Surgical Approach to Pancreatic Cancer

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Disclosures

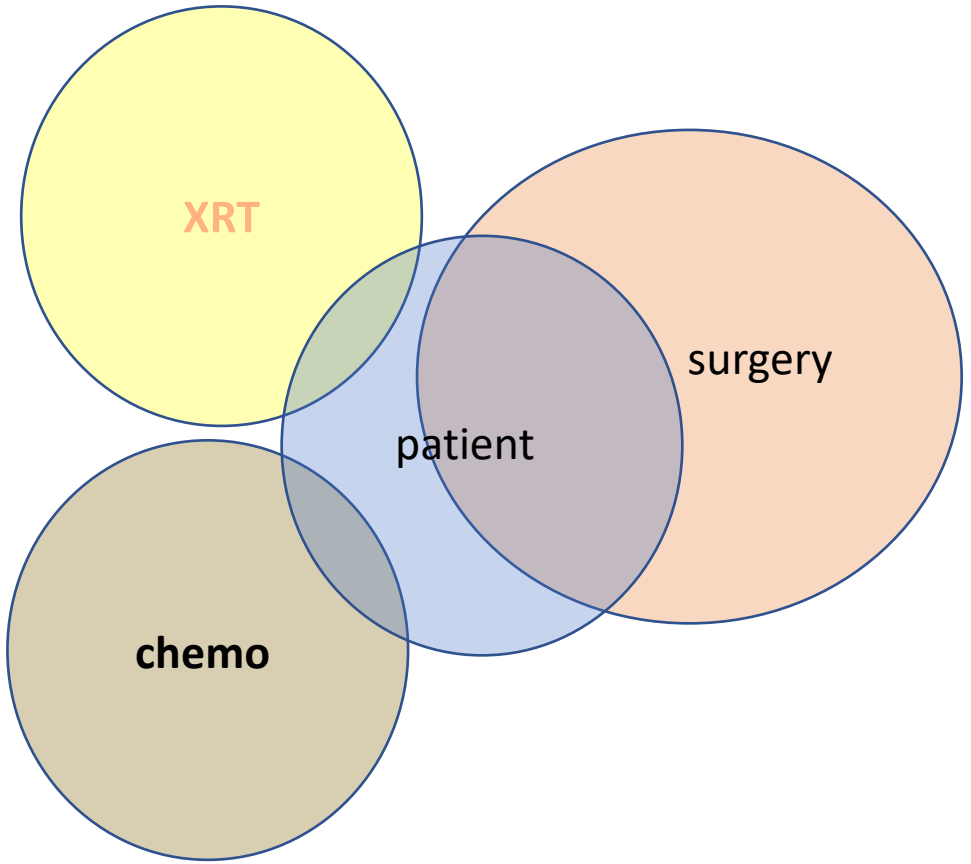
- Consultant for Angiodynamics
- Consultant for Ethicon
- Consultant for SIRTEX

Outline of talk

- Defining resectability of pancreatic cancer
- Importance of margins
- Role of chemo – pre/post?
- Technical aspects of surgery

Pancreatic cancer

- Terrible disease
- Poor survival:
  - 20% at 2 years
  - 5% at 5 years
- Surgery is biggest bang for the buck


XRT
surgery
patient
chemo

When do we do surgery?

Anatomic resectablility:

- SMV
- SMA
- Celiac

Oncologic factors:

- CA 19-9
- ? mets

Patient factors:

- Recent MI
- PS

Categories:

- Resectable
- Borderline resectable (BRPDAC)
- Locally advanced
- Metastatic

MUST know

Resectable:

- Clear planes
- R0 resection expected

Borderline resectable:

- R1 expected

Locally advanced:

- Cannot take out at this time

Metastatic:

- Distant disease

Categories of BRPC

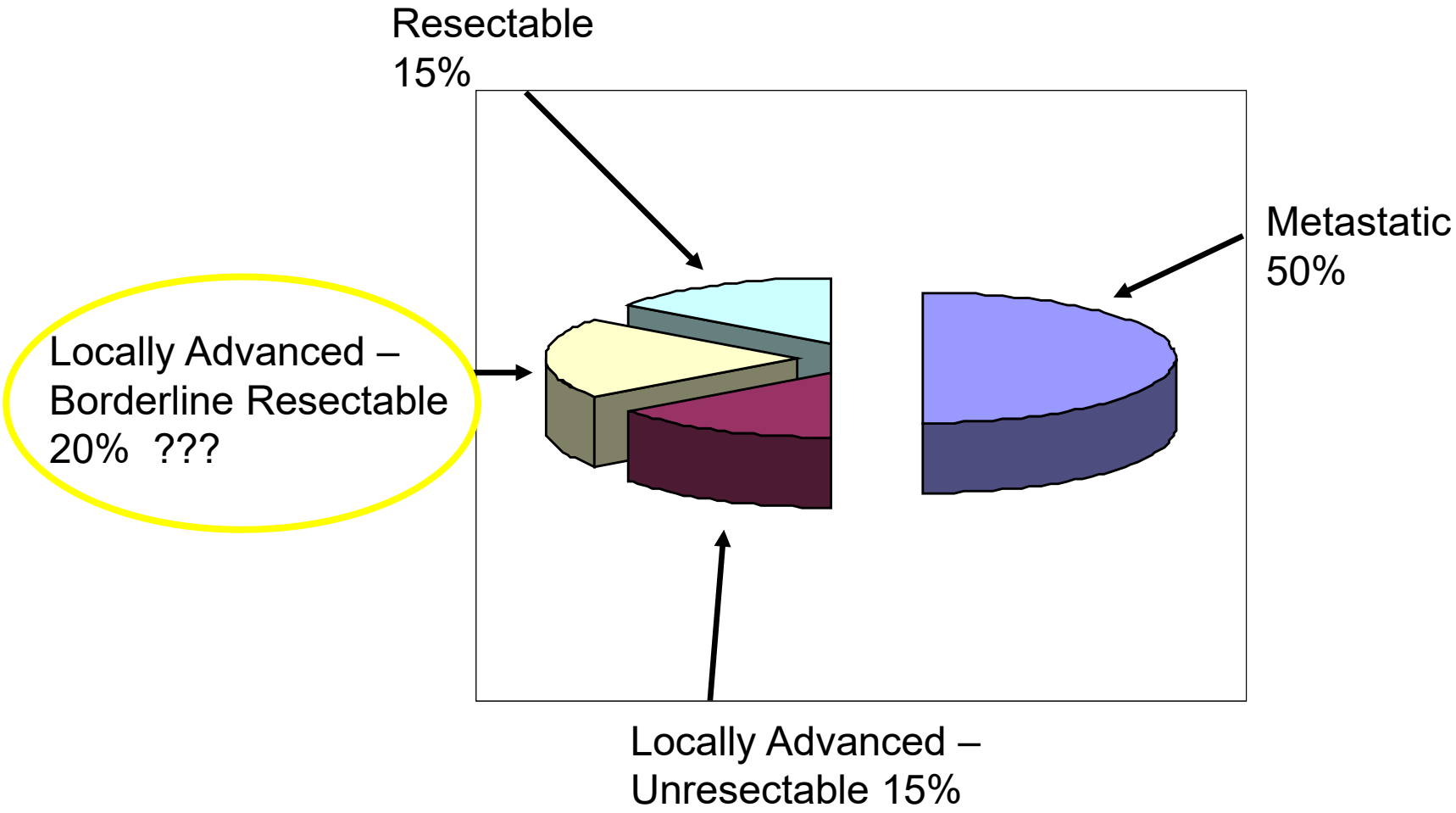
	A	B	C
category	ANATOMIC	BIOLOGIC	CONDITIONAL
example	Arterial involvement	Elevated CA 19-9>500	Recent MI

Katz, et al, J Am Col Surg, 2008

Anatomic factors:

- SMV/ PV confluence:
  - ? Reconstructable disease
- SMA:
  - >180 degree?
- Extent into pancreas:
  - Where does the PD change size?
- Proximal extent into bile duct:
  - Rare to be an issue with distal CBD lesion / Panc ca

Distribution of Pancreatic Cancer

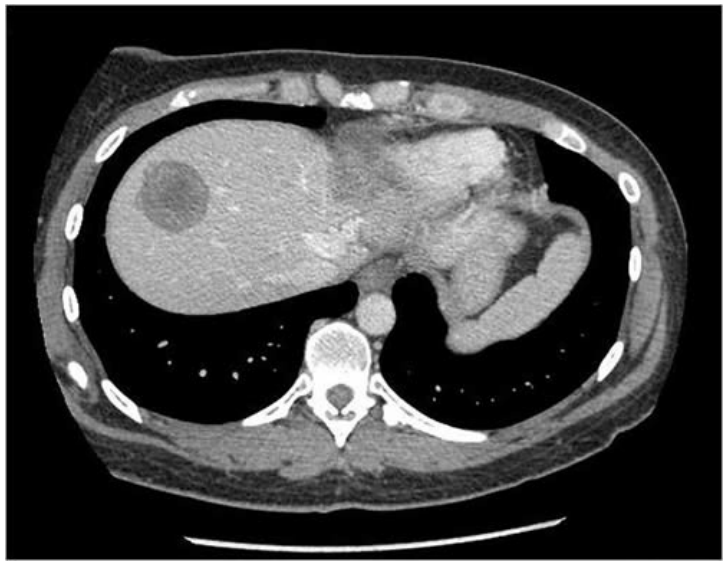


What is BRPC

TABLE 1. Definitions of BRPC

	MDACC[9]	Alliance trial[10]	AHPBA/SSAT/ SSO[11]
Portal vein (PV)/superior mesenteric vein (SMV)	Occlusion	Interface between tumor and vessel measuring *180° or greater* of the circumference of the vessel wall, and/or reconstructable occlusion	Abutment, encasement, or occlusion
Celiac artery	Abutment	Interface between tumor and vessel measuring *less than 180°* of the circumference of the vessel wall	No abutment or encasement
Common hepatic artery	Abutment or short encasement	Reconstructable, short-segment interface between tumor and vessel of any degree	Abutment or short-segment encasement
Superior mesenteric artery (SMA)	Abutment	Interface between tumor and vessel measuring *less than 180°* of the circumference of the vessel wall	Abutment

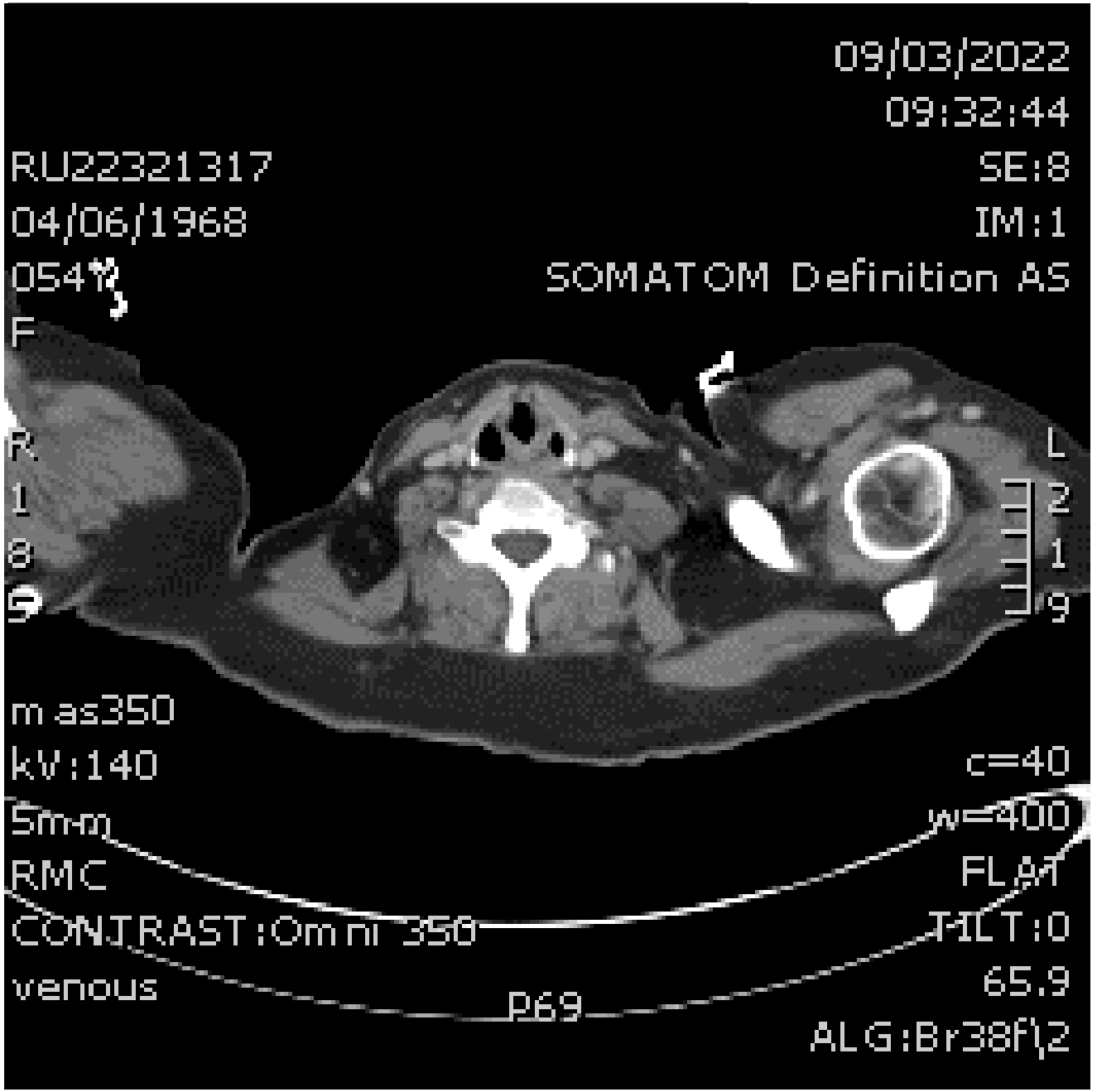
MDACC MD Anderson Cancer Center, *AHPBA* Americas Hepato-Pancreato-Biliary Association, *SSAT* Society for Surgery of the Alimentary Tract, *SSO* Society of Surgical Oncology

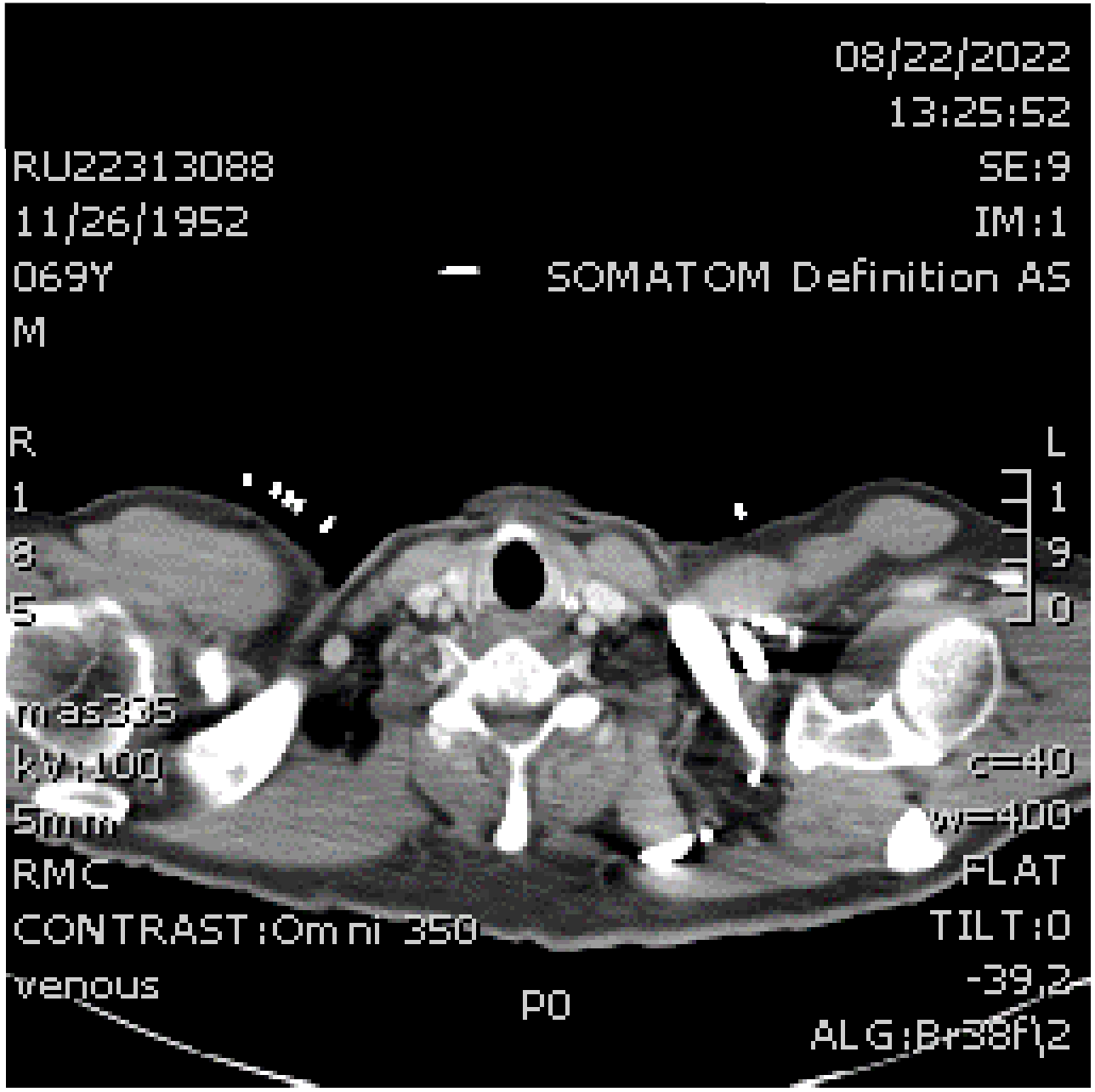


- Tumor relationship with SMV/PV, SMA, hepatic artery, celiac axis
- <u>Resectable tumor:</u>
  - No “involvement” of any above structures
- <u>Unresectable tumor:</u>
  - Distant disease
  - Locally advanced

- <u>Locally Advanced – Unresectable tumor</u>
  - >180^{o} involvement SMA (50%)
  - Extension to celiac axis
  - HA encasement not amenable to reconstruction
  - SMV/PV encasement not amenable to reconstruction

Resectable lesion

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IM:1
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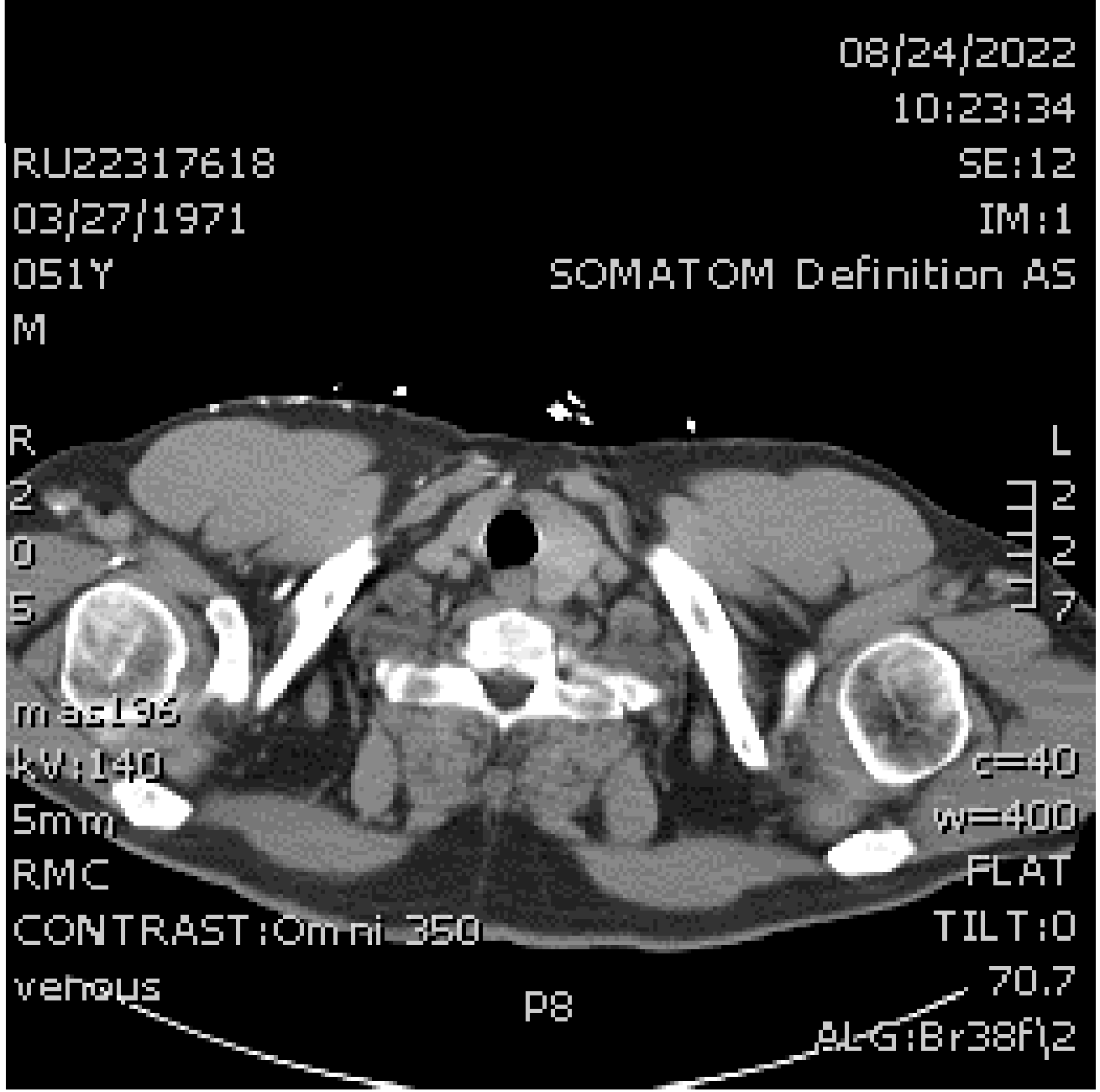
venous
-39.2
P0
ALG:B+38f\2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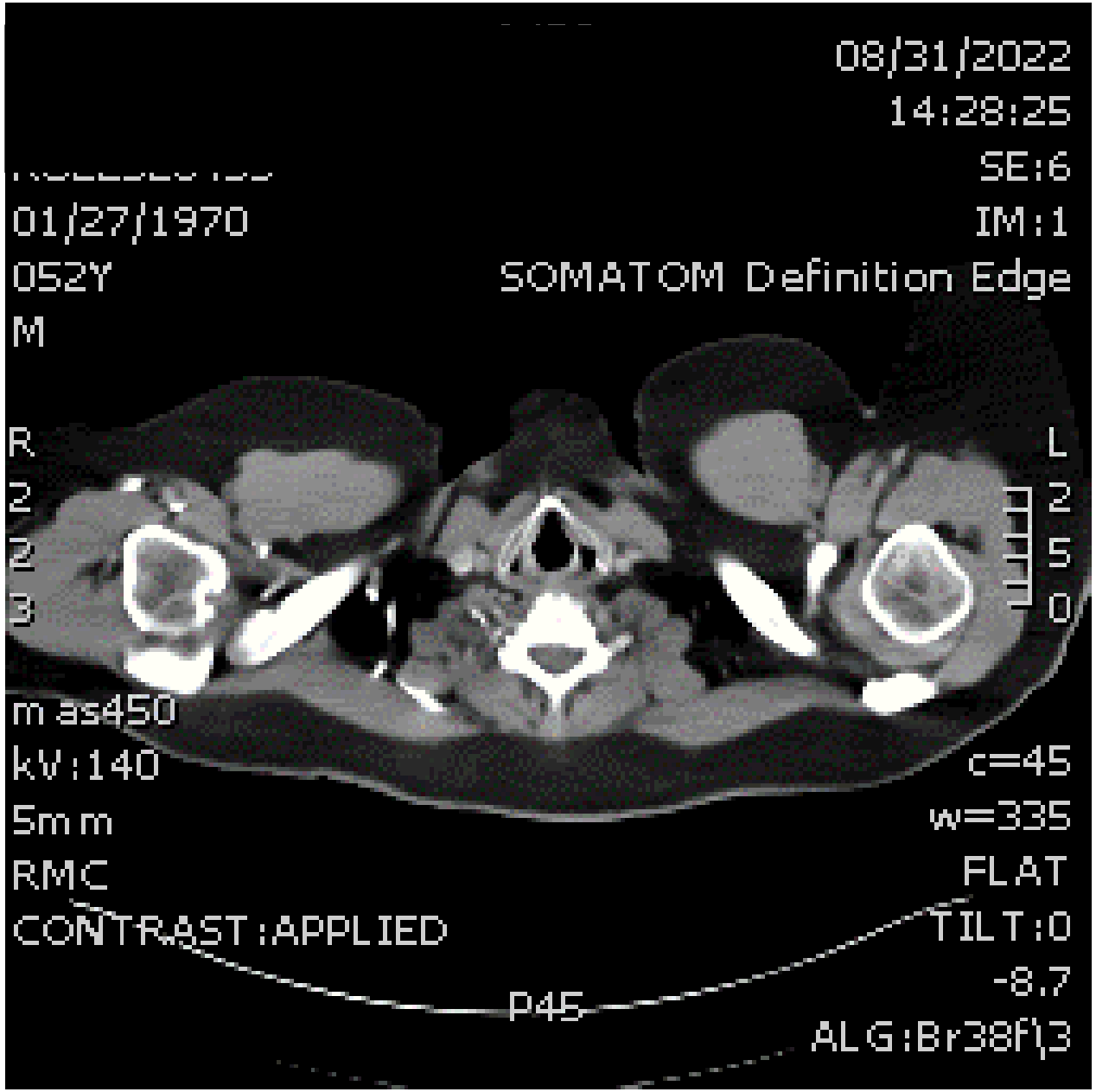
venous
70.7
P8
ALG:Br38f\2

BRPDAC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M
SOMATOM Definition Edge
R
L
mas450
kV:140
5mm
RMC
CONTRAST:APPLIED
c=45
w=335
FLAT
TILT:0
-8.7
P45
ALG:Br38f\3

So what do we do with resectable lesion?

- NCCN guidelines allows resect if able
- Open for neoadjuvant treatment:
  - ALLIANCE TRIAL
  - Initial data suggests lower R1 rate/ N1 rate
- BUT no clear evidence that neoadjuvant treatment results in BETTER OS

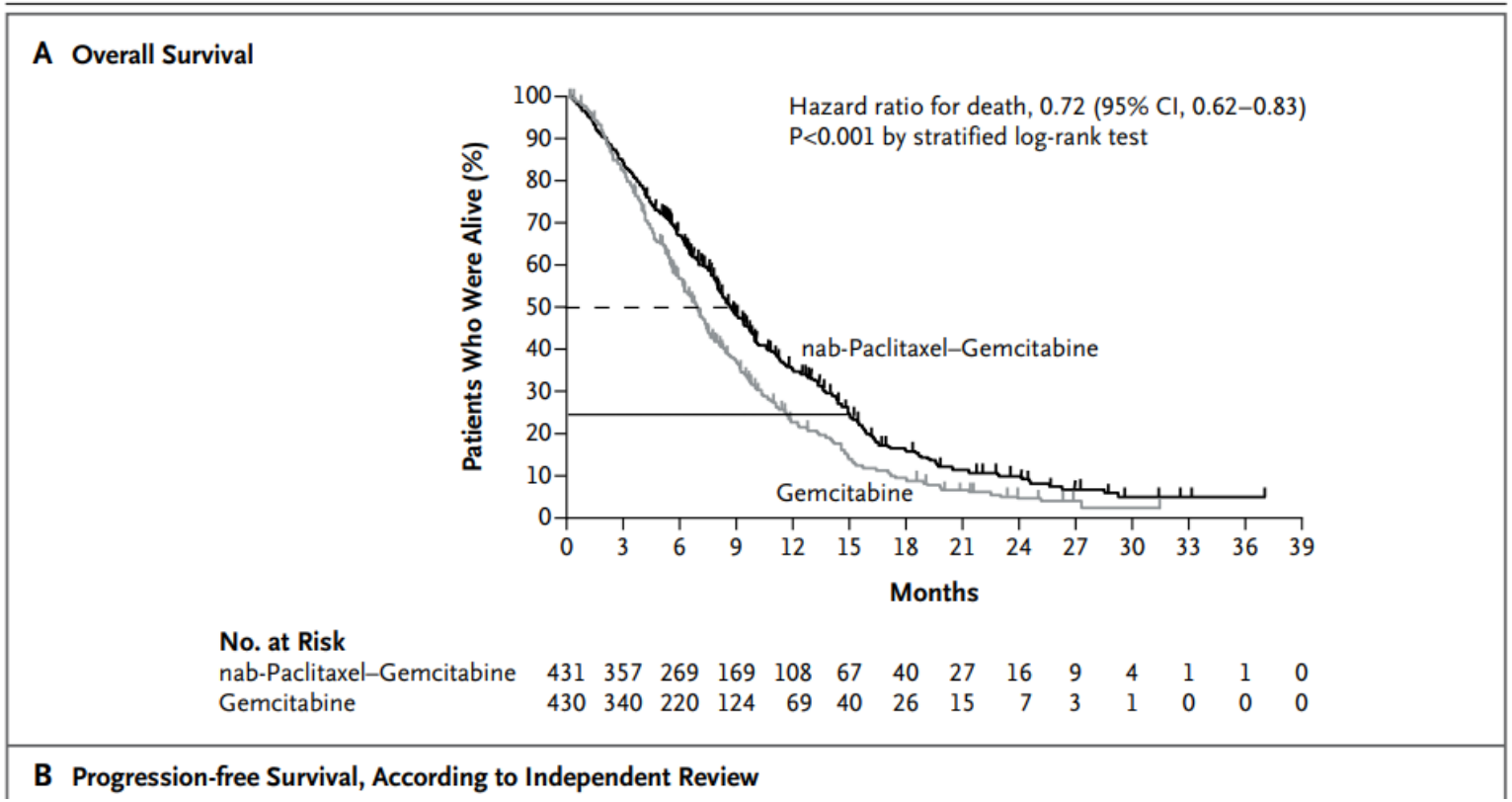
Neoadjuvant Therapy : Advantages

1. Identification of patients with occult metastatic disease
2. Completion of therapy
3. Reduce incidence of positive margins
4. Reduce incidence of pancreatic leak
5. Oxygen delivery
6. Radiation of “specimen” vs. anastomoses

USING DATA FROM METASTATIC PANC CA

Van Hoff- Nab/Pacli+gem vs Gem*

INCREASED SURVIVAL IN PANCREATIC CANCER



Van hoff et al, NEJM 2013

NEOADJUVANT TREATMENT

Neoadjuvant treatment and panc ca

- Chemo:
  - FU
  - Gem/Nab-PAc
  - FOLFIRINOX
- XRT:
  - Standard (6 week)
  - SBRT (5 days)
- Future:
  - Immunotherapy
  - Check point inhibitors

TABLE 2 Summary of clinical studies

Study group	Time frame	Study design	Primary endpoint	Result from intention-to-treat analysis	Strength	Weakness
Korean trial	2012–2014	Neoadjuvant gem CRT versus upfront surgery	2-year survival rate	Neoadjuvant arm had better 2-year survival rate (21 vs. 12 months)	The first multicenter RCT	Early termination of study; single-agent chemotherapy
Dutch PREOPANC	2013–2017	Neoadjuvant gem/gem CRT versus upfront surgery	Overall survival (OS)	Neoadjuvant arm had better overall survival (17.6 vs. 13.2 months)	Multicenter RCT	Mixed resectable and BRPC patients; combined single-agent chemotherapy and CRT
MGH study	2012–2016	Single-arm neoadjuvant FOLFIRINOX	R0 resection rate	31 patients (97%) achieved R0 resection	Multiagent chemotherapy; total neoadjuvant design	Single-arm phase II study
A021501	2016–2020	Neoadjuvant FOLFIRINOX versus FOLIRINOX plus hypofractionated radiation therapy	18-month overall survival (OS)	The radiation treatment arm was prematurely closed due to poor R0 resection rate	Multiagent chemotherapy; "pick-a-winner" approach; National Clinical Trials Network cooperative group study	Significant variance of surgical quality in resecting BRPC among the cooperative group

Gem gemcitabine, *FOLFIRINOX* fluorouracil, irinotecan, and oxaliplatin, *CRT* chemoradiotherapy, *RCT* randomized clinical trial

Jun He, et al, Ann Surg Onc, 2021

PREOPANC TRIAL

- 248 pts randomly assigned
  - Gem/Gem XRT
    120
  - Surgery first
    128

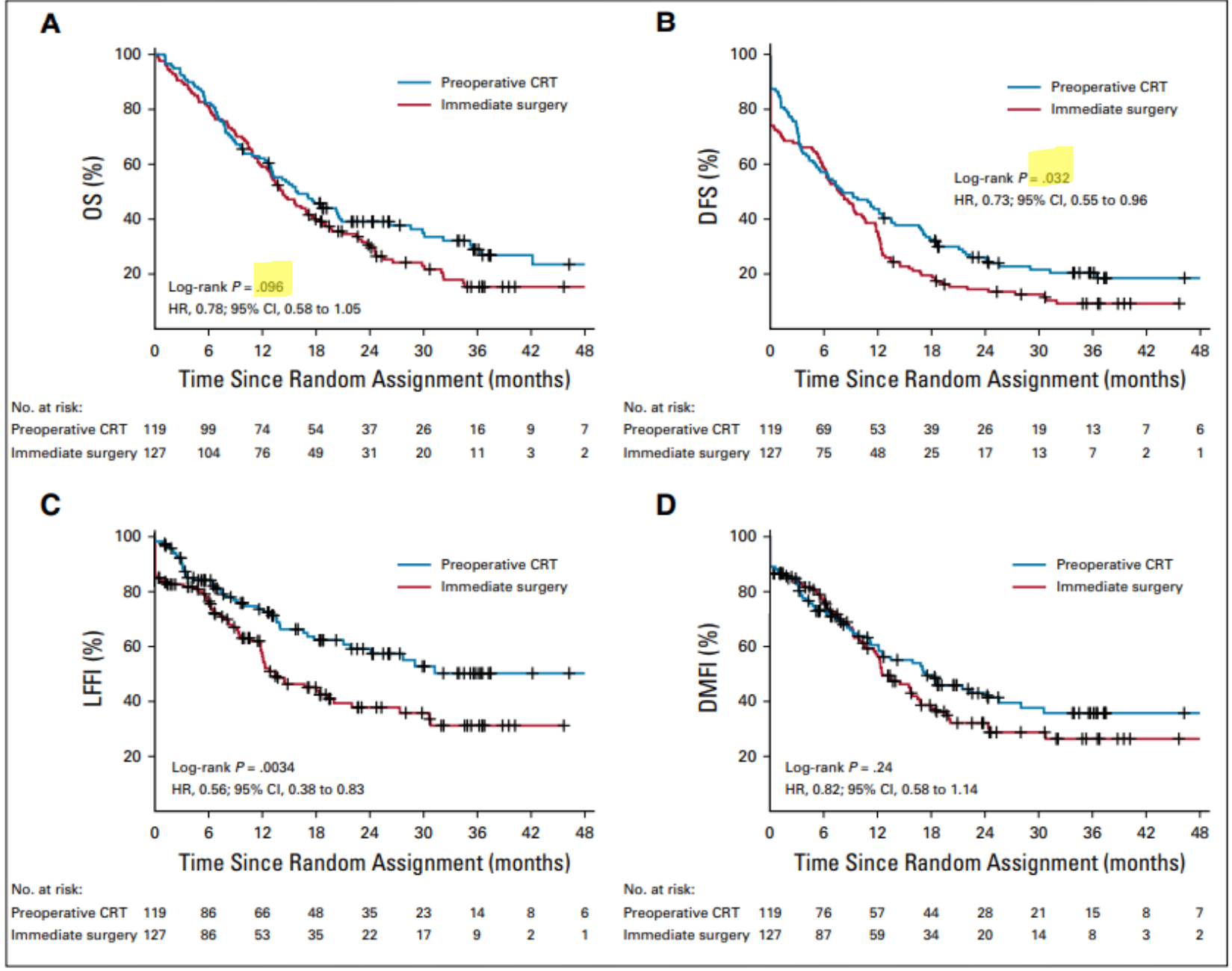


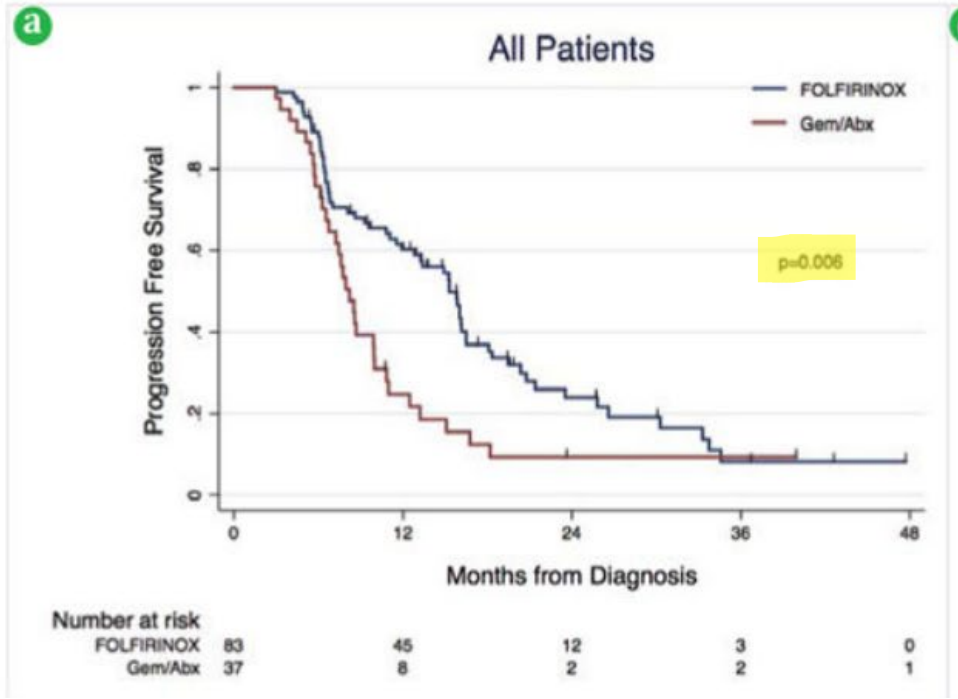
FIG 2. (A) Overall survival (OS), (B) disease-free survival (DFI), (C) locoregional failure–free interval (LFFI), and (D) distant metastasis–free interval (DMFI) in 246 patients randomly assigned to preoperative chemoradiotherapy (CRT; 119 patients) or immediate surgery (127 patients) according to intention-to-treat analysis. Tick marks indicate censored observations. HR, hazard ratio.

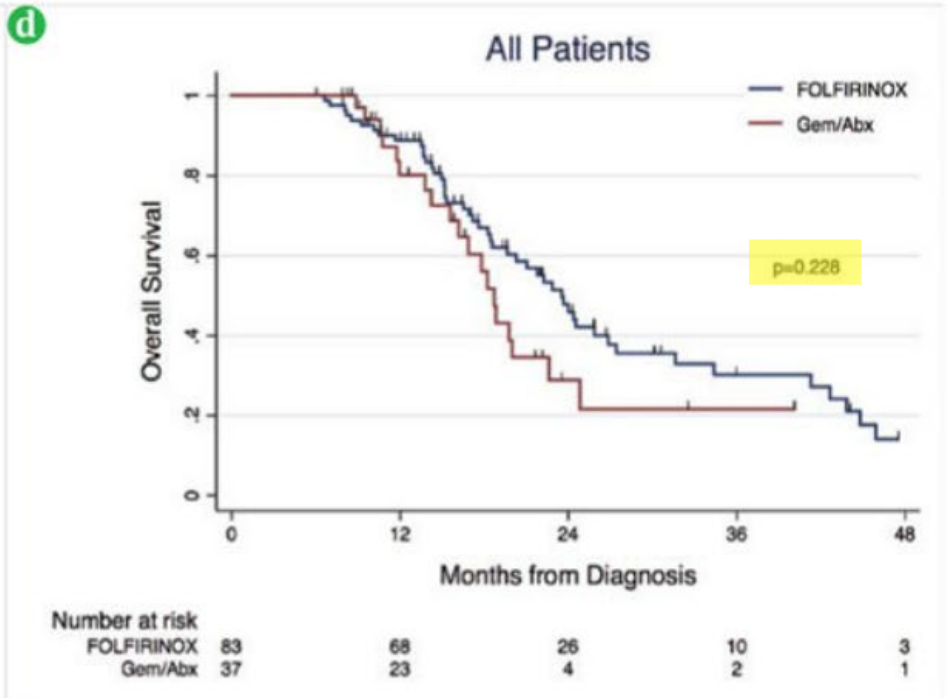
TABLE 2. Intention-to-Treat Analyses of Primary and Secondary End Points for Both Treatment Groups

Outcome	Preoperative CRT (n = 119)	Immediate Surgery (n = 127)	HR (95% CI)	*P*
Primary				
Median OS, months	16.0	14.3	0.78 (0.58 to 1.05)	.0960
Secondary				
Median DFS, months	8.1	7.7	0.73 (0.55 to 0.96)	.0320
Median LFFI, months	NR	13.4	0.56 (0.38 to 0.83)	.0034
Median DMFI, months	17.4	12.5	0.82 (0.58 to 1.14)	.2400
	No. (%)	**No. (%)**	**OR (95% CI)**	
Resection rate	72 of 119 (61)	92 of 127 (72)	0.58 (0.34 to 1.00)	.0580
R0 rate	51 of 72 (71)	37 of 92 (40)	3.61 (1.87 to 6.97)	< .0010
Safety				
Patients with SAEs (all grades)	62 of 119 (52)	52 of 127 (41)	1.57 (0.95 to 2.60)	.0960

Abbreviations: CRT, chemoradiotherapy; DFS, disease-free survival; DMFI, distant metastasis–free interval; HR, hazard ratio; LFFI, locoregional failure–free interval; NR, not reached; OR, odds ratio; OS, overall survival; SAE, serious adverse event.

Neoadjuvant data re Gem/A vs FOLFIRINOX: the Colorado experience*





*Chapman et al, JOP March 2018

Conclusion:

- No benefit to NACRT in resectable/BRPC
- Improved R0 status/ Node + status

What do we do adjuvantly?

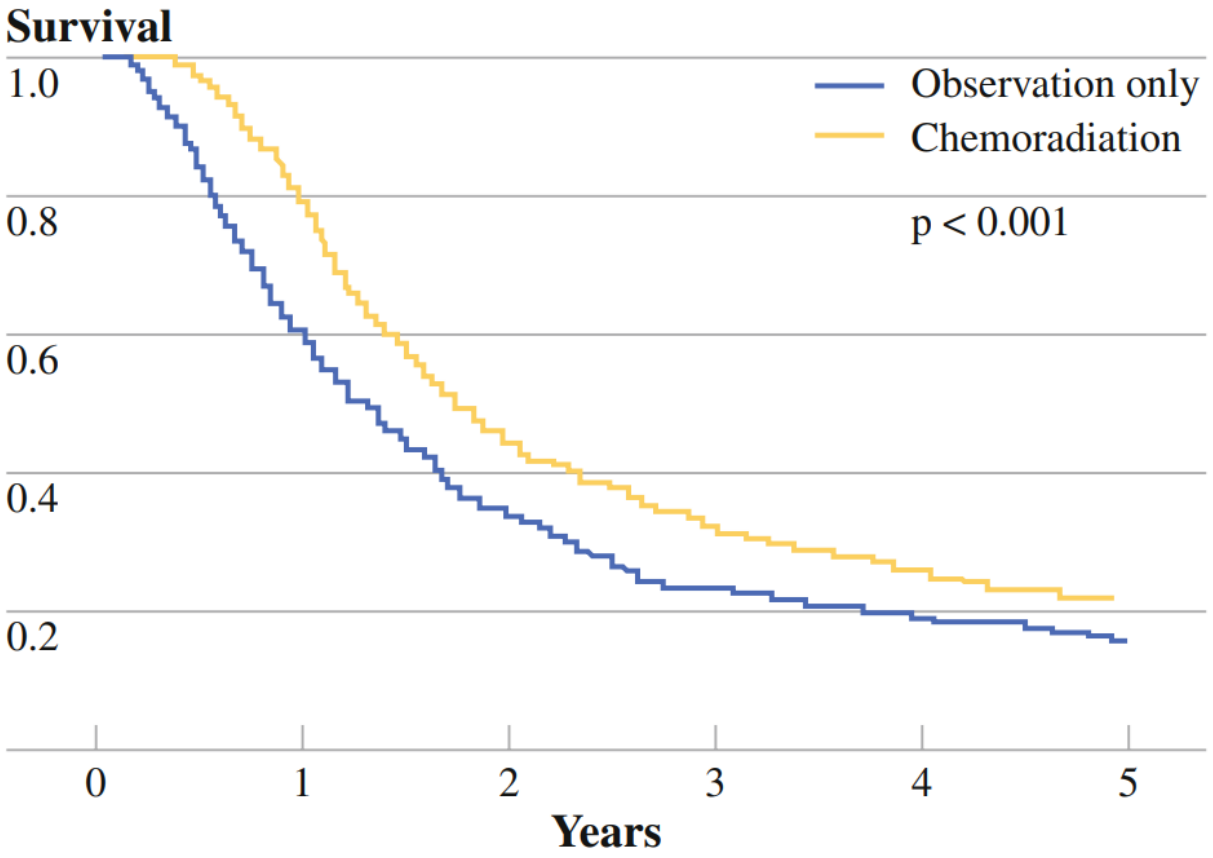
Chemo rads- JH/ Mayo experience*

Chemo alone:

- Gem
- FU/Gem
- Gem/Nab
- FOLFIRINOX

*Hsu et al, Ann Surg Onc, 2010

Hopkins/ Mayo experience with adjuvant chemo/XRT



Conclusion

- FU and XRT increased OS in the adjuvant setting

Then entered FOLFIRINOX

- We knew that there was metastatic data to support this
- The question was whether it would work adjuvantly

PROTÉGÉ GROUP

- 493 pts resected panc ca
- Randomized to :
  - FOLFIRINOXX 24 WEEKS
  - GEMX 24 WEEKS

- Conroy et al, NEJM, 2018

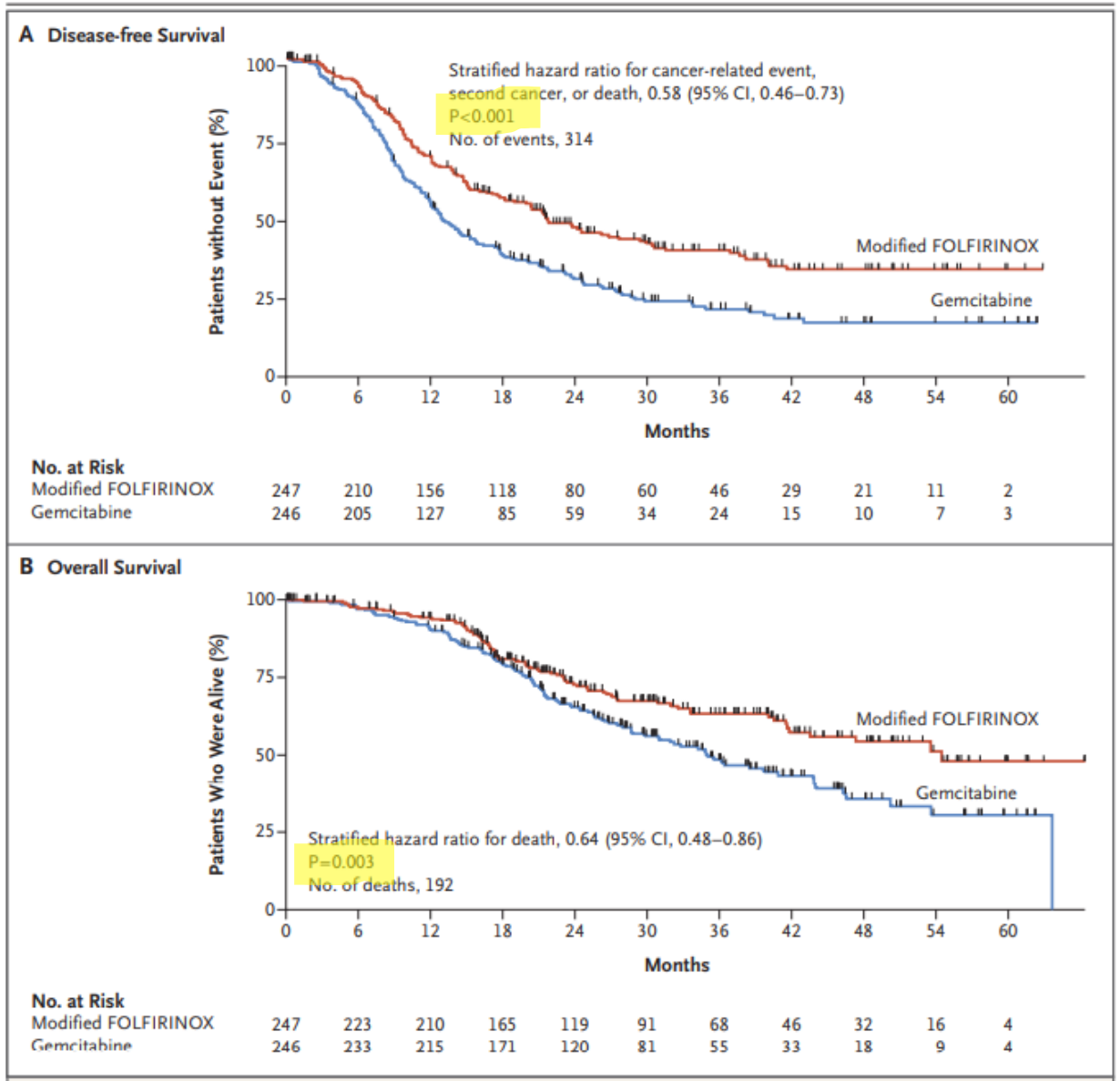


Figure 2. Kaplan–Meier Estimates of Disease-free Survival and Overall Survival in the Intention-to-Treat Population, According to Treatment Group.

The median disease-free survival was 21.6 months in the modified-FOLFIRINOX group, as compared with 12.8 months

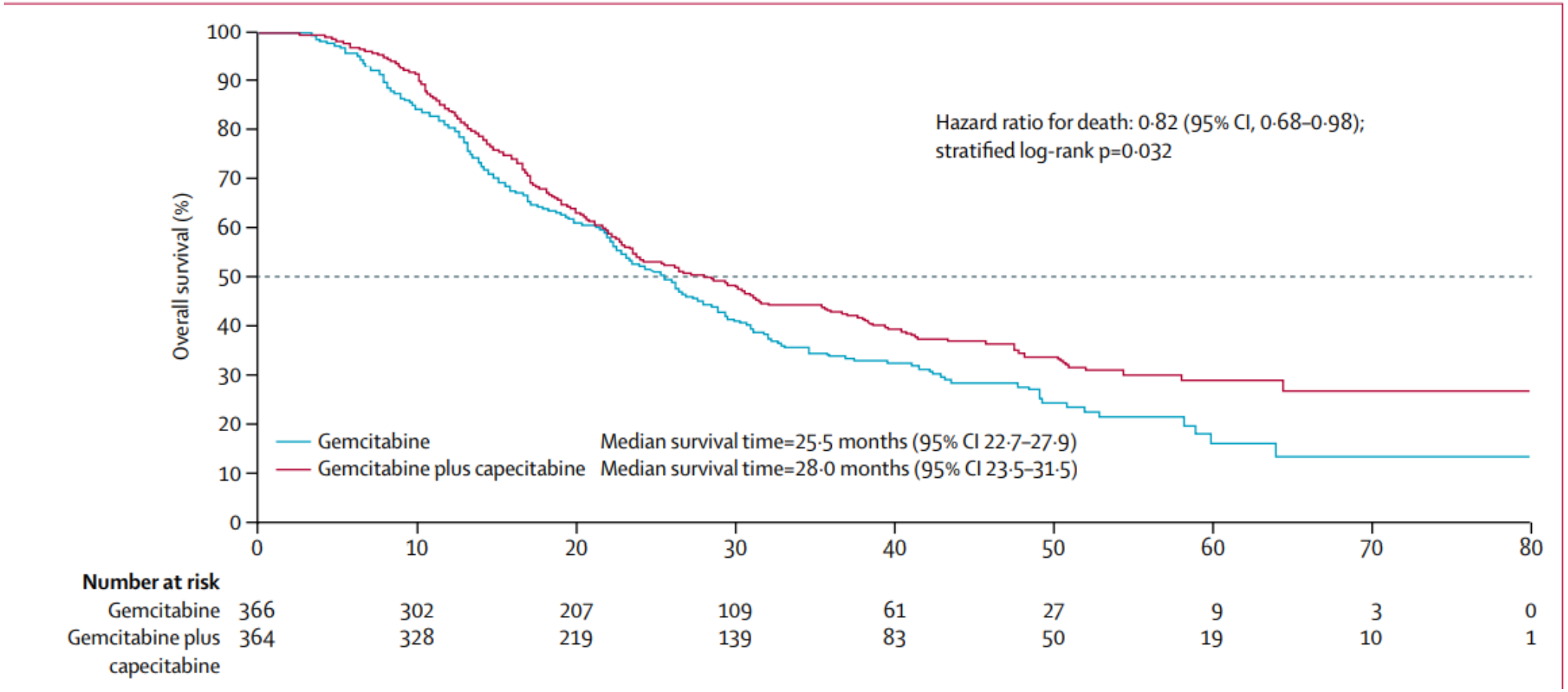
ESPAC-4

- Gem/ Cap compared with Gem
- Neoptolemos et al , Lancet, March 2017

ESPAC-4

- 794 pts post resection
- R1 or R0
- Randomized to :
    - Gem
    - Gem /cap

Overall survival better with G/C



SO IN SUMMARY

- No clear consensus on NAT in RESECTABLE PDAC
- Adjuvant therapy improves survival in RESECTED PDAC:
  - FOLFIRINOX
  - Gem/Nab-pac
  - FU/Gem

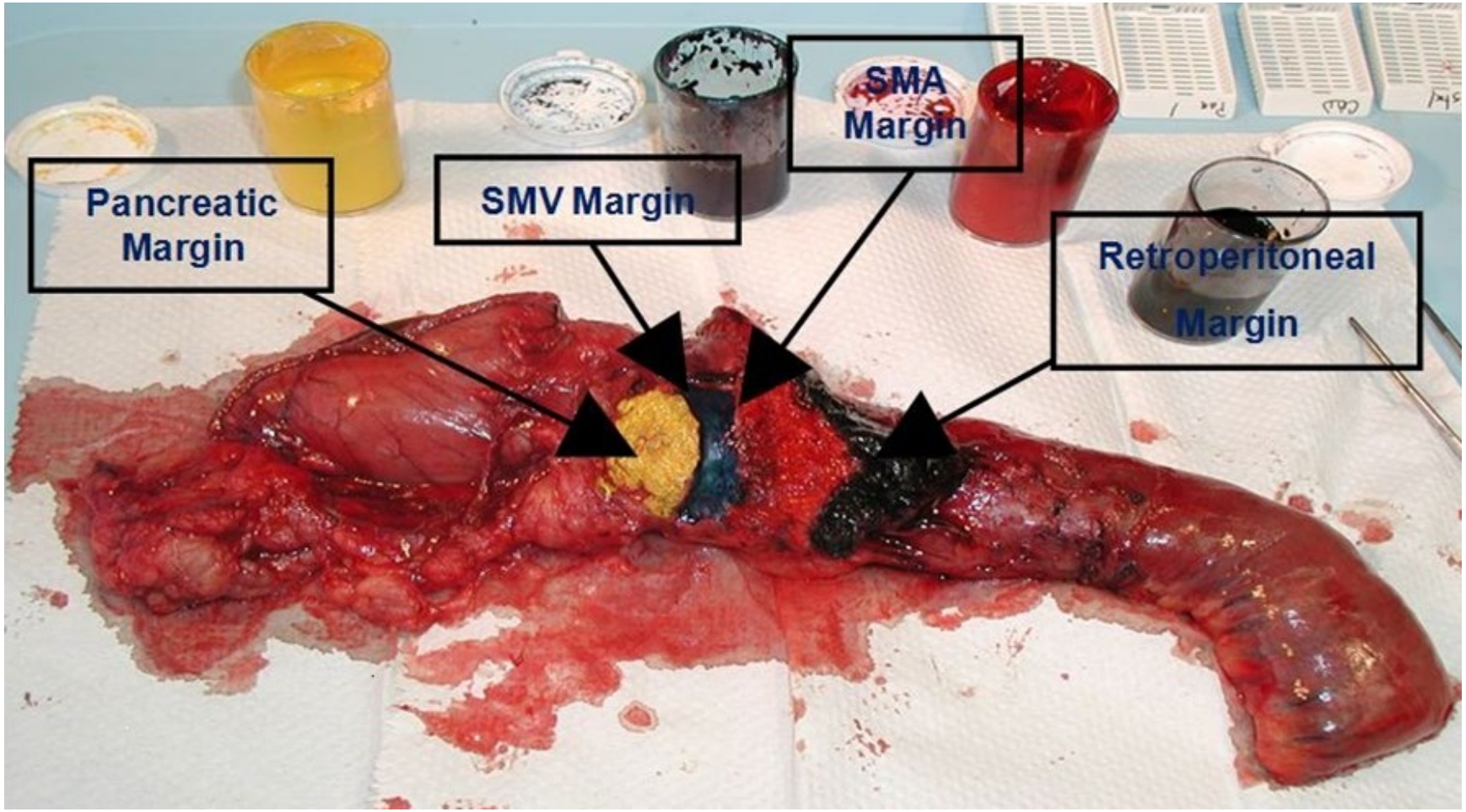
So what about margins?

- Most data suggests that margins status does impact on survival
- How we assess margins differs:
  - Europeans <1mm= R1*
  - USA- no tumor on ink
- Verbeke et al, HPB 2008,11:18-24

US centers generally ink

- Retroperitoneal
- Bile duct
- Pancreas
- SMV

Our protocol



More + margins if you look

But what does this mean?

Table 1 Survival data following curative and non-curative surgical resection for pancreatic cancer

Reference (First author/ year)	No of patients	RM status	R1 rate (%)	Median survival R1/R2 (months)	Median survival R0 R0 (months)
Menon (2009)[20]	27	R1	82	14	>55
Westgaard (2008)[36]	40	R1	45	11	16
Raut (2007)[17]	360	R1	17	22	28
Verbeke (2006)[16]	26	R1	85	11	37
Neoptolemos (2001)[5]	541	R1	19	11	17
Benassai (2000)[13]	75	R1, R2	20	9	17
Sohn (2000)[14]	616	R1	30	12	19
Millikan (1999)[12]	84	R1	29	8	17
Nishimura (1997)[11]	157	R1, R2	45	6	12
Sperti (1996)[10]	113	R1, R2	17	7	14
Nitecki (1995)[9]	174	R2	16	9	NA
Yeo (1995)[8]	201	R1, R2	29	10	18
Willett (1993)[7]	72	R1	51	12	20

R0: clear margins; R1: microscopic margin involvement, R2: gross margin involvement.

Can resection of the SMV help decrease + margins?

Our data:

- Looked at PD from 2005-11
- 98 pts for cancer
- R1 rate 23.4%
- Smv +-23 pts
- SMV+/SMA+: 11 pts (47.8%)
- SMV+/SMA-: 12 pts (52.2%)

Table 1: Entire Patient Cohort characteristics:

Our data re margins:

	R0 group SMV Margin Negative (N=75)	R1 group SMV Margin Positive (N=23)	P value
Patient Characteristics			
Male	41 (54.67%)	8 (34.78%)	P=0.095 [NS]
Female	34 (45.33%)	15 (65.22%)	P=0.095 [NS]
Median Age at Surgery (Years)	70 [42-88]	70 [48-84]	P=0.2844 [NS]
Median Charlson Comorbidity Index	6 [3-10]	6 [3-9]	P=0.8047 [NS]
Median ASA Class Index	3 [2-4]	3 [2-4]	P=0.9214 [NS]
Median Length of Hospital Stay (Days)	12 [2-40]	13 [7-24]	P=0.7557 [NS]
Median Body Mass Index ($kg/m^{2)}$	25.3 [14.3-40.5]	23.4 [17.3-39.2]	P=0.5464 [NS]
Operative Characteristics			
Median Operative Time (hours)	3.45 [1.42-5.49]	3.13 [2.16-4.33]	P=0.0003 [S]
Median Estimated Blood Loss (ml)	400 [100-2500]	350 [200-1500]	P=0.9656 [NS]

You are operating on sick pts!
UNRECOGNIZED FIBROSIS

World J Surg (2017) 41:2854–2857
DOI 10.1007/s00268-017-4101-9

World Journal of Surgery

ORIGINAL SCIENTIFIC REPORT

Undiagnosed Liver Fibrosis in Patients Undergoing Pancreatoduodenectomy for Pancreatic Adenocarcinoma

Andrew Gdowski[1] · Houssam Osman[2] · Umar Butt[2] · Steve Foster[3] · Dhiresh Rohan Jeyarajah[2,4]

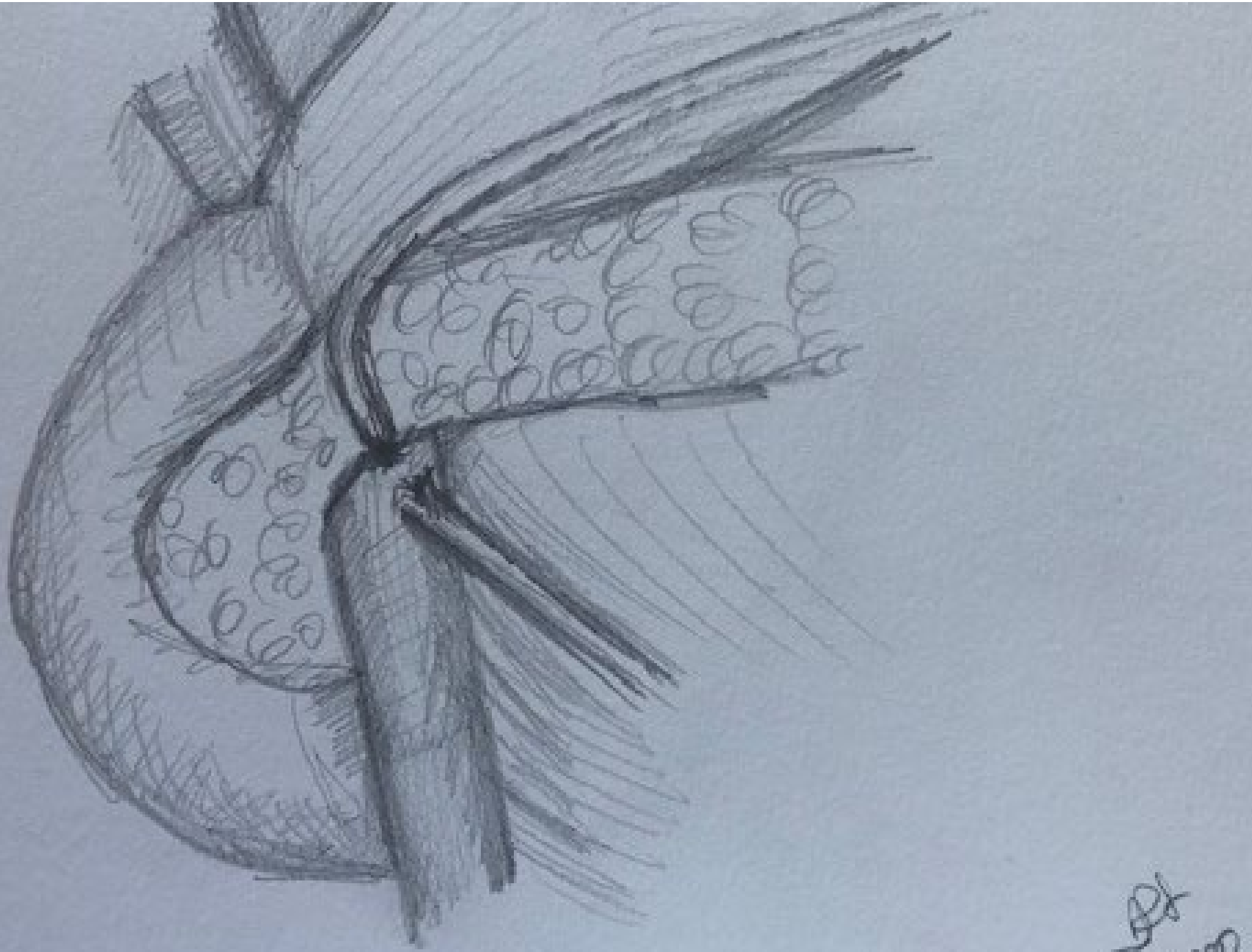
Published online: 17 July 2017

Table 1 Patient demographics

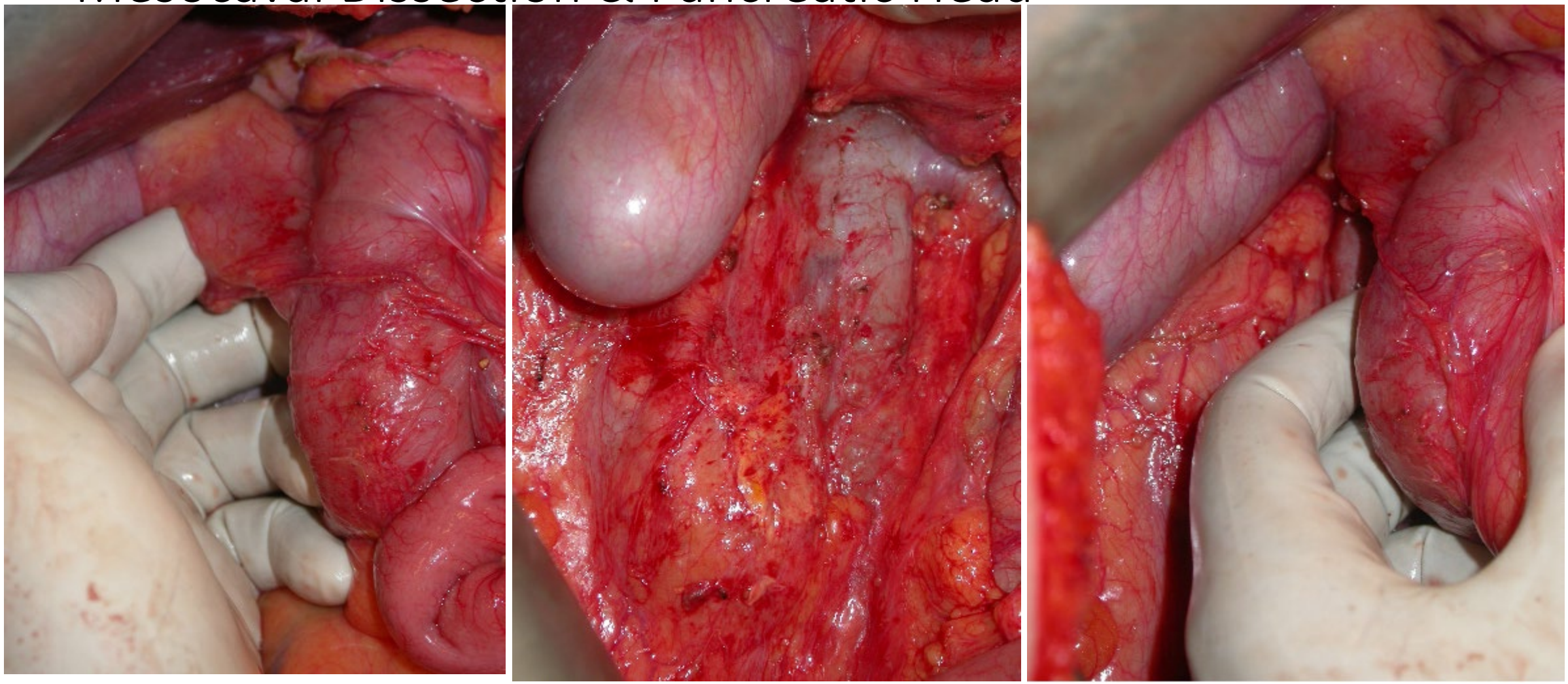
Characteristic	Fibrosis Stage 0–1 $n = 19$	Fibrosis Stage ≥2 $n = 17$
Average age (SD)	62.7 (7.9)	70.5 (6.5)
Stented (%)	12 (63.2)	9 (52.9)
Non-stented (%)	7 (36.8)	8 (47.1)
Bile obstruction (%)	10 (52.6)	15 (88.2)
Steatosis (%)	10 (52.6)	6 (35.3)
Adenocarcinoma (%)	15 (78.9)	17 (100)
Neuroendocrine (%)	3 (17.6)	0 (0)
Chronic lymphocytic leukemia/small lymphocytic lymphoma (%)	1 (5.3)	0 (0)
Tumor staging		
Stage 1 (%)	2 (10.5)	1 (5.8)
Stage 2 (%)	14 (73.7)	13 (76.5)
Stage 3 (%)	1 (5.3)	2 (11.8)
Stage 4 (%)	0 (0)	0 (0)
Positive surgical margin (%)	6 (31.6)	9 (52.9)

So lets talk surgery and technique

Principles of the Whipple:



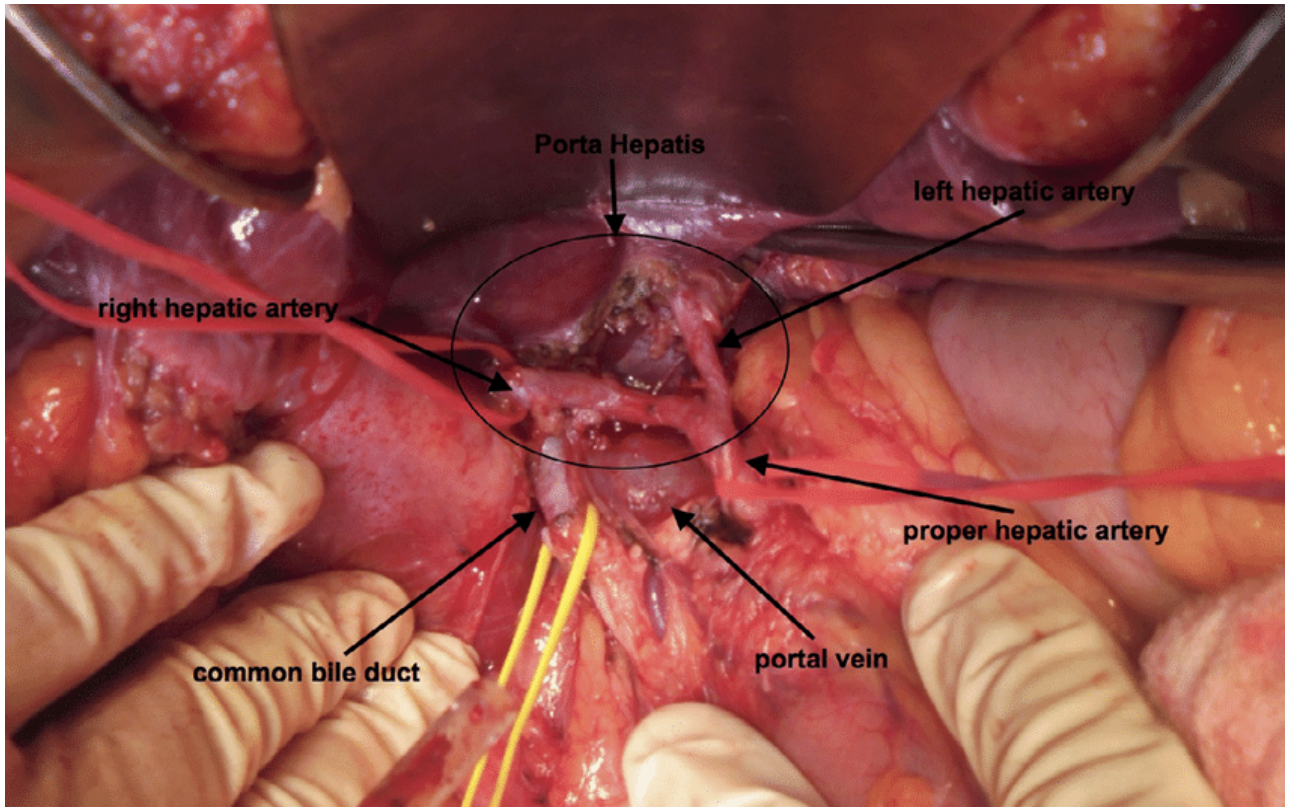
Mesocaval Dissection & Pancreatic Head



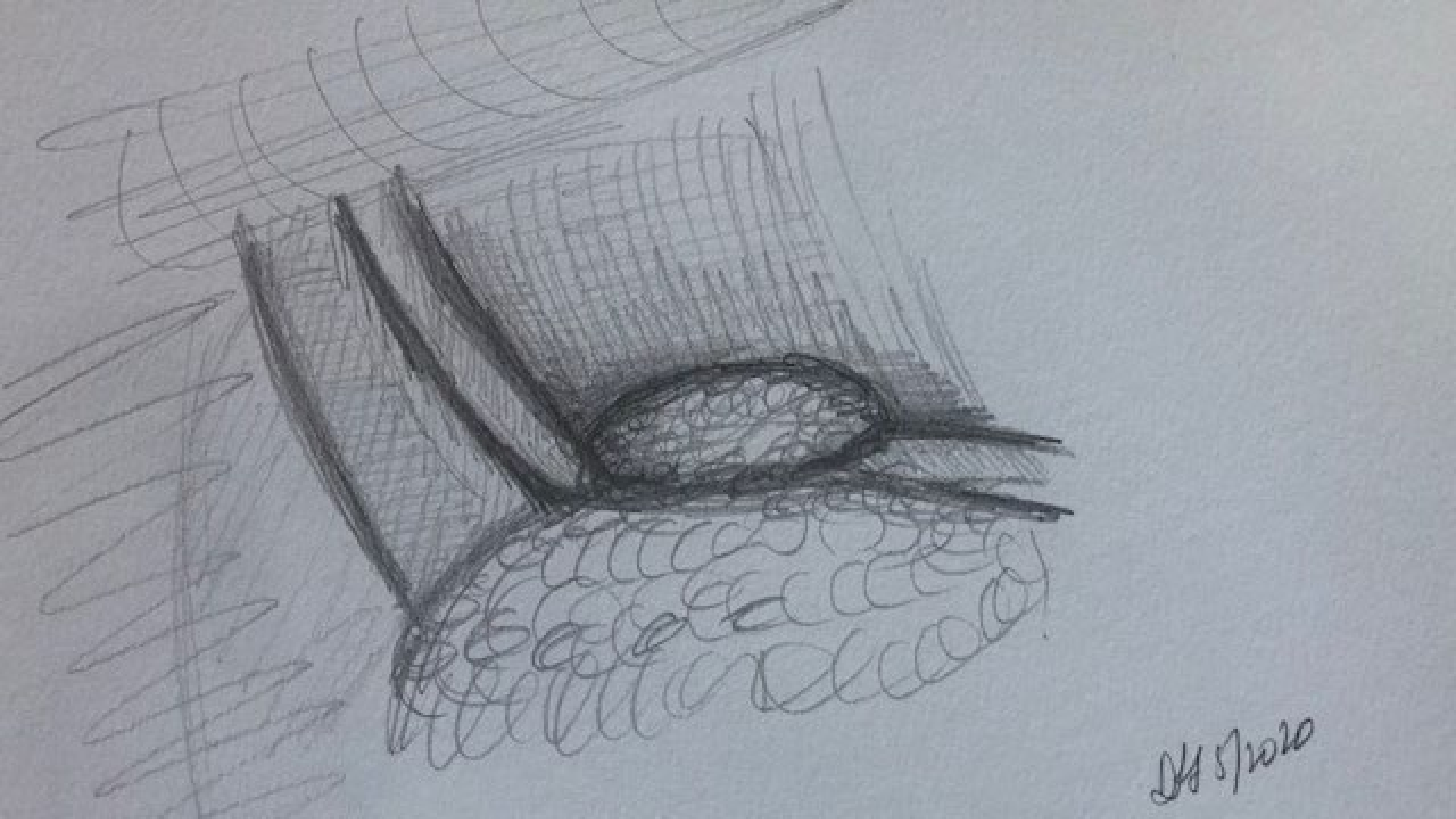
Dissection

Dissect the porta hepatis

What is this porta hepatis and what are the structures affiliated with it?



https://www.researchgate.net/figure/Relationship-of-the-common-bile-duct-inside-the-Porta-Hepatis-Supraduodenal-segment_fig2_327630709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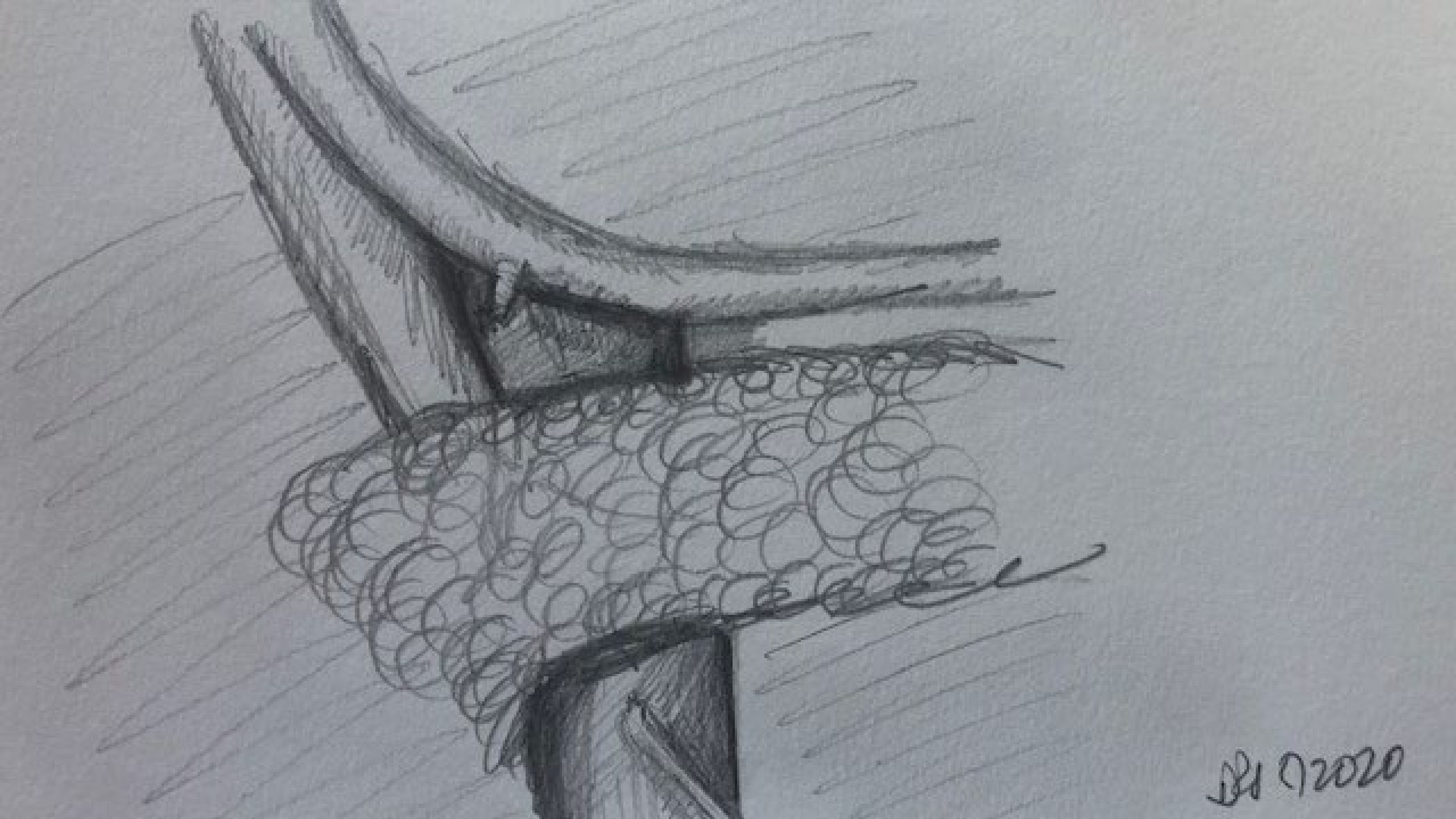
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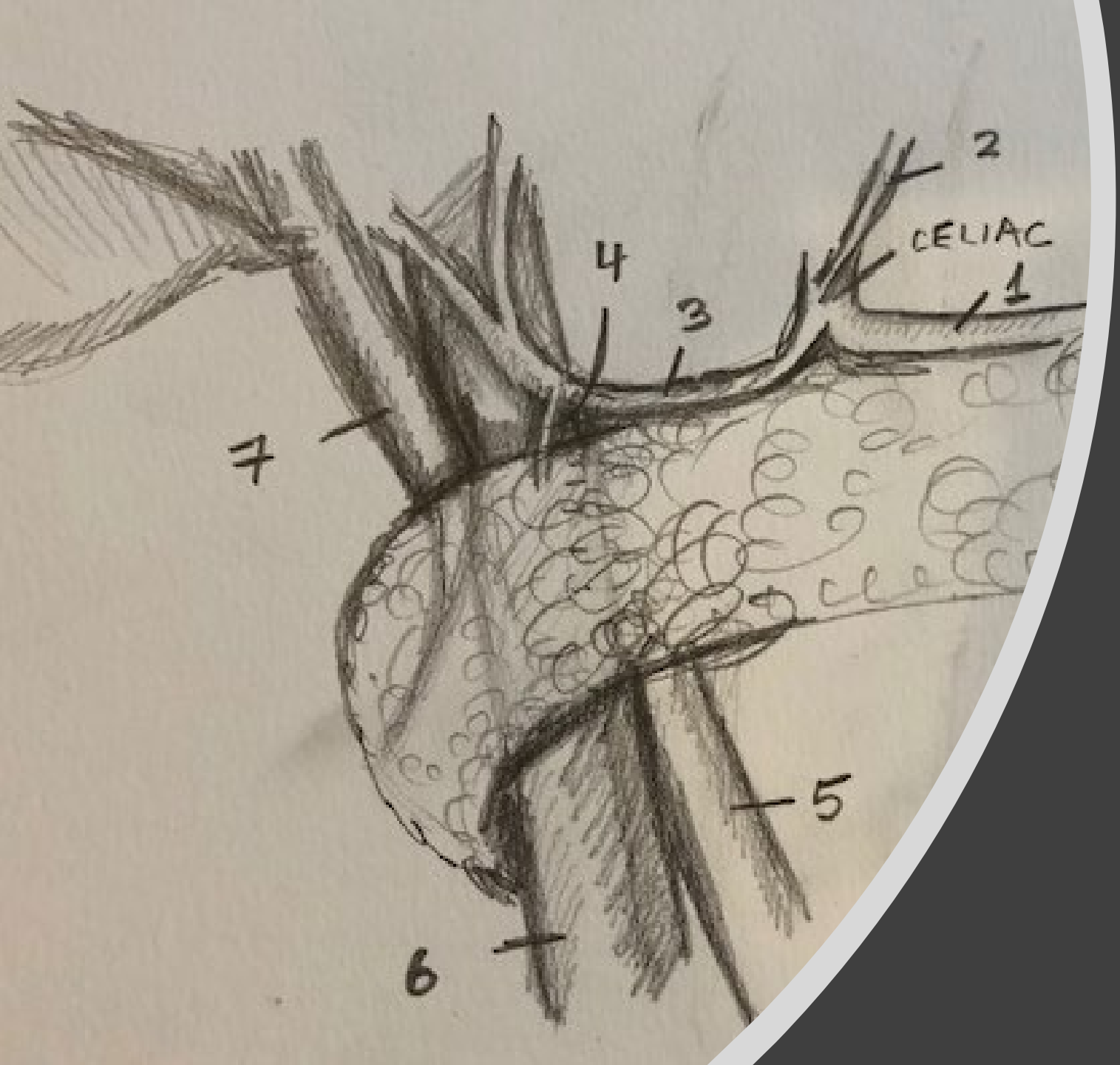
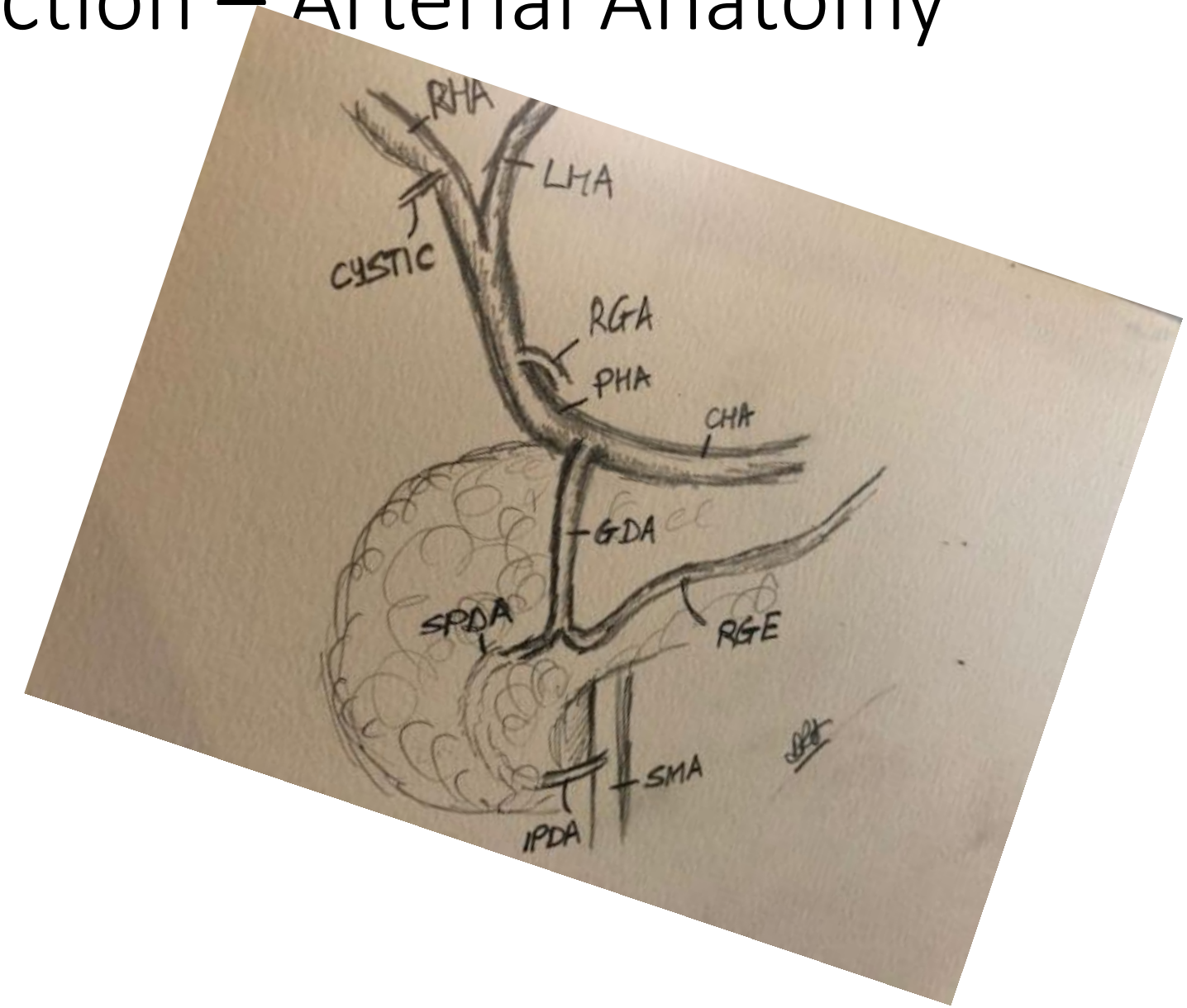
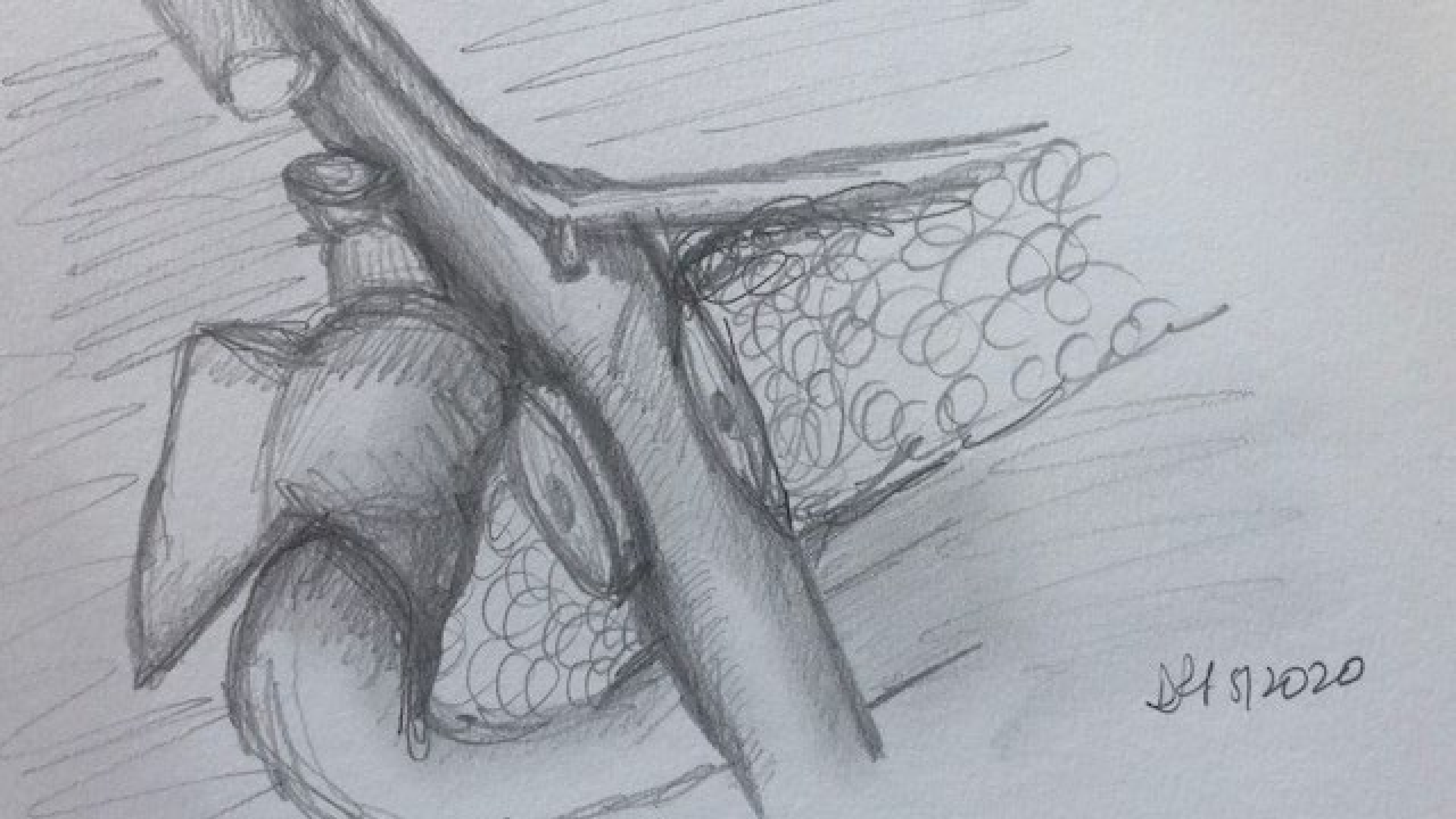


Dissection – Arterial Anatomy

Dissection – Arterial Anatomy

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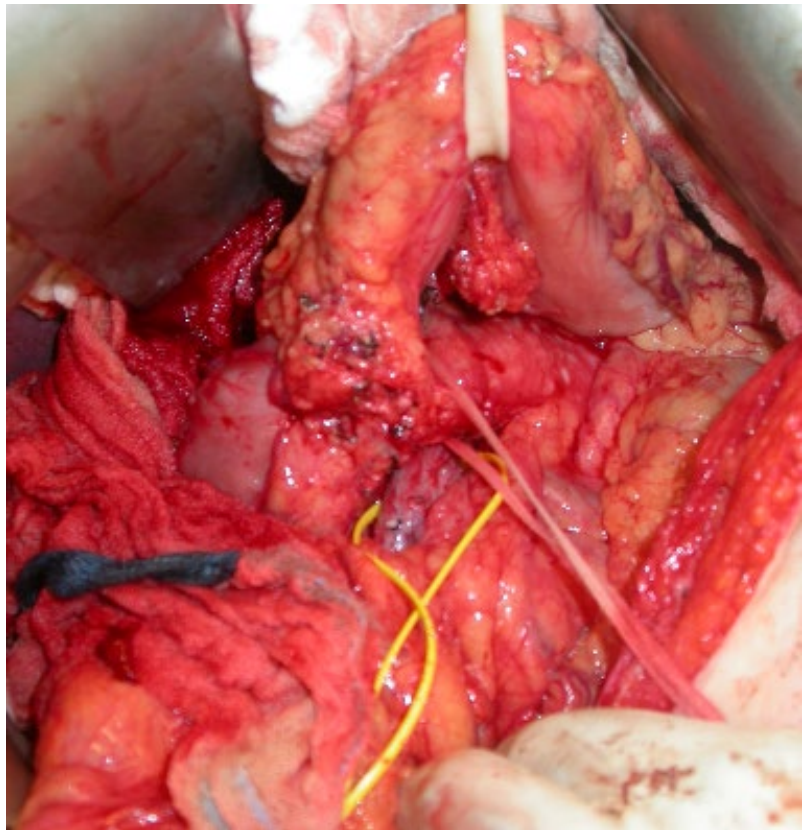
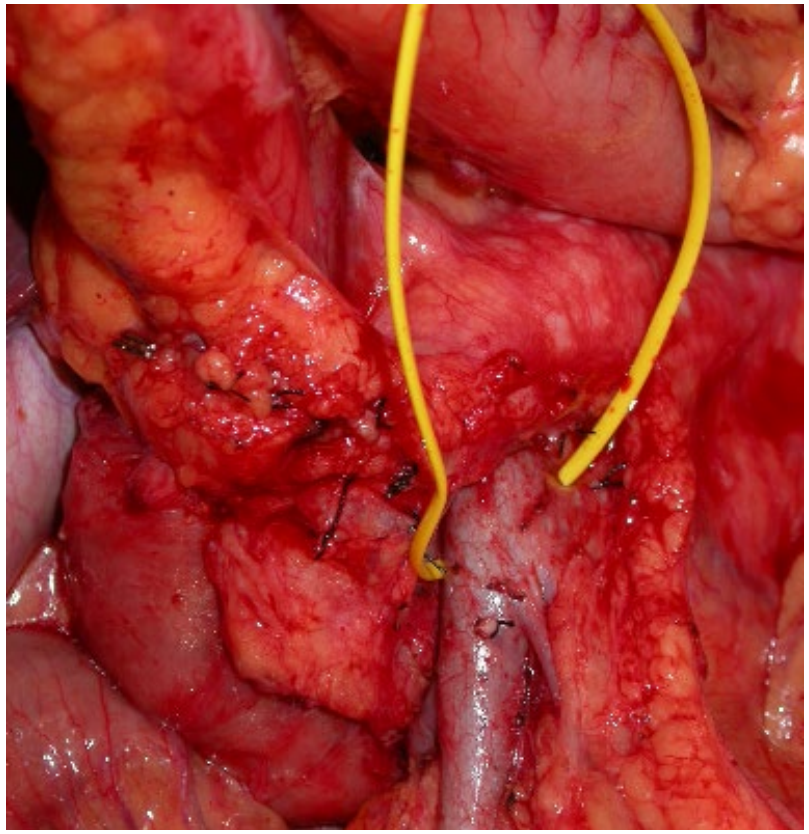
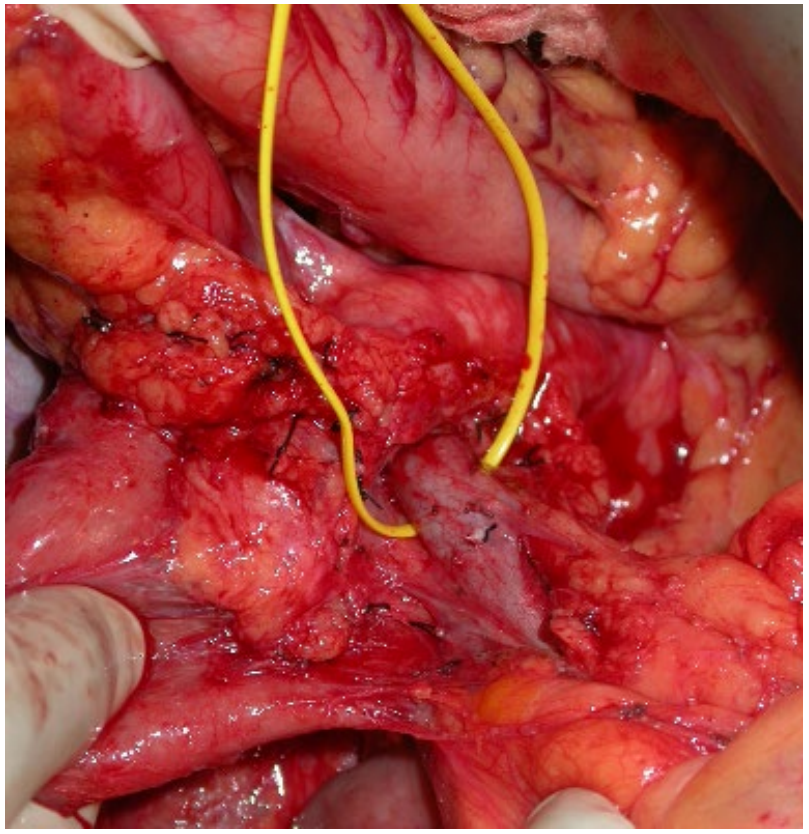
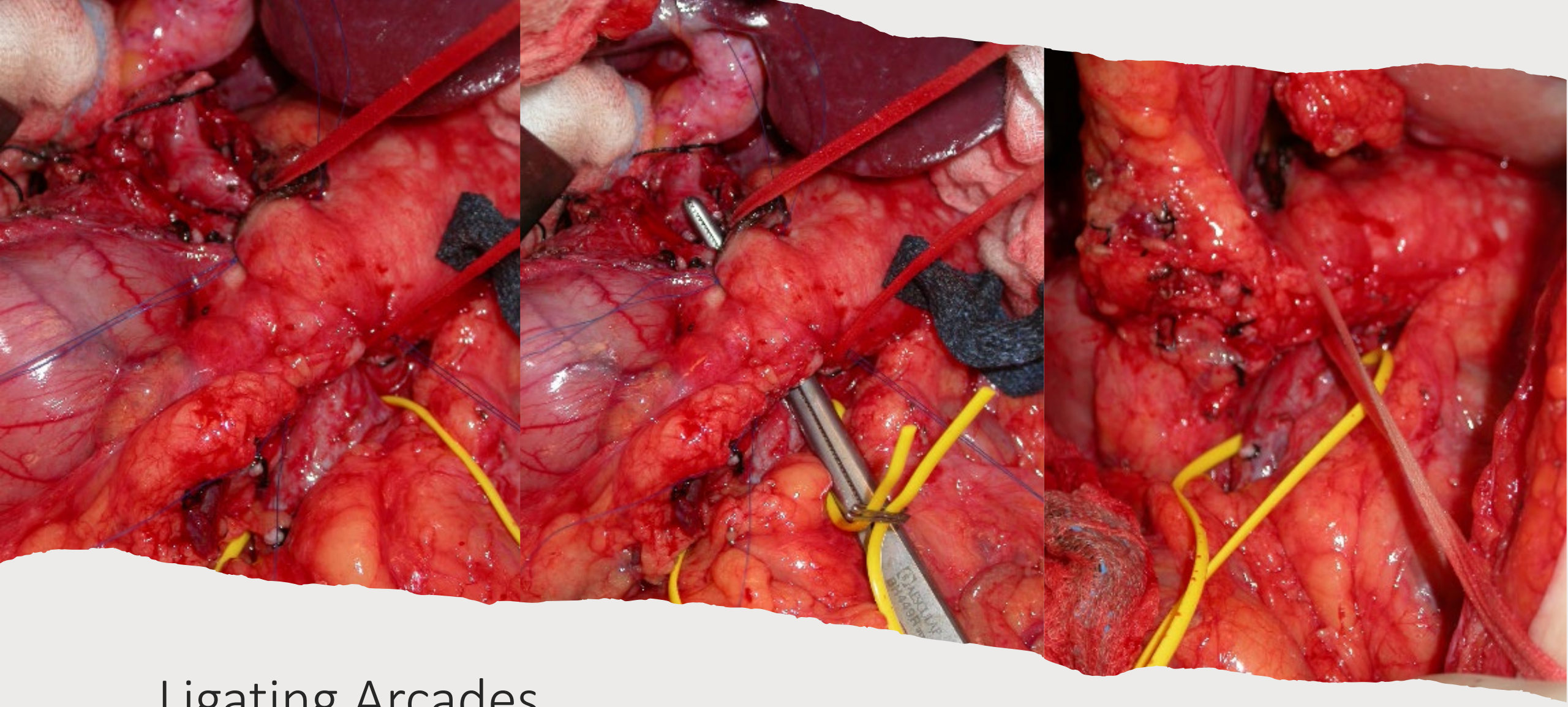
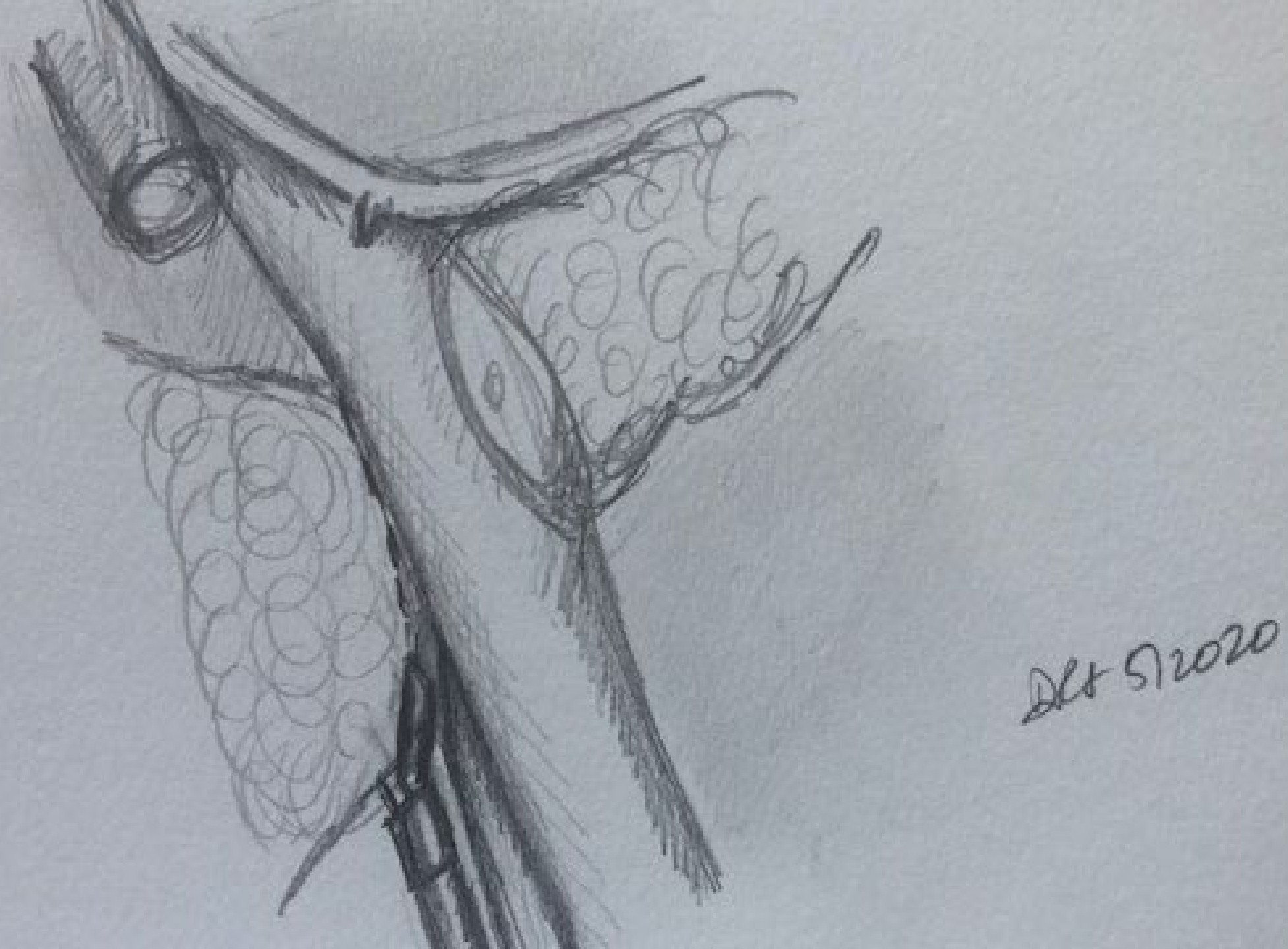




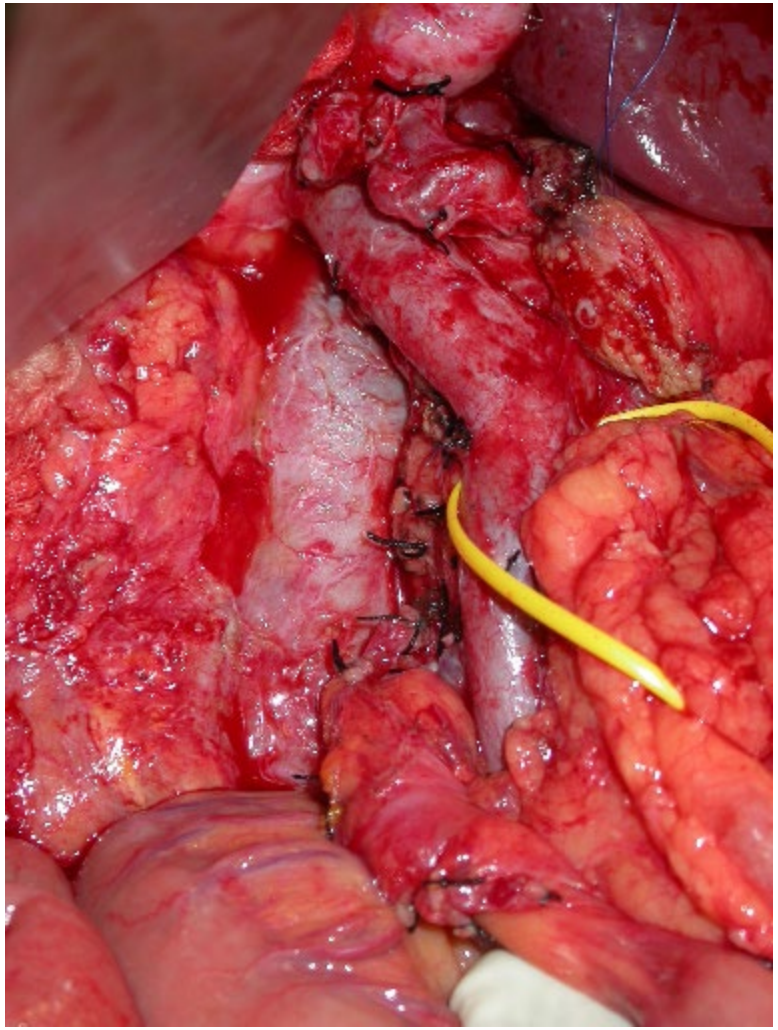
Pancreatic Head & Superior Mesenteric Vein

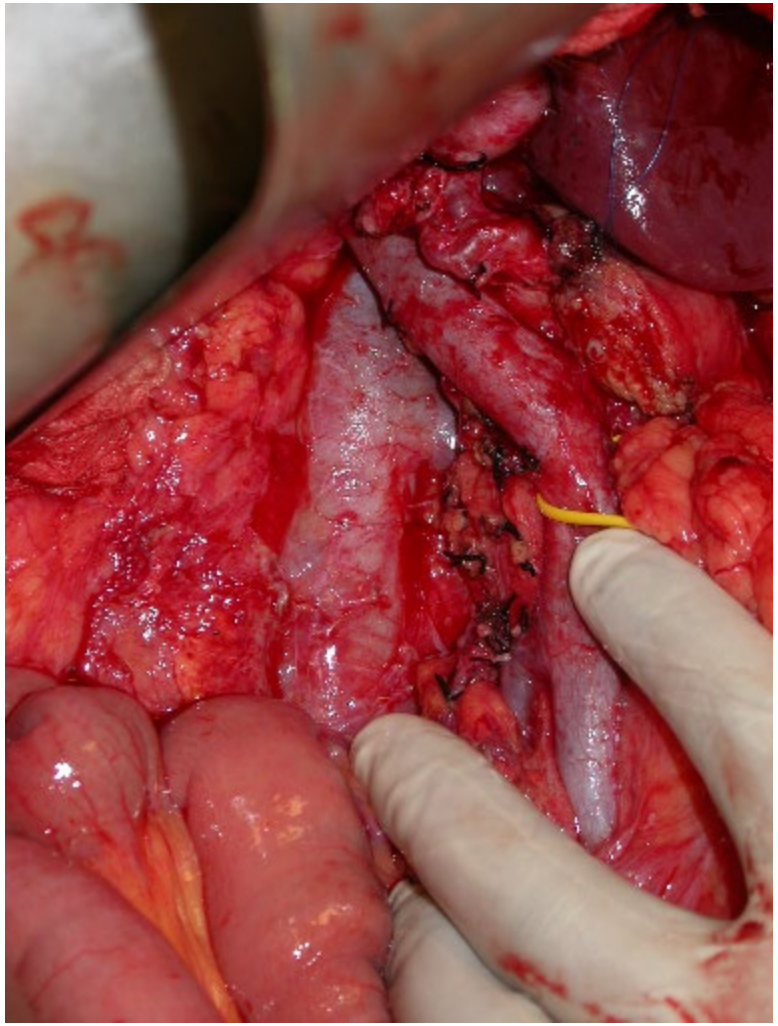


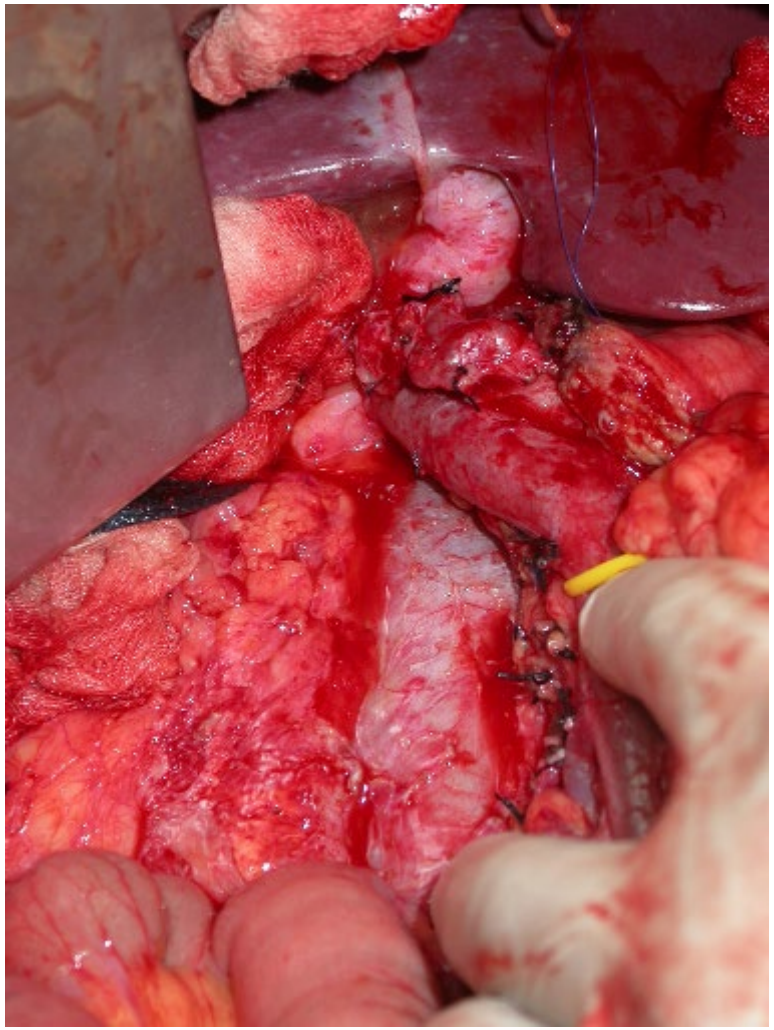
Ligating Arcades


DLt 5/2020

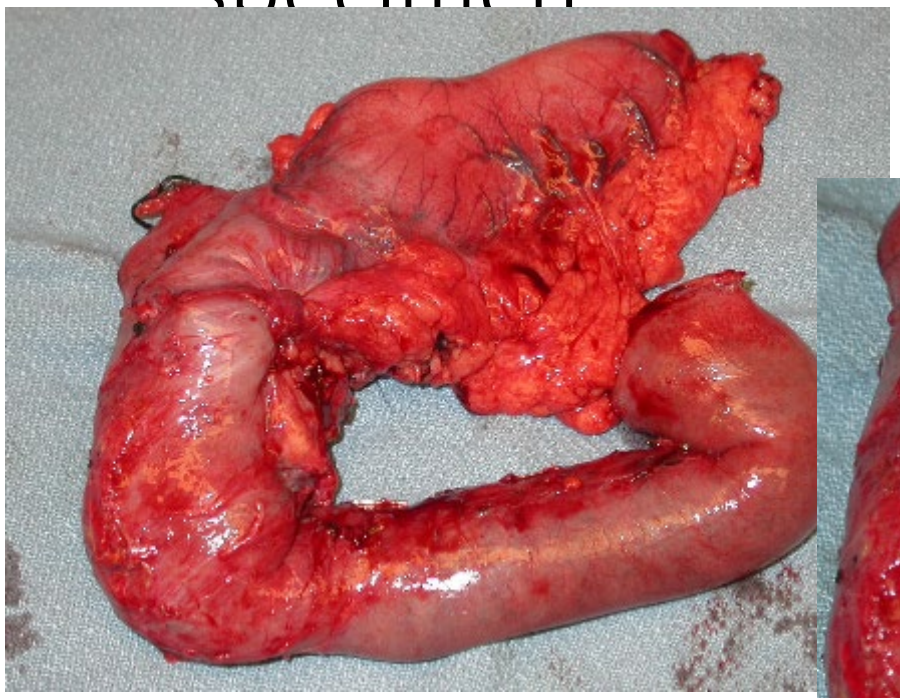
Pancreatic Head Divided & Portal Vein

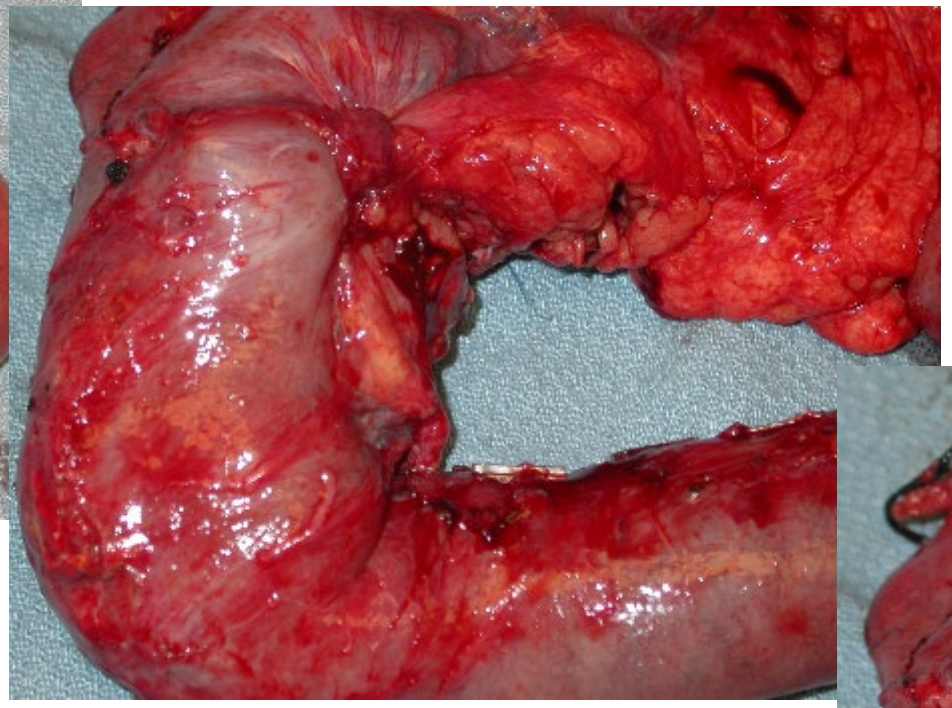


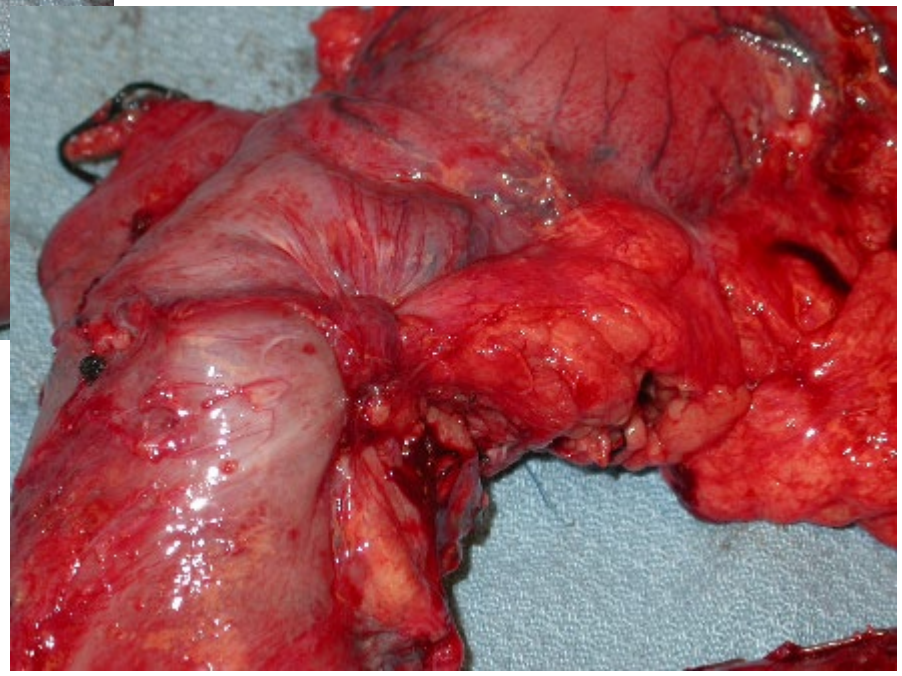




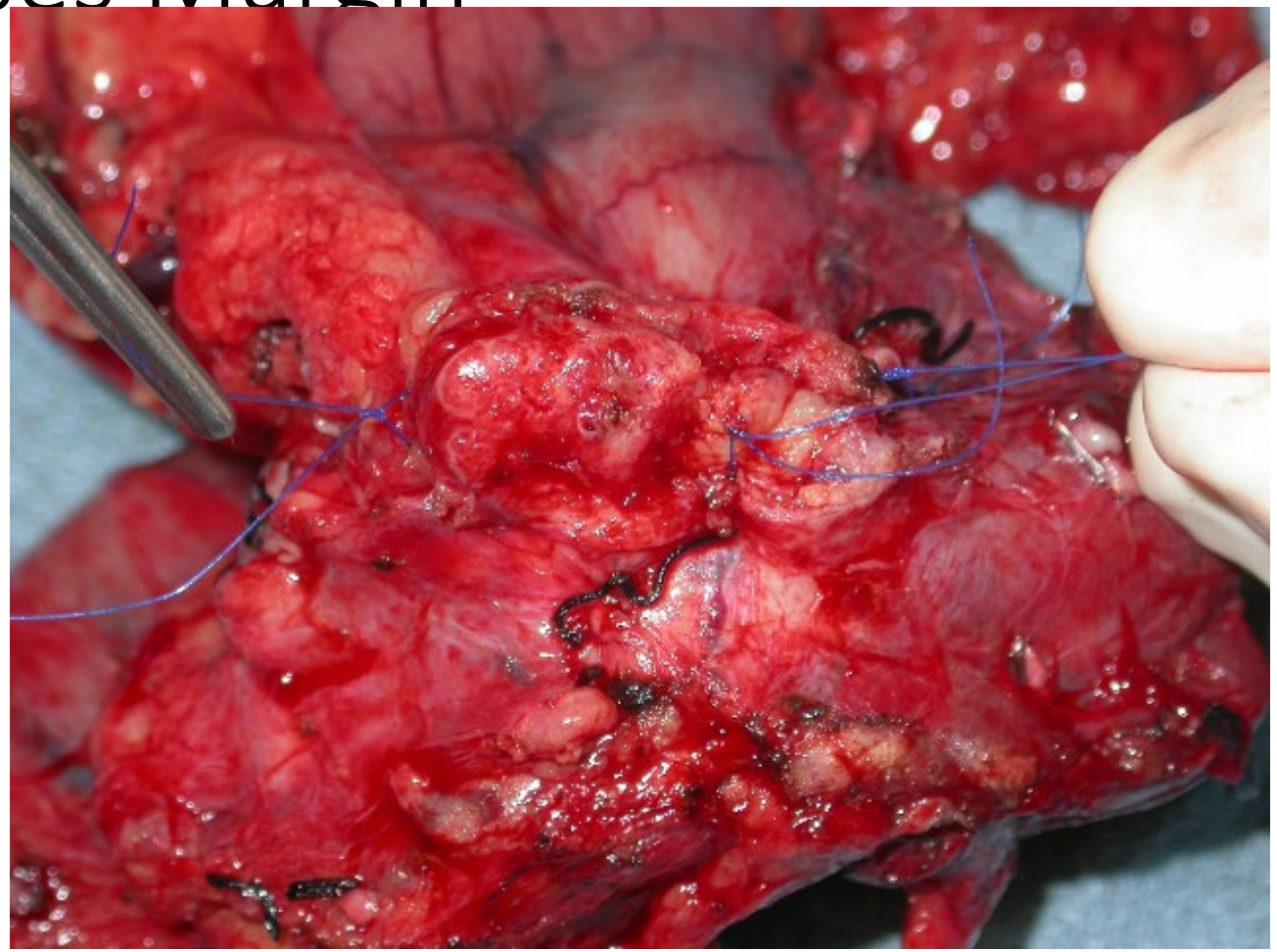
specimen

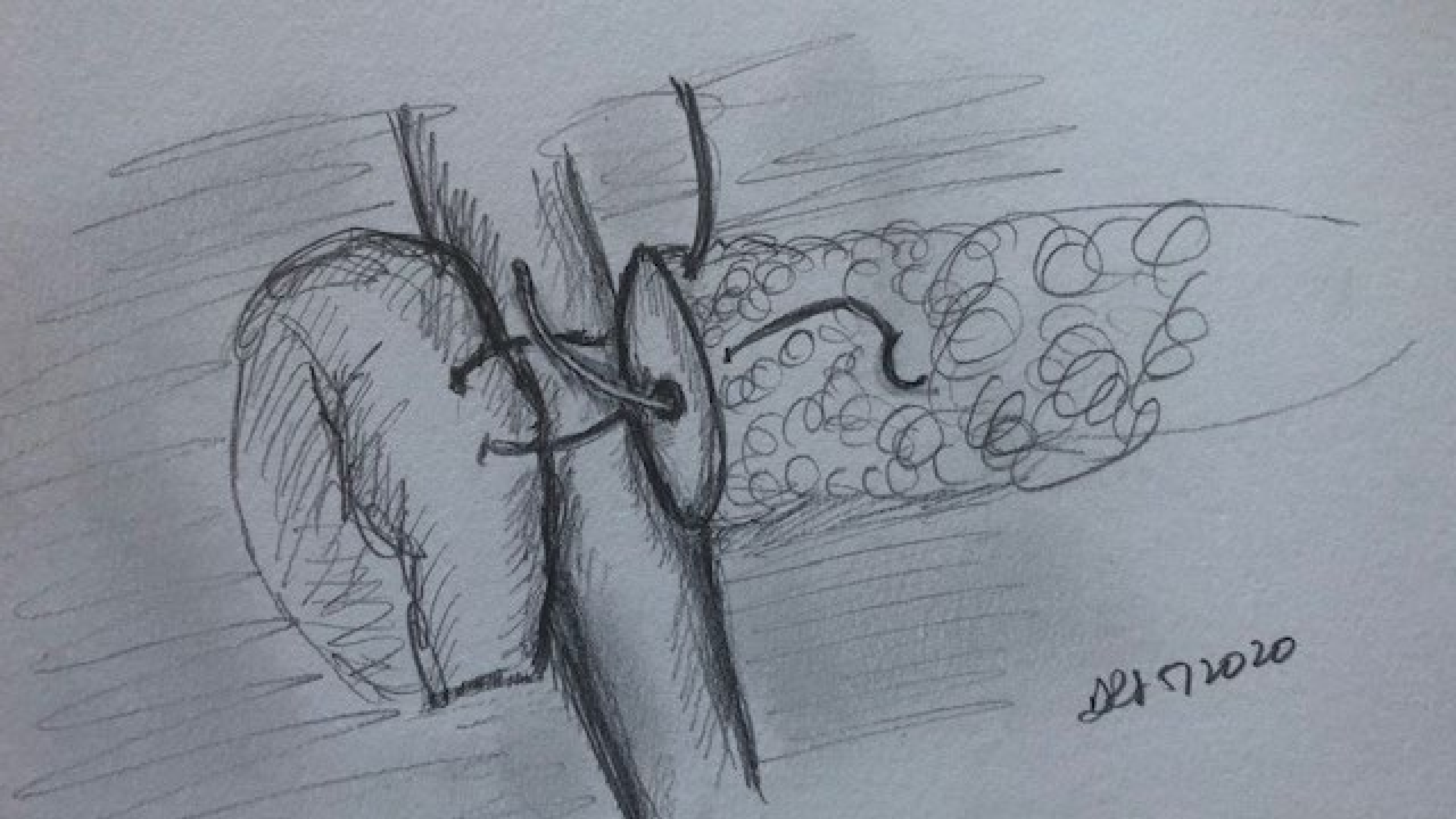


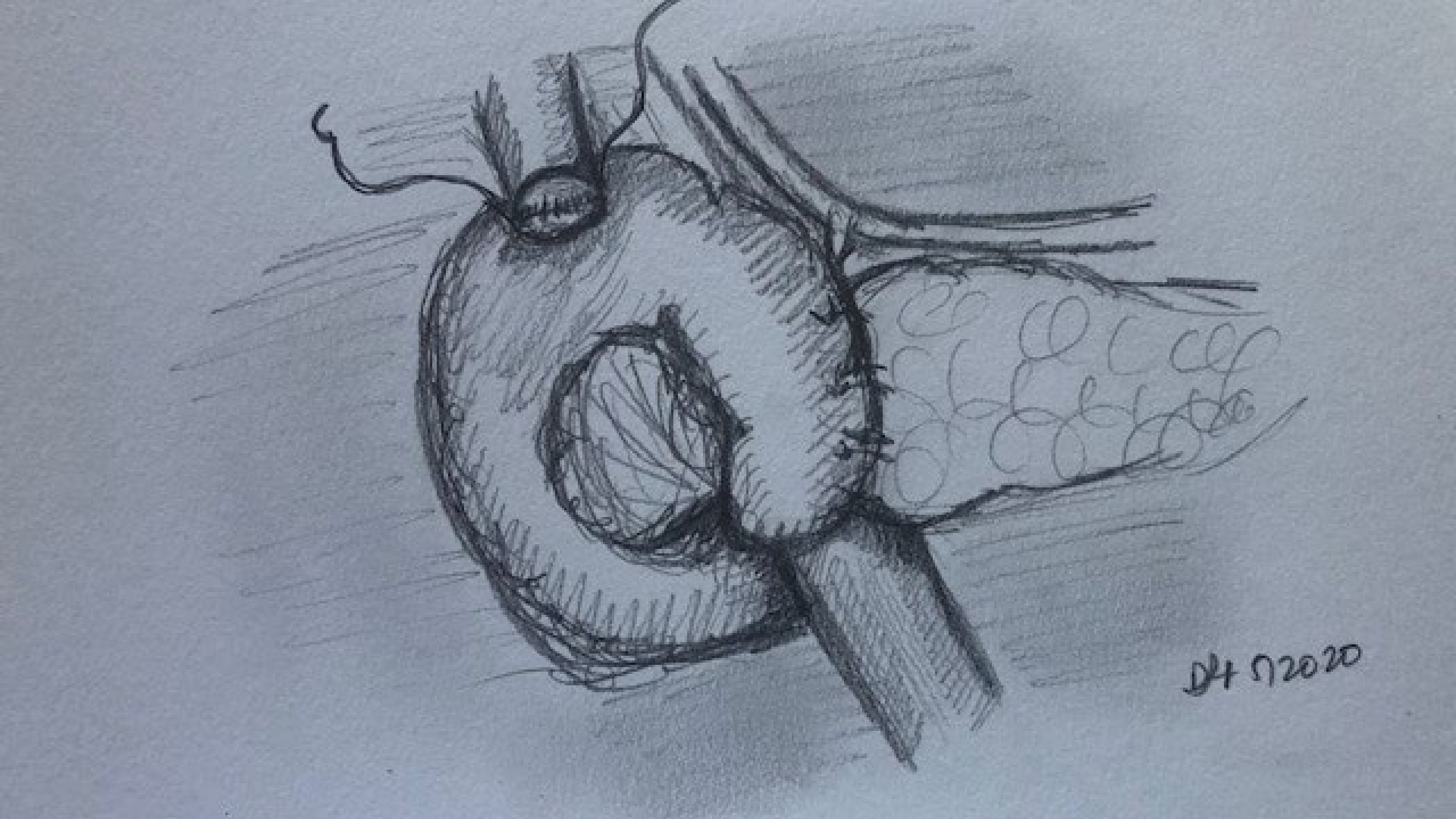




Pancreases Margin




2020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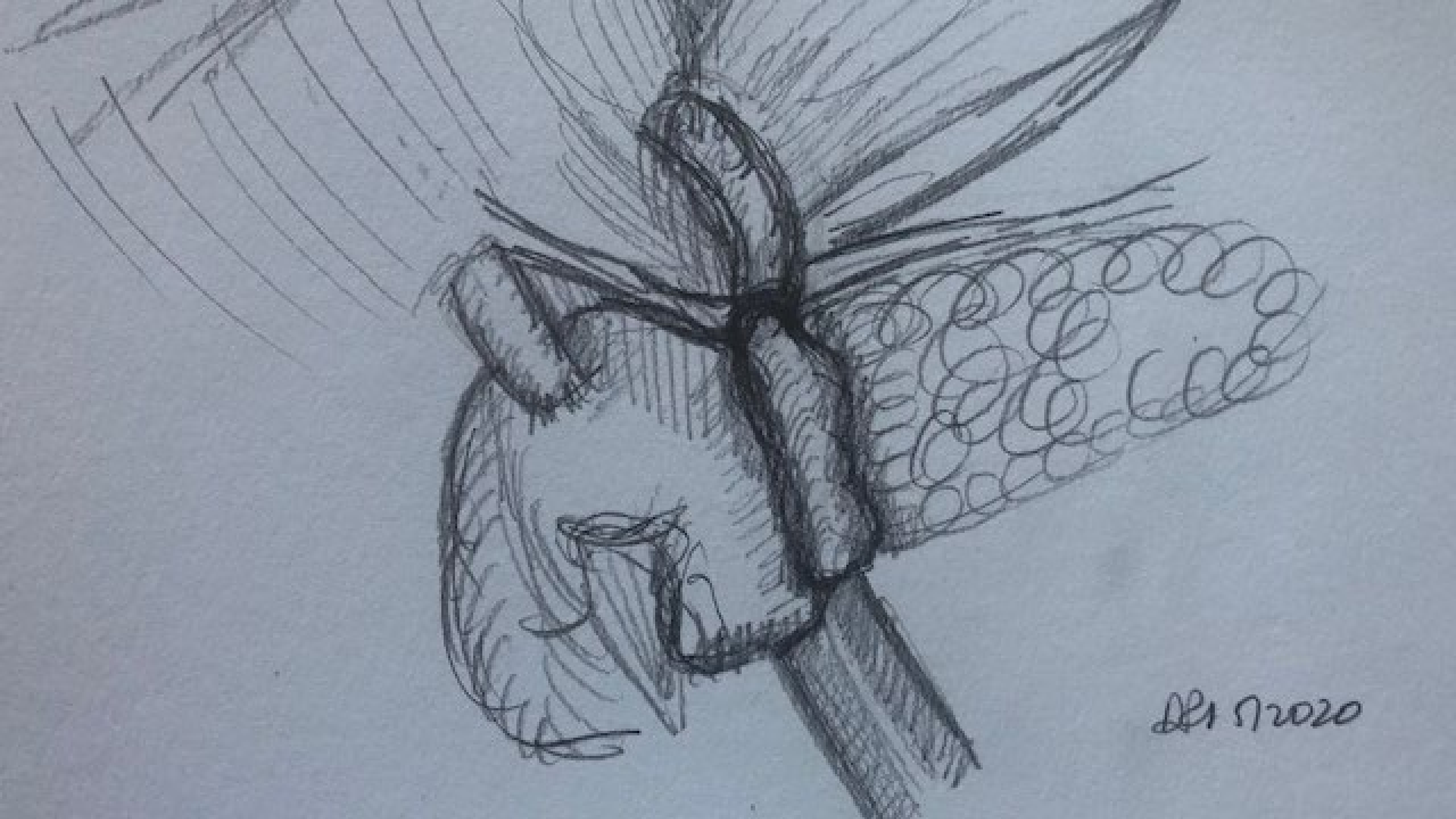
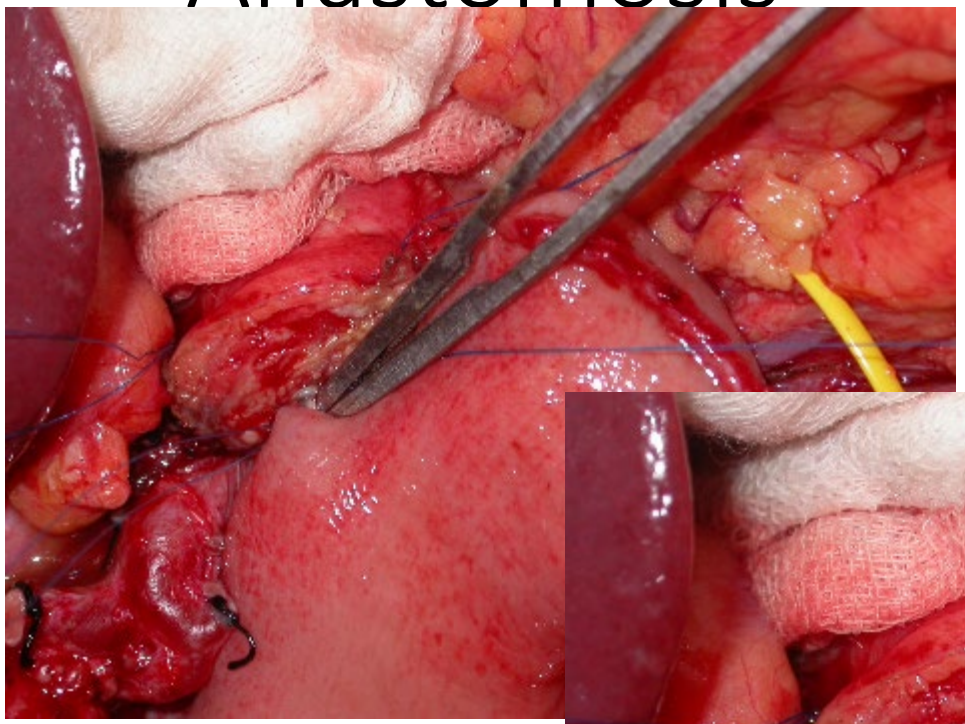
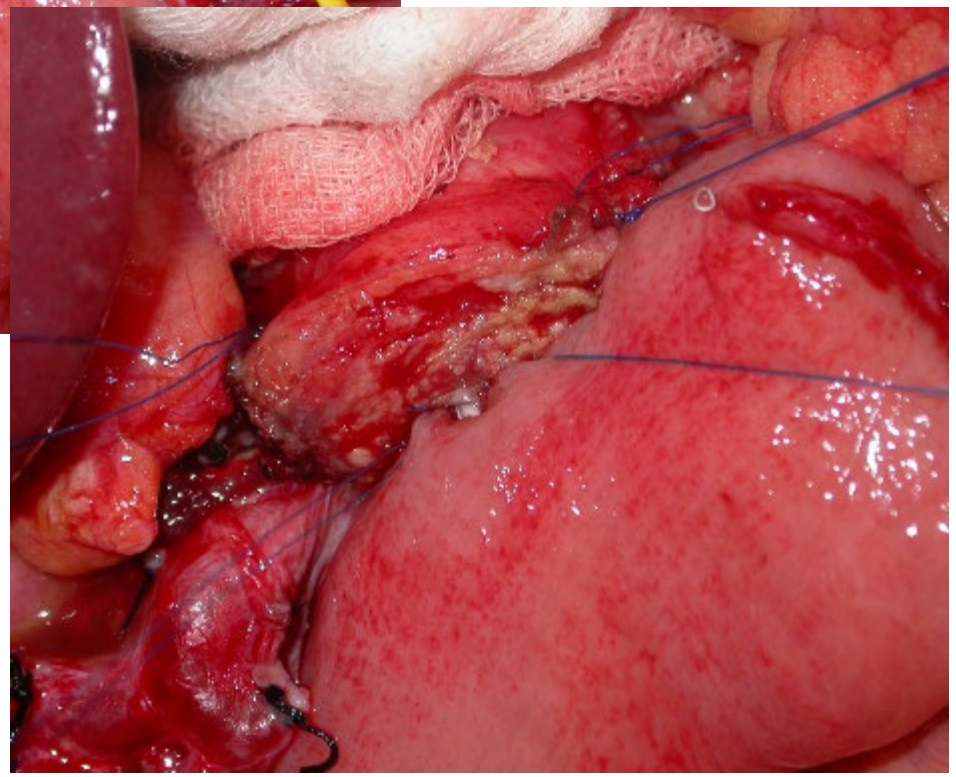
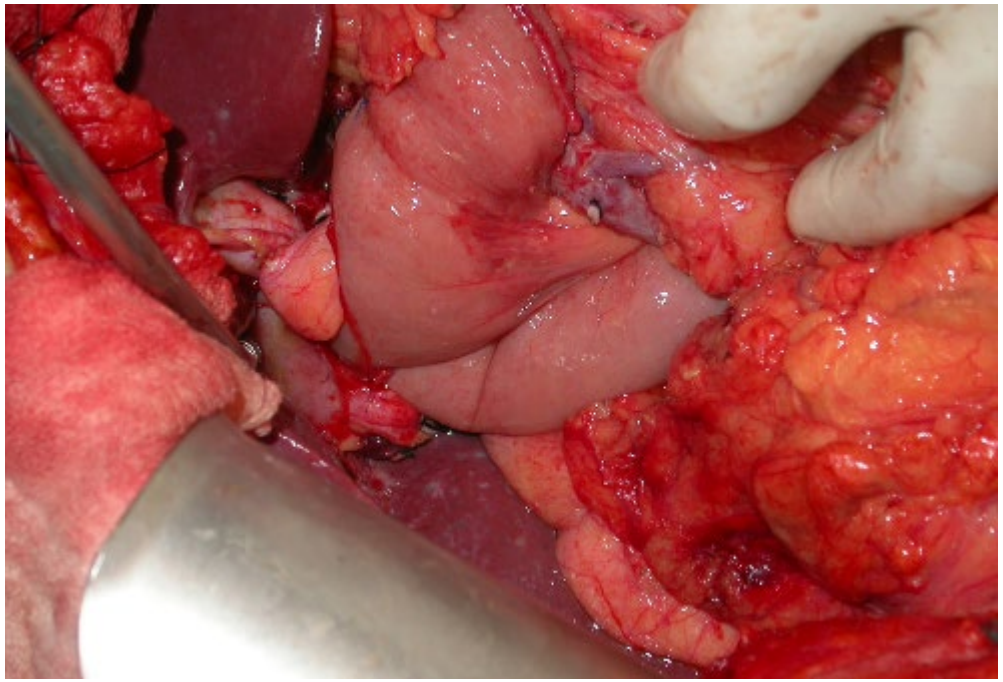

DB 17 2020

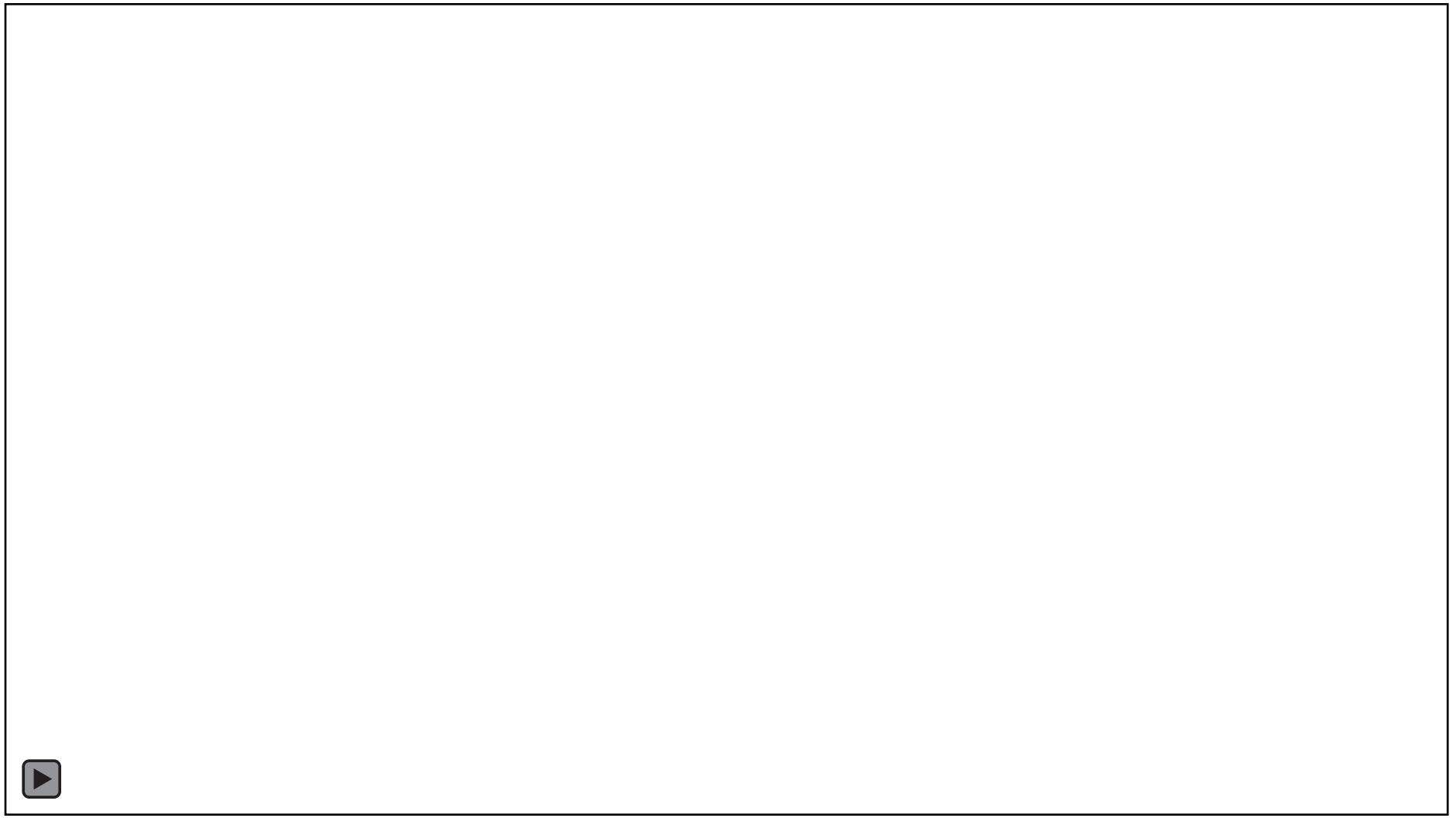
Anastomosis







How I do a robotic Whipple:



Can collateral robotic surgery help the learning curve?

The learning curve

World J Surg
https://doi.org/10.1007/s00268-020-05861-z

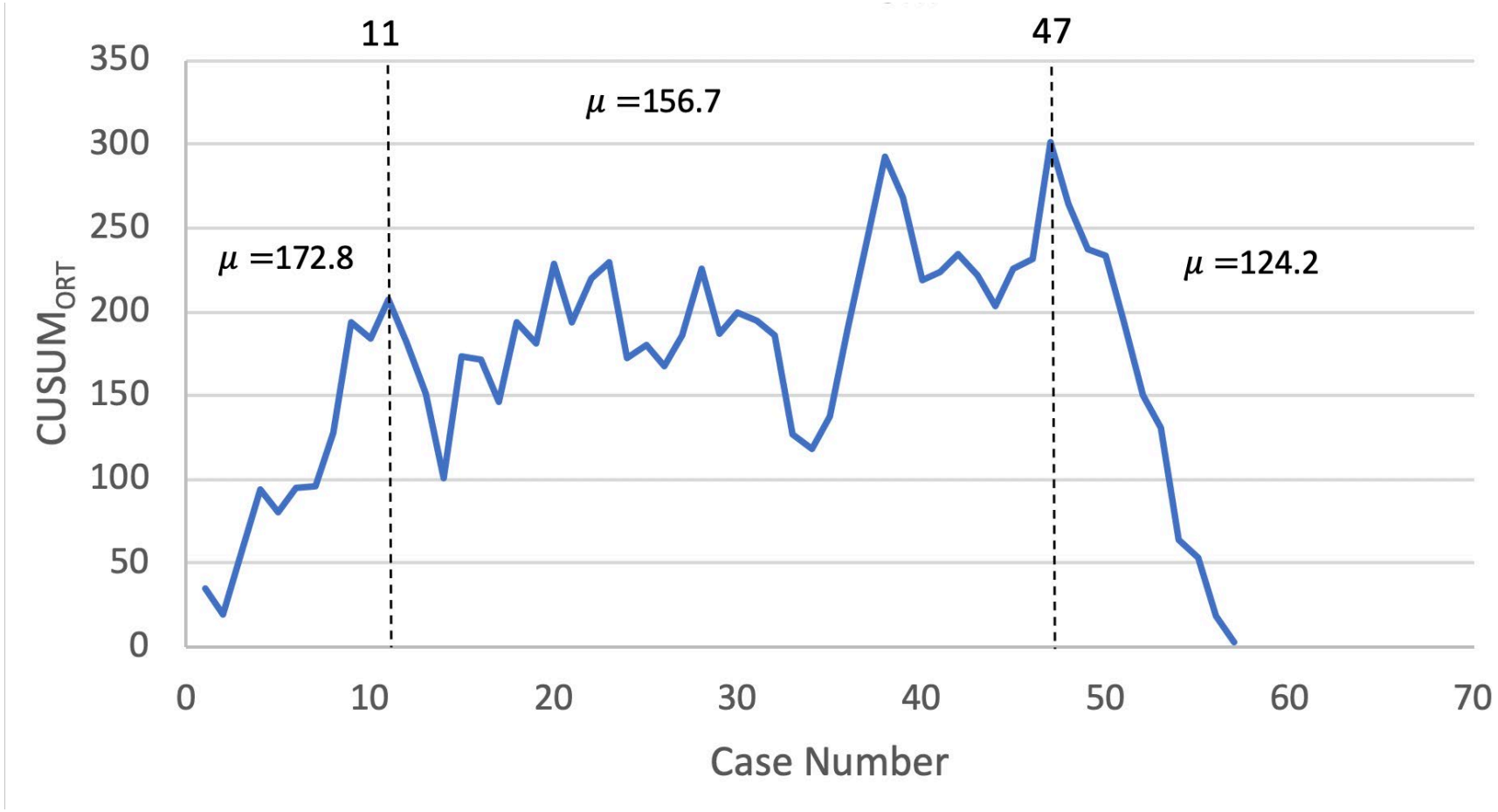
ORIGINAL SCIENTIFIC REPORT

Overcoming the Arduous Transition for Robotic Hepatopancreatobiliary Cases: A Multi-Procedure Learning Curve Study Utilizing CUSUM Analysis

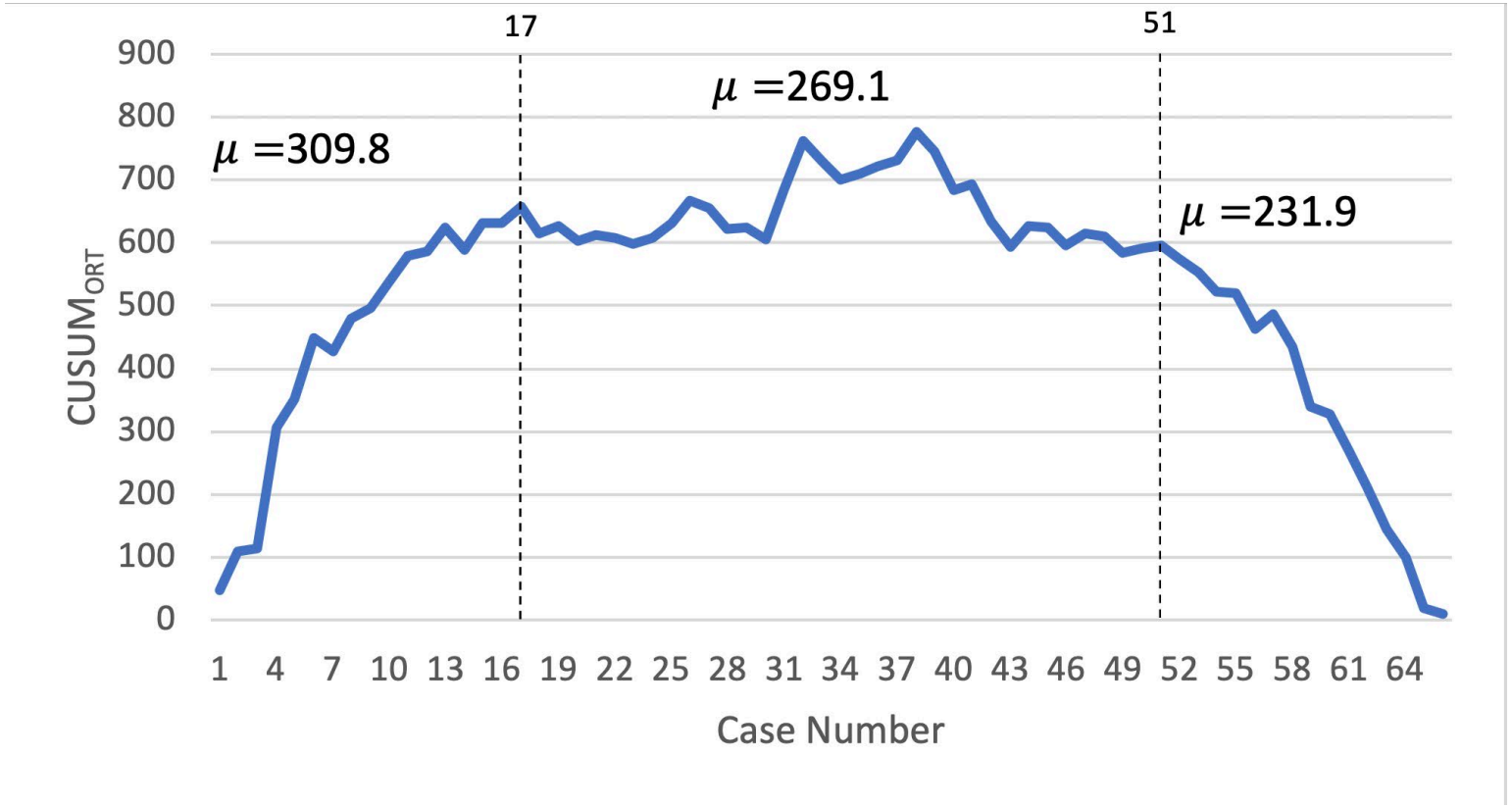
Joseph S. Lim[1,2] · Terence Jackson[1] · James Kurtz[1,3] · Edward E. Cho[1,4] · Shyam Vedantam[1] · Kei Nagatomo[1] · Houssam Osman[1] · Dhiresh Rohan Jeyarajah[1,4]

Accepted: 25 October 2020

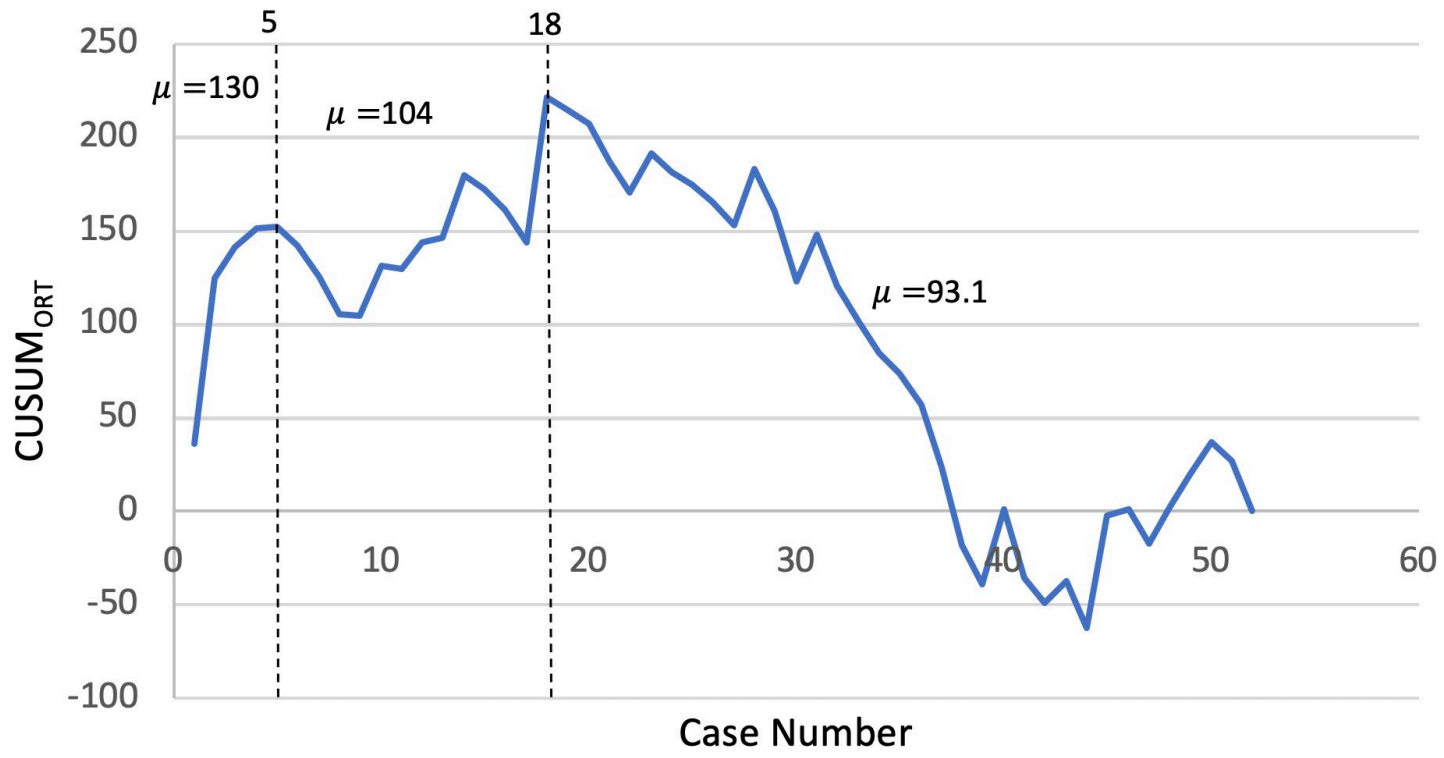
Learning curve can be overcome -RDP



RPD


17
51
μ =309.8
μ =269.1
μ =231.9
900
800
700
600
500
400
300
200
100
0
CUSUM$_{ORT}$
1 4 7 10 13 16 19 22 25 28 31 34 37 40 43 46 49 52 55 58 61 64
Case Number

Robotic Heller

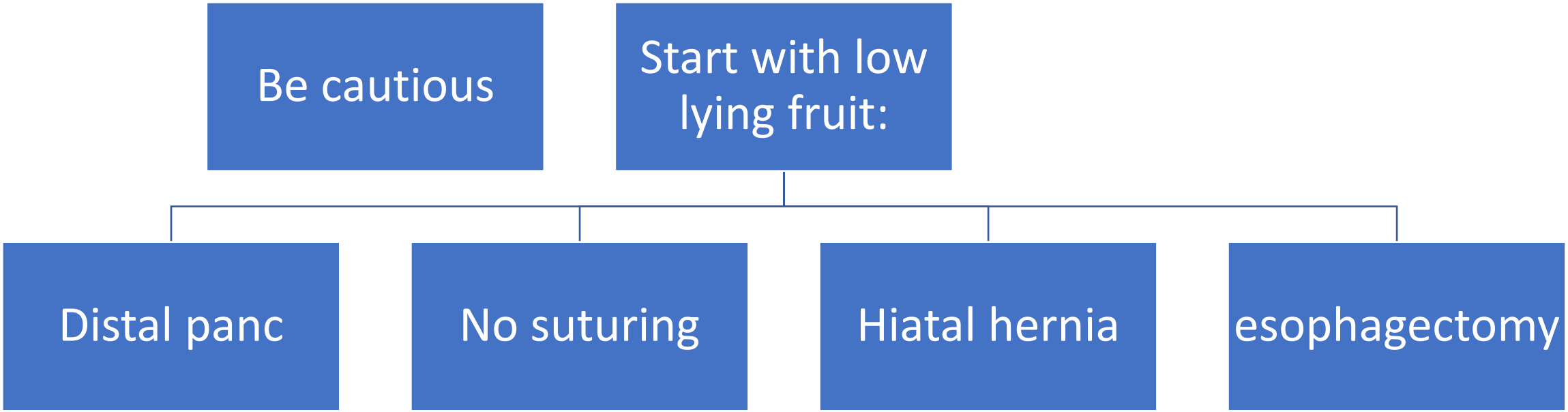


Our conclusion:

Robotic PD can be learned

But slope depends on experience in the surgery AND experience with other robotic procedures

My advice:


Be cautious
Start with low lying fruit:
Distal panc
No suturing
Hiatal hernia
esophagectomy

What is the data re open/ MIS Whipple?

Lap versus Open DP- LEOPARD 1

- Lap versus open DP
- Experience in lap DP
- High volume Dutch Centers

- Rooij, et al, Annals of Surgery, Jan 2019

TABLE 4. Postoperative Complications

	Minimally Invasive Distal Pancreatectomy (n = 51)	Open distal Pancreatectomy (n = 57)	Relative Risk (95% CI)	*P*
Complications Clavien–Dindo grade ≥III	13 (25)	21 (38)	0.69 (0.39–1.24)	0.21
IIIa	10 (20)	15 (27)		
IIIb	1 (2)	2 (4)		
IVa	2 (4)	3 (5)		
IVb	0 (0)	2 (4)		
V	0 (0)	0 (0)		
Postoperative pancreatic fistula	20 (39)	13 (23)	1.72 (0.96–3.09)	0.07
Grade B	17 (33)	12 (21)		
Grade C	3 (6)	1 (2)		
Increased drain amylase/lipase level day 3*	28 (55)	31 (54)	1.01 (0.72–1.42)	0.96
Percutaneous catheter drainage	11 (22)	11 (20)	1.12 (0.53–2.36)	0.77
Postoperative delayed gastric emptying	3 (6)	11 (19)	0.30 (0.09–1.03)	0.04
Grade B	0 (0)	7 (13)		
Grade C	3 (6)	4 (7)		
Endoscopic feeding tube placement	4 (8)	14 (25)	0.32 (0.11–0.91)	0.02
Postoperative bleeding	2 (4)	2 (4)	1.12 (0.16–7.65)	>0.99
Grade B	2 (4)	1 (2)		
Grade C	0 (0)	1 (2)		
Endovascular coiling	0 (0)	2 (4)		0.50
Surgical re-intervention	1 (2)	3 (5)	0.37 (0.04–3.47)	0.62
Surgical site infection	2 (4)	3 (5)	0.75 (0.13–4.28)	0.74
Unplanned ICU admission	5 (10)	6 (11)	0.93 (0.30–2.87)	0.90
Length of initial hospital stay, median (IQR), d	6 (4–7)	8 (6–9)		<0.001
Readmission	15 (29)	14 (25)	1.20 (0.64–2.23)	0.57
Length of total hospital stay, median (IQR), d	6 (4–13)	8 (6–12)		0.004
Mortality	0 (0)	1 (2)		>0.99

Analyzed according to intention-to-treat. Data are expressed as median (IQR), or number (%).

*Drain amylase/lipase level higher than three times the upper level of normal serum amylase/lipase on postoperative day three.

TABLE 2. Time to Functional Recovery (Primary Outcome)

	Minimally Invasive Distal Pancreatectomy (n = 51)	Open Distal Pancreatectomy (n = 57)	*P*
Time to functional recovery, median (IQR), d	4 (3–6)	6 (5–8)	<0.001
Restored mobility	4 (2–5)	5 (3–6)	0.01
Reached adequate pain control with oral medication	3 (2–3)	4 (3–5)	<0.001
Reached at least 50% required caloric intake	3 (2–5)	6 (4–7)	<0.001
No need for fluid administration	3 (2–5)	4 (3–6)	0.001
No signs of infection	4 (3–6)	6 (5–8)	<0.001

Analyzed according to intention-to-treat. All outcomes are expressed in days, as medians (IQR).
IQR, interquartile range.

Leopard 2 Study:

- Dutch trial
- 4 centers
- Had to have done >20 lap PD
- Center must do>20PD/yr

- n Hilst, Lancet, March 2019

Leopard 2 study-time to functional recovery

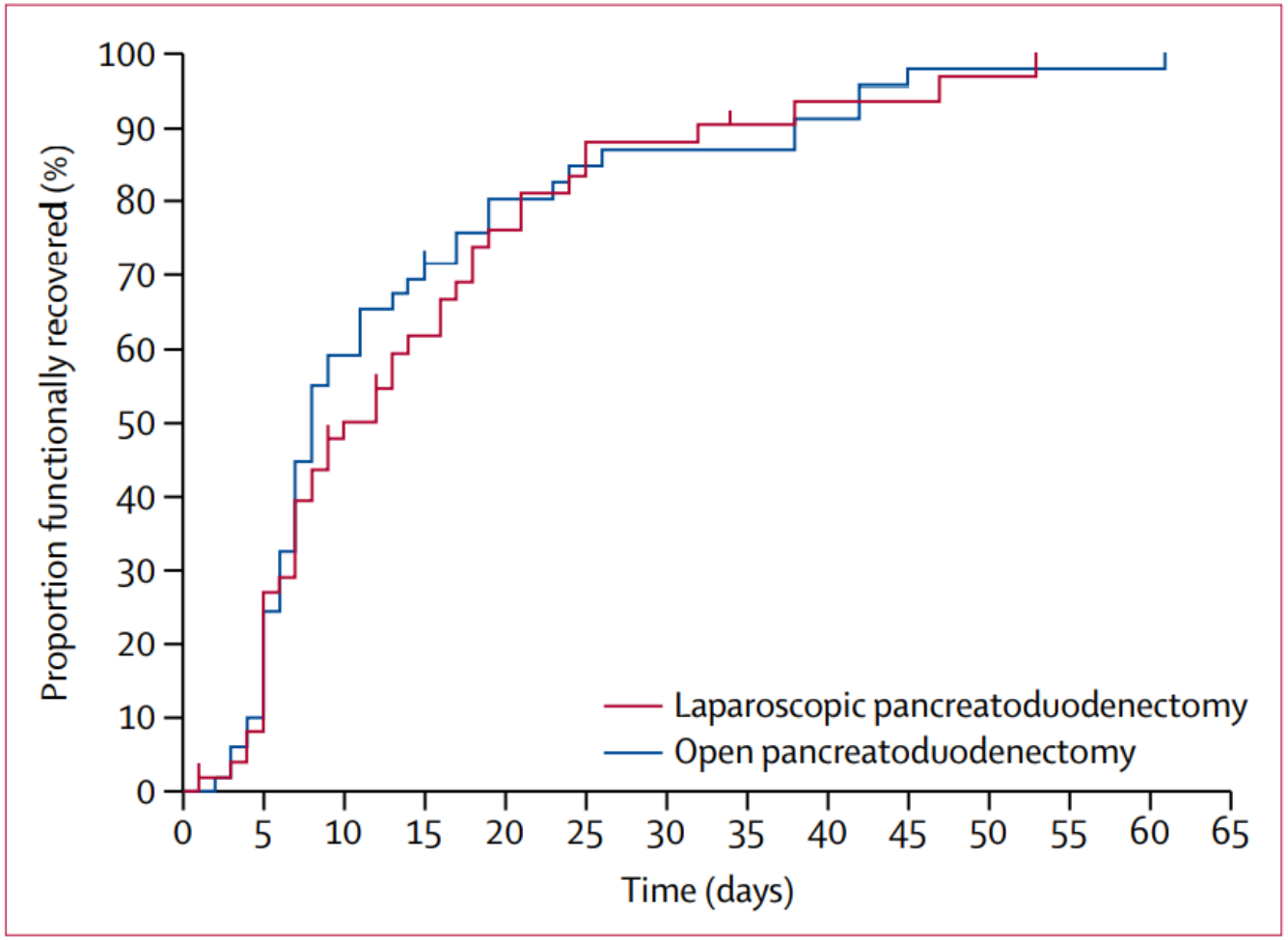
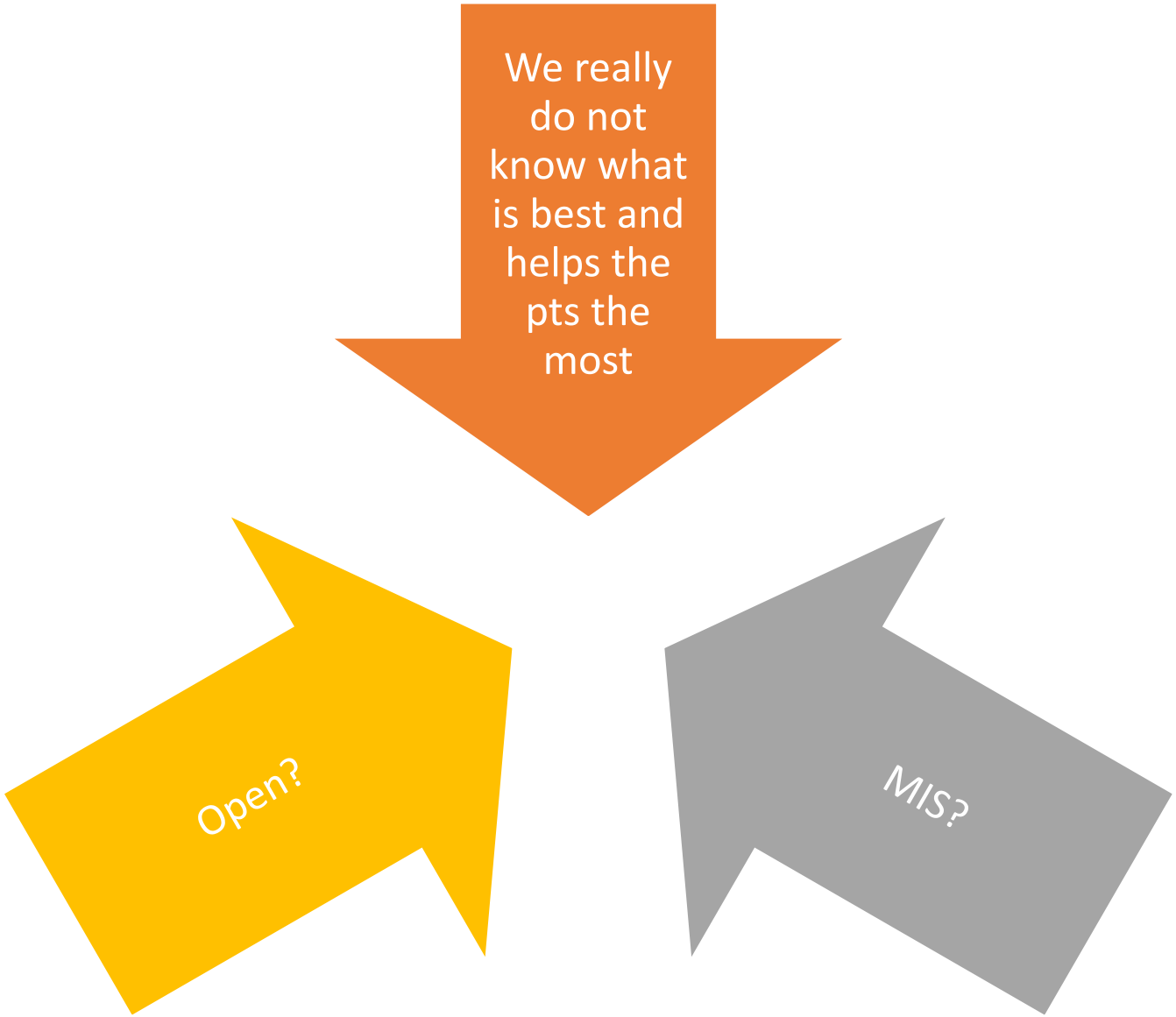


Figure 2: **Time to functional recovery**

Van Hilst, Lancet, March 2019

Leopard 2 Study:

	Open (n=50)	Lap (n=49)
Mortality	2%	10%
Cause of death	Hemorrhage=1	Hemorrhage=2 Bowel ischemia=2 Grade C panc fistula=1



So in summary:

So in summary:

- Resectable/ BRPDAC/ Locally advanced PDAC
- Role of chemo- NAT and adjuvantly
- Importance of margins
- Surgical technique and learning curves