Objectives to Review:

- AJCC 8th edition Pancreatic Adenocarcinoma Changes
  - T based on size
  - N based on number of lymph nodes
- AJCC 8th edition Neuroendocrine Neoplasms
  - Well Differentiated Neuroendocrine Tumor WHO Grade 1-3 of 3
  - Poorly Differentiated Neuroendocrine Carcinoma (WHO Grade 3 of 3)
  - Differential Diagnoses to Consider in the Work-up
- Additional Diagnostic Changes to Implement in the Future
  - Cystic Lesions – Dysplasia
  - Differential Diagnoses to Consider in the Work-up
Pancreatic Ductal Adenocarcinoma
AJCC 8th Edition Definitions: T is Focused on Size

T1: 7th ed. - 2 cm or less limited to pancreas
   - 8th edition has subcategories:
     • T1a ≤ 0.5 cm
     • T1b > 0.5 cm ≤ 1.0 cm
     • T1c > 1.0 cm ≤ 2.0 cm

T2: 7th ed. - >2 cm limited to the pancreas
   - 8th edition >2 cm and ≤ 4 cm

T3: 7th ed. - Invasion into the peripancreatic tissue
   - 8th edition >4 cm

T4: 7th ed. - unresectable
   - 8th edition: less emphasis on term "unresectable" in the definition as this is subjective and changing
   - Better to define as extent of invasion: tumor involves celiac axis, superior mesenteric artery and/or common hepatic artery

Pancreatic Ductal Adenocarcinoma:
Problems with AJCC 7th Edition: T3 as Extension Beyond the Pancreas

T3 – “Extension beyond the pancreas” is non discriminating

• Saka/Adsay et al: overall 96% of their cases were pT3 (223 cases)
• Thin pancreas so most carcinomas have a component that extends to a surface
• Pancreas does not have a capsule and the soft tissue often makes deep invaginations between lobules throughout the pancreas
• Chronic pancreatitis can obliterate the border between the pancreatic parenchyma and extra-pancreatic soft tissue

Pancreatic Ductal Adenocarcinoma:
Problems with AJCC 7th edition: T3

T3 – “Extension beyond the pancreas” is not reproducible with regard to outcome

Allen/Mino-Kenudson et al paper: T3N0 7th edition: Median survival difference between center 1 and center 2 was 13 months. This is with expert pancreatic pathologists. (0.50 OS 24 months vs 37 months)

Median survival in PDAC with ‘resectable’ disease is 20.1 to 23.6 months
Pancreatic Ductal Adenocarcinoma: Problems with AJCC 7th edition: T3

T3 – “extension beyond the pancreas” non-discriminating
- Saka/Adsay et al paper: overall 96% of their cases were pT3 (223 cases)
- Thin pancreas so most carcinomas have a component that extends to a surface
- Pancreas does not have a capsule and the soft tissue often makes deep invaginations between lobules throughout the pancreas
- Chronic pancreatitis can obliterate the border between the pancreatic parenchyma and extra-pancreatic soft tissue

T3 – “extension beyond the pancreas” not reproducible with regard to outcome
- Allen/Mino-Kenudson et al paper: T3N0 7th edition: Median survival difference between center 1 and center 2 was 13 months. This is with expert pancreatic pathologists. (.5 probability of overall survival is 24 months vs 37 months)

Thus, T3 lacks prognostic correlation and is not helpful


Comparison of survival between proposed (size based) T stages: T3 defined by >4 cm proposed

Pancreatic Ductal Adenocarcinoma: Proposal for Size Focused T Category:
- Documented to be successful in many solid organ cancers (breast, lung etc.)
  - Mirrors size for Neuroendocrine Tumors (Practical)
  - Numerous studies have found size to be a strong prognosticator
Pancreatic Ductal Adenocarcinoma: Proposal for Size Focused T Category:

Performed recursive partitioning on a training set for size and nodal status
Implemented on a testing set for assessment

Pancreatic Ductal Adenocarcinoma:

AJCC 8th Edition Size Focused
T1-3 N0 M0
Overall Survival (525 pts)

Excluded from patient cohort:
Neoadjuvant treated patients
R1/R2 resections
Not PDAC

Pancreatic Ductal Adenocarcinoma:

AJCC 8th Edition N Category
Tx N1-2 M0
Overall Survival
Pancreatic Ductal Adenocarcinoma:
Seems comparatively reproducible

T3 N0 by 7th edition
T3 N0 by 8th edition

Neoadjuvant Treatment in PDAC
Contemporary approach has focused on borderline resectable disease
Potential to downsize tumor and convert to resectable status (15-40%)
Increase likelihood of a margin-free resection (R0)
Selects surgery for those with more stable or therapy responsive disease
Possible treatment of micrometastases at an earlier stage
Surgery following neoadjuvant treatment appears safe

Difficulty Assessing Size After Neoadjuvant Treatment
Boundary difficult to assess during gross examination:
Therapy induced diffuse fibrosis and chronic pancreatitis
(of both the tumor bed and adjacent non neoplastic pancreas/soft tissue)

Tumor bed difficult to assess during microscopic examination:
Decrease in overall cellularity with a heterogeneous response resulting in nests of surviving tumor separated by unknown distance
Are size based criteria still prognostic after neoadjuvant treatment:
Neoadjuvant Pancreatic Ductal Adenocarcinoma:

- Taking previously classified ypT3 (7th ed.) cases and reclassifying based on 8th ed. size criteria
- ypT1a and ypT1b had better DFS and OS
- No significant difference in DFS or OS between ypT1c, ypT2, and ypT3 (p > 0.05) – promote cutoff at 1.0 cm

Neoadjuvant Pancreatic Ductal Adenocarcinoma: Measuring for Size

Small Residual Cancer (single slide) is easy

Scattered amongst several slides you encounter islands of tumor?
Measuring for Size: Whole Mount?

Summary: Pancreatic Ductal Adenocarcinoma
AJCC 8th Edition Definitions: Focused on Size/Count LN

T1: 7th ed. - 2 cm or less limited to pancreas
   - 8th edition has subcategories:
     - T1a ≤ 0.5 cm; T1b > 0.5 cm ≤ 1.0 cm; T1c > 1.0 cm ≤ 2.0 cm
T2: 7th ed. - >2 cm limited to pancreas
   - 8th edition >2 cm and ≤ 4 cm
T3: 7th ed. - Invasion into peripancreatic tissue
   - 8th edition >4 cm
T4: 7th ed. - unresectable
   - 8th edition Less emphasis on term “unresectable” in the definition as this is subjective and changing
     - Better to define as extent of invasion: Tumor involves celiac axis, superior mesenteric artery and/or common hepatic artery

Neuroendocrine Neoplasms of the Pancreas
Neuroendocrine Neoplasms as **Two Different Diseases**

**Neuroendocrine Tumor vs Carcinoma**

- **Grade 1 / Grade 2 Neuroendocrine TUMOR (Well Differentiated NET)**
  - Cytologically bland
  - Synaptophysin and chromogranin often diffusely positive
  - Inactivating mutations in DAXX and ATRX and mutations in MEN1 are in WD NET
  - Perhaps progressive, prolonged prognosis

- **Small and Large Cell Neuroendocrine CARCINOMA (Poorly Differentiated NEC)**
  - Cytologically ugly
  - May have less diffuse to focal synaptophysin and chromogranin
  - Inactivation TP53 and Rb/p16 pathways frequent in these carcinomas
  - Poor Prognosis

---

### Serologic and Radiologic Considerations

- **WD NET (Grade 1 and Grade 2)**
  - Elevated CgA
  - May have hormonal symptoms if functional (insulinoma, gastrinoma)
  - Somatostatin receptor imaging high avidity – 68Ga DOTATATE (Netspot) or OctreoScan
  - 18FDG PET has a range of avidity

- **PD NEC (Small Cell or Large Cell)**
  - Normal serum CgA markers; maybe elevated carcinoma markers (CA19-9)
  - Hormonal symptoms rare (look into paraneoplastic syndromes if present)
  - Somatostatin receptor imaging often no to low avidity – 68Ga DOTATATE or OctreoScan
  - 18FDG PET high avidity

---

### Table by CAP/AJCC - based on 7th ed. criteria

<table>
<thead>
<tr>
<th>Classification</th>
<th>WHO/Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Well differentiated neuroendocrine tumors, grade 1</td>
<td>G1</td>
<td>≤ 50 mitoses per 10 HPF, no necrosis/eosinophils</td>
</tr>
<tr>
<td>Well differentiated neuroendocrine tumors, grade 2</td>
<td>G2</td>
<td>50 to 500 mitoses per 10 HPF, no necrosis/eosinophils</td>
</tr>
<tr>
<td>Poor differentiated neuroendocrine carcinomas, grade 3</td>
<td>G3</td>
<td>≥ 500 mitoses per 10 HPF, necrosis/eosinophils</td>
</tr>
</tbody>
</table>

---

**PROBLEM:**

- WHO 2010 Digestive System Blue Book and 7th edition AICC:
  - Definition of Poorly Differentiated Neuroendocrine CARCINOMA encompasses a large and heterogeneous group of diseases; they don’t all look or behave as though they belong
Neuroendocrine Neoplasms as **Two Different** Diseases

<table>
<thead>
<tr>
<th>Classification</th>
<th>WHO Grade</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly differentiated neuroendocrine tumor, grade 1</td>
<td>G1</td>
<td>≤ 6 million per 6 HFP; ≤ 1% mitotic rate ≤ 2%</td>
</tr>
<tr>
<td>Poorly differentiated neuroendocrine tumor, grade 2</td>
<td>G2</td>
<td>3–6 million per 6 HFP; ≤ 2% mitotic rate ≤ 25%</td>
</tr>
<tr>
<td>Poorly differentiated neuroendocrine tumors (4)</td>
<td>G3</td>
<td>≤ 6 million per 6 HFP; ≤ 1% mitotic rate ≤ 10%</td>
</tr>
</tbody>
</table>

**PROBLEM:**

- WHO 2010 Digestive System Blue Book and 7th edition AJCC:

- Definition of Poorly Differentiated Neuroendocrine CARCINOMA encompasses a large and heterogeneous group of diseases; they don’t all look or behave as though they belong

- These are not all typical large and small cell neuroendocrine carcinomas.

Impetus to Examine the G3 Category of Neuroendocrine Neoplasms: NORDIC NEC Study

252 patients from 12 Nordic hospitals looking at predictive and prognostic markers in advanced GI NEC patients.

**Conclusion:**

- It may not be correct to consider all GI-NEC as one single disease entity.

- This was concluded on a retrospective study irrespective of morphology and site of origin.
Well-Differentiated Neuroendocrine Tumor Grade 3

AJCC 8th ed. Recommended Grading System for WD Gastroenteropancreatic Neuroendocrine Tumors

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mitotic Rate (per 10 HPF)</th>
<th>Ki-67 index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G1</td>
<td>&lt;2</td>
<td>&lt;2</td>
</tr>
<tr>
<td>G2</td>
<td>3 to 20</td>
<td>3 to 20</td>
</tr>
<tr>
<td>G3</td>
<td>&gt;20</td>
<td>&gt;20</td>
</tr>
</tbody>
</table>

Added a WD NET Grade 3 (without an upper limit) and disposed of PD NEC as a part of this table.

AJCC 8th edition and WHO 2017 Endocrine Organs Blue Book have incorporated this diagnosis.

Footnote in new CAP synoptic reporting template:

Small group of WD NET with a Ki-67 index >20% and a mitotic rate >20 per 10 HPF with the typical morphology of WD NET. AJCC 8th Ed and WHO 2017 blue book of endocrine tumors classify these as “well differentiated neuroendocrine tumor, grade 3.”

*These may also be seen in the literature referred to as grade discordant NET.

Grade Discordant Neuroendocrine Tumors

All Cases

Cases with Distant Metastasis Only
**Well-Differentiated Neuroendocrine Tumor Grade 3**

May be HETEROGENEOUS:

WD NET may have a background of G1/G2 NET with an area of high grade transformation (with both proliferative rate and mitotic index >20%)

---

- **WD NET Grade 3**
  - Nested/organoid and trabecular architecture surrounded by vessels
  - Abundant cytoplasm and stippled chromatin
- **PD NEC – Small Cell Carcinoma**
  - Fusiform nuclei lacking nucleoli, molding
  - Tumor necrosis
  - Stromal desmoplasia
- **PD NEC – Large Cell Carcinoma**
  - Expansile and irregular nests with peripheral palisading
  - Tumor necrosis

---

**A Practical Approach to the Classification of WHO Grade 3 (G3) Well-differentiated Neuroendocrine Tumor (WD-NET) and Poorly Differentiated Neuroendocrine Carcinoma (PD-NEC) of the Pancreas**

Laura H. Tang, MD, PhD, Oliva Bannari, MD, Allison J. Suo, BS, and David S. Kimura, MD

- Poor disagreement among expert pathologists at blindly diagnosing WD NET G3 from PD NEC SCLC/CC based on morphology alone
- 33% concordance among 3 expert pathologists based on morphology of a single slide
- Helpful Ancillary Studies: With immunohistochemistry (molecular and proliferate rate) and resection material (other histologic components present) came to a consensus and survival curves support the final designation
No agreement or determine the subclassification on 62% of the cases by H+E morphology alone of a single slide (ambiguous)

Every biopsy failed to achieve consensus (n=8)

Resections, Ki-67 and molecular IHC to arrive at a final consensus diagnosis → correlate

Morphologic criteria, proliferative rate, molecular alterations together with clinicoradiologic information:

- Time course (rapid deterioration) and other clinicoradiologic features
- Low grade WD (G1/G2) NET elsewhere in tumor OR coexisting conventional carcinoma elsewhere in tumor
- DAXX or ATRX loss in 44% WD NET (not seen in carcinomas) this cohort 10/20
- TPS3, KRAS, p16, RB1, SMAD4 in 91% BC PD NEC and 50-60% LC PD NEC (also in PDAC); this cohort 11/12

Molecular IHC

- Abnormal p53 and loss of Rb and SMAD4 (A,B,C respectively) observed in majority PD-NEC

- Loss of DAXX (D) or ATRX expression observed in 40-50% of WD-NET


• Abnormal p53 and loss of Rb and SMAD4 (A,B,C respectively)
  observed in majority PD-NEC

• Loss of DAXX (D) or ATRX expression observed in 40-50% of WD-NET

32% of WD NET G3 had Ki-67 >55% and 33% of PD NEC had Ki-67 <55%

No absolute cutoff value can sufficiently distinguish these two categories

Platinum-based therapy: CR or PR 37% of PD NEC vs 10% WD panNET G3

Alkylating agents: CR or PR in 50% of PD NEC and WD panNET G3

Cytotoxic therapy traditionally reserved for high grade tumors; however, most trials are not randomized, in small patient populations, and comprise a heterogeneous cohort.

Consideration of a more targeted therapy may be helpful.
FDA approved PRRT (peptide receptor radionuclide therapy): lutetium (Lu) 177 dotatate (DOTA+octreotate) for somatostatin receptor positive GEP-NETs (with octreotide LAR) – radiolabeled somatostatin analogue delivers targeted radiation

NETTER-1 study looked at metastatic midgut NET (Grade 1 and Grade 2); Progression Free Survival at month 20 was 65.2% vs 10.8% in the control group (octreotide LAR alone)

Tx implemented in Europe for several years; case reports with G3 WD panNETs
76 year old F with a 1.6 cm pancreatic tail mass and numerous liver metastases; liver biopsy

If you are considering a Neuroendocrine Carcinoma, Large Cell Morphology...

• But your synaptophysin and chromogranin are negative
  • This is your lipase and chymotrypsin

ACINAR CELL CARCINOMA
65 year old F with a 8.5 cm well circumscribed mass in the pancreatic body

If you are considering a WD NET G3:
• But your synaptophysin and chromogranin come back negative...
• And, your chymotrypsin and Bcl-10 → positive

ACINAR CELL CARCINOMA
Apical eosinophilic cytoplasm, nuclear polarization

Acinar Cell Carcinoma
• Acinar differentiation is defined as the production of pancreatic exocrine enzymes by the neoplastic cells
• Historically (prior to our ancillary studies), rare patients with pancreatic cancer would present (develop) disseminated fat necrosis in their subcutaneous tissue along with polyarthralgia → classic lipase hypersecretion syndrome; now reported to occur only rarely, in <10% of cases
• Gross: Relatively circumscribed expansile growth
• Various architectural patterns: Acinar and solid are the most common, occasionally trabecular
• IHC for trypsin and chymotrypsin
  • Reported to be most sensitive
• IHC for lipase (65% of cases are positive) and bcl-10 are optional
• IHC for amylase is not useful
• Overall 5 year survival rate of 43% (72% if resectable and 22% if metastatic)
On the Horizon: Changes to Cyst Dysplasia Classifications
From Three to Two Tiers of Dysplasia

- Intraductal Papillary Mucinous Neoplasm (IPMN)
- Mucinous Cystic Neoplasm (MCN)
- Pancreatic Intraepithelial Neoplasm (PanIN)

- Mild and Moderate/Intermediate → Low Grade Dysplasia
  - No immediate clinical consequence, poorly reproducible
- Severe/Carcinoma in Situ → High Grade Dysplasia
  - May be clinically relevant

IPMN: Low to High Grade Dysplasia to Carcinoma

Pathologic Evaluation and Reporting of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Other Tumoral Intraepithelial Neoplasms of Pancreatobiliary Tract

Recommendations of Verona Consensus Meeting

- The term "minimally invasive" should be avoided; instead, invasion size with stage and substaging of T1 (1a, b, c; 0.5, >0.5–1, >1 cm) is to be documented.
- Largest diameter of the invasion, not the distance from the nearest duct, is to be used.

- Approximately 30% of IPMNs reveal invasion
  - PDAC, large (≥2.5 cm), main duct, mural nodule, solid component

IPMN with PDAC: 5-year survival 30-50%
PDAC without PDAC: 5-year survival 70-90%
MUCINOUS CYSTIC NEOPLASM
LOW GRADE

Females: Males 20:1
Body or Tail of Pancreas
No communication with the duct system
15-30% Invasive PDAC
MCN with no PDAC: 5 year survival ~100%

Cysts Encountered in Daily Practice:
They aren’t all neoplastic precursors

Simple Mucinous Cyst:
No known pancreatic duct obstruction

Retention Cyst:
In the presence of a pancreatic duct obstruction

Lymphoepithelial Cyst
Cysts Encountered in Daily Practice: They aren’t all neoplastic precursors

Pseudocyst

Acinar Cell Cystadenoma / Acinar Cystic Transformation

Thank you!

Questions?
References


