Chapter 8. Grading (and Classification) Systems Quick Reference: Solid Tumors

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*(*All subsections are by these authors, unless specified otherwise)*

Grading of Adenocarcinoma, NOS[a]	
	Fraction of tumor composed of glands
Well differentiated (Grade 1)	>95%
Moderately differentiated (Grade 2)	50–95%
Poorly differentiated (Grade 3)	<50%

- Applies mainly to adenocarcinomas of the gastrointestinal tract (esophagus, stomach, bowel, anus).
- Undifferentiated CA applies to carcinomas that are so poorly differentiated that they cannot be identified as adenoCA vs. SqCC vs. others. Small cell and large cell neuroendocrine carcinomas are always high grade.
- Grade is usually assigned based on the least differentiated area.

[a]Note that this is a "rule of thumb," and more detailed grading systems for individual organs (incorporating other features such as cytologic pleomorphism, necrosis, mitoses, etc.) are either available or being developed. However, the loss of glandular architecture is a general hallmark of poor differentiation in adenocarcinomas. Exception is micropapillary pattern, which in carcinomas of virtually all sites is a high-grade pattern.

References: [1, 2]

Grading of Squamous Cell Carcinoma (SqCC), NOS		
	Nuclear pleomorphism and mitoses (including atypical mitoses)	Keratinization and intercellular bridges
Well differentiated (Grade 1)	Absent	Abundant
Moderately differentiated (Grade 2)	Intermediate	Intermediate
Poorly differentiated (Grade 3)	Abundant	Nearly absent

- Applies to SqCC of any site: the head and neck, lung, abdominal organs (esophagus, bladder), skin, etc.
- There is no widely accepted quantitative definition of grading in SqCC. As a "rule of thumb," WD SqCC are said to closely resemble normal squamous epithelium, whereas PD SqCC are those in which squamous origin can be barely discerned.
- It is generally emphasized that the grade should be assigned based on nuclear features rather than degree of keratinization, although the two almost always go together. Nevertheless, the degree of keratinization is usually expressed by designating a SqCC as "keratinizing" vs. "nonkeratinizing" separately from the grade.
- HPV-related SqCC of the oropharynx should not be graded [3].
- As for adenocarcinoma, grade is assigned based on the least differentiated area.
- In contrast to adenocarcinoma, grade does not appear to be a strong predictive factor in SqCC, particularly of the head and neck.

References: [4, 5]

N. Rekhtman et al., *Quick Reference Handbook for Surgical Pathologists*, https://doi.org/10.1007/978-3-319-97508-5_8

Breast

Elston[a] Grading of Infiltrating Breast Cancer		
Parameter	**Point score**	**Final score** (add point scores in rows 1, 2, and 3) **and corresponding grade**
1. Tubule formation (% composed of tubules)		**3–5 points → Grade I** (well differentiated) **6–7 points → Grade II** (moderately differentiated) **8–9 points → Grade III** (poorly differentiated)
• ≥75%	1	
• 10–75%	2	
• <10%	3	
2. Nuclear pleomorphism[1]		
• Mild	1	
• Moderate	2	
• Severe	3	
3. Mitoses[2] (per mm²)		
• ≤3	1	
• 4–7	2	
• ≥8	3	

1. Nuclei are evaluated at the periphery of the tumor or in the area with highest nuclear grade:
   Mild pleomorphism: uniform nuclei, size similar to normal duct cells.
   Moderate and severe pleomorphism: increasing severity of nuclear enlargement, size and shape variability, clumping (vesicular) of chromatin, and prominence of nucleoli.
2. Mitotic count should be performed in the most mitotically active part of carcinoma, which is usually at the periphery of the tumor.
   Mitotic count should be done in 10 HPFs (40X objective, i.e., 400X field). The actual size of 400X field is microscope-dependent and should be measured with stage micrometer. For a table with conversion between field size, mitotic count, and point score, see Reference [6].

Note: Lobular carcinoma is always given 3 points for lack of tubule formation. It is still usually Elston grade I or II, as nuclei generally get 1–2 points and mitotic count gets 1 point. An exception to this is pleomorphic lobular carcinoma, which by definition has marked nuclear atypia (nuclear score of 3), making it at least Elston grade II. Ductal carcinoma is more commonly Elston grade II or III. Tubular cancer is by definition grade I.

[a]"Elston grade" is mercifully short for "Elston-Ellis modification of Scarff-Bloom-Richardson" grading system (or Nottingham combined histological grade).

References: [1, 6, 7]

Van Nuys Nuclear Grading of Ductal Carcinoma In Situ (DCIS)			
	Nuclear size	**Mitoses per 10 HPF**	**Nuclear pleomorphism[a]**
Grade 1	<1.5 RBC or normal duct cell	Rare	Mild
Grade 2	1–2 RBC	Sparse	Moderate
Grade 3	>2.5 RBC	Frequent	Severe

[a]Nuclear pleomorphism is graded as described above for invasive lesions.

Notes:
1. The most recent WHO grading scheme is based on nuclear grade alone, without incorporating necrosis. Similarly, CAP recommends using the same nuclear grading scheme and reporting the presence or absence of necrosis, instead of combining the features of both. When present, necrosis should be described as focal (punctate) or central ("comedo"), the latter of which is generally reserved for grade 3 lesions.
2. Architectural histopathologic features are not taken into account for grading purposes but should be reported as they have prognostic significance.
3. LCIS is not generally graded.

Reference: [1, 6]

Grading of Phyllodes Tumor					
	Stromal cellularity	**Stromal overgrowth (4X field is all stroma)**	**Stromal pleomorphism**	**Infiltrative border**	**Mitoses/10 HPF**
Benign	Mild	–	None to minimal	–	<5
Borderline/low-grade malignant	Moderate	– (or very focal)	Mild to moderate	F+	5–9
Malignant[a]	Marked	+	Marked	+	>10

[a]Malignant heterologous elements may be present in a malignant phyllodes tumor but never seen in benign or borderline lesions.

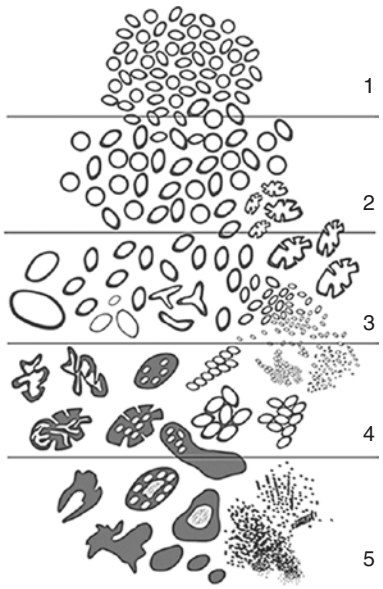
References: [1, 8]

Genitourinary Tract: Prostate

Gleason Grading of Prostate Cancer

The Gleason system is a five-tier system based entirely on architectural pattern; nuclear features are not factored in. The grade is reported as a sum of the most prevalent (primary) and second most prevalent (secondary) pattern to obtain a "combined Gleason grade" or "Gleason score." For example, a tumor with primary Gleason pattern 3 and secondary Gleason pattern 4 is reported as Gleason score 3 + 4 = 7. Note that in this example, 3 and 4 are "Gleason patterns," and 7 is a "Gleason score."

Gleason pattern 1	• Non-infiltrative nodule • Round to oval back-to-back glands • Exceedingly rare diagnosis, usually seen on TURP specimens
Gleason pattern 2	• Fairly well-circumscribed nodule, but minimal infiltration is allowed • Glands are more loosely arranged and not as uniform as those in pattern 1 • Exceedingly rare diagnosis, usually but not always in transition zone
Gleason pattern 3	• Clearly infiltrative pattern (unlike patterns 1 and 2) • Glands vary in size and shape • All glands are distinct, such that one can draw a mental circle around each gland • Microcystic, atrophic pattern, branching, and pseudohyperplastic glands are now recognized as pattern 3 • PIN-like ductal adenocarcinoma
Gleason pattern 4	• Glands are no longer separate as seen in patterns 1–3 (**one cannot draw a mental circle around each gland**): glands are fused, poorly defined, cribriform, or glomeruloid • All cribriform glands are now considered pattern 4 • Ductal adenocarcinoma (except PIN-like variant, which is graded as pattern 3, and ductal adenocarcinoma with necrosis, which is graded as pattern 5)
Gleason pattern 5	• Cells in solid nests and sheets, rosettes, cords, or single cells with virtually no glandular differentiation • Nests of tumor with central "comedonecrosis" are also classified as pattern 5
Not graded	• Small cell prostate carcinoma • Adenocarcinoma with Paneth cell-like differentiation (by criteria, would be graded 5 + 5 but behaves like 3 + 3)



Weinzerl | Visual Media
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Because clinical decisions are based primarily on the total Gleason score, several modifications to the traditional Gleason grading have been proposed to better convey the severity of disease:

1. "5% cutoff rule": If lower-grade pattern occupies <5% of the tumor, it can be ignored. For example, a 4 + 3 = 7 in traditional Gleason grading should be diagnosed as 4 + 4 = 8, if pattern 3 comprises <5% of the tumor. The highest-grade pattern is included in the score **regardless** of its quantity.
2. When three Gleason patterns (e.g., 3, 4, 5) are present, the Gleason score is derived by adding the most prevalent and the highest grades. This is true on biopsies regardless of the amount of the highest-grade pattern (5 in this case). On resections, however, this applies only when the highest-grade pattern comprises >5% of the tumor.
3. Gleason patterns 1 and 2 are essentially historical, in that they are no longer assigned on biopsy and exceedingly rarely on resection. In fact, the current WHO urges against assigning Gleason scores 2–5 on biopsy due to low reproducibility, poor correlation with final grade on resection, and potentially misleading prognosis.

Illustration from: *Am J Surg Pathol* 2016, 40(2): 244–252; Epstein JI; The 2014 ISUP Consensus Conference on Gleason Grading of Prostatic Carcinoma; with permission from © Wolters Kluwer Health 2016

Abbreviations: *PIN* prostatic intraepithelial neoplasia, *TURP* transurethral resection of the prostate

Reference: [9]

Prostate Cancer Prognostic Grade Groups[a]

Grade group	Gleason score (patterns)
1	≤6
2	7 (3 + 4)
3	7 (4 + 3)
4	8 (4 + 4; 3 + 5; 5 + 3)
5	9–10

[a]Based on the most recent multi-institutional data, prostate cancer has been assigned into grade groups (1–5), each associated with a unique prognosis, and thus a distinct therapeutic approach. The WHO recommends to report both Gleason grade and grade group in a surgical pathology report, which is now done by most GU pathologists. Reference: [9]

Grading of Prostatic Intraepithelial Neoplasia (PIN)[a]

	Nuclear cytology
LGPIN (low-grade prostatic intraepithelial neoplasia)	Enlarged, marked size variation; Normal chromatin pattern; Rare prominent nucleoli (<10% of cells)
HGPIN (high-grade prostatic intraepithelial neoplasia)	Enlarged, mild to moderate size variation; hyperchromasia and chromatin clumping; prominent nucleoli

[a]Although not part of grading criteria, integrity of the basal cell layer is another helpful distinguishing feature of LG versus HG PIN. While it is intact in LGPIN, it is often disrupted or attenuated in HGPIN.

Reference: [10]

Genitourinary Tract: Kidney and Bladder

WHO (2014)/ISUP Grading of Renal Cell Carcinoma		
	Nucleoli (400X magnification)	**Nucleoli (100X magnification)**
Grade 1	Absent or inconspicuous	Absent
Grade 2	Conspicuous and eosinophilic	Visible but not prominent
Grade 3	Prominent	Conspicuous and eosinophilic
Grade 4[a]	Prominent	Prominent

[a]Rather than nucleolar prominence, Grade 4 is defined by marked nuclear pleomorphism, multinucleated giant cells, and/or rhabdoid and/or sarcomatoid differentiation.

- Tumors are graded by the worst area, however focal
- Grading is applied to clear cell and papillary RCC
- Collecting duct carcinoma is ISUP grades 3–4
- Chromophobe RCC is generally not graded
- Oncocytoma is benign and therefore not graded

Reference: [10]

Nephroblastoma (Wilms Tumor): Criteria for Anaplasia (unfavorable histology)
1. Nucleomegaly (at least 3X enlargement).
2. Nuclear hyperchromasia.
3. Atypical mitoses (large and multipolar).
Note: Anaplasia predicts resistance to chemotherapy and inherent aggressiveness, the latter of which has been reflected in more recent data [11]. Reference: [10]

The WHO (2004)/ISUP Consensus Classification of Non invasive (*In Situ*) Papillary Urothelial Neoplasms (see http://pathology.jhu.edu/tutorials/bladder/ for tutorial)

	Urothelial thickness	**Cellular disorganization: loss of polarity, crowding**	**Pleomorphism**[4]	**Mitoses**	**Fusion and branching of papillae (soft feature)**
Papilloma	Normal (<7 layers)	Absent (perfectly orderly, identical to normal)	Absent	Absent	None
PUNLMP[1]	Increased	Absent (perfectly orderly, identical to normal)	Absent	Rare, basal	Rare
LGPUC[2]	Increased	Minimal	Mild	Occasional, at any level	Occasional
HGPUC[3]	Increased	Prominent	Moderate to severe	Frequent, at any level	Frequent

1. **PUNLMP** (papillary urothelial neoplasm of low malignant potential): cells may be uniformly enlarged, but they are identical to each other in all fields and are perfectly oriented (orderly).
2. **LGPUC** (low-grade papillary urothelial carcinoma): overall low-power appearance is orderly, but there is distinctive variation of architectural and/or cytological features.
3. **HGPUC** (high-grade papillary urothelial carcinoma): distinctive pleomorphism and loss of polarity/crowding. Necrosis and cellular discohesion, when present, are specific to HGPUC.
4. Pleomorphism refers to nuclear enlargement, hyperchromasia, variation in size and shape, and prominence of nucleoli. Nuclear grooves, a feature of normal urothelium, are preserved in PUNLMP but are lost in carcinomas (low-grade and high-grade).

"**5% rule**": Grade is assigned based on the highest-grade area, unless it is <5% of the tumor (presence of a small higher-grade area may be mentioned in a note).

References: [10, 12]

The WHO (2004)/ISUP Consensus Classification of Flat *In Situ* Urothelial Neoplasms (see http://pathology.jhu.edu/tutorials/bladder/ for tutorial)

Dysplasia	Some features of CIS are present but fall short of the threshold for CIS (cytology similar to LGPUC). Uncommon diagnosis.
Carcinoma in situ (CIS)	Nucleomegaly (nuclei are **5X** the size of stromal lymphocytes vs. normal urothelium is 2–3X), pleomorphism, 1–2 irregular nucleoli, nuclear crowding, loss of polarity (cytology similar to HGPUC).

References: [10, 12]

Abbreviations: *PUC* papillary urothelial carcinoma (*LG* low grade, *HG* high grade), *ISUP* International Society of Urological Pathology

Head and Neck

by Justin A. Bishop

Grading of Thyroid Carcinomas	
Well differentiated[1]	Papillary carcinoma[2] Follicular carcinoma[3] • Minimally invasive • Encapsulated angioinvasive • Widely invasive
"Moderately differentiated"	None[4]
Poorly differentiated	Insular, solid, or trabecular architecture + no papillary nuclear features + one of these three: Convoluted nuclei, elevated mitoses (≥3/10 HPF), or necrosis[5]
Anaplastic (undifferentiated)	Minimal or no thyroid differentiation. Includes squamoid, pleomorphic/giant-cell, and spindled variants

1. Medullary carcinoma has a significantly worse prognosis than papillary or follicular carcinoma and is not graded. As a result, when you hear the term "well-differentiated thyroid cancer," it refers to just the papillary and follicular types.
2. Tall cell, columnar cell, hobnail, and diffuse sclerosing variants have a worse prognosis and should be mentioned in the report.
3. In widely invasive follicular carcinoma, there is typically no capsule to evaluate because the cancer has pretty much blown past it as invasive nodules in the parenchyma. The term "minimally invasive" should be limited to cases that have capsular invasion only [13]. For encapsulated angioinvasive follicular carcinomas, the number of foci of vascular invasion should be reported (if <4, the prognosis is good).
4. Some regard the high-risk variants of papillary CA as well as widely invasive follicular CA as "moderately differentiated" thyroid carcinoma [14]. We do not use this designation at our institutions, and it is not recognized in modern classification schemes.
5. The criteria listed above are from the 2006 Turin proposal [15] which were encoded into the 2017 WHO classification [16]. However, at some institutions the criteria are less strict, requiring only elevated mitoses (>4/10 HPF) *or* necrosis [17]. Regardless of what criteria are used to diagnose poorly differentiated carcinoma, the presence of the high-grade features (elevated mitoses or necrosis) in a follicular or papillary carcinoma should be mentioned.

Grading of Salivary Gland Carcinomas[1]			
Low-grade	**Intermediate-grade**	**High-grade**	**Variable grade**
Acinic cell carcinoma Polymorphous adenocarcinoma Basal cell adenocarcinoma Epithelial-myoepithelial carcinoma Secretory carcinoma Clear cell carcinoma	Adenoid cystic carcinoma[2] Myoepithelial carcinoma	Salivary duct carcinoma Neuroendocrine carcinomas Large cell undifferentiated carcinoma Lymphoepithelial carcinoma Primary squamous cell carcinoma	Mucoepidermoid carcinoma (see table below) Adenocarcinoma, NOS[3] Carcinoma ex-pleomorphic adenoma[4] Intraductal carcinoma[5]

1. Most salivary gland carcinomas have a default grade for typical examples, but tumors should be "upgraded" if they show more aggressive histologic features (e.g., basal cell adenocarcinoma with a highly infiltrative pattern, necrosis, and marked pleomorphism would be regarded as high-grade). Moreover, virtually all types of low- or intermediate-grade carcinoma may rarely exhibit high-grade transformation ("dedifferentiation") into a high-grade adenocarcinoma NOS or large cell undifferentiated carcinoma.
2. Although classic adenoid cystic carcinoma is generally considered an intermediate-grade carcinoma, tumors with solid areas (especially >30%) behave worse (more like high-grade). The approximate percentage of solid pattern should be noted.
3. Adenocarcinoma, NOS, is graded low, intermediate, or high-grade based on cytological features, presence/absence of necrosis, and degree of invasiveness.
4. The type of carcinoma arising in the mixed tumor should be graded as it would if it had arisen de novo.
5. Intraductal carcinoma is the salivary analogue to breast ductal carcinoma in situ. It should be graded as low, intermediate, or high-grade based on cellular features and necrosis but has an excellent prognosis in its pure form (i.e., no invasive component).

References: [5, 18]

Mucoepidermoid Carcinoma, AFIP Grading System		
Histopathological feature	**Point value**	**Total point score** (add points in point value column) **and corresponding tumor grade**
Cystic component <20%	2	0–4 → **Low-grade** 5–6 → **Intermediate-grade** >7 → **High-grade**
Neural invasion	2	
Necrosis	3	
>4 mitoses per 10 HPF	3	
Anaplasia	4	

This is the most widely used grading scheme, but the WHO classification does not endorse any specific grading system.

References: [5, 18]

Evaluation of Autoimmune Sialiadenitis (Sjögren Syndrome) in Labial Biopsy		
Grade	**Amount of inflammation** (lymphocytes, plasma cells, histiocytes)	**Likelihood of Sjögren Syndrome**
0	Absent	Nondiagnostic
1	Slight infiltrate	Nondiagnostic
2	Moderate infiltrate (less than 1 focus[a] per 4 mm^2)	Nondiagnostic
3	One focus per 4 mm^2	Suggestive
4	More than one focus per 4 mm^2	Diagnostic

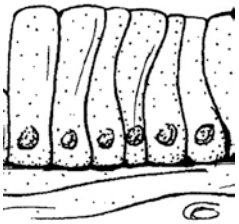
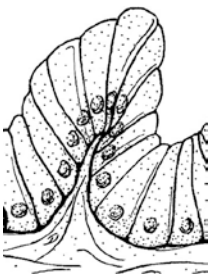
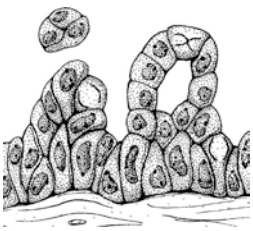
[a]"Focus" is defined as an aggregate containing at least 50 lymphocytes, plasma cells, or macrophages.

There is a lack of standardization among oral pathologists' grading for Sjögren syndrome. Another common approach is the American College of Rheumatology recommendation which consists of focus score = (number of foci*4)/(area of glandular tissue present in mm2), with a focus score ≥1 being supportive of Sjögren syndrome if other required criteria are met [19].

References: [20, 21]

Pancreas and Biliary Tree

Grading of Pancreatic Intraepithelial Neoplasia (PanIN) and Pancreatic Cystic Mucinous Neoplasms (IPMN and MCN)

Terminology for PanIN, IPMN, and MCN			Cytology	Architecture	Illustration
WHO 2010		**Revised 2015**			
PanIN-1A	IPMN/MCN – Low-grade dysplasia	**Low-grade PanIN, IPMN, or MCN**	Small bland cuboidal basally located nuclei	Flat	 PanIN-1A
PanIN-1B				Papillary	 PanIN-1B
PanIN-2	IPMN/MCN – Moderate dysplasia		– Moderate pleomorphism (↑N/C ratio, prominent nucleoli) – Stratified nuclei some rising to luminal surface	Usually papillary	 PanIN-2
PanIN-3	IPMN/MCN – Severe dysplasia	**High-grade PanIN, IPMN, or MCN**	– Severe pleomorphism (as in carcinoma) – Loss of nuclear polarity – Dystrophic goblet cells (goblet cells with flipped polarity – nuclei oriented toward the lumen and mucinous cytoplasm toward the basement membrane) – Atypical mitoses	Papillary or micropapillary, luminal budding, fusion of micropapillae, cribriforming + necrosis (Even with bland cytology, complex architecture supports PanIN-3)	 PanIN-3

The currently recommended reporting terminology is based on the revised 2015 classification of the neoplastic precursor lesions. The former terminology (based on WHO 2010 classification) may still be included in reports as a supplementation and indicated in parentheses pending the new WHO classification revision. Low-grade PanINs do not need to be reported, especially in the absence of invasive carcinoma, due to the lack of proven clinical significance of these lesions.

Rule of thumb: Dysplasia in pancreatic ducts is graded a step above of how you would grade dysplasia in a colon adenoma, such that low-grade dysplasia (typical adenoma) in the colon = moderate dysplasia in the pancreas.

The key distinguishing features of PanIN vs. IPMN vs. MCN are:
- PanIN – usually <5 mm, radiologically occult
- IPMN – grossly visible (usually >1 cm), associated with pancreatic duct (main or branch), mucin extrusion at the papilla
- MCN – almost exclusively women, not connected to pancreatic duct, associated with ovarian-type stroma

References: https://pathology.jhu.edu/pc/professionals/DuctLesions.php [22–27]

Illustration adapted from Cornish TC and Hruban RH. Surg Pathol Clin 2011[28]; with permission from © Surg Pathol Clin

Abbreviations: *PanIN* pancreatic intraepithelial neoplasia, *IPMN* intraductal papillary mucinous neoplasm, *MCN* mucinous cystic neoplasm

Esophagus

Grading of Dysplasia in Barrett Mucosa				
	Architectural atypia[a]	**Cytologic atypia**[b]	**Surface maturation**	**Inflammation**
NFD (reactive)	None[1]	None	Present	Variable
IFD	None to minimal	Mild	Present	Frequent
LGD	Minimal	Moderate	Absent	Minimal
HGD	Prominent	Severe (loss of nuclear polarity)	Absent	Minimal

[a]**Architectural atypia** = glandular crowding and complexity (budding, branching, contour irregularity, papillary projections into the lumen)
[b]**Cytologic atypia** = ↑N/C ratio, hyperchromasia, ↑nucleoli, stratified nuclei, loss of mucin

1. In cases of regenerative changes, particularly in the setting of marked inflammation, variable degrees of architectural atypia may be seen, but in the presence of surface maturation, preserved N/C ratio, and lack of significant cytologic atypia (other than prominent nucleoli), this should not be interpreted as dysplasia.

Abbreviations: *HGD* high-grade dysplasia, *IFD* indefinite for dysplasia, *LGD* low-grade dysplasia, *NFD* negative for dysplasia

References: [29, 30]

Liver Biopsy

Grading and Staging of Chronic Viral Hepatitis

Grade = Lymphocytic inflammation and "necrosis[a]" (indicates "activity")
- Portal inflammation
- Periportal inflammation/necrosis (= interface activity = piecemeal necrosis[a])
- Lobular inflammation/necrosis

increasing severity

Stage = Fibrosis (indicates "chronicity")
- Portal fibrosis
- Bridging fibrosis (early → established)
- Cirrhosis

increasing severity

[a]Note that "necrosis" does not manifest as necrotic debris in the setting of viral hepatitis but rather as replacement of hepatic parenchyma by lymphocytes.

There are multiple scoring systems in use to quantify the above parameters. These are nicely reviewed (with diagrams) in Reference [31].

Neuroendocrine Neoplasms

Pulmonary Neuroendocrine Neoplasms, WHO 2015			
	Mitoses per 2 mm²	**Necrosis**	**Ki67 (Mib1)[a]**
Typical carcinoid (=low grade; G1)	<2	Absent	<2%
Atypical carcinoid (=intermediate grade; G2)	2–10	Focal	<20% (mean 10%)
Neuroendocrine carcinoma (small-cell and large-cell type) (=high grade; G3)	>10	Extensive	20–100% (mean for small cell >80%)

For consistent reporting, the grading criteria require assessment of mitotic index within a 2 mm² area. The number of HPFs (high-power fields) per 2 mm² varies among microscopes and has to be individually calculated.
[a]Ki67 is not part of the WHO 2014 criteria, but it is very helpful in small crushed biopsies where distinction of carcinoid tumors and small cell carcinoma can be difficult.
Carcinoid tumorlet is defined by size of ≤0.5 cm.

References: [32, 33]

Pancreatic (WHO 2017) and GI (WHO 2010) Neuroendocrine Neoplasms			
	Mitoses per 10 HPF	**Ki67**	**Morphology**
Well differentiated (= NETs): NET, grade 1 NET, grade 2 NET, grade 3 (for pancreas only)[1]	 <2 2–20 >20	 <3% 3–20% >20%	Look like carcinoid of any site
Poorly differentiated (= NECs): NEC, small cell type, grade 3 NEC, large cell type, grade 3	>20	>20%	Look like small cell or large cell neuroendocrine carcinomas of any site
MANEC (GI), MiNEN (pancreas)[2]	NA	NA	Mixed neuroendocrine and carcinomatous neoplastic components (at least 30% each)

1. Well-differentiated grade 3 category is currently unique to the pancreatic NETs (PanNETs). This separates NETs with elevated proliferation rate from neuroendocrine carcinomas (NECs) that are morphologically, genetically, and prognostically distinct. Although not currently in use for the remainder of the GI tract or the lung, these changes are likely forthcoming in these organ systems.

2. Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN) category has replaced mixed adenoneuroendocrine carcinoma (MANEC) in the pancreatic WHO criteria to account for well-differentiated entities in this category and entities with components other than adenocarcinoma (e.g., squamous cell carcinoma, acinar cell carcinoma).

Notes:

- Grading requires a mitotic count in at least 50 HPF (with 1 HPF = 0.2 mm², 10 HPF = 2 mm², and a Ki67 index as a percentage of at least 500 cells counted in "hot spots." Get your coffee ready!!
- If the mitotic rate and Ki67 index differ, use the higher of the two.
- Even though NECs are included as grade 3, in reality they are NOT graded. They are by definition and always high grade.
- "Micro" neuroendocrine proliferations are considered benign and include pancreatic neuroendocrine microadenoma (≤0.5 cm) and gastric carcinoid (ECL cell) tumorlet (≤0.5 cm).
- For pancreatic NETs, additional feature associated with prognosis is the type of hypersecretory syndrome:
  - Insulinoma – better prognosis (may be related to earlier detection due to symptoms)
  - Glucagonoma – worse prognosis
- For GI NETs, additional prognostic features include:
  - Anatomic location: bad (colon, esophagus), good (appendix, rectum), intermediate (small bowel, stomach)
  - Clinical setting (for gastric NETs): tumors arising in the setting of hypergastrinemia (Zollinger-Ellison syndrome/MEN1 or autoimmune metaplastic atrophic gastritis/pernicious anemia) have excellent prognosis, whereas sporadic tumors are aggressive
  - Size and depth of invasion which are a part of the staging system

References: [24, 34]

Abbreviations: *NE* neuroendocrine, *NET* neuroendocrine tumor, *NEC* neuroendocrine carcinoma

Neuroblastoma

Neuroblastoma: Revised Shimada Grading System (Not Graded if Metastatic or Posttreatment)			
Designation	Histology		Prognosis
Ganglioneuroma, maturing	**Stroma-rich**[1,2] (Schwannian stroma >50%)	No microscopic nodules of NB cells	FH
Ganglioneuroblastoma, intermixed		Microscopic nodules of NB cells present	FH
Ganglioneuroblastoma, nodular		Macroscopic (gross) nodules of NB cells present	UH/FH
Undifferentiated neuroblastoma	**Stroma-poor** (Schwannian stroma <50%)	No ganglion cells; No neuropil	Always UH (any age)
Poorly differentiated neuroblastoma		<5% ganglion cells; Neuropil present	UH if age >1.5 yrs or MKI[3] >4% Otherwise FH
Differentiating neuroblastoma		>5% ganglion cells; Neuropil present	UH if any of the following: – Age >5 yrs or – Age 1.5–5 yrs plus MKI >2% or – Age <1.5 yrs plus MKI >4% Otherwise FH

1. Schwannian stroma consists of spindle cells, which resemble schwannoma or neurofibroma. In contrast, neuropil consists of fibrillary processes similar to the kind seen in ependymoma.
2. Stroma-rich neuroblastomas generally have >50% ganglion cells, but this feature is not a criterion in grading of ganglioneuroblastoma.
3. MKI (mitosis-karyorrhexis index): percentage of mitotic and karyorrhectic cells based on a 5000-cell count (2% is 100 of 5000 cells, and 4% is 200 of 5000 cells). A 900-cell count is sometimes mercifully applied (2% is 19 of 900 cells, and 4% is 36 of 900 cells).
   Sample sign-out: "Neuroblastoma, stroma poor, differentiating, low MKI."

Abbreviations: *FH* favorable histology, *MKI* mitosis-karyorrhexis index, *NB* neuroblast, *UH* unfavorable histology

Reference: [35]

Olfactory Neuroblastoma, Hyams Grading System				
	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Architecture	Lobular	Lobular	Variable	Variable
Mitotic activity	Absent	Present	Prominent	Marked
Nuclear pleomorphism	Absent	Moderate	Prominent	Marked
Necrosis	Absent	Absent	+/– Present	Common
Fibrillary matrix	Prominent	Present	Minimal	Absent
Rosette type	Homer Wright	Homer Wright	Flexner-Wintersteiner	Flexner-Wintersteiner

The four-tiered system may be simplified into low grade (Hyams grades 1 and 2) and high grade (Hyams grade 3 and 4).

Reference: [5]

Sarcoma Grading (Not for the Faint of Heart!)

by Youran Zou & Justin A. Bishop

There are two main systems, the NCI system and the French Federation of Cancer Centers (FNCLCC or "French") system.

French Grading System for Soft Tissue Sarcomas		
Parameter	Point score	
1. Tissue differentiation (how closely the tumor resembles the tissue from which it arose) **see table below** • Tumors closely resembling normal mesenchymal tissue (i.e., difficult to distinguish from a benign tumor), e.g., well-differentiated leiomyosarcoma • Tumors of a definite histologic type, e.g., myxoid liposarcoma • Tumors that are embryonal, poorly differentiated, or of uncertain histologic type	1 2 3	
2. Mitoses • 0–9/10 HPF • 10–19/10 HPF • ≥ 20/10 HPF	1 2 3	
3. Tumor necrosis • No necrosis at all • <50% • ≥50%	0 1 2	
	Final score (combined point score) and corresponding grade	
	2–3 points = Grade 1	Low-grade
	4–5 points = Grade 2	High-grade
	6–8 points = Grade 3	
• A high-power field is = 0.1744 mm^2. • Sectioning the tumor at least 1 section/2 cm is recommended. Reference:[36]		

For the most commonly encountered sarcomas (assuming you know what type it is!), the differentiation score can simply be looked up in this table:

Histology-Specific Tumor Differentiation Scores	
Sarcoma	**Score**
Adipocytic	
Myxoid liposarcoma	2
High-grade myxoid (round cell) liposarcoma	3
Pleomorphic liposarcoma	3
Dedifferentiated liposarcoma	3
Fibrous/Fibrohistiocytic	
Well-differentiated fibrosarcoma	1
Conventional fibrosarcoma	2
Poorly differentiated Fibrosarcoma	3
Myxofibrosarcoma	2
Undifferentiated (spindle cell and pleomorphic) sarcoma	3
Smooth muscle	
Well-differentiated leiomyosarcoma	1
Conventional leiomyosarcoma	2
Poorly differentiated/pleomorphic leiomyosarcoma	3
Others/unknown	
Synovial sarcoma	3
Ewing sarcoma	3
Mesenchymal chondrosarcoma	3
Extraskeletal osteosarcoma	3
Extrarenal rhabdoid tumor	3
References: [36, 37]	

But unfortunately it's not that simple. In practice, some of the sarcomas are high-grade or low-grade by definition. Also, the French Federation of Cancer Centers Sarcoma Group "doesn't recommend" grading a few of the common sarcomas. This is really confusing, since most of the "differentiation charts" include these sarcomas that they don't recommend grading.

So basically, for these tumors, you *can* go through the fun process of grading them by counting up the points, but it would be a waste of time because (1) for some sarcomas, you will always get to a certain grade (i.e., they are either high-grade or low-grade by definition) or (2) applying a grade would be misleading because the actual prognosis doesn't match it.

Sarcomas for Which Grading Is Generally Not Recommended or Not Necessary	
Sarcoma	**Reason**
Alveolar and embryonal rhabdomyosarcoma (except for botryoid and spindle cell variants)	Grade 3 by definition
Ewing sarcoma	Grade 3 by definition
Angiosarcoma	Grade 3 by definition
Desmoplastic small round cell tumor	Grade 3 by definition
Extrarenal rhabdoid tumor	Grade 3 by definition
Extraskeletal osteosarcoma	Grade 3 by definition
Mesenchymal chondrosarcoma	Grade 3 by definition
Infantile fibrosarcoma	Grade 1 by definition (has a good prognosis, but if grade strictly applied, would be high)
DFSP	Tumors of intermediate malignancy that are low-grade by definition
Well-differentiated liposarcoma	
MPNST and dedifferentiated liposarcoma	Grading is controversial
Extraskeletal myxoid chondrosarcoma	Grade does not predict outcome. Would be low-grade based on histology but meets late in 40% of cases.
Alveolar soft part sarcoma	Considered by many experts to be "ungradable" but usually managed as high-grade sarcomas. Would often meet histologic criteria for low-grade but often metastasize long term (within 10–20 years).
Clear cell sarcoma	
Epithelioid sarcoma	
"Low-grade" fibromyxoid sarcoma	
Abbreviations: *DFSP* dermatofibrosarcoma protuberans, *MPNST* malignant peripheral nerve sheath tumor References: [37–42]	

Central Nervous System

by Marina K Baine & Tejus A. Bale

Tips and Tricks: WHO Grading of CNS Tumors[1]	
Grade I	Most sellar tumors None of the oligodendrogliomas
Grade II	You're on your own
Grade III	All tumors with "anaplastic" in the name: Anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic pleomorphic xanthoastrocytoma, anaplastic ependymoma, anaplastic ganglioglioma, and anaplastic (malignant) meningioma
Grade IV [2]	All embryonal tumors: Medulloblastoma (all subtypes), embryonal tumor with multilayered rosettes C19MC-altered, medulloepithelioma, CNS embryonal tumor NOS, atypical teratoid/rhabdoid tumor, CNS embryonal tumor with rhabdoid features Most tumors with "blastoma" in the name[3] (e.g., glioblastoma, pineoblastoma, medulloblastoma, etc.)

1. Grading of CNS tumors relies on histologic features and tumor classification.
2. The remaining **two** Grade IV entities are diffuse midline glioma, H3 K27 M-mutant (predominantly pediatric), and malignant peripheral nerve sheath tumor (MPNST), which can be WHO grade IV but has its own clinically unvalidated and marginally reproducible grading system.
3. Exceptions are hemangioblastoma (WHO grade I) and myofibroblastoma, which is a rare (in CNS) benign mesenchymal neoplasm.

Astrocytic and Oligodendroglial Neoplasms: WHO Grading System

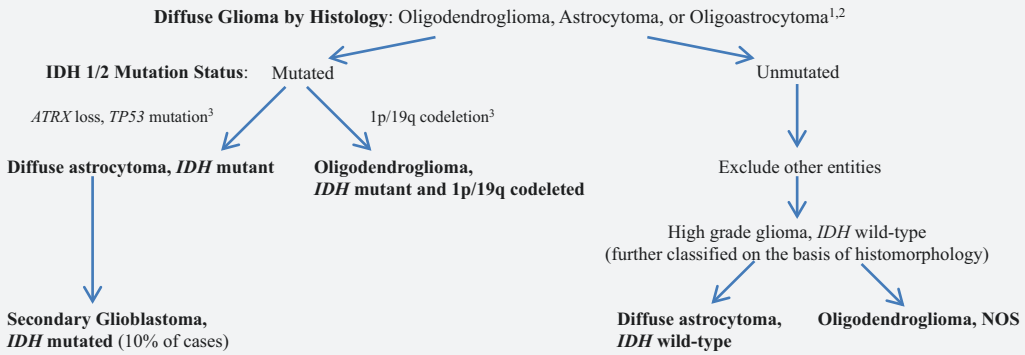
WHO grade	Histology					Other features
	Atypia	Cellularity	Ki67[1]	Mitoses	Necrosis +/– MVP	
I [2]	Variable but generally minimal	Variable but generally low	Variable but generally <4%	Minimal mitotic activity	–	"Rosenthal fibers" Possibility of cure after complete resection
II [3]	↑	↑	<4% astrocytic <5% oligodendroglial	Minimal-rare mitotic activity (see below)	–	Infiltrative and often recur despite low proliferative activity Some progress to grades III and IV
III	↑↑	↑↑	5–10% astrocytic 6–10% oligodendroglial	Readily identifiable mitoses; in a small biopsy **even one is enough!**	– or + [1]	Most patients require adjuvant chemotherapy and radiation High rate of recurrence and/or progression
IV	↑↑/↑↑↑	↑↑↑	>10%	Brisk mitotic activity	+	Widespread infiltration with high incidence of craniospinal spread Rapid pre- and postoperative disease evolution with fatal outcome

1. There are no definitive criteria for proliferative index assessment for oligodendroglioma grading, but generally a cutoff of 5% is used to distinguish WHO grades II and III. If a tumor is truly an oligodendroglioma, 1p19q co-deleted, then even mitosis, necrosis, and MVP still only make it to anaplastic oligodendroglioma, grade III. The same histologic features in an astrocytoma would amount to GBM, WHO grade IV.
2. WHO grade I tumors are a unique category composed of heterogeneous group of tumors with a known benign course.
3. Pleomorphic xanthoastrocytoma (PXA) (grade II) is an exception, often with MVP and/or necrosis, and defined by nuclear pleomorphism, but consistent with its grade, it has low proliferative activity (<5 mitoses/10 HPF, and Ki67 < 1%).

Abbreviations: *MVP* microvascular proliferation

Reference: [43]

High-Grade Gliomas: WHO Classification



1. Genotype trumps morphology!

2. If genetic testing is not done or is inconclusive, the diagnosis is made based on histomorphology with the NOS designation (i.e., diffuse astrocytoma, NOS, oligodendroglioma, NOS or glioblastoma, NOS).
3. ATRX loss and *TP53* mutation are characteristic of IDH-mutated diffuse astrocytoma, but NOT required for the diagnosis. 1p/19q codeletion, however, MUST be present for the diagnosis of oligodendroglioma. When two molecularly distinct populations are seen in a single tumor, oligoastrocytoma may be diagnosed (rare reports); or in the absence of diagnostic molecular testing, oligoastrocytoma, NOS, may be diagnosed (provisional diagnosis).

Reference: [43]

Central Nervous System: 2

Ependymal Tumors: WHO Grading System[1]

Tumor type	WHO grade	Histology			
		Cytology	Mitotic activity	Cellularity	Palisading necrosis and/or MVP
Subependymoma	**I**	Unique slow-growing mitotically inactive tumors with a generally benign course			
Myxopapillary ependymoma					
Ependymoma[2]	**II**	Bland	Low	↑ – ↑↑	–/+ [3]
Ependymoma, *RELA* fusion-positive[4]					
Anaplastic ependymoma	**III**	High N:C ratio	Brisk	↑↑↑	–

1. Among grades II and III ependymomas, the grade does not appear to correlate with tumor aggressiveness or survival. It is therefore rarely used for treatment stratification. Stay tuned for the likely extinction of histologic grading of ependymomas!
2. Including papillary, clear cell, and tanycytic variants.
3. Classic ependymoma may have areas of geographic necrosis, but palisading necrosis and MVP are only focal.
4. Ependymoma with *RELA* fusion is histologically indistinct from other ependymomas and is graded based on above histopathologic features. Regardless of grade, it carries the worst prognosis.

Abbreviations: *N:C ratio* nuclear-to-cytoplasmic ratio

Reference: [43]

Meningioma: WHO Grading System

Grade I	Lack of higher-grade features
Grade II (atypical)[1]	Any 1 of the 3 criteria: 1. ≥4 mitoses/10 HPF or 2. Brain invasion 3. At least three of the following features: • Sheet-like growth (i.e., loss of lobular architecture) with uninterrupted patternless growth • Prominent nucleoli • Hypercellularity • Small cells with high N:C ratio • Foci of spontaneous necrosis
Grade III (anaplastic/malignant)[2]	Frankly malignant cytology (like that of a carcinoma, melanoma, or undifferentiated pleomorphic sarcoma) and/or ≥20 mitoses/10 HPF (0.16 mm^2)

1. Clear cell and chordoid meningioma are always grade II. An alternative grading approach combines hypercellularity with ≥5 mitoses/10 HPF.
2. Papillary and rhabdoid meningioma are always grade III.

Note: Bone invasion does not raise the grade.

Reference: [43]

Gynecologic Tract

Endometrioid Adenocarcinoma: FIGO Grading	
	% solid growth
Grade 1 (well differentiated)	<5%
Grade 2 (moderately differentiated)	6–50%
Grade 3 (poorly differentiated)	>50%

- Squamoid areas are not counted as solid growth.
- Presence of severe nuclear atypia (grade 3 nuclei) raises the grade by one.

Reference: [44]

Smooth Muscle Neoplasms of the Uterus			
	Mitoses per 10 HPF	Atypia	Coagulative necrosis
Leiomyoma or cellular leiomyoma (increased cellularity)	<5	–	–
Atypical leiomyoma (aka symplastic, pleomorphic, or bizarre)	<10	+	–
Mitotically active leiomyoma	≥5	–	–
Leiomyosarcoma (diagnosis requires at least 2 of 3 features)[1]	>10	+	+

1. When only one of three features is present, the diagnosis of STUMP is made. In a STUMP, however, no more than 15 mitoses per 10 HPF are permissible, but mitotically active STUMP may display some focal atypia.

References: [44–47]

Epithelioid Smooth Muscle Neoplasms of the Uterus			
	Mitoses per 10 HPF	Atypia	Coagulative necrosis
Epithelioid leiomyoma	<5	Minimal	–
Epithelioid STUMP	<5	Moderate to severe	–
Epithelioid leiomyosarcoma	>5[1]	Moderate to severe	+[1]

1. Presence of either >5 mitoses/10 HPF or necrosis qualifies for the diagnosis of leiomyosarcoma.

Reference: [47]

Endometrial Stromal Sarcomas			
	Mitotic activity (mitoses per 10 HPF)	Atypia	Coagulative necrosis
Low-grade	Low (usually <5)	None to minimal	–/+
High-grade	High (>10)	Mild to moderate	+
Undifferentiated	Very high (usually >20)	Severe[1]	+

1. Undifferentiated stromal sarcomas typically display marked pleomorphism, bearing no resemblance to endometrial stroma.

Reference: [46]

Grading of Immature Ovarian Teratomas	
	Fields occupied by immature neuroepithelial elements
Grade I	<1 LPF (4X objective)
Grade II	1–3 LPF
Grade III	>3 LPF

Rule of thumb: grade I, if immature areas are hard to find; grade III, easy to find.

Reference: [46]

Abbreviations: *FIGO* International Federation of Gynecology and Obstetrics, *STUMP* smooth muscle tumor of uncertain malignant potential

Gynecologic Tract: 2

Dating of Endometrium[a] *By Diana Weedman Molavi*	
Proliferative endometrium cannot be dated. The first secretory change occurs, on average, on day 16 or so of a 28-day cycle. This change is the appearance of clear secretory vacuoles at the base of the epithelial cells, below the nuclei. When you see just a few of these in a generally proliferative endometrium, it is called interval endometrium. Beyond that day, specific histologic criteria are:	
From day 16 to day 20, the glands are the most helpful feature.	
Day 16	Subnuclear vacuoles, pseudostratified nuclei
Day 17	Subnuclear vacuoles but with an orderly row of nuclei
Day 18	Vacuoles above and below nuclei (the "piano key" look)
Day 19	Vacuoles diminishing, only above nuclei; orderly row of nuclei, no mitoses
Day 20	Peak secretions in lumen and ragged luminal border, vacuoles rare
From day 21 to 28, the glands stay pretty much the same – they are exhausted and appear low columnar with orderly nuclei, no mitoses, and ragged luminal edges. They may also have degenerative apical vacuoles – tricky to discern from day 19 to 20. After day 21, the stroma is the key.	
Day 21	Stromal edema begins, secretion continues
Day 22	Peak stromal edema with naked nuclei
Day 23	Spiral arteries become prominent
Day 24	Periarteriolar cuffing with predecidua (stromal cells around the arteries begin to get plump pink cytoplasm, creating a pink halo around the vessels)
Day 25	Predecidual change under the surface epithelium
Day 26	Decidual islands coalesce; polys begin to infiltrate stroma
Day 27	Lots of polys in a solid sheet of decidua, with focal necrosis and hemorrhage
Day 28	Prominent necrosis, hemorrhage, clumping, and breakup
[a]Note: The reliability of endometrial dating is controversial.	

Grading and Staging of Infections in the Placenta		
Stage (Reflects Duration)		
	Chorioamnionitis (Maternal neutrophils involving the membranes)	**Funisitis** (Fetal neutrophils migrating from fetal vessels into the umbilical cord and/or chorionic plate)
Stage I	**Subchorionitis** (neutrophils line up beneath the chorion) and **chorionitis** (neutrophils involve the chorion)	**Umbilical phlebitis** (neutrophils in the wall of umbilical vein) or **chorionic vasculitis** (neutrophils in the wall of vessels located in the chorionic plate)
Stage II	**Chorioamnionitis**: neutrophils extend into the amnion	**Umbilical arteritis:** neutrophils in the wall of umbilical arteries
Stage III	**Necrotizing chorioamnionitis:** above plus reactive amnion or necrosis or amniotic basement membrane thickening or band-like inflammation	**Necrotizing funisitis**: neutrophils extend into Wharton jelly and form microabscesses or band-like inflammation
Grade (Reflects Severity)		
Grade I	Mild to moderate	
Grade II	Severe (such as subchorionic microabscesses)	
Note that chorioamnionitis represents a maternal response to infection, whereas funisitis fetal response to infection. Funisitis usually develops later than chorioamnionitis.		
References: [48, 49]		

Transplant Pathology

Grading of Cellular Lung Allograft Rejection, (2007 Update) International Society for Heart and Lung Transplantation (ISHLT) system [reported as, e.g., ISHLT A_0B_x]	
Grade of rejection	**Histologic features**
Acute rejection	
Grade A0 (no rejection)	
Grade A1 (minimal rejection)	Infrequent, scattered perivascular lymphocytes forming a ring 2–3 cells thick
Grade A2 (mild rejection)	More frequent perivascular lymphocytes readily seen at low power (4X objective), cuffing the vessels and expanding the perivascular interstitium
Grade A3 (moderate rejection)	Lymphocytes extend into alveolar septa and airspaces
Grade A4 (severe rejection)	Diffuse interstitial lymphoid infiltrate with diffuse alveolar damage, hemorrhage, and/or necrosis
Bronchial/bronchiolar inflammation	
Grade B0 (no airway inflammation)	
Grade B1R (low grade)	Mononuclear cells within the submucosa of bronchioles without evidence of epithelial damage or intraepithelial infiltration (combines former B1 and B2 categories)
Grade B2R (high grade)	Mononuclear cells are increased in number, are larger, and accompanied by more eosinophils and plasmacytoid cells (but not many neutrophils, which would make you think infection). Also there is epithelial damage (e.g., necrosis, metaplasia) and intraepithelial lymphocytes.
Grade Bx (ungradable)	No evaluable bronchial tissue
Chronic rejection (obliterative bronchiolitis)	
Grade C0	Bronchiolar obliteration absent
Grade C1	Bronchiolar obliteration via fibrosis present. Often subtle and/or focal (a trichrome stain can be helpful).
Chronic vascular rejection	
Grade D	Thickening of arteries and veins, similar to the coronary artery disease seen in transplanted hearts. Not applicable to transbronchial biopsies.
At least five pieces of alveolated lung parenchyma each containing bronchioles and >100 air sacs are defined as sufficient to rule out rejection by ISHLT criteria. Reference: [50]	

Staging of Antibody-Mediated Rejection (AMR) of Lung Transplant International Society for Heart and Lung Transplantation (ISHLT) System	
Criteria	**Description of criteria**
Donor-specific antibodies (DSAs)	High serum antibody titer
Pathology	Neutrophilic capillaritis[1] and/or margination[2] Acute lung injury with or without diffuse alveolar damage and endothelialitis
C4d IHC[3]	>50% capillary staining

Note: There are three stages of AMR, which are defined based on the number of met criteria: definite (all three criteria), probable (any two of three), and possible (any one of three).

1. Neutrophilic capillaritis can be patchy or diffuse and is defined as a dense neutrophilic septal infiltrate with neutrophilic karyorrhexis and fibrin with or without microvascular fibrin thrombi, alveolar hemorrhage, and neutrophil spillover into adjacent airspaces.
2. Neutrophilic margination is characterized by both septal and interstitial neutrophilic capillary infiltration in the absence of karyorrhexis and fibrin.
3. Aside from characteristic pathologic findings described above, additional histopathologic indications for C4d IHC include high-grade acute or cellular rejection (≥A3, B2R, or C1) and persistent/recurrent ACR (any A grade or grade B1R). Furthermore, in the absence of any histologic findings, clinical graft dysfunction or newly detected DSA positivity warrants C4d IHC evaluation.

References: [51, 52]

Grading of Acute Graft-versus-Host Disease (GVHD) in Intestinal (Usually Rectal) Biopsy	
Grade I	Rare apoptotic cells (approximately >3 per crypt; normal is ≤1 per crypt)
Grade II	Loss of individual crypts
Grade III	Loss of two or more contiguous crypts
Grade IV	Complete loss of crypts; mucosal ulceration (neuroendocrine cells are relatively spared from the damages of GVHD, and they may appear as little nests)
Chemotherapy-related changes may be indistinguishable (best not to biopsy <20 days post-BMT). Mycophenolate mofetil immunosuppression therapy, among other etiologies, may also mimic acute GVHD histologically. References: [53, 54]	

Transplant Pathology: 2

Grading of Acute Graft-versus-Host Disease (GVHD) in Skin Biopsy	
Grade I	Vacuolization of the basal layer
Grade II	Above + dyskeratotic/necrotic keratinocytes
Grade III	Above + subepidermal clefting
Grade IV	Above + necrosis and separation of epidermis

Drug reaction looks virtually indistinguishable from GVHD and must be ruled out on clinical grounds. A soft feature that favors GVHD is dyskeratotic cells on hair follicles. Lymphocytes are either absent or minimal in GVHD (unlike drug reaction). Eosinophils favor drug reaction.

With advents of immunosuppression, finding GVHD >grade I is very rare. Thus, this grading system is largely of historical value.

Reference: [55]

Criteria for Acute Cellular Liver Allograft Rejection	
Criteria	**Description**
1. **Portal inflammation**	Lymphocytes with admixed neutrophils and eosinophils involving portal tracts
2. **Ductulitis**	Lymphocytes involving bile ducts with evidence of bile duct damage
3. **Endothelialitis**	Subendothelial and perivenular lymphocytes involving portal and/or hepatic venules

The diagnosis of rejection requires at least two of the three above criteria. The severity of rejection is further qualified as "mild, moderate, or severe" based on intensity of inflammation and the number of involved structures.

Similar to lung transplant, evaluation for acute antibody-mediated rejection (AMR) of liver transplants involves both clinical (elevated serum DSAs), C4d IHC, and histologic criteria, the latter of which are meticulously scored based on degree and extent of portal and periportal endothelial injury (hypertrophy, endotheliitis, and dilation). Other causes, such as obstructive cholangiopathy or reperfusion injury, must be excluded.

Criteria for evaluation of chronic AMR are not as well-defined, making this entity particularly difficult to diagnose.

References: [56, 57]

The Good the Bad and the Ugly:

Prognostic Features in Neoplasms with Difficult-to-Predict Behavior

Adrenocortical Neoplasms

The only definitive criteria for malignancy are distant metastasis and/or local invasion, but various histologic criteria have been devised to predict an aggressive phenotype (Weiss criteria for classical adrenocortical tumors and Lin-Weiss-Bisceglia criteria for oncocytic neoplasms are listed below).

- **Weiss criteria** for histologic assessment of malignancy in adrenocortical neoplasms: [58, 59]
  1. >5 mitoses per 50 HPF*
  2. Atypical mitoses*
  3. Venous invasion*
  4. Sinusoidal invasion
  5. Capsular invasion
  6. Nuclear pleomorphism (equivalent to renal ISUP nuclear grades III and IV)
  7. Clear cells representing <25% of tumor cells (>75% eosinophilic cells)
  8. Diffuse architecture (>33% of tumor)
  9. Necrosis

Malignant tumors have ≥3 of the above criteria, whereas benign tumors have <2. In addition, the *asterisked criteria are found exclusively in malignant tumors. Weiss criteria cannot be applied to oncocytic adrenal tumors because high nuclear grade, <25% clear cells and diffuse architecture are intrinsic features of these tumors regardless of their behavior. Modified criteria have therefore been proposed based on several case series (see Lin-Weiss-Bisceglia criteria below).

- **Lin-Weiss-Bisceglia criteria** for histologic assessment of malignancy in **oncocytic** adrenocortical neoplasms: [60, 61]

Major criteria
1. >5 mitoses per 50 HPF
2. Atypical mitoses
3. Venous invasion

Minor criteria
1. Weight >200 g and/or size >10 cm
2. Necrosis (microscopic)
3. Capsular invasion
4. Sinusoidal invasion

The presence of one major criterion indicates malignancy. In the absence of major criteria, the presence of any of the minor criteria indicates borderline malignant potential. Lack of any of the above features is consistent with benignity.

- Other criteria: Ki67 >5–20% [16]. It is recommended that Ki67 should be scored in a hot spot area within 500–2000 cells, similar to GI neuroendocrine neoplasms [62]. Furthermore, Ki67 has been determined to be an important prognostic marker [63, 64] and should therefore be reported for all adrenocortical carcinomas.
- Helsinki score (3 x mitotic rate/50 HPF + 5 x presence of necrosis + Ki67 index) recently developed, and appears to be superior to the Weiss criteria for predicting malignant behavior [65, 66]. Given its simplicity and accuracy, it is likely to replace Weiss criteria in the future. Stay tuned!

Note: According to some reports, the criteria for malignancy in pediatric tumors should have a higher threshold [16], and additional parameters have impact on prognosis [67, 68].

Pheochromocytoma and Paraganglioma

Ten percent of cases are considered to be malignant. The only definitive criterion for malignancy is distant metastasis. Local invasiveness is not an unequivocal malignant feature. Aggressive behavior is impossible to predict based on any histologic features, but the following two sets of criteria incorporate features that have been associated with malignancy:

PASS (Pheochromocytoma of the adrenal gland scaled score) [69]

- Extension into adjacent adipose tissue [2 points]
- Confluent tumor necrosis (may occur in benign) [2 points]
- Expanded large nests (>3 times the normal "Zellballen" size) and diffuse growth [2 points]
- Increased cellularity [2 points]
- Increased mitoses (>3 mitoses per 10 HPF) [2 points]
- Atypical mitotic figs. [2 points]
- Tumor cell spindling (including focal) [2 points]
- Vascular invasion [1 point]
- Capsular invasion [1 point]
- Profound nuclear atypia with macronucleoli [1 point] and hyperchromasia [1 point] (may occur in benign)

Applies to pheochromocytoma only due to distinctive histologic features. All tumors with subsequent malignant behavior had a PASS ≥4 at initial diagnosis. However, not all tumors with PASS ≥4 subsequently metastasized.

GAPP (Grading system for adrenal Pheochromocytoma and Paraganglioma) [70]

- Histological pattern:
  - Zellballen [0 points]
  - Large, irregular cell nests [1 point]
  - Pseudorosette [1 point]
- Cellularity:
  - Low (<150 cells/U[a]) [0 points]
  - Moderate (150–250 cells/U) [1 point]
  - High (>250 cells/U) [3 points]
- Confluent tumor necrosis [2 points, if present]
- Vascular or capsular invasion [1 point, if present]
- Ki67 (%):
  - <1 [0 points]
  - 1–3 [1 point]
  - >3 [2 points]
- Catecholamine type:
  - Norepinephrine type [1 point]
  - All others [0 points]

The majority of tumors with GAPP <3 (well differentiated) have benign behavior (<4% metastatic rate and 100% 5-year survival). Moderately differentiated (GAPP 3–6) and poorly differentiated (GAPP 7–10) tumors are associated with intermediate and high risk of metastasis and 5-year mortality, respectively.

Other factors: Tumor size >5 cm; *SDHB* mutation (lack of SDHB IHC staining)
Both scoring systems are included in the new WHO classification (2017) for reference, but more recent data has demonstrated **GAPP** to be **superior** to PASS.

[a]U, number of cells in a 10 mm^2 area observed at high power (X400)

References: [16, 69, 70]

The Good the Bad and the Ugly: 2

Parathyroid Neoplasms

The only definitive criteria for malignancy are distant metastasis and/or local invasion. Features that have been associated with malignant behavior include:

- Thick fibrous bands (present in 90% of carcinomas but low specificity)
- Thick capsule
- Infiltrative growth (with adherence to the thyroid and/or soft tissue extension)
- Capsular invasion[a] (present in 2/3 of carcinomas)
- Vascular invasion[a]
- Perineural invasion (pathognomic but present in only 5% of the cases)
- Tumor necrosis
- >5 mitoses per 50 HPF or Ki67 >6%
- Atypical mitotic figures
- Diffuse, marked pleomorphism with macronucleoli (may occur in benign)
- Spindling of tumor cells
- Large size (mean size 3 cm, mean weight 12 g)
- Complete loss of parafibromin immunoexpression (also seen in adenomas of the hyperparathyroidism-jaw tumor syndrome) [71]

[a]Vascular and capsular invasion are assessed using the same criteria as those applied to thyroid follicular carcinoma: vascular invasion should be present within or beyond the tumor capsule, and capsular invasion should be completely penetrating.

Reference: [72]

Gastrointestinal Stromal Tumor (GIST), AFIP Risk Stratification Scheme

Tumor parameters		*Risk of poor outcome by site*			
Size (cm)	**Mitotic rate**	**Stomach**	**Jejunum/ileum**	**Duodenum**	**Rectum**
≤2	≤5 per 5 mm^2	None	None	None	None
>2–5		Very low	Low	Low	Low
>5–10		Low	Moderate	High	High
>10		Moderate	High		
≤2	>5 per 5 mm^2	None	High	Insufficient data	High
>2–5		Moderate		High	
>5–10		High			
>10					

Key poor prognostic factors in GIST are large tumor size, extragastric location, and high mitotic rate. NIH consensus criteria and AFIP criteria for risk stratification of disease recurrence after surgical resection of GIST incorporate these three main prognostic features. Tumor rupture has also been associated with high risk of relapse (80–100%), irrespective of other risk factors [73], and was subsequently incorporated into the modified NIH consensus scheme. Of these three main existing schemes, the AFIP system is favored by the National Comprehensive Cancer Network, the College of American Pathologists, and the European Society for Medical Oncology and was adopted by the AJCC staging manual for clinical practice guidelines [74].

Reference: [75]

Solitary Fibrous Tumor (SFT)

Proposed histologic criteria for malignancy in pleural SFT include [76]:

- High cellularity (crowded, overlapping nuclei)
- >4 mitoses per 10 HPF
- Pleomorphism
- Hemorrhage
- Necrosis

Resectability is the single most important indicator of clinical outcome (regardless of "histologic malignancy"). Size >10 cm also predicts worse outcome. These criteria have also been applied to extrapleural SFT [77].

Reference: [78]

Sertoli and Leydig Cell Tumors[1]

- Size >5 cm
- >5 mitoses per 10 HPF[2]
- Necrosis
- Moderate to severe nuclear pleomorphism/cytologic atypia
- Vascular invasion
- Infiltrative borders/extraprostatic extension

1. Generally, all features are present concurrently in the malignant Sertoli cell tumors. The vast majority of malignant Leydig cell tumors display ≥2 of the above features. Overall, 5% of neoplasms are malignant.
2. The mitotic criteria for malignant Leydig cell tumors are >3 mitoses per 10 HPF.

Reference: [10]

The Good the Bad and the Ugly: 3

PEComas (Perivascular Epithelioid Cell Tumors)[1]		
	Folpe criteria (2005) [79]	**Modified Folpe criteria (2015)** [80]
Benign	Absence of the features listed below	≤1 of the following features: – Invasive edge – Size 5–9 cm – Mitotic rate 2–3/50 HPF – Vascular invasion
Uncertain malignant potential	1 of the following features: – Nuclear pleomorphism/multinucleated giant cells[2] – Size >5cm[3]	1 of the following features: – Marked atypia – Size ≥10 cm – Mitotic count ≥4/HPF
Malignant	≥2 of the following features: – >5 cm – Infiltrative – High nuclear grade and cellularity – Mitotic rate ≥1/50 HPF – Necrosis – Vascular invasion	Any necrosis or ≥2 of the above features

1. PEComas include a variety of tumors with special names: angiomyolipoma (kidney and other sites); clear cell "sugar" tumor (lung); lymphangioleiomyomatosis or LAM (lung); several unusual visceral, intra-abdominal, and soft tissue/bone tumors (clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres, abdominopelvic sarcoma of perivascular epithelioid cells, etc.), plus "PEComa" with no special name, soft tissue/bone, visceral, GYN tract, skin.

   Criteria for predicting malignant potential have been modified over the years. While the original Folpe criteria were designed on the basis of both soft tissue and GYN PEComas, the later criteria (Schoolmeester and modified Folpe) were established based on GYN tumors only. Nonetheless, it is currently recommended to apply **modified Folpe criteria** to categorize the tumors as above and to apply the more stringent Schoolmeester criteria [81] to determine which of the **malignant** tumors are likely to **recur early** [80].

2. "Symplastic" PEComa suggested to be likely benign, but this is uncertain due to few reported cases.

3. It is essential to thoroughly sample large tumors.

References: [79–82]