RECENT ADVANCES IN PACREATIC NEOPLASMS

DrTK Marumo
GIT/HPB Surgeon
Charlotte Maxeke
JohannesburgAcademic Hospital

CONTENT:

- GENETICS
- EARLY DIAGNOSIS
- CHEMOTHERAPY
  - NEOADJUVANT
  - ADJUVANT
  - PRIMARY
  - PALLIATIVE

- SURGICAL TECHNIQUE
- EUS

- PALLIATIVE
  - BYPASS VS ENDOSCOPIC THERAPY
  - IRREVERSIBLE ELETROPORATION/NANOKNIFE

The Way

Personalised medicine

MDT-multidisciplinary TEAM

Patient centered TEAM

Dedicated Surgical team

AIM-cure with minimal morbidity and mortality

-Improve quality of life and prolong survival.

Meticulous planning-Preoperative imaging

-Operative strategy

-Prevention of complications

Treat the FAMILY

Pancreatic ductal adenocarcinoma cancer is the 12th most common cancer in the United States, and pancreatic cancer deaths have been increasing steadily over the past few years.

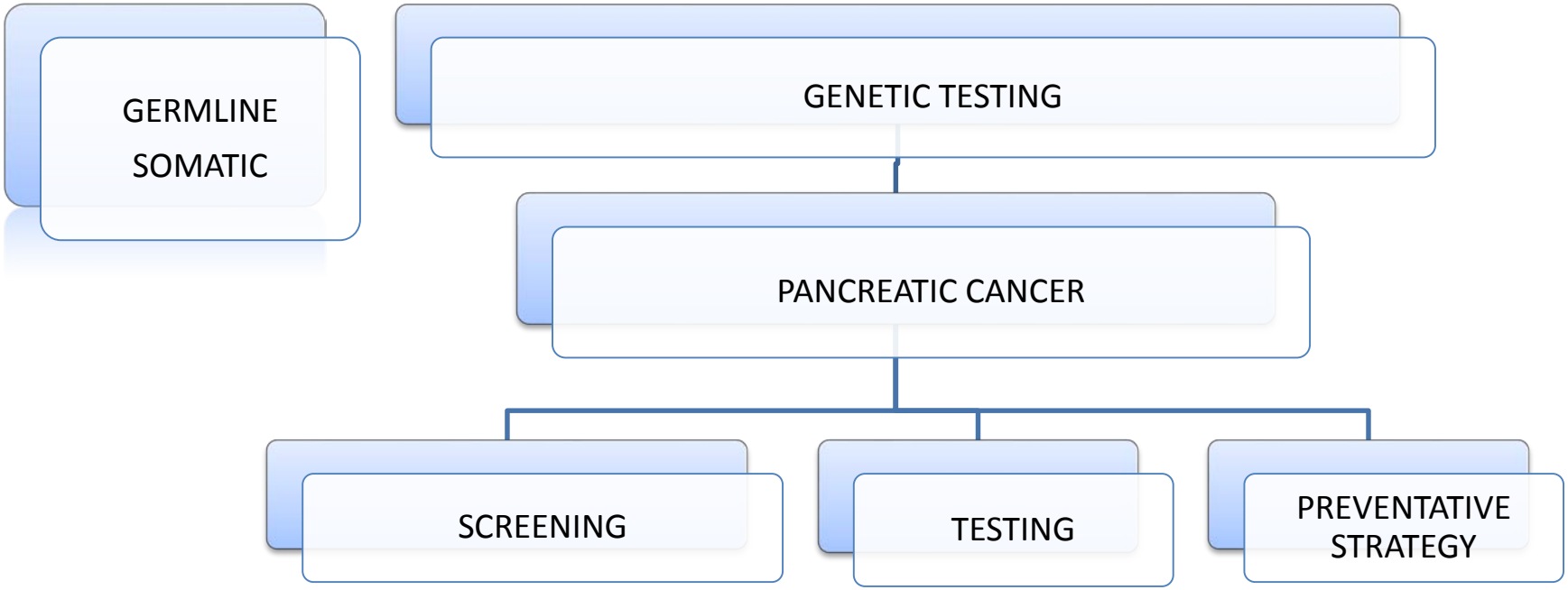
The genetics and other molecular aspects of pancreatic cancer have been well-characterized, with recent progress toward subtyping pancreatic tumors, with potential implications for therapy.

The greatest risk factor for pancreatic cancer is a strong family history; environmental and medical factors have been associated (tobacco use and a history of chronic pancreatitis).

There is no established method of early detection, and pancreatic cancer is frequently diagnosed in late stages.

Immunotherapy and targeting DNA repair deficiency in a subset of tumors are promising areas of research and may yield improved outcomes in the near future.

GENETICS

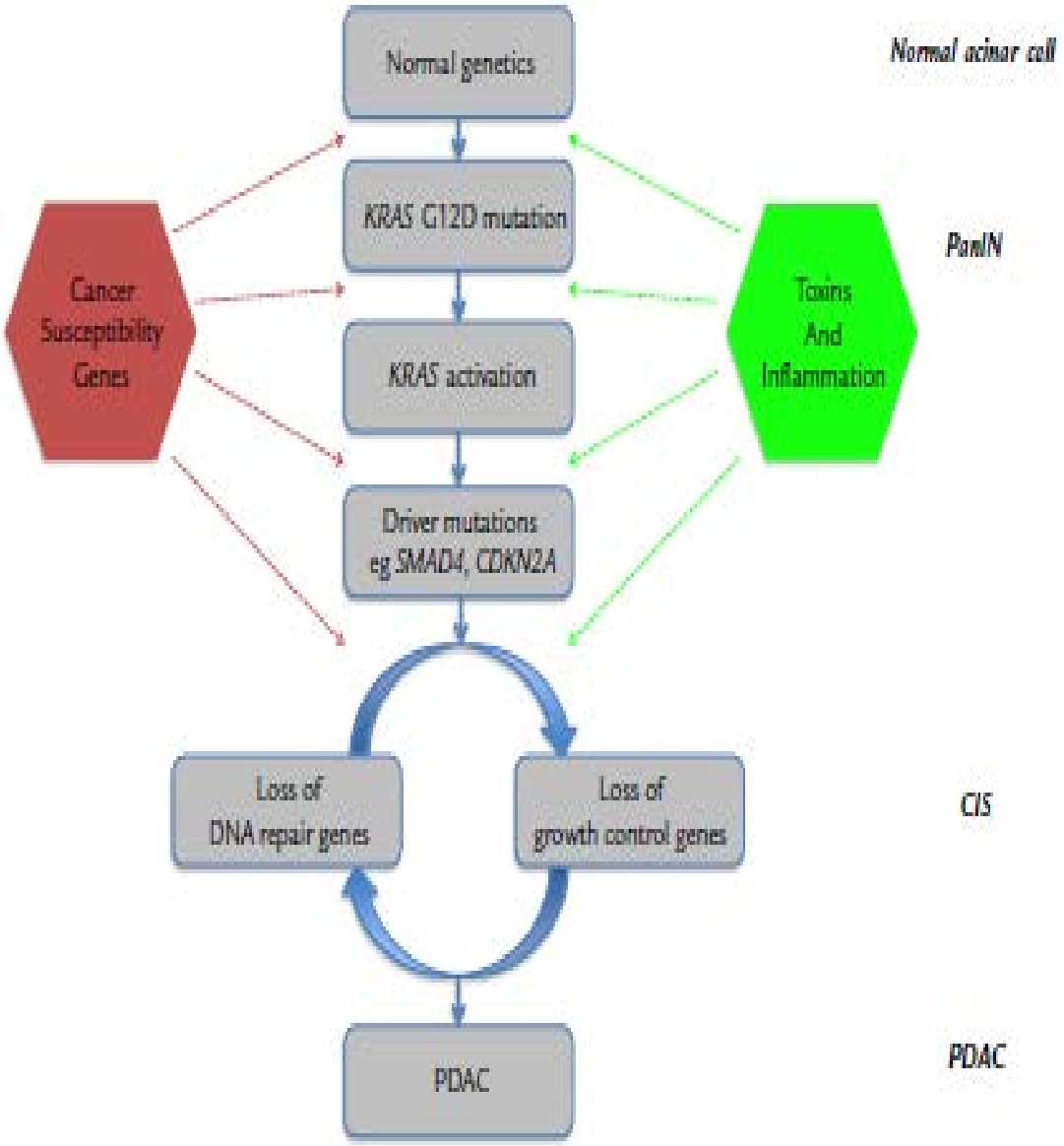


- 10% PDAC associated with Germline mutation
- Germline mutations informs treatment options and identifies high risk individuals inother cancers

- Data on Pancreatic Cancer genetics is emerging
- PDAC has higher incidence rates in developed countries and among African Americans **???**
- Overall 5 yrs survival in 2012 – 7.2%

  2013 – 3.6%

  1975 – 3%
- Localized disease –
  - Resectable :
    - 5 year survival rate in 27%


Normal genetics
Normal acinar cell
KRAS G12D mutation
PanIN
Cancer Susceptibility Genes
Toxins And Inflammation
KRAS activation
Driver mutations eg SMAD4, CDKN2A
Loss of DNA repair genes
Loss of growth control genes
CIS
PDAC
PDAC

CLEAR SCREENING GUIDELINES OT OTHER BRCA ASSOCIATED MALIGNANT TUMOURS

	Prevalence in all pancreatic cancer patients (unselected)	Prevalence in patients with family history of PDAC	Risk of PDAC if positive
APC		< 5%	1.7%
ATM	0.9%–1%	2.4%	
BRCA1	0.4%–1%	1.2–2.6%	1.3–3.6%
BRCA2	0.7%–4%	2.9–17%	4.5–5%
CDKN2A		2.5–21%	10–28%
EPCAM			3.7–13.9%
MLH1	0.4%	2.8%	
MSH2	0.7%	5.5%	
MSH6	0.4%	2.8%	
PALB2	3.0%	0.6–3.7%	
PMS2			3.7–13.9%
STK11			11–36%
TP53	0.4%		9.5%

Indentified Germline mutation associated with PDAC

Table 3. Hereditary Syndromes Associated With Pancreatic Adenocarcinoma

Syndrome	Relative risk of pancreatic cancer	Gene	Yield of testing in FPC kindreds who do not meet criteria for known syndromes, %	Major-associated cancers
Familial atypical multiple mole melanoma	13- to 39-fold[133–135]	*CDKN2A*	0–20[136–138]	Melanoma
Familial breast and ovarian	2-fold[57]	*BRCA1*	0–6[9,44,137]	Breast
	3- to 9-fold[139,140]	*BRCA2*	0–6[9,44,137]	Ovary
Familial adenomatous polyposis	5-fold[59]	*APC*	Unknown	Colon
Lynch syndrome	9- to 11-fold[61,62]	*MLH1*	<1[44]	Colon
		MSH2	<1[44]	Endometrial
		MSH6	<1[44]	
		PMS2	Unknown	
Peutz-Jeghers syndrome	Up to 132-fold[63]	*STK11/LKB1*	0[138]	GI
				Breast
Li-Fraumeni syndrome	7-fold[65]	*p53*	<1[44]	Sarcomas
				Breast
				Brain
				Adrenocortical
Hereditary pancreatitis	53- to 70-fold[17,21]	*PRSS1*	Unknown	Pancreas
ATM carrier (ataxia telangiectasia)	3-fold[68]	*ATM*	1–2.4[44,69]	Breast
				Colon
				Pancreas
PALB2 carrier (Fanconi anemia)	Unknown	*PALB2*	0 to 5[137,138,141]	Breast
				Pancreas

FPC, familial pancreatic cancer; GI, gastrointestinal.

- Genetic testing has 2 primary purposes
  1. Germline testing to identify at risk individual
  2. Somatic and germline testing to identify potential targets of treatment
- Genetic testing has been hindered by unclear definition of target population at risk and the absence of proven low risk screening strategies
  - E.g. PDAC is not included in the Amsterdam or Bethesda guidelines that define Lynch Syndrome even though these individual have a higher PDAC risk than the general population.
  - The role of PDAC screening for BRCA cancers is unclear despite increased rates of PDAC

SCREENING STRATEGIES FOR HIGH RISK PDAC

		International Cancer of the Pancreas Screening (CAPS) Consortium	American College of Gastroenterology (ACG)	National Comprehensive Cancer Network® (NCCN®)
Family History		• ≥ 3 close relatives (at least 1 first degree) with PDAC • ≥ 2 first degree relatives with PDAC • Start age 50, Q1-2Y EUS or MRI	• Start age 50, Q1Y, EUS or MRI or MRCP	
Cancer Syndromes	BRCA	• ≥ 1 first degree relative with PDAC • ≥ 2 close relatives with PDAC • Start age 50, Q1-2Y EUS or MRI		
	Lynch	• ≥ 1 first degree relative with PDAC • Start age 50, Q1-2Y EUS or MRI	• ≥ 1 FDR • Startage 50, Q1-2Y EUS or MRI	
	Peutz-Jegher	• All patients • Start younger, Q1-2Y EUS or MRI	• All patients • Start age 30, Q1-2Y EUS or MRCP	• All patients • Start age 30-35, Q1-2Y EUS or MRCP
	Li Fraumeni			• Annual whole body MRI
	FAMMM			

COMPARATIVE GUIDELINES FOR PDAC GENETIC TESTING

		American College of Medical Genetics and Genomics (ACMG)	American College of Gastroenterology (ACG)
Heritage		Ashkenazi Jewish heritage (BRCA testing only)	N/A
Family History		≥ 2 cases of PDAC in close relatives (BRCA testing only)	• ≥ 2 relatives with PDAC, where one is a first degree relative • ≥ 3 relatives with PDAC
Co-morbidities		N/A	History of hereditary pancreatitis
Cancer Syndromes	**BRCA**	≥ 2 cases of breast, ovarian, and/or aggressive prostate cancer in close relatives	N/A
	Lynch	PDAC and 2 other cases of any Lynch syndrome-associated cancer in the same person or close relatives	Evaluation for Peutz-Jeghers, Lynch, and hereditary pancreatitis genes should be considered if personal and/or family history criteria are met for the syndrome
	Peutz-Jegher	PDAC and ≥ 1 Peutz-Jegherpolyp in the same person	
	FAMMM	• 3 cases of PDAC and/or melanoma in close relatives • PDAC and melanoma in the same person	
Other			Testing should include analysis of BRCA 1 and 2, CDKN2A, PALB2, and ATM

CHEMO PREVENTION

- No proven intervention to reduce risk of developing PDAC other than healthy lifestyle choices
- Several Medications have pre-clinical and in vitro data indicative of potential application in risk reduction.
- Metformin – recent meta-analysis found that it reduced PDAC risk among diabetic patients.
- Metformin-Currently tested to reduce the risk of breast cancer and HCC among patients with obesity and impaired glucose tolerance.

- Angiotensin receptor blockers
  - In vitro models revealed the blocking the Renin Angiotensin system reduces the proliferation of Pancreatic Cancer
  - Losartin being studied with Folfirinox (ongoing trial)
  - COX – 2 inhibitors
    - Mooted as potential mechanism for in vitro suppression of tumour growth
  - Aspirin
    - Reduces development of Adeno….. Polyps and colon cancer
    - Restrospectively found benefit but due to lower prevalence of PDAC overall risk benefit use in these setting is likely to be lower

Criteria defining tumour resectability status according to NCCN guidelines, version 2.2015 [10].

Resectability status	Arterial involvement	Venous involvement
Resectable	No contact with coeliac axis (CA), superior mesenteric artery (SMA), or common hepatic artery (CHA)	No contact with the superior mesenteric vein (SMV), or portal vein (PV) or ≤180° contact without vein contour irregularity
Borderline resectable	**Pancreatic head/uncinate process** • Solid tumour in contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction • Solid tumour contact with the SMA of ≤180° • Presence of variant arterial anatomy (ex: accessory right hepatic artery...) and the presence and degree of tumour contact should be noted if present as it may affect surgical planning	• Solid tumour in contact >180° with the SMV or PV, or in contact ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessels proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction • Solid tumour contact with the inferior vena cava (IVC)

Pancreatic body/tail

- Solid tumour contact ≤180° with the CA
- Solid tumour contact >180° with the CA without involvement of the aorta and with intact and uninvolved gastroduodenal artery (some members prefer this criteria to be in the unresectable category)

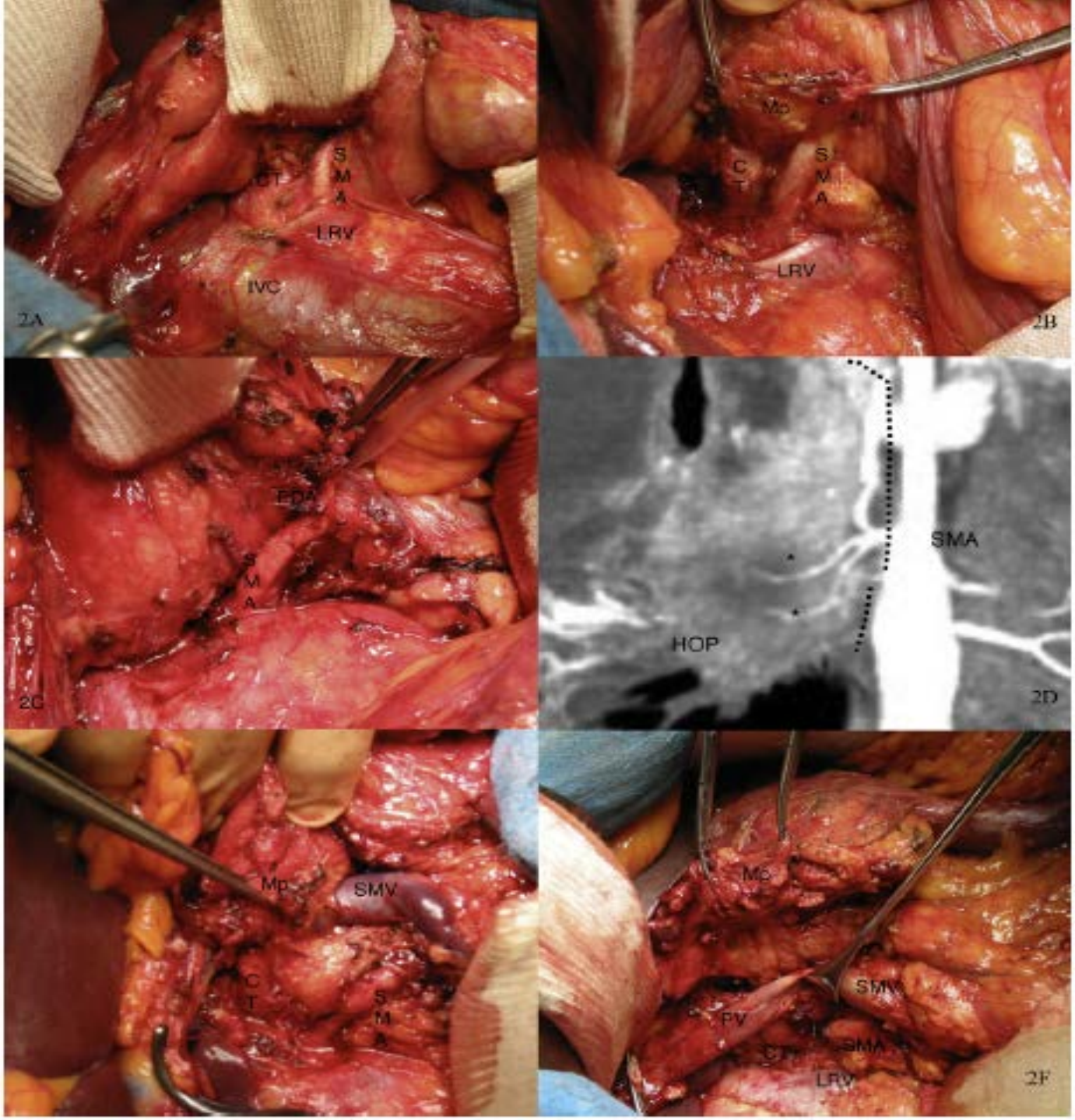
Unresectable	• Distant metastasis	**Head/uncinate process**
	Head/uncinate process	• Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)
	• Solid tumour contact with SMA >180° • Solid tumour contact with the CA >180° • Solid tumour contact with the first jejunal SMA branch	• Contact with most of the proximal draining jejunal branch into the SMV
	Body and tail	**Body and tail**
	• Solid tumour contact >180° with the SMA or CA • Solid tumour contact with the CA and aortic involvement	• Unreconstructible SMV/PV due to tumour involvement or occlusion (can be due to tumour or bland thrombus)

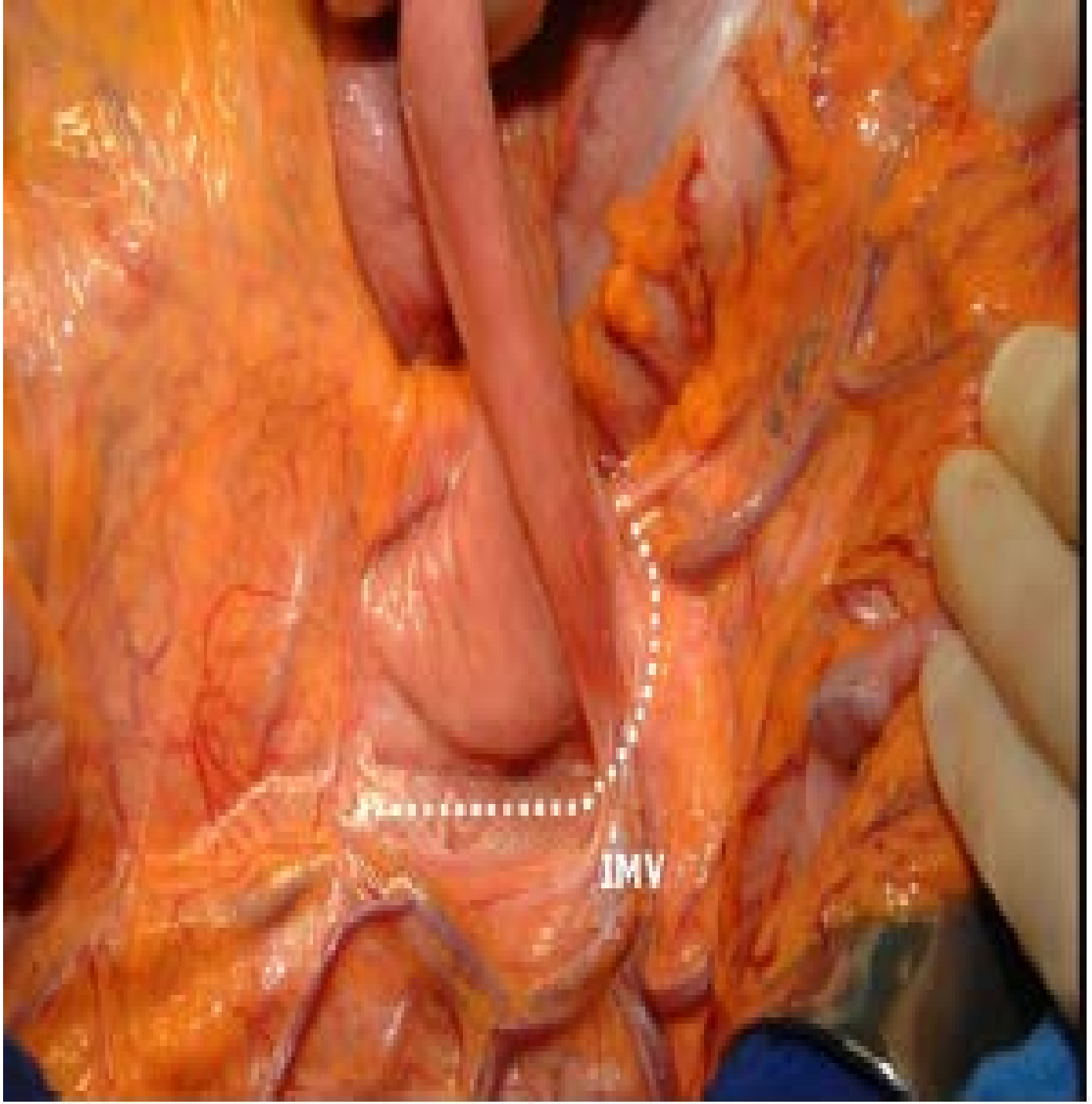
Artery first approach

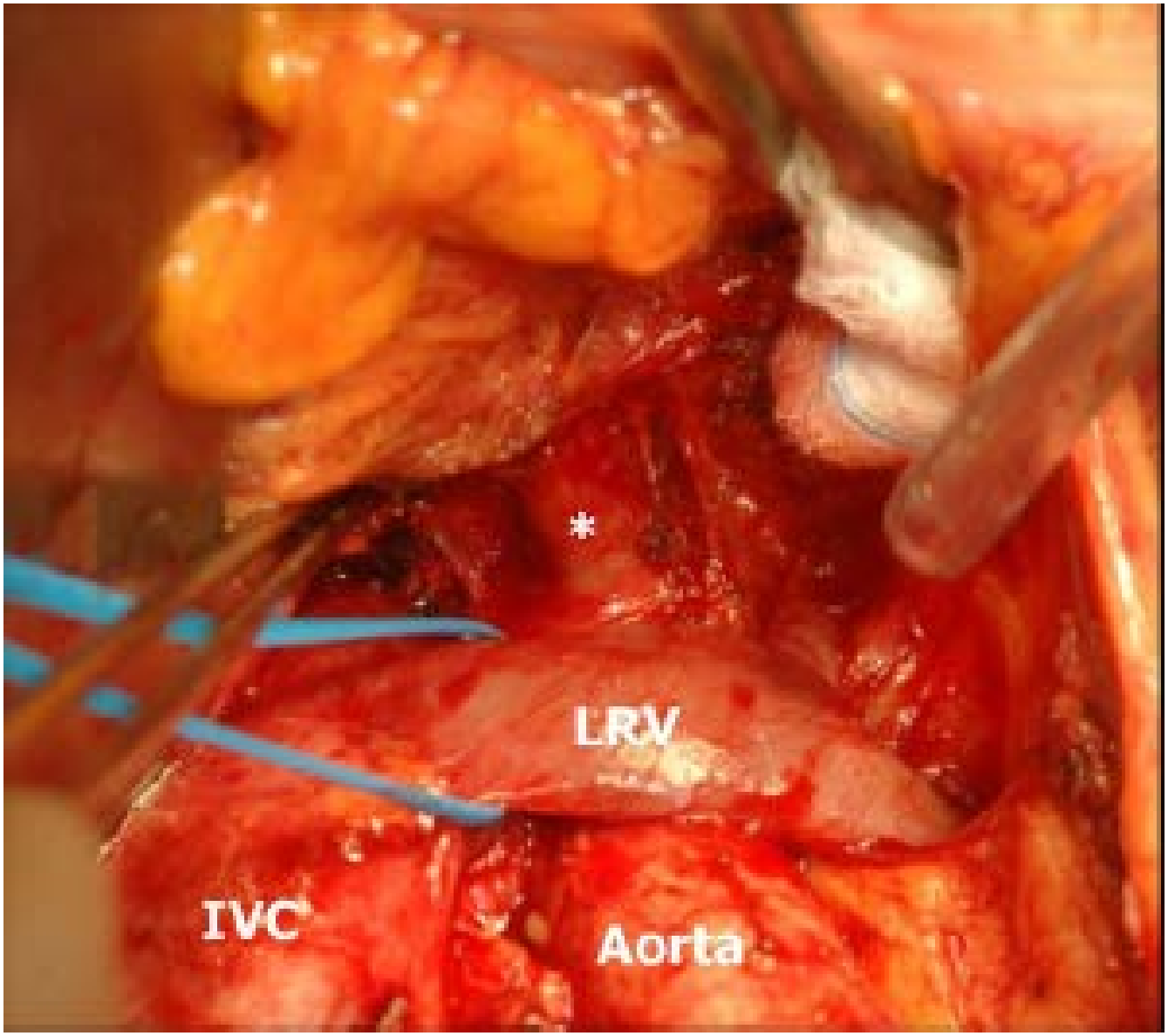
Surgical procedures

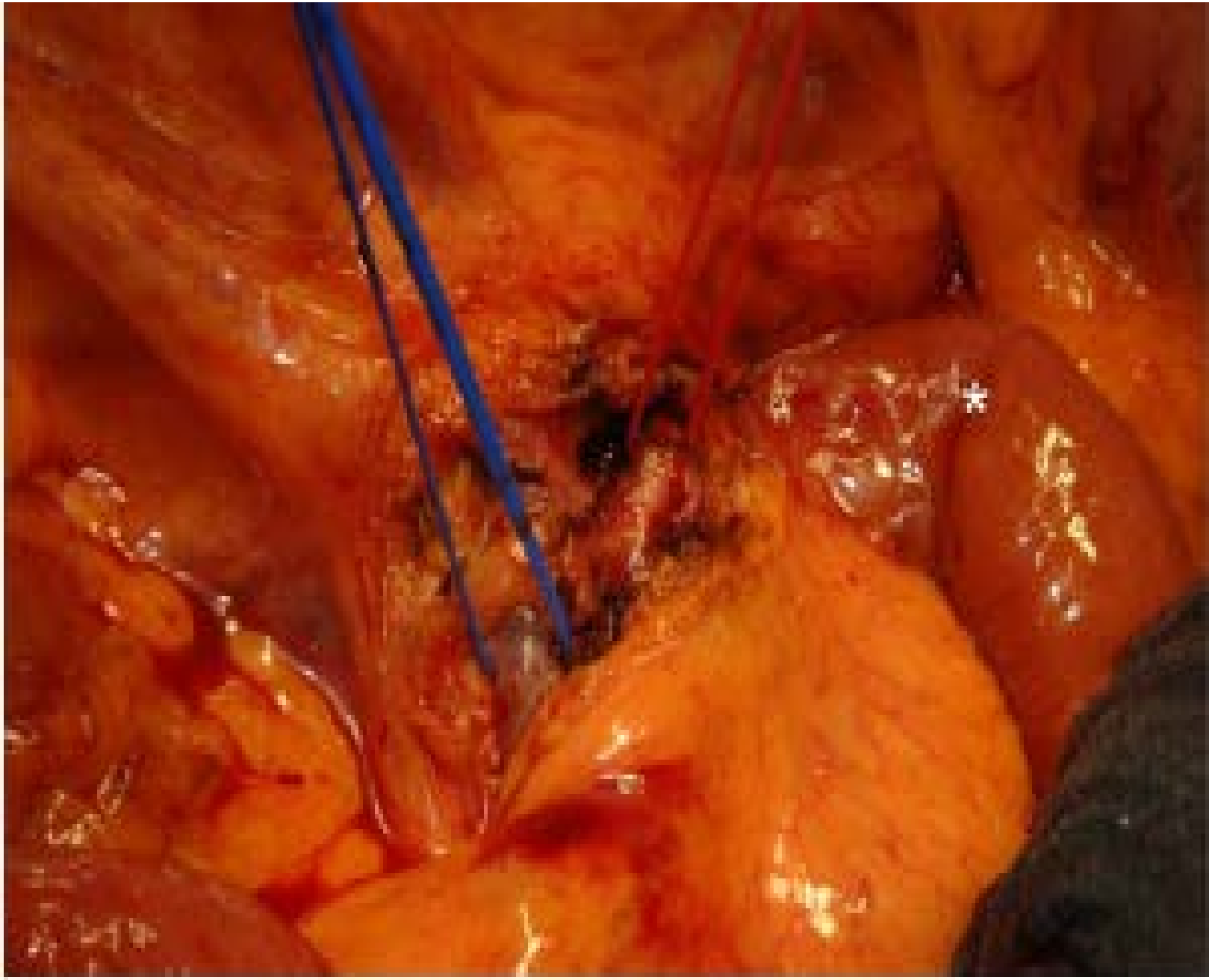
Laparotomy was performed with exploration of the abdominal cavity and intra-operative ultrasonography ensuring the absence of a contraindication for surgical resection.

Key points for exposure included a large mobilization of the right hepatic flexure of the colon followed by an extended Kocher's maneuver allowing the exposure of the infra-hepatic inferior vena cava (IVC) and the distal portion of the left renal vein (LRV).

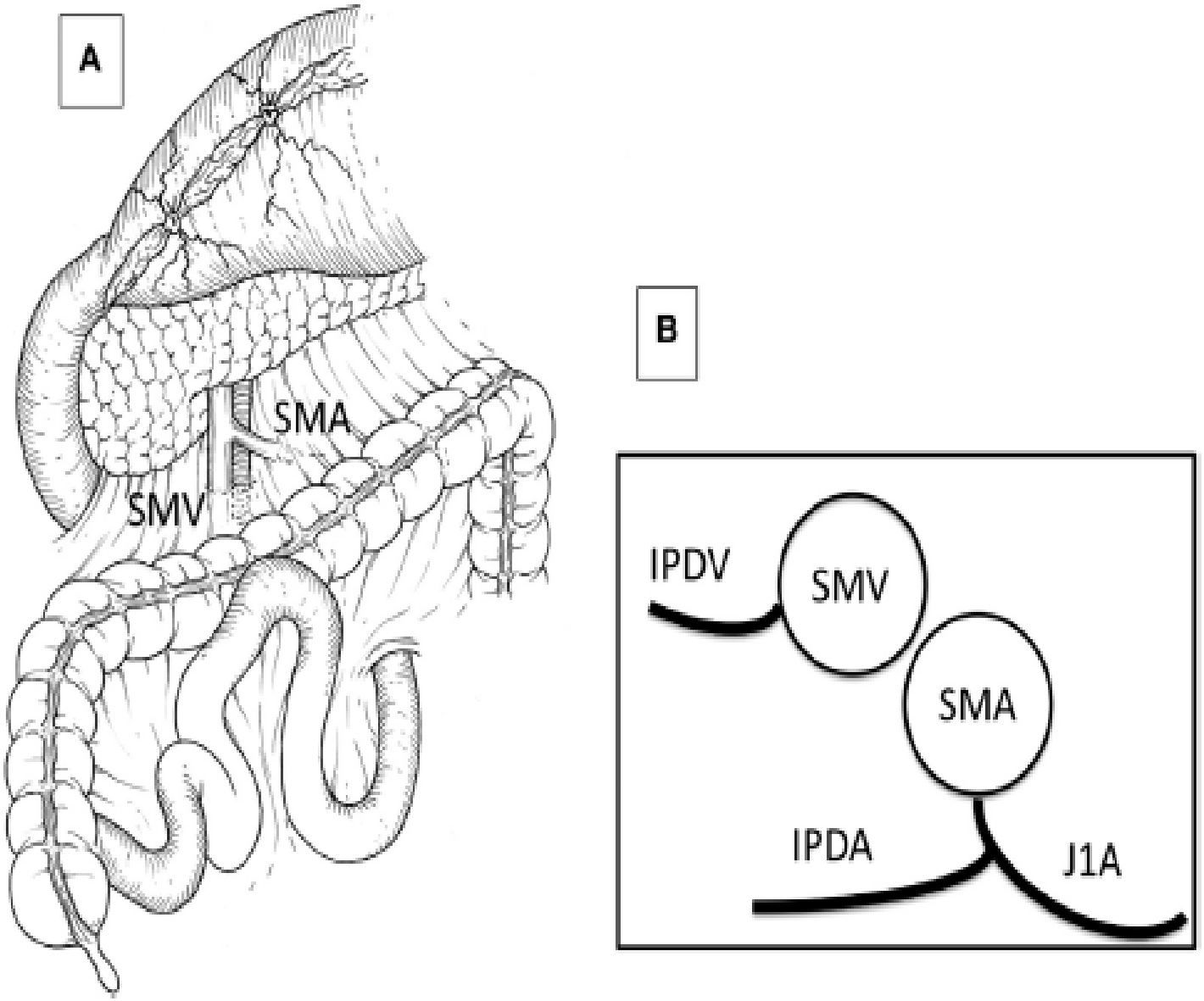

SMA
LRV
IVC
2A
Mp
CT
SMA
LRV
2B
PDA
SMA
2C
SMA
HOP
2D
Mp
SMV
CT
SMA
Mp
SMV
PV
CT
SMA
LRV
2F

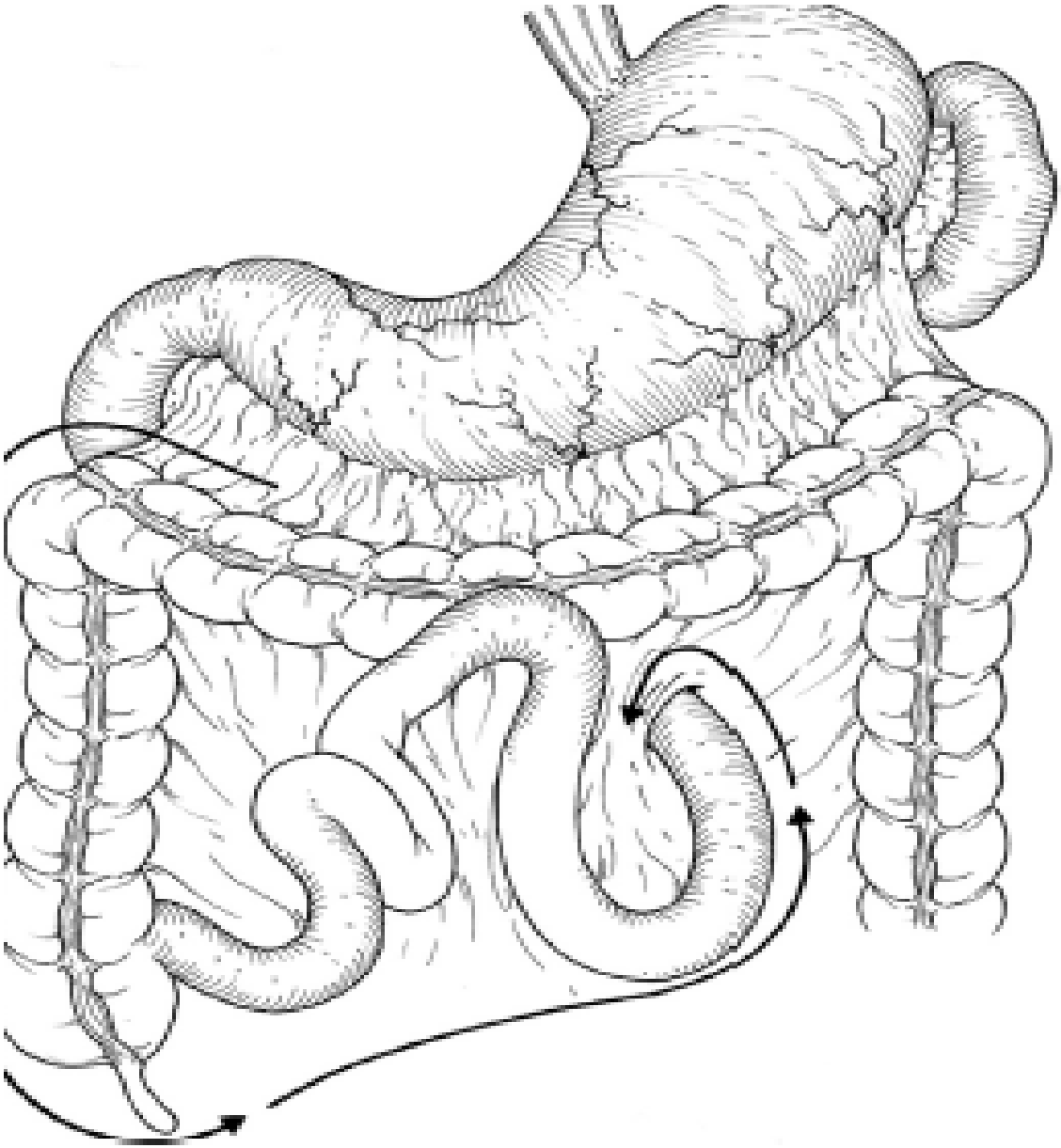

IMV

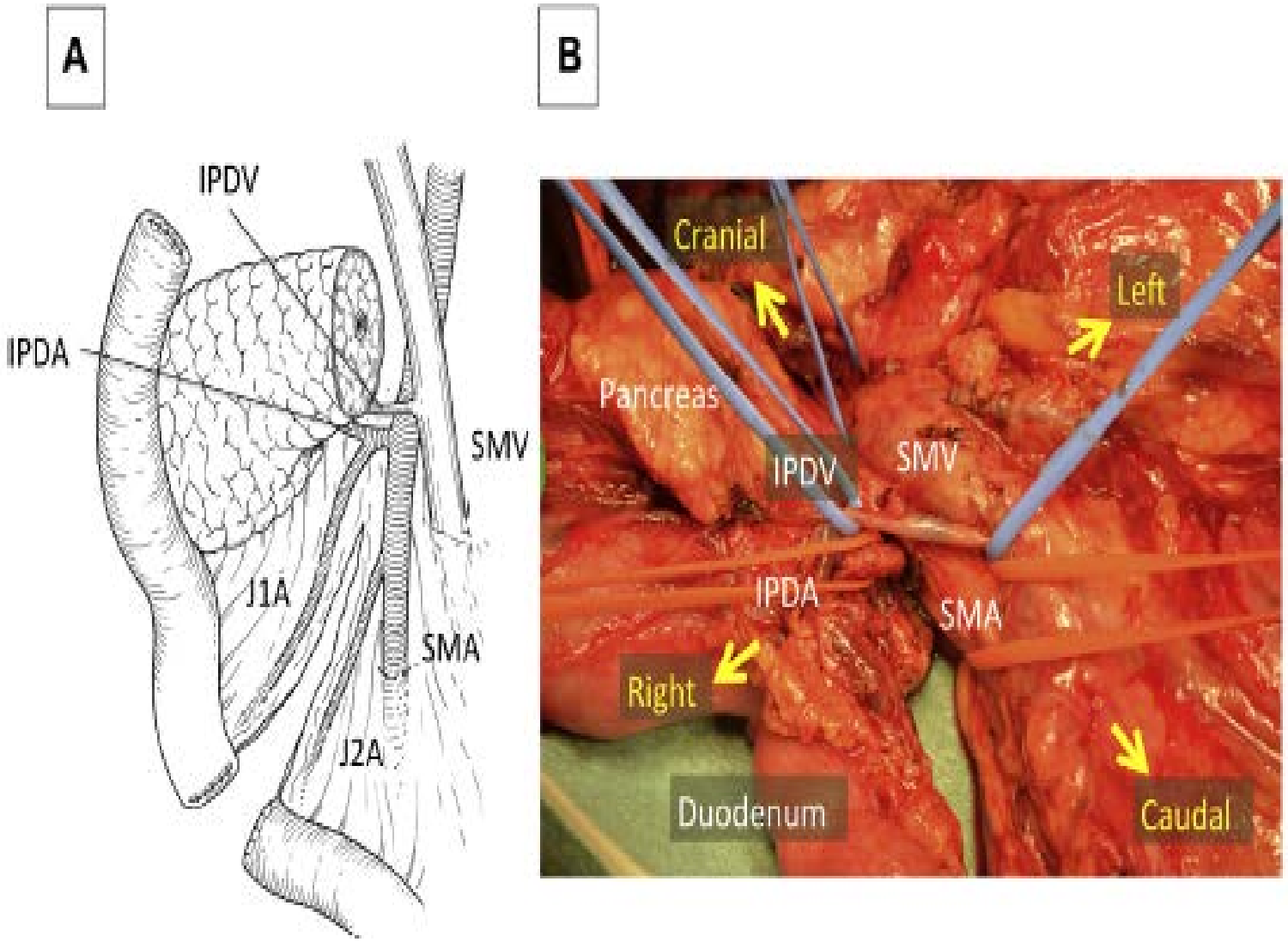

*
LRV
IVC
Aorta



Intestinal derotation procedure for facilitating pancreatoduodenectomy






A
IPDV
IPDA
SMV
J1A
SMA
J2A
B
Cranial
Left
Pancreas
IPDV
SMV
IPDA
SMA
Right
Duodenum
Caudal

Neoadjuvant chemotherapy

- 3 meta-analyses published
- Gillian et al-111 trials
- -no separate analysis of BRPC and LAPC
- -Overall resection rate 33%
- -Median survival in resectable patients with neoadjuvant therapy(20.5months)vs primary resection(23.3),Comparable

- 3rdmeta-analysis –Folforinox in BRPCor LAPC
- -253patients +/- DXT
- -BRPCresection rate 68.5%
- -R0 resection 69.5%
- -new standard of care in FIT patients
- -Such patients to be included in clinical trials
- -High toxicity rate

Neodadjuvant therapy in resectable PC

Overall survival improved with neoadjuvant therapy vs upfront resection in resectable pancreatic cancer

Median survival was 26months in neodajuvant grp vs 21 months in the upfront resection grp

pT3/T4-73%vs86%

Positive lymph nodes-48%vs 73%

Positive resection margin 17%vs24%

- Despite decades of research on the systemic therapy for advanced PDAC only 2 combination cytotoxic chemotherapy regimens have produced a clinical meaningful survival benefit compared to single agent Gemcytabine in 1st line setting.

Folfirinox : leucovorin; 5 Fu; Irinotecan and Oxaliplatin

- Improved survival 11.1 vs 6.8 months
- Improved quality of life of life at 6 months
  - » 31% vs 61%

2. Combination - Nab paclitaxeland Gemcytabine Vs Gemcytabine alone

» Improved survival rate 8.5 months Vs 6.7 Months

- Only targeted agent approved for PDAC treatment :
  - Oral EGFR Inhibitor
  - Erlotineb

} Improved survival by 10 days

2. Combination - Nab Paditaxel and Gematabine Vs Gematabine alone

» Improved survival rate 8.5 months Vs 6.7 Months

- Only targeted agent approved for PDAC treatment :
  - Oral EGFR Inhibitor
  - Erlotineb

} Improved survival by 10 days

Irreversible electroporation

- Delivers high voltage current to tumour cells.
- Creates multiple holes in the cell membrane
- Irrreversibly damages cellular homeostsis
- Resultant celluler death
- Very little effect on vascular structures
- Suited for LAPC without metastases with vascular invasion
-