

Gross examination of pancreaticobiliary cancer specimens

Dr Vlad Maksymov MD, PhD, FRCPC
OPA meeting
September 17 2017



Learning Objectives

- Review issues related to the surgical anatomy and gross examination of the pancreaticoduodenectomy pancreaticobiliary cancer / specimen.
- Review and discuss existing terminology for margins and the need for standardized assessment of these specimens (as well as, discuss the role of standardized terminology amongst pathologists, radiologists, surgeons and oncologists in the optimal care of patients with pancreaticobiliary cancer).
- Discuss how gross examination of pancreaticoduodenectomy/pancreaticobiliary cancer specimen affects synoptic reporting.
- At the end of the session, the participants will be able to answer questions for self assessment.

Pancreaticoduodenectomy

- Pylorus preserving PD
 - Standard/classic PD (Whipple procedure)
 - “Extended” PD (includes dissection of retroperitoneal and aorta-caval lymph nodes (used in Asia) (A Nakao, et al, 2004))
 - Total PD Pancreaticoduodenectomy
- (PD) specimen present a challenge for surgical pathologists because of the relative rarity of these specimens, combined with anatomic complexity (V V Adsay, et al, 2014)

PD specimen contains:

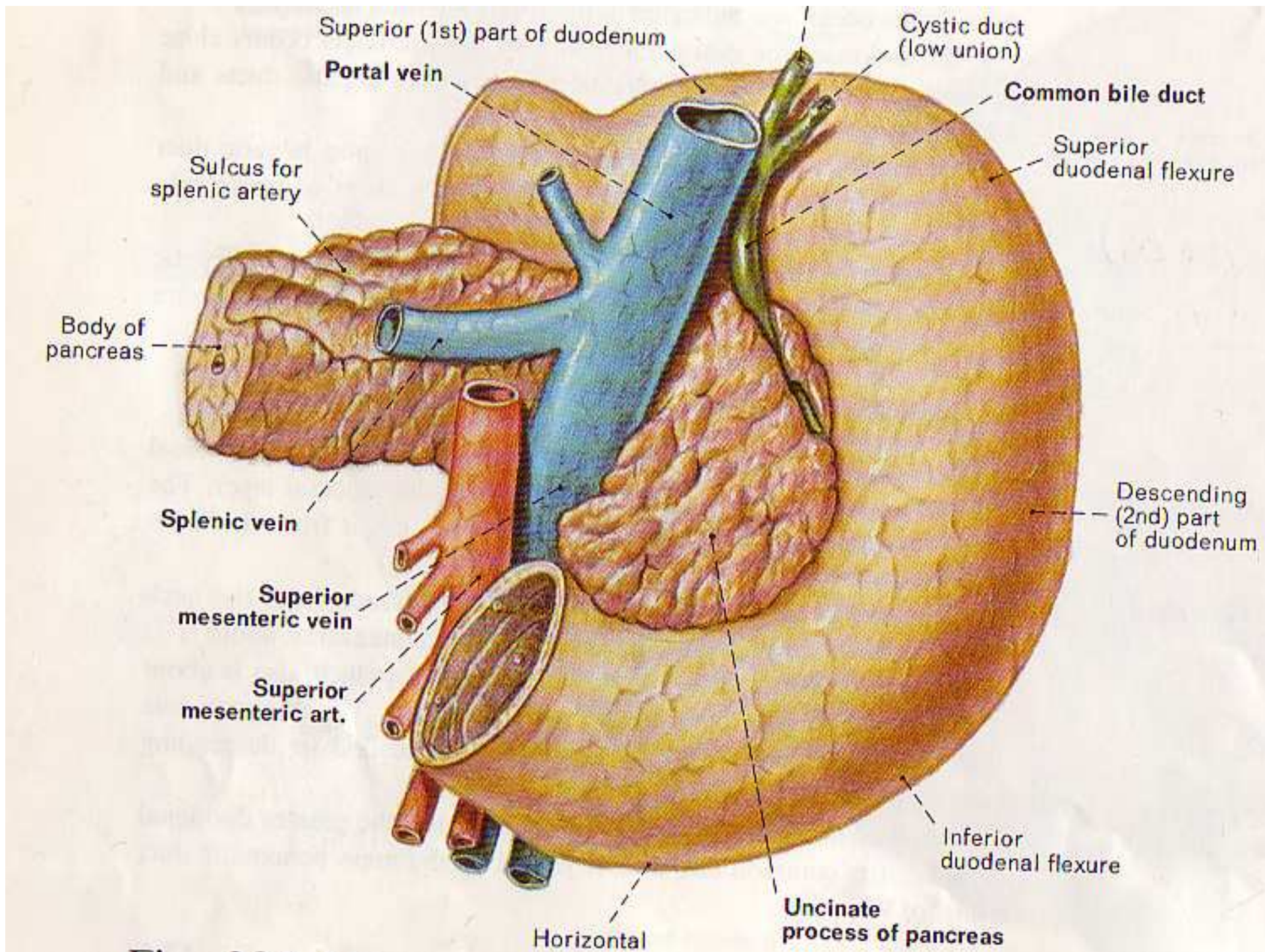
- Pancreatic head
- Most of duodenum (sometimes portion of jejunum)
- Distal segment of the common bile duct (CBD)
- If standard (classic) PD it also contains the pylorus and a segment of the stomach antrum (this become less common/NV Adsay, et al, 2014)
- If pylorus preserving PD - (no pylorus and antrum)
- Gallbladder and cystic duct

Whipple surgery involves following steps:

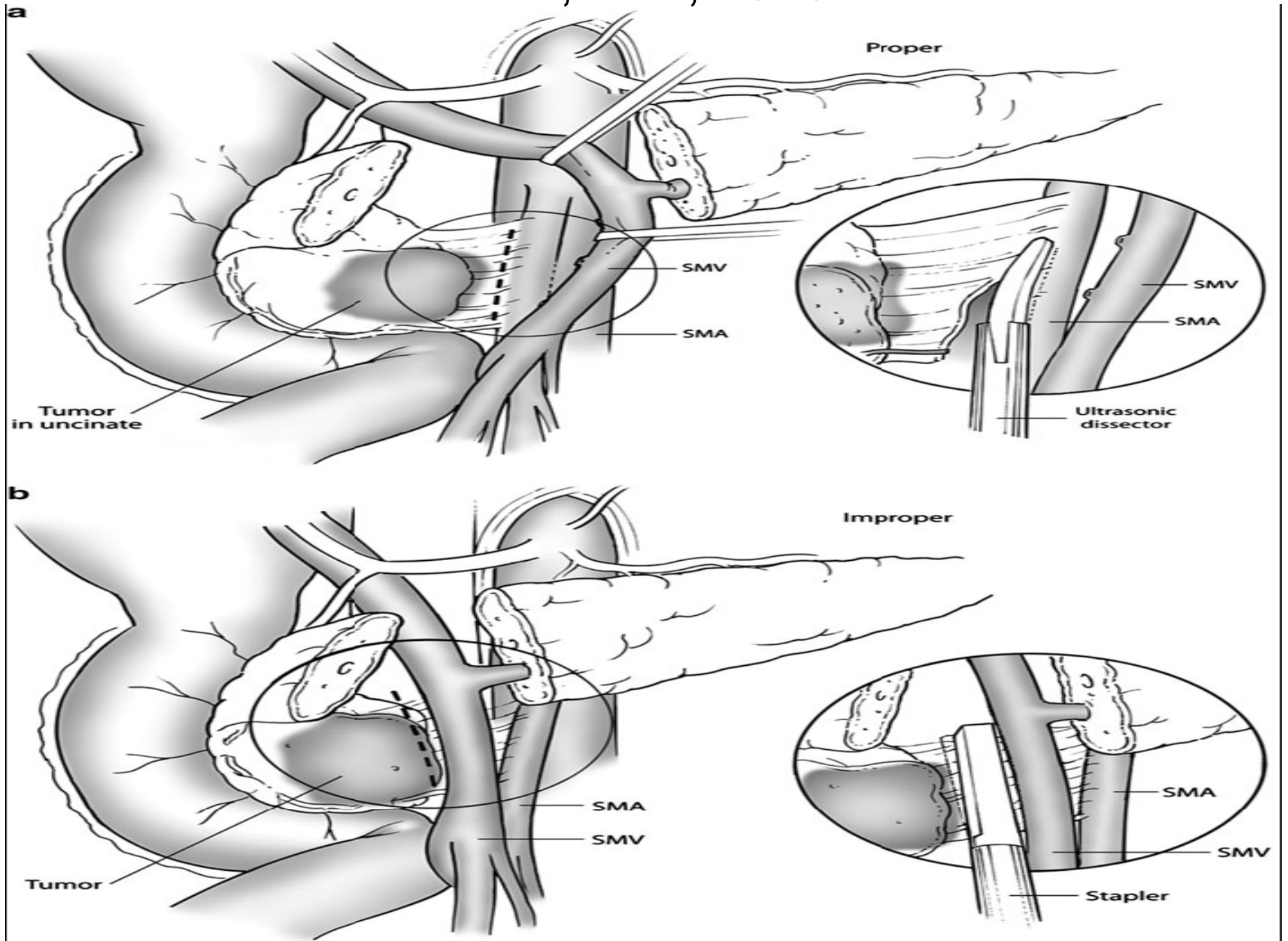
- The pancreatic neck is transected from the body of the pancreas
- The pancreatic head is *dissected* from the retroperitoneal soft tissues, including Superior Mesenteric/Portal Vein (SMV) and Superior Mesenteric Artery (SMA)
- SMV usually came out freely/relatively easily unless there is direct invasion of SMV or fibrous adhesions
- In the posterior-inferior aspect of the uncinate process the pancreatic tissues is *dissected* from the retroperitoneal soft tissues just right lateral along SMA.
- Common Hepatic Duct (often still called CBD) is transected at/above the union between the Cystic and Common Hepatic Duct and anastomosed to the jejunum.

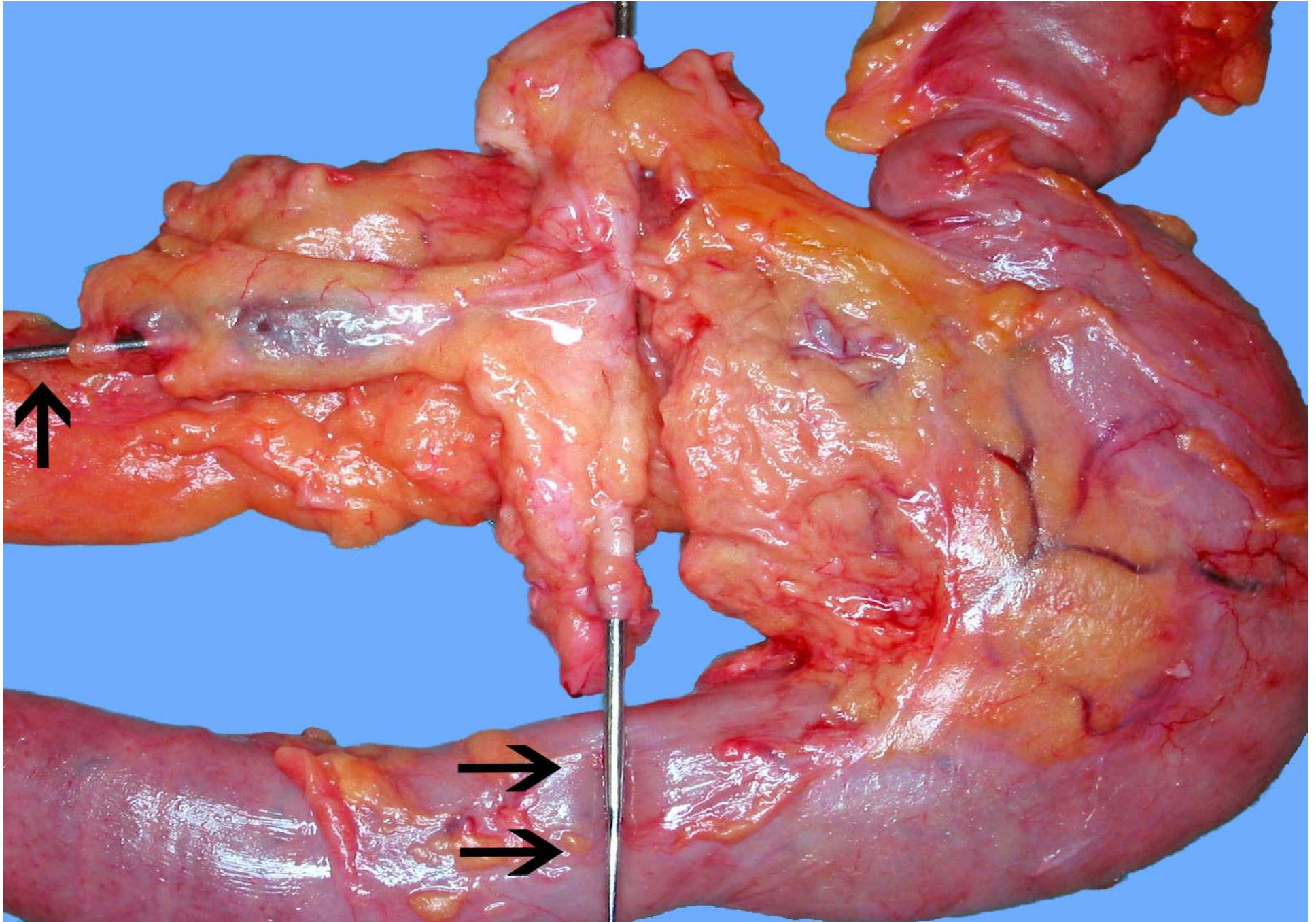
Whipple surgery:

- For a pylorus preserving PD the duodenum is transected 1-2 cm distal to the pylorus
- For standard/classic PD the antrum is transected
- For both types of PD, the proximal jejunum is transected approximately 5 to 10 cm distal to ligament of Treitz.
- Extended PD includes dissection of retroperitoneal and aorta-caval lymph nodes (used in Asia) (A Nakao, et al, 2004)



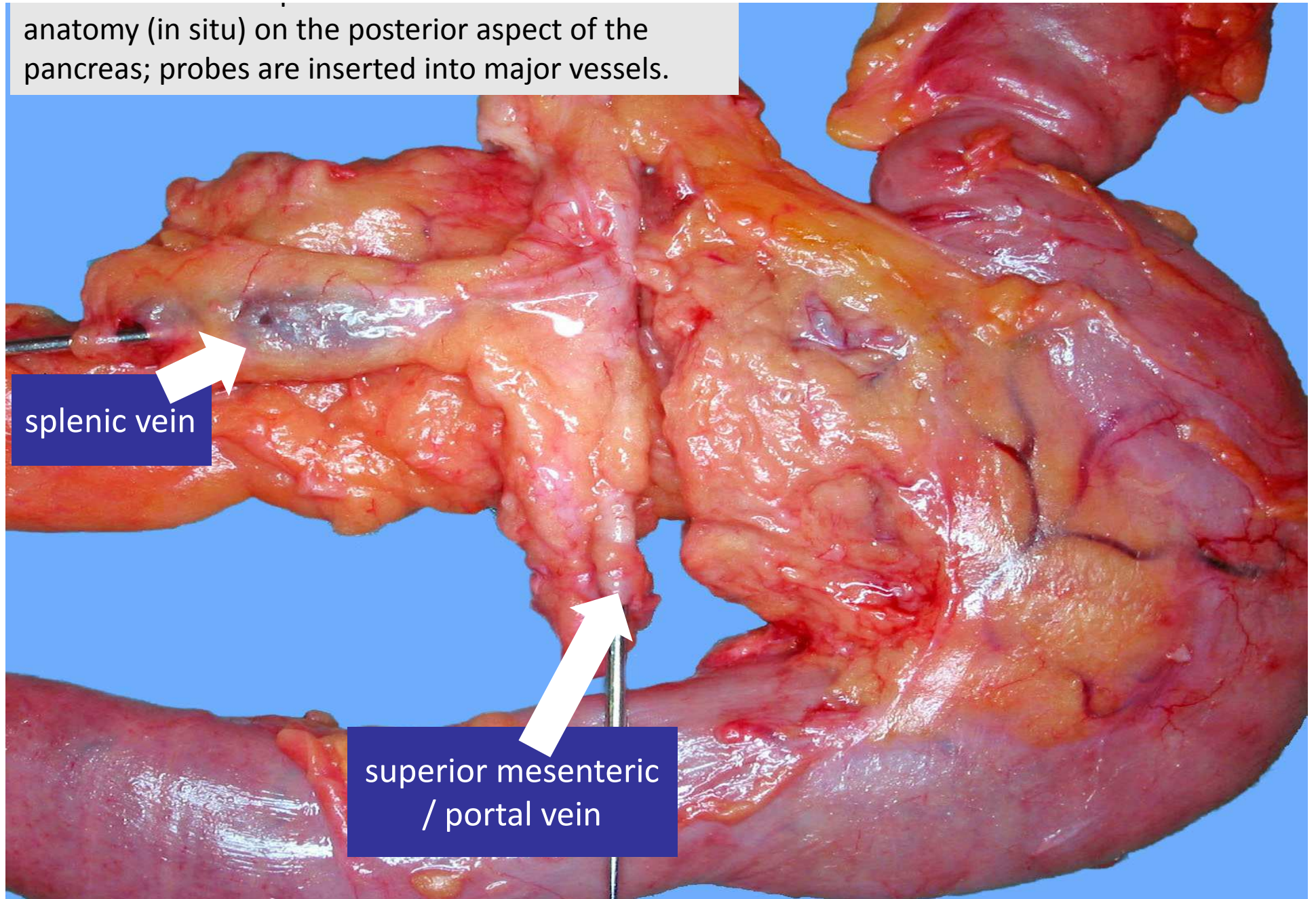
M Katz, et al, 2010





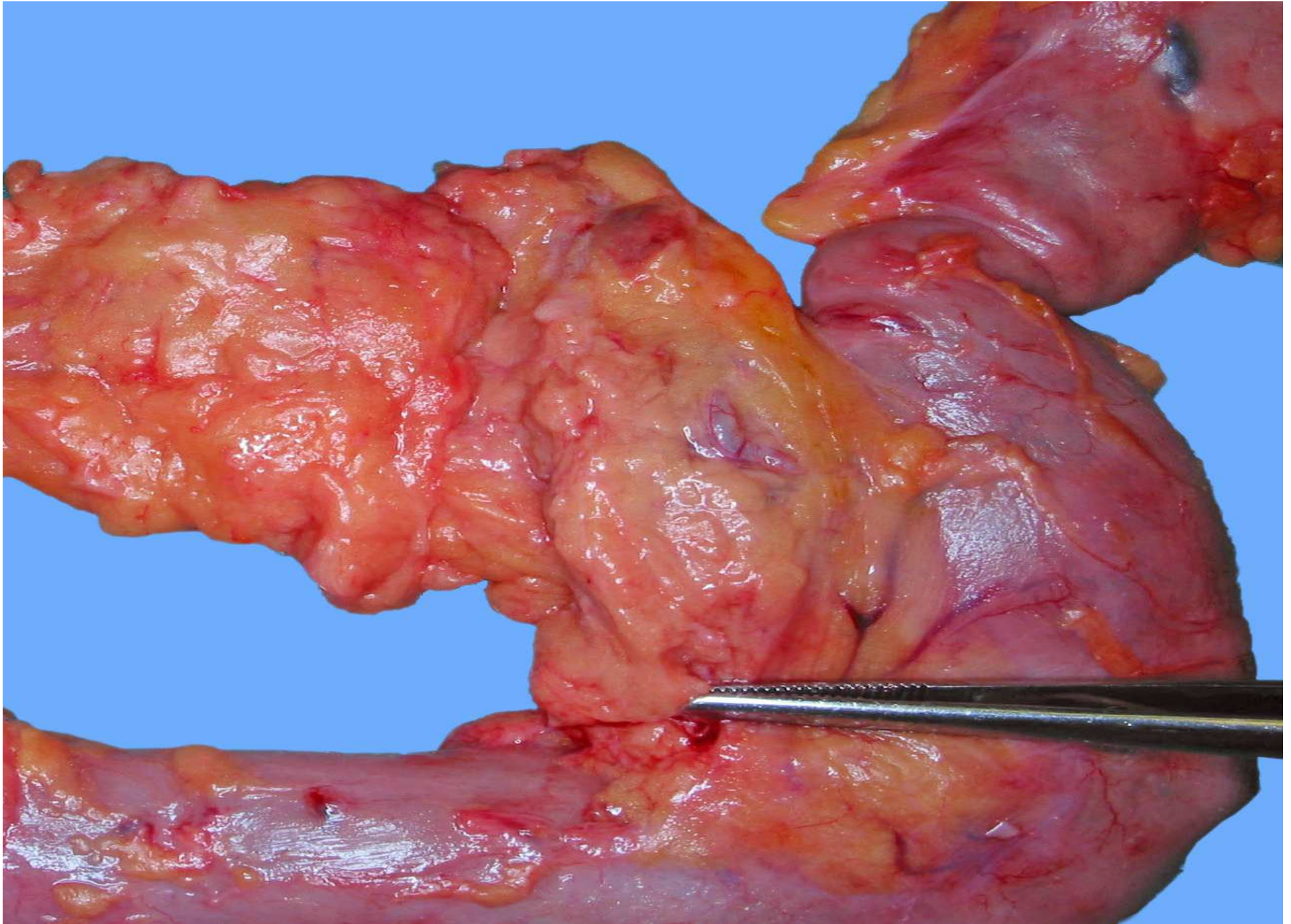
Khalifa MA, Maksymov V, Rowsell C. Virchow's Arch. 2009

anatomy (in situ) on the posterior aspect of the pancreas; probes are inserted into major vessels.



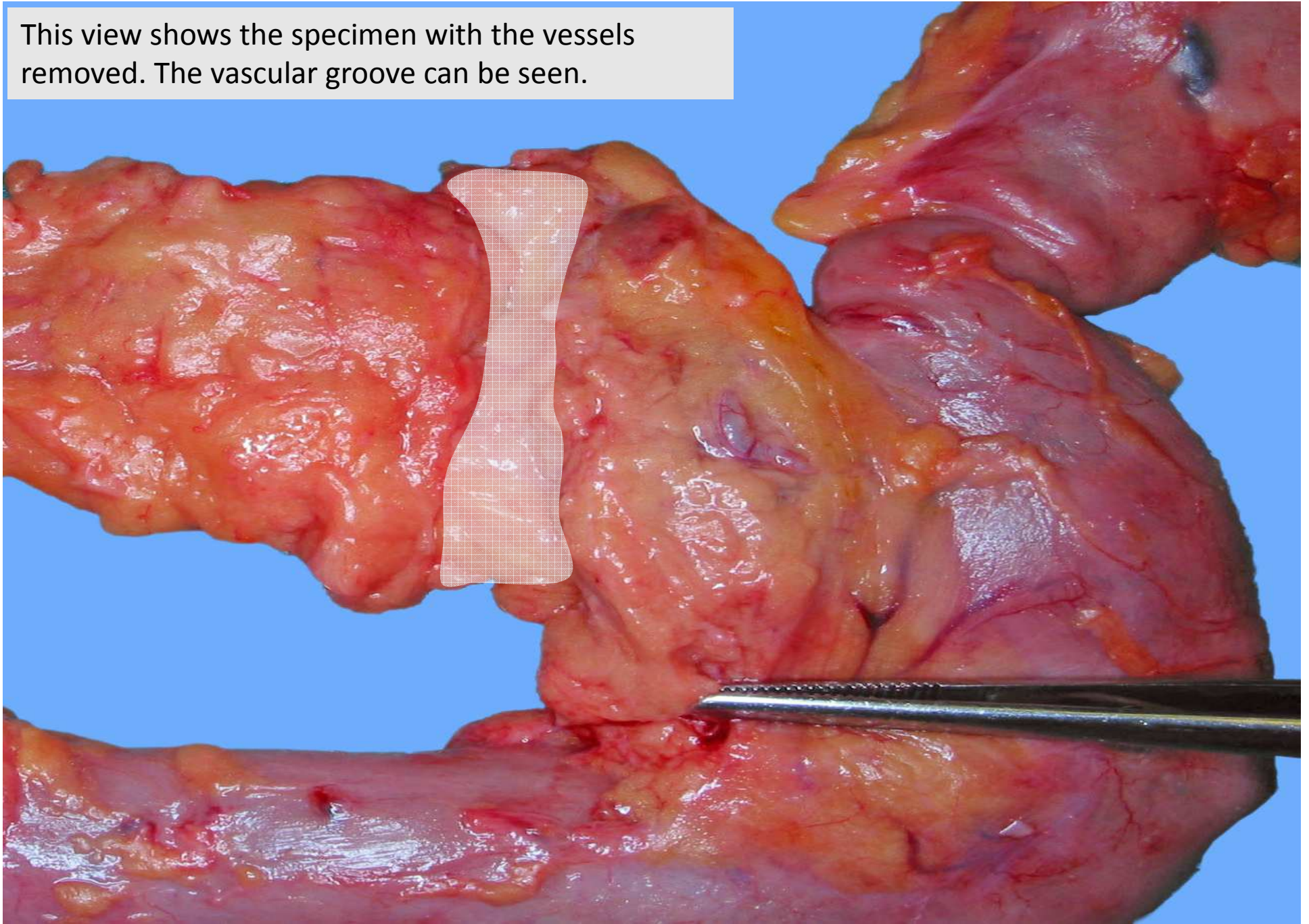
splenic vein

superior mesenteric
/ portal vein



Khalifa MA, Maksymov V, Rowsell C. Virchow's Arch. 2009

This view shows the specimen with the vessels removed. The vascular groove can be seen.



Typically surgical margins of the PD specimen

- Luminal (proximal gastric and distal duodenal/jejunal)
- Pancreatic (also known as distal pancreatic (DP), it results from transecting the pancreatic neck)
- Bile duct (BD)
- Anterior margin
- Retroperitoneal (RP RM) (also known as radial) or uncinata margin
- American Joint Committee on Cancer(2009) cancer staging manual recommends using the term SMA margin instead retroperitoneal or uncinata margin

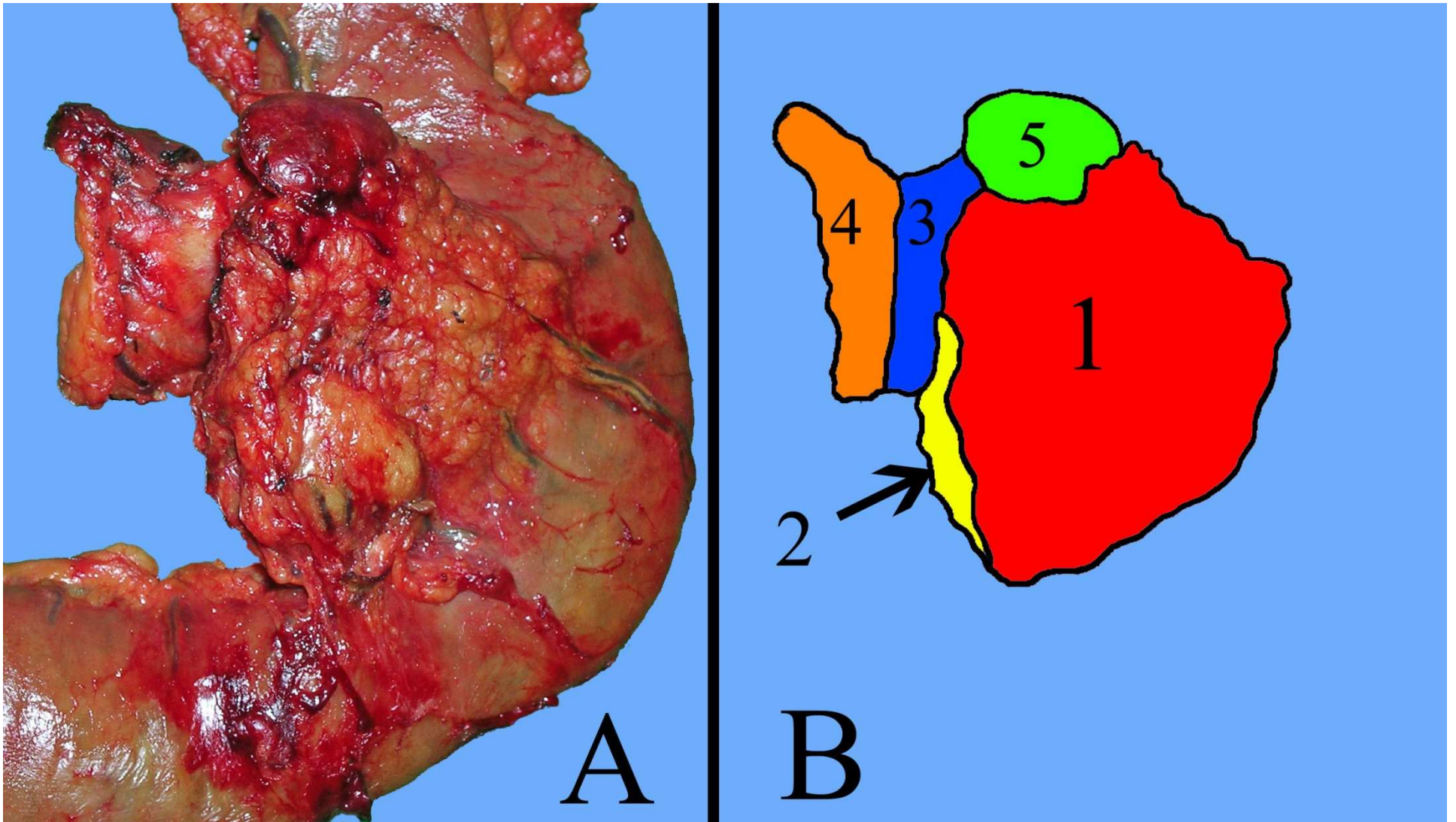
Anatomic mapping of the retroperitoneal margin
(RPM) M Khallifa, V Maksymov, C Rowsell, Virchows
Archiv, 2009)

- RPM margin is actually a combination of surfaces/margins facing to the different anatomical structures (combination of the dissection and resection margins)
 - Uncinate (SMA) margin (resection).
 - Posterior surface of uncinata process (dissection margin).
 - SMV/Vascular groove (dissection margin).
- Goal: to develop approach allowing to identify involvement of the SMV or SMA and give feedback to the surgeons and radiologists

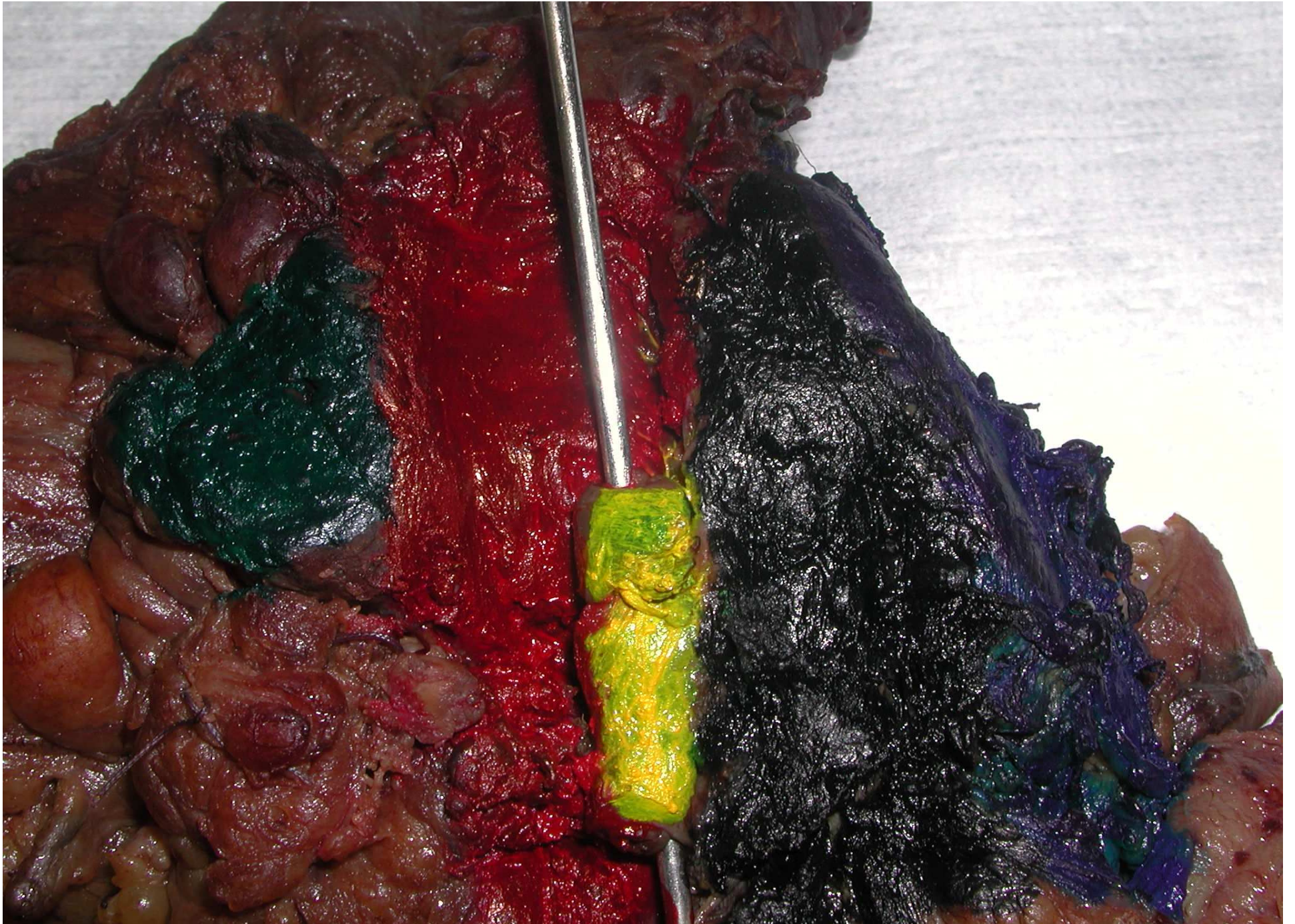
Resection versus Dissection margin

(Khalifa M A, Maksymov V , Rowsell C H, 2009)

- Resection margin- results from the surgeon's resection (using a sharp knife or blade).
- Dissection margin– results from the separation of the pancreas using the hand and/or scissors or similar tools).
 - Mobilization Margin (Jamieson, N Nigel, et al, 2010)



Khalifa MA, Maksymov V, Rowsell C, Virchow's Arch, 2009



Maksymov V, Hogan M, Khalifa MA, 2012

“Margin” versus “free surfaces”

(N V Adsay, et al, 2014 and personal communication)

- Manually dissected (by surgeon) compartments are regarded as “margin”, and those that come off readily and are serosa covered are regarded as “free surfaces”
- Prefer to refer to only the posterior-inferior aspect of the uncinate process as margin to posterior-right aspect of the pancreatic head as free surface
- “free surfaces “ are similar to “dissection margin” as per (Khalifa M A, Maksymov V , Rowsell C H, 2009)

Posterior free surfaces

(N V Adsay, et al, 2014 and personal communication)

- Not true margin in the sense that
- 1) There is nothing the surgeon can do about them (they cannot go any further, or they cannot change their approach in order to take more next time etc; because this tissue more or less peels off readily.
- 2) These surfaces are akin to radial “surfaces” in any other organ including the serosal surface.... this tissue clearly has a *different covering* than the true/real unciniate margin.

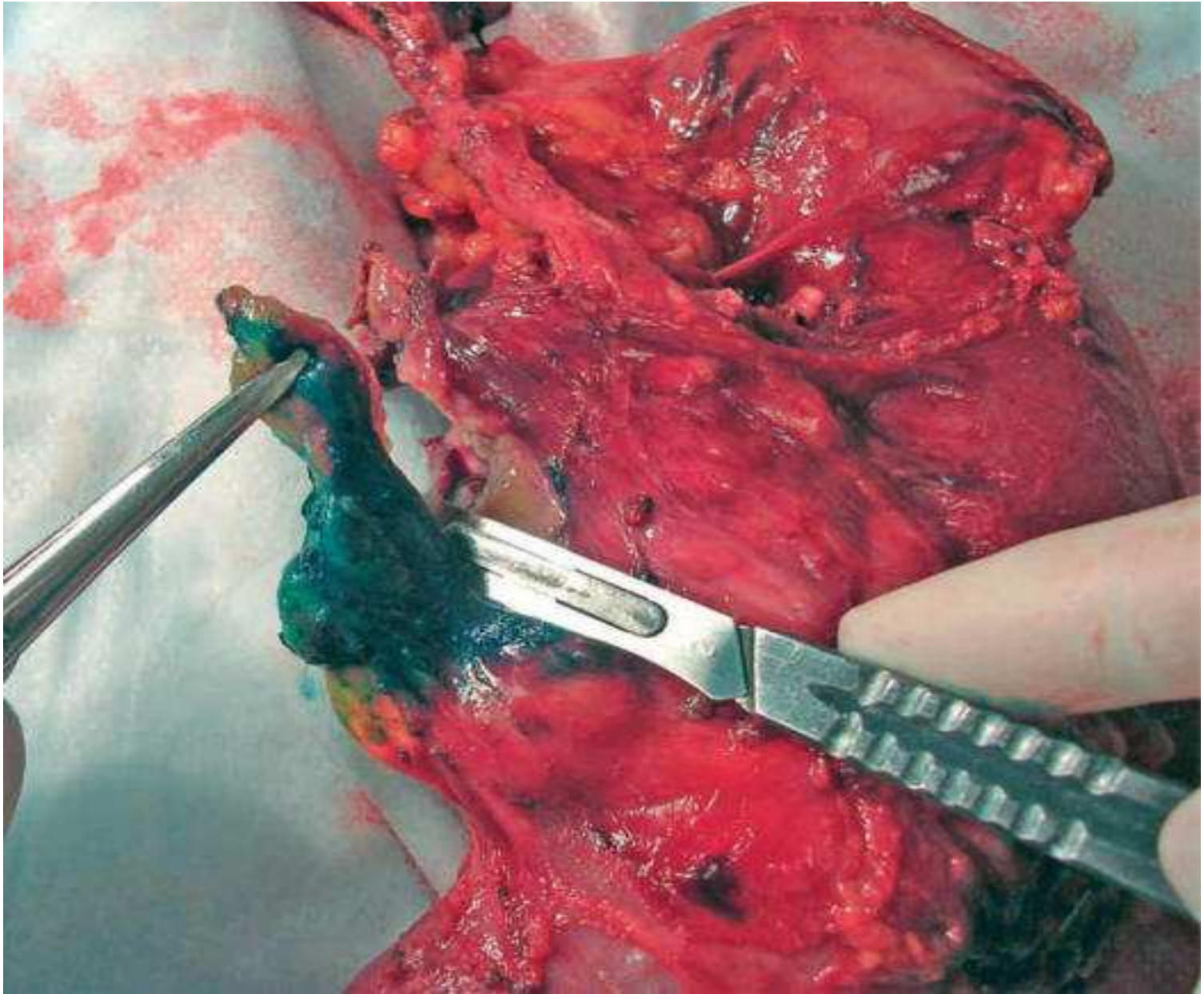
Anterior free surfaces

(N V Adsay, et al, 2014)

- Anterior pancreaticoduodenal junctional region: the anterior free surface typically contains abundant adipose tissue and is convex in appearance.
- Anterior versus posterior free surfaces (N V Adsay, personal communication): “it become clear most people had some sort of protocol for posterior free surfaces but nothing for anterior free surfaces....self-contradictory, considering that these 2 surfaces biologically are very similar and ought to be sampled and treated with the same principles”.

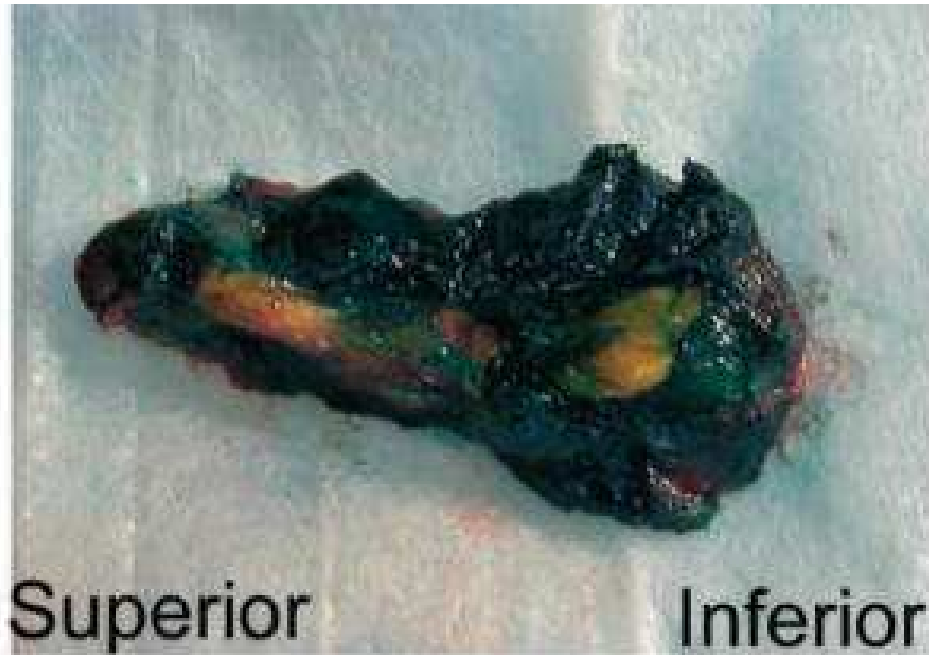
Uncinate margin (SMA margin)

- The posterior-inferior aspect of the uncinate process
- Cut surface/stapled surface produced by surgeons using different tools dissecting uncinate process from SMA
- Bumpy appearance (contrary to vascular bed)
- Very vascular areas (can see staples, sutures)
- Some consider as “mesopancreas” (adipose tissue rich in peripheral nerves and vessels)
- Facing to SMA/right lateral to SMA
- Surgeons use different tools to do skeletonization of SMA
- Exposed pancreatic tissue – indicator of not complete skeletonization



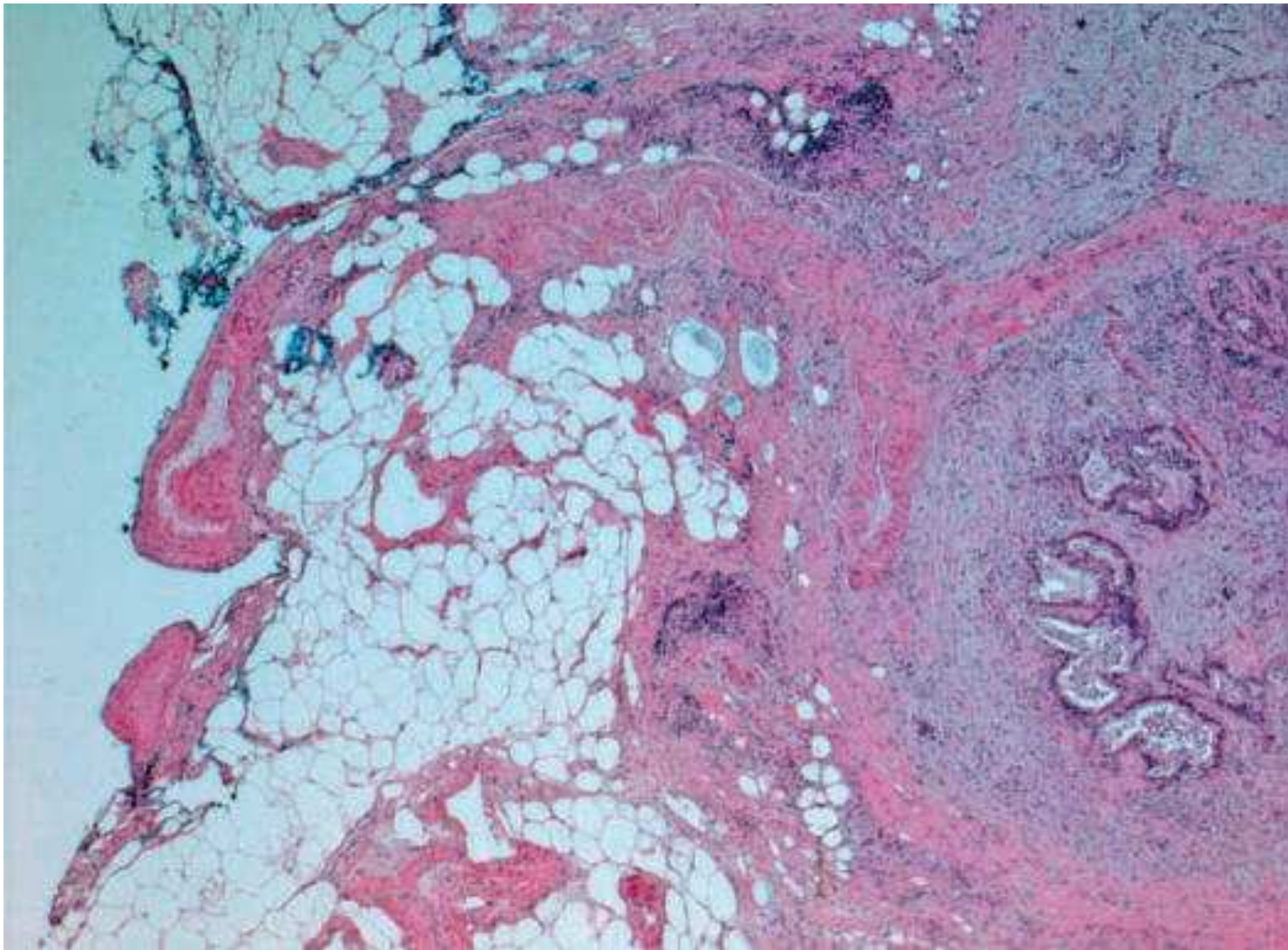
M. A. Khalifa, V. Maksymov, C. H. Rowsell, and S. Hanna. *HPB (Oxford)*. 2007; 9(2): 146–149

A



B





M. A. Khalifa, V. Maksymov, C. H. Rowsell, and S. Hanna. *HPB (Oxford)*. 2007; 9(2): 146–149

Frozen sections issues

(M. A. Khalifa, V. Maksymov, C. H. Rowsell, and S. Hanna. HPB (Oxford). 2007; 9(2): 146–149)

- Surgical technique for a PD resection involves clearance of all tissue along the portal vein/SMV and along the right of SMA
- FS on SMA margin typically unhelpful as artery provides the absolute boundary
- FS on neck and bile duct resection margin may be appropriate

Superior Mesenteric Vein/Vascular groove margin/surface

- Concavity where the SMV/PV comes in contact with retroperitoneal surface of the pancreas
- In the majority of cases, pathologist recognize it as a concave depression with a smooth, glistening surface immediately to the left (posterior view) of the uncinate process

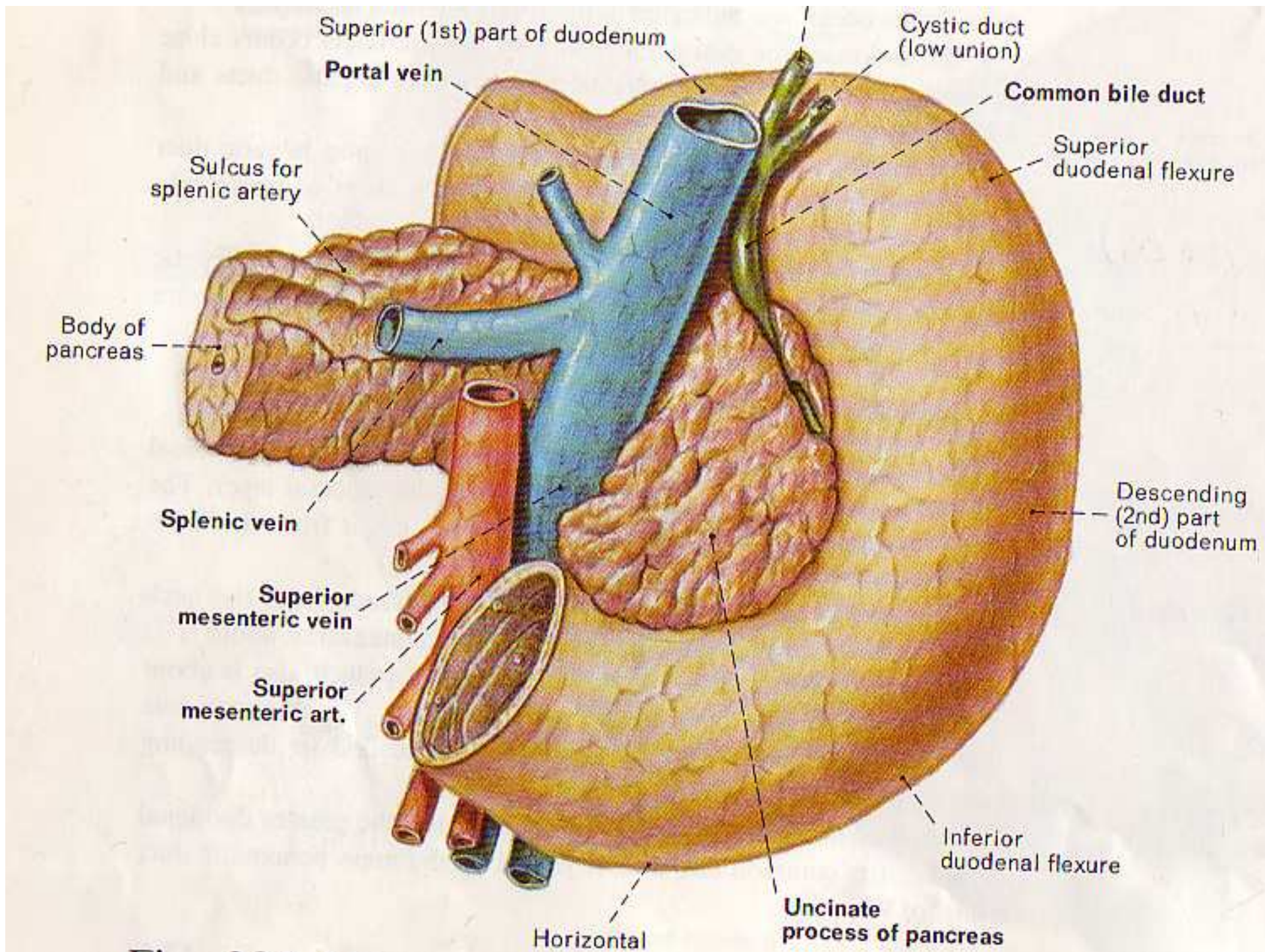


TABLE 1. Structures on the Surfaces of a PD

Term in This Study	Synonyms	Reporting Recommendation (Authors' Approach)	Reporting Recommendation (American Joint Committee on Cancer ¹⁷)	Reporting Recommendation (College of American Pathologists, as of October 1, 2013 ¹⁸)	Reporting Recommendation (Royal College Pathologists ¹⁹ and Verbeke et al ¹¹)	Reporting Recommendation (Esposito et al, ²⁰ Schlitter and Esposito ²¹ and Maksymov et al ¹³)
CBD margin		Margin	Margin	Margin	Margin	Margin
Pancreatic neck margin (Figs. 1, 2)	Pancreatic duct margin Distal resection margin	Margin	Margin	Margin	Margin	Margin
Uncinate margin (Figs. 1, 2, 5)	Superior mesenteric artery margin Retroperitoneal margin Inferior-posterior margin Inferior-posterior retroperitoneal margin Mesopancreatic margin Medial margin Radial margin	Margin	Margin	Margin	Margin	Margin
Vascular bed (Figs. 1, 2)	Vascular groove Superior mesenteric/portal vein margin	Surface*	—	Surface† (Part of the deep retroperitoneal posterior surface)	Margin	Margin‡
Anterior free surface (Fig. 3)	Anterior margin	Surface	—	—	Margin	Margin§
Posterior free surface (Figs. 3, 9)	(Part of) uncinata margin (Part of) retroperitoneal margin Deep retroperitoneal posterior surface Inferior vena cava margin	Surface	Posterior pancreatic margin (NOT the retroperitoneal margin)	Surface†	Margin	Margin

*The authors ink and take 1 perpendicular section from the vascular bed with the closest tumor and report it as vascular bed surface.

†The American Joint Committee on Cancer and College of American Pathologists protocols recommend inking the posterior (free) surface of the pancreas including the vascular groove (bed) and submission of sections through the tumor at its closest approach to this surface.

‡It is regarded as a part of the medial (uncinate) margin by Esposito et al,²⁰ Schlitter and Esposito.²¹

§In Maksymov et al's¹³ opinion, the anterior margin is present in a pylorus-preserving PD and absent in a standard Whipple procedure.

Maksymov V, Hogan M, Khalifa MA 2012

Margin	CAP	RCPUK Verbeke	Leeds Protocol/ Verbeke et al	Anatomical based mapping / authors approach
SMAM/uncinate (retroperitoneal) margin	+	+	-	+
SMVM	-	+	-	+
Medial*	-	-	+	-
Posterior	-	+	+	+
PNM	+	+	+	+
BDM	+	+	+	+
Anterior	-	+	+	+/-***
Other**	+	-	-	-

“Medial circumferential resection margin, the part of the surface of the pancreatic head that faces the superior mesenteric vessels “

* * following description is available in CAP Cancer protocols. Pancreas (exocrine), 2012: “deep retroperitoneal posterior surface of the pancreas...recommend inking the posterior surface of the pancreas and submission of sections through the tumor at its closest approach to this surface”

*** In author’s opinion anterior margin present in pylorus preserving pancreaticoduodenectomy and absent in standard Whipple procedure

MARGIN INVOLVEMENT (Maksymov V, Hogan M, Khalifa MA 2012)

Margin	Based on CAP approach	Based on our approach	
		(0 mm rule)	(1 mm rule)
SMA (uncinate)	9** (36.0%)	9** (36.0%)	14 (56.0%)
SMV (groove)	-	9 (36.0%)	18 (72.0%)
Posterior surface of UP	-	1 (4.0%)	5 (20.0%)
Pancreatic neck	1 (4.0%)	1 (4.0%)	1 (4.0%)
BDM	1 (4.0%)	1 (4.0%)	1 (4.0%)
Total R1	9 (36.0%)*	14 (56.0%)*	20 (80.0%)*

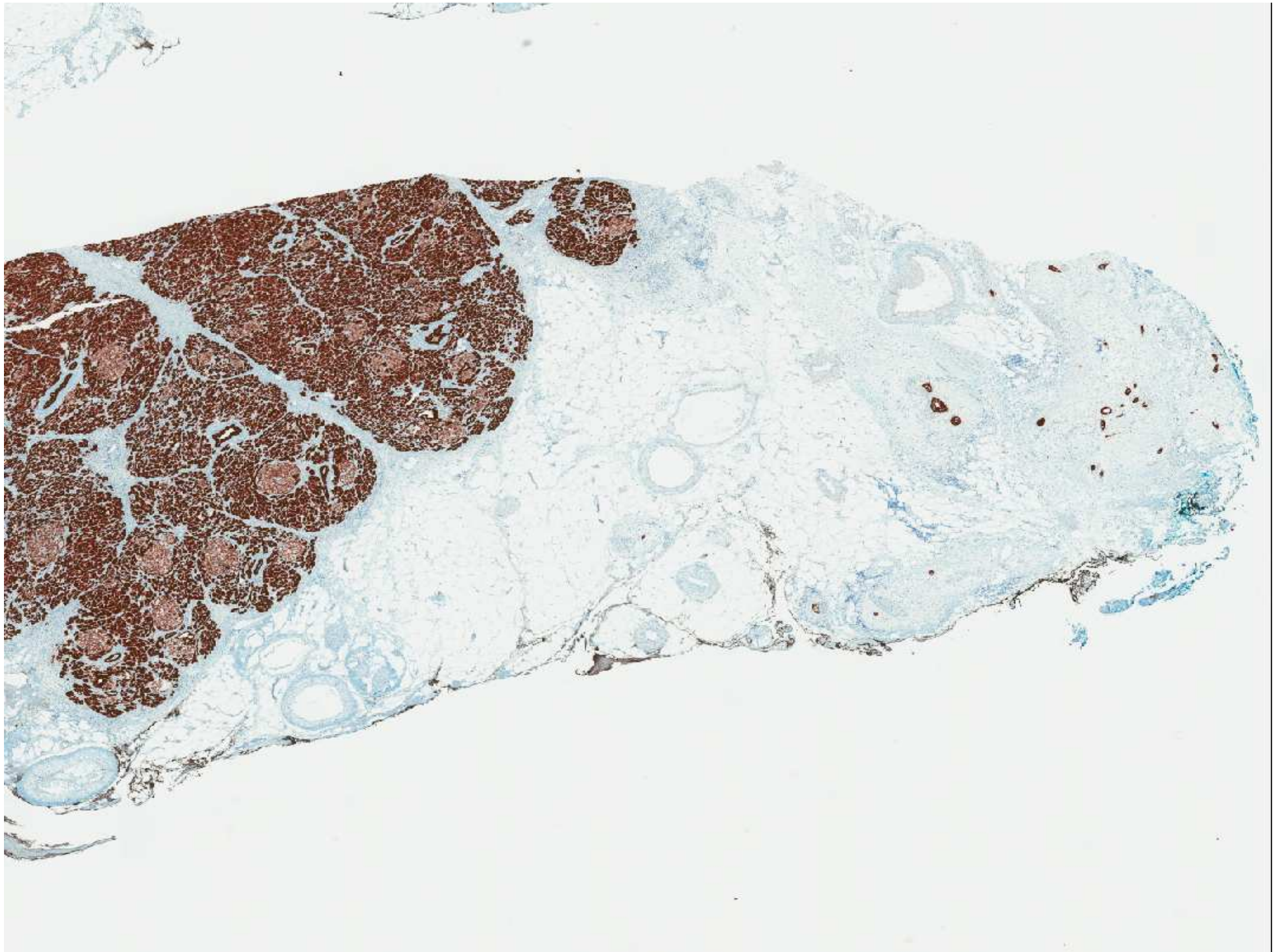
* Due to multifocality of resection margin involvement within the same specimen in some patients, the total number of involved margin exceeds the total number of R1 cases.

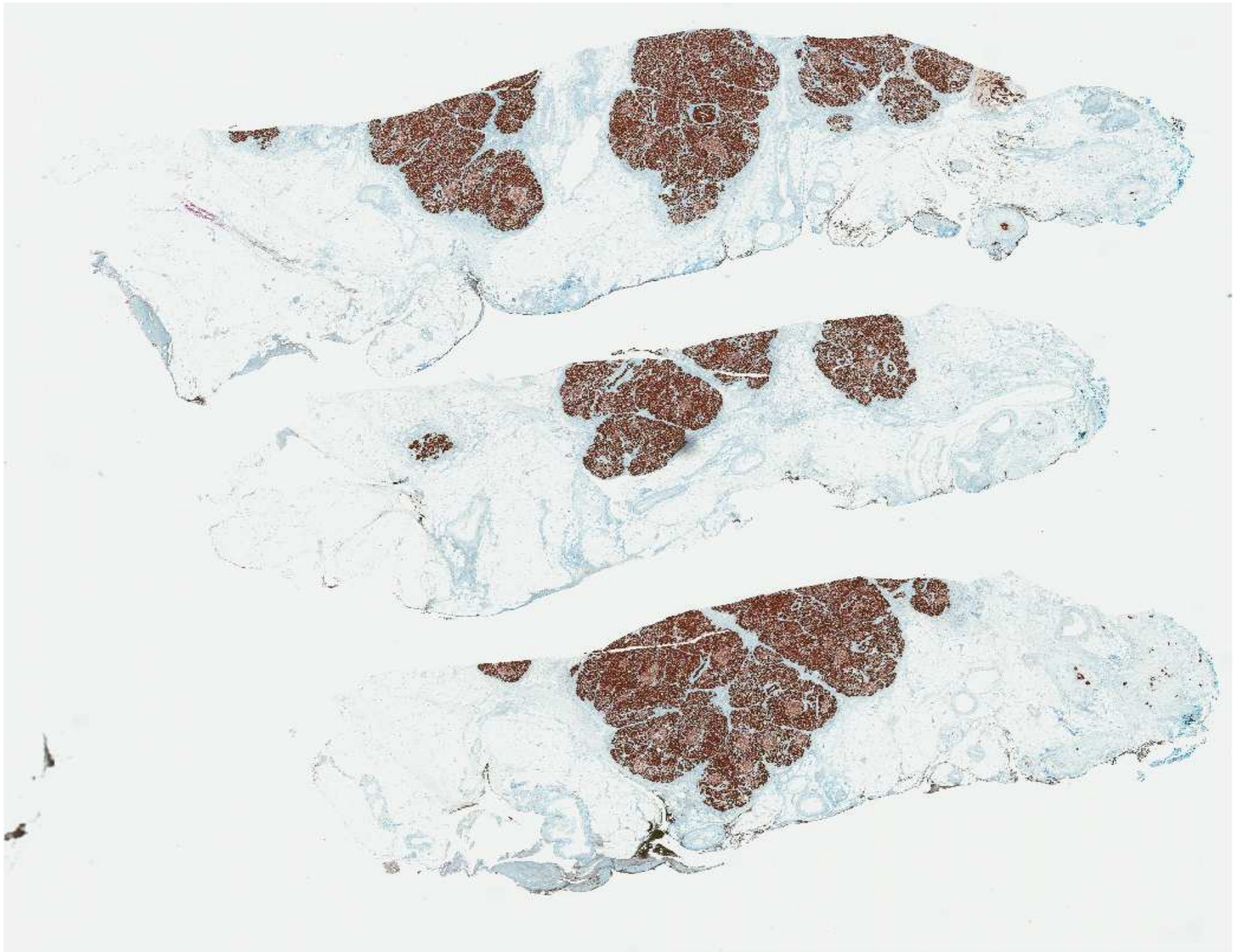
** In one more case, the SMAM was involved by metastatic carcinoma in a lymph node and this case was not included since it was considered as locoregional metastasis

The above findings illustrate that different approaches to the assessment and reporting retroperitoneal margin can change the results and adversely affect the final statistics used in pancreatic cancer studies and clinical trials.

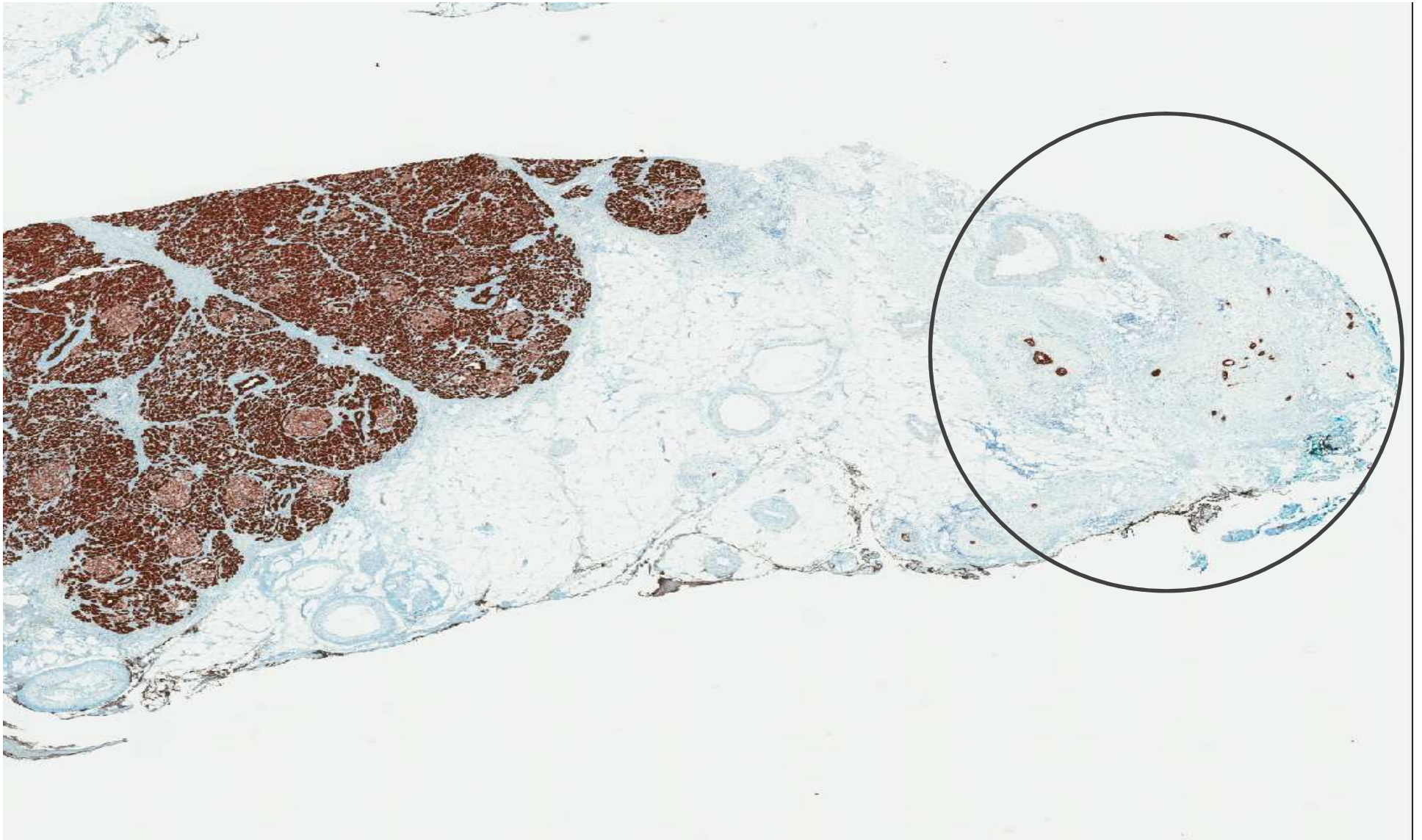
Highlight needs for standardized assessment of the PD specimen

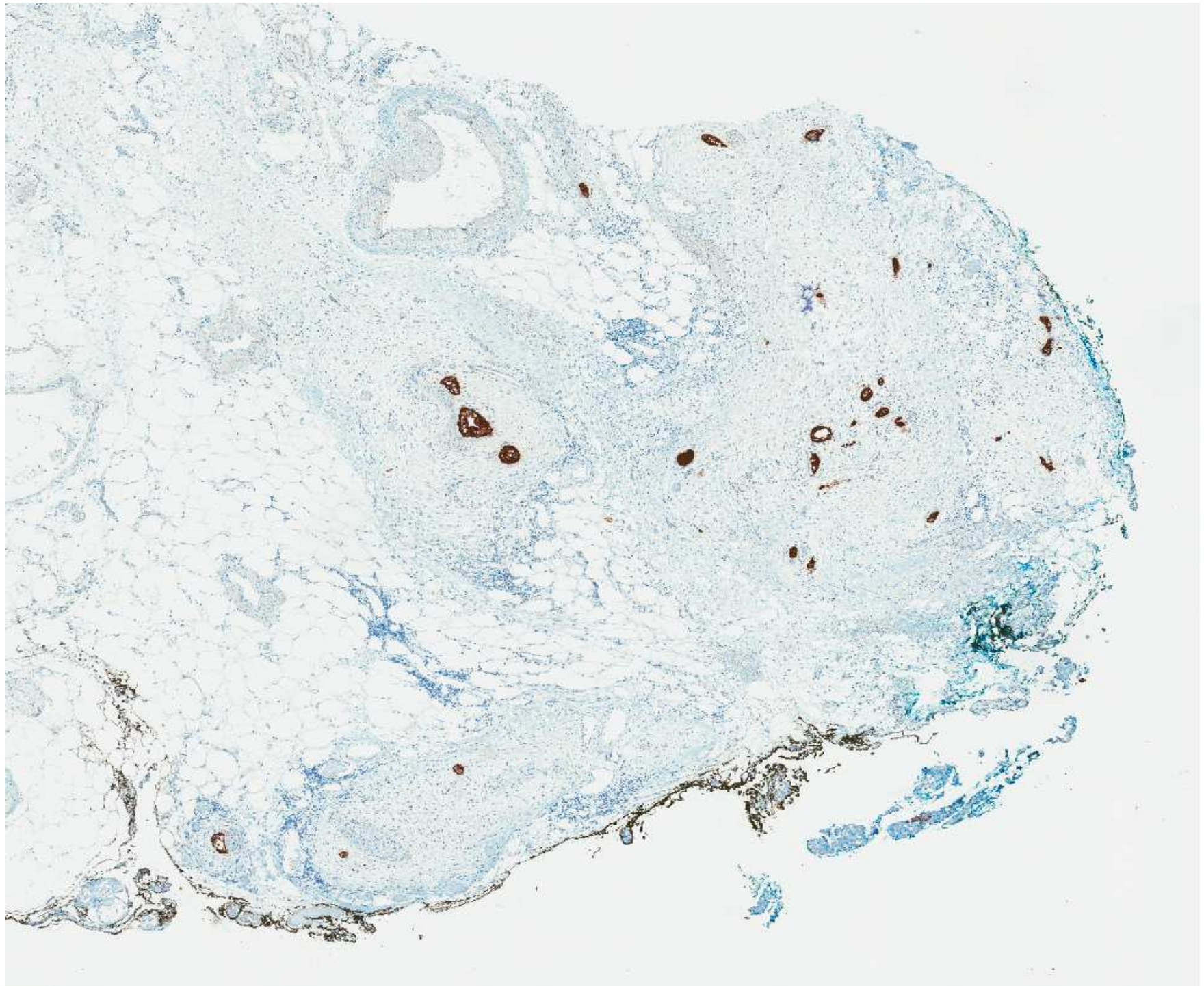
- Gross examination is poorly reliable in the:
 - assessment of the maximal dimension of the tumor
 - selection of the sections to assess margin status
 - Identification of lymph nodes
 - Solution: extensive sampling or submission in total





In this same study, invasion of the peripancreatic adipose tissue by single malignant glands are present (circle). NB: Invasion can't be identified on gross examination or with CT imaging.

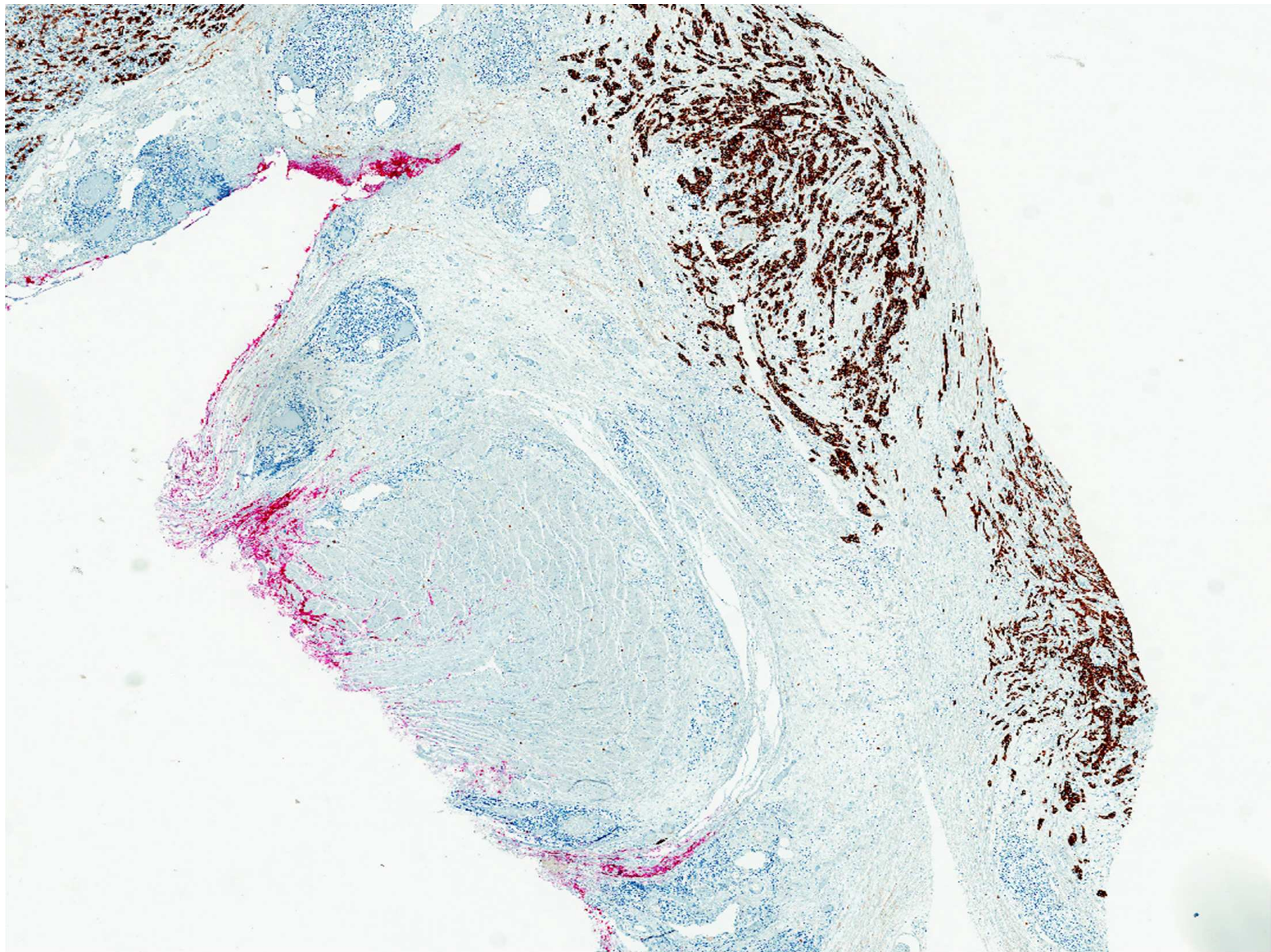


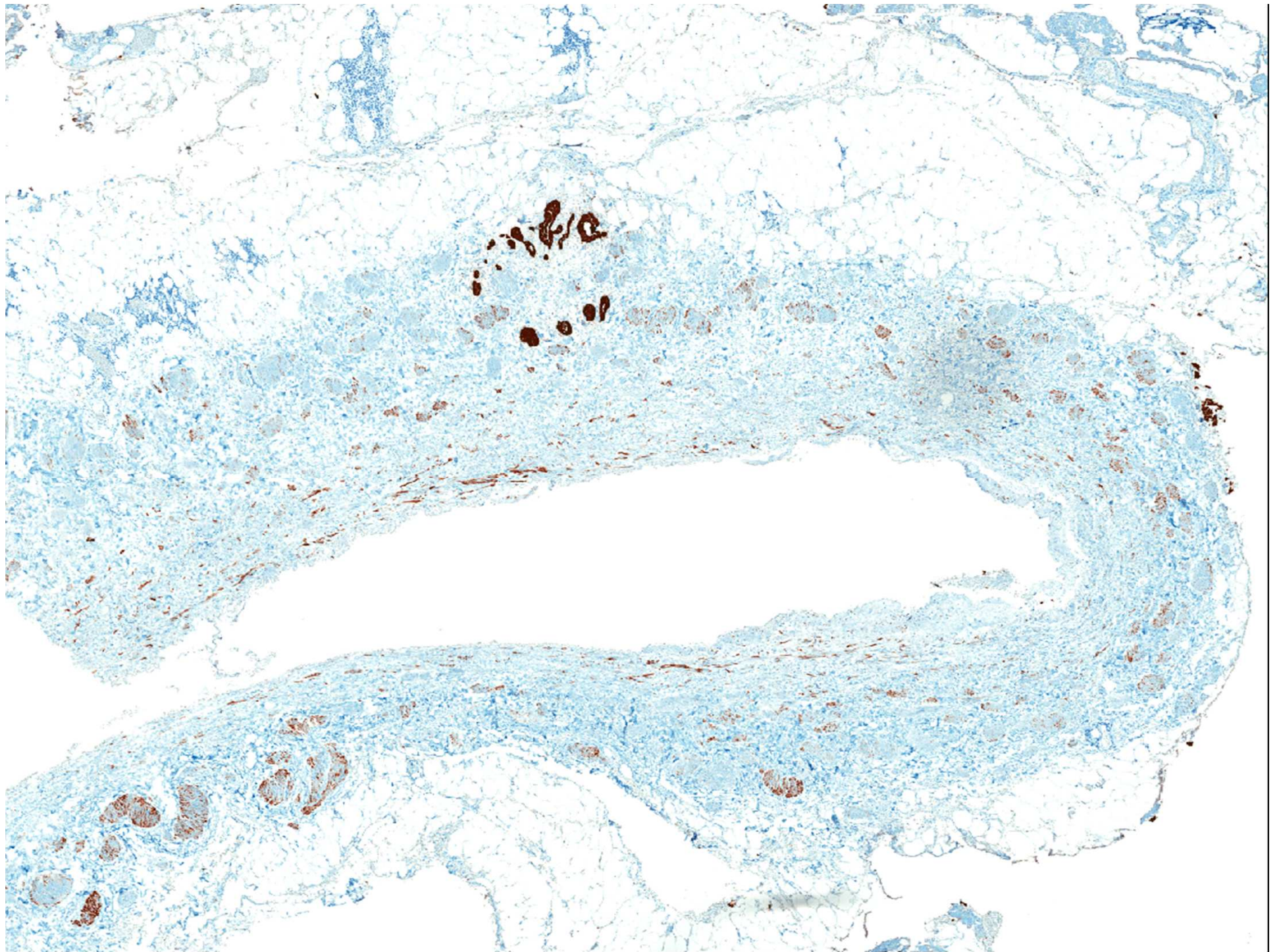


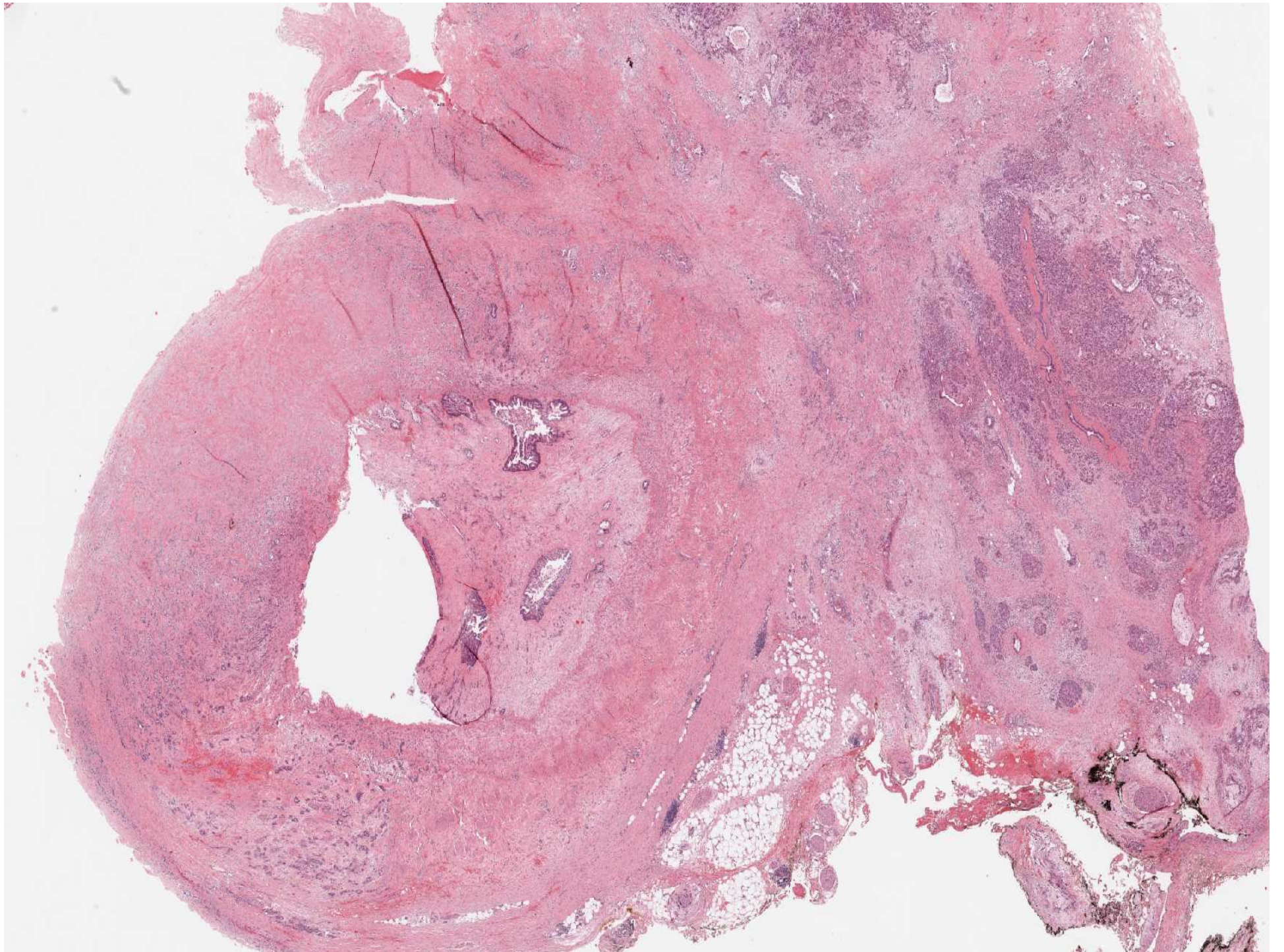
Integrating pathology and radiology disciplines: an emerging opportunity?

James Sorace et al. BMC Medicine 2012,10:100

- Pathology and radiology form the core of cancer diagnosis, yet the workflow's of both specialties remain *ad hoc* and occur in separate “*silos*”, with no direct linkage... between reporting system.
- ...isolation of radiology and pathology workflows can be detrimental to the quality and outcomes of patient care
- The opportunity has emerged to develop an integrated reporting system that supports both specialties...







- Results indicate that even if radiologically confirmed tumor contact with SMV/PV confluence is less than 50% or even 25% adenocarcinoma will most likely be identified at the SMVM or within 1 mm (if margin submitted in total for microscopic examination)

Patient	Pathologic status	Pre-operative radiology (circumference involvement)
+ Microscopic evidence of adenocarcinoma present at the margin		
- Adenocarcinoma is microscopically identified more than 1 mm from margin		
1	+	Contact (obliterated)
2	+	Contact (50-75%)
3	+	Contact (50%)
4	+	Contact (25-50%)
5	+	Contact (25%)
6	+	Contact (25%)
7	+	Contact (25%)
8	+	Separate, 2 mm from tumor
9	1 mm	Contact (50%)
10	1 mm	Contact (50%)
11	1 mm	Contact (25-50%)
12	1 mm	Contact (25-50%)
13	1 mm	Contact (25%)
14	1 mm	Separate, 2 mm from tumor
15	1 mm	Separate, 3 mm from tumor
16	1 mm	Separate, 13 mm from tumor
17	-	Separate, 8 mm from tumor
18	-	Separate, 8 mm from tumor
19	-	Separate 16 mm from tumor
20	-	Separate 20 mm from tumor

V Maksymov et al, American Journal of Clinical Pathology, Volume 138, Issue suppl_2, 1 November 2012, Pages A038, Published: 23 October 2015. Presented at the Annual Meeting of the American Society of Clinical Pathology, 2012, Boston, USA.

Complete correlation between preoperative imaging and microscopy (with the exception of one patient)

Tumors were identified at or within 1 mm from SMVM even in patients where the radiologist identified less than 25% circumferential tumor contact with SMV/PV confluence

Results indicate that even if radiologically confirmed tumor contact with SMV/PV confluence is less than 50% or even 25% adenocarcinoma will most likely be identified at the SMVM or within 1 mm (if margin submitted in total for microscopic examination);

V Maksymov, M Khalifa, D Divaris and D Driman (2013) advocate for changes to the CAP checklist such that the following margins are evaluated in all PD specimens (changes in red):

___ Proximal margin (gastric or duodenal)

___ Distal margin (distal duodenal)

___ SMA margin

___ SMV / vascular groove margin/surface

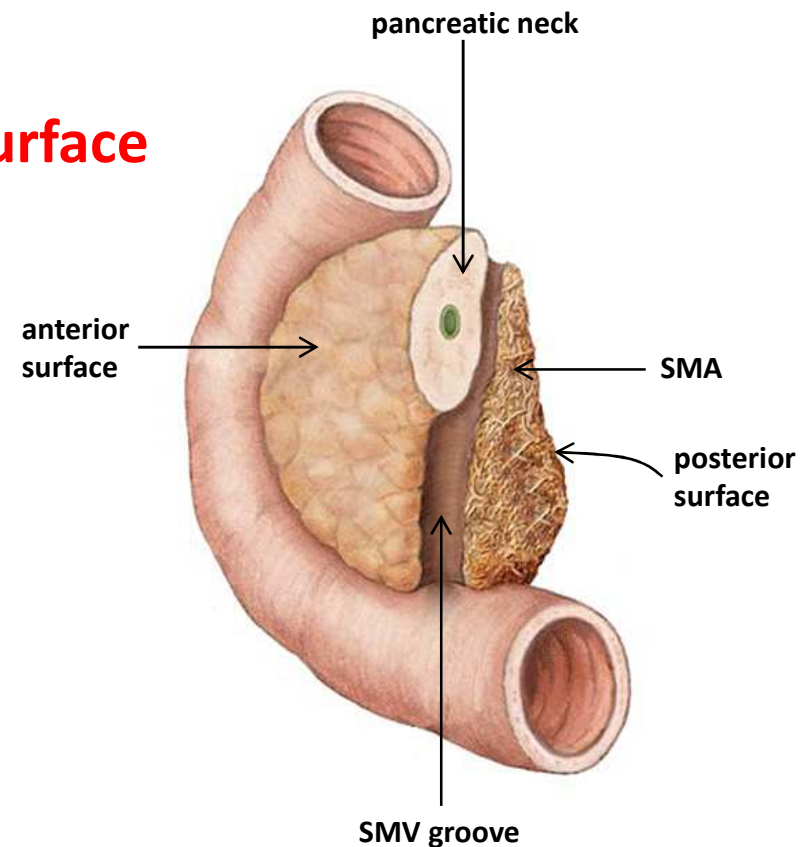
___ Posterior margin/surface

___ Anterior margin/surface

(NB: controversial, for discussion)

___ Bile duct margin

___ Pancreatic resection margin



Suggested unified reporting of the margins

- ___ Margin(s) involved by invasive carcinoma
- ___ Proximal **resection** margin (gastric or duodenal)
- ___ Distal **resection** margin (distal duodenal)
- ___ **SMA/Uncinate process (retroperitoneal) resection** margin (nonperitonealized surface of the uncinate process)
- ___ **SMV/Vascular groove dissection margin/surface**
- ___ Bile duct **resection** margin
- ___ **Pancreatic resection margin**
- ___ Other (specify): _____
- ___ Invasive carcinoma involves **other** posterior retroperitoneal surface of pancreas



Uncinate (retroperitoneal/superior mesenteric artery) margin

- Margin(s) involved by invasive carcinoma
 - Proximal margin (gastric or duodenal)
 - Distal margin (distal duodenal)
 - Uncinate process (retroperitoneal) margin (non-peritonealized surface of the uncinata process)
 - Bile duct margin
 - Pancreatic resection margin
 - Other (specify): _____

Pancreatic neck/parenchymal resection margin

+ Invasive carcinoma involves posterior retroperitoneal surface of pancreas **DELETE**

Microscopic Tumor Extension (select all that apply)

- Cannot be assessed
- No evidence of primary tumor
- No invasion (carcinoma in situ/high-grade dysplasia, includes pancreatic intraepithelial neoplasia III)
- Tumor is confined to pancreas
- Tumor invades ampulla of Vater or sphincter of Oddi
- Tumor invades duodenal wall
- Tumor invades peripancreatic soft tissues
 - + Tumor invades retroperitoneal soft tissue
 - + Tumor invades mesenteric adipose tissue
 - + Tumor invades mesocolon
 - + Tumor invades other peripancreatic soft tissue (specify): _____
 - + Tumor invades extrapancreatic common bile duct
- Tumor invades other adjacent organs or structures (specify): _____

- + Tumor involves posterior surface of pancreas
- + Tumor involves anterior surface of pancreas
- + Tumor involves vascular bed/groove (corresponding to superior mesenteric vein/portal vein)

ADDED

Positive margin definition:

- UK, Japan, Australia:
 - 1 mm or less (1 mm rule)
- College of American Pathologist (2013 edition)
 - malignant cells at the margin (0 mm rule)
- Controversial data for many reasons.

Importance: radiation oncologist - radiation or no?

Why it is important?

Reporting of SMV/groove/margin/surface involvement:

- Tumor present microscopically at the SMV surface margin (SMA margin negative) – radiation?

Why it is important?

Pathologic reporting of
SMV/groove/margin/surface involvement:

- important for quality assurance, including feedback to the radiologist and surgeons who makes preoperative and intraoperative decisions as to the separation of the vessel from pancreatic head, especially in borderline resectable cases

Main methods/protocols

1. Axial slicing method (no duct dissection)

(Leeds Pathology Protocol (LEEPP), Menon KV, Gomez D, Smith AM, Anthony A, Verbeke CS. HPB (Oxford), 2009; Verbeke CS, Gladhaug IP. B J Surg 2012)

2. Duct dissection method.

3. Combination (combine approach to grossing).

Combined approach.

- Shaved all margin (5-10 mm in thickness) and serially sectioned perpendicular to margins and submitted in total, oriented.

Advantages: definite margin status and increase number of identified lymph nodes.

- Ampulla of Vater removed in block and sectioned longitudinally along long axis of CBD, submitted in total.

Advantages: important to distinguish between pancreatic, ampullary and distal bile duct cancer.

- Remaining specimen – serial slicing in axial plane (or other planes if necessary)

Pathologic staging (exocrine pancreas) (Based

on AJCC/UICC TNM, 7th edition

Protocol web posting date: August 2016

- Primary Tumor (pT)
- ___ pTX: Cannot be assessed
- ___ pT0: No evidence of primary tumor
- ___ pTis: Carcinoma in situ
- ___ pT1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
- ___ pT2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
- ___ pT3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- ___ pT4: Tumor involves the celiac axis or the superior mesenteric artery

Pathologic staging (exocrine pancreas) (June 2017, includes pTMN requirements from the 8th edition, AJCC Staging manual)

- ___ pT1: Tumor ≤ 2 cm in greatest dimension
- ___ pT1a: Tumor ≤ 0.5 cm in greatest dimension
- ___ pT1b: Tumor > 0.5 cm and < 1 cm in greatest dimension
- ___ pT1c: Tumor 1–2 cm in greatest dimension
- ___ pT2: Tumor > 2 cm and ≤ 4 cm in greatest dimension
- ___ pT3: Tumor > 4 cm in greatest dimension
- ___ pT4: Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery

Tumor size

- The T categories T1-T3 are defined by tumor size as it provides better prognostic stratification than classification based on extension into peripancreatic tissue (8th Edition AJCC). (Lim JE, Chien MW, Earle CC. Ann Surg. 2003;237(1):74-85. Matsumoto G, Muta M, Tsuruta K, Horiguchi S, Karasawa K, Okamoto A. Pancreatology. 2007;7(2-3):167-173. Moon HJ, An JY, Heo JS, Choi SH, Joh JW, Kim YI. Pancreas. 2006;32(1):37-43. Saka B, Balci S, Basturk O, et al. Ann Surg Oncol. 2016;23(6):2010-2018. Allen PJ, Kuk D, Castillo CF, et al. Ann Surg. 2017;265(1):185-191.)
- Tumor size is determined by measurement of the gross lesion and should be corroborated on microscopic assessment. (8th Edition AJCC).

V Maksymov, D Driman. World Pancreas Forum, Switzerland, 2017***

- Pancreatic ductal adenocarcinoma was diagnosed in 30 cases.
- Extension of tumor into peripancreatic fat identified in all cases (pT3, based on 7th edition of AJCC).
- According to the new 8th Edition of AJCC size based criteria, these cases would have been reported as follows: pT3 (n=4) and pT2 (n=26).
- The average size of tumor was 3.2 cm.
- In our series, a finding of invasion of peripancreatic fat by single glands without desmoplasia was common and as result the true maximum dimension was most likely bigger than size measured on macroscopic examination or radiological assessment.

*** The winner of travel grant

Conclusion

- The following discussion illustrate that different approaches to the assessment and reporting can completely change statistics and affect final understanding in all scientific trials etc.
- Standardized assessment of PD specimens now must include assessment of SMV dissection margin/surface (not only Uncinate process (SMA) resection margin). It is important for interdisciplinary collaboration) and quality assurance:
 - 1) feedback for the radiology team
 - 2) for the surgeon who is planning/making decision before and during the surgery to proceed with the separation of the SMV/PV from RP surface or not or perform wedge resection/en block resection of SMV/PV

Which anatomical structure (s) are facing to the Uncinate process (retroperitoneal) margin in the human body?

- A) Superior Mesenteric Artery and Superior Mesenteric Vein
- B) Vena cava Inferior
- C) Superior Mesenteric Artery
- D) Superior Mesenteric Vein

Which term is best in the description of the Superior Mesenteric Vein Margin?

- A) Resection margin
- B) Surface /Dissection margin
- C) Retroperitoneal margin

Which term is suggested by AJCC (Cancer Staging Manual, Seventh Edition) to be used instead of Uncinate process margin?

- A) Posterior pancreatic margin
- B) Superior Mesenteric Artery margin
- C) Retroperitoneal margin