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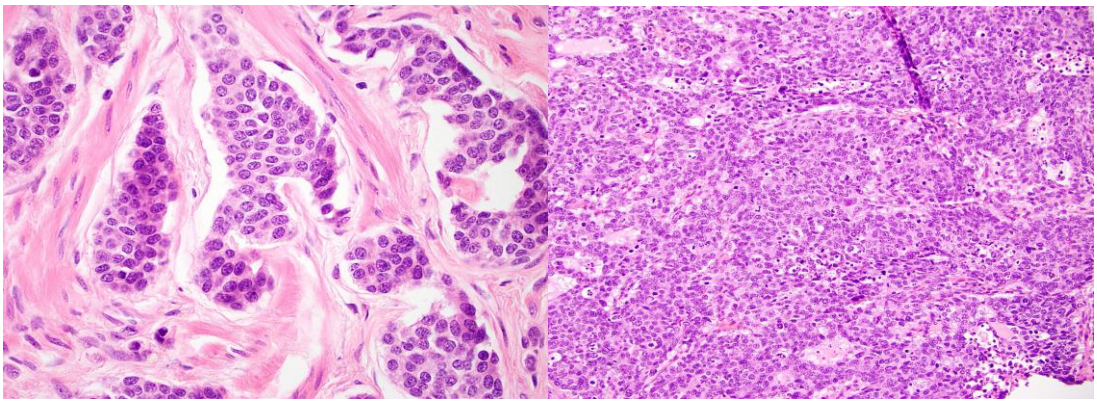
Tweetorial on Gastroenteropancreatic Neuroendocrine Neoplasms

1. Inspired by @smlungpathguy's amazing #Tweetorial on carcinoid tumor of the lung from a while back, I thought I'd try one on gastroenteropancreatic neuroendocrine neoplasms. Here we go! #pathology #gipath

2. The short version is that neuroendocrine neoplasms of the stomach, intestine, and pancreas basically fit into one of two diagnoses: "well-differentiated neuroendocrine tumor" (WD-NET; ye olde 'carcinoid' of lore) and "poorly differentiated neuroendocrine carcinoma" (PD-NEC)

3. Step one is to pick one of those two diagnoses, based PURELY on H&E. It's usually straightforward (carcinoid morphology = WD-NET, ugly badness = PD-NEC), but it can occasionally be a bit tricky. Necrosis is not considered a reliable feature in isolation to distinguish the two.



5. (Yes, there are a few rare organ-specific outliers ... I will cover those later. All the rest of the time, you've got either a WD-NET or a PD-NEC.)

6. You can do IHC to confirm neuroendocrine phenotype. Stick to synaptophysin and chromogranin whenever possible. CD56 is iffy (not terribly sensitive or specific), and I've only ever used it when I was desperate to call something neuroendocrine.

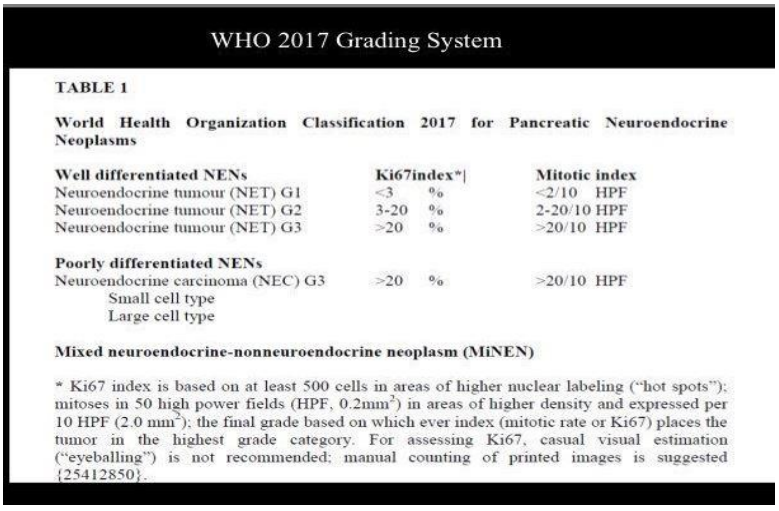
7. Anyway, after you've got the dx, you pick the stage. This is done using WHO/ENETS criteria and based on Ki67 index and mitotic count. "Eyeballing" is probably ok for cases blatantly on either end of the low/high spectrum, but for anything else, you've got to put the time in.

8. For Ki67 count, look at the hottest (brownest) area on the IHC slide, and count between 500 and 2,000 cells, then report the positive number as a percentage. (I count any convincing nuclear staining as positive.) Don't count lymphs by mistake!

9. For mitotic count, you should count the number of mitoses in 10 square mm (probably about 40 high-power fields, but check your microscope and calculate to be sure), then divide by 5 and report the average number in 2 square mm.

10. Sometimes a biopsy will not give you enough material to reach ... In that case, just do your best, and re-grade on the resection specimen (probably a good idea in general anyway).

11. Once you have the Ki67 and the mitotic rate, use this handy dandy chart, and you've got a grade! If the two are discrepant (eg, Ki67 says grade 2 but mitoses say grade 1), pick the HIGHER grade.



WHO 2017 Grading System

TABLE 1

World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms

Well differentiated NENs	**Ki67index*|**	**Mitotic index**
Neuroendocrine tumour (NET) G1	<3 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20 %	>20/10 HPF
Poorly differentiated NENs		
Neuroendocrine carcinoma (NEC) G3	>20 %	>20/10 HPF
Small cell type		
Large cell type		
Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)		

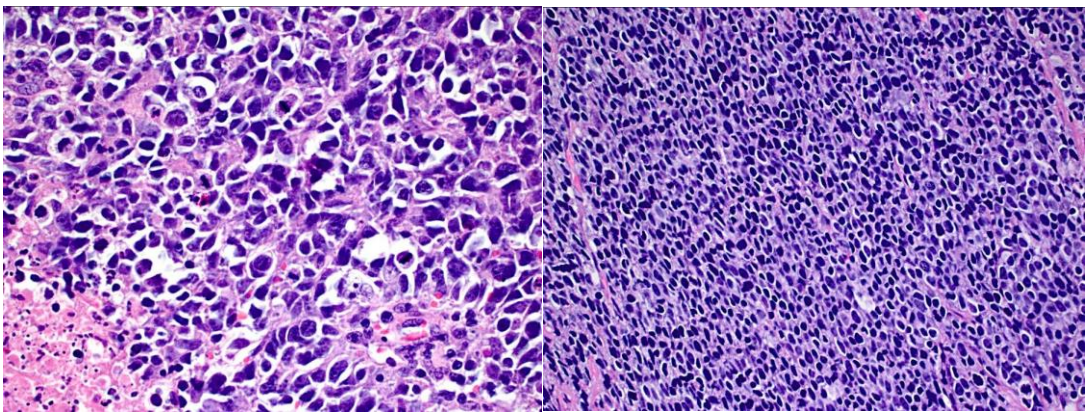
* Ki67 index is based on at least 500 cells in areas of higher nuclear labeling ("hot spots"); mitoses in 50 high power fields (HPF, 0.2mm^2) in areas of higher density and expressed per 10 HPF (2.0 mm^2); the final grade based on which ever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation ("eyeballing") is not recommended; manual counting of printed images is suggested {25412850}.

12. WD-NETs can be ANY grade – 1, 2, or 3. This is official for pancreas with the new WHO 2017 Endocrine blue book. Gastrointestinal WD-NETs still technically use 2010 WHO criteria (which say only grade 1 or 2), but this will be updated next edition.

13. (If you're reading these posts and take away only one thing, have it be that last one. WD-NET can be grade 3!)

14. PD-NECs are basically always grade 3, with Ki67 usually 60% or more. (The few grade 3 WD-NETs I've seen have had a Ki67 of maybe 25%.) It's been recommended that we not bother saying "grade 3" for NECs, since it's implied and can cause confusion. https://bit.ly/2U5PyIt

15. NECs can be subcategorized into large-cell NEC and small-cell NEC. I feel like most GI NECs are "intermediate cell", so I err on the side of calling them large-cell. Small-cell NECs (resembling the same tumor in the lung) are not terribly common in the GI tract.

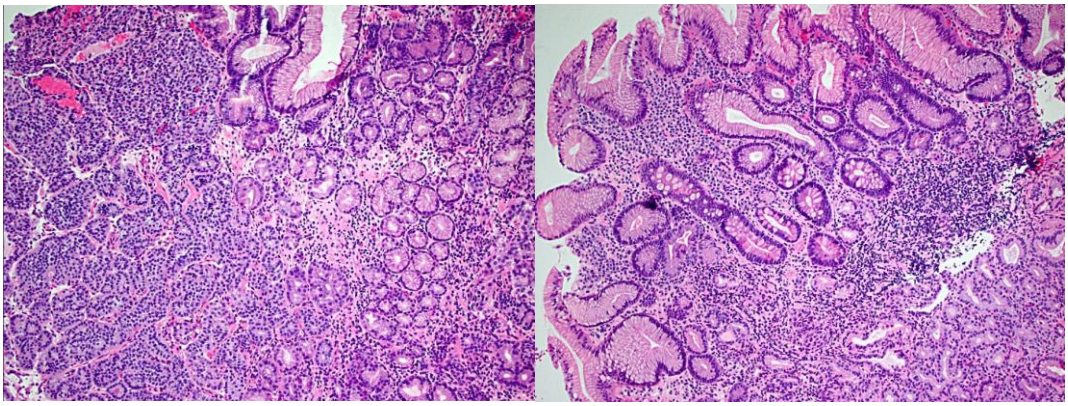


16. Both large-cell and small-cell GI NECs behave badly and are fairly similar, no matter what organ they arise in. There's not a ton of site-specific details to try to remember.

17. WD-NETs, on the other hand, are a different story! Buckle up as we go organ by
organ ...

18. Esophageal NETs are really rare. Never seen one. I hope they're indolent!

19. Gastric NETs fall into one of three categories. Group 1 tumors arise in autoimmune gastritis. They are generally benign and can be multifocal (due to field effect). Background neuroendocrine hyperplasia is common (either linear or nodular ... the distinction is academic).



20. My rule of thumb: If the endoscopist sees a lesion grossly, call it a NET. If you just pick it up via chromogranin staining on a 'flat' mucosal biopsy, call it neuroendocrine hyperplasia.

21. Group 2 NETs occur in Zollinger-Ellison syndrome. Much less common. Also often multifocal. A bit more aggressive than group 1 NETs, but not horrible.

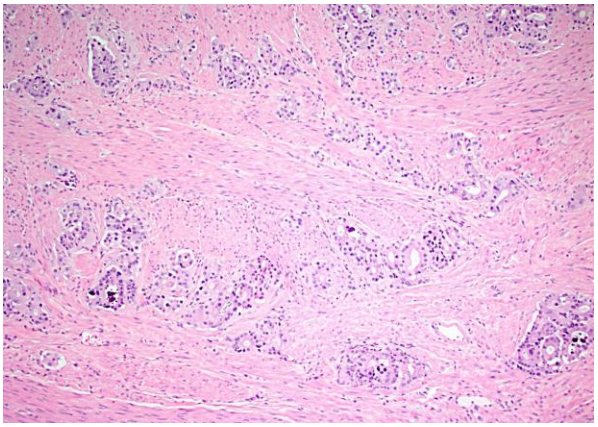
22. Group 3 gastric NETs are the bad actors. They are sporadic, with no known etiology. I've personally only ever seen them pop up in gastric bypass specimens. These have the highest propensity to recur, metastasize, and do harm to the patient.

23. The CAP protocol for gastric NETs has a good table summarizing the different types of NETs there. https://bit.ly/2zKHuEy

24. Good time for this side note ... AJCC 8th edition staging now has different criteria for WD-NETs in each organ. Each one has a corresponding CAP protocol. (PD-NECs follow the adenocarcinoma staging criteria in whatever organ.)

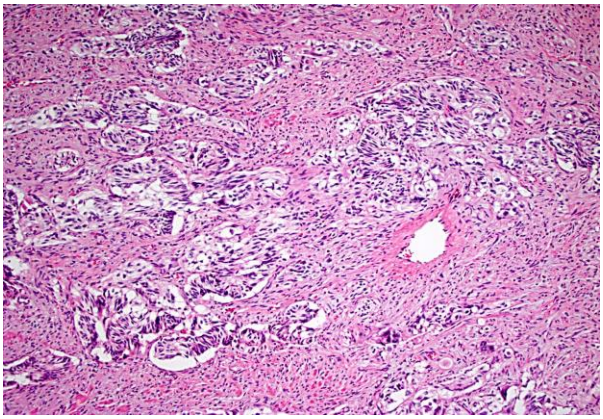
25. Duodenal NETs are uncommon and a bit more aggressive than group 1 stomach NETs. In particular, gastrinomas can metastasize to lymph nodes early in the disease course. For the most part, they're bland and straightforward, with one fun exception!

26. Duodenal/ampullary somatostatinoma usually arises in NF1 patients. It looks pseudoglandular and has lots of psammoma bodies. Don't be fooled!



27. btw, "somatostatinoma" and similar hormone-based diagnoses should be granted based on CLINICAL behavior. IHC staining isn't specific or reliable enough – NETs without clinical gastrinoma symptoms (for example) may still stain for gastrin.

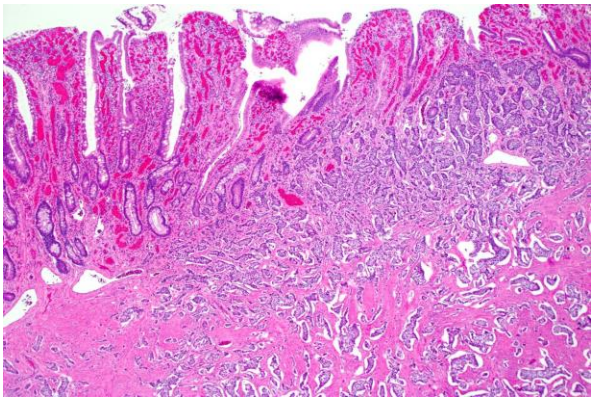
28. Site-specific outlier #1: gangliocytic paraganglioma (GP) is a weird, rare triphasic neoplasm that usually occurs in the duodenum/ampulla. It has epithelioid/endocrine cells, spindle/Schwann cells, and ganglion cells.



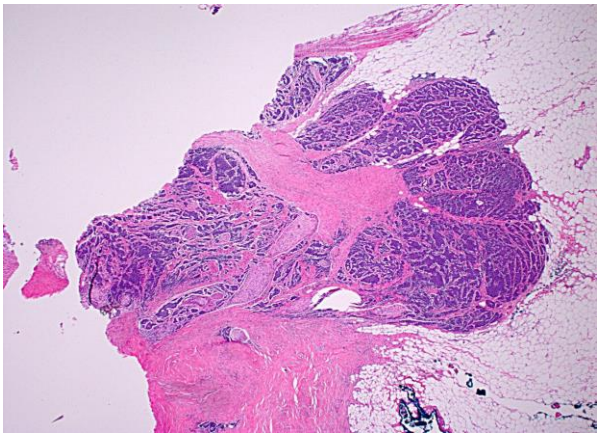
29. Typical neuroendocrine markers will highlight the epithelioid cells and the ganglion cells. S100 will highlight the spindle cells and the ganglion cells.

30. GP is mostly indolent, though it can sometimes spread to lymph nodes, and very very rarely metastasize widely and kill the patient.

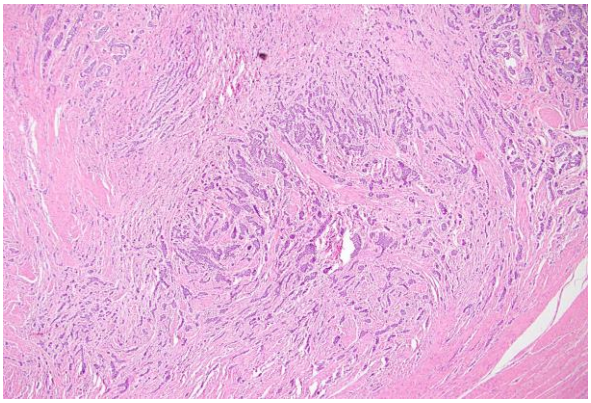
31. Speaking of killing the patient, jejunal/ileal (midgut) NETs are meaner than duodenal NETs. They love to metastasize, even when small. They can also be multifocal. Patients with advanced disease can live for years or decades but eventually succumb.



32. Like colorectal carcinoma, midgut NETs love to create mesenteric tumor deposits. These are now part of AJCC staging and are a worse prognostic indicator than nodal mets. Look for irregular contour and entrapped nerves and vessels. https://bit.ly/2zKI3hE

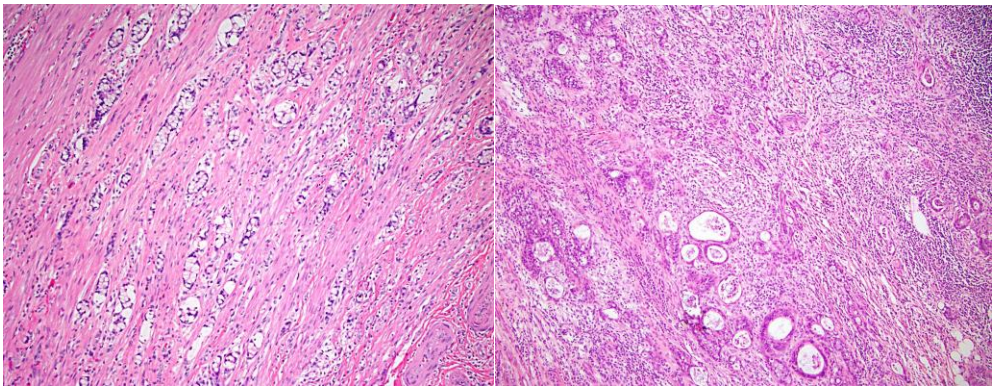


33. Appendix NETs are also midgut, but they don't act too badly. Many of them are small, incidental, and indolent. Always bisect and submit the tip of the appendix!



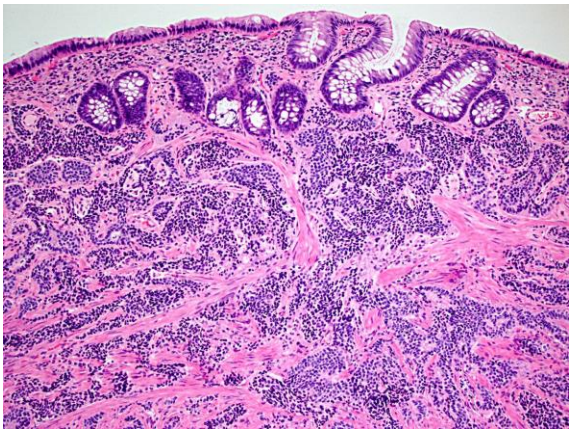
34. Even if they are large and metastatic, appendix NETs basically never do anything worse than jumping to locoregional lymph nodes.

35. Site-specific outlier #2 (sorta): goblet cell carcinoid is going to be called GOBLET CELL CARCINOMA in the upcoming WHO GI blue book. Thank goodness! These things are weird. Here are two good recent papers: https://bit.ly/2zczhsl https://bit.ly/2ATMzKk

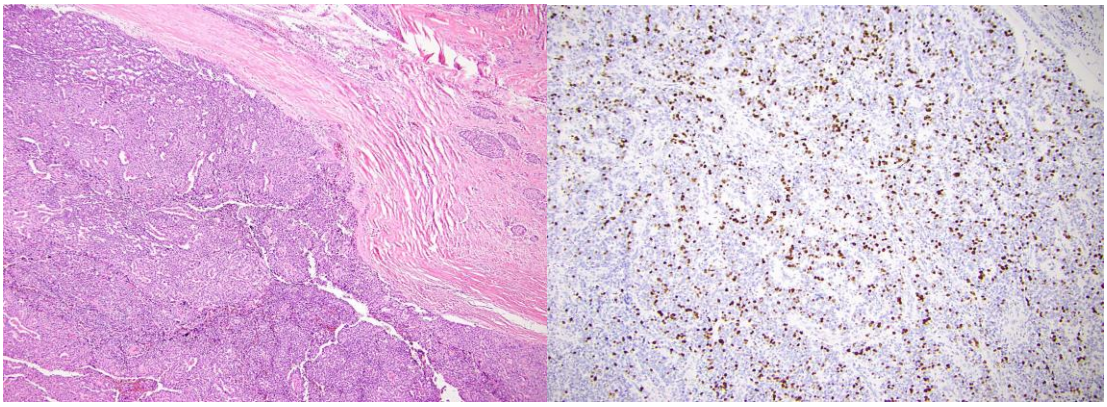


36. NETs are rare in the colon proper – I've only seen two or so. They occur more often in patient with IBD and can actually act aggressively.

37. In contrast, the rectum is a common spot for NETs. Large ones can be bad actors and cause significant morbidity and mortality, but most are small and cured by polypectomy/TEMS (and what seems like eternal follow-up with negative bx.) These can be PSAP-positive, so be careful.



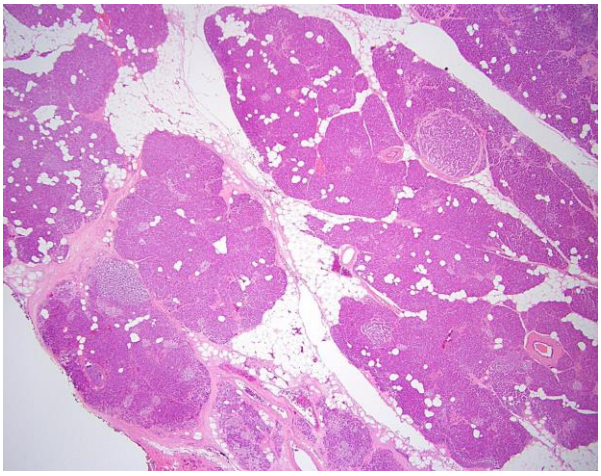
38. I did not forget the pancreas! NETs there have more character than in most other digestive organs. They're the most common pancreatic malignancy after PDAC, and they are G3 more commonly than elsewhere (this is where G3 NETs were first studied). https://bit.ly/2REw10l



39. If they are functional (insulinoma, glucagonoma, etc.), they come to clinical attention earlier, and get resected when smaller. Nonfunctional ones grow larger and have more time to metastasize. (However, gastrinomas and glucagonomas also love to metastasize.)

40. Lots of syndromes are associated with pancreatic NETs! Patients with von Hippel-Lindau, NF1, tuberous sclerosis, and MEN1 are all at increased risk for these tumors.

41. Site-specific outlier #3: patients, especially those with VHL or MEN1, may also have background "neuroendocrine microadenomas" or "carcinoid tumorlets" in their resected pancreas specimens. They are < 0.5 cm and don't appear to cause harm.



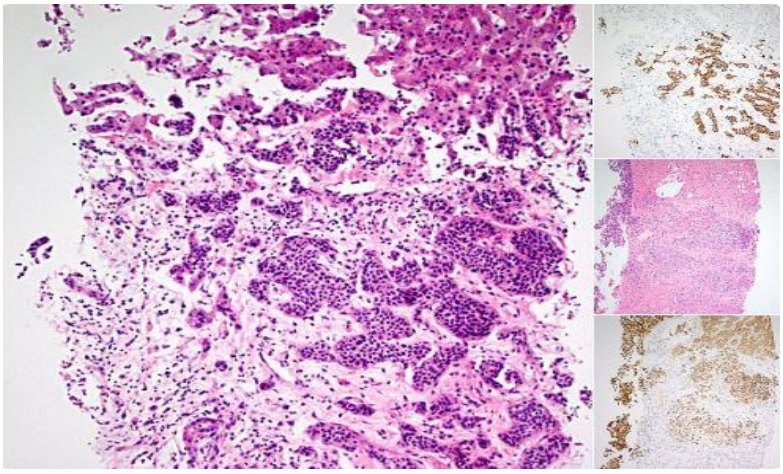
42. Pancreas NETs are also more interesting from a molecular perspective than other GI NETs. Just ask @PancPathologist! They have mutations in MUTYH, CHEK2, BRCA2, MEN1, and VHL, and late aggressive tumors lose DAXX and ATRX.

43. What about the liver? There are reports of primary neuroendocrine neoplasms of the liver (@DraEosina and I are working on one, so I am guilty), but I think most of them are probably small bowel mets where the primary was never really found.

44. Note: Be sure to grade liver mets, even if you know the grade of the primary NET. The metastases may be higher grade! https://bit.ly/2zNJYSD

45. So can IHC help determine the site of origin of a metastatic neuroendocrine tumor? Kinda ...

46. A good panel is TTF1 (lung), CDX2 (GI tract), and polyclonal PAX8 (pancreas). If you have Islet1 IHC, use that instead of PAX8. These are NOT as specific as for adenocarcinomas, so take results w/ a grain of salt. (pix 1,2 = GI met; pix 3,4 = lung met) https://bit.ly/2BVT7tR



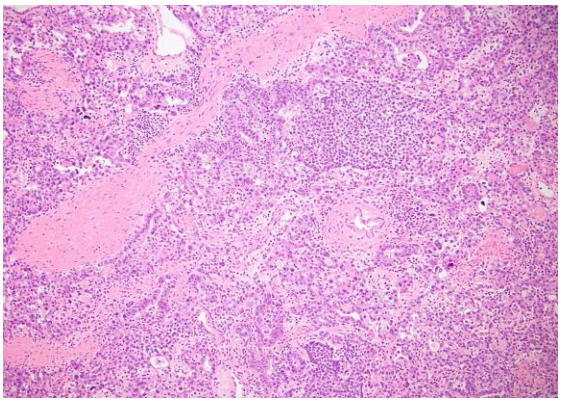
47. Also, in my experience, those IHC markers are even less helpful for NEC than for NET. Those nasty NECs can express whatever the heck they want.

48. Not much more to say about GI tract NECs, honestly. They have poor survival rates and are treated clinically with platinum-based chemo, rather than somatostatin analogues and targeted therapy. Again, I don't think of them differently depending on organ of origin, unlike NETs.

49. Final point to consider is neoplasms with both a neuroendocrine and a non-neuroendocrine component (>30% of each). The old term for these (more or less) is MANEC – mixed adenoneuroendocrine carcinoma. This term is DEAD per the new WHO.

50. The new term is MiNEN, meaning mixed neuroendocrine-non-neuroendocrine neoplasms (I guess MiNEN sounds better than MiNENNEN). The non-NE component can be adenocarcinoma, squamous cell carcinoma, etc.

51. The neuroendocrine component can be NET or NEC. These are hard to truly pin down because they are so unusual and heterogeneous. The more aggressive component probably drives behavior.



52. I think that's enough for now. Excited to see what the future holds! Any questions? #pathology #gipath