Challenges in Pancreatobiliary Pathology

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Introduction

- **Numbers of pancreaticoduodenectomies (PDs) rapidly increased in the 1990s; John Cameron performed 2000 PDs, first 1000 over a period of 34yrs, second 1000 over a period of 9yrs**

Cameron & He. J Am Coll Surg 2015; 220: 530-6

- **Assessment of PD resection specimens**
- **Diagnostic entities & differential diagnoses**
- **Resection margins and status**
- **Assessment of cystic neoplasms**
- **Precursor lesions***
- **TNM staging***

Precursor lesions

- PanINs, intraductal papillary mucinous neoplasms (IPMNs), mucinous cystic neoplasms (MCNs)
- Baltimore consensus meeting has proposed **two-tiered** histology classification system (WHO 2010 is 3-tiered)

- PanIN: **low-grade PanIN** (currently PanINs-1A, 1B &2)
  high-grade PanIN (currently PanIN-3)
- IPMN: **IPMN, low-grade** (currently IPMN with LGD or IGD)
  IPMN, high-grade (currently IPMN with HGD)
- MCN: **MCN, low-grade** (currently MCN with LGD or IGD)
  MCN, high-grade (currently MCN with HGD)

Basturk O et al. Am J Surg Pathol 2015; 39 (12): 1730-41

UICC TNM7 - pancreatic cancer

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ[a]
T1	Tumor limited to pancreas, 2 cm or less in greatest dimension
T2	Tumor limited to pancreas, more than 2 cm in greatest dimension
T3	Tumor extends beyond pancreas, but without involvement of celiac axis or superior mesenteric artery
T4	Tumor involves celiac axis or superior mesenteric artery

- **Based on tumour size and extension**
- **Combination of macroscopy & microscopy**

T1 - tumour ≤2cm

- 'Minimally' invasive PDACs are detected in IPMNs, intraductal tubulopapillary neoplasms and MCNs
- What is 'minimally invasive'?:

'≤5mm in depth'

'Minute focus/foci of invasion'

'Cancer discovered only on microscopy'

'T1 cancer'

- Suggested now that this term 'minimally invasive' is abandoned

Pancreas - subdivide T1

- **Proposed subdividing T1 into**

pT1a ≤0.5cm

pT1b >0.5 & ≤1cm

pT1c >1-2cm

for cancers arising in IPMNs, ITPNs and MCNs

Tanaka M et al. Pancreatology 2012; 12: 183-97

Adsay et al. Ann Surg 2016; 263(1): 162-77

T2 &T3 - pancreatic cancer

- Tumour limited to (T2) or extends beyond (T3) pancreas
- Pancreas has no capsule
- Often invaginations of peripancreatic (fatty) tissue between lobules (does not equate to peripancreatic (T3) invasion)
- Distinction between pancreatic and extrapancreatic soft tissue can be obscured by fibrosis (tumour or chronic pancreatitis)
- Careful examination, 95% of cases are T3
- Suggested that tumour size becomes defining parameter for T3

Adsay et al. Sem Diagn Pathol 2012; 29: 127-41

Invasion of intrapancreatic BD?

Regional Lymph Nodes

The regional lymph nodes are the peripancreatic nodes, which may be subdivided as follows:

Superior	Superior to head and body
Inferior	Inferior to head and body
Anterior	Anterior pancreaticoduodenal, pyloric (for tumours of head only), and proximal mesenteric
Posterior	Posterior pancreaticoduodenal, common bile duct, and proximal mesenteric
Splenic	Hilum of spleen and tail of pancreas (for tumours of body and tail only)
Coeliac	(for tumours of head only)

TNM Clinical Classification

T – Primary Tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour
Tis Carcinoma in situ

T1 Tumour limited to the pancreas, 2 cm or less in greatest dimension
T2 Tumour limited to the pancreas, more than 2 cm in greatest dimension
T3 Tumour extends directly into any of the following: duodenum, bile duct, peripancreatic tissues[1]
T4 Tumour extends directly into any of the following: stomach, spleen, colon, adjacent large vessels[2]

Note: 1. Peripancreatic tissues include the surrounding retroperitoneal fat (retroperitoneal soft tissue or retroperitoneal space), including mesentery (mesenteric fat), mesocolon, greater and lesser omentum, and peritoneum. Direct invasion to bile ducts and duodenum includes involvement of ampulla of Vater.
2. Adjacent large vessels are the portal vein, coeliac artery, and superior mesenteric and common hepatic arteries and veins (not splenic vessels).

N – Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
N1a Metastasis in a single regional lymph node
N1b Metastasis in multiple regional lymph nodes

M – Distant Metastasis

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

pTNM Pathological Classification

The pT, pN, and pM categories correspond to the T, N, and M categories.

pN0 Histological examination of a regional lymphadenectomy specimen will ordinarily include 10 or more lymph nodes.

G Histopathological Grading

See definitions on page 52.

UICC TNM 5

UICC TNM7 – pancreatic cancer

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UICC TNM7

Invasion beyond pancreas?

- **Invasion of IP bile duct or EP bile duct, or of ampulla, by PDAC is still regarded by some as invasion 'beyond' the pancreas (ie. pT3)**
- **IP-bile duct involvement by PDAC is common, even with small tumours**
- ***AFIP 2007*: Involvement of IP-bile duct by PDAC does not signify extension beyond pancreas (ie. pT1 or pT2), but involvement of EP-bile duct does (pT3)**
- ***College of American Pathologists 2012*: pT3 if involves EP-bile duct or ampulla**
- **One person's T2 is someone else's T3…….**

Invasion of SMV or portal vein?

- Resection of tangential or segmental part of superior mesenteric vein (SMV) or porta vein (PV) during PD or total pancreatectomy is a safe surgical procedure
- But not specified in TNM7
- Extension beyond pancreas, most would consider it pT3 but should it be T4?

AJCC TNM8 pancreatic cancer

T1 tumour ≤ 2cm in greatest dimension

- T1a tumour ≤0.5cm
- T1b tumour >0.5cm and <1cm
- T1c tumour 1-2cm

T2 tumour >2cm and ≤4cm in greatest dimension

T3 tumour >4cm in greatest dimension

T4 tumour involves coeliac axis, SMA, and/or common hepatic artery, regardless of size

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AJCC TNM8 pancreatic cancer

- Deals with small cancers in cystic lesions (T1)
- Objective size criteria (T2 & T3) have replaced the need to subjectively identify invasion of the peripancreatic soft tissue
- Size criteria removed controversy over invasion of IP and/or EP bile duct being T3 or not

Saka B et al. Ann Surg Oncol 2016; 23: 2010-8

Allen PJ et al. Ann Surg 2016. May 9 [Epub ahead of print]

- Invasion of SMV and/or PV does not influence T staging

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N staging – pancreatic cancer

- LN metastases occur in >70% of PDAC resections
- Regional LN status is one of the most important predictors of outcome after surgical resection
- 5yr SR falls from ~40% to less than 10% when there are LN metastases at surgical resection

Zacharias et al. J Gastroint Surg 2007; 11: 350-6

- Lymph node ratio (number of +ve LNs: total number of LNs examined) of >20% correlates with a poorer survival
- What is a positive LN? A discrete tumour deposit in a LN that is not contiguous with main tumour mass

What about direct invasion of LN?

- Occurs alone without true LN metastasis in 9-20% of pancreas resections
- Some authors do not think that direct invasion equates to a true LN metastasis; tumour cells do not yet have ability to grow & survive within lymphatic channels

Pai et al. Am J Surg Pathol 2011; 35: 228-34

- Gene expression profiling of lung squamous cell cancer suggested that tumours with direct invasion of LNs are genomically different to those with true lymphatic spread, but similar to LN-negative tumours

Larsen et al. Eur Resp J 2007; 30: 21-5

Direct invasion of LN

- **Direct invasion (34m) poorer survival than N0 (57m)**

  Buc et al. Eur J Surg Oncol 2014; 40: 1578-85

- **Direct invasion equivalent survival to 'true' N1**

  Konstantinidis et al. J Gastroint Surg 2010; 14: 261-7

  Buc et al. Eur J Surg Oncol 2014; 40: 1578-85

- **Current guidelines of RCPath UK, AJCC and Australia: direct invasion of a LN is considered a LN metastasis (pN1)**

- **Recent meta-analysis has shown that extra-nodal extension is very common and associated with poor prognosis in PDAC**

  Luchini et al. Eur J Gastroenterol Hepatol 2016 ; 28: 205-9

How many LNs should be assessed?

- Inadequate LN sampling results in understaging
- pN0 with <11-12 LNs sampled had similar SR to patients with a single positive LN

House et al. J Gastrointest Surg 2007; 11: 1549-55

Huebner et al. J Gastrointest Surg 2012; 16: 920-6

- ≥10 (UICC TNM 7th edn)
- ≥12 (AJCC 7th edn & Australia reporting protocol)
- ≥15 (CAP – proposed; 'needs further study')
- ≥15 (RCPath)

Sierzega et al. Pancreas 2006; 33: 240-5

Han et al. Pancreas 2006; 32: 271-5

Tomlinson et al Arch Surg 2007; 142: 767-73

- ≥13-16

Valsangkar et al. J Gastroint Surg 2013; 17: 257-66

N – Regional Lymph Nodes

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1–N3	Increasing involvement of regional lymph nodes

M – Distant Metastasis*

M0	No distant metastasis
M1	Distant metastasis

Note: *The MX category is considered to be inappropriate as clinical assessment of metastasis can be based on physical examination alone. (The use of MX may result in exclusion from staging.)

The category M1 may be further specified according to the following notation:

Pulmonary	PUL (C34)	Bone marrow	MAR (C42.1)
Osseous	OSS (C40, 41)	Pleura	PLE (C38.4)
Hepatic	HEP (C22)	Peritoneum	PER (C48.1,2)
Brain	BRA (C71)	Adrenals	ADR (C74)
Lymph nodes	LYM (C77)	Skin	SKI (C44)
Others	OTH		

Subdivisions of TNM

Subdivisions of some main categories are available for those who need greater specificity (e.g., T1a, T1b, or N2a, N2b).

UICC TNM7

Number of positive LNs?

- ***TNM 5th edn (1997) - pancreas***

  N0 - no regional LN metastasis

  N1a - metastasis in a single regional LN

  N1b - metastasis in multiple regional LNs

  Hermanek P. Eur J Surg Oncol 1991; 17: 167-72

- **Most authors not found significant survival differences between these groups**
- ***TNM 6th edn (2002) & 7th edn (2009)***

  N0 - no regional LN metastasis

  N1 - regional LN metastasis

Number of positive LNs?

- **Overall survival significantly influenced by number of positive LNs:**

N0 = 31m

1LN = 22.3m

2LN = 16m

>2LNs = 15m

- **Separate 1LN met from ≥2LN mets**

Konstantinidis et al. J Gastroint Surg 2010; 14: 261-7

Number of positive LNs?

- (Median LN count of 24)

N0 = 33m

1LN = 31m

2-3LN = 26m

4-7LN = 22m

≥8 LN = 18m

- Was superior to LN ratio in predicting survival
- Suggest 3 categories for LN metastases:

N1 (for 1LN+), N2 (2-7LN+), N3 (≥8LN+)

Strobel et al. Ann Surg 2015; 261: 961-9

AJCC TNM8 – pancreatic cancer

- Nodal involvement includes direct extension or metastasis to peripancreatic LNs
- Minimum of 12 LNs recommended to accurately stage N0
- Total number of positive LNs outperformed LN ratio when sufficient numbers of LNs obtained and evaluated
- N category now similar to other GI sites

Nx	regional LNs cannot be assessed
N0	no regional LN metastases
N1	metastasis in 1-3 regional LNs
N2	metastasis in 4 or more LNs

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Distal bile duct cancer

- Distinction from PDAC can be challenging
- Symmetrical tumour around the CBD is more likely to be distal BD cancer
- Eccentric tumour with epicentre away from IP-BD is more likely to be a PDAC
- Prominent (in-situ component) biliary intraepithelial neoplasia (BilIN) or a biliary intraductal tubular/tubulopapillary neoplasm indicate a BD origin
- Challenges with TNM7 for distal BD cancer

UICC TNM7 – distal bile duct cancer

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour confined to the bile duct
T2	Tumour invades beyond the wall of the bile duct
T3	Tumour invades the gallbladder, liver, pancreas, duodenum, or other adjacent organs
T4	Tumour involves the coeliac axis or the superior mesenteric artery

- **BD does not have a well-defined muscle layer and transition to periductal tissues is not sharply demarcated**
- **Fibrosis (stenting, tumour or bx) further blurs the transition to periductal soft tissues**
- **Suggested that depth of invasion is a better predictor of prognosis**

Hong S-M et al. Surgery 2009; 146: 250-7

AJCC TNM8 distal BD cancer

T1	tumour invades the BD wall with a depth of <5mm
T2	tumour invades the BD wall with a depth of 5-12mm
T3	tumour invades the BD wall with a depth of >12mm
T4	tumour involves coeliac axis, SMA, and/or common hepatic artery

Nx	regional LNs cannot be assessed
N0	no regional LN metastases
N1	metastasis in 1-3 regional LNs
N2	metastasis in 4 or more LNs

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UICC TNM7 - ampulla of Vater

T – Primary Tumour

TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour limited to ampulla of Vater or sphincter of Oddi
T2	Tumour invades duodenal wall
T3	Tumour invades pancreas
T4	Tumour invades peripancreatic soft tissues, or other adjacent organs or structures

- **TNM7 does not reflect complex anatomy of AoV**

Adsay et al. Sem Diagn Pathol 2012; 29: 127-41

- **AoV is not covered entirely by duodenum, then pancreas, then peripancreatic soft tissues**
- **AoV cancers posteriorly invade periduodenal & peripancreatic tissues and duodenal serosa without having to invade through the pancreas**

AJCC TNM8 ampulla of Vater

T1 tumour limited to ampulla of Vater or sphincter of Oddi or tumour invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa

T1a tumour limited to ampulla of Vater or sphincter of Oddi

T1b tumour invades beyond the sphincter of Oddi (perisphincteric invasion) and/or into the duodenal submucosa

T2 tumour invades into the muscularis propria of the duodenum

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AJCC TNM8 ampulla of Vater

T3 tumour directly invades the pancreas (up to 0.5cm) or tumour extends more than 0.5cm into the pancreas, or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the coeliac axis or SMA

T3a tumour directly invades the pancreas (up to 0.5cm)

T3b tumour extends more than 0.5cm into the pancreas, or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the coeliac axis or SMA

T4 tumour involves coeliac axis, SMA, and/or common hepatic artery, irrespective of size

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AJCC TNM8 ampulla of Vater

Nx regional LNs cannot be assessed
N0 no regional LN metastases
N1 metastasis in 1-3 regional LNs
N2 metastasis in 4 or more LNs

Balci S et al. Ann Surg Oncol 2015; 22: 4392-4401
Kang HJ et al. Surgery 2014; 155: 74-84

Summary

- Two-tiered classification system for grading dysplasia in PanIN, IPMN, MCN (what will next WHO edn state?)

- TNM8 pancreas: T1a/1b/1c subdivisions
  T2 2-4cm
  T3 >4cm

- TNM8 distal BD: T1 <5mm depth
  T2 5-12mm depth
  T3 >12mm depth

Summary

- **TNM8 Ampulla of Vater:**

T1 limited to AoV / sphincter of Oddi, and/or invades into duodenal submucosa,

T2 invades into the muscularis propria of the duodenum

T3 invades pancreas (≤0.5cm or >0.5cm) or extends into peripancreatic or periduodenal tissue or duodenal serosa without involvement of the coeliac axis or SMA

N1 mets in 1-3 regional LNs

N2 mets in 4 or more LNs

Future challenges…

- **Implementation of AJCC TNM8 cancer staging system is being delayed until 1st Jan 2018**

  AJCC announcement 14th November 2016

- **UICC TNM8 imminent**

- **3rd edition RCPath pancreas/distal bile duct/ampulla of Vater dataset (consultation just closed)**