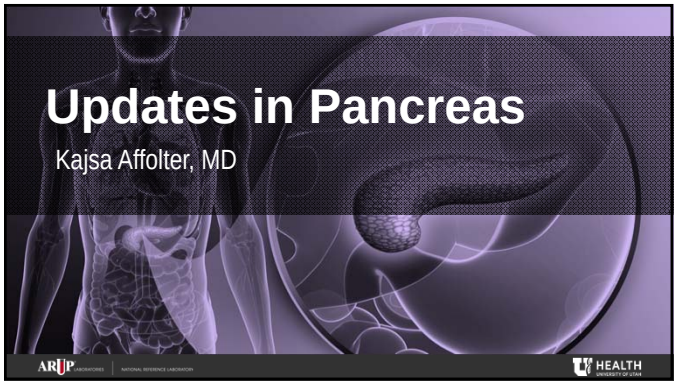


Objectives to Review:

- 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

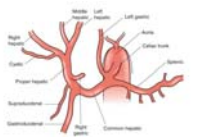
Pancreatic Ductal Adenocarcinoma
AJCC 8th Edition Definitions: T is Focused on Size

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**



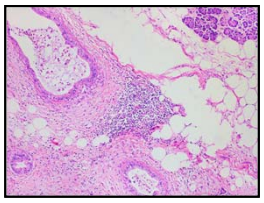
From Blumgart LH, Hann LE: Surgical and radiologic anatomy of the liver and biliary tract. In Blumgart LH, Fong Y [eds]: Surgery of the liver and biliary tract, London, 2000, WB Saunders, pp 3–34.

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

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



ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

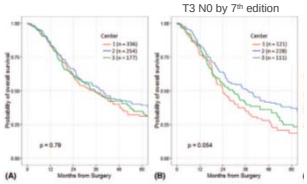
Pancreatic Ductal Adenocarcinoma:
Problems with AJCC 7th edition: T3

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

T3 N0 by 7th edition



Overall survival of 767 patients who underwent resection for node-negative pancreatic cancer. A, Overall survival stratified by institution. B, Overall survival of T3, N0 patients (AJCC 7th edition) stratified by institution.

Allen et al Annals of Surgery Volume 265, Number 1, January 2017

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

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

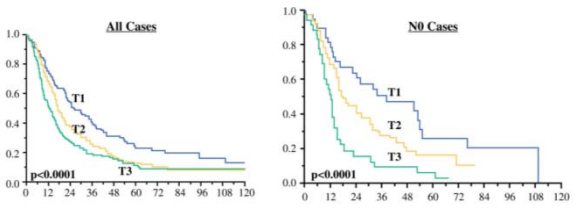
T3 – "extension beyond the pancreas" not reproducible with regard to outcome

- 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

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

Saka et al. Pancreatic Adenocarcinoma is Spread to the Peripancreatic Soft Tissue in the Majority of Resected Cases, Rendering the AJCC T-Stage Protocol (7th Ed.) Inapplicable and Insignificant: A Size-Based Staging System is More Valid and Clinically Relevant. Ann Surg Oncol. 2016



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

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

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

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

Pancreatic Ductal Adenocarcinoma: Proposal for Size Focused T Category:

ORIGINAL ARTICLE

Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma

Peter J. Allen, MD, Deborah Kuk, ScM,† Carlos Fernandez-del Castillo, MD,‡ Ozer Basturk, MD,§ Christopher L. Wolfgang, MD, PhD,¶ John L. Cameron, MD,¶ Keith D. Lillemoe, MD,‡ Cristina R. Ferrone, MD,‡ Vicente Morales-Oyarvide, MD, MPH,‡ Jin He, MD, PhD,¶ Matthew J. Weiss, MD,¶ Ralph H. Hruban, MD,|| Mithat Gönen, PhD,† David S. Klimstra, MD,§ and Mari Mino-Kenudson, MD***

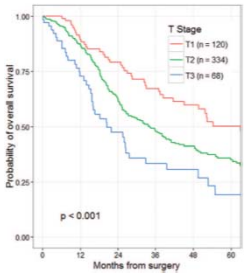
Performed recursive partitioning on a training set for size and nodal status

Implemented on a testing set for assessment

Pancreatic Ductal Adenocarcinoma:

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

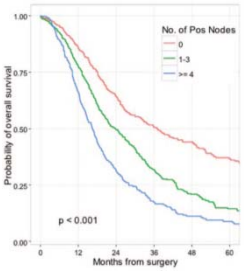
Excluded from patient cohort:
Neoadjuvant treated patients
R1/R2 resections
Not PDAC



Allen et al *Annals of Surgery* Volume 265, Number 1, January 2017

Pancreatic Ductal Adenocarcinoma:

AJCC 8th Edition N Category
Tx N1-2 M0
Overall Survival

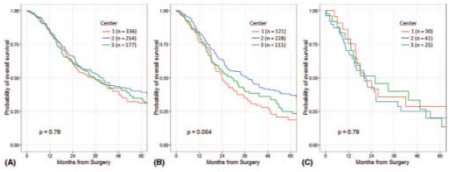


Allen et al *Annals of Surgery* Volume 265, Number 1, January 2017

Pancreatic Ductal Adenocarcinoma:

Seems comparatively reproducible

T3 N0 by 7th edition T3 N0 by8th edition



Allen et al Annals of Surgery Volume 265, Number 1, January 2017

ARUP | HEALTH

Neoadjuvant Treatment in PDAC

Contemporary approach has focused on borderline resectable disease

Borderline Resectable[2]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction; • Solid tumor contact with the SMA of ≤180°; • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be should be noted if present as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some members prefer this criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction. • Solid tumor contact with the inferior vena cava (IVC).

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

ARUP | HEALTH

Difficulty Assessing Size After Neoadjuvant Treatment

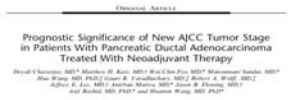
Boundary difficult to assess during gross examination:
Therapy induced diffuse fibrosis and chronic pancreatitis
(of both the tumor bed and adjacent non neoplastic pancreas/soft tissue)

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:

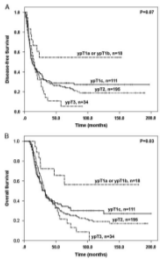
ARUP | HEALTH

Neoadjuvant Pancreatic Ductal Adenocarcinoma:


Original Article

Prognostic Significance of New AJCC Tumor Stage in Patients With Pancreatic Ductal Adenocarcinoma Treated With Neoadjuvant Therapy

- 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

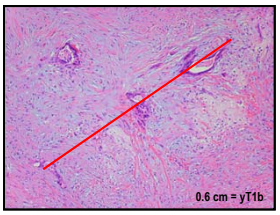


Chatterjee D, *Am J Surg Pathol.* 2017

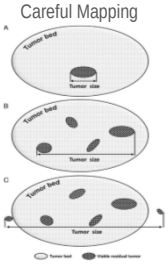
ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

Neoadjuvant Pancreatic Ductal Adenocarcinoma: Measuring for Size

Small Residual Cancer (single slide) is easy



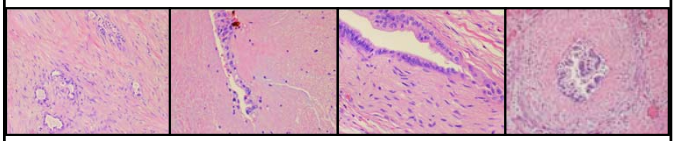
Careful Mapping



Chatterjee D, *Am J Surg Pathol.* 2017

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

Scattered amongst several slides you encounter islands of tumor?

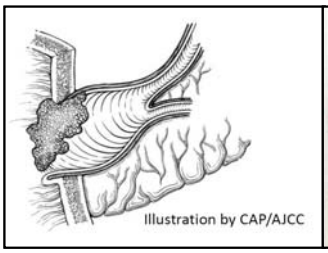


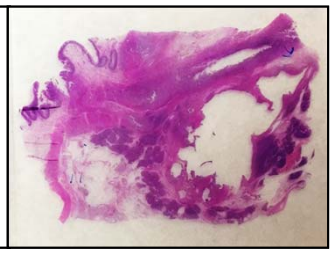
SLIDE 2 | SLIDE 6 | SLIDE 8 | SLIDE 11

5 slides representative of 5 mm adjacent sections – 2.5 cm - ypT2

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

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 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**

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

Neuroendocrine Neoplasms as Two Different Diseases
Neuroendocrine Tumor vs Carcinoma
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

Neuroendocrine Neoplasms as Two Different Diseases

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

Classification	WHO Grade	Features
Well-differentiated neuroendocrine tumor, grade 1	G1	<2 mitoses per 10 HPF; Ki-67 labeling index ≤2%
Well-differentiated neuroendocrine tumor, grade 2	G2	2 to 20 mitoses per 10 HPF; Ki-67 labeling index 3%-20%
Poorly differentiated neuroendocrine carcinoma (small cell carcinoma or large cell endocrine carcinoma), grade 3[#]	G3	>20 mitoses per 10 HPF; Ki-67 labeling index >20%

- 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

Neuroendocrine Neoplasms as Two Different Diseases

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

Classification	WHO Grade	Features
Well-differentiated neuroendocrine tumor, grade 1	G1	<2 mitoses per 10 HPF; Ki-67 labeling index ≤2%
Well-differentiated neuroendocrine tumor, grade 2	G2	2 to 20 mitoses per 10 HPF; Ki-67 labeling index 3%–20%
Poorly differentiated neuroendocrine carcinoma (small cell carcinoma or large cell endocrine carcinoma), grade 3[#]	G3	>20 mitoses per 10 HPF; Ki-67 labeling index >20%

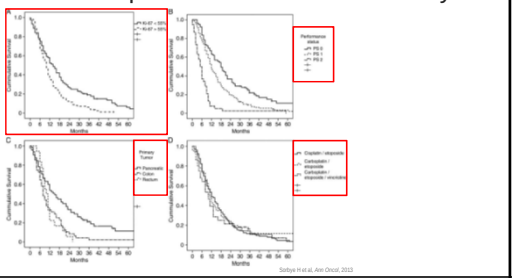
- PROBLEM:
- WHO 2010 Digestive System Blue Book and 7th edition AJCC:

- 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

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

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



Sorbye H et al. Ann Oncol, 2013

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

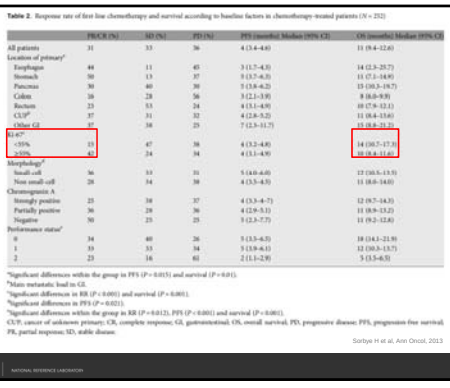


Table 2. Response rate of first-line chemotherapy and survival according to baseline factors in chemotherapy-treated patients (*N* = 252)

	PR/CR (%)	SD (%)	PD (%)	PFS (months) Median (95% CI)	OS (months) Median (95% CI)
All patients	31	33	36	4 (3.4–4.6)	11 (9.4–12.6)
Location of primary[a]					
Esophagus	44	11	45	5 (3.7–8.3)	14 (2.3–25.7)
Stomach	50	13	37	5 (3.7–6.3)	11 (7.1–14.9)
Pancreas	30	40	30	5 (3.8–6.2)	15 (10.3–19.7)
Colon	16	28	56	3 (2.1–3.9)	8 (6.0–9.9)
Rectum	23	53	24	4 (3.1–4.9)	10 (7.9–12.1)
CUP[b]	37	31	32	4 (2.8–5.2)	11 (8.4–13.6)
Other GI	37	38	25	7 (2.3–11.7)	15 (8.8–21.2)
Ki-67[c]					
<55%	53	47	38	6 (3.2–8.8)	14 (10.7–17.3)
≥55%	15	24	34	4 (3.1–4.9)	10 (8.4–11.6)
Morphology[d]					
Small cell	36	33	31	5 (4.0–6.0)	12 (10.5–13.5)
Non small cell	28	34	38	4 (3.3–4.3)	11 (8.0–14.0)
Chromogranin A					
Strongly positive	25	38	37	4 (3.3–4.7)	12 (9.7–14.3)
Partially positive	36	28	36	4 (2.9–5.1)	11 (8.9–13.2)
Negative	50	25	25	5 (2.3–7.7)	11 (9.2–12.8)
Performance status[e]					
0	34	40	26	5 (3.5–6.5)	18 (14.1–21.9)
1	33	33	34	5 (3.9–6.1)	12 (10.3–13.7)
2	23	16	61	2 (1.1–2.9)	5 (3.5–6.5)

[a]Significant differences within the group in PFS ($P = 0.015$) and survival ($P = 0.01$).
[b]Main metastatic load in GI.
[c]Significant differences in RR ($P < 0.001$) and survival ($P = 0.001$).
[d]Significant differences in PFS ($P = 0.021$).
[e]Significant differences within the group in RR ($P = 0.012$), PFS ($P < 0.001$) and survival ($P < 0.001$).
CUP, cancer of unknown primary; CR, complete response; GI, gastrointestinal; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Sorbye H et al. Ann Oncol, 2013

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.

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

Well-Differentiated Neuroendocrine Tumor Grade 3

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

Grade	Mitotic Rate (per 10 HPF)	Ki-67 index (%)
Well-differentiated neuroendocrine tumor, G1	<2	<3
Well-differentiated neuroendocrine tumor, G2	2 to 20	3 to 20
Well-differentiated neuroendocrine tumor, G3	>20	>20

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:

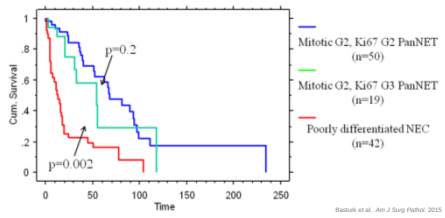
Small group of WD NET with a Ki-67 index >20% and a mitotic rate <20 per 10 HPF with the typical morphology of WD NET. AJCC 8th Ed and WHO-2017 blue book of endocrine tumors classify these as "well differentiated neuroendocrine tumor, grade 3."

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

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

Grade Discordant Neuroendocrine Tumors

All Cases

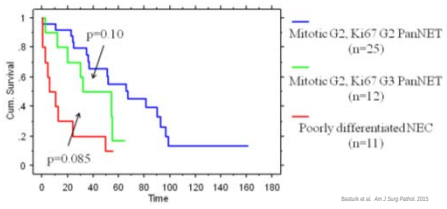


Basturk et al. *Am J Surg Pathol.* 2015

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

Grade Discordant Neuroendocrine Tumors

Cases with Distant Metastasis Only



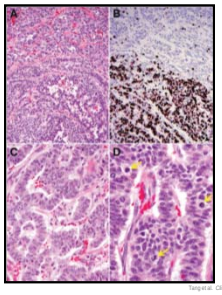
Basturk et al. *Am J Surg Pathol.* 2015

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

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%)

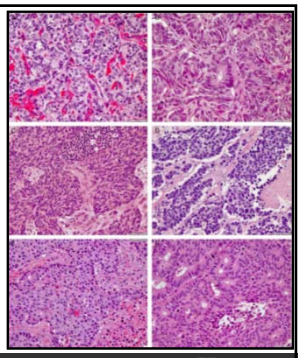


Tang et al. *Clin Cancer Res.* 2016

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

- 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

Tang et al. *Am J Surg Pathol*. 2016



ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

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

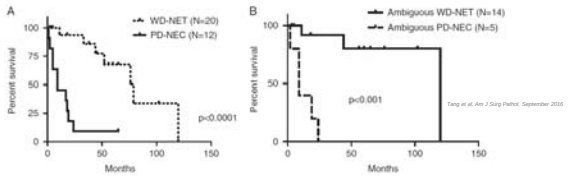
Laura H. Tang, MD, PhD, Olca Basturk, MD, Jillian J. Sue, BSc, and David S. Klimstra, MD

- Poor disagreement among expert pathologists at blindly diagnosing WD NET G3 from PD NEC SCC/LCC 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

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

- 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

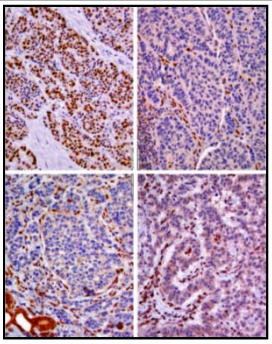


Morphologic criteria, proliferative rate, molecular alterations together with clinicoradiologic information:

- 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 carcinoma); this cohort 10/20
- TP53, KRAS, p16, RB1, SMAD4 in 91% SC 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

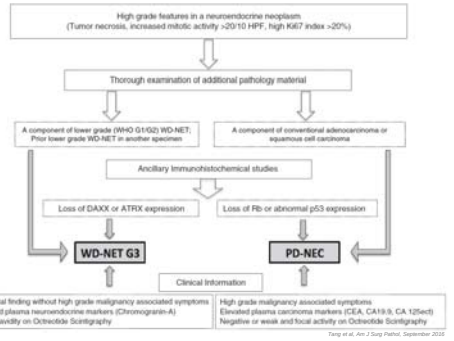


Tang et al, Am J Surg Pathol, September 2016

Initial Consensus	IHC Abnormalities	Ki67%	Other Histologic Components	Confirmed Classification
WD-NET		50	G1,G2 WD-NET	WD-NET
WD-NET	DAXX	70	G1,G2 WD-NET	WD-NET
WD-NET	ATRX	50	G1,G2 WD-NET	WD-NET
WD-NET		40	G1,G2 WD-NET	WD-NET
WD-NET	DAXX	35	G1,G2 WD-NET	WD-NET
WD-NET		32	G1,G2 WD-NET	WD-NET
Ambiguous		35	G1,G2 WD-NET	WD-NET
Ambiguous		65	G1,G2 WD-NET	WD-NET
Ambiguous	DAXX	50	G1,G2 WD-NET	WD-NET
Ambiguous	ATRX	35	G1,G2 WD-NET	WD-NET
Ambiguous	DAXX	30	G1,G2 WD-NET	WD-NET
Ambiguous		60	G1,G2 WD-NET	WD-NET
Ambiguous	ATRX	40		WD-NET
Ambiguous	DAXX	80	G1,G2 WD-NET	WD-NET
Ambiguous	DAXX	40	G1,G2 WD-NET	WD-NET
Ambiguous		30	G1,G2 WD-NET	WD-NET
Ambiguous		60	G1,G2 WD-NET	WD-NET
Ambiguous		50	G1,G2 WD-NET	WD-NET
Ambiguous		70	G1,G2 WD-NET	WD-NET
Ambiguous	p53/Rb	85		PD-NEC
Ambiguous	p53/SMAD4	30	Ductal adenocarcinoma	PD-NEC
Ambiguous	p53/Rb	70		PD-NEC
Ambiguous	p53/Rb	85		PD-NEC
Ambiguous	p53	60		PD-NEC
Ambiguous		70		Undetermined
PD-NEC-LCC	DAXX	66	G1,G2 WD-NET	WD-NET
PD-NEC-LCC	Rb	44		PD-NEC
PD-NEC-LCC		26	Ductal adenocarcinoma	PD-NEC
PD-NEC-SCC	p53	80	Ductal adenocarcinoma	PD-NEC
PD-NEC-SCC	Rb	90		PD-NEC
PD-NEC-SCC	p53/Rb	94	Ductal adenocarcinoma	PD-NEC
PD-NEC	Rb	84		PD-NEC
PD-NEC	p53	88		PD-NEC

Tang et al. Am J Surg Pathol. September 2016

- **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**



Tang et al. Am J Surg Pathol. September 2016

Diagnosis Impacts the Prognosis, but Does it Impact Treatment Options?

Table 2. Response rate of first line chemotherapy and survival according to baseline factors in chemotherapy treated patients (N = 202)

NORDIC Sorbye H et al. Ann Oncol. 2013

	PR/CR (%)	SD (%)	PD (%)	PFS (months) Median (95% CI)	OS (months) Median (95% CI)
Ki-67					
<55%	15	47	38	4 (3.2-4.8)	14 (10.7-17.3)
≥55%	42	24	34	4 (3.1-4.9)	10 (8.4-11.6)

Treatment Response and Outcomes of Grade 3 Pancreatic Neuroendocrine Neoplasms Based on Morphology
Well Differentiated Versus Poorly Differentiated Pancreas • Volume 46, Number 3, March 2017

Nitya Raj, MD, Emily Valentino, BA,* Marinela Capanu, PhD,† Laura H. Tang, MD, PhD,‡ Olca Basturk, MD,‡ Brian R. Untch, MD,§ Peter J. Allen, MD,‖ David S. Klimstra, MD,‡ and Diane Reidy-Lagunes, MD, MS**

- 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.

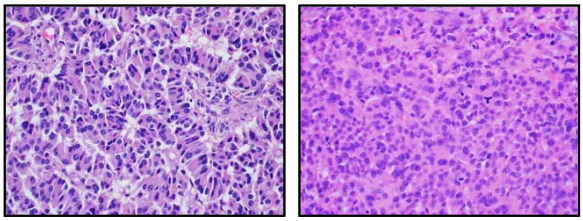
Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

Jonathan Strosberg, M.D., Ghassan El-Haddad, M.D., Edward Wolin, M.D., Andrew Hendifar, M.D., James Yao, M.D., Beth Chasen, M.D., Erik Mittra, M.D., Ph.D., Pamela L. Kunz, M.D., Matthew H. Kulke, M.D., Heather Jacene, M.D., David Bushnell, M.D., Thomas M. O'Dorisio, M.D., Richard P. Baum, M.D., Harshad R. Kulkarni, M.D., Martyn Caplin, M.D., Rachida Lebtahi, M.D., Timothy Hobday, M.D., Ebrahim Delpassand, M.D., Eric Van Cutsem, M.D., Ph.D., Al Benson, M.D., et al., for the NETTER-1 Trial Investigators*

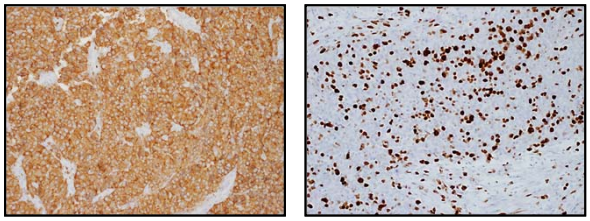
- FDA approved PRRT (peptide receptor radionuclide therapy): lutetium (Lu) 177 dotatate (DOTA+octreotate) for somatostatin receptor positive GEP-NETs (with octreotide LAR) – radiolabeled somatostatin analogue delivers targeted radiation
- NETTER-1 study looked at metastatic midgut NET (Grade 1 and Grade 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

ARUP | HEALTH

Pancreatic Tail Mass in 56 Year-Old Male



ARUP | HEALTH



Synaptophysin Diffusely Positive

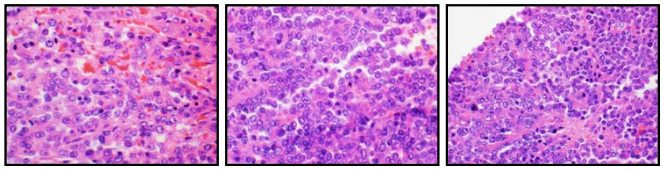
Ki-67 proliferative rate of 30%

WD Pancreatic Neuroendocrine Tumor, WHO Grade 3

ARUP | HEALTH

76 year old F with a 1.6 cm pancreatic tail mass and numerous liver metastases; liver biopsy

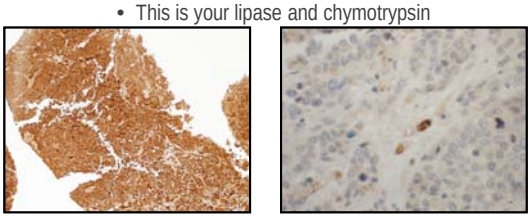
76 year old F with a 1.6 cm pancreatic tail mass and multiple liver masses; liver biopsy



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

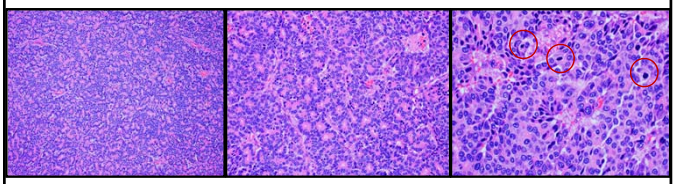
If you are considering a Neuroendocrine Carcinoma, Large Cell Morphology…

- 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

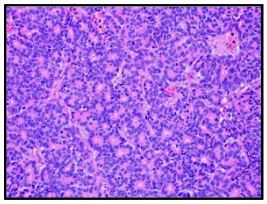


If you are considering a WD NET G3:

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

A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas

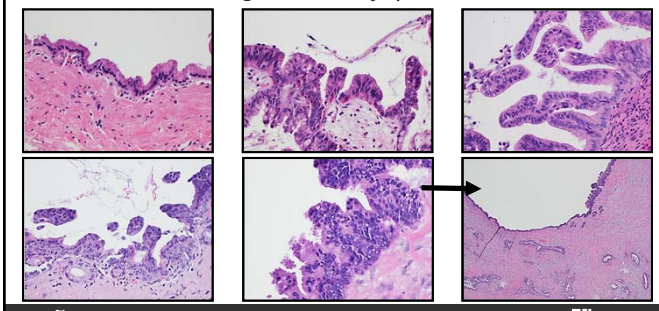
Am J Surg Pathol • Volume 39, Number 12, December 2015

- 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

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

IPMN: Low to High Grade Dysplasia to Carcinoma



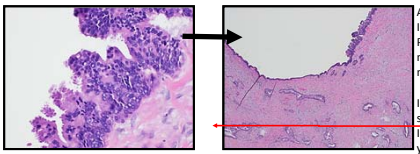
ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

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

(*Ann Surg* 2016;263:162–177)

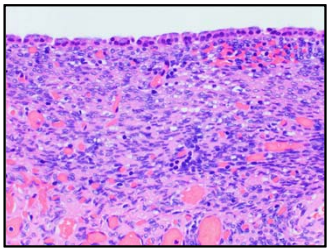
- The term "minimally invasive" should be avoided; instead, invasion size with stage and substaging of T1 (1a, b, c; 0.5, >0.5–1, >1 cm) is to be documented.
- Largest diameter of the invasion, not the distance from the nearest duct, is to be used.



Approximately 30% of IPMNs reveal invasive PDAC; large (>3.0 cm), main duct, mural nodule, solid component

IPMN with PDAC: 5 year survival 30-50%
IPMN without PDAC: 5 year survival 70-90%

ARUP LABORATORIES | NATIONAL REFERENCE LABORATORY — HEALTH UNIVERSITY OF UTAH

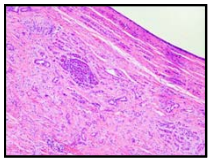


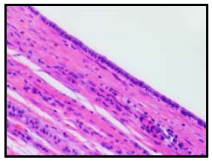
MUCINOUS CYSTIC NEOPLASM LOW GRADE

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%

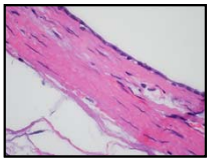
ARUP | HEALTH

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





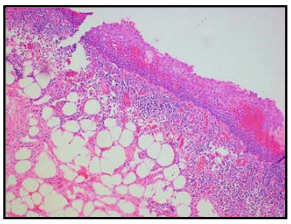
Simple Mucinous Cyst:
No known pancreatic duct obstruction

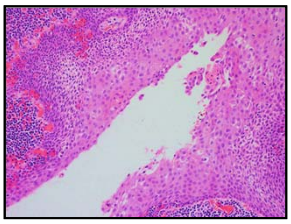


Retention Cyst:
In the presence of a pancreatic duct obstruction

ARUP | HEALTH

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

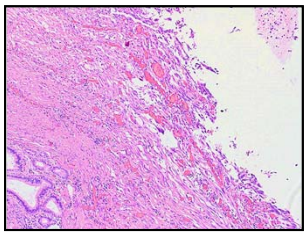




Lymphoepithelial Cyst

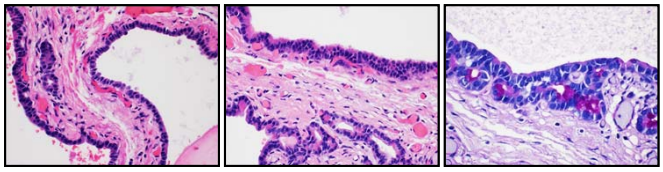
ARUP | HEALTH

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



Pseudocyst

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



Acinar Cell Cystadenoma / Acinar Cystic Transformation

Thank you!

Questions?

References

- Sorbye H, Welin S, Langer SW, Vestermark LW, Holt N, Osterlund P, Dueland S, Hofsli E, Guren MG, Ohrling K, Birkemeyer E, Thiis-Evensen E, Biagini M, Gronbaek H, Soveri LM, Olsen IH, Federspiel B, Assmus J, Janson ET, Knigge U. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. Ann Oncol. 2013 Jan;24(1):152-60. doi: 10.1093/annonc/mds276. Epub 2012 Sep 11. PubMed PMID: 22967994.
- Basturk O, Yang Z, Tang LH, Hruban RH, Adsay V, McCall CM, Krasinskas AM, Jang KT, Frankel WL, Balci S, Sigel C, Klimstra DS. The high-grade (WHO G3) pancreatic neuroendocrine tumor category is morphologically and biologically heterogenous and includes both well differentiated and poorly differentiated neoplasms. Am J Surg Pathol. 2015 May;39(5):683-90. doi: 10.1097/PAS.0000000000000408. PubMed PMID: 25723112; PubMed Central PMCID: PMC4398606.
- Tang LH, Untch BR, Reidy DL, O'Reilly E, Dhall D, Jih L, Basturk O, Allen PJ, Klimstra DS. Well-Differentiated Neuroendocrine Tumors with a Morphologically Apparent High-Grade Component: A Pathway Distinct from Poorly Differentiated Neuroendocrine Carcinomas. Clin Cancer Res. 2016 Feb 15;22(4):1011-7.
- Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, Lillemoe KD, Ferrone CR, Morales-Oyarvide V, He J, Weiss MJ, Hruban RH, Gönen M, Klimstra DS, Mino-Kenudson M. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. Ann Surg. 2017 Jan;265(1):185-191.
- Chatterjee D, Katz MH, Foo WC, Sundar M, Wang H, Varadhachary GR, Wolff RA, Lee JE, Maitra A, Fleming JB, Rashid A, Wang H. Prognostic Significance of New AJCC Tumor Stage in Patients With Pancreatic Ductal Adenocarcinoma Treated With Neoadjuvant Therapy. Am J Surg Pathol. 2017 Aug;41(8):1097-1104.
- Klimstra DS, Adsay V. Acinar neoplasms of the pancreas-A summary of 25 years of research. Semin Diagn Pathol. 2016 Sep;33(5):307-18.
- Basturk O, Hong SM, Wood LD, Adsay NV, Albores-Saavedra J, Biankin AV, Brosens LA, Fukushima N, Goggins M, Hruban RH, Kato Y, Klimstra DS, Klöppel G, Krasinskas A, Longnecker DS, Matthaei H, Offerhaus GJ, Shimizu M, Takaori K, Terris B, Yachida S, Esposito I, Furukawa T; Baltimore Consensus Meeting. A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas. Am J Surg Pathol. 2015 Dec;39(12):1730-41.
- Tang LH, Basturk O, Sue JJ, Klimstra DS. 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. Am J Surg Pathol. 2016 Sep;40(9):1192-202.