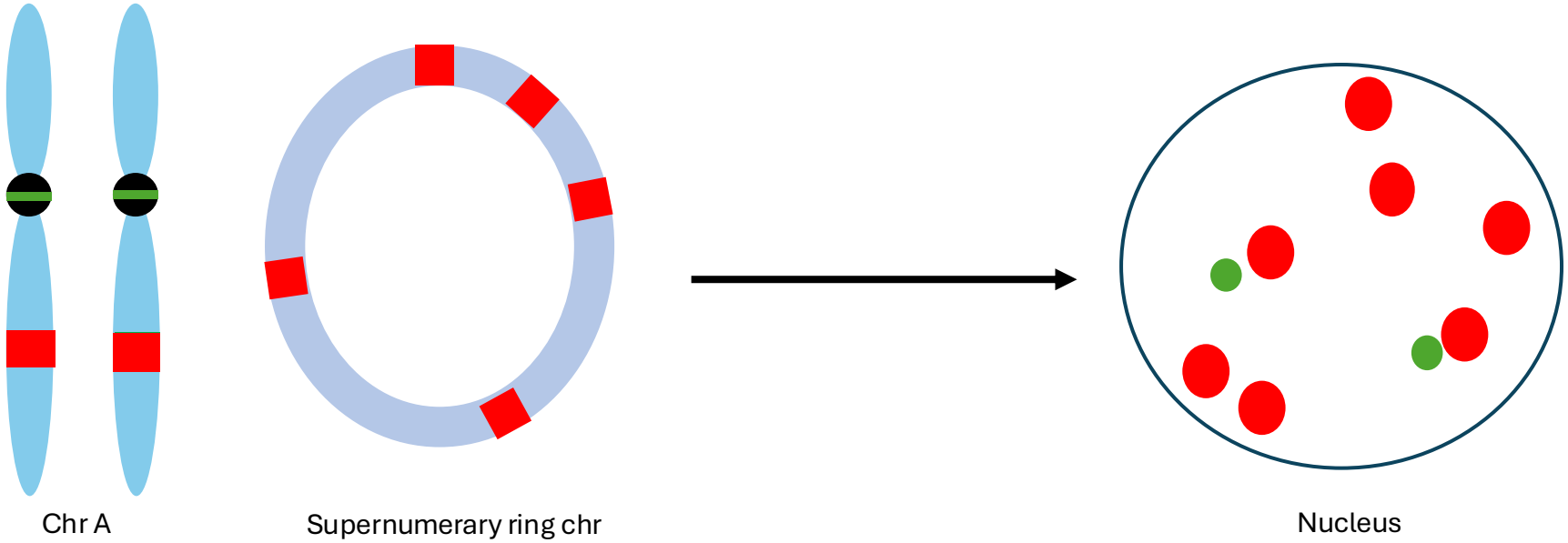
Types of Molecular Aberrations

- Mutations
  - DNA bases: substitutions, deletions, insertions
  - *KIT* mutations in GIST
- Rearrangement
  - Gene amplification: *MDM2* (ALT/WDLPS/DDLPS)
  - Gene deletions: *SMARCB1* (epithelioid sarcoma)
  - Gene translocations:
    - 1983 Ewing sarcoma: *EWSR1*
    - *DDIT3* (MLPS), *FUS, WT1*
- Complex karyotypes
  - Multiple chromosomal duplications, deletions, rearrangements
    - Undifferentiated pleomorphic sarcoma, leiomyosarcoma

Fluorescence in situ Hybridization (FISH): *MDM2* Amplification



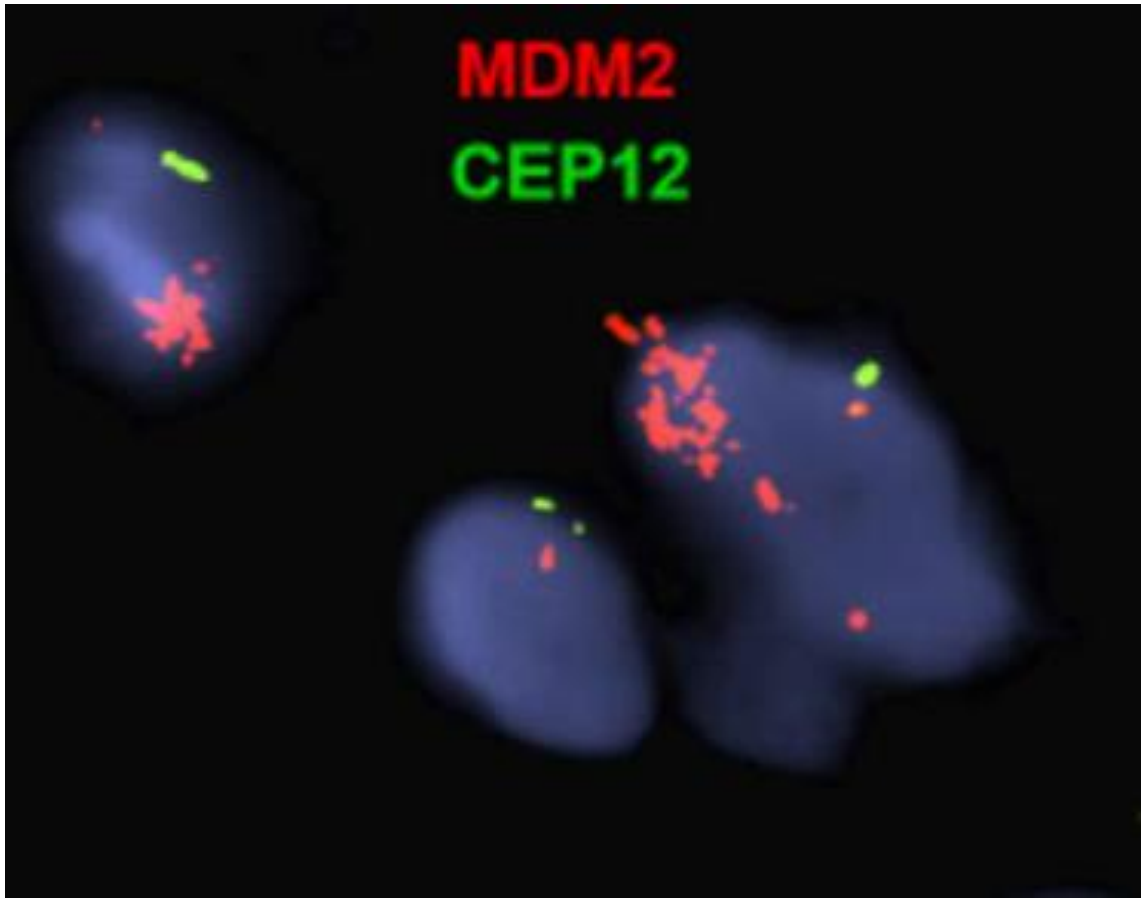
Normal copy numbers of both centromere and gene



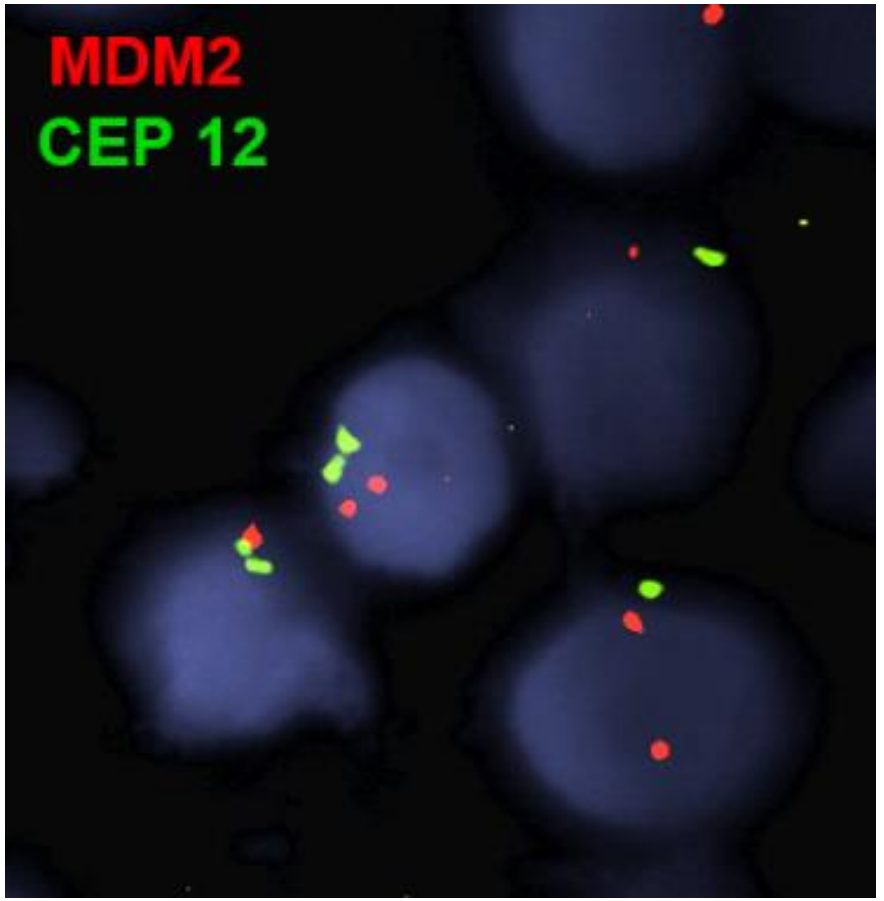
Gene/centromere ratio >2 demonstrates amplified gene

Time: 5-7 days

MDM2 FISH



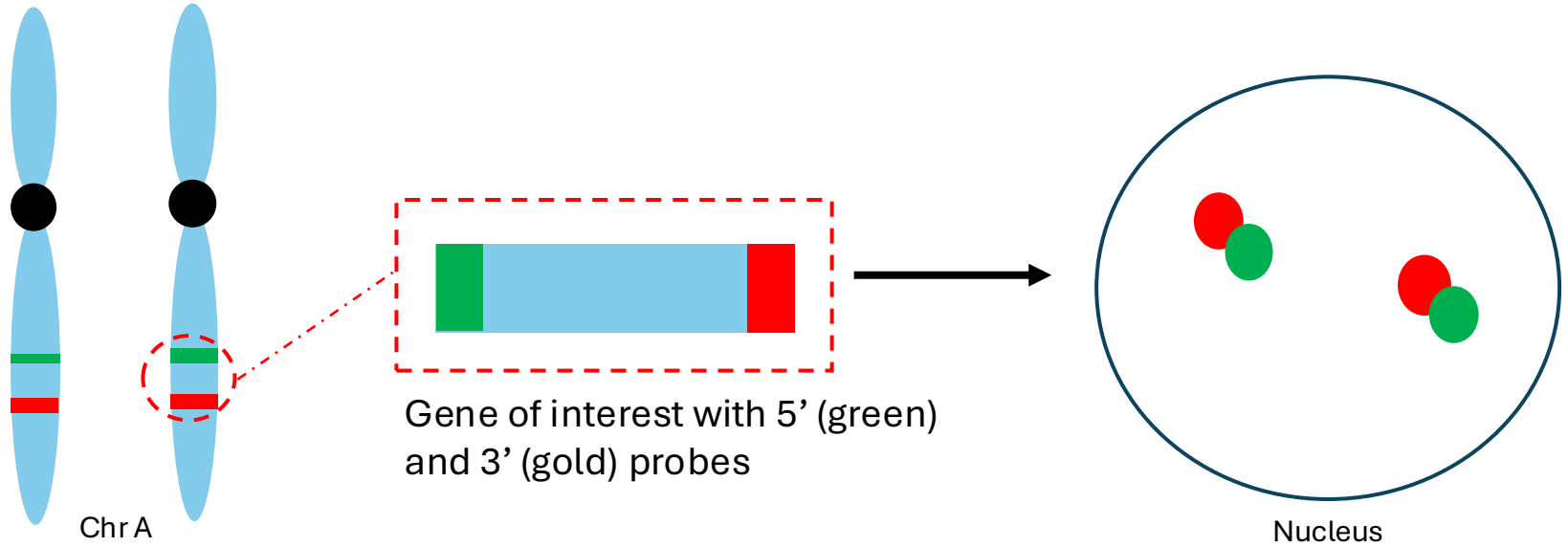
Amplified



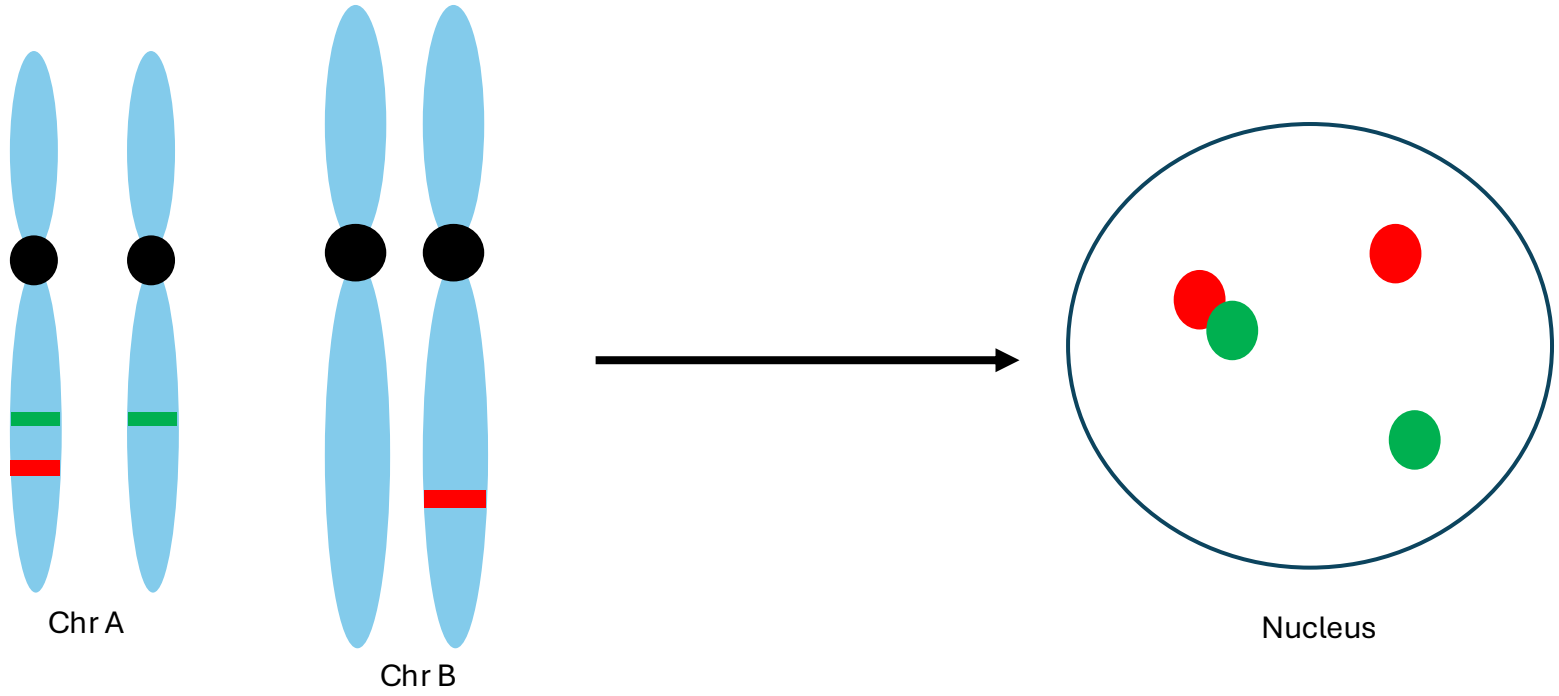
Not Amplified

Time: 5-7 days

Fluorescence in situ Hybridization (FISH): *DDIT3* Translocation



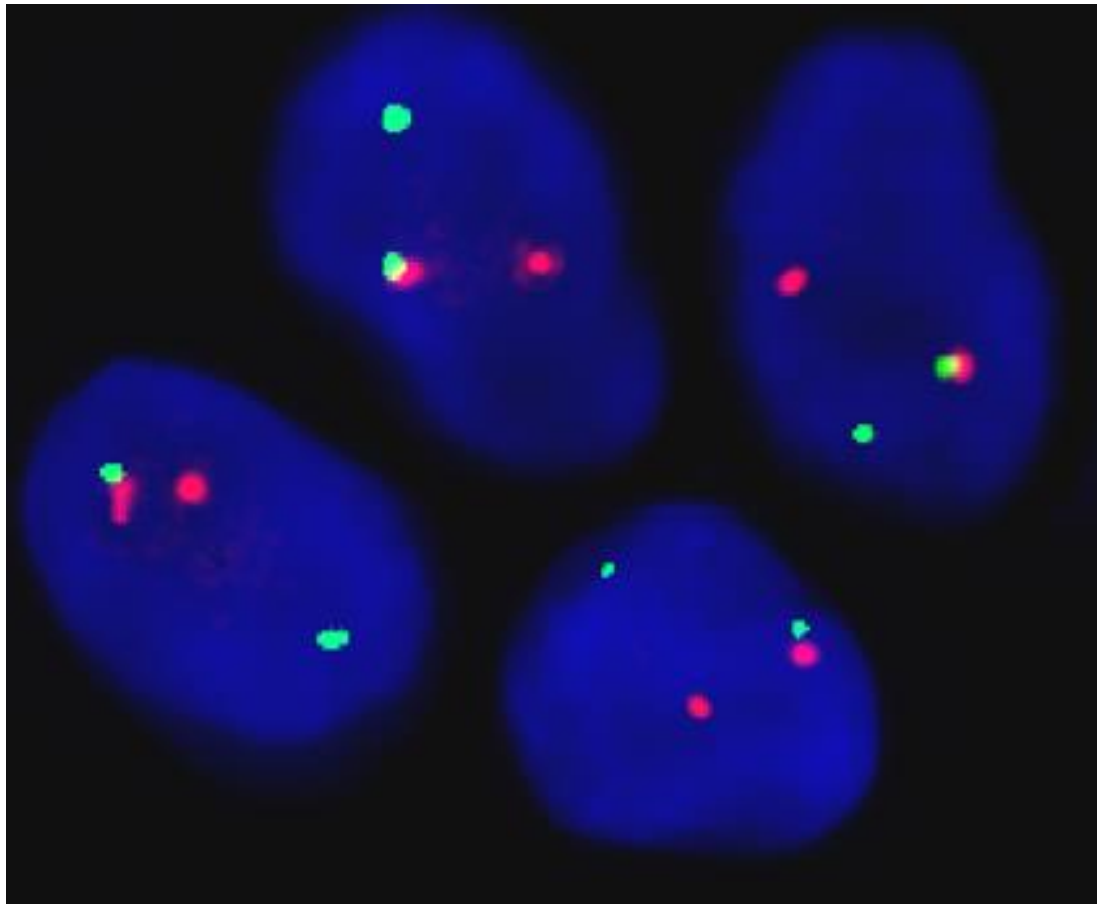
Two fused, normal signals



One fused signal and one split signal, indicating translocation

Time: 5-7 days

DDIT3 FISH

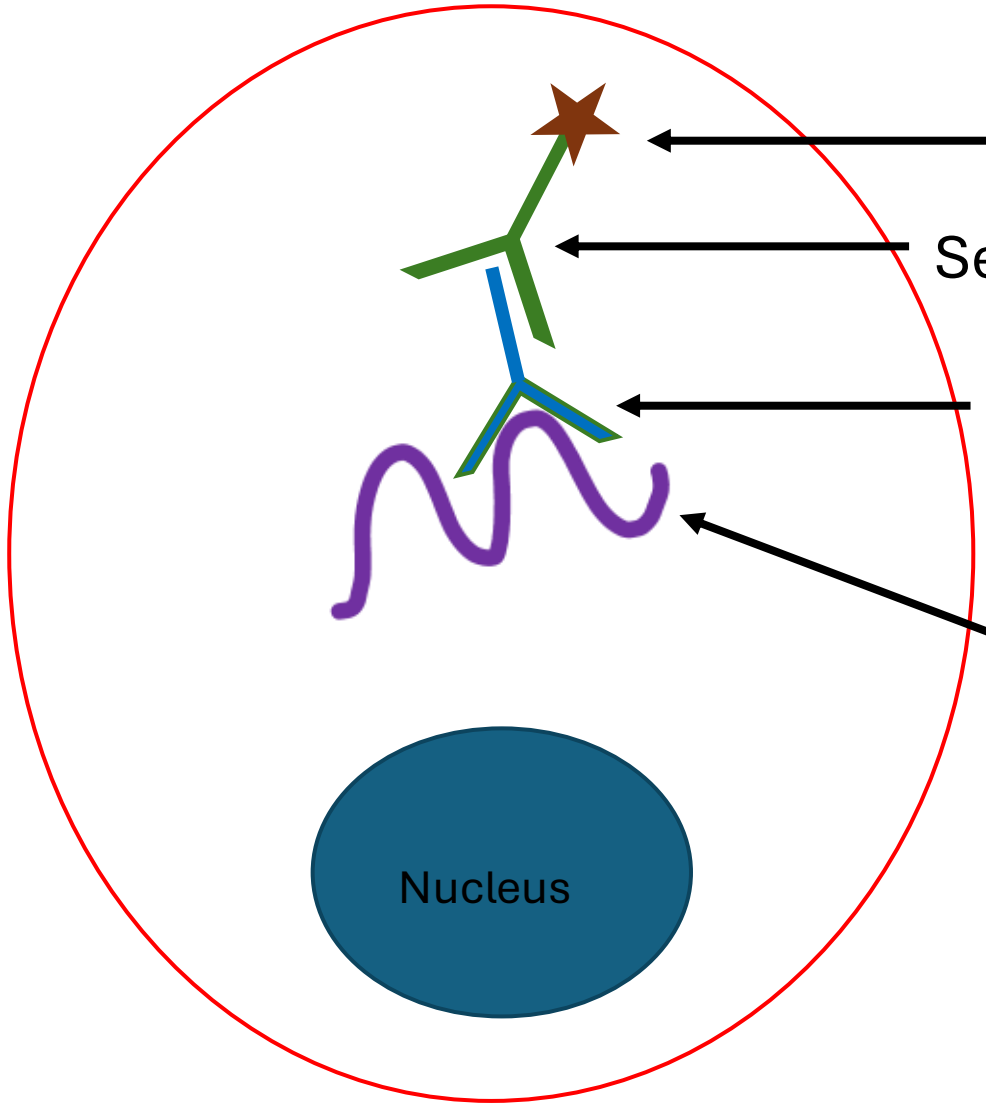


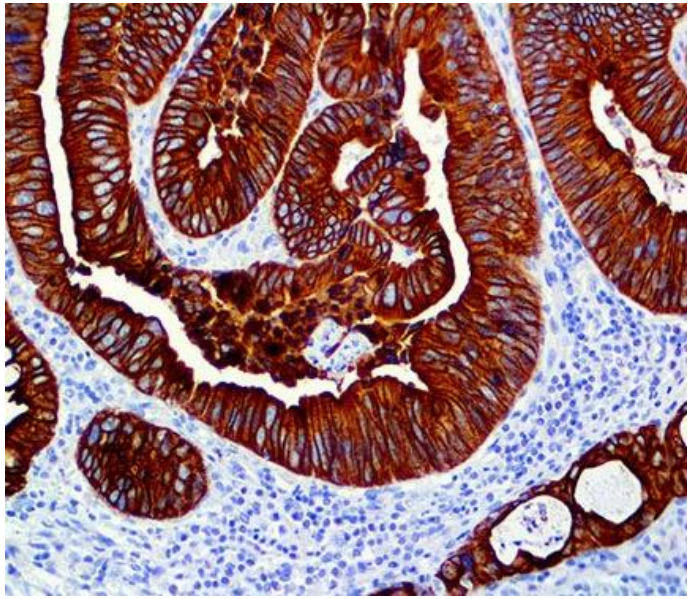
Narendra S, et al. *Diagn Mol Pathol*. 2011 Dec;20(4):218-24.

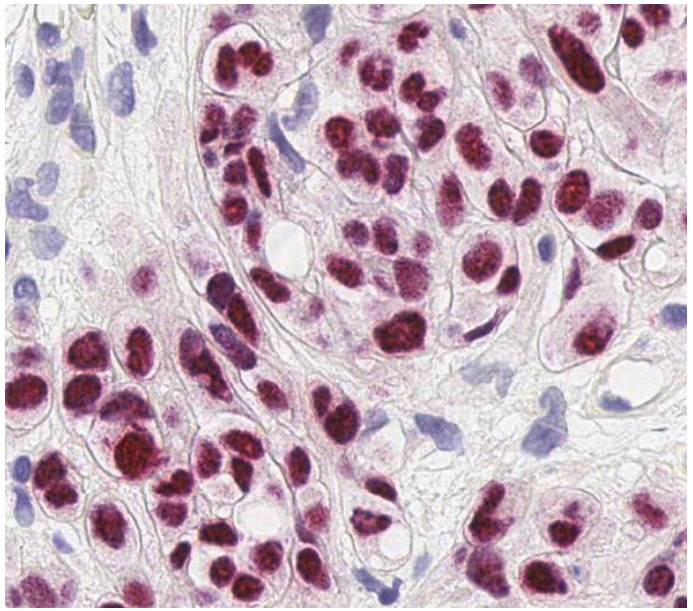
Luckily, we don’t have to rely just on FISH and have a more rapid test

Time: 5-7 days

Immunohistochemistry (IHC)

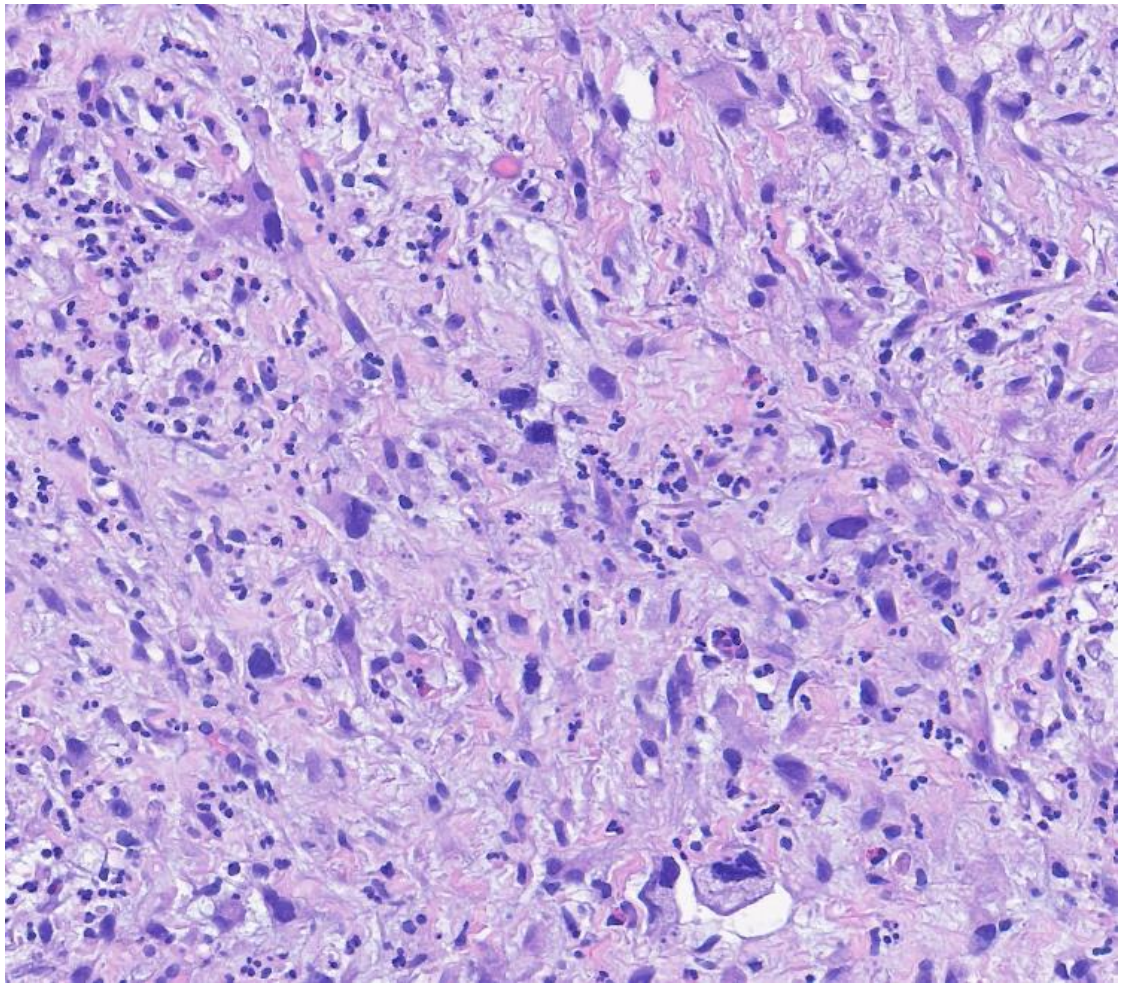


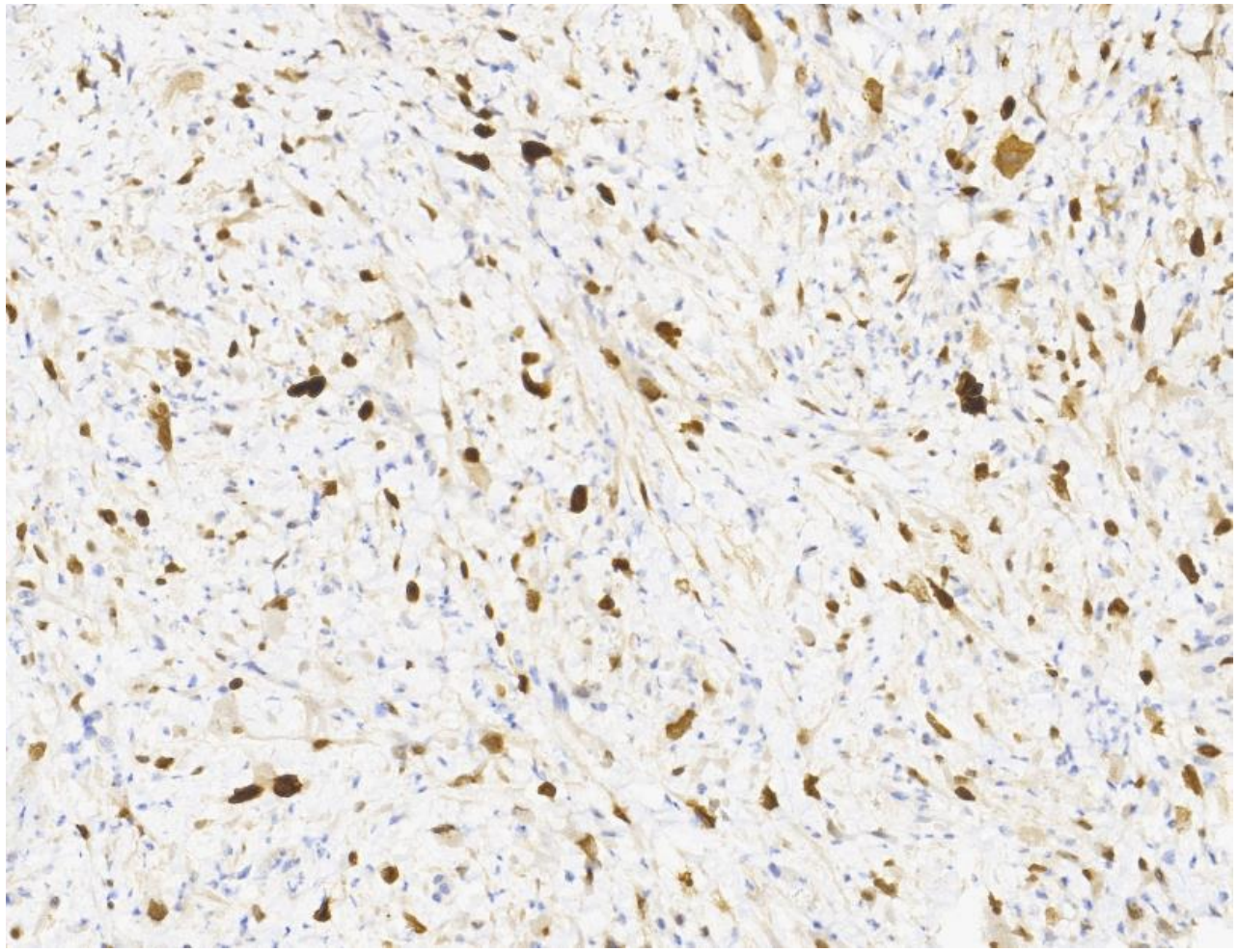




Time from H&E slides to IHC: 8-24 hours

Biopsy of Thigh Mass: MDM2 IHC





DDIT3 IHC works in same (nuclear) manner

Questions?

LIPOSARCOMA SUPPORT NETWORK

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