

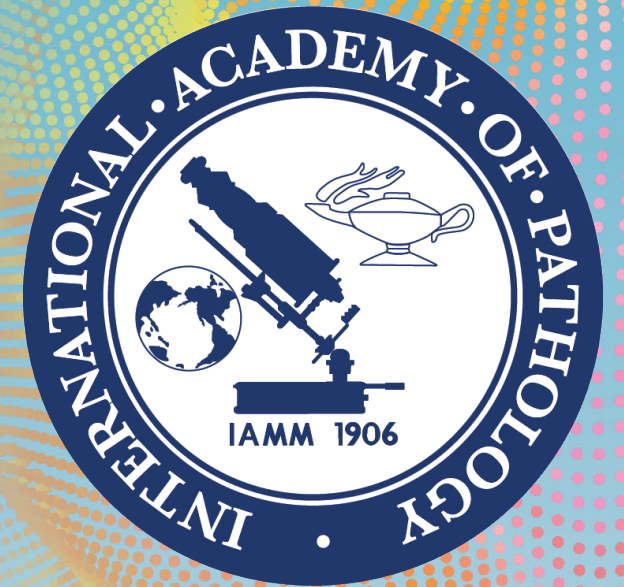
The robustness of grading pleural mesothelioma outside of specialist centres

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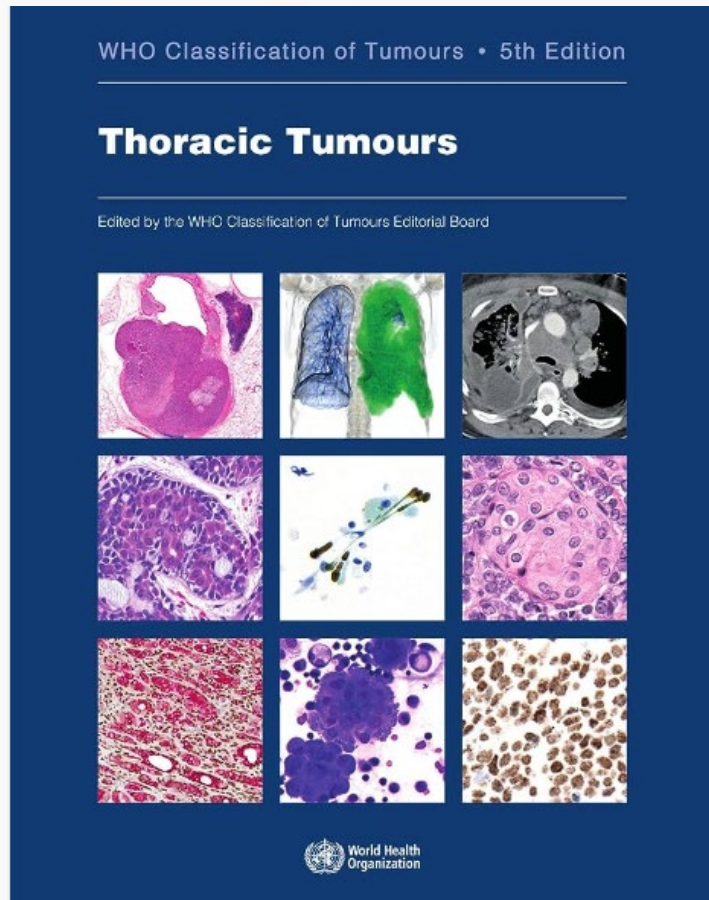
Flinders University

Adelaide, South Australia



Disclosure of Relevant Financial Relationships

No relevant financial relationships



Pleural mesothelioma an enigma

Significant changes:

- Nuclear grading system introduced
- Recommendation to record grade in diagnostic reports
- Grading incorporated in ICCR & USCAP guidelines on histological reporting




Nuclear grading in epithelioid mesothelioma

EURACAN/IASLC recommendations adopted by the WHO

	Nuclear grade	Grading method	Other prognostic factors
Kadota et al. 2012 (pleural)	Nuclear grade p < 0.001	3 tier	Nuclear atypia, Mitotic count
Rosen et al. 2018 (pleural)	Nuclear grade p < 0.0001	3 tier	Mitotic count, Nuclear atypia, Mitosis–Necrosis score, Necrosis
Zhang et al. 2020 (pleural)	Three-tier nuclear grade p < 0.001 Two-tier nuclear grade p = 0.001	3 tier 2 tier	Mitosis–Necrosis score
Bilecz et al. 2020 (pleural)	Three-tier nuclear grade p < 0.001	3 tier	Mitosis–Necrosis score
Paajanen et al. 2020 (pleural)	Nuclear grade p < 0.001	3 tier	Growth pattern
Forest et al. 2021 (pleural)	Tumor grading p < 0.001	2 tier	Predominant architectural pattern
Turk et al. 2022 (pleural)	Nuclear grade p < 0.001 Histopathological grade p=0.023	3 tier 2 tier	Severe atypia
Chapel et al. 2021 (peritoneal)	Nuclear grade p < 0.001	3 tier	
Pezzuto et al. 2021 (peritoneal)	Nuclear grade p=0.003	2 tier	p16 deletion
Benzerdjeb et al. 2021 (peritoneal)	Nuclear grade p<0.001 Combined grade p<0.001	3 tier 3 tier	Necrosis, Mitotic counts

Authors	Grading method	Multiparametric approaches
Pelosi et al. 2018 (pleural)	Pathologic Grading System (PGS)	includes mitoses, necrosis, histological subtype, & Ki67
Fuchs et al. (pleural)	Mesothelioma Weighted Grading Scheme	includes atypia, mitoses, necrosis, histological subtype, age & BAP1 (IHC) results

Reliability of assessing morphologic features with prognostic significance in cytology specimens of epithelioid diffuse pleural mesothelioma and implications for cytopathology reporting

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Francis M. Bodd MS² | Michael D. Offin MD^{4,5}  | Natasha Rekhtman MD, PhD² |
Marjorie G. Zauderer MD^{4,5} | William D. Travis MD² | Prasad S. Adusumilli MD¹  |
Jennifer L. Sauter MD² 

WHO Tumour grade

Nuclear Atypia Score: mild (1), moderate (2), severe (3)

Mitotic Count: 0-1/2 sq mm (1), 2-4 mitosis/2 sq mm (2), >5/2 sq mm (3)

Necrosis: present or absent

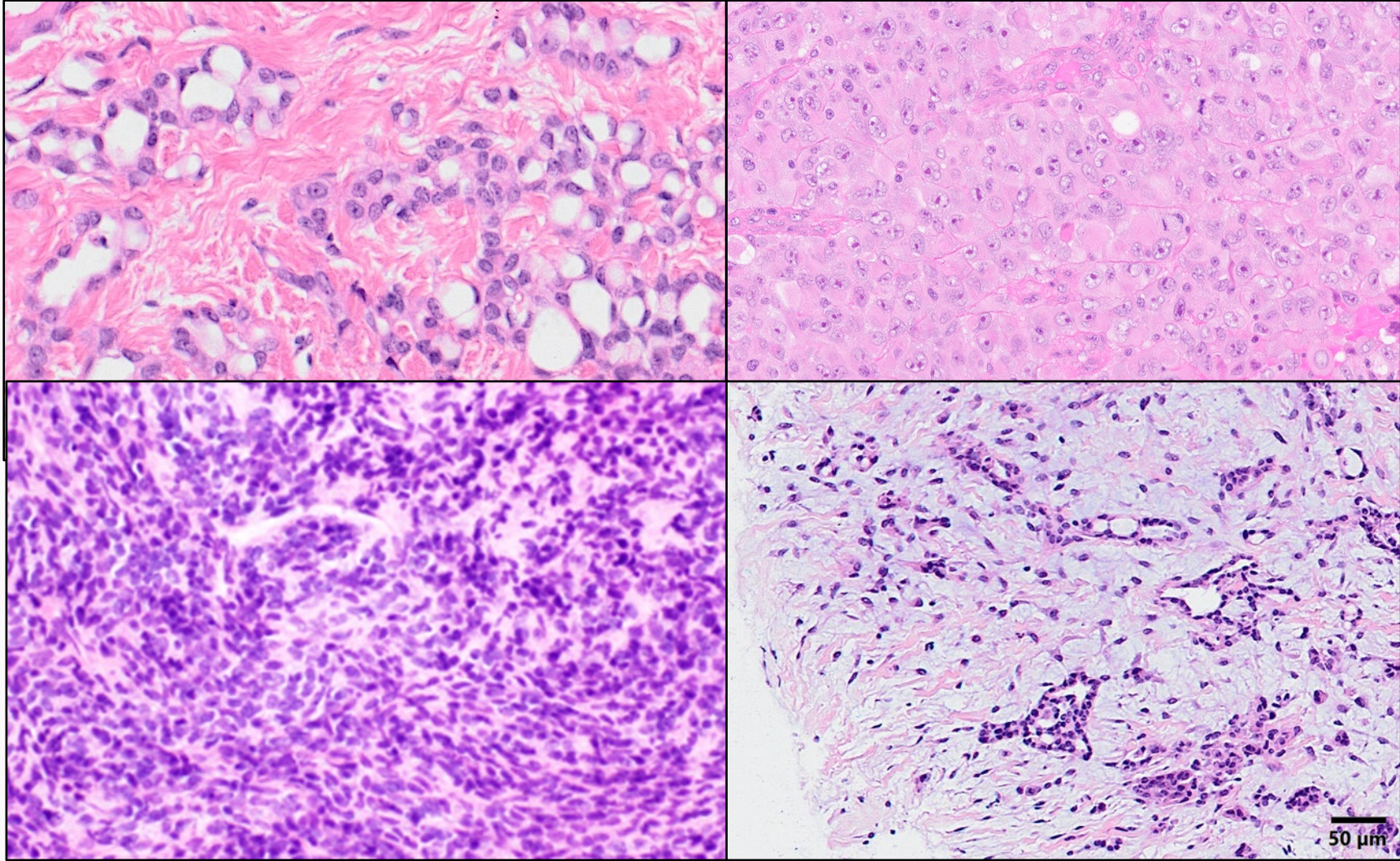
3-tier Nuclear Grade:

- Sum of nuclear atypia and mitotic count
 - grade I (2-3), grade II (4-5) and grade III (6)
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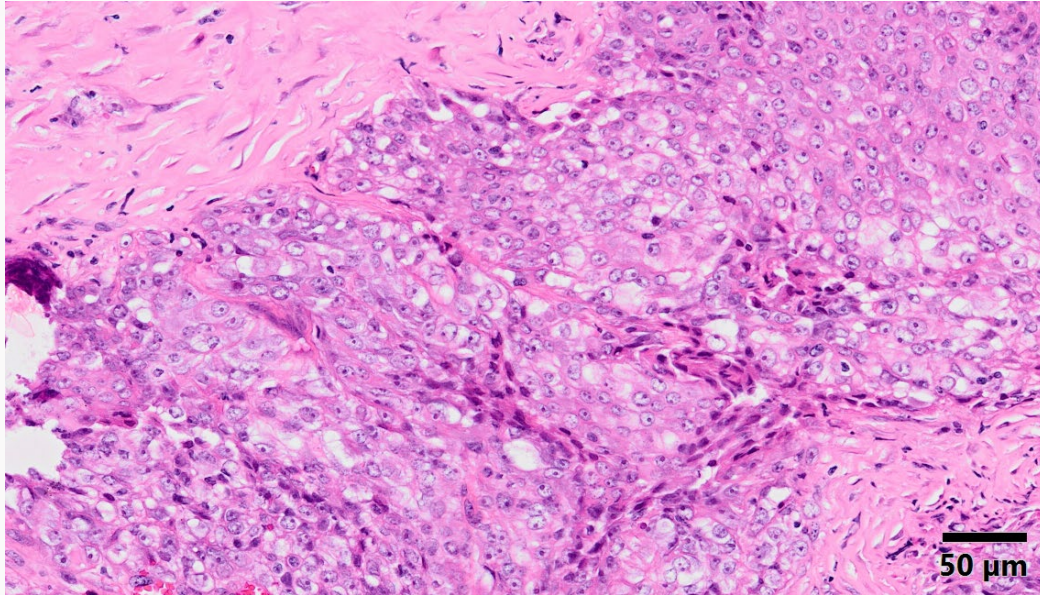
2-tier Grade:

- **Low grade:** grade I and II tumours without necrosis.
 - **High grade:** grade II with necrosis and grade III with or without necrosis.
-

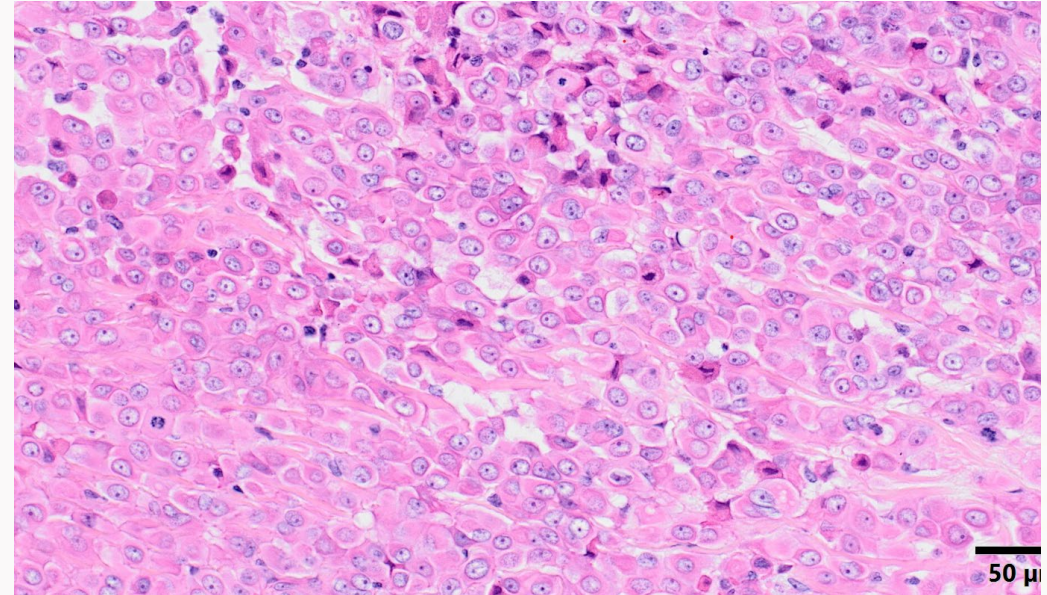
Pattern/features	Favourable	Unfavourable
Architectural patterns <ul style="list-style-type: none"> • Tubulolopapillary • Trabecular • Adenomatoid • Solid • Micropapillary 	Architectural patterns <ul style="list-style-type: none"> • Tubulopapillary • Trabecular • Adenomatoid 	Architectural patterns <ul style="list-style-type: none"> • Solid (> 50%) • Micropapillary
Cytological features <ul style="list-style-type: none"> • Rhabdoid • Deciduoid • Small-cell • Clear-cell • Signet ring • Lymphohistiocytoid • Pleomorphic 	Cytological features <ul style="list-style-type: none"> • Lymphohistiocytoid • Low nuclear grade 	Cytological features <ul style="list-style-type: none"> • Rhabdoid • Pleomorphic • High nuclear grade
Stromal features <ul style="list-style-type: none"> • Myxoid 	Stromal features Myxoid (if predominant, i.e., when > 50% of tumour with < 50% solid pattern contains myxoid stroma)	Stromal features Necrosis (included in grading)



Solid



Solid pattern and Deciduoid features



Two tier grading system incorporated in the WHO classification of tumours (2021)

Box 2.01 Nuclear grading of pleural diffuse epithelioid mesothelioma

Nuclear grade:

Nuclear atypia score: _____ 1 for mild, 2 for moderate, 3 for severe

Mitotic count score: _____ 1 for low (≤ 1 mitosis/ 2 mm^2), 2 for intermediate (2–4 mitoses/ 2 mm^2), 3 for high (≥ 5 mitoses/ 2 mm^2)

Sum: _____ 2 or 3 = nuclear grade I, 4 or 5 = nuclear grade II, 6 = nuclear grade III

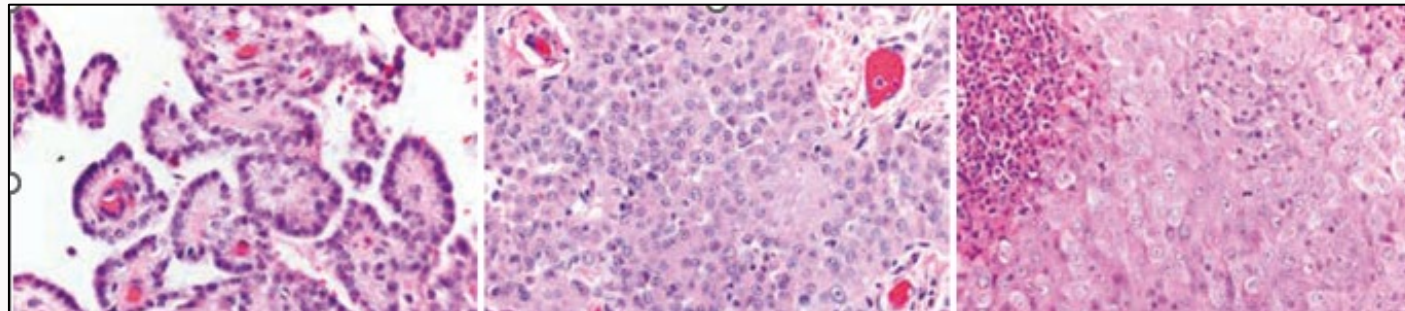
Necrosis: present/absent

Overall tumour grade:

Low grade = nuclear grades I and II without necrosis

High grade = nuclear grade II with necrosis, nuclear grade III with or without necrosis

From the WHO classification of thoracic tumours (2021)



Examples of nuclear atypia scores 1-3 in epithelioid mesothelioma

Methods

50 Epithelioid mesothelioma

3-tier nuclear grade	2-tier overall tumour grade
Grade I=8	Low grade=32
Grade II=32	High grade=18
Grade III=10	

Predominantly tubulopapillary, trabecular or both
2 deciduoid, 3 myxoid stroma, 3 solid, 2 small cell & 1 pleomorphic

Survey – RCPA, IMiG, PPS on RCPAQAP (& video link)
Slides scanned on OlympusVS200
Slides viewed on SectraUniview
Anonymous responses

Analysis – Consensus scores
Weighted kappa and Accuracy

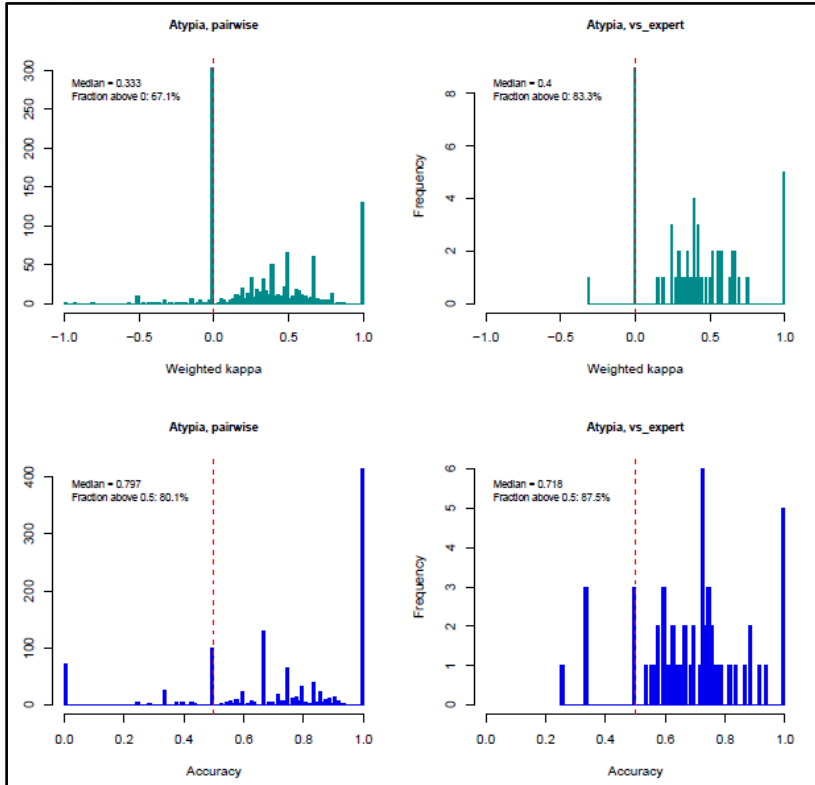
$$\text{Accuracy} = \frac{\text{TP} + \text{TN}}{\text{TP} + \text{TN} + \text{FP} + \text{FN}}$$

Agreement with expert pathologist's scores and grading 50 epithelioid mesothelioma

	Agreement	%
Atypia	35/50	70
Mitoses	28/50	56
Nuclear grade (3-tier)	36/50	72
Necrosis	42/50	84
Overall grade (2-tier)	45/50	90

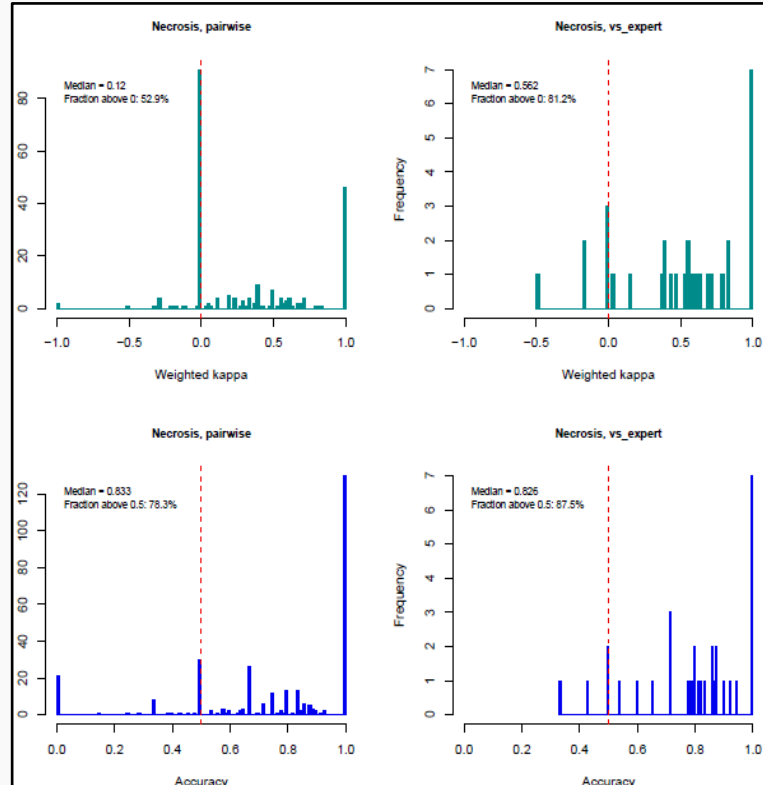
Weighted kappa and Accuracy

ATYPIA



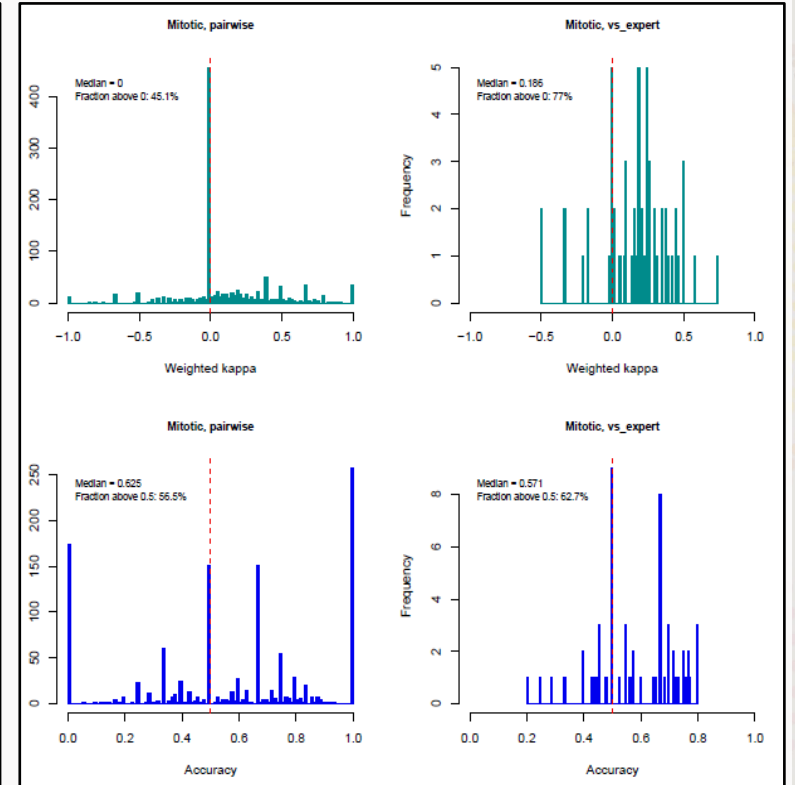
Median 0.718

NECROSIS



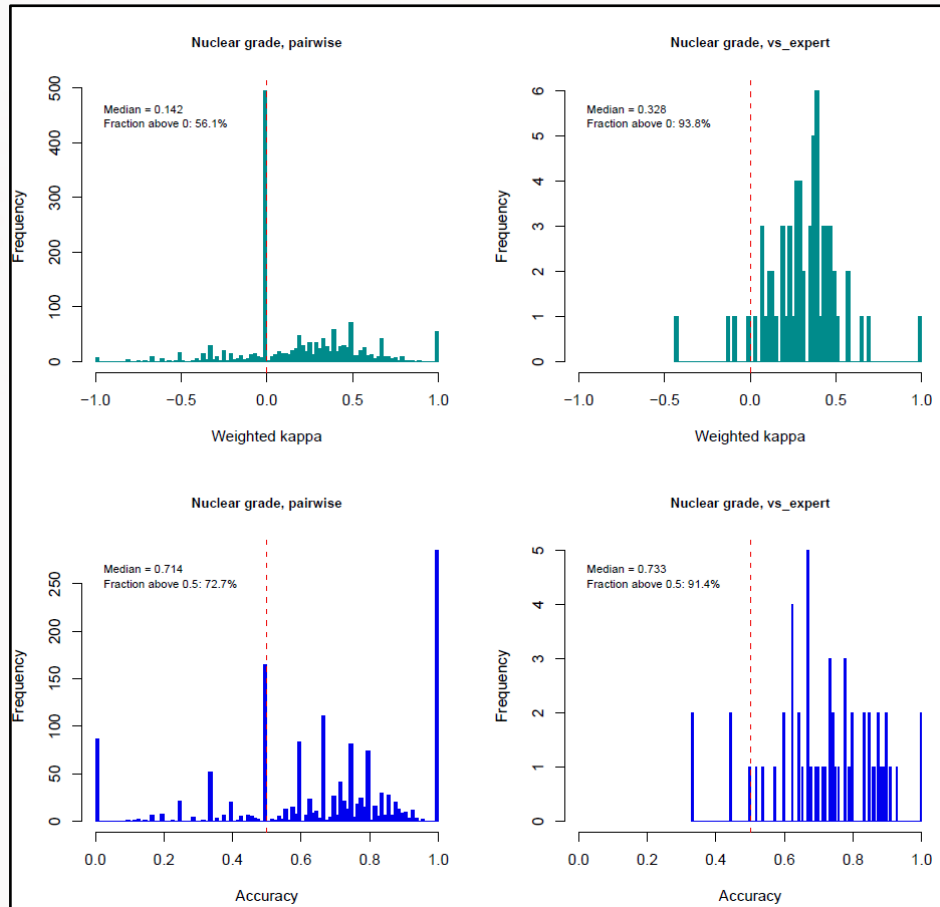
Median 0.826

MITOTIC COUNTS



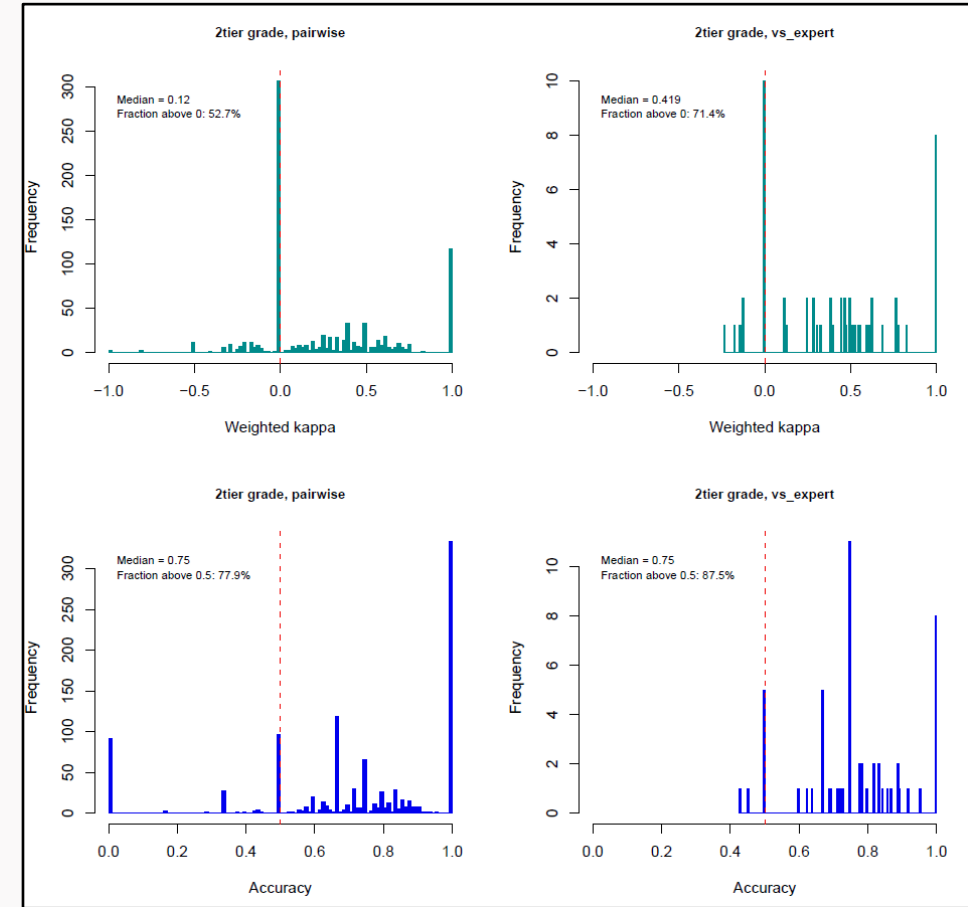
Median 0.571

3-TIER NUCLEAR GRADE



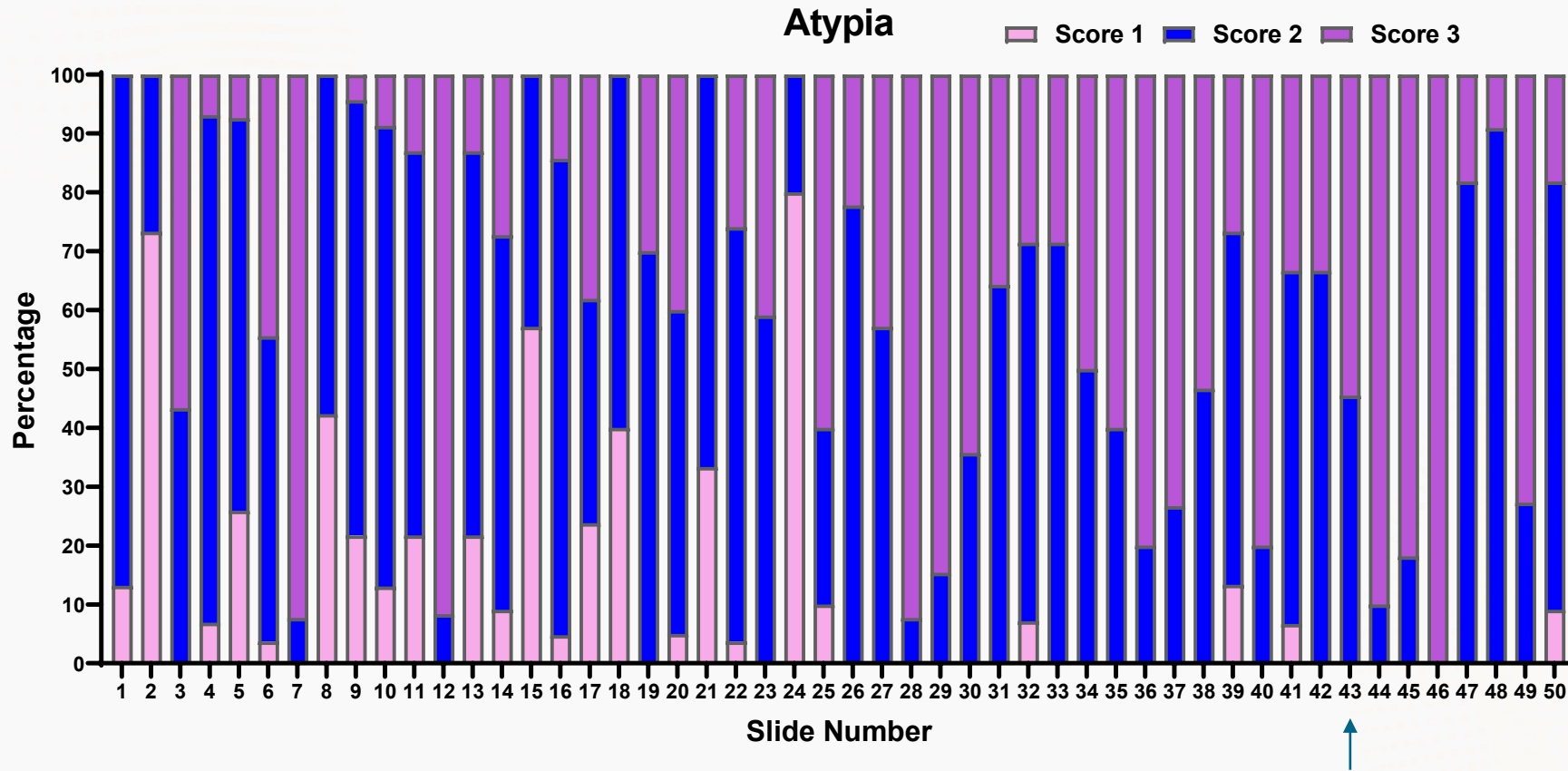
Median 0.733

2-TIER NUCLEAR GRADE

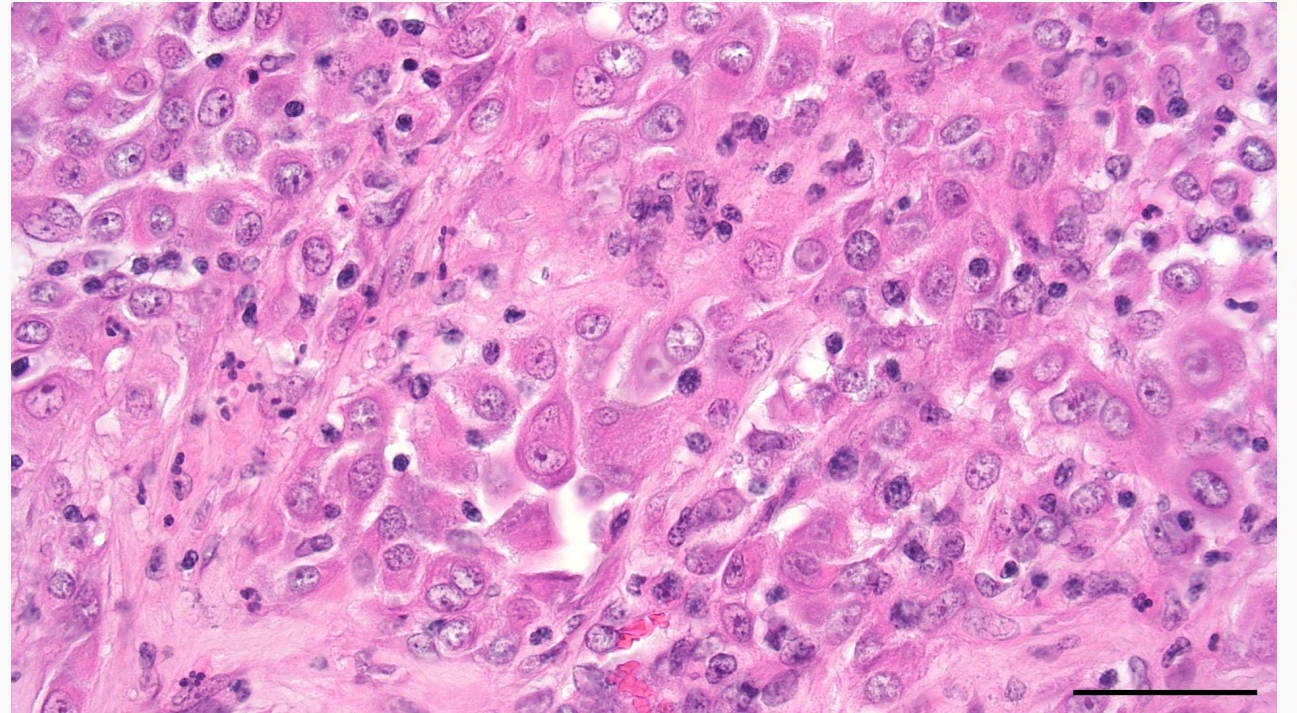
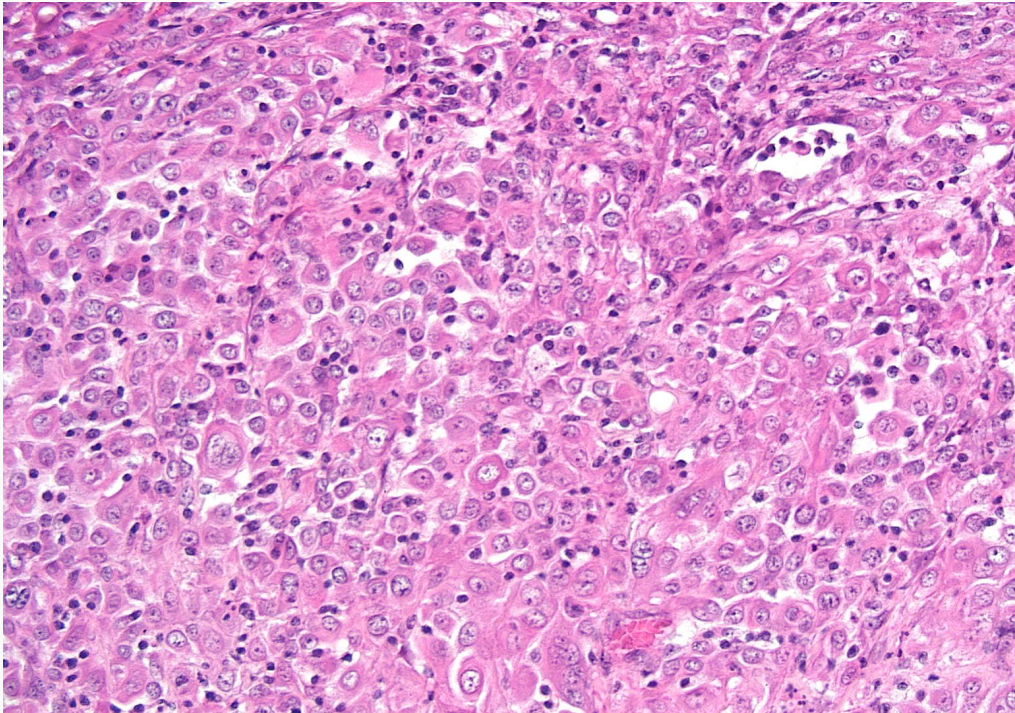


Median 0.75

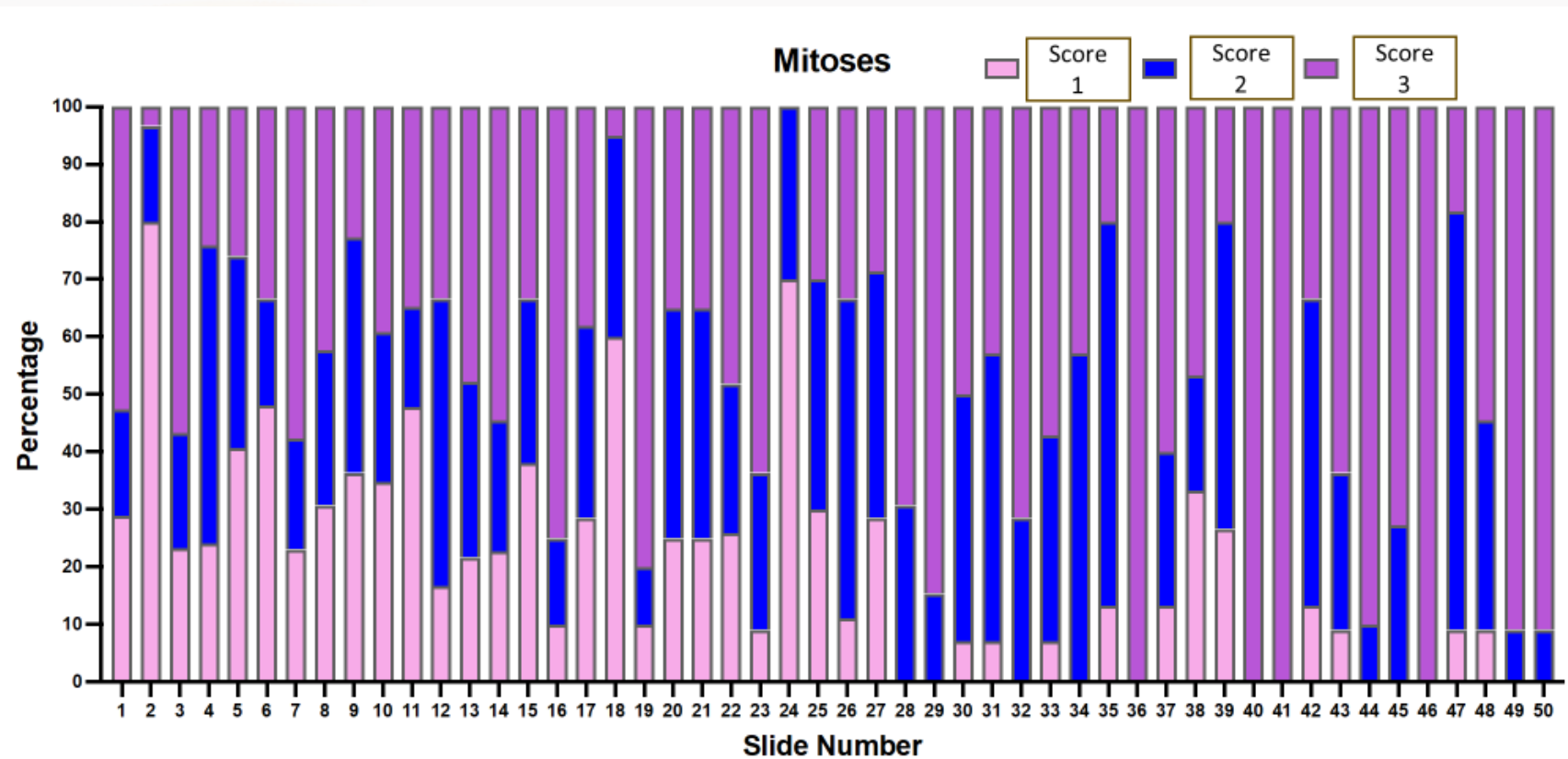
Scores on Atypia



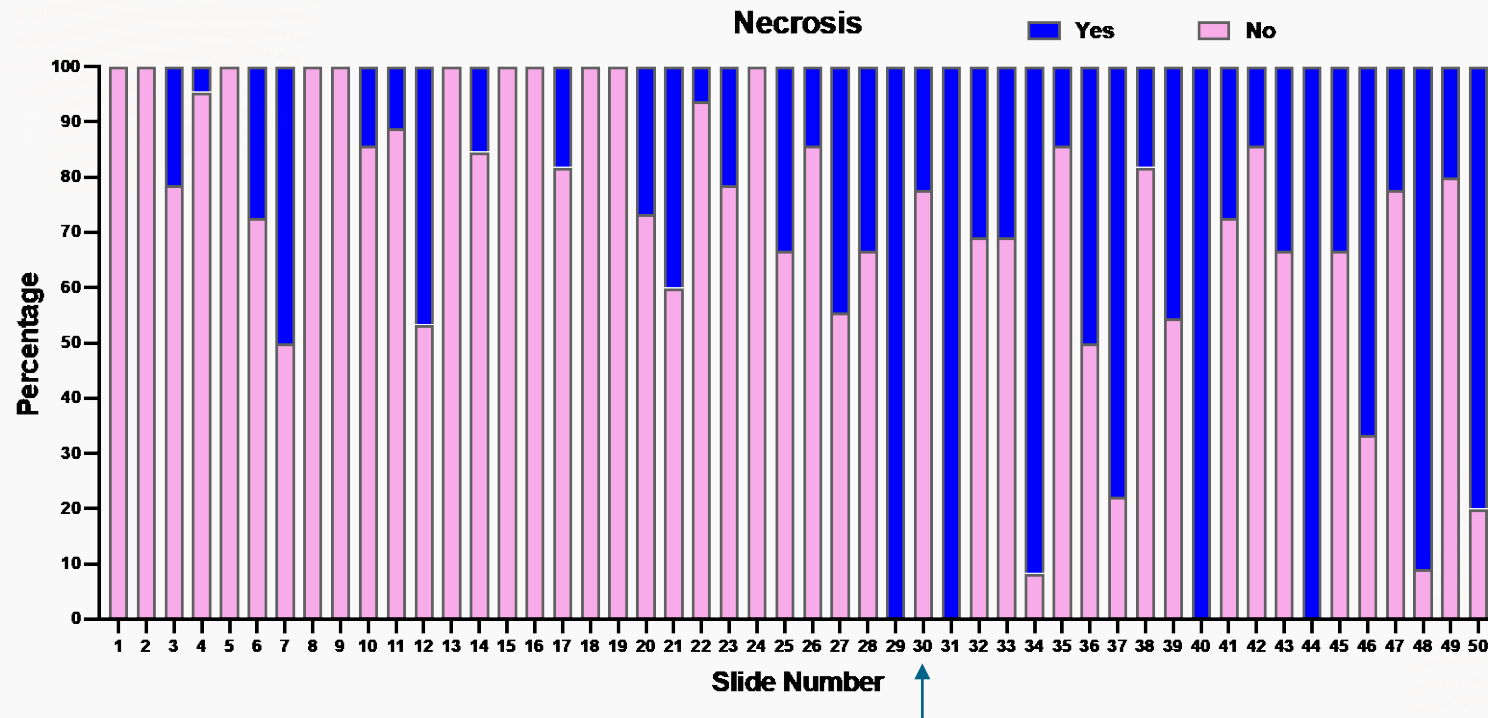
Discordance between Atypia scores 2 and 3 (55 vs 45%)



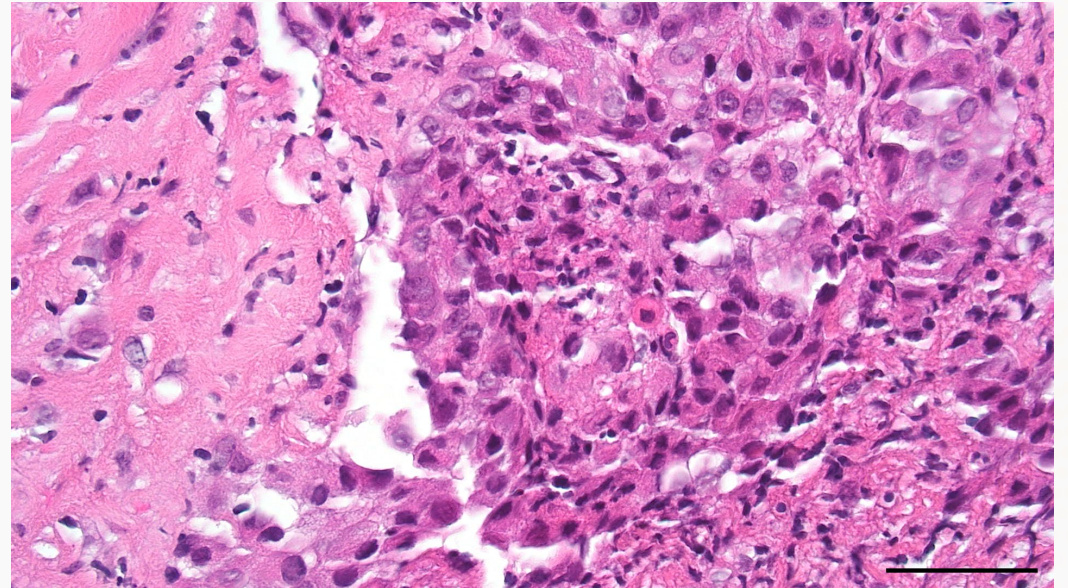
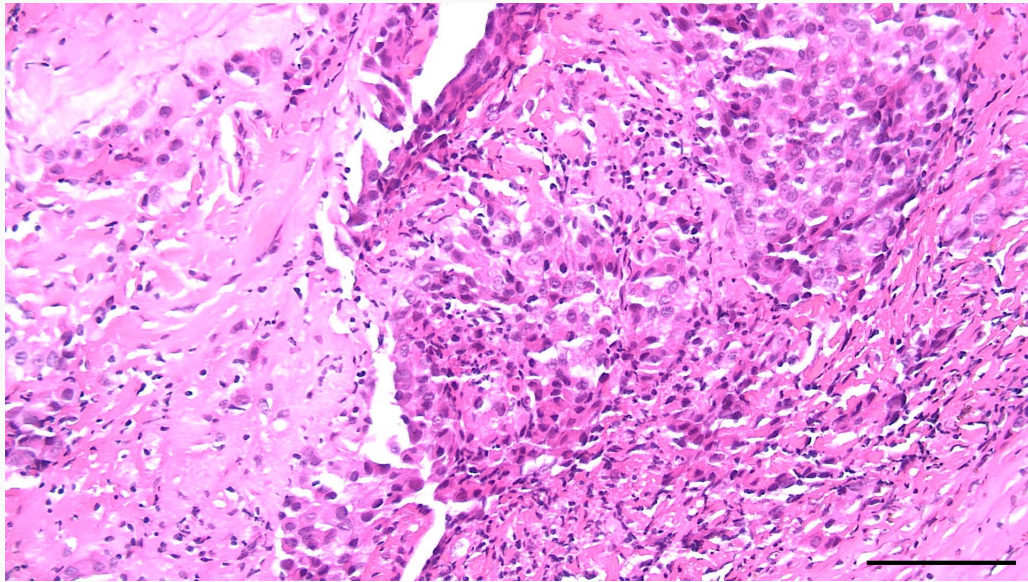
Scores on Mitotic counts



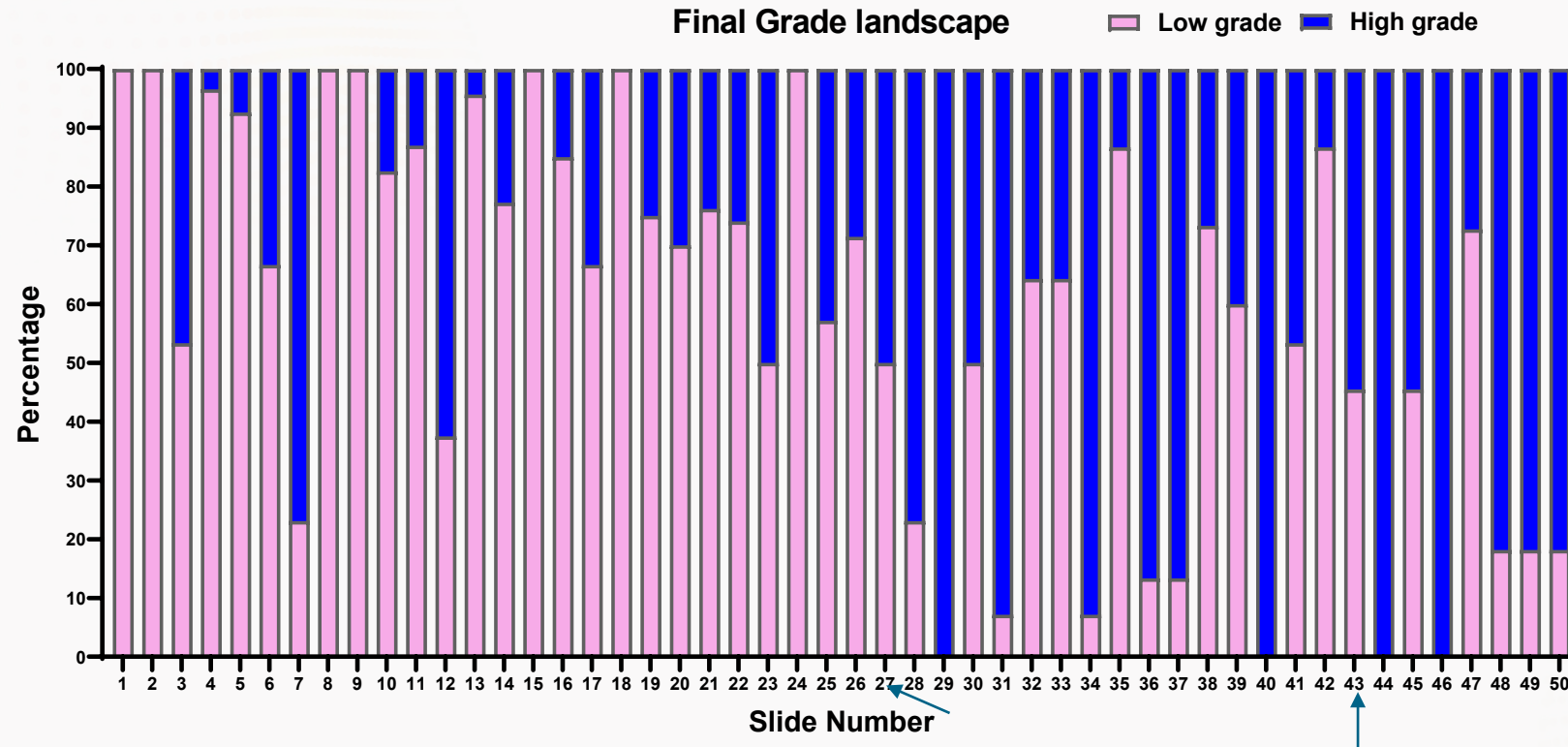
Scores on Necrosis



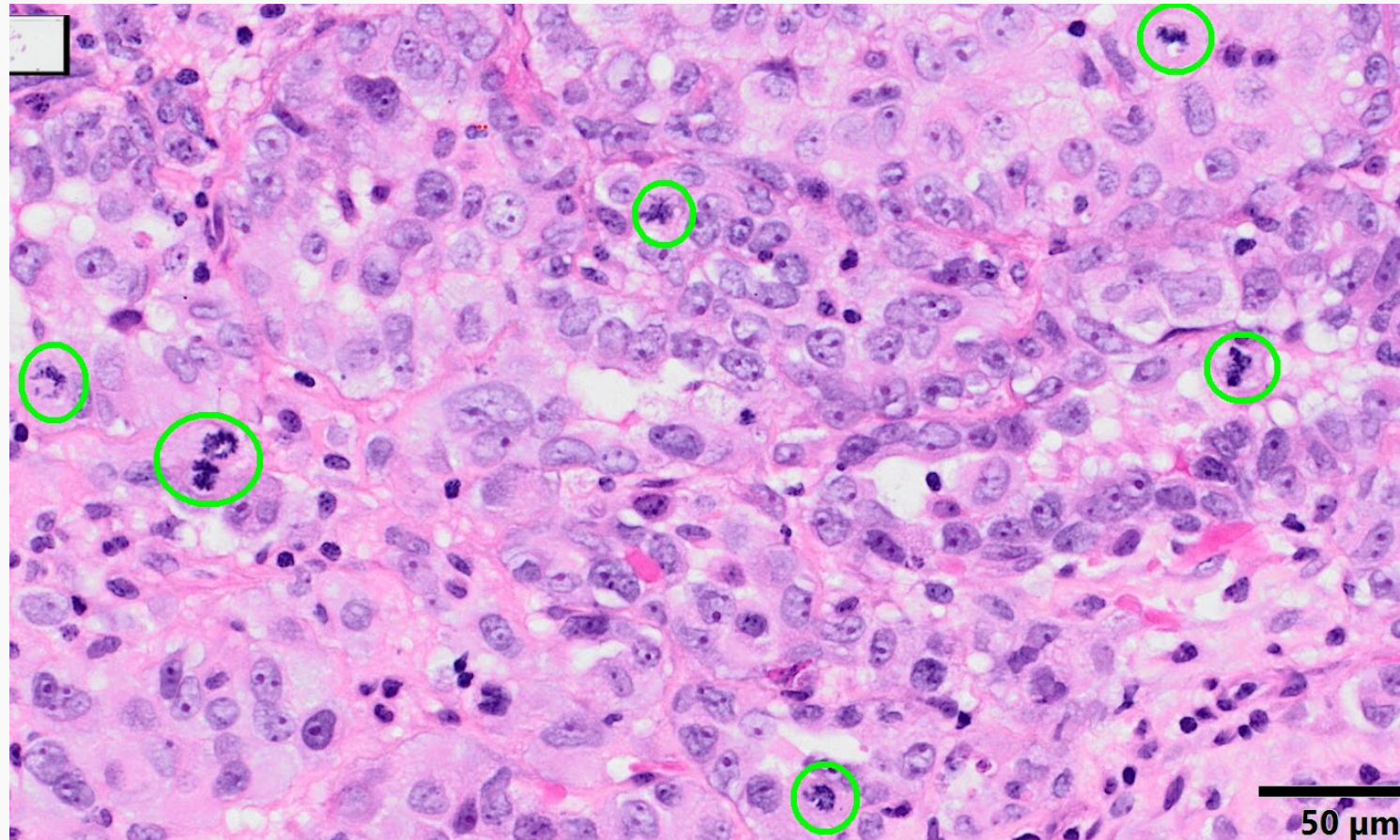
Discordance in necrosis scores (78 vs 22%)



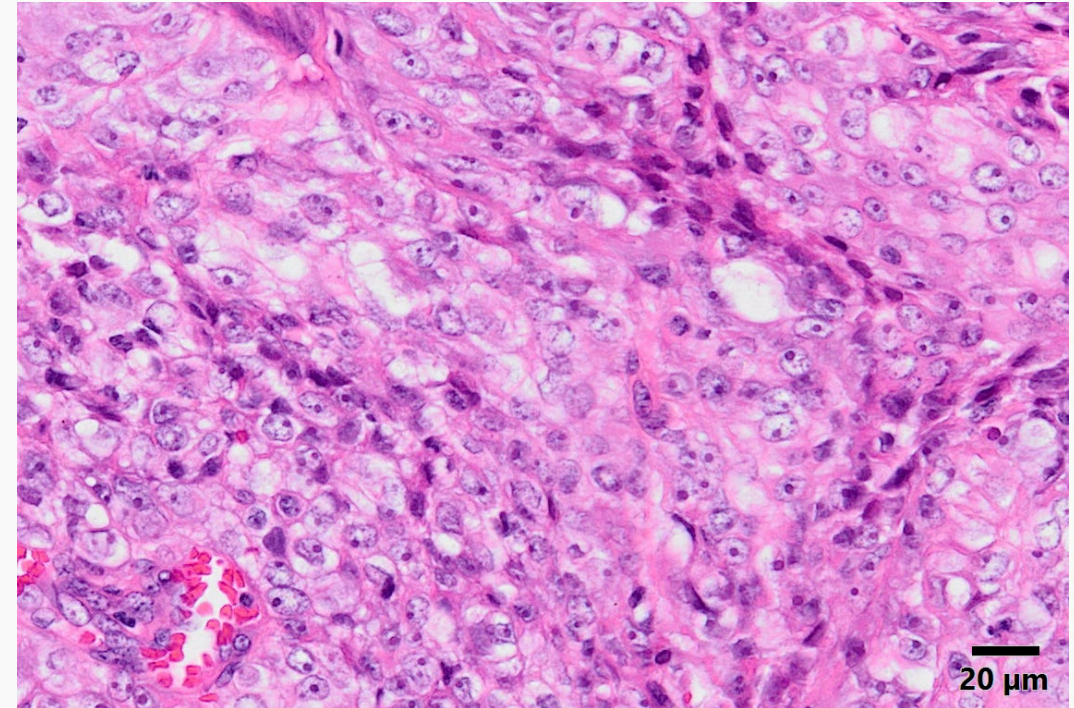
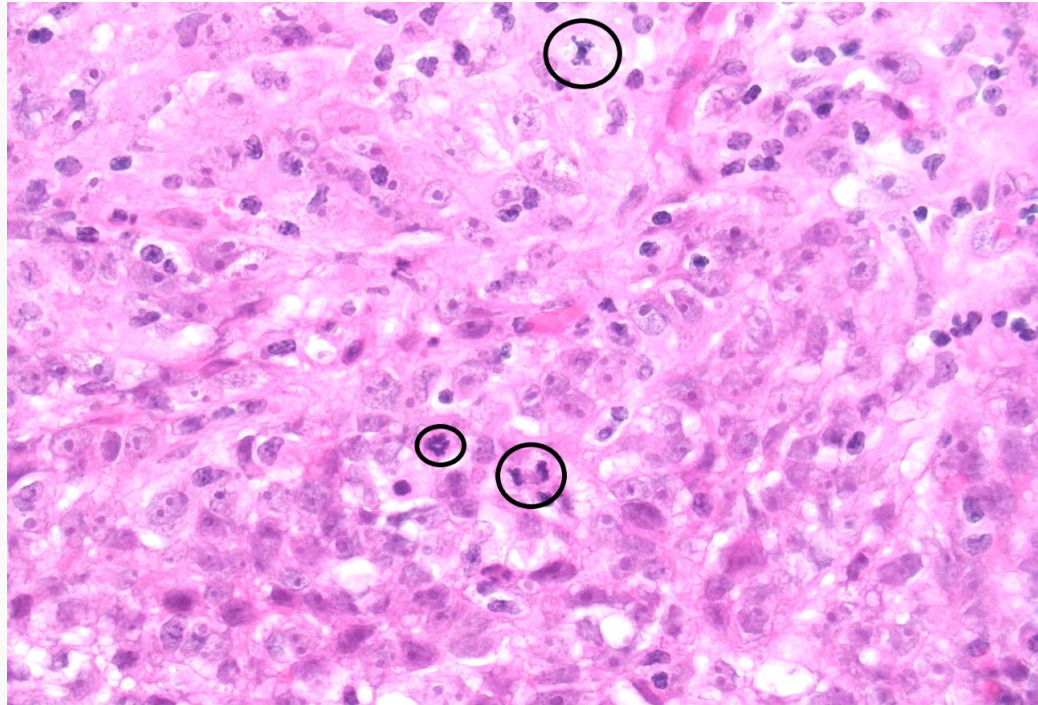
Final tumour grade



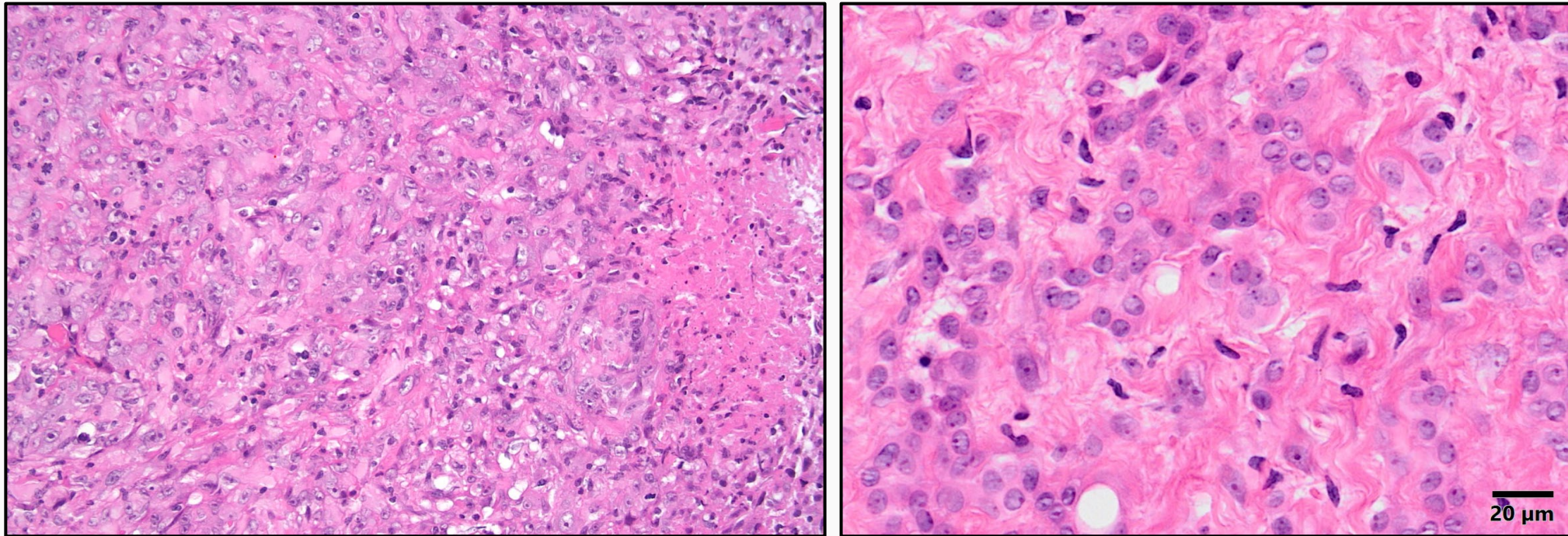
Slide 43 Low Grade A+M=5, no necrosis



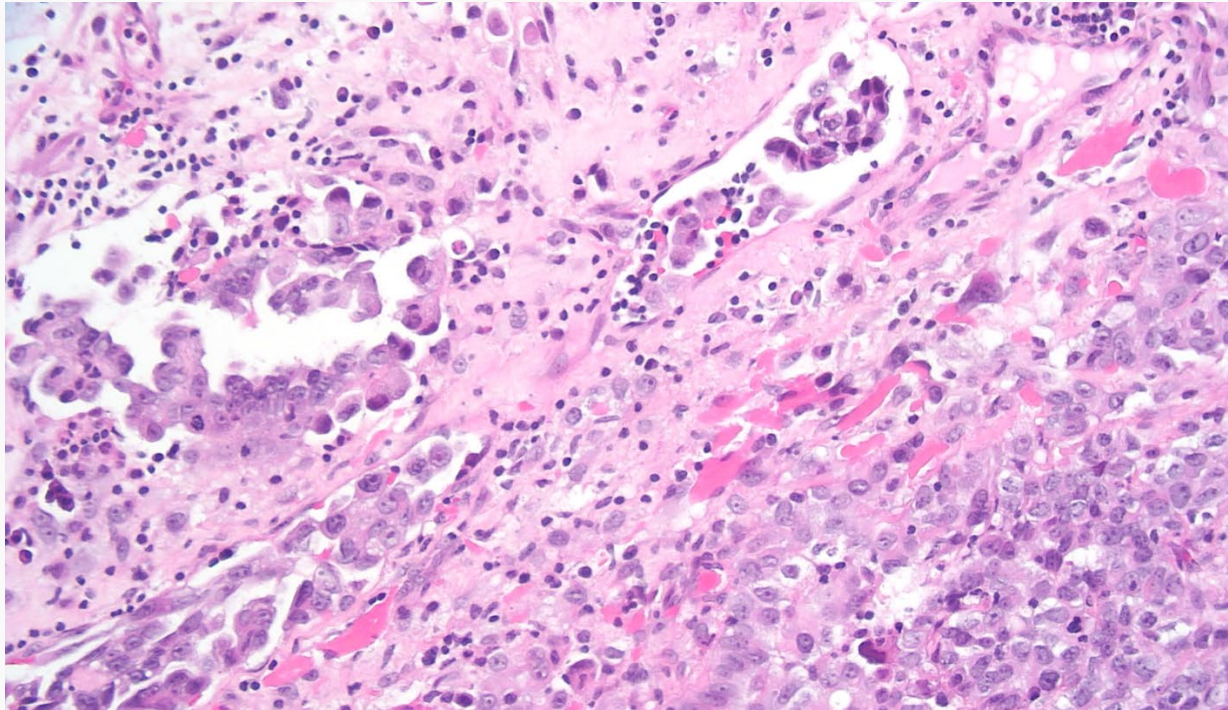
Slide 27 High Grade (43 vs 57%)



Full concordance when morphology is typical



Lymphovascular invasion-Low grade?



Future questions

- Role of grade in predicting treatment outcomes
- Primary & metastasis
- Other predictive histological factors

Conclusion

Overall grading is robust and accurate

Concordance in grading despite variance in individual parameters & use of virtual slides

More training (Difficulty choosing hotspots in tumours/Heterogenous morphology)

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Questions?

Thank You

