

SOCIETAD CATALANA DE CIRURGIA
Barcelona, October 2013

**SURGICAL TREATMENT OF
PANCREATIC CANCER: FROM MAJOR
RESECTION TO CELLULAR SURGERY**

Prof. Claudio Bassi FACS,FRCS,FEBS
Verona, Italy



“Personal” convictions and “focal” today questions ...

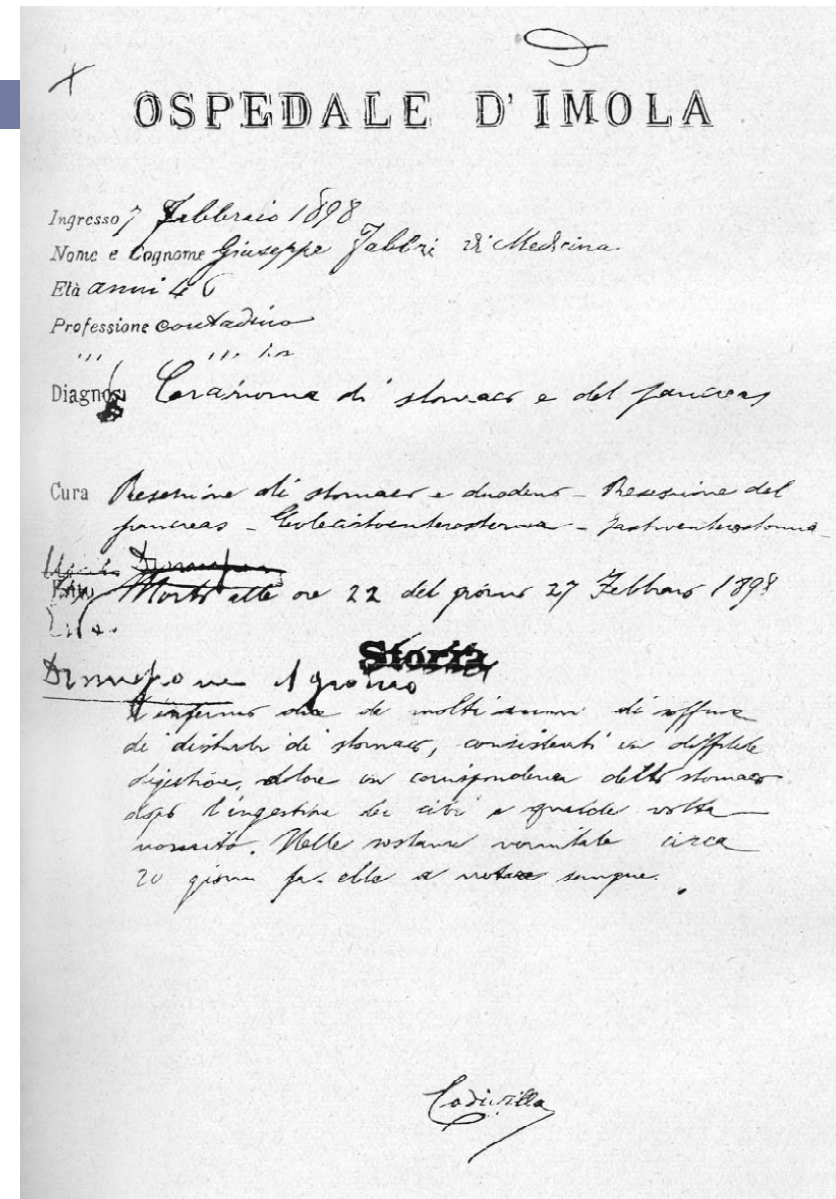
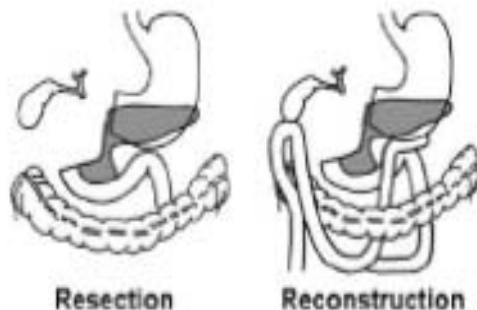
- **Still devastating, not curable but treatable disease ...**
- **Better survival ... (from cancer to chronicity ...)**
- **Systemic disease since the very beginning ...**
- **CH is the “basic treatment” ... but “when” within the “multimodality setting”?**
- **Role of surgery: radical (R0) ... and “adjuvant”?**
- **Role of the surgeon today... in between “major” resection and cell “minor” resection ...**

The history of major resection begins in Italy

February 9th 1898, Imola Hospital

Alessandro Codivilla performed on a 46 years old man a distal gastrectomy extended to the second/third duodenal portions and pancreatic head for a pancreatic cancer. Reconstruction consisted on a gastro-jejunoastomy and cholecysto-jejunostomy. No pancreatic anastomosis was carried out.

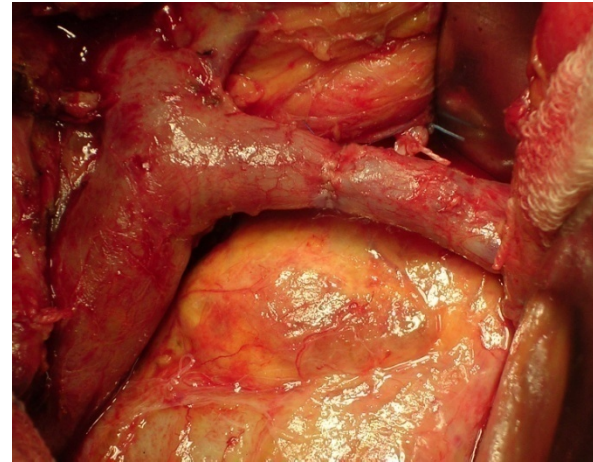
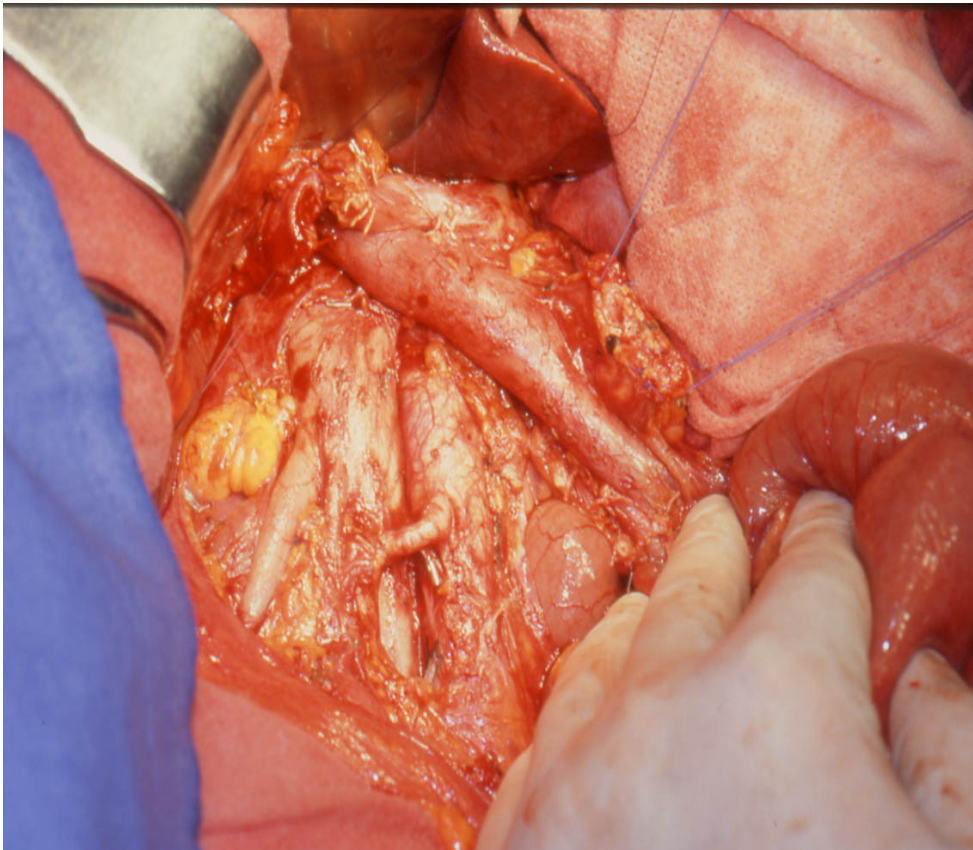
The patient died on postoperative day 18 for a presumed pancreatic fistula and cachexia.



PROF. DR. MED.
WALTER KAUSCH



**Surgical Oncology for Ductal Cancer is ... always
the same since Kausch - Whipple original
procedure!**



Lymphadenectomy standard vs. extensive

Author	Year	Survival	Morbidity	Mortality
Yeo	2002	n. d.	29 % vs. 43 % (p = 0.01)	n. d.
Mukaiya	1998	n. d.	n. e.	n. v.
Pedrazzoli	1998	n. d.*	n. d.	n. d.

* Positive for N+ pts

Lymphadenectomy standard vs.extensive

Author	Year	Survival	Morbidity	Mortality
Nguyen TC	2005	n. d.	n.d.	n.d.
Nimura H	2004	n.d.	n.d.	n.d.
Yeo CJ	2005	n.d.	n.d.	n.d.

Systematic review of outcome of synchronous portal-superior mesenteric vein resection during pancreatectomy for cancer.

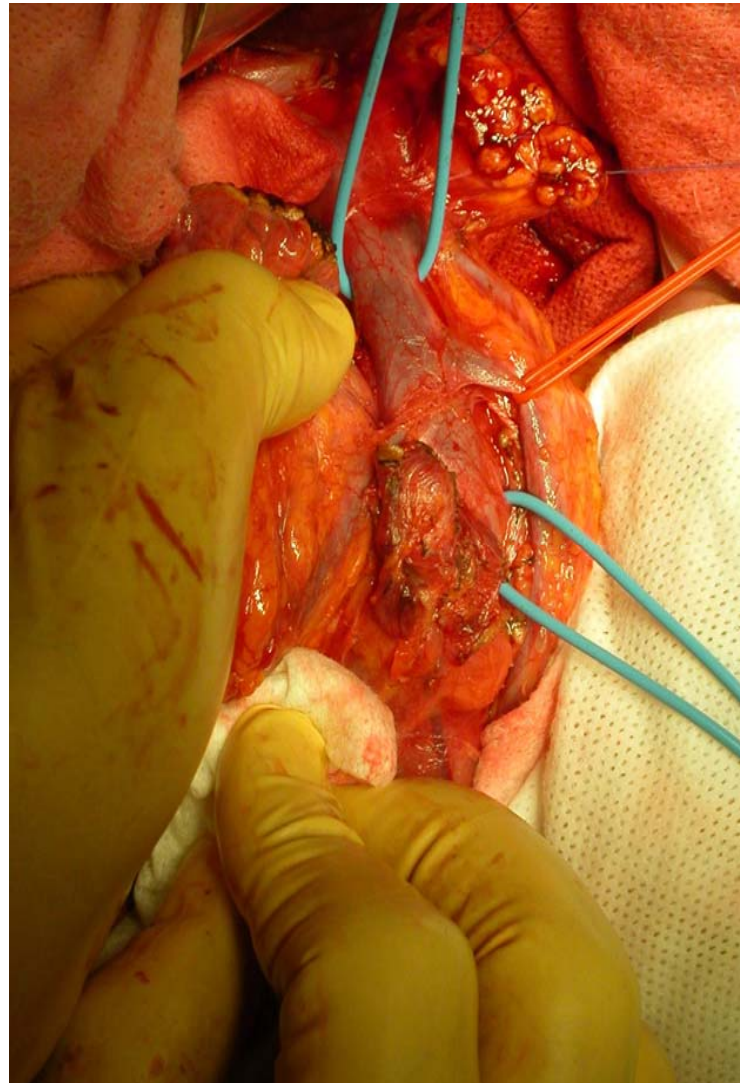
Siriwardana HP and Siriwardena AK **Br J Surg. 2006, 93:662-73**

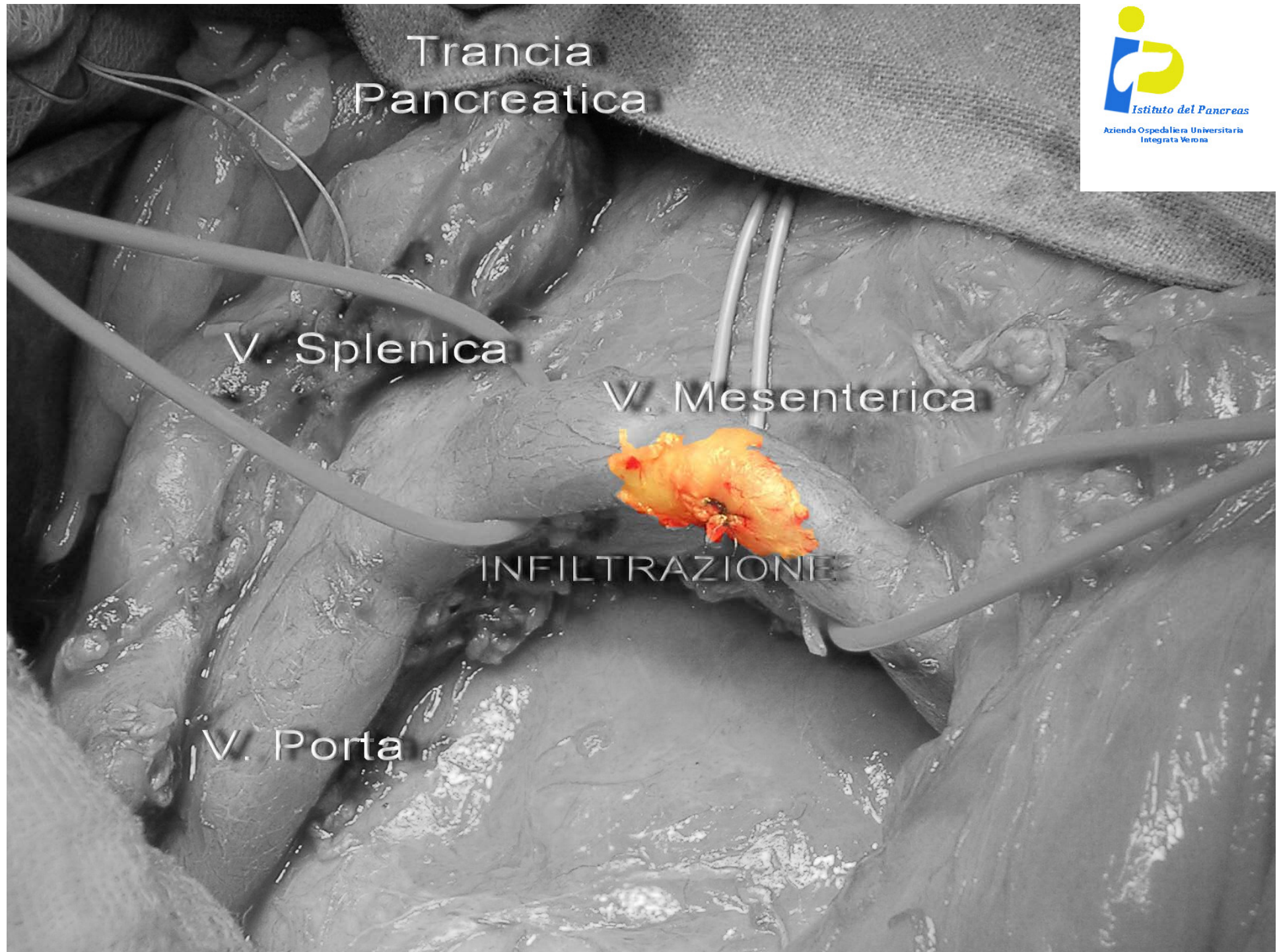
NEED of Portal Vein Replacement in Ductal Cancer

Venous involvement is a function of tumour location more than an indicator of aggressive tumor biology ...”

Fuhrman, Ann Surg 1996

Role ...or better, NEED of Portal Vein Replacement in Ductal Cancer



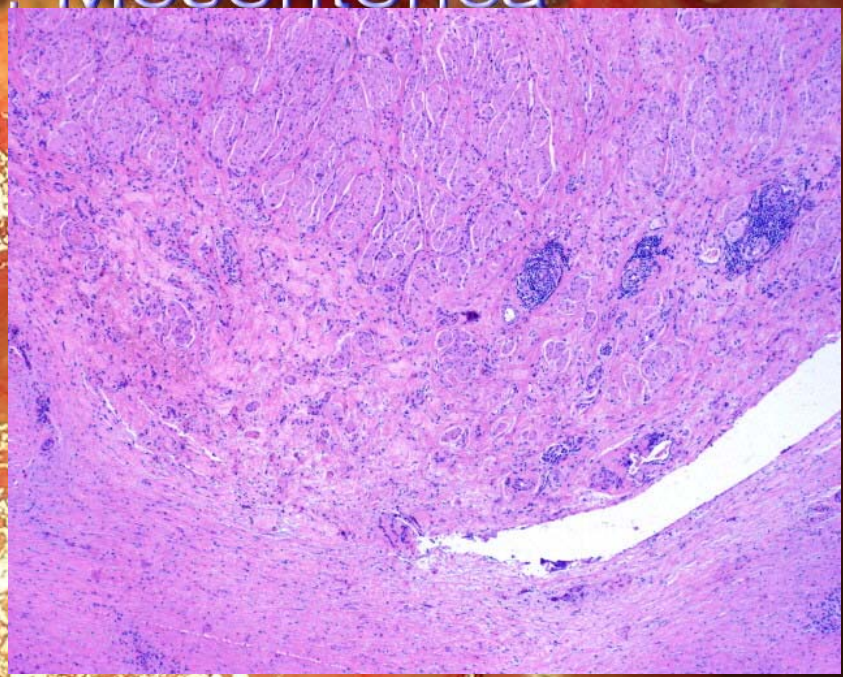
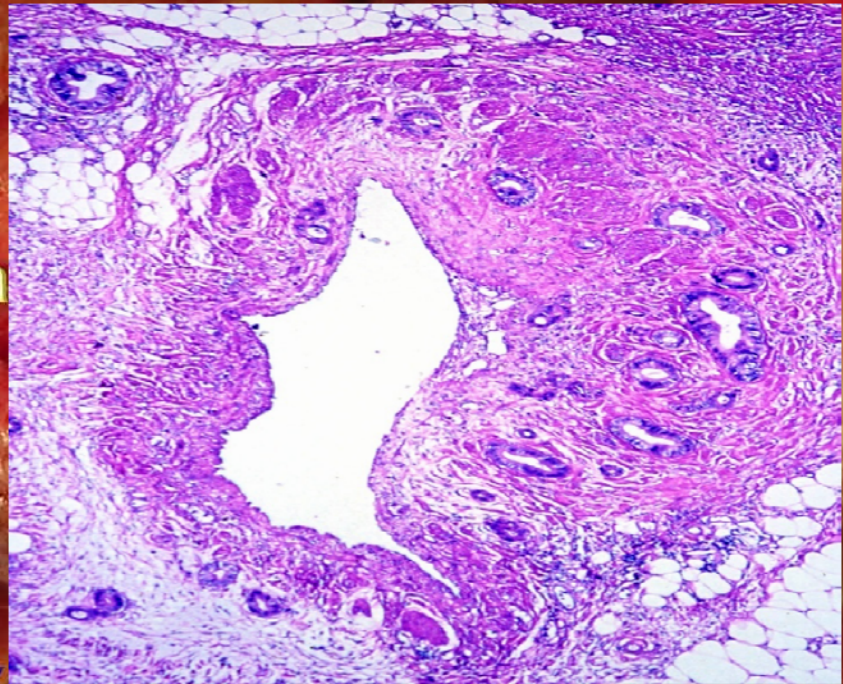


V. Splenica

Ana

V. Porta

V. Mesenterica



WHAT IS THE CONCEPT OF THE STANDARD PANCREATECTOMY TODAY ?



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WHAT IS THE CONCEPT OF THE STANDARD PANCREATECTOMY TODAY ?

Ann Surg 2012;256(5):675-9.

Ultrasonic dissection versus conventional dissection techniques in pancreatic surgery: a randomized multicentre study.

Uzunoglu FG, Stehr A, Fink JA, et al

...the use of an ultrasonic dissection device did not significantly reduce overall operation time and did not significantly increase the costs of surgery. Analysis of secondary endpoints revealed no difference in postoperative course.

WHAT IS THE CONCEPT OF THE STANDARD PANCREATECTOMY TODAY ?

NOT ONLY OPERATIVE TRADITIONS CHANGE...

REVIEW

Perioperative Management of Patients Undergoing Pancreatic Resection: Implementation of a Care Plan in a Tertiary-Care Center

ROBERTO SALVIA, PhD,* GIUSEPPE MALLEO, MD, GIOVANNI BUTTURINI, PhD, MARCO DAL MOLIN, MD,
ALESSANDRO ESPOSITO, MD, GIOVANNI MARCHEGIANI, MD, SALVATORE PAIELLA, MD,
ANNA MALPAGA, MD, MARTINA FONTANA, MD, BEATRICE PERSONI, BSN, AND
CLAUDIO BASSI, MD, FRCS, FACS

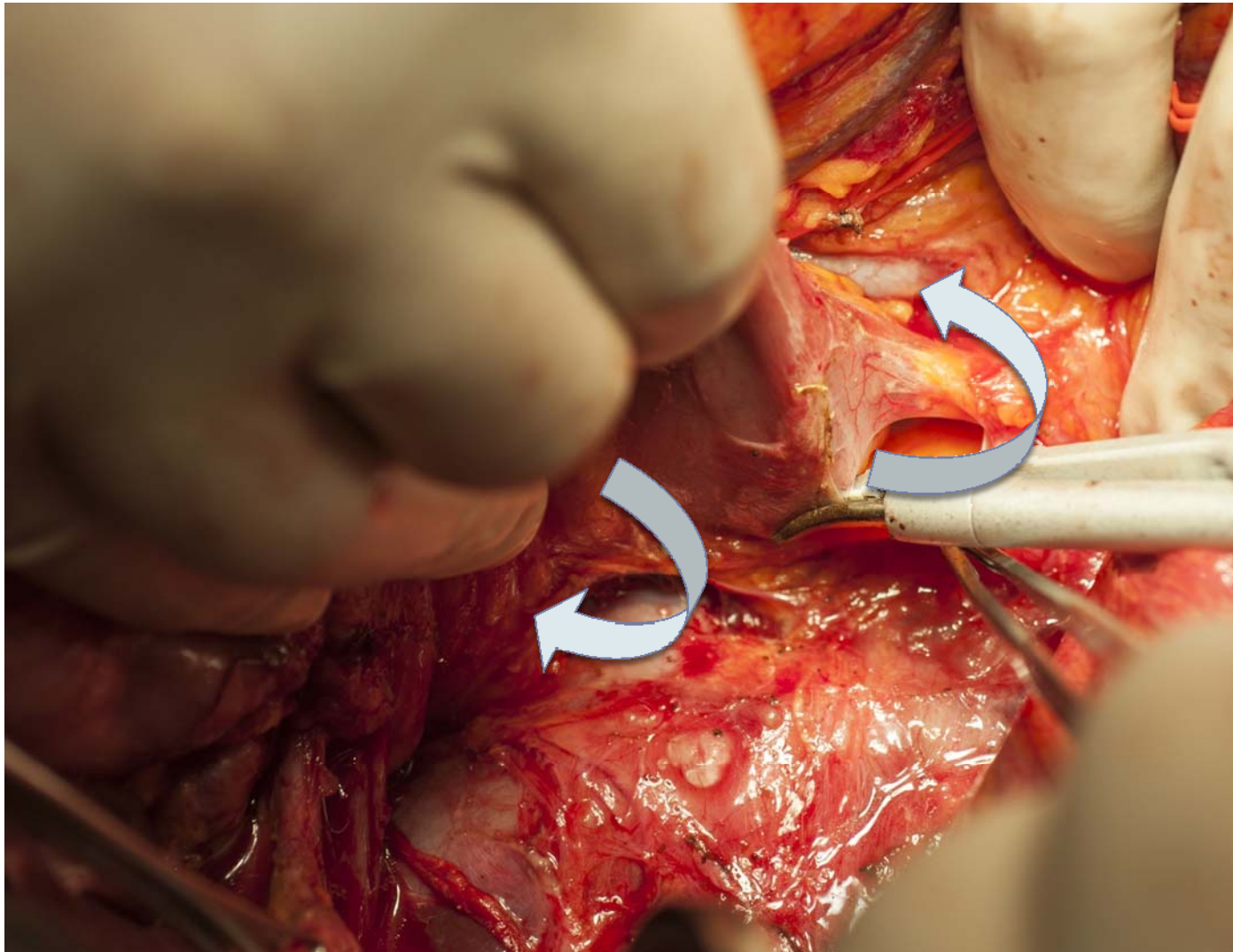
Department of Surgery and Oncology, Pancreas Institute, University of Verona, Verona, Italy

JSO 2013

Dogma Revolution !!!

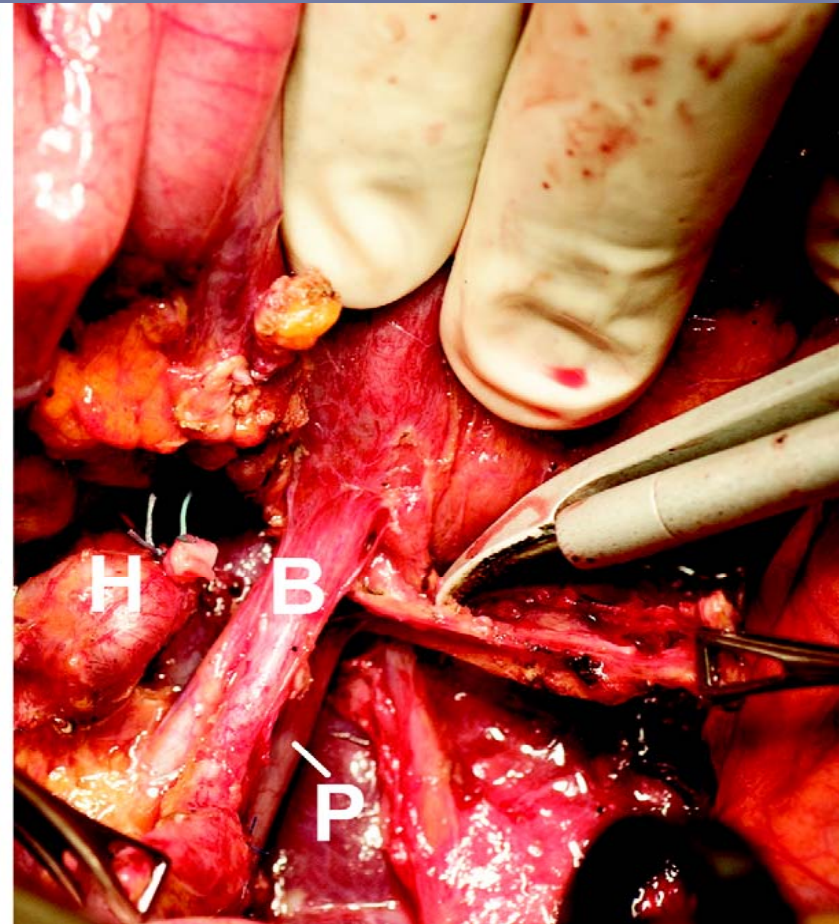
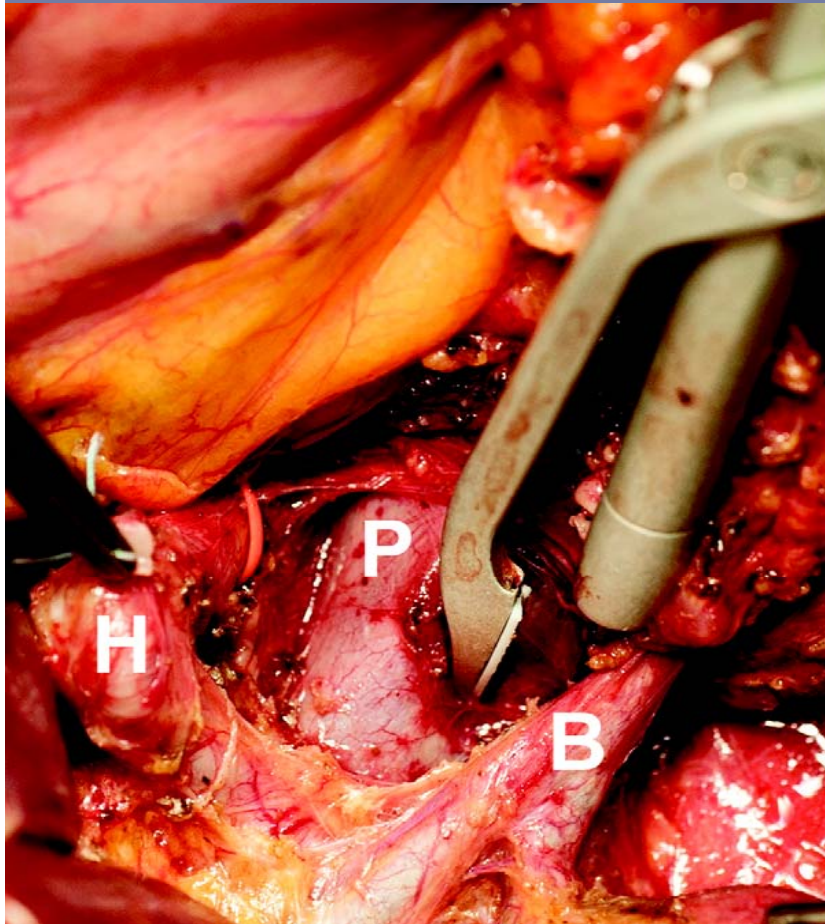


WIDE KOCKER MANOEUVRE



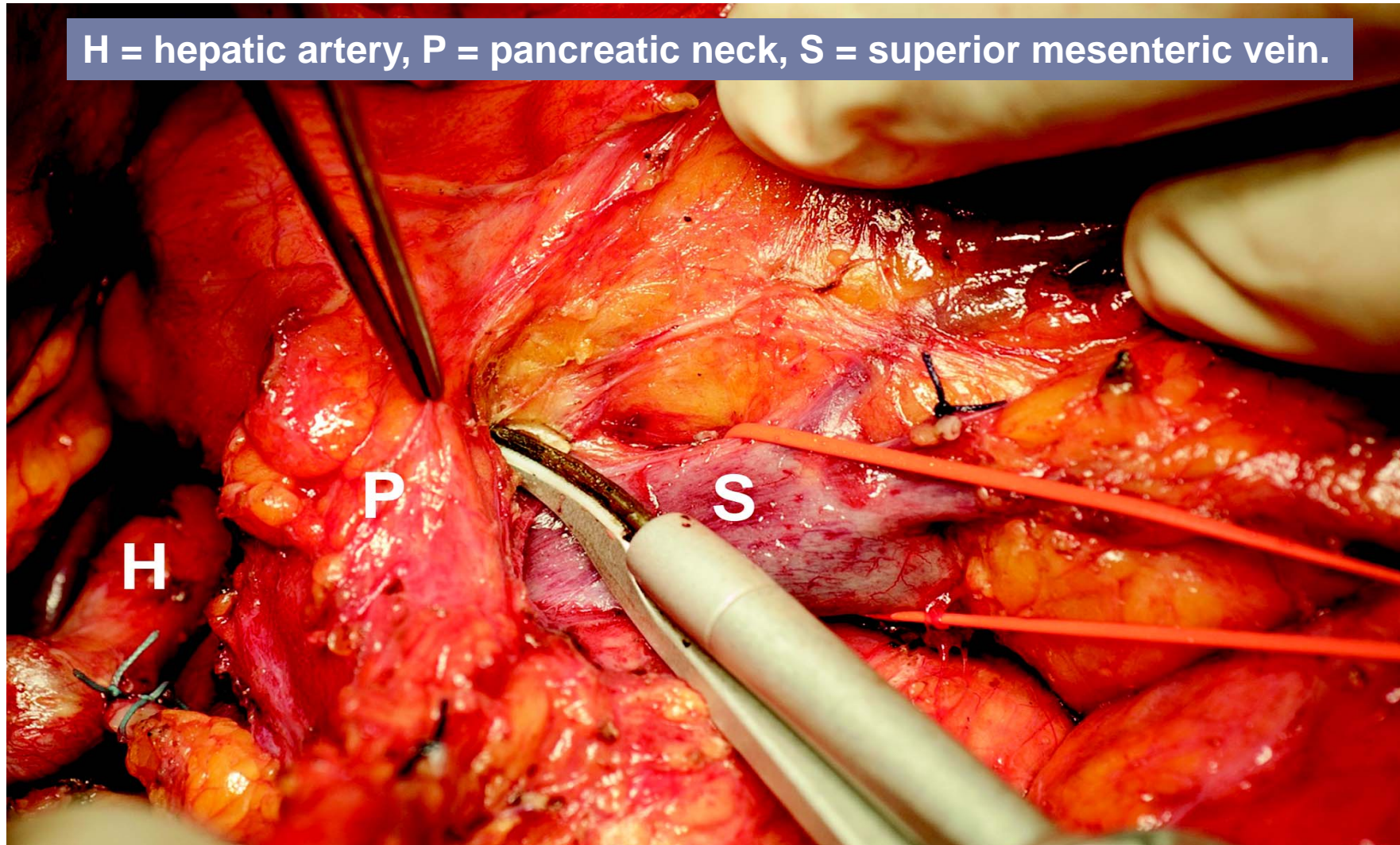
SUPERIOR MARGIN AND HEPATODUODENAL LIGAMENT

H = hepatic artery, P = portal vein, B = bile duct.



DISSECTION OF SMV AT THE PANCREATIC INFERIOR MARGIN

H = hepatic artery, P = pancreatic neck, S = superior mesenteric vein.



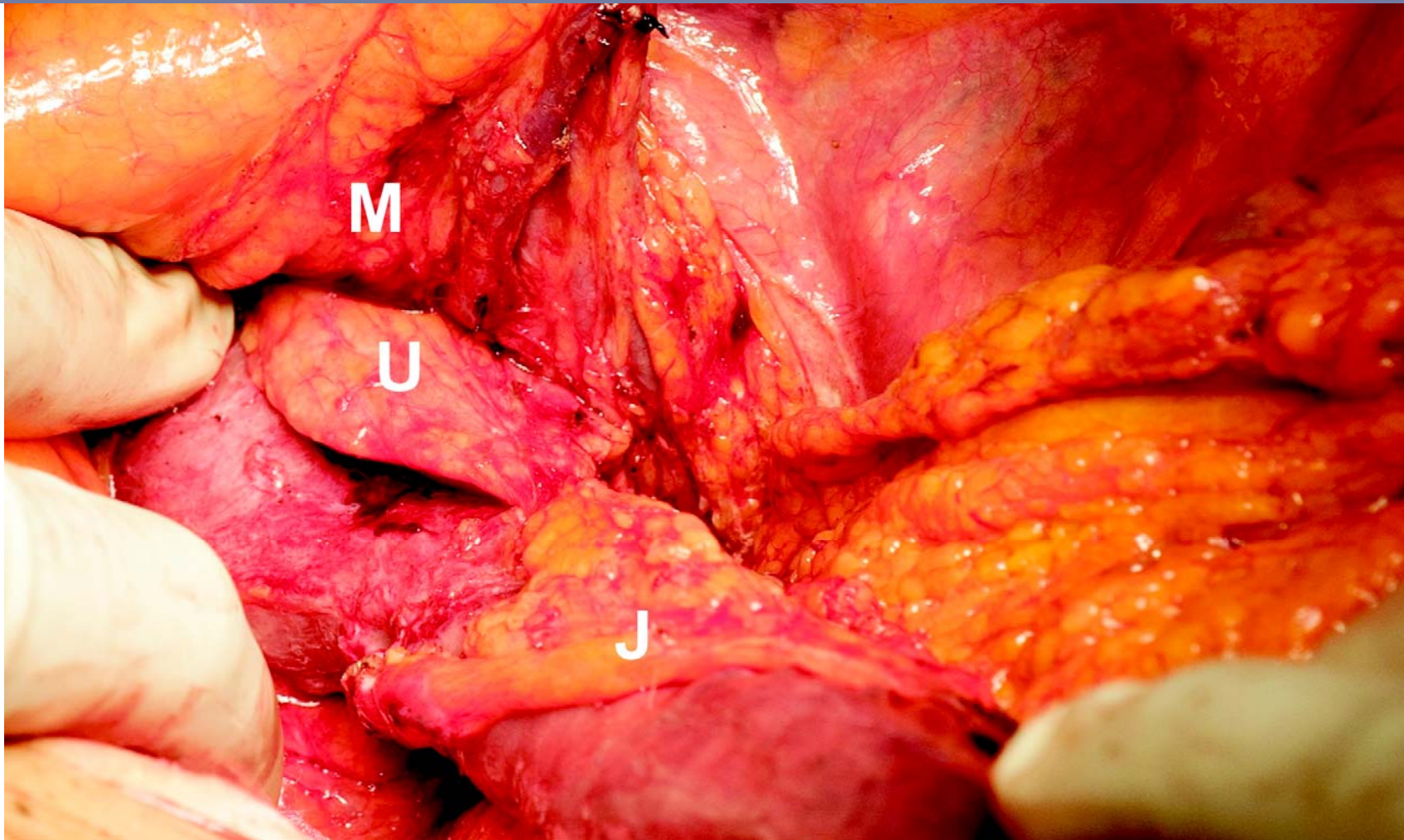
RETROPANCREATIC TUNNEL AND POINT OF NO-RETURN

KEY STEPS

- Retropancreatic tunnel gently developed
- Division of right gastric and gastroepiploic vessels at the pylorus
- Division of the duodenum
- Stitching of pancreatic arterial arcades
- Division of the pancreatic neck (resection margin for frozen section)
- Division of the common bile duct (this can be also done at the end of procedure)

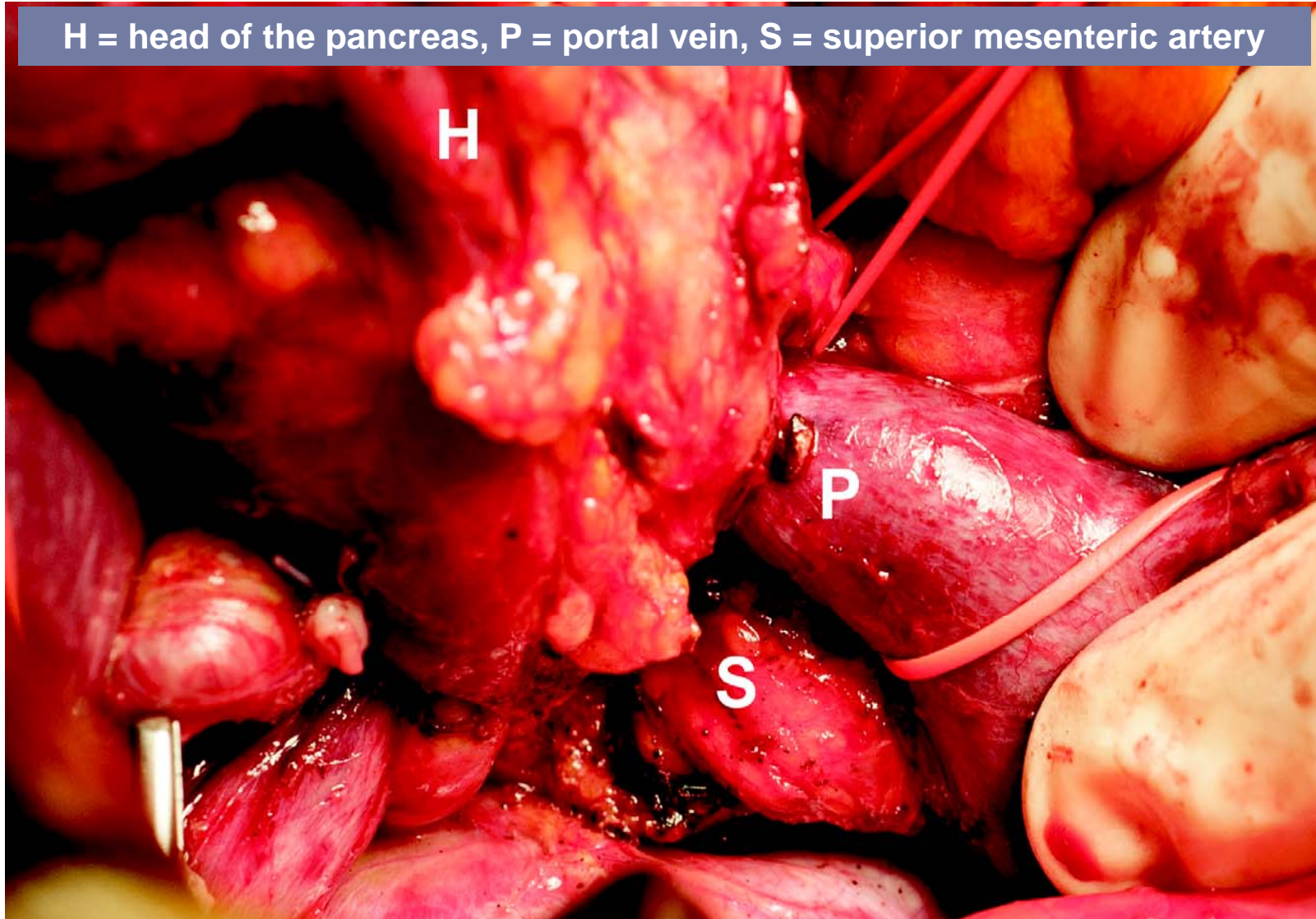
DISCONNECTION OF THE FIRST JEJUNAL LOOP

M = mesentery root, U = uncinate process, J = jejunal loop (disconnected).

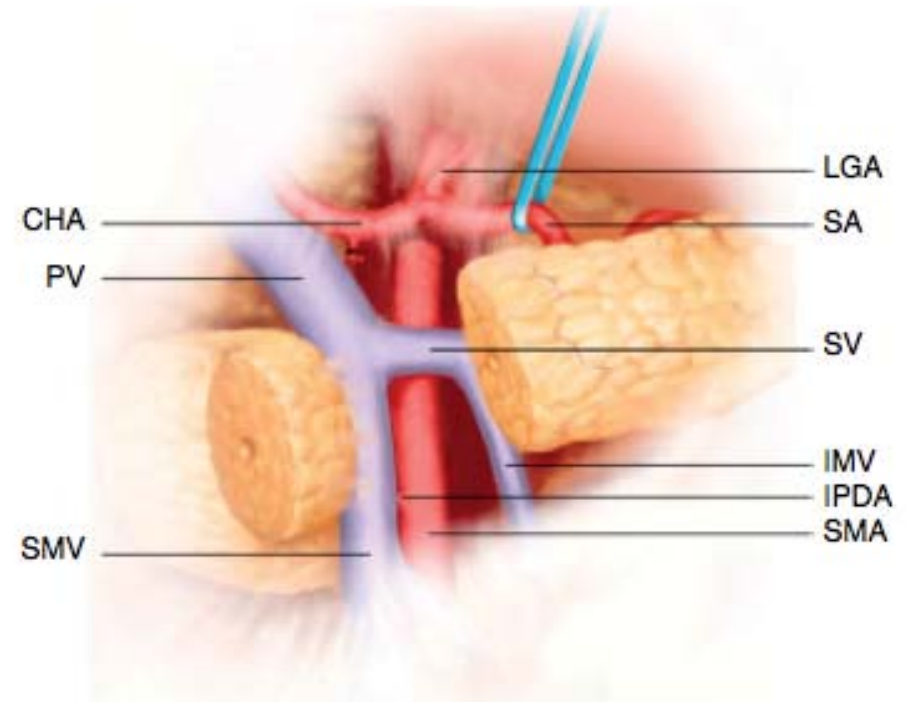
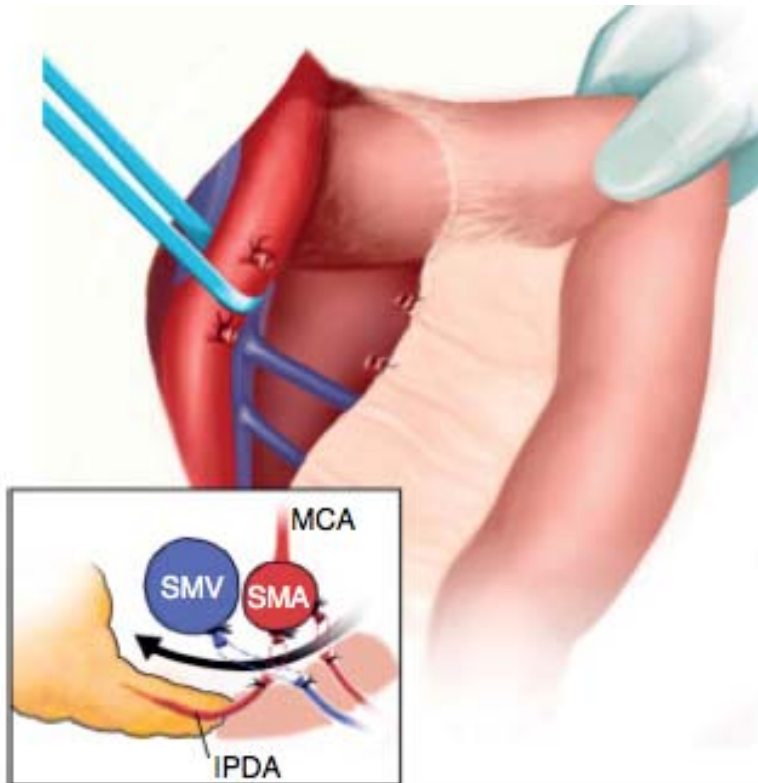


DIVISION OF RETROPORTAL LAMINA

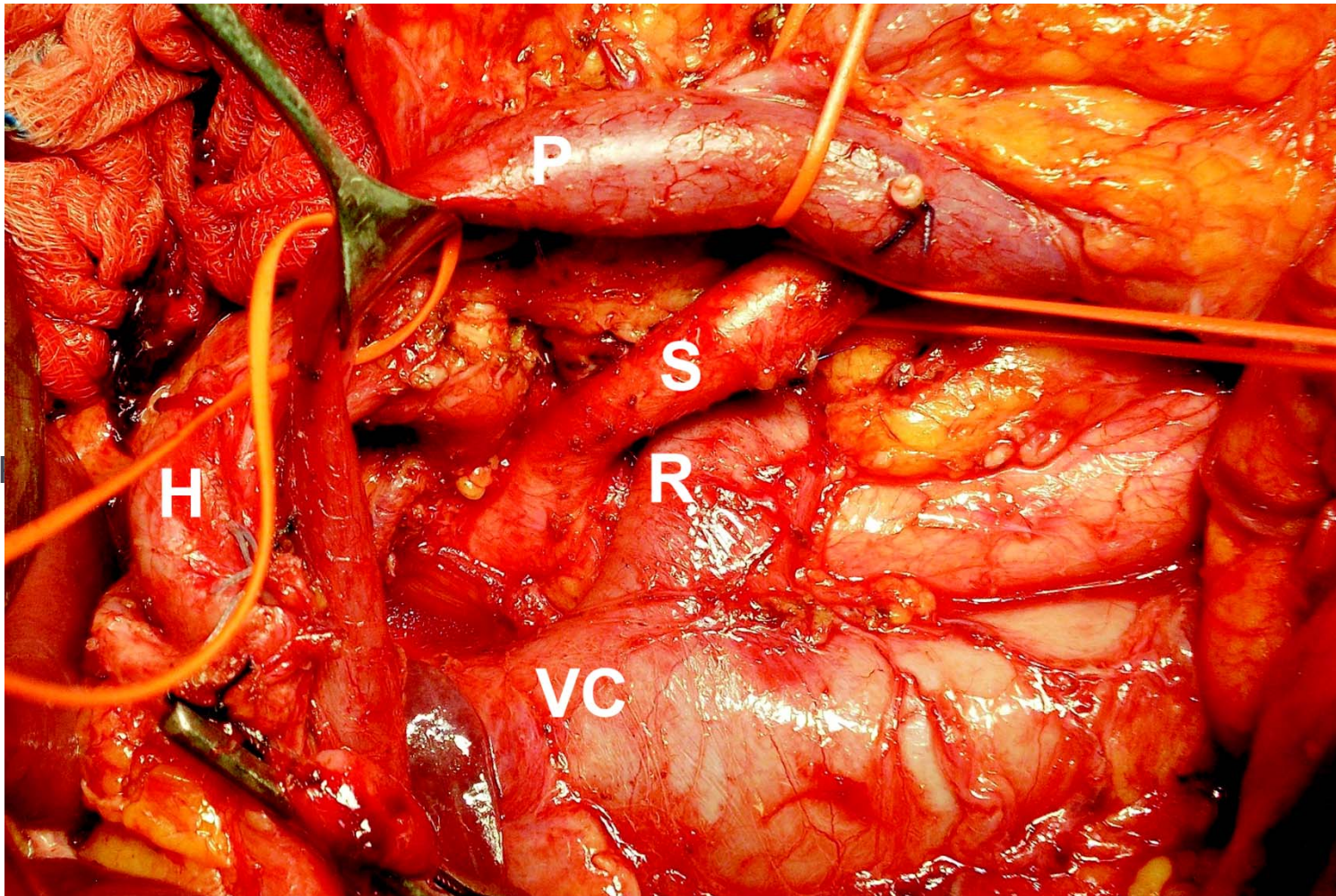
H = head of the pancreas, P = portal vein, S = superior mesenteric artery



CIRCUMFERENTIAL DISSECTION OF SMA



CIRCUMFERENTIAL DISSECTION OF SMA





EXTENSION OF LYMPH NODE DISSECTION

**Definition of a standard lymphadenectomy in surgery for PDAC
A consensus statement by the international study group on
pancreatic surgery (ISGPS). Garda, Verona April 2013 –
SUBMITTED**

**Standard lymphadenectomy for
pancreaticoduodenectomy should strive
to resect lymph node stations no. 5, 6, 8a, 12a,
12b, 12p, 13a, 13b, 14, 17a and 17b.**

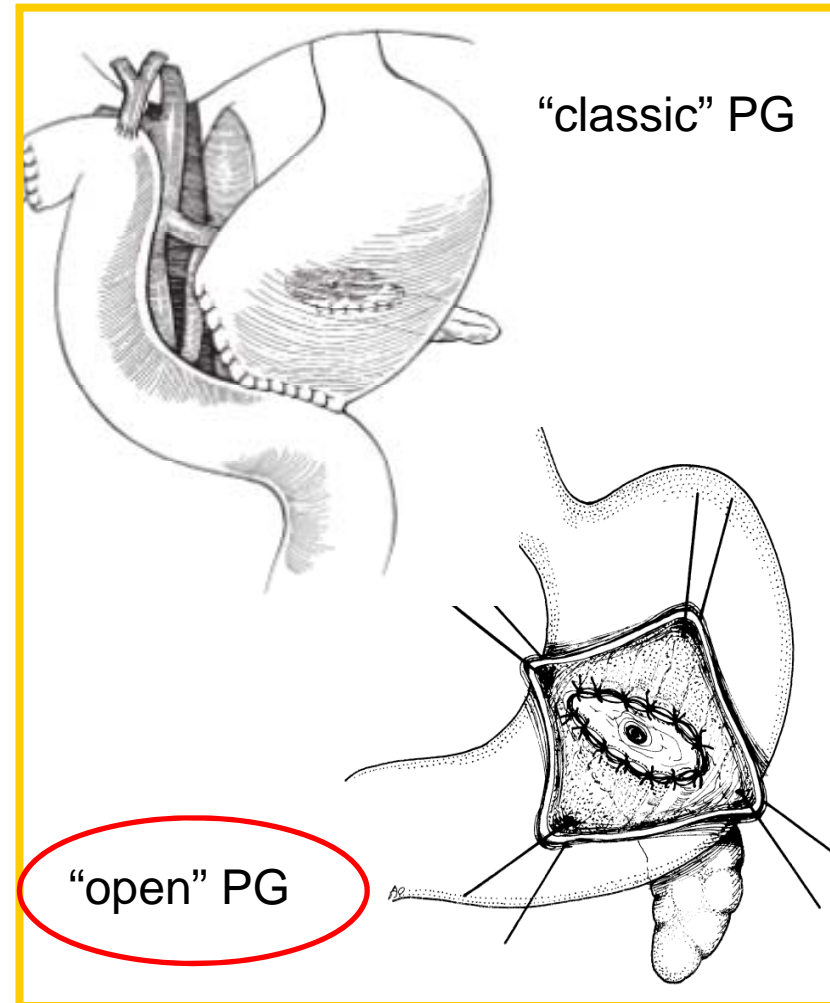
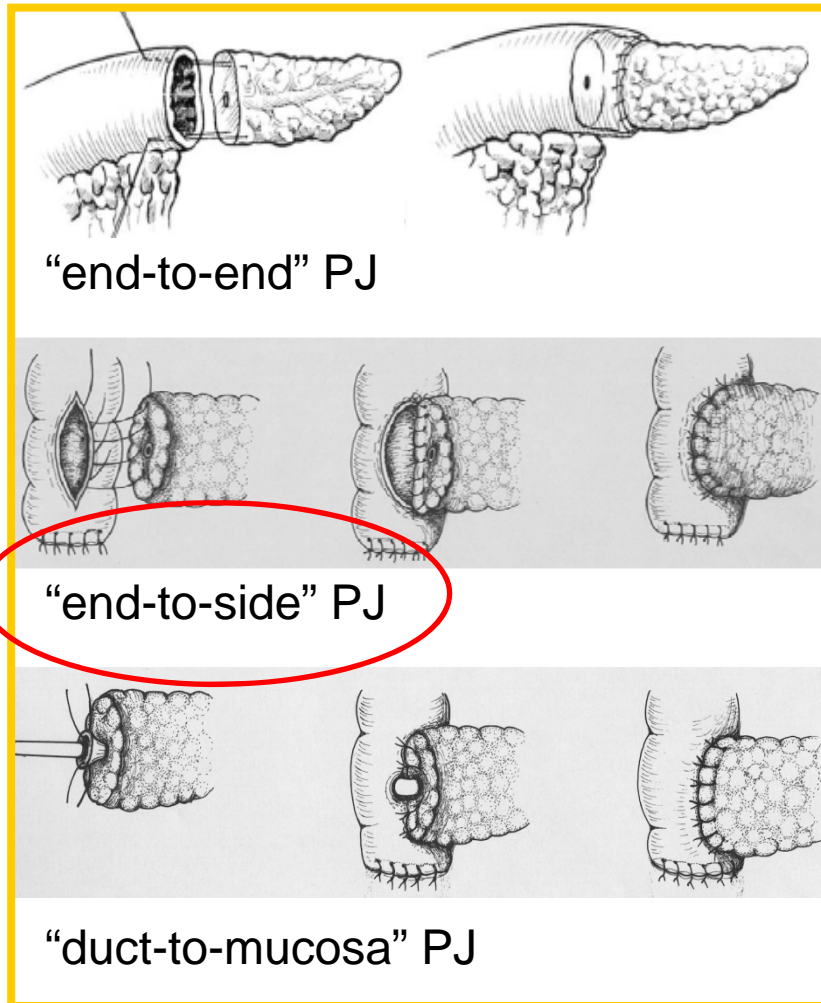


RESECTION COMPLETED!

And now...

RECONSTRUCTION!

The “dilemma” of pancreatic anastomosis



[Ann Surg. 2008 Dec;248:930-8.](#)

Pancreatogastrostomy with gastric partition after pylorus-preserving pancreaticoduodenectomy versus conventional pancreatojejunostomy: a prospective randomized study.

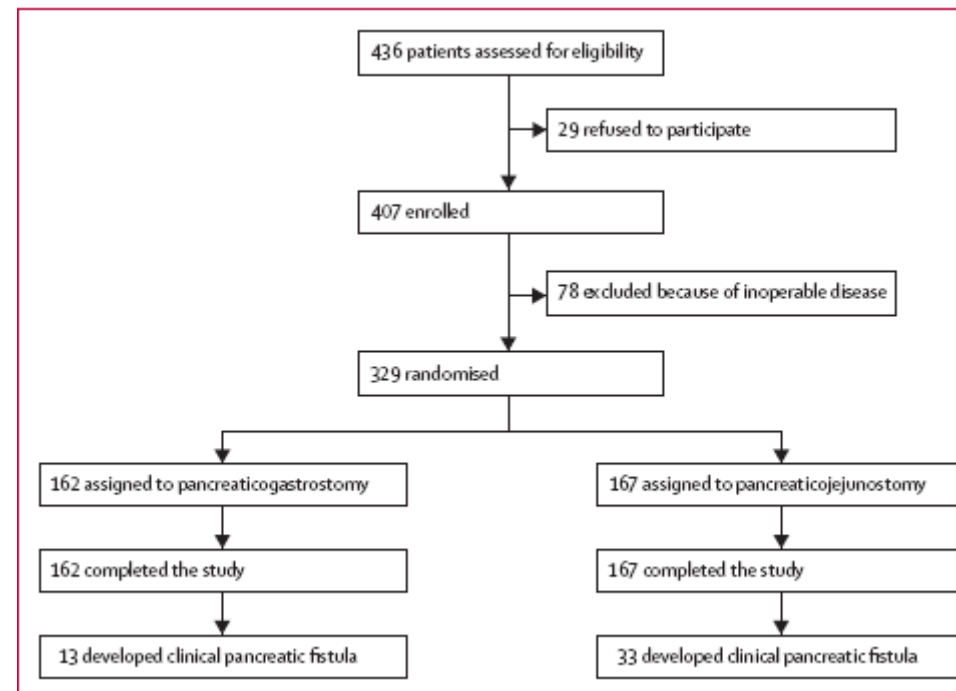
[Fernández-Cruz L et al](#)

- **New technique; the gastroepiploic arcade is preserved. Gastric partition was performed using 2 endo-Gia staplers along the greater curvature of the stomach, 3 cm from the border. This gastric segment, 10 to 12 cm in length is placed in close proximity to the cut edge of the pancreatic stump. An end-to-side, duct-to-mucosa anastomosis (with pancreatic duct stent) is constructed.**
- **RESULTS:**
- **The incidence of pancreatic fistula was 4% after PPPD-GP and 18% after PPPD-PJ (P < 0.01). The mean + SD hospital stay was 12 +/- 2 days after PPPD-GP and 16 +/- 3 days after PPPD-PJ.**
- **CONCLUSIONS:**
- **This study shows that PPPD-GP can be performed safely and is associated with less complication than PPPD-PJ. The advantage of this technique over other PG techniques is that the anastomosis is outside the area of the stomach where the contents empty into the jejunum, but pancreatic juice drains directly into the stomach**

Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial



Baki Topal, Steffen Fieuws, Raymond Aerts, Joseph Weerts, Tom Feryn, Geert Roeyen, Claude Bertrand, Catherine Hubert, Marc Janssens, Jean Closset, on behalf of the Belgian Section of Hepatobiliary and Pancreatic Surgery





Pancreaticojejunostomy versus pancreaticogastrostomy reconstruction after pancreaticoduodenectomy for pancreatic or periampullary tumours: a multicentre randomised trial



NEWS & VIEWS

PANCREAS

Reconstruction methods after pancreaticoduodenectomy

Giuseppe Malleo and Claudio Bassi

Pancreaticojejunostomy and pancreaticogastrostomy are both used for reconstruction after pancreaticoduodenectomy; which method is best is still debated. A nationwide multicentre randomized clinical trial that compared these two types of reconstruction has demonstrated that pancreaticogastrostomy is associated with a substantially lower rate of clinically relevant postoperative pancreatic fistula than pancreaticojejunostomy.

Malleo, G. & Bassi, C. *Nat. Rev. Gastroenterol. Hepatol.* advance online publication 25 June 2013; doi:10.1038/nrgastro.2013.114

than pancreaticojejunostomy.

Malleo, G. & Bassi, C. *Nat. Rev. Gastroenterol. Hepatol.* advance online publication 25 June 2013; doi:10.1038/nrgastro.2013.114

pancreaticojejunostomy group than in the pancreaticogastrostomy group.

The study by Topal and co-workers is the largest multicentre randomized trial comparing the principal reconstruction methods after pancreaticoduodenectomy to date. The study design is pragmatic with respect to certain technical aspects. All the anastomoses were performed using an end-to-side telescoped technique (into the jejunum or the posterior wall of the stomach), but the type and thickness of the suture materials and the number of suture layers were based on the surgeon's judgment. In our opinion, this variability is unavoidable in a multicentre setting and might not be a major point affecting the interpretation of the results.

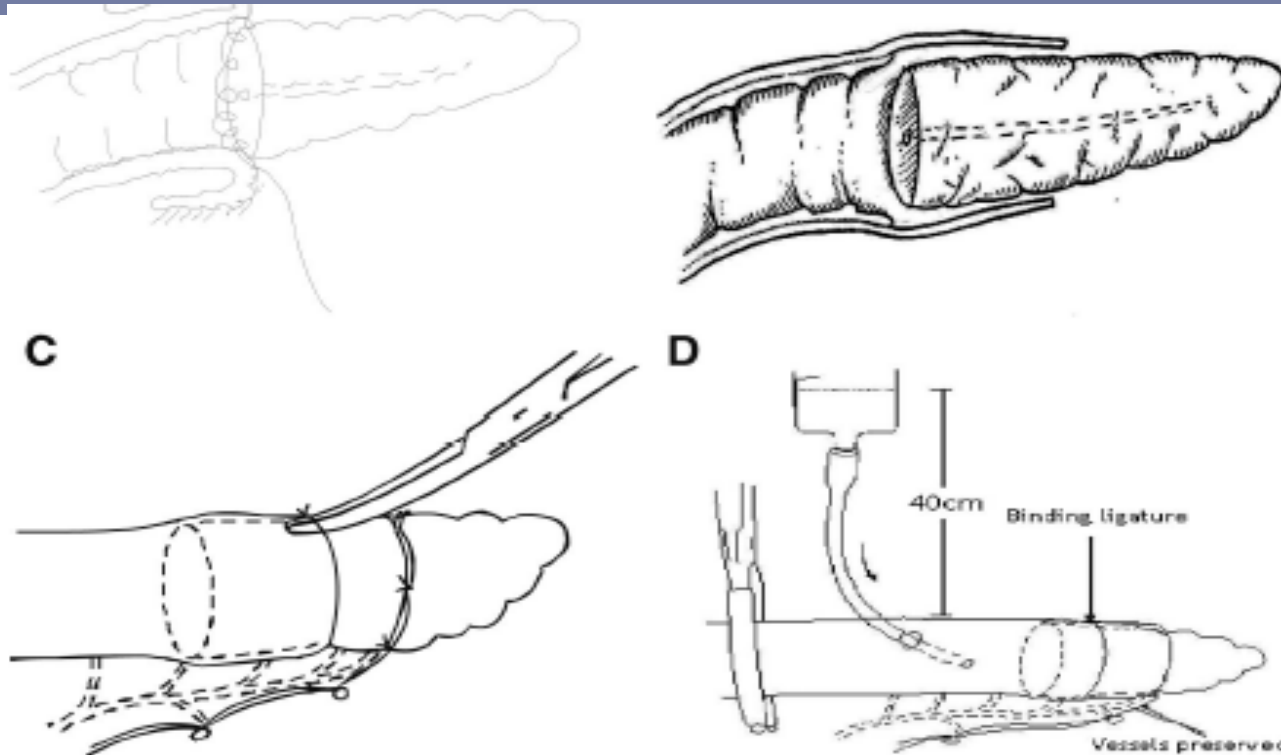
on the surgeon's judgment. In our opinion, this variability is unavoidable in a multicentre setting and might not be a major point affecting the interpretation of the results.



Conventional Versus Binding Pancreaticojejunostomy After Pancreaticoduodenectomy A Prospective Randomized Trial

Shu You Peng et al.

(*Ann Surg* 2007;245: 692–698)



The overall p.o. complications developed in 37% in the conventional group compared with 24.5% in the binding group (P 0.048). Seven patients (6.3%) died in the conventional group compared with 3 patients (2.8%) in the binding group (P 0.37).

My answer is

Bassi C et al (Surgery, 2003 – Ann Surg, 2005 – J Gastroint Surg, 2006)

- From EBM (Evidence-based medicine)

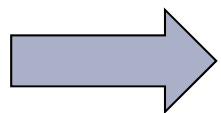


PJ and PG show similar results
(Wente M et al. Am J Surg, 2007)



DO NOT use glues!

- From ExBM (Experience-based medicine)



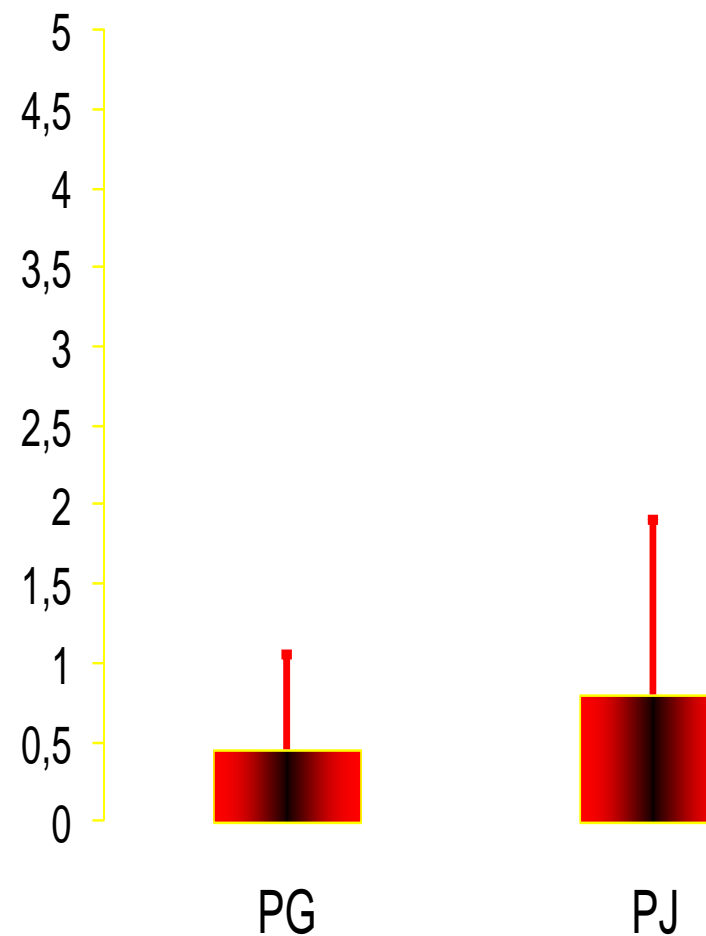
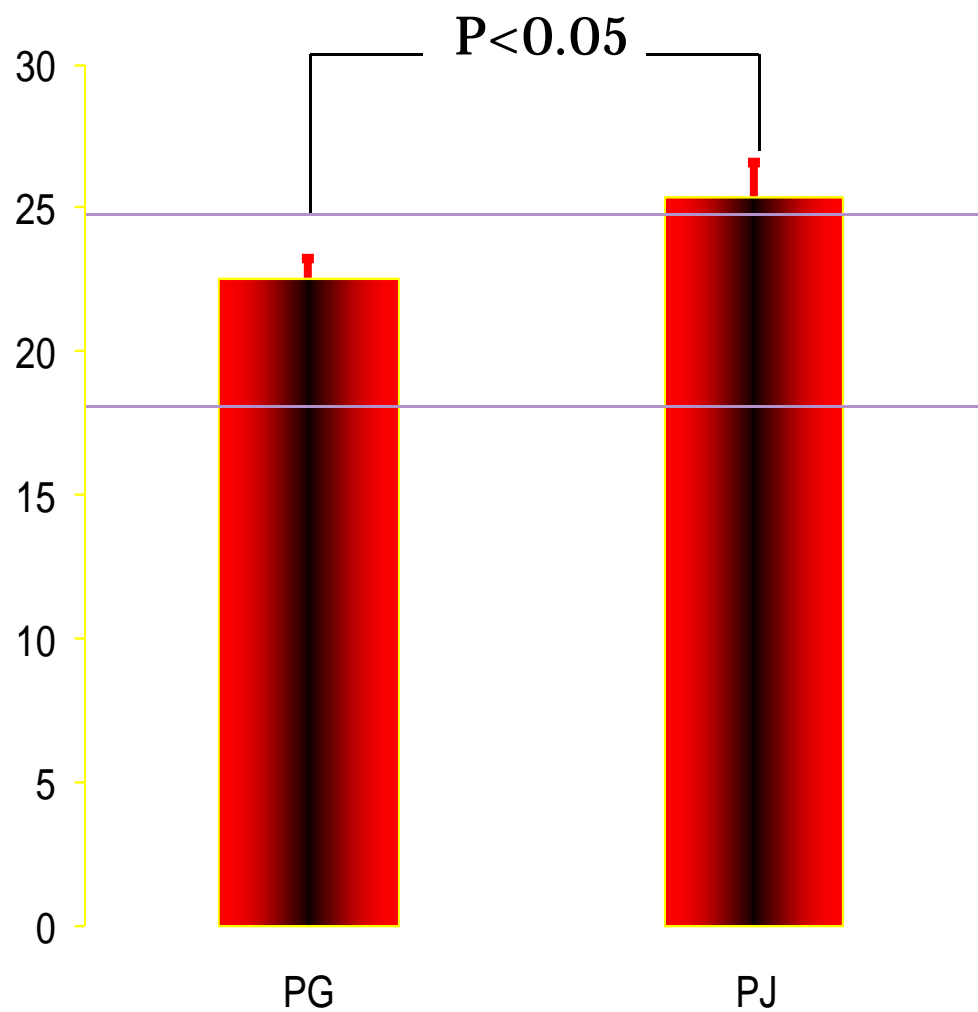
Hard pancreas? I do end-to-side pancreaticojejunostomy
Soft Pancreas? I do open pancreaticogastrostomy



Mobilize the gland

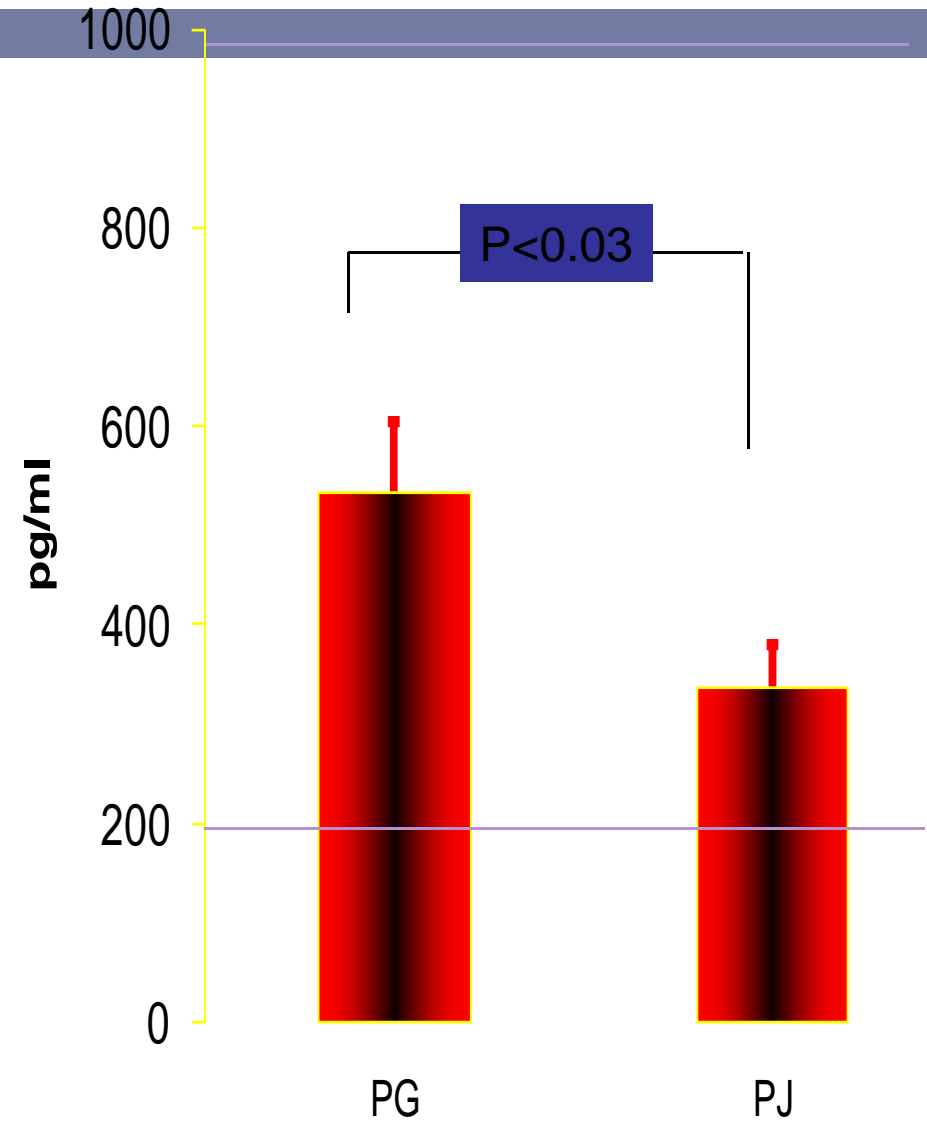
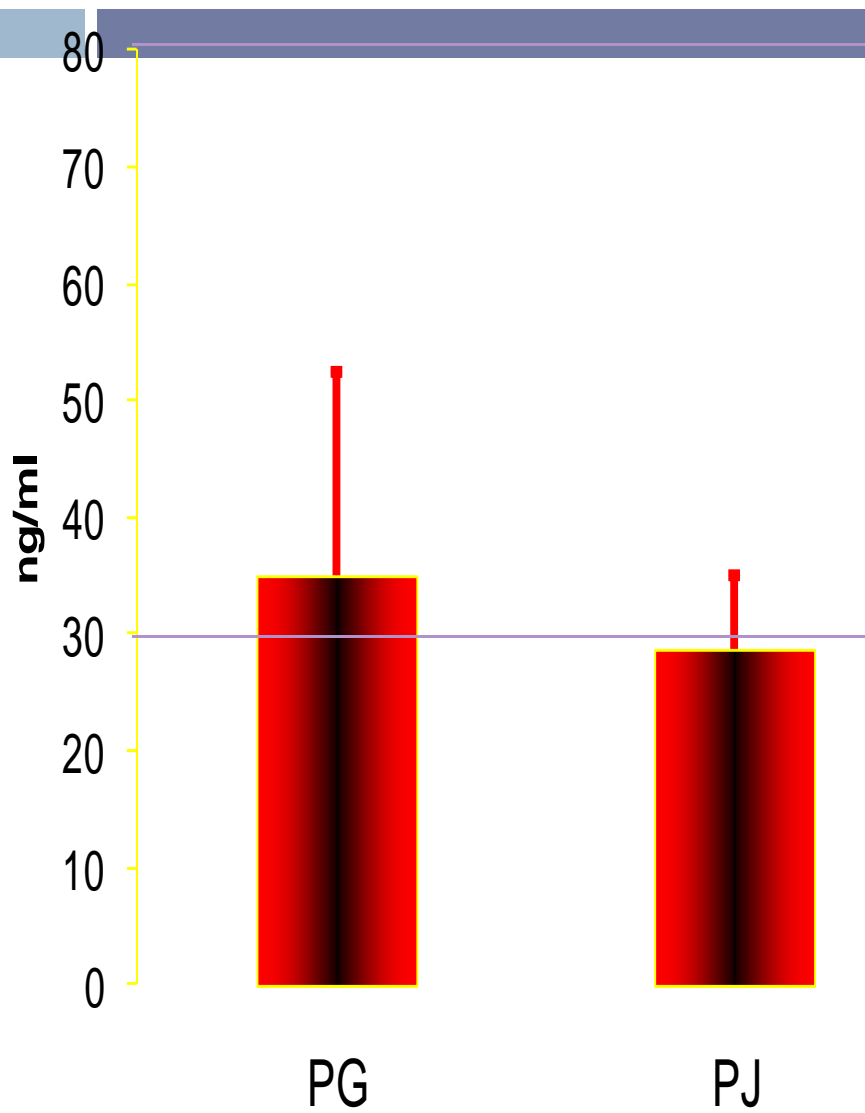
BMI attuale

Differenza BMI



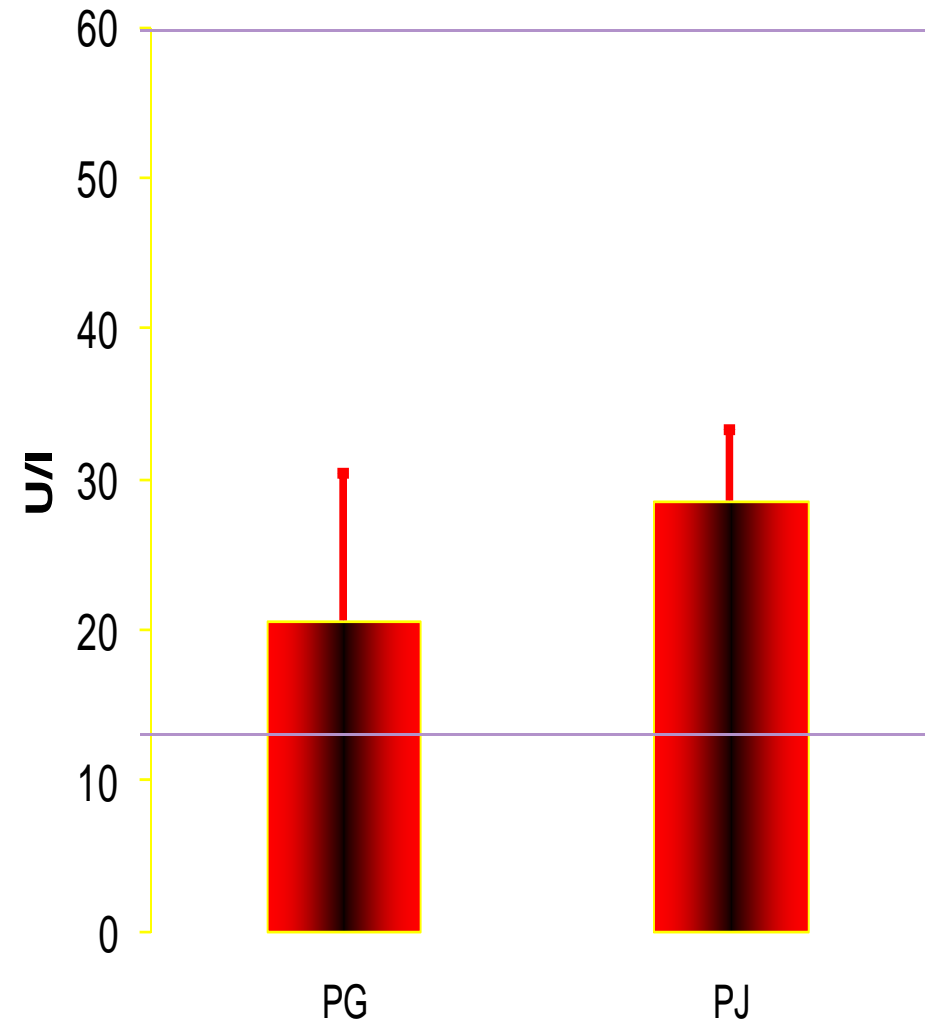
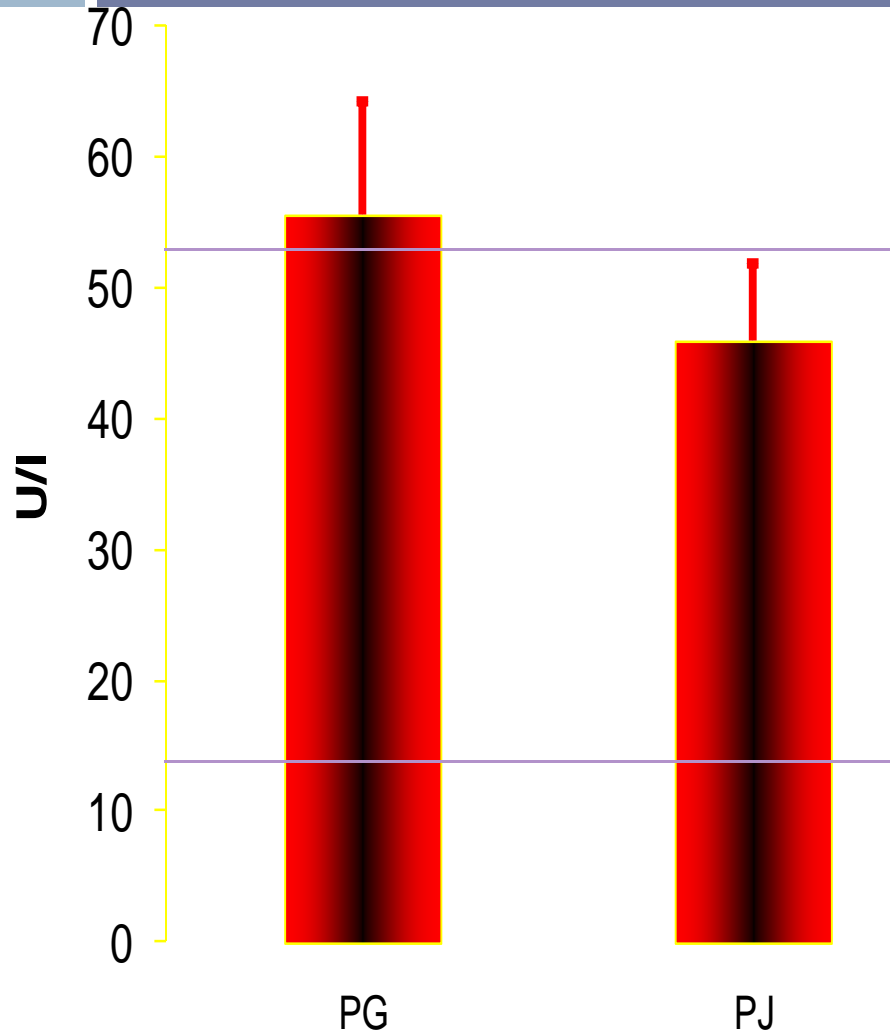
Vit D

Vit B₁₂

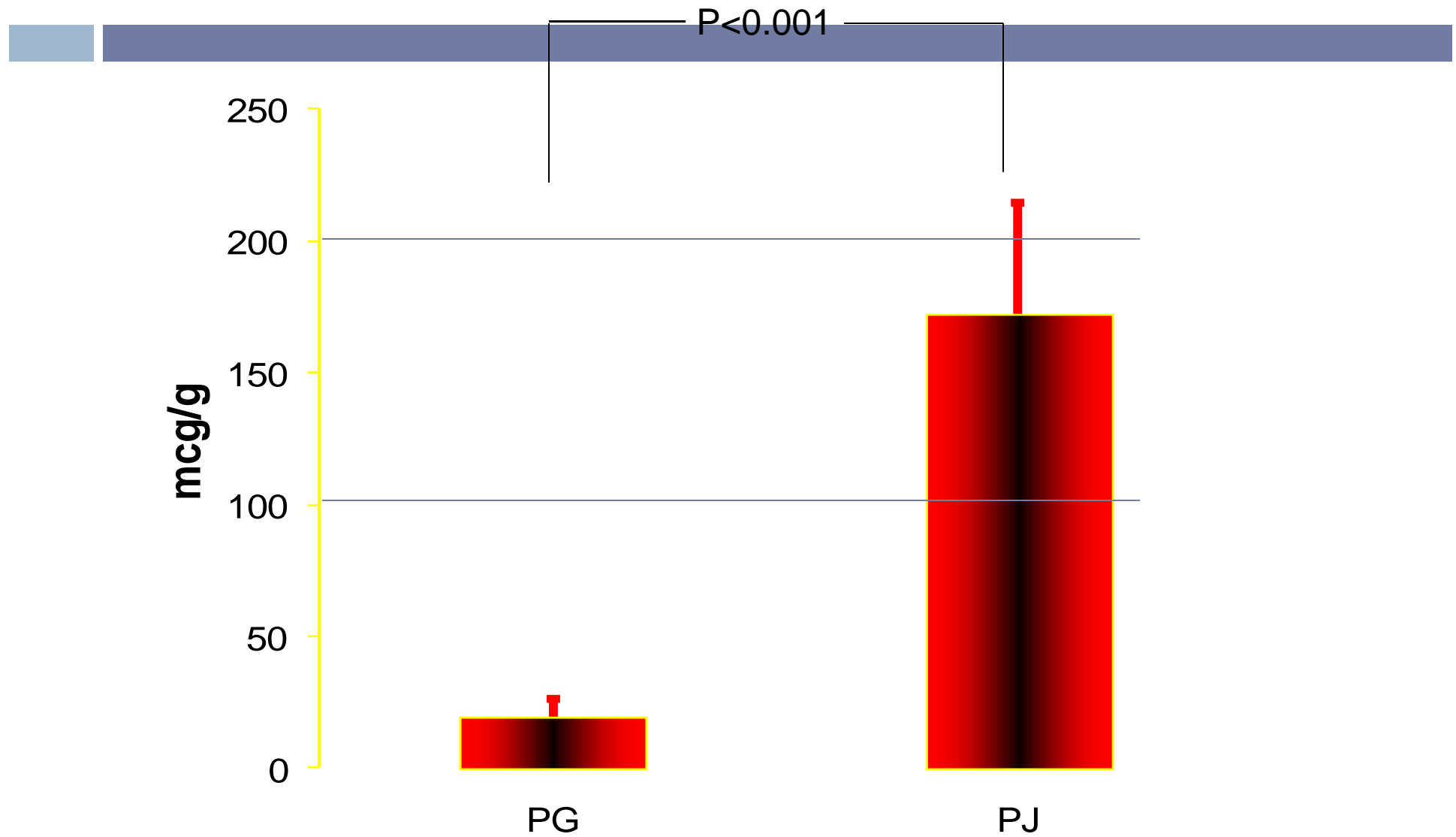


p-Ams

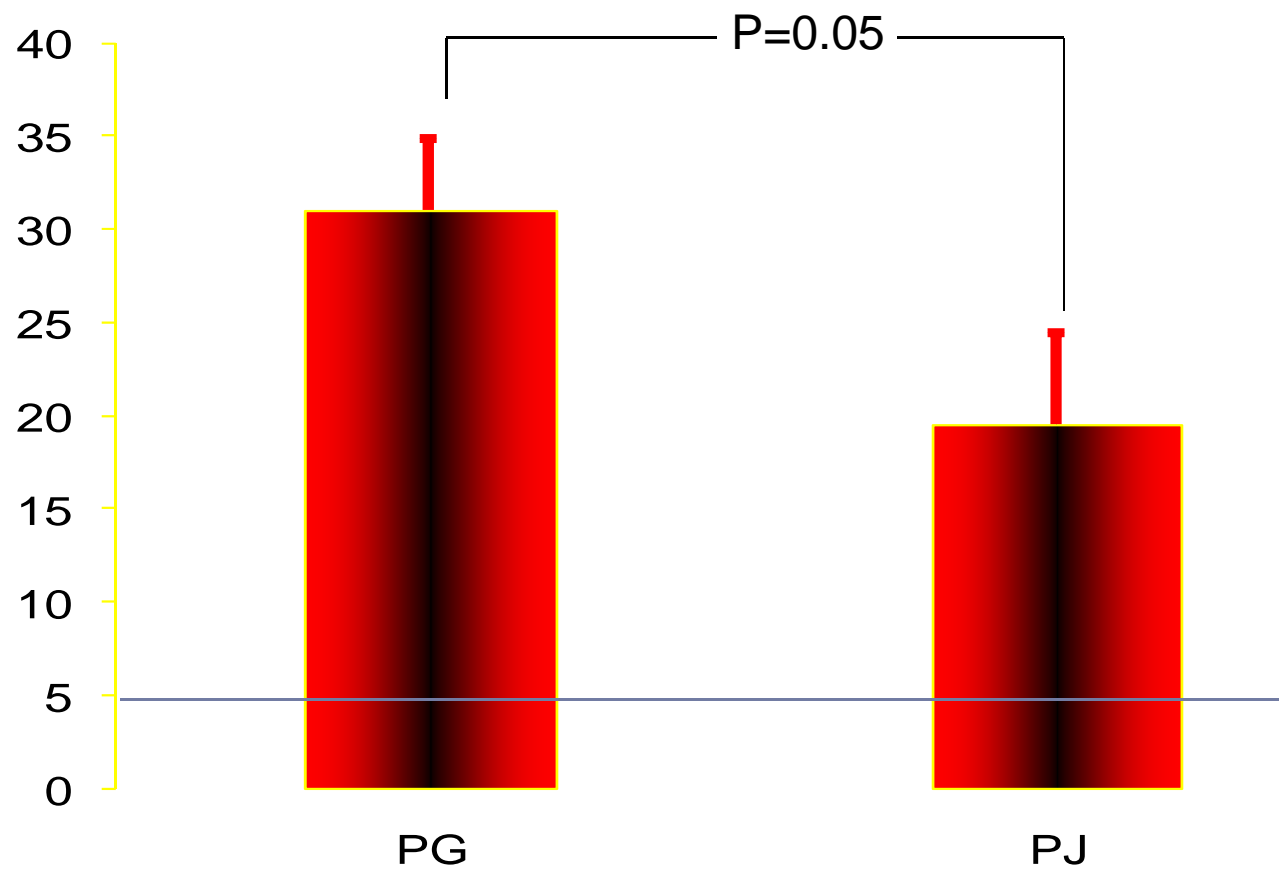
Lipasi



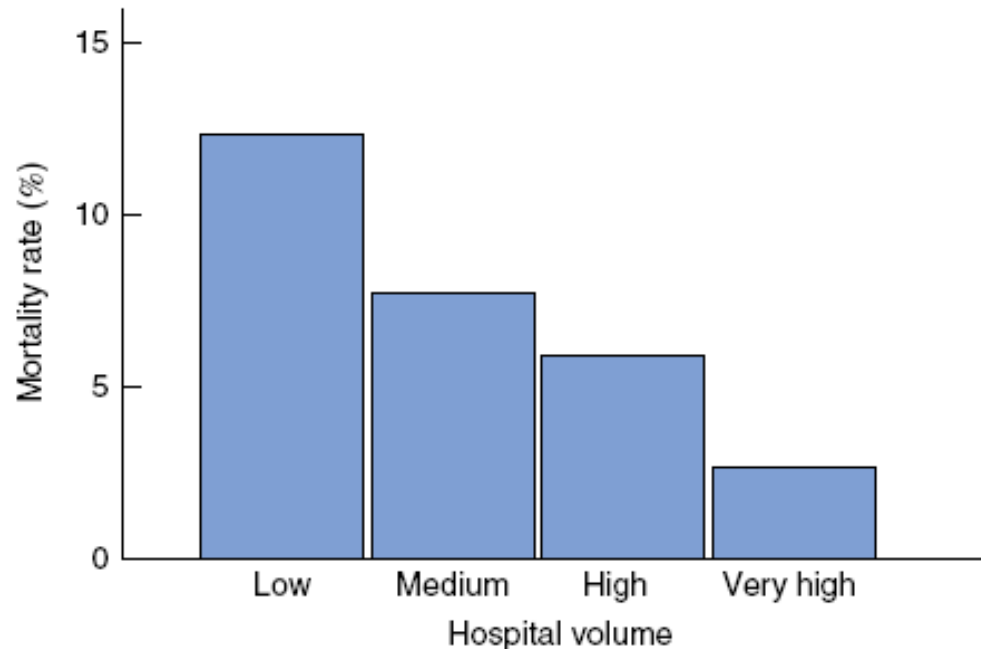
Elastasi 1



Steatorrea



Pancreaticoduodenectomy: the Italian situation



“If all patients had received the standard of treatment offered by the two very high-volume hospitals (Verona and S.Raffaele Hospital, Milan), **68.0% of operative deaths (87 of 128) would have been prevented**, and **4647 days** of hospital stay **would have been saved in 2003.**”

Balzano et al. Br J Surg. 2008;95:357-62

... and not only the surgeon ... also the whole team !!!

ITALIAN SITUATION

Procedure	Low volume	High volume
	%	%
DCP	12.4	2.6
DP	3.8	0
TP (!?)	23.7 (!?)	0 (!!)
Others	9.9	0



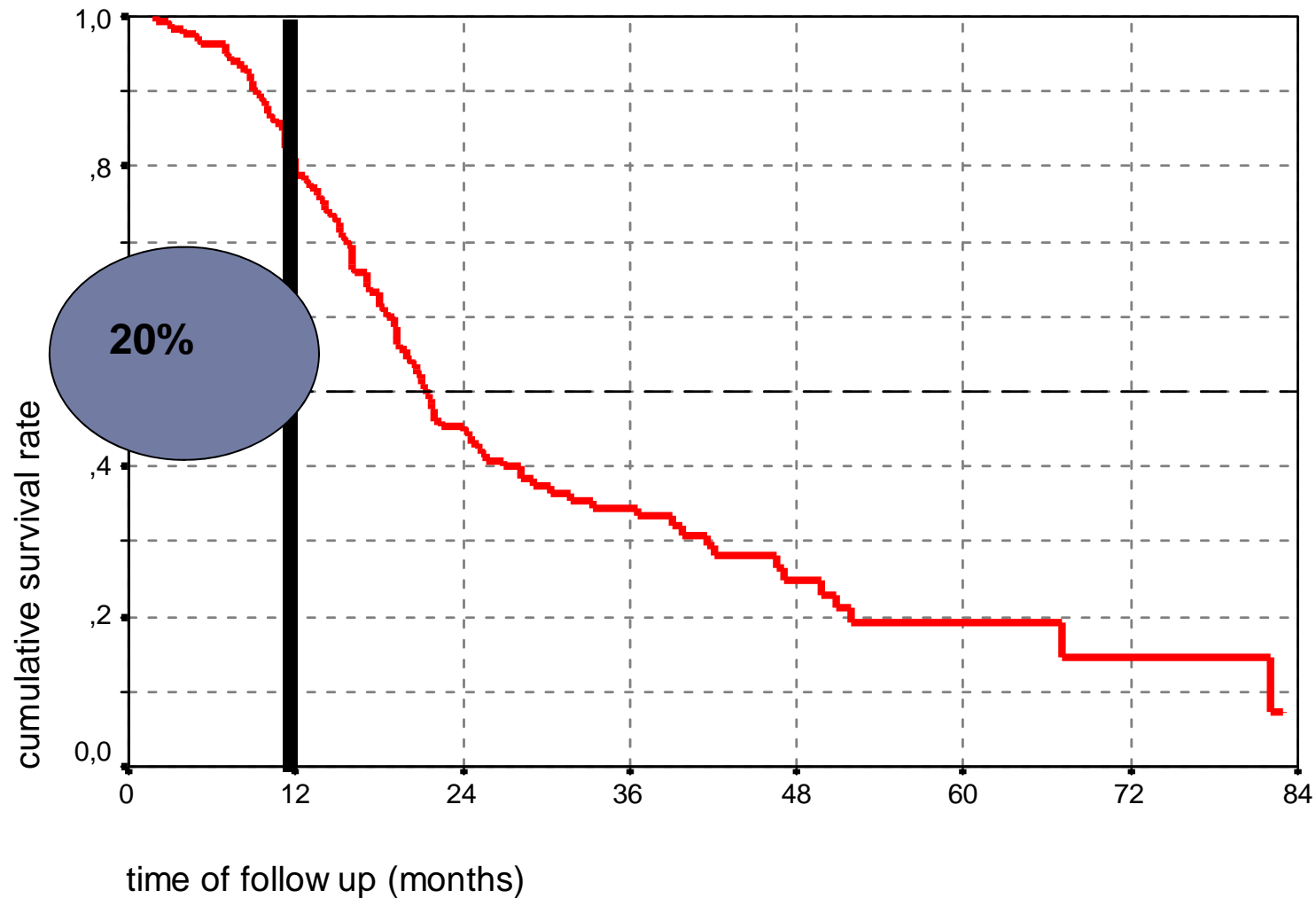
VOLUME AND OUTCOME (2012)



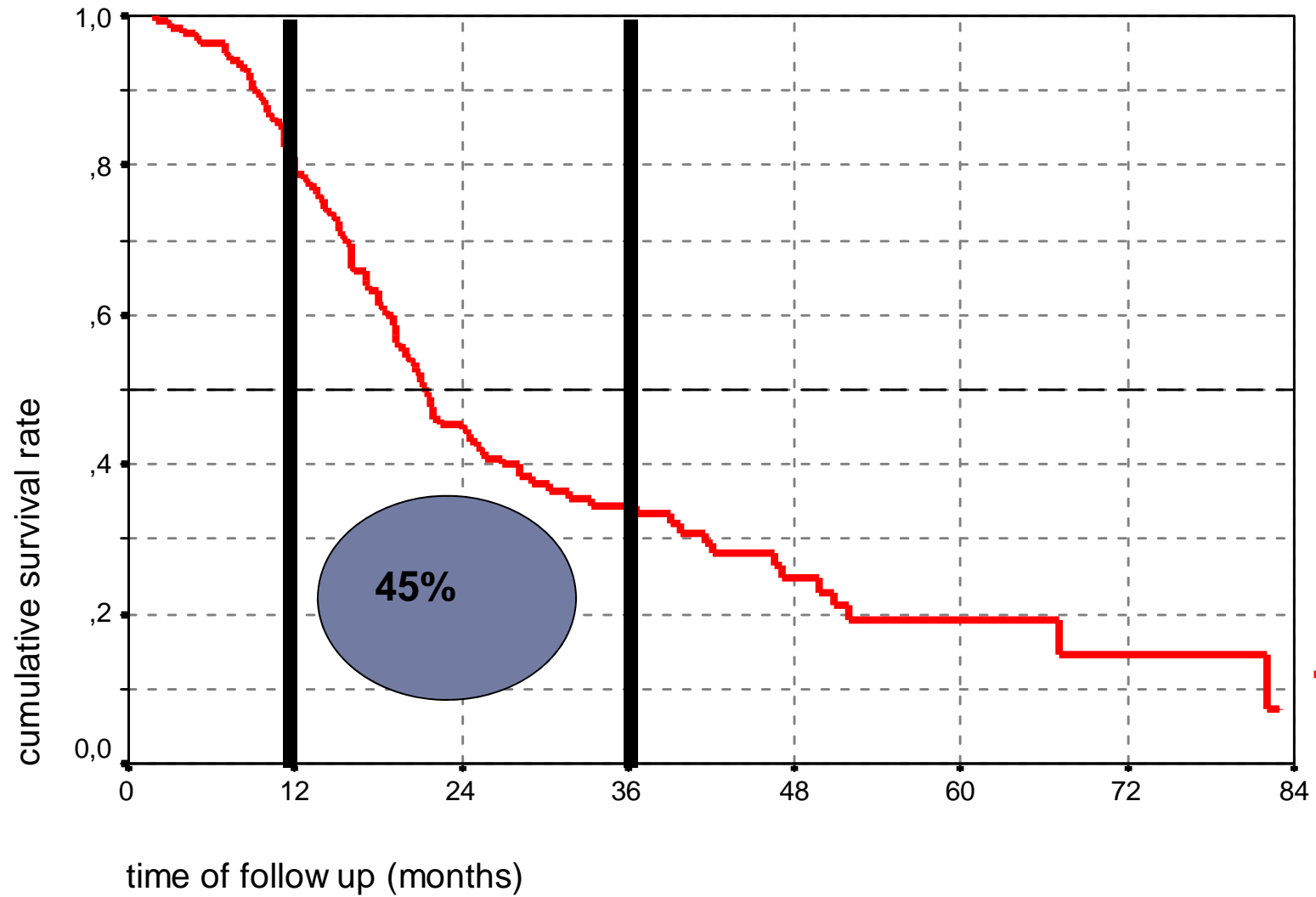
THE VERONA-PESCHIERA SURGICAL NETWORK

PANCREATIC RESECTIONS	380
Pancreaticoduodenectomy	247
Distal Pancreatectomy	90
Total pancreatectomy	19
Enucleation	10
Middle segment pancreatectomy	13
Other atypical resection (uncinatectomy)	1
Mortality	2.0%
Overall morbidity	45.3%
Reoperation	10.0%
Pancreatic fistula	24.0%
Abdominal collection	24.9%
Post-pancreatectomy hemorrhage	11.0%
Delayed gastric emptying	7.4%

WRONG INDICATION!



Surgery plays a role, but ...



Surgey is not enough !!!

...at the beginning of any P.C. discussion is that "surgery is the only chance for cure ..."

This statement should be modified to "Radical surgery is the first step to prolong survival in patients with P.C."

W. Traverso 2004

THE MULTIMODALITY'!

ESPAC-1

EUROPEAN STUDY GROUP FOR
PANCREATIC CANCER - TRIAL 1

Adjuvant Therapy in resected Pancreatic Cancer

NEMJ 2004

Adjuvant therapy



“Surgeon, you’re not alone!”

GISTG

EORTC

ESPAC-1

CONKO-001

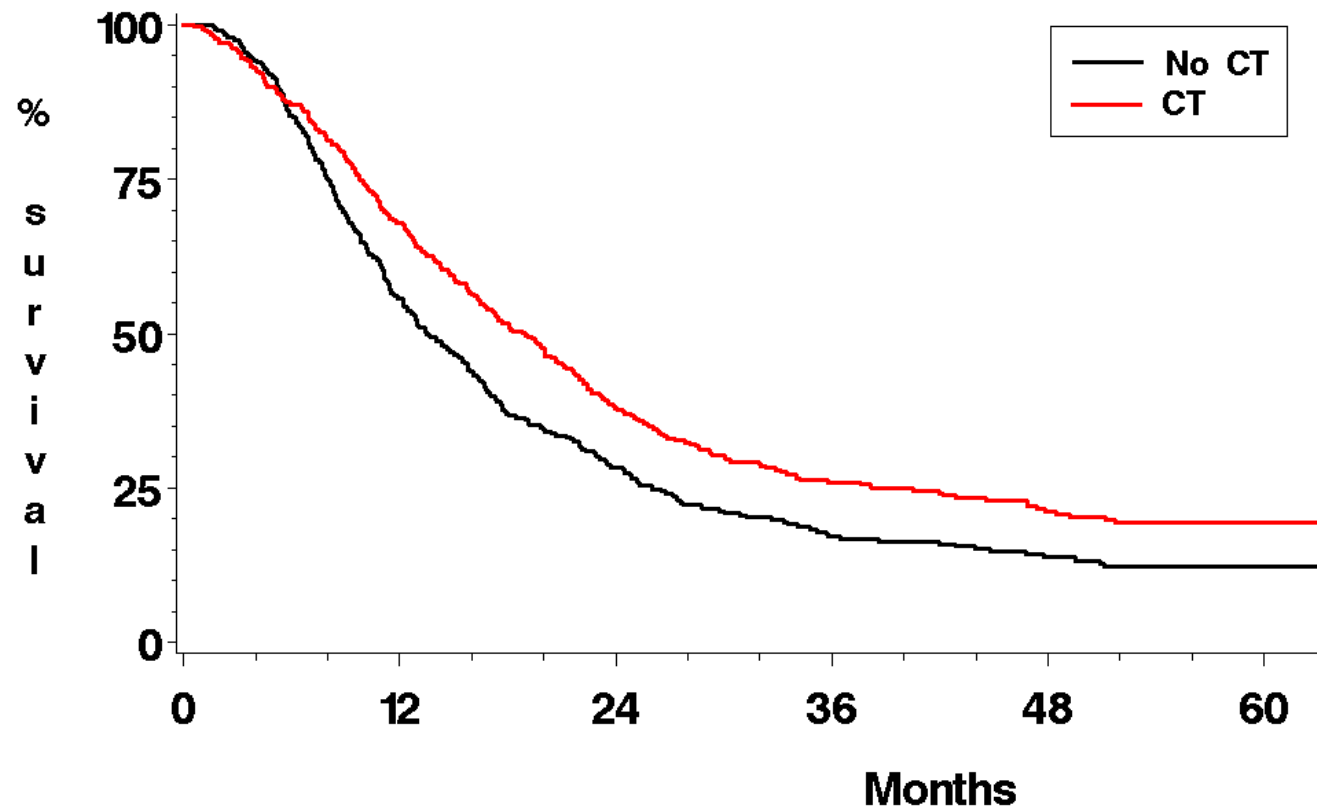
RTOG 97-04

Meta-Analysis of Randomised Adjuvant Therapy Trials for Pancreatic Cancer

Br J Cancer. 2005 Apr 25;92(8):1372-81

Survival by Adjuvant Chemotherapy

Pooled Data from Norwegian, Japanese and ESPAC trials



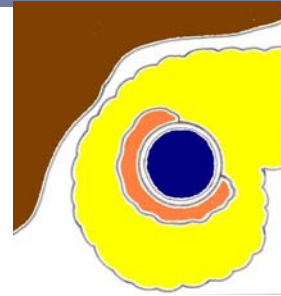
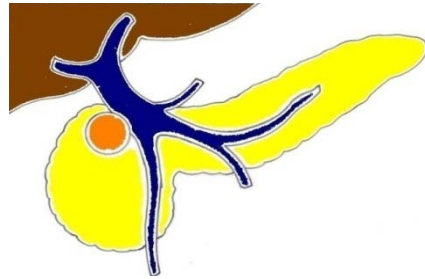
No. at Risk							
No CT	338	184	88	44	29	16	
CT	348	230	125	75	49	33	

THE MULTIMODALITY'!

MANDATORY !!!

**Adjuvant Therapy in resected
Pancreatic Cancer**

“Boderline” & LAPC: whenever vassels involvement is ...



RADICAL SURGERY IS NOT FEASIBLE !



Locally advanced pancreatic carcinoma (LAPC) “best treatment”: chemo & radiotherapy

**Median progression free survival (mPFS) =
6-10 mo**

Median Overall survival (mOS) = 11-15 mo

No treatment, mOS = 6 mo

Gillen et al, PLoS Med, Apr 2010, Vol7, Iss4

Huguet et al., J Clin Oncol 25:326-331, 2007

Krishnan et al, Cancer 110: 47-55, 2007

THE TECHNIQUE: from patient 1 to 50

Original article

Feasibility and safety of radiofrequency ablation for locally advanced pancreatic cancer

R. Girelli¹, I. Frigerio¹, R. Salvia³, E. Barbi², P. Tinazzi Martini² and C. Bassi³

¹Hepatopancreatobiliary Unit and ²Department of Radiology, Pederzoli Clinic, Peschiera del Garda–Verona, and ³Department of Surgery, GB Rossi Hospital, University of Verona, Verona, Italy

Correspondence to: Professor C. Bassi, Surgical and Gastroenterological Department, 'GB Rossi' Borgo Roma Hospital, University of Verona, 37134 – Verona, Italy (e-mail: claudio.bassi@univr.it)

British Journal of Surgery 2010; **97**: 220–225

SLIGHT MODIFICATION TO THE TECHNIQUE IN THE FOLLOWING YEARS WITHOUT CHANGING THE GROSS STRUCTURE

VERONA/PESCHIERA GROUP RFA 2007- 2012

250 PATIENTS

M/F	166/84
MEDIAN AGE	64 yo
TUMOR SITE head/body tail	187/63
TUMOR SIZE median (IQR)	35mm (30-48)
median SURVIVAL	19.5 months
RELATED MORBILITY	10%
MORTALITY	2%

WS

1999 10/19
2000 6/14
2001 7/14

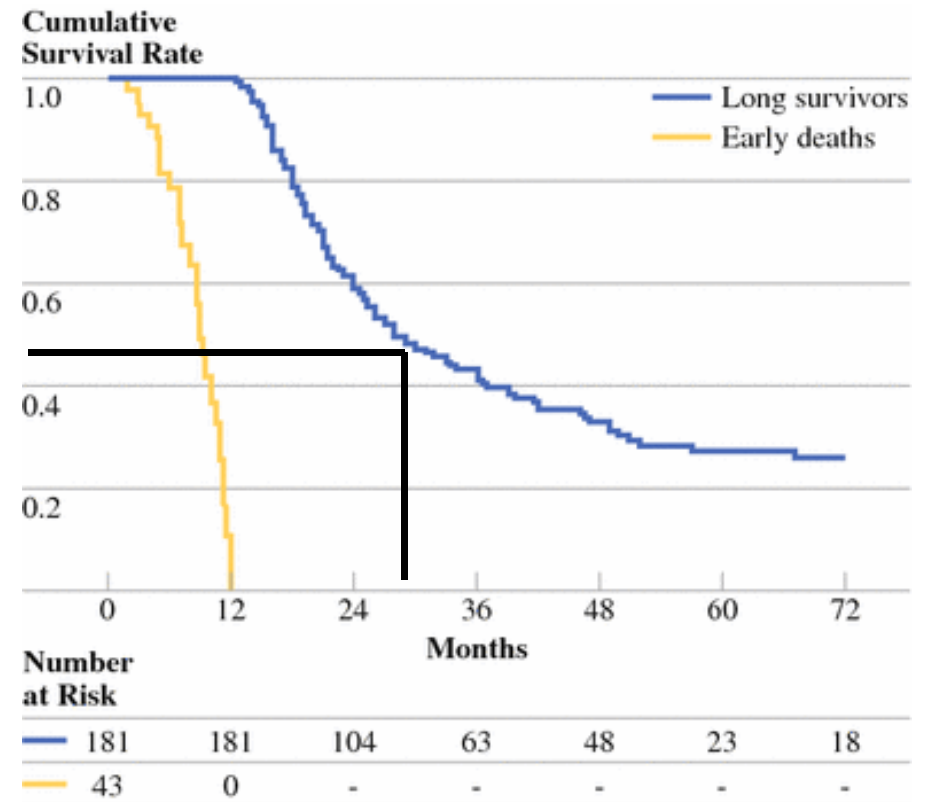
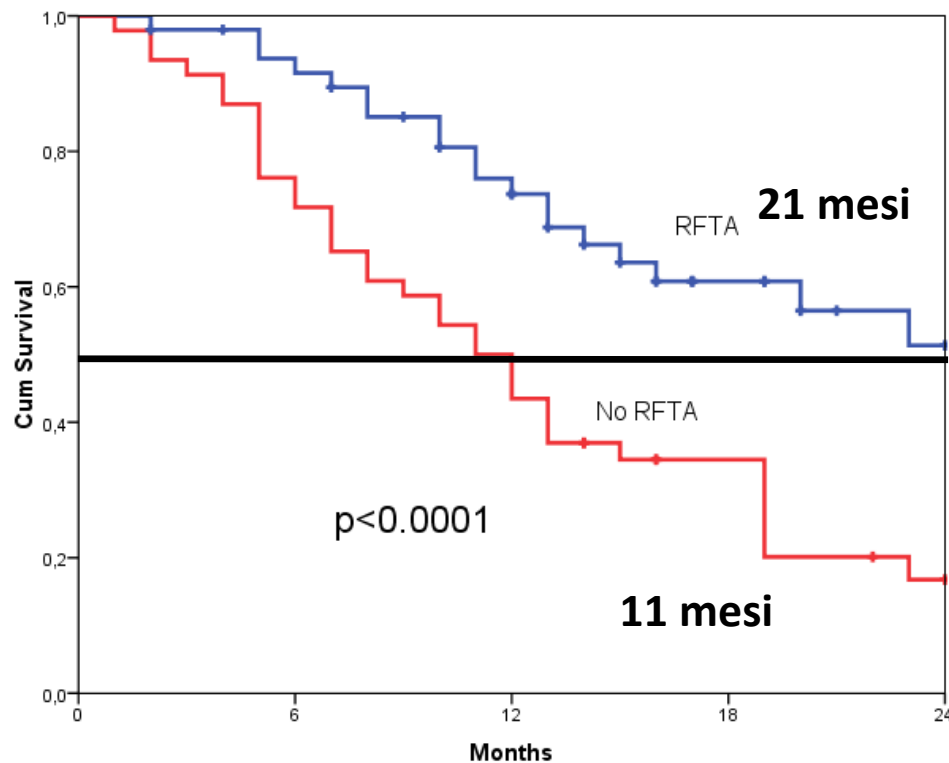
CAUTION

**THIS MACHINE
HAS NO BRAIN
USE YOUR OWN**



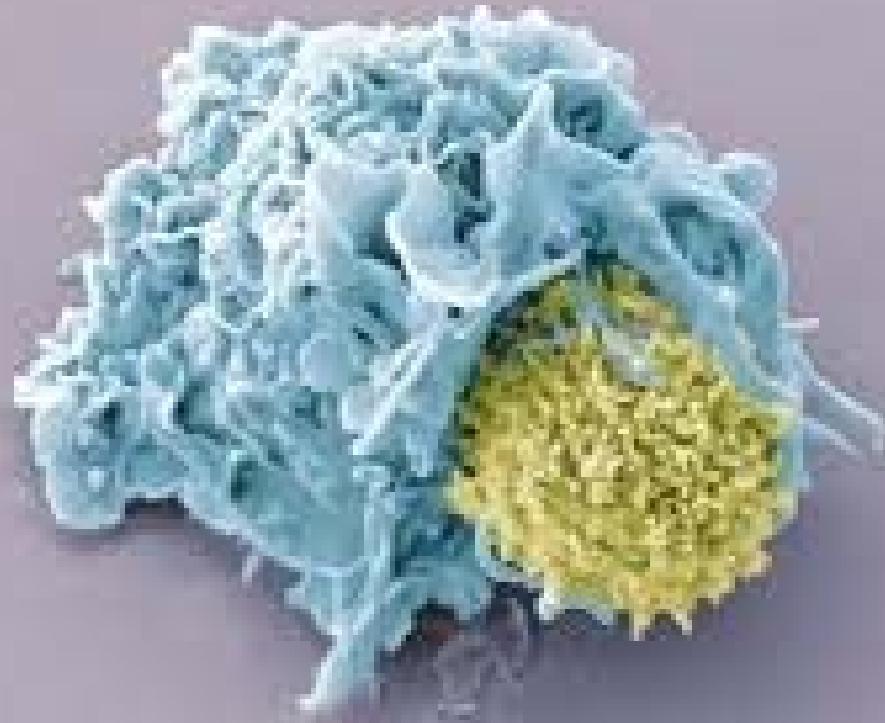
Can we do it?

Disease specific survival



Barugola et al; Resectable Pancreatic Cancer: Who Really Benefits From Resection? Ann Surg Oncol 2009

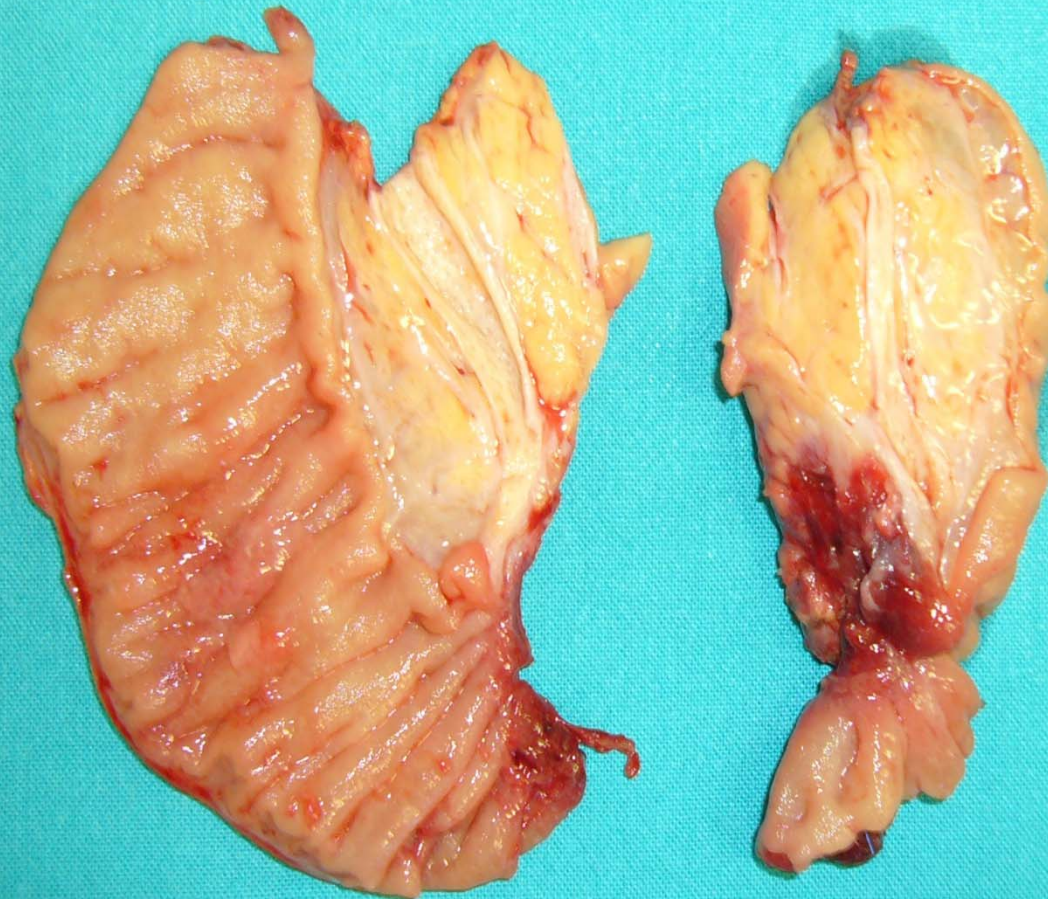
IMMUNOMODULATION ?



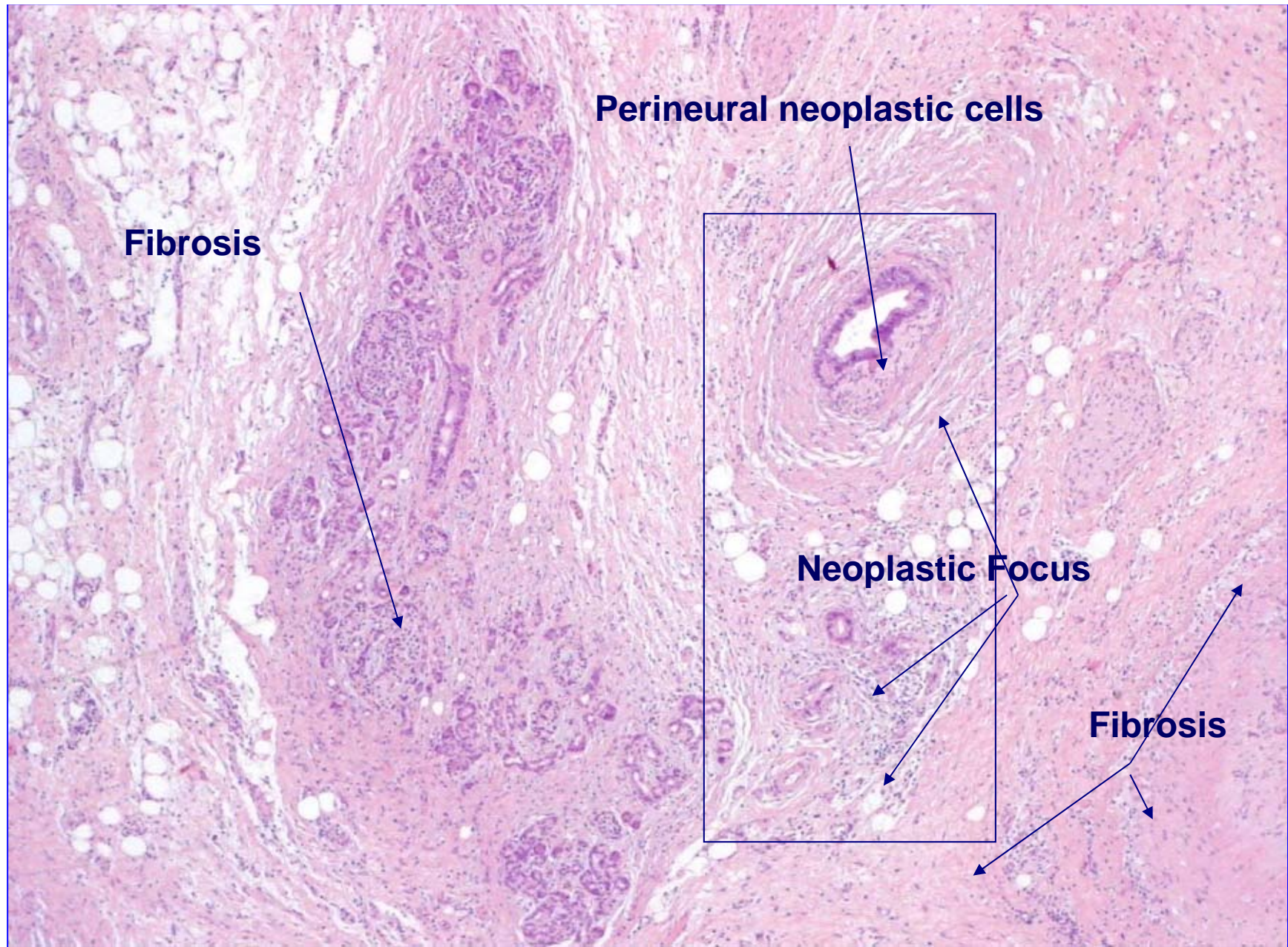
IMMUNOMODULATION ???

- Den Brok et al Efficient loading of dendritic cells following cryo and radiofrequency ablation in combination with immune modulation induces anti-tumour immunity British Journal of Cancer (2006) 95, 896 – 905
- Martijn H et al. In Situ Tumor Ablation Creates an Antigen Source for the Generation of Antitumor Immunity Cancer Research 64, 4024–4029, 2004
- Matuszewski M et al. Impact of radiofrequency ablation on PBMC subpopulation in patients with renal cell carcinoma Urologic Oncology 46:78,2010
- Dromi SA et al. Radiofrequency Ablatio Induces Antigen-presenting Cell Infiltration and Amplification of Weak Tumor-induced Immunity Radiology: 251:58, 2009
- Napoletano C et al. RFA strongly modulates the immune system and anti-tumor immune responses in metastatic liver patients Intational Journal of Oncology 32: 481-490, 2008
- Li-Song T et al. RFA, heat shock protein 70 and potential anti-tumor immunity in hepatic and pancreatic cancer: a minireview. Hepatobiliary Pancreat Dis Int 9:361-365,2010

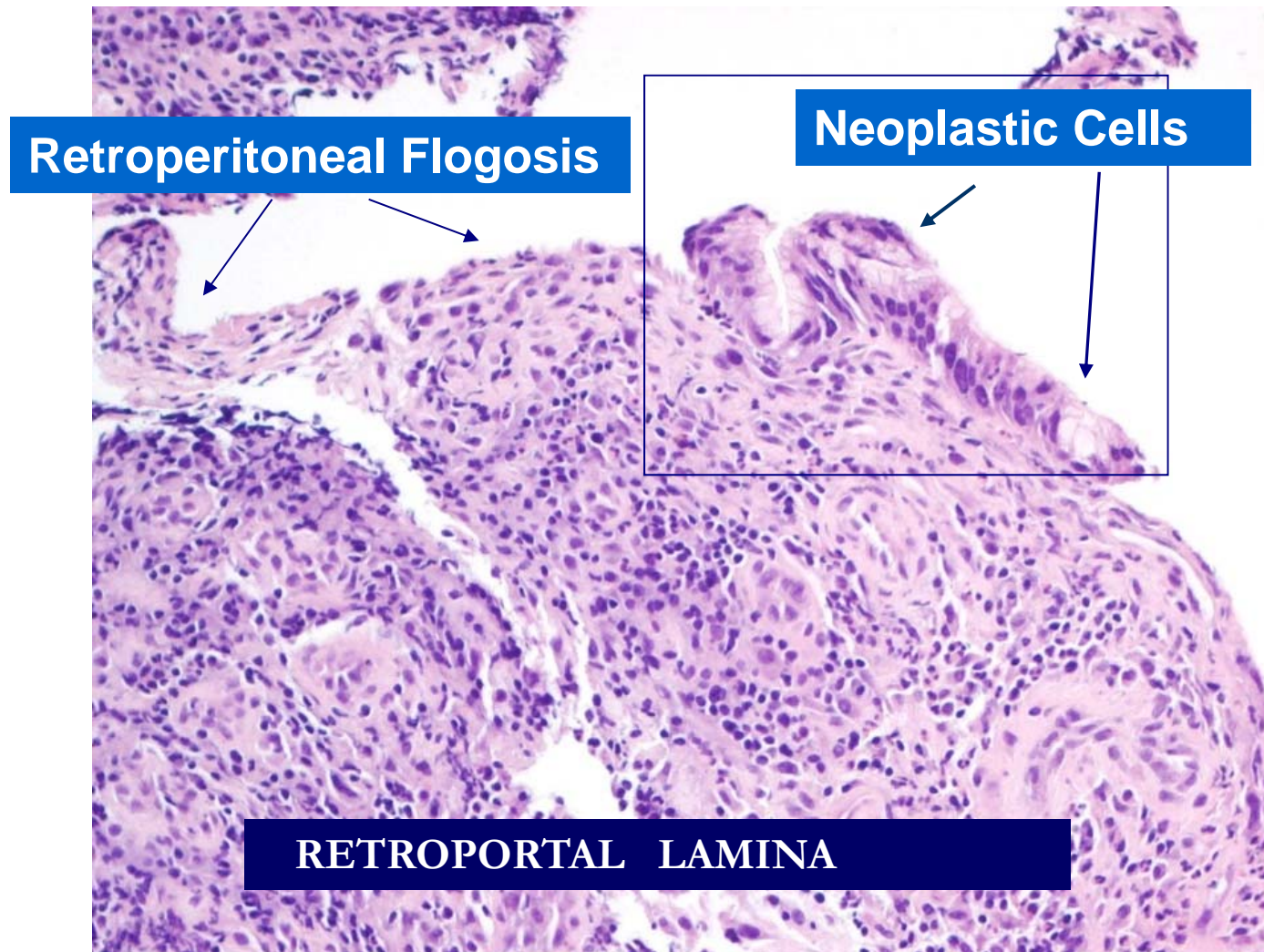
4 cm. Size uncinata process carcinoma



after two months 2 cm. "HARD AREA"

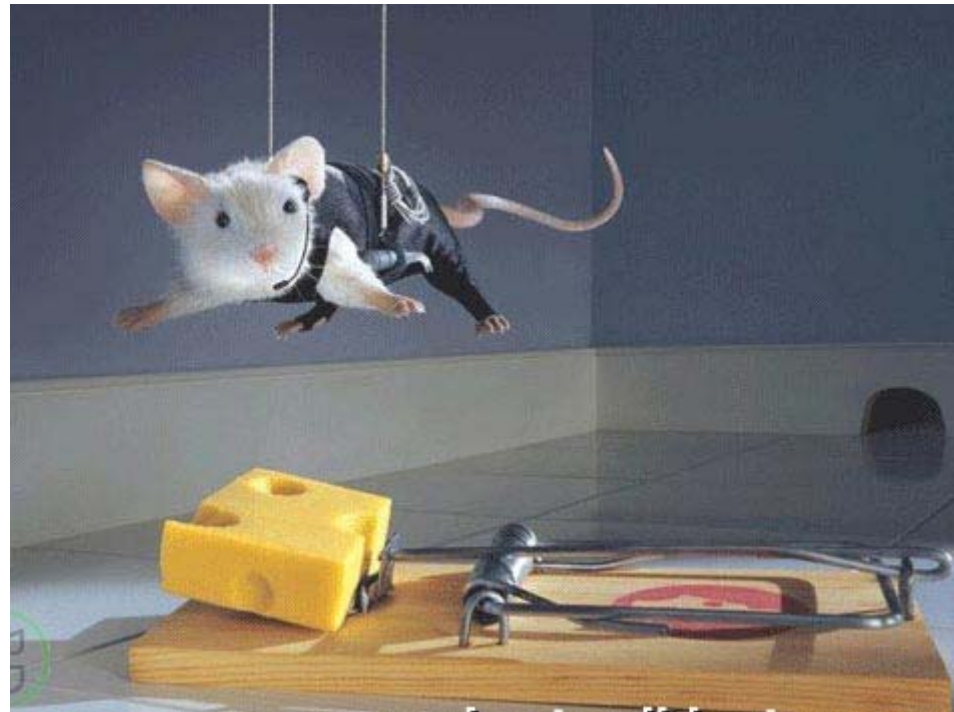


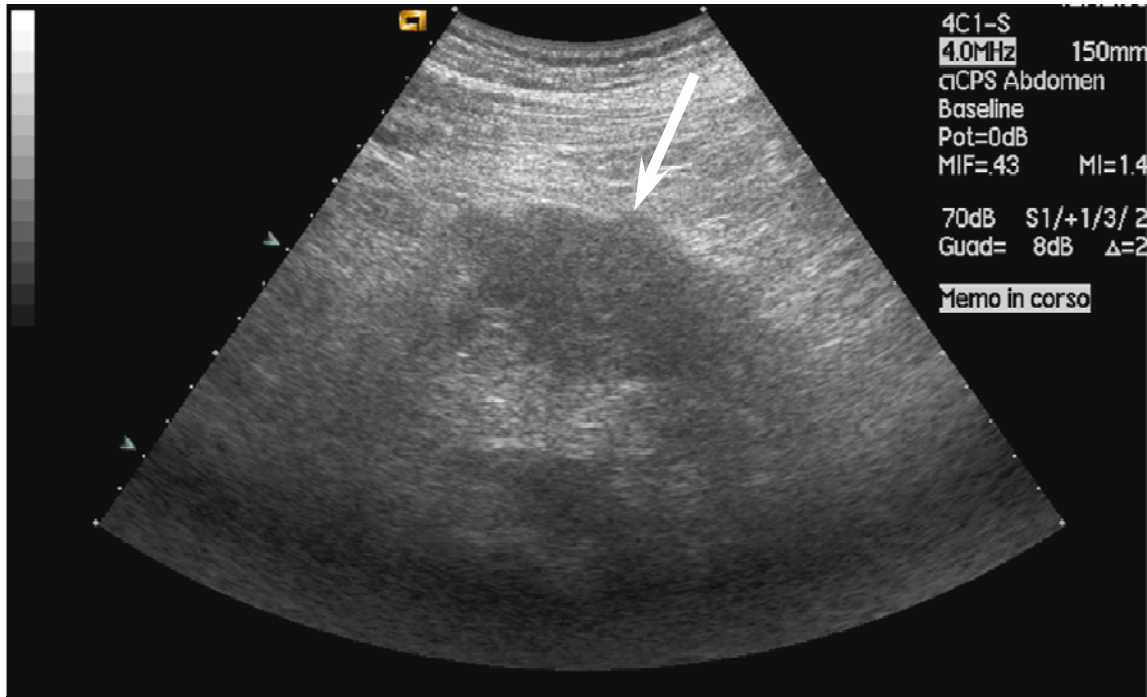
8 mm. area



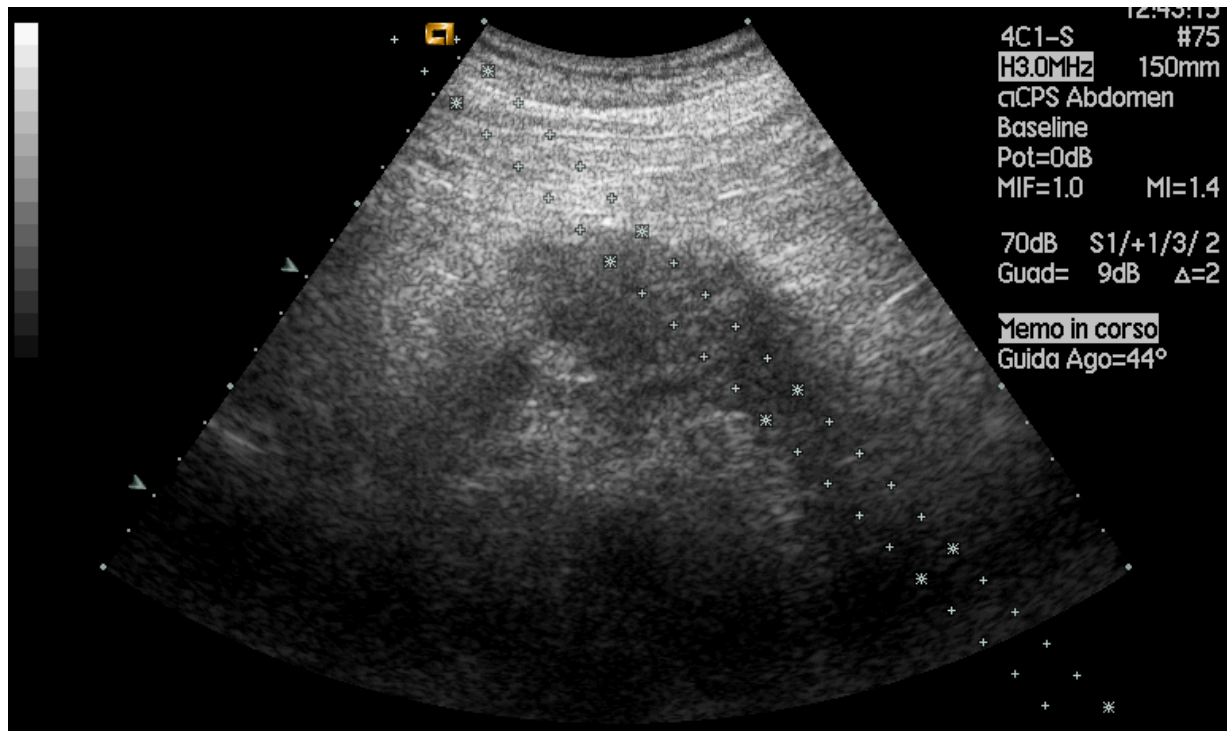
37 ms Follow up : N+

To prolong survival in LAPC is not a mission impossible !



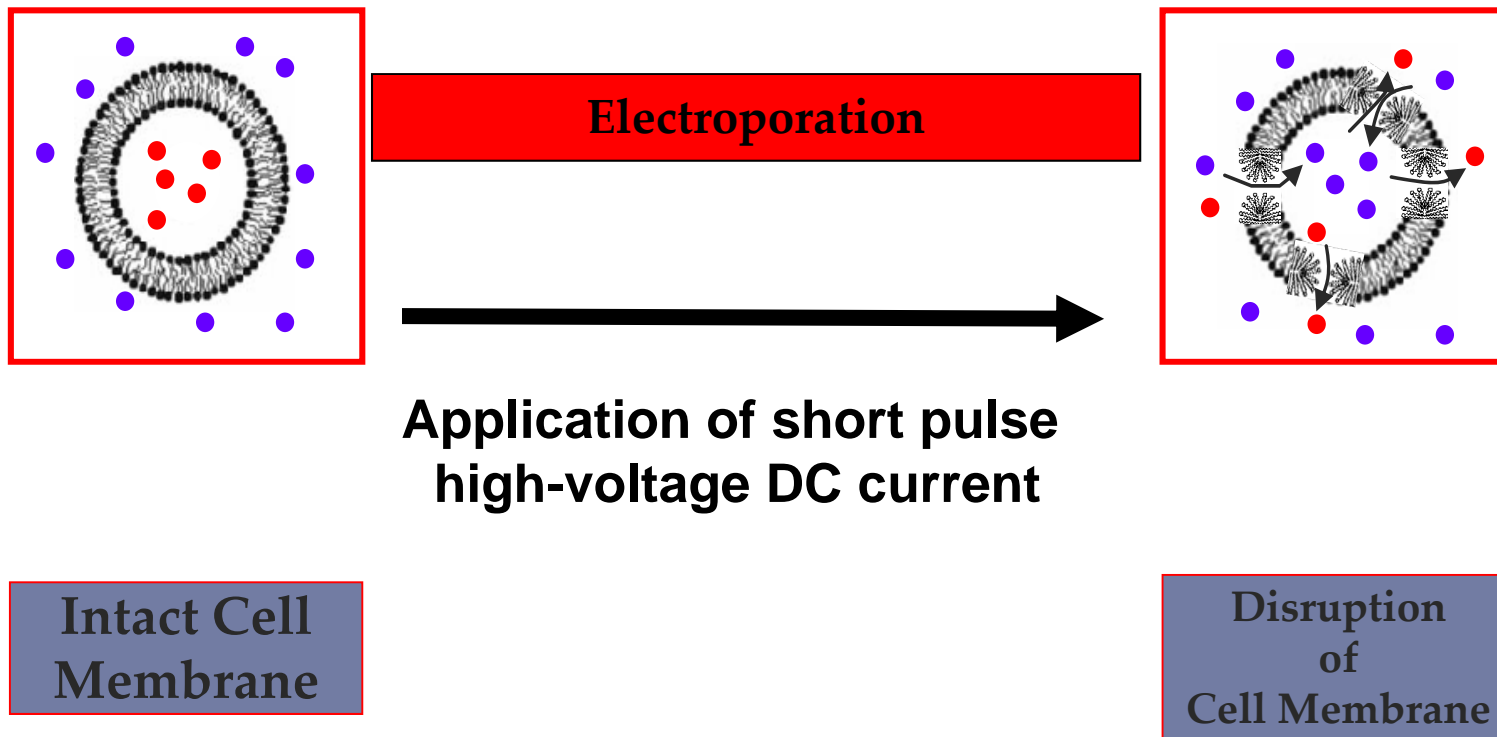


RFA approccio percutaneo



To avoid thermal injuries CELLULAR SURGERY

ELECTROPORATION is a technique that increases the permeability of cell membranes by changing the transmembrane potential resulting in disruption of the cell membrane



PECULIAR CHARACTERISTICS OF IRE

Irreversible disruption of cell membrane integrity without pharmacological addition injury

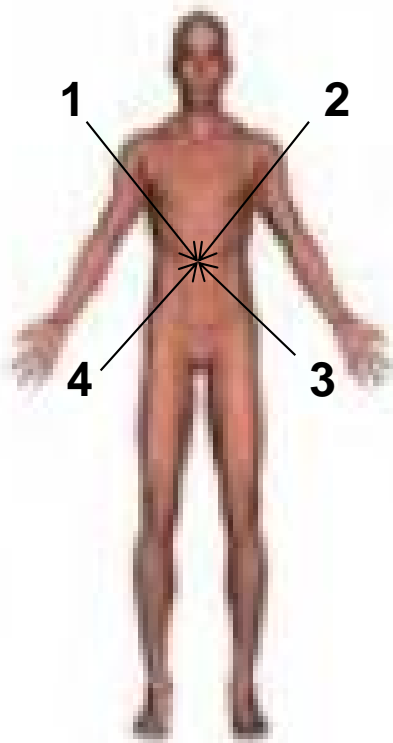
Non-thermal technique

Cells in the ablation region are destroyed but the underlying matrix is not damaged



NanoKnife IRE Procedure

Anterior Probe Placement into 1.5 x 3.0 x 1.5 lesion

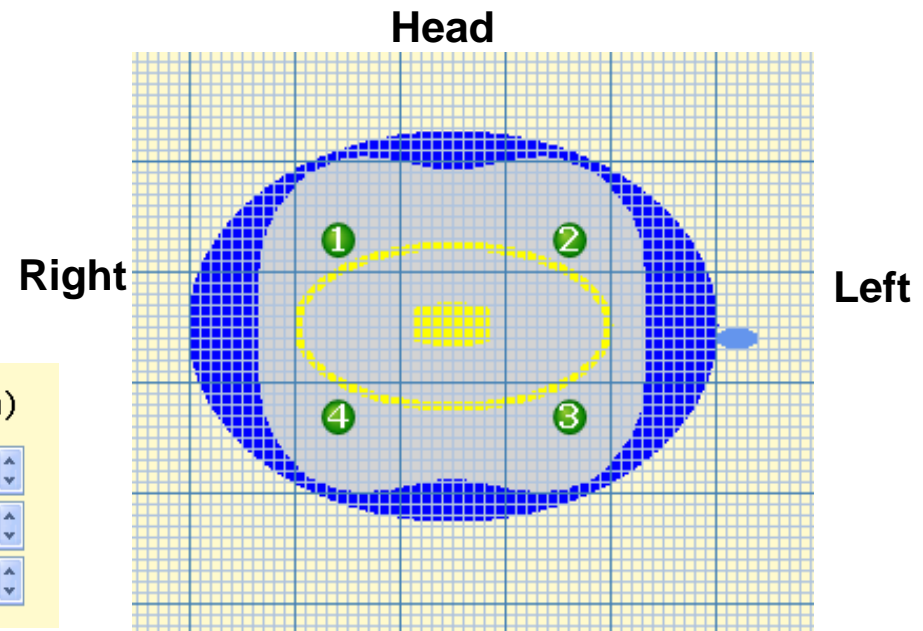


Lesion zone (cm)

Length:

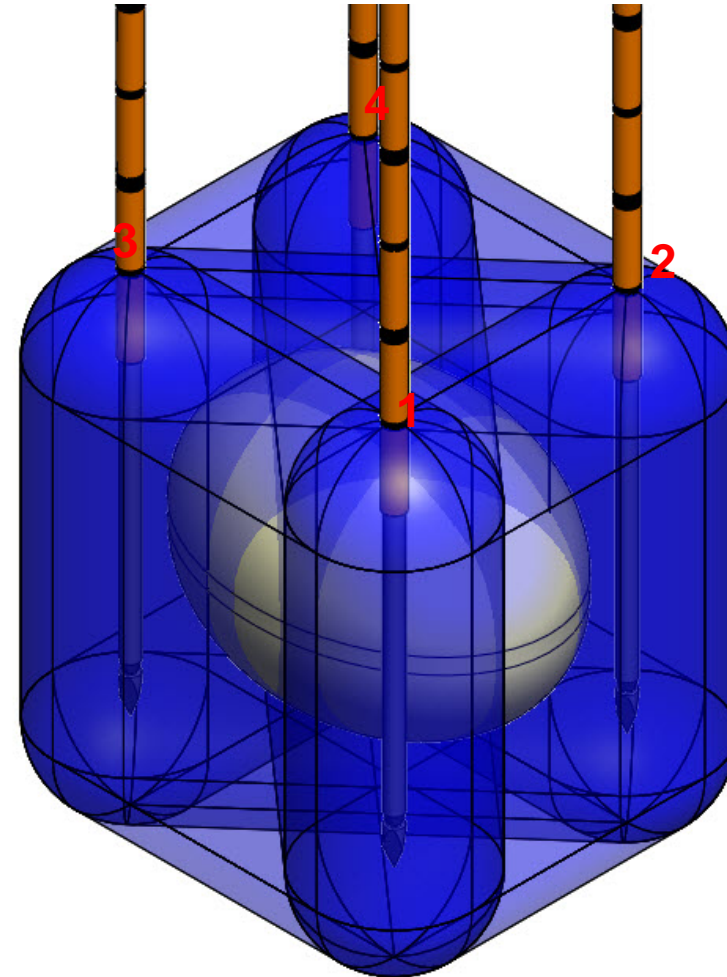
Width:

Depth:



Case - IRE Treatment

Probe (+)	Probe (-)	Voltage	Pulse Length	N. Pulses	V/cm	Distance
1	4	3000	100	90	1500	2.2
2	3	3000	100	90	1500	2.2
2	4	2550	100	90	1500	1.7
3	1	2550	100	90	1500	1.7
3	4	2250	100	90	1500	1.5
1	2	2250	100	90	1500	1.5



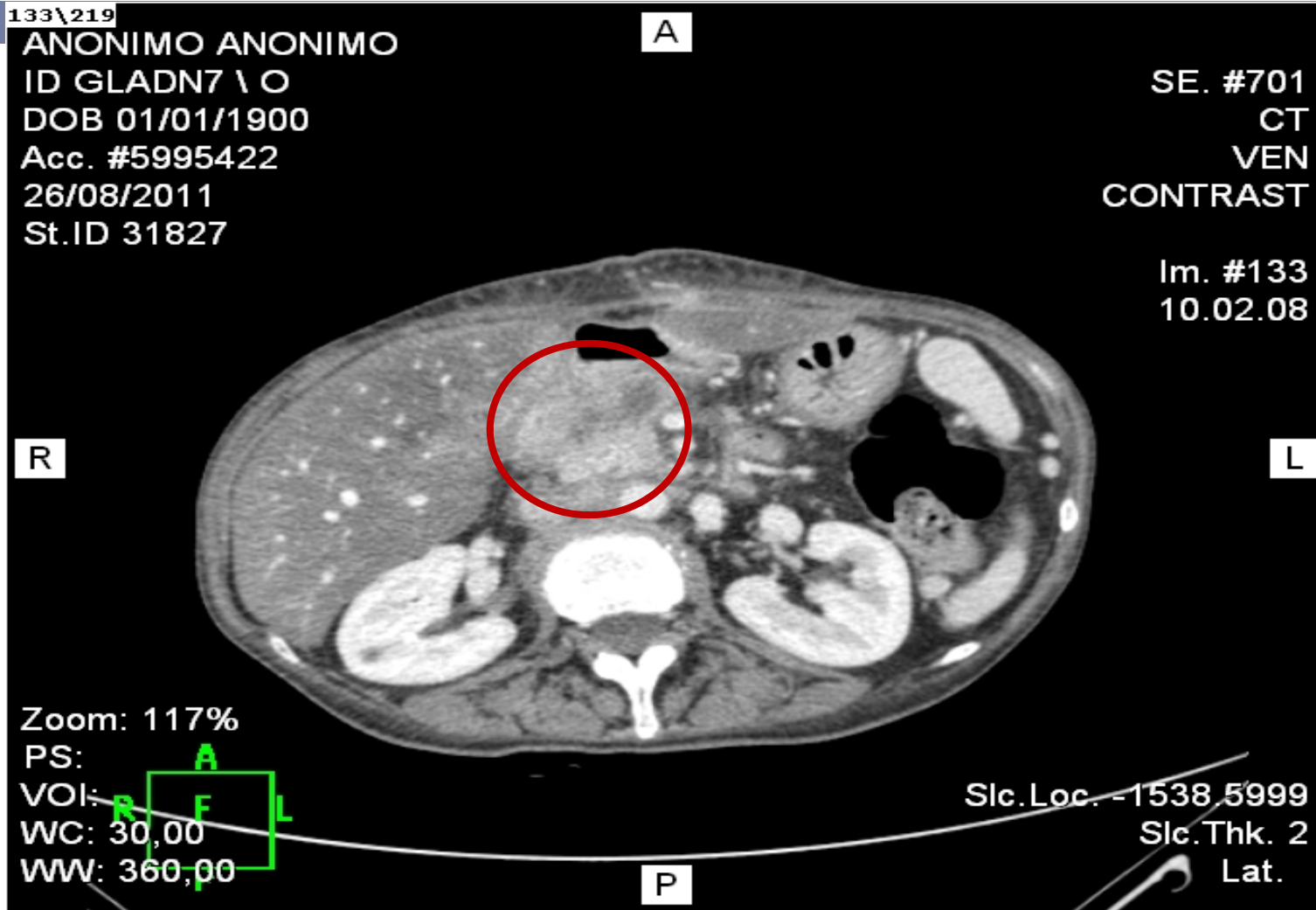
Procedures features

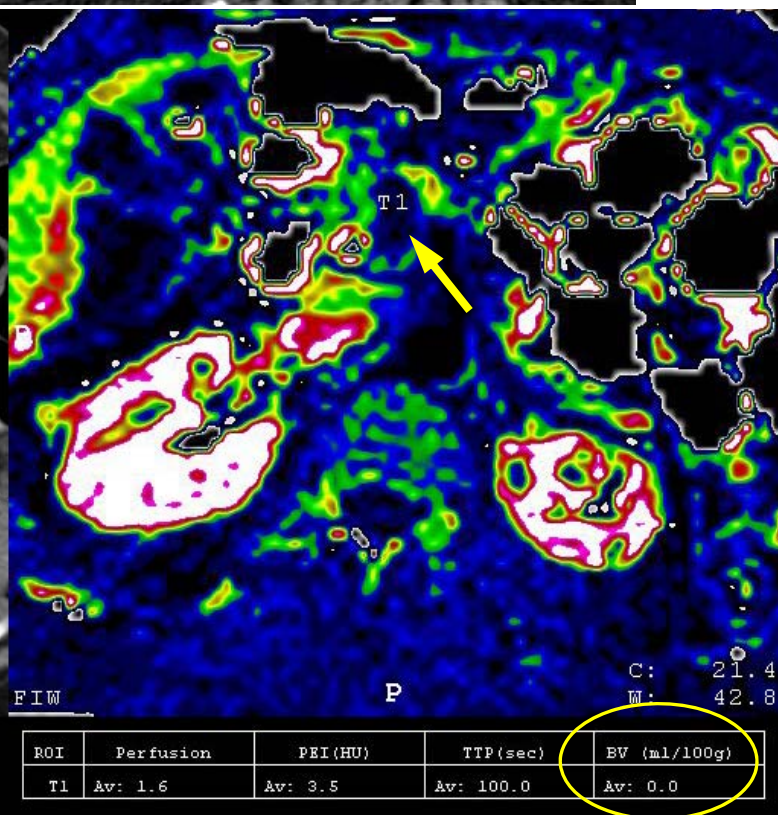
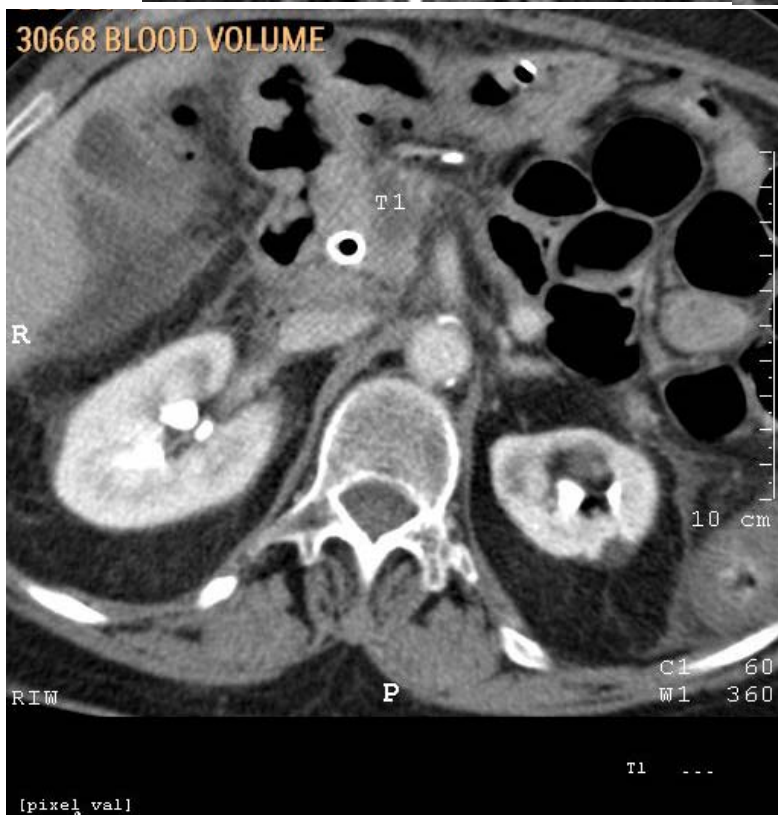
PT ID	Lenght of operation (min)	Energy Delivery time (min)	Electrodes (n)	Type of Electrodes	Procedure-Related Intraop- complication	Transfu sion	Associated surgical procedures
01	295	50	5	Monopolar	No	No	No
02	300	65	4	Monopolar	No	No	No
03	265	34	4	Monopolar	No	No	No
04	160	50	5	Monopolar	No	No	No
05	240	11	1	Bipolar	No	No	No
06	300	130	6	Monopolar	Yes	No	No
07	315	48	2	Monopolar	No	No	No
08	255	70	4	Monopolar	No	No	No
09	230	27	3	Monopolar	No	No	No
10	460	27	5	Monopolar	No	No	Yes
Median	280	49	4				

#2: pre-procedure CT-scan

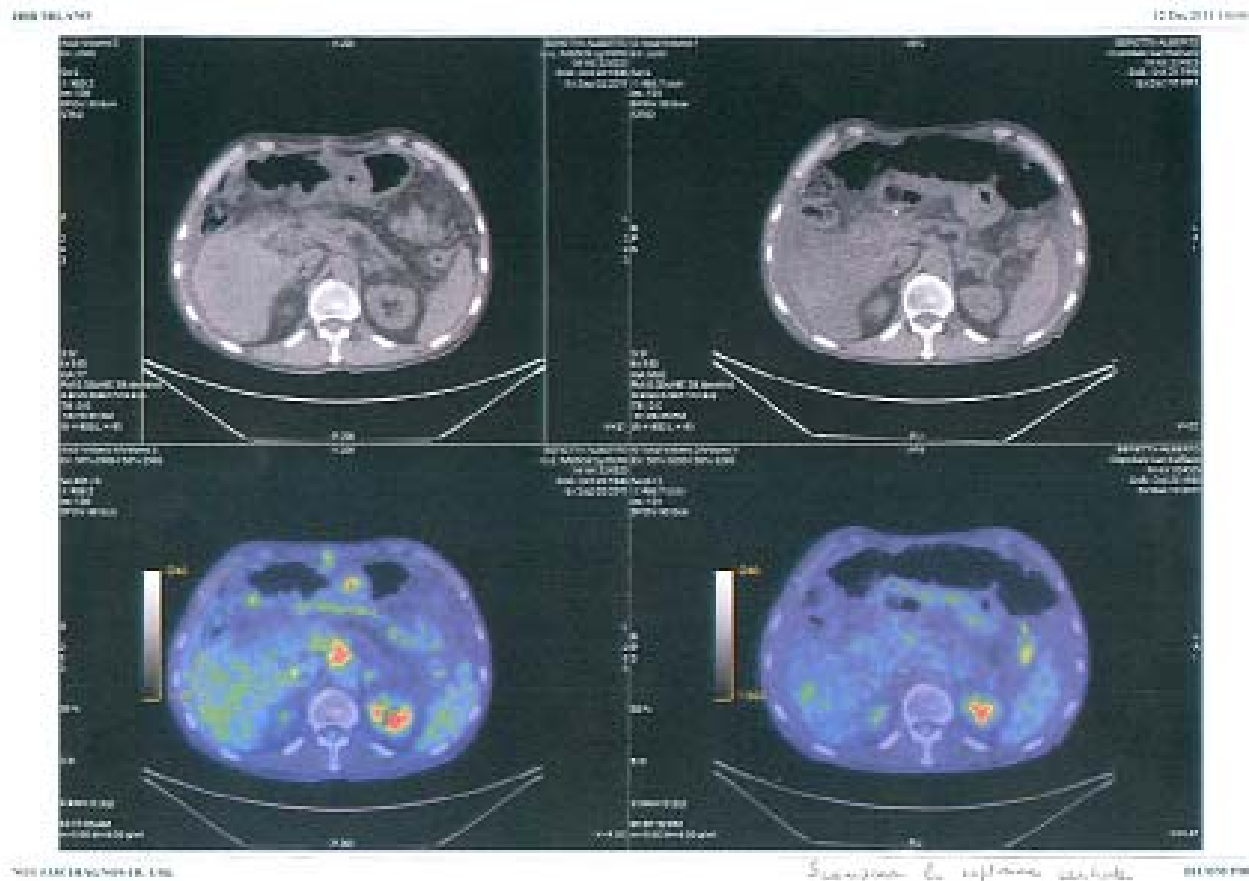


#2: 30th POD CT-scan





Further possible indication: LOCAL RECURRENCE



“Personal” convictions and “focal” today questions ...

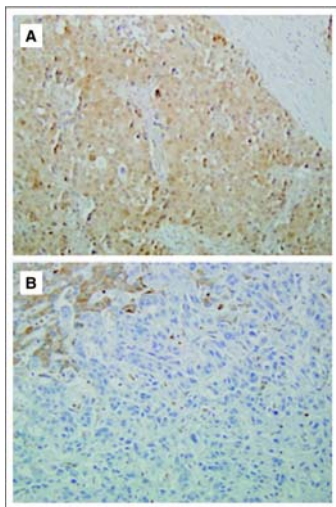
- **Still devastating, not curable but treatable disease ...**
- **Better survival ... (from cancer to chronicity ...)**
- **Systemic disease since the very beginning ...**
- **CH is the “basic treatment” ... but “when” within the “multimodality setting”?**
- **Role of surgery: radical (R0) ... and “adjuvant”?**
- **Role of the surgeon ...**

Final Conclusions for today pancreatic surgeon

MORE DATA ARE STILL NEEDED!

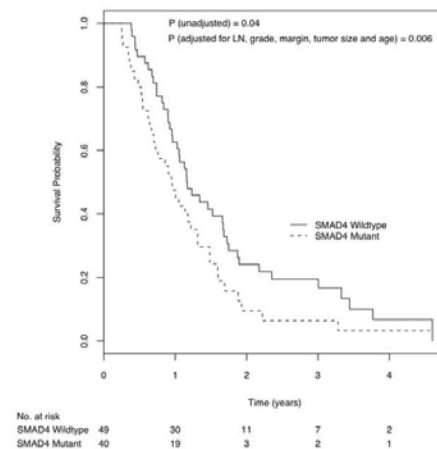
I dream an ideal world based on “traslational surgery” ...

Pre operative biopsy to all ...



Positive Dpc4 immunolabeling in LAPC associated with limited metastatic disease burden ... (UP FRONT RESECTION or ...)

Loss of Dpc4 immunolabeling in a primary carcinoma associated with widespread metastatic disease ... (NEOADJUVANT?)



SMAD 4 loss or intact ...





Thanks for your attention

1st Announcement

International Symposium on PANCREAS CANCER 2014

Verona | 3-5 JULY 2014

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ORGANIZING COMMITTEE

Claudio Bassi, Giampaolo Tortora, Aldo Scarpa, Kyoichi Takaori, Roberto Coppola,
Vincent Picozzi, Richard Kozarek, William Traverso, Andrew Blankin



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