Pancreas Transplantation in Norway: An update – NTPG 081215

High number of technical complications, but the successful cases are very awarding - the patient becomes abruptly:

- Free from Insulin
- Free from Dialysis (SPK)

Intentional increase in number of PTx's performed during recent years - and a high rate of solitary PTx

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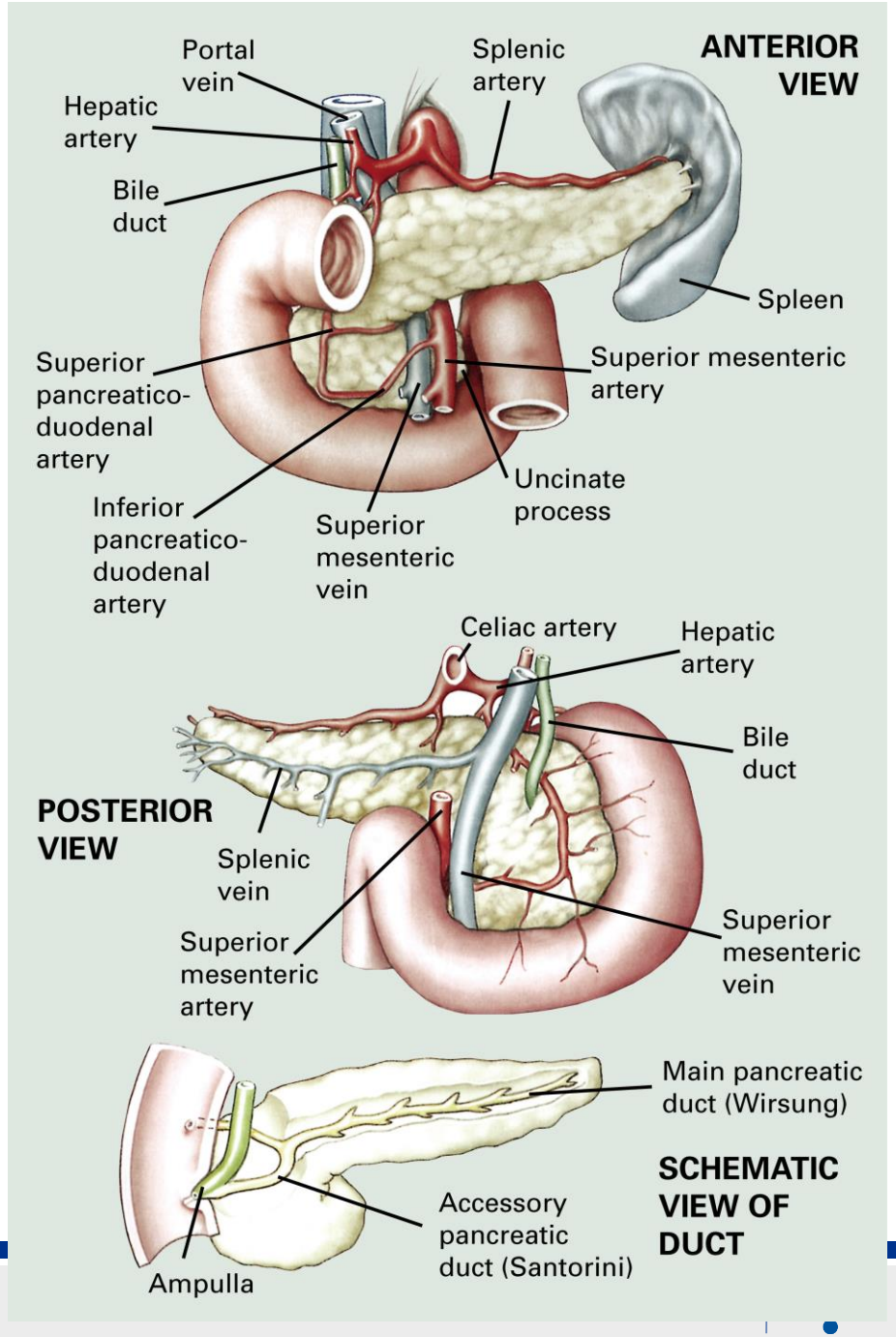
NORWAY

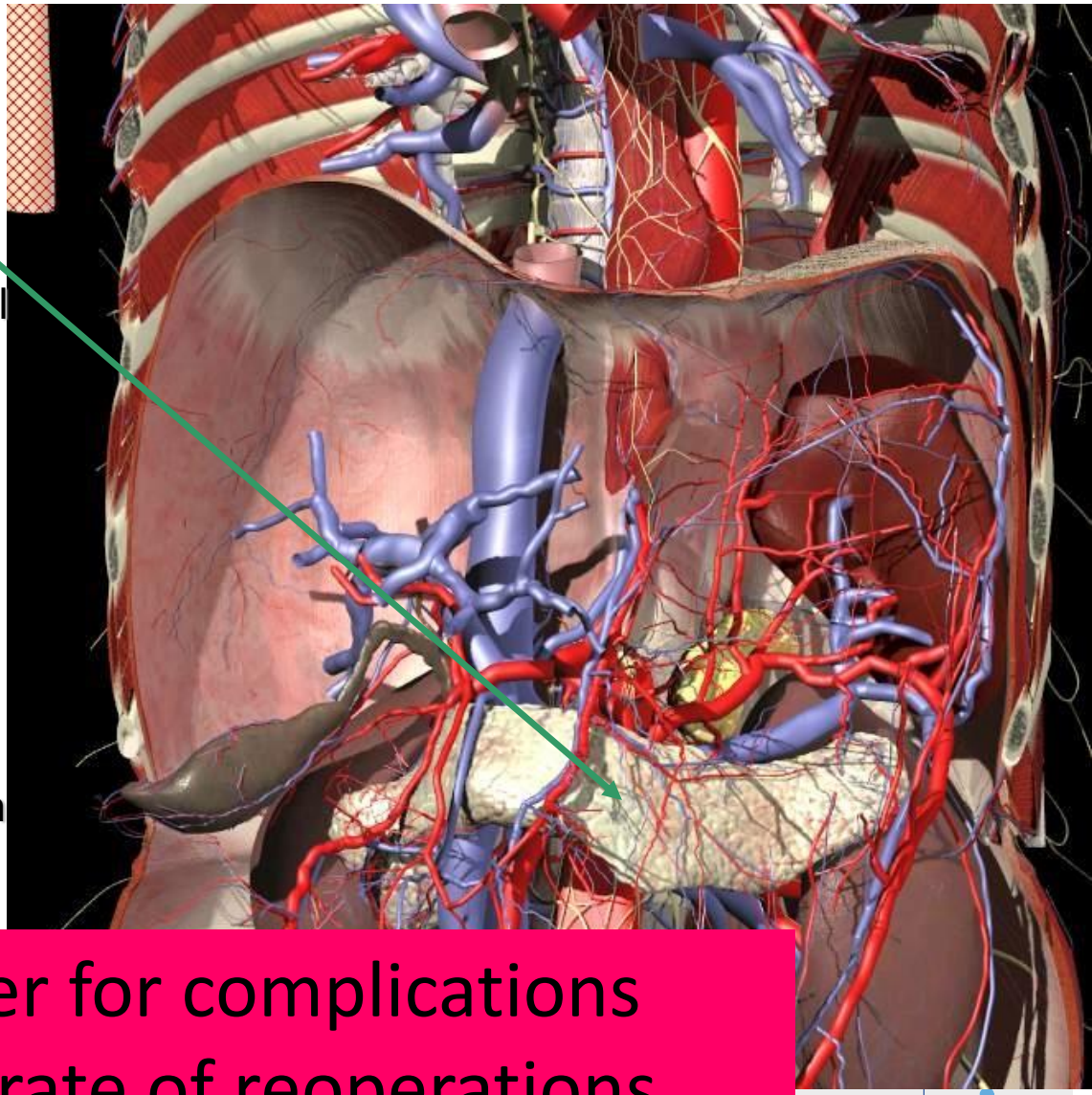
PANCREAS-Tx
Anatomy

- *Technically demanding; localisation; organ relation; vessels*
- *The desired Insulin-producing β-cells only account for 1-3 %*
- *> 95 % "unwanted" potent enzyme-package !!*



PANCREAS-Tx: Problems

- Surgery
  - Difficult, fragile Tx-organ
    - Potent enzyme-package
    - Fragile tissue/thin capsule
    - On the posterior abd. wall
    - Adhered to the duodenum
    - Complex vascular supply
  - ***Atraumatic tecnique*** essential
  - Challenging hemostasis
- Anticoagulation
  - High risk of thrombosis
    - ”Oversized” central vessels
  - Delicate balance between bleeding and thrombosis
- Immunology; Rejection
  - High-levelled immunosuppresion required
- Infections

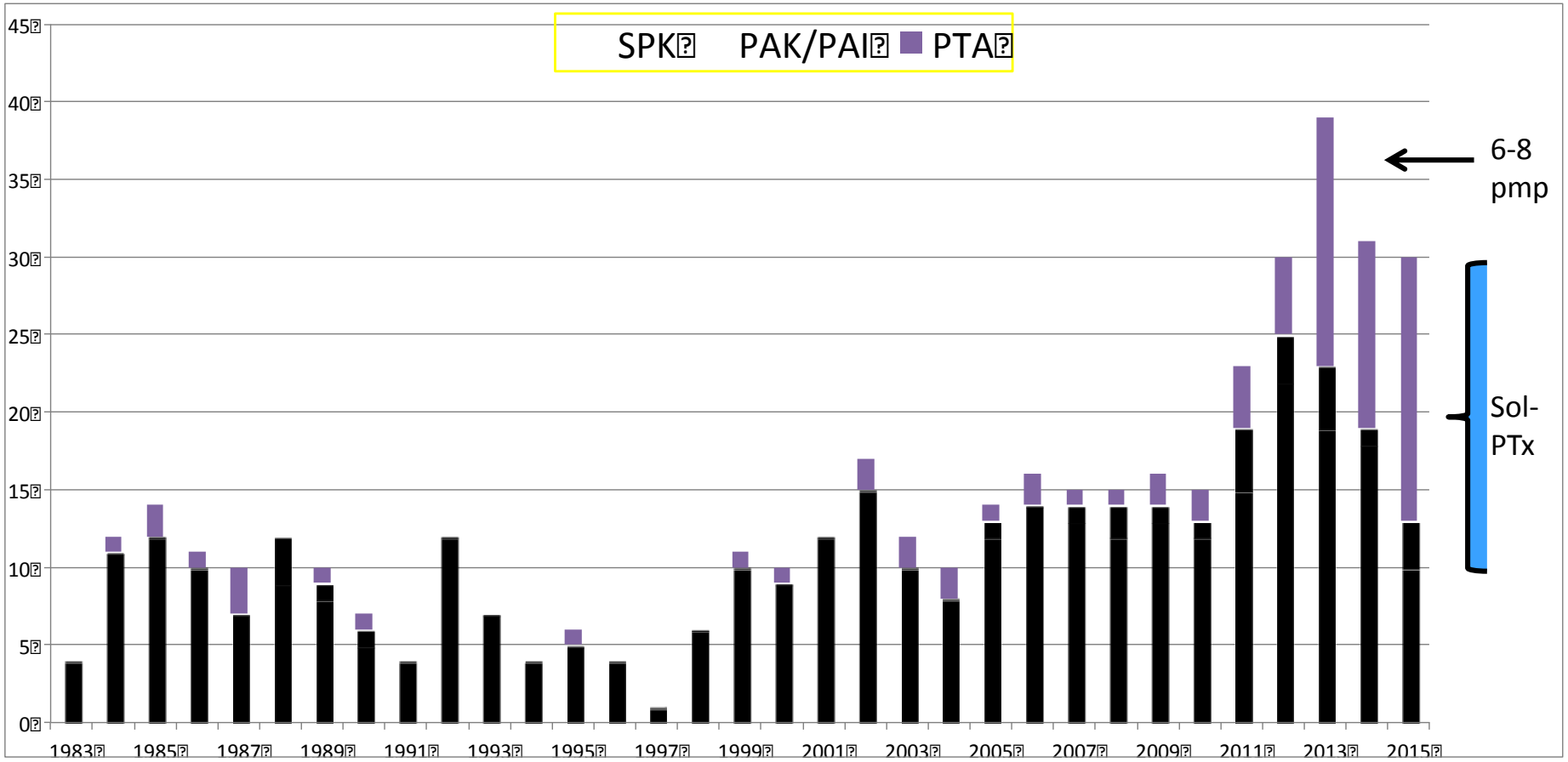


Major danger for complications
- High rate of reoperations

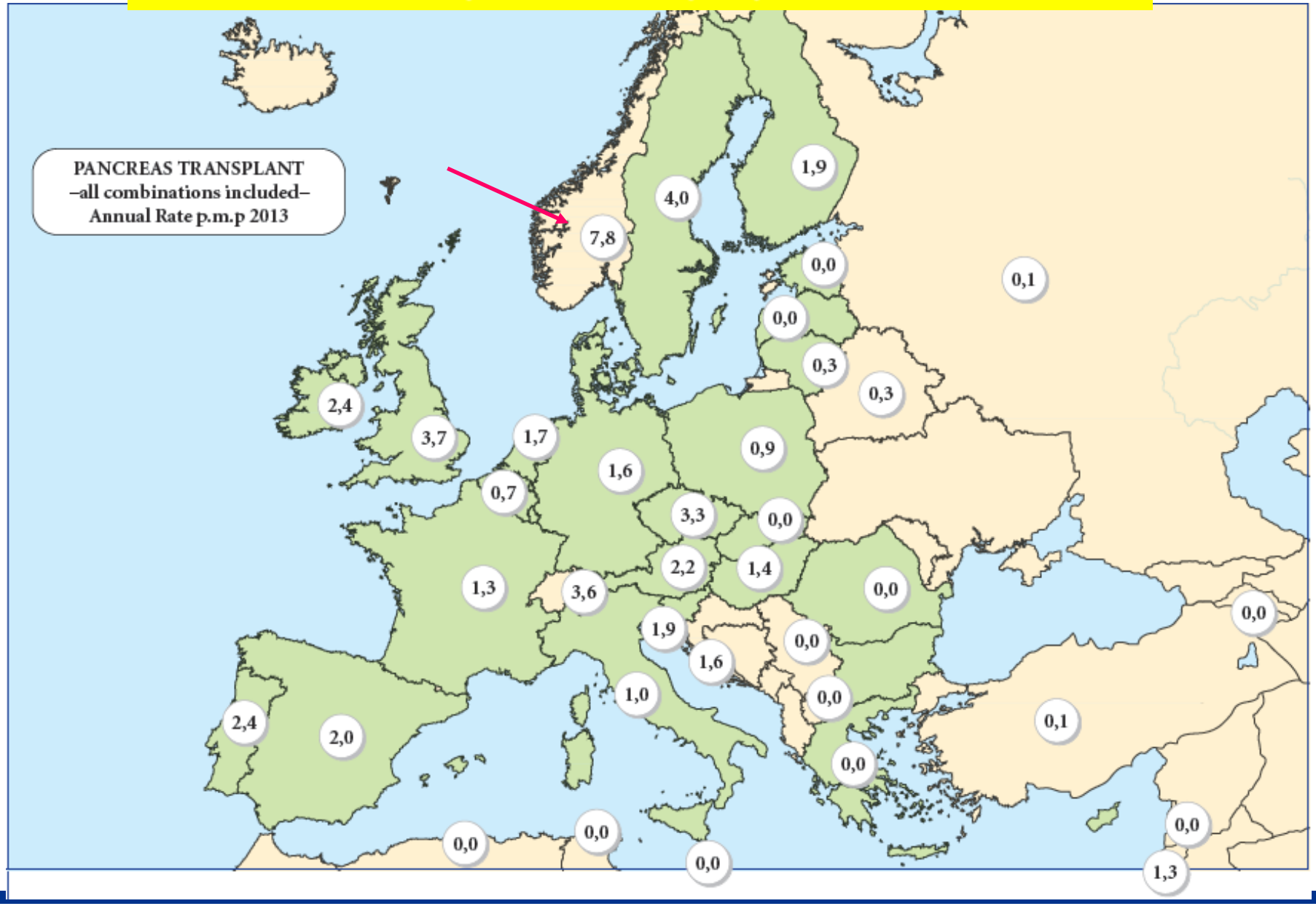
PANCREAS-Tx: Types/Indications

- Simultaneous Pancreas- + Kidney-Tx (SPK)
  - Uremic DM pats < 50-60 years should be offered SPK
  - Traditionally better results with SPK than Sol-PTx
- Solitary Pancreas-Tx (Sol-PTx)
  - Selected non-uremic DM pats should be offered solitary PTx (”brittle DM”, ”unawareness”)
    - Pancreas-Tx alone (PTA)
    - Pancreas-Tx after previous Kidney-Tx (PAK) and/or previous Islet-Tx (PAI)
      - Allready on immunosuppression

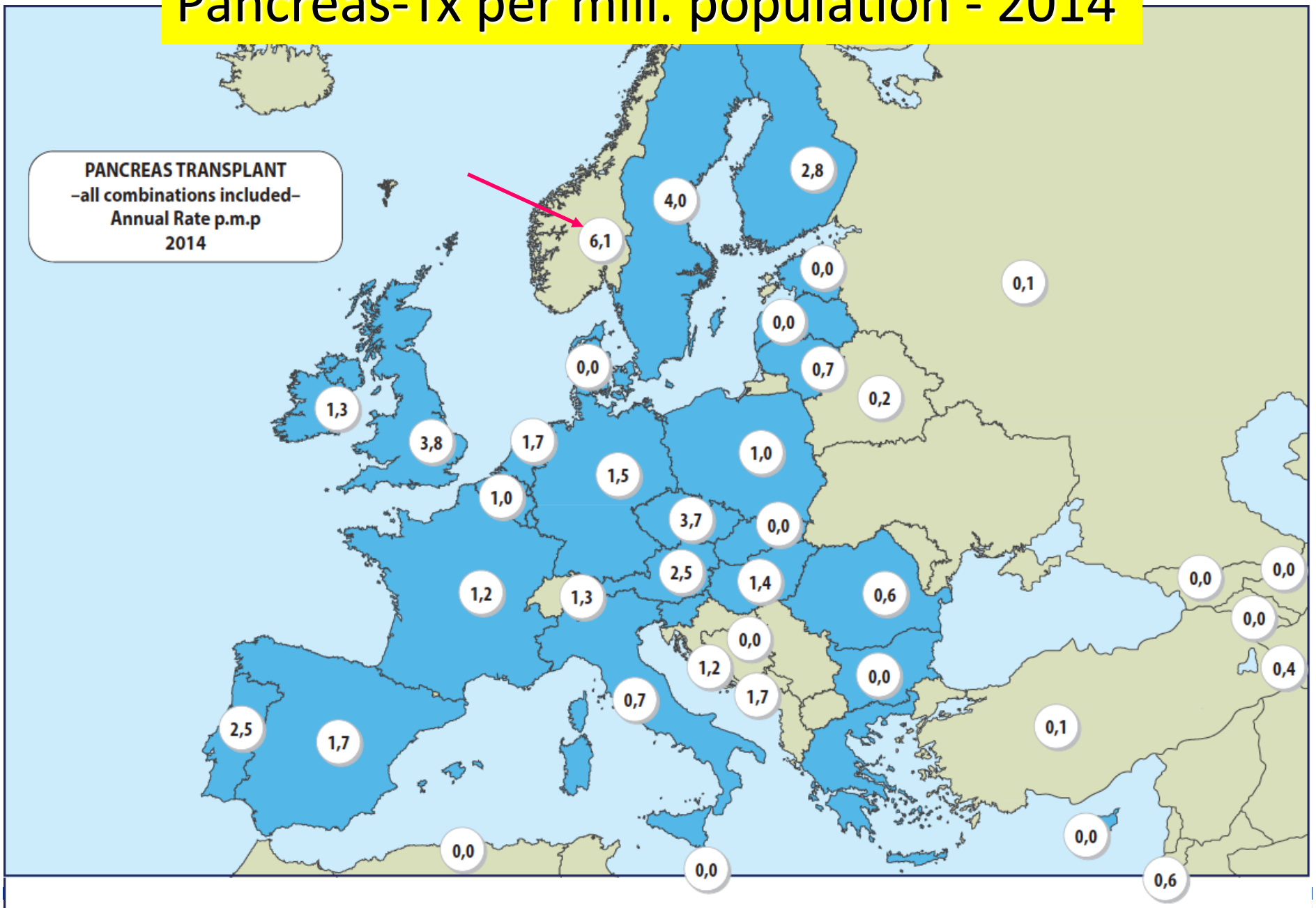
Number/type of PTx in Norway 1983-2015



Pancreas-Tx per mill. population - 2013

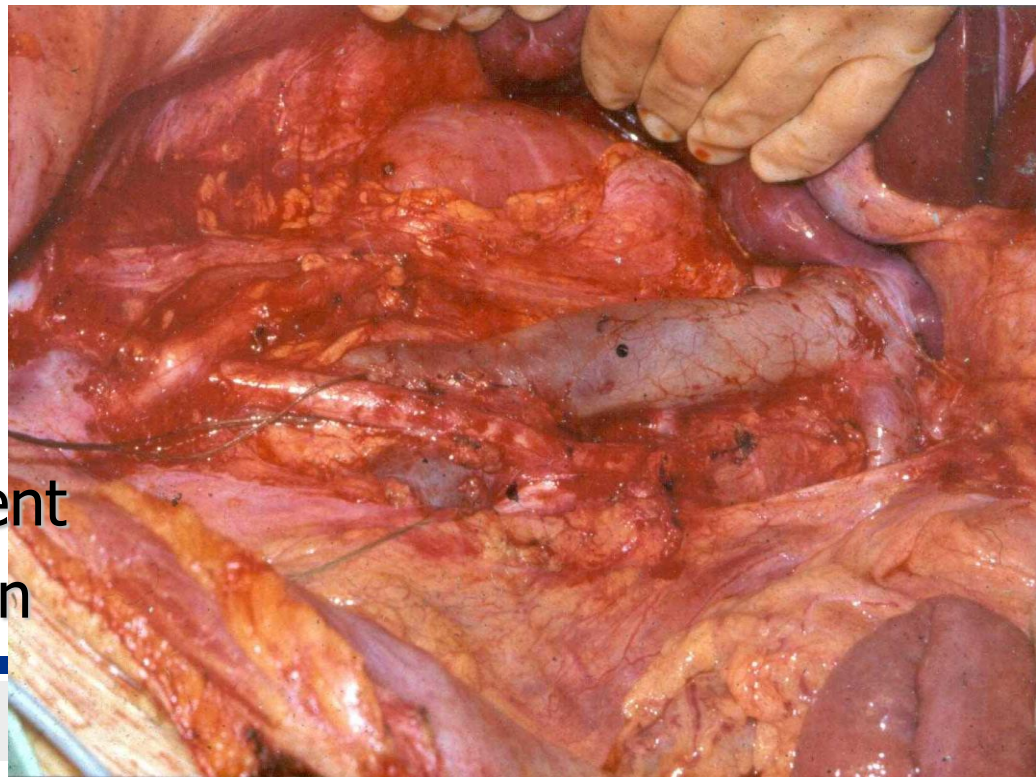


Pancreas-Tx per mill. population - 2014



PANCREAS-Tx in Norway
Surgical tecnique: Explantation

- The handling of pancreas during removal is demanding and decisive !!
  - Atraumatic technique is essential (”no touch”)
- LigaSure – Technically a quantum leap !
- Vessels
  - Preferably coeliac trunk and sup. mes. art. on common aortic segment
  - Preferably long portal vein

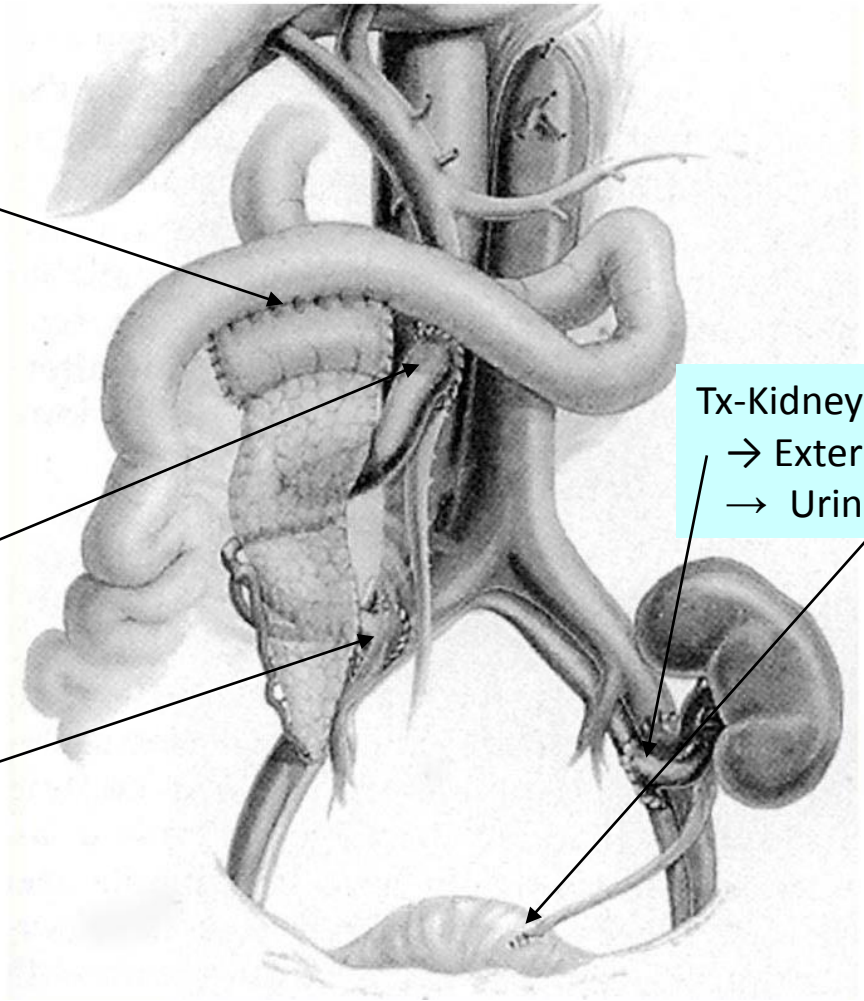


Surgical technique: Transplantation Simultaneous Pancreas + Kidney Tx (SPK)

Entero-anastomosis:
Tx-duodenum → Jejunum

Systemic venous anastomosis:
Portal Vein → Vena Cava

Arterial anastomosis:
Coeliac Trunk + Sup Mes Art on common aortic patch → Comm Iliac Art dxt

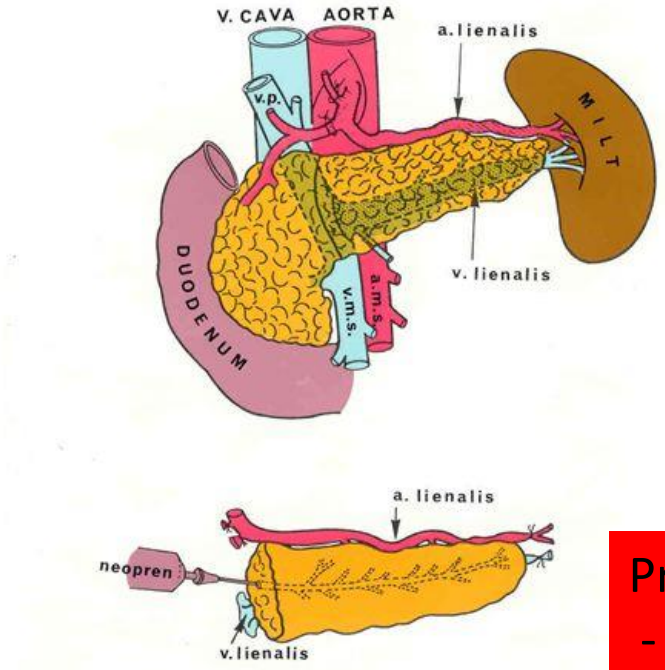


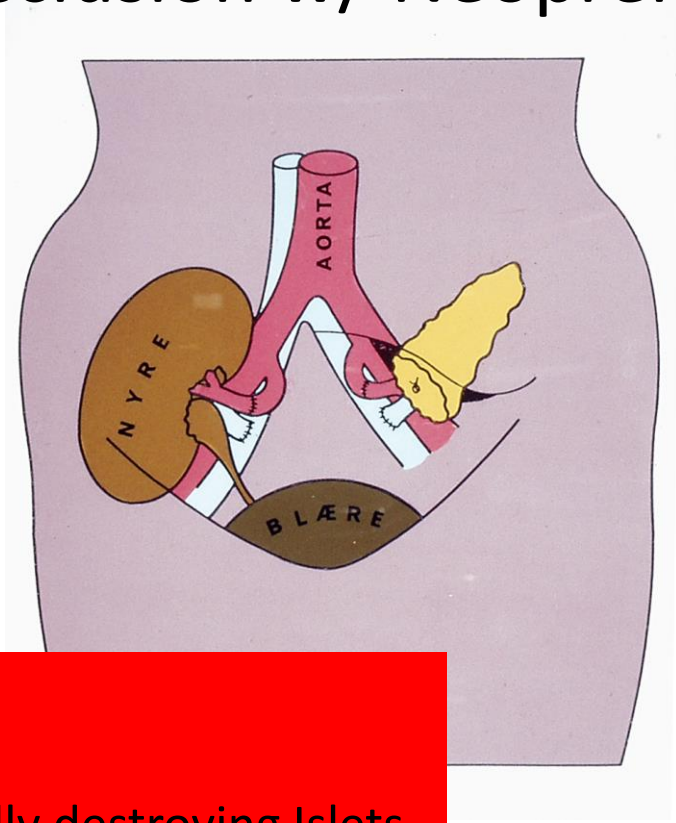
Tx-Kidney anastomoses:
→ External Iliac Vein/Artery
→ Urinary bladder

Pancreas-Tx in Norway: HISTORY

Technique 1: 1983-1988

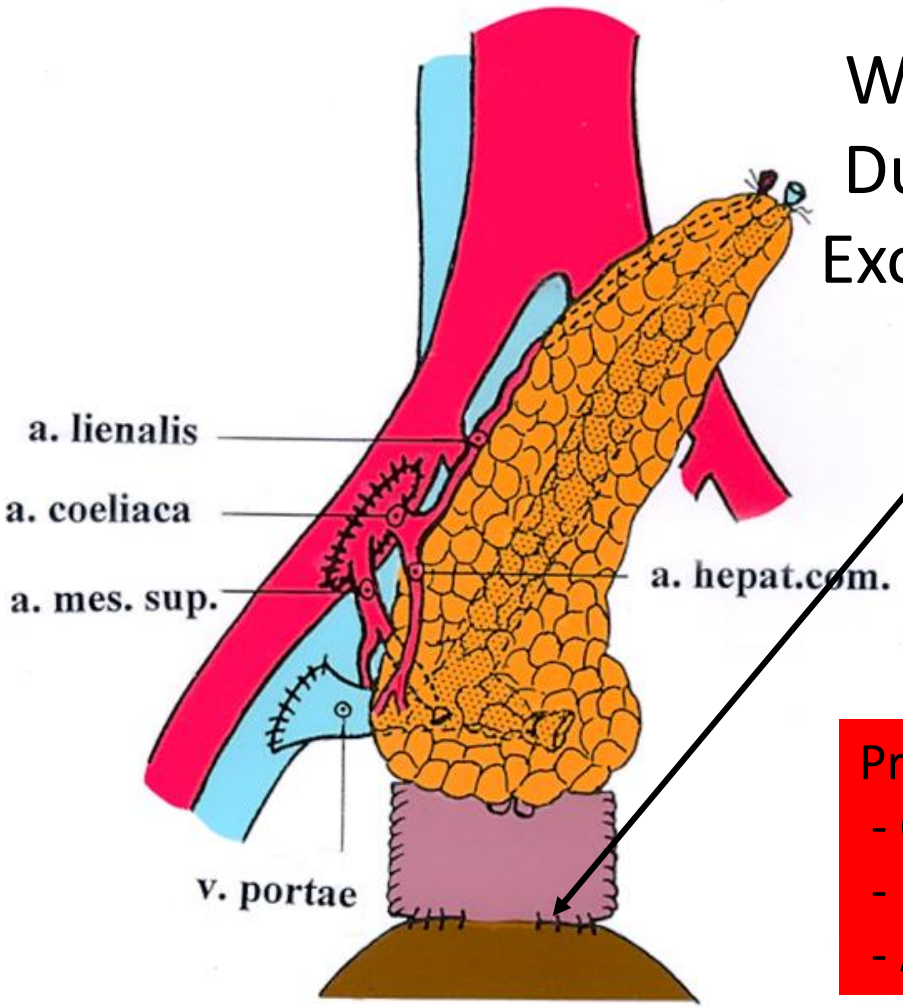
Segmental pancreas - Duct-occlusion w/ Neopren





Problems:
- Fibrosis
  -- Eventually destroying Islets
- Exocine leakage/fistulas

Pancreas-Tx in Norway: HISTORY
Technique 2: 1988-1997

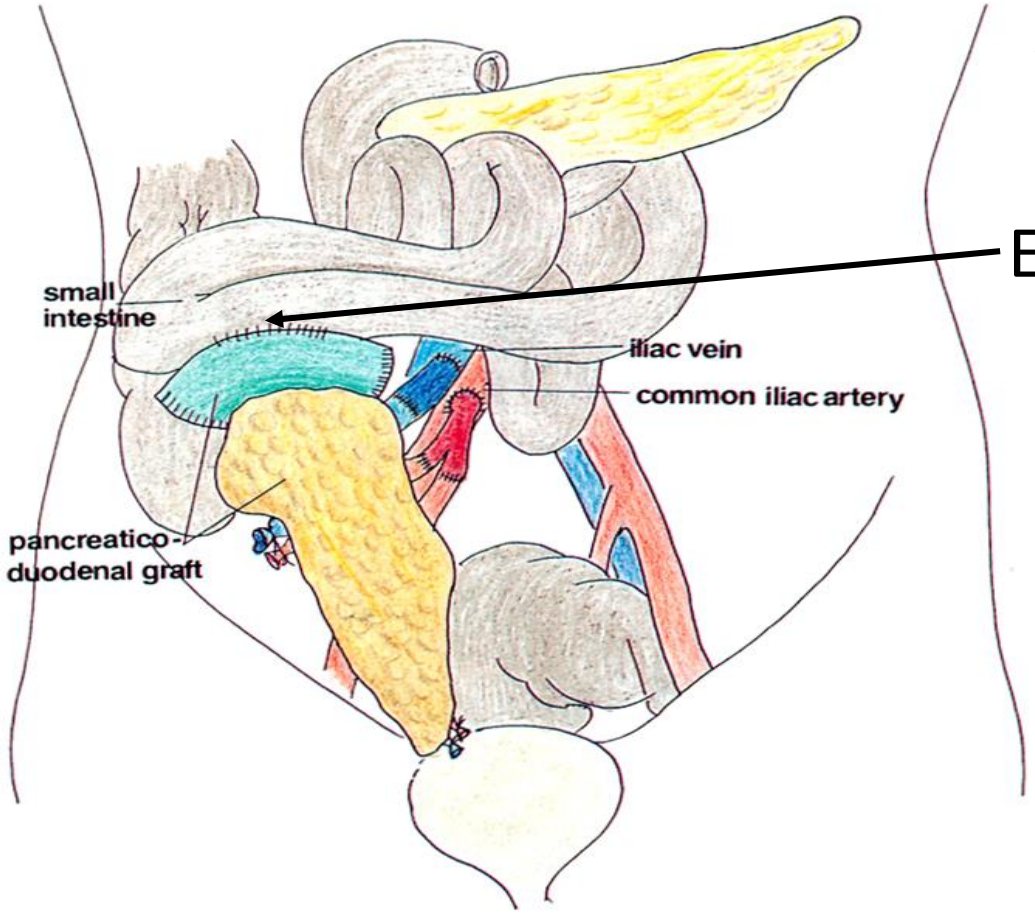


Whole pancreas w/
Duodenal segment:
Exocrine drainage → Urinary bladder

Problems:
- Chemical cystitis
- Metabolic acidosis
- Amylase-counts illusionary

Pancreas-Tx in Norway: HISTORY

Technique 3: 1997 -

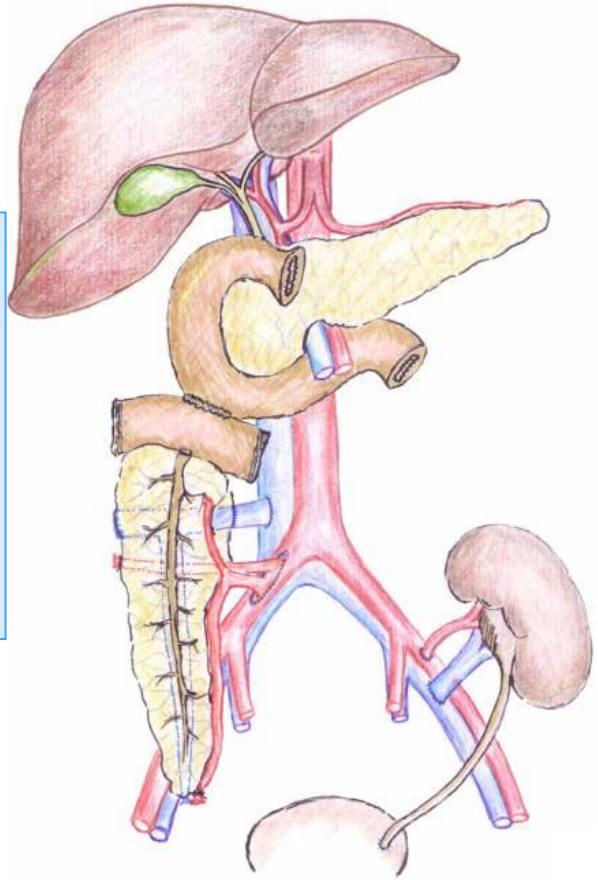


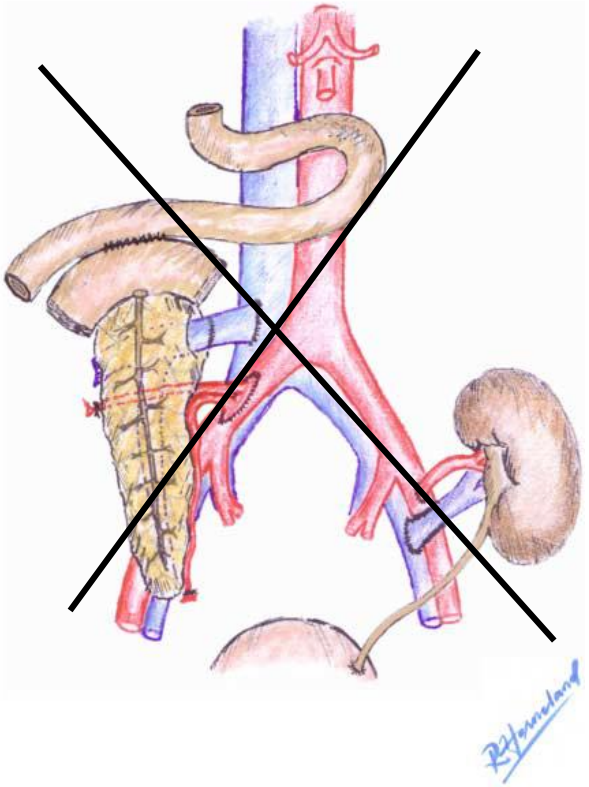
Whole pancreas w/ Duodenal segment Exocrine drainage → Jejunum

Pancreas-Tx in Norway: HISTORY

Enteroanastomosis: Duodenoduodenostomy 2012-

Benefits:
- Easier endoscopic access for 'scheduled' and 'ad hoc' biopsies
- In case of exocrine leakage: Allows for stenting of the pancreatic duct





Lindahl et al., Diabetologia, 2013

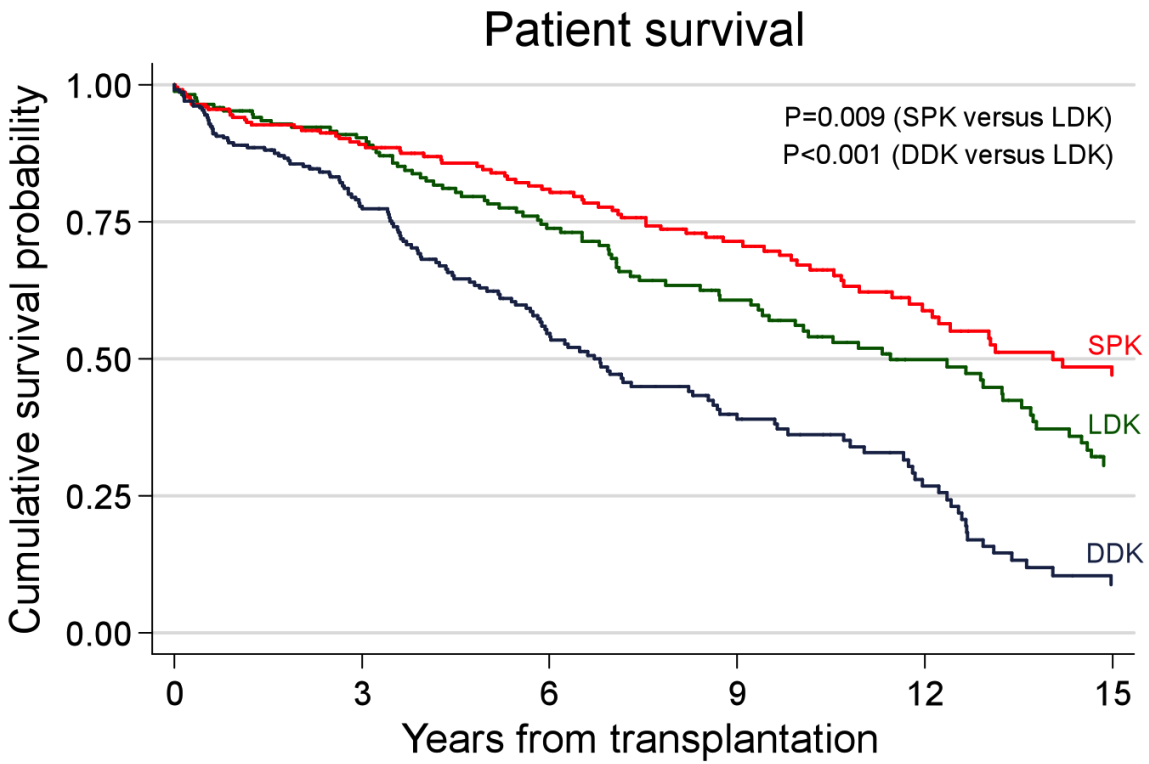
Diabetologia (2013) 56:1364–1371
DOI 10.1007/s00125-013-2888-y

ARTICLE

Improved patient survival with simultaneous pancreas and kidney transplantation in recipients with diabetic end-stage renal disease

J. P. Lindahl · A. Hartmann · R. Horneland · H. Holdaas · A. V. Reisæter · K. Midtvedt · T. Leivestad · O. Øyen · T. Jenssen

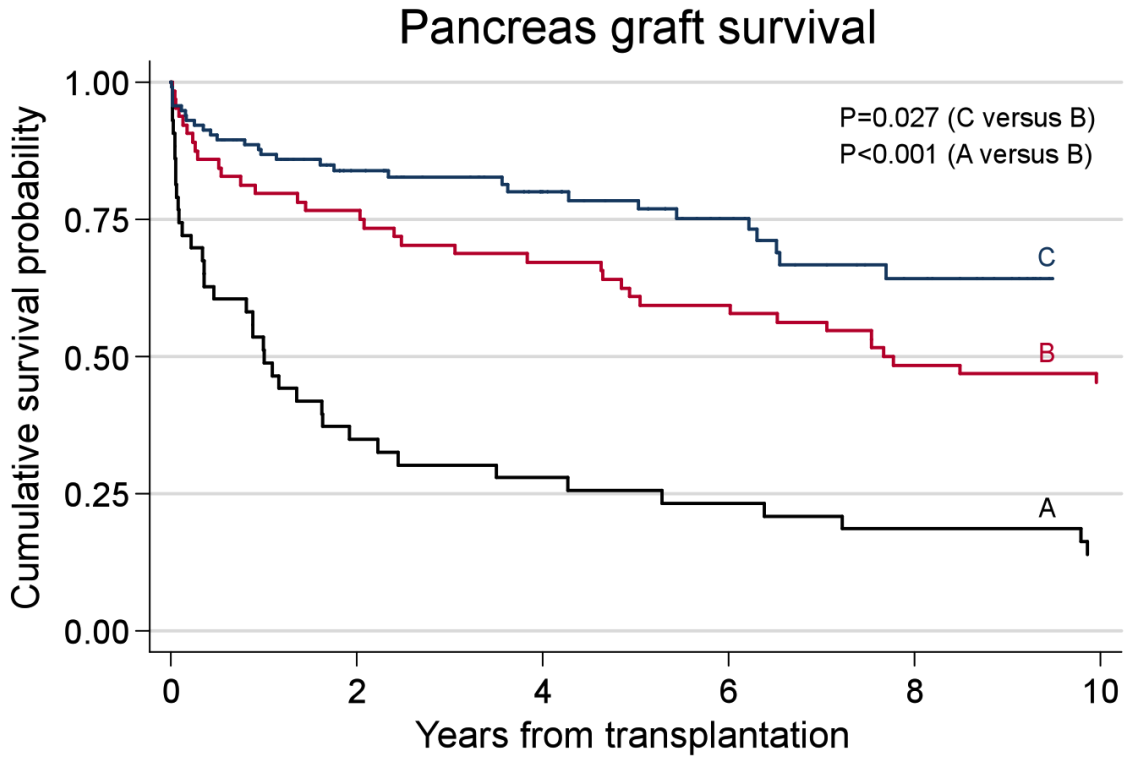
PTx in Norway: Results I (Lindahl et al. 2013)



Patients at risk:

LDK	171	140	99	66	41	20
SPK	222	168	129	90	51	33
DDK	237	147	84	44	22	5

PTx in Norway: Results II (Lindahl et al. 2013)



Patients at risk:

A. 1983-1987	43	15	12	10	8	6
B. 1988-1999	64	49	43	38	31	29
C. 2000-2010	115	76	56	39	23	9

PTx in Norway: Risk factors for death (Lindahl et al. 2013)

Cox regression analysis of risk factors for **patient death**.

	Univariate analysis			Multivariate analysis Model 1			Multivariate analysis Model 2		
	HR	95% CI	*p*-value	HR	95% CI	*p*-value	HR	95% CI	*p*-value
Recipient age	1.03	1.02-1.04	<0.001	1.03	1.02-1.04	<0.001	1.03	1.02-1.04	<0.001
Recipient gender	1.06	0.83-1.34	0.65						
Treatment LDK (*n*=171) SPK (*n*=222) DDK (*n*=237)	 0.68 1.82	 Reference 0.51-0.91 1.39-2.37	 0.010 <0.001	 0.70 1.29	 Reference 0.52-0.95 0.96-1.75	 0.02 0.094	 0.84 1.41	 0.60-1.18 1.04-1.93	 0.32 0.029
Time on dialysis	1.0006	1.0002-1.0009	0.001	1.001	1.000-1.001	0.001	1.001	1.000-1.001	0.001
Transplant era 1983-1999 (*n*=304) 2000-2010 (*n*=326)	0.57	0.43-0.77	<0.001	0.41	0.30-0.56	<0.001	0.40	0.30-0.55	<0.001
Donor age	1.01	1.01-1.02	<0.001				1.01	1.00-1.02	0.018

PTx in Norway: Conclusions I (Lindahl et al. 2013)

- Recipients receiving SPK have superior patient survival compared to both LDK and DDK
- Significantly improved graft and patient survival during the last decade
- Significant effect on patient death by:
  - Transplant era
  - Time on dialysis
  - Donor age
  - Recipient age

Horneland et al., Am J Transpl, 2015

American Journal of Transplantation 2014; XX: 1–9
Wiley Periodicals Inc.

doi: 10.1111/ajt.12953

Brief Communication

Pancreas Transplantation With Enteroanastomosis to Native Duodenum Poses Technical Challenges—But Offers Improved Endoscopic Access for Scheduled Biopsies and Therapeutic Interventions

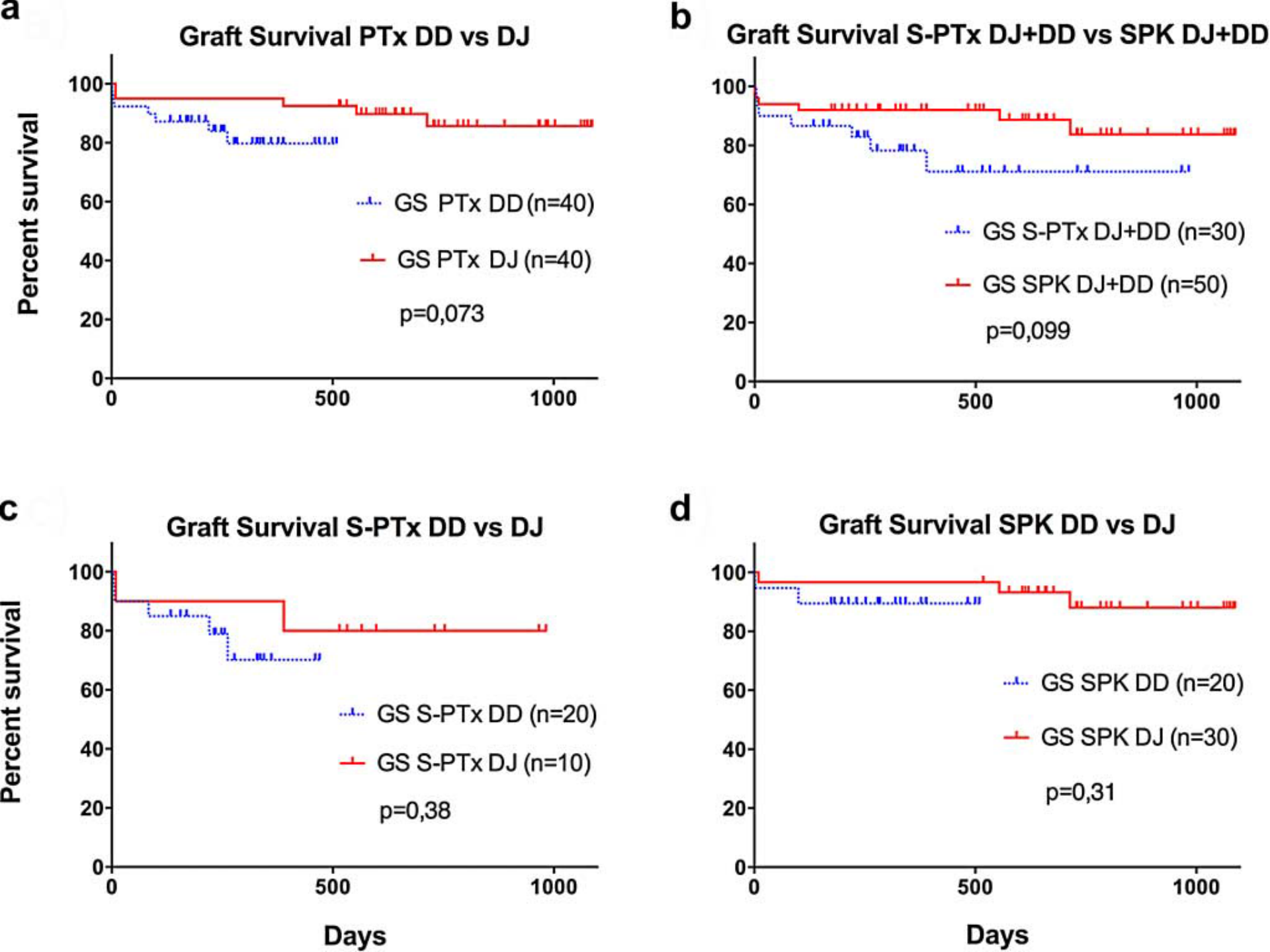
R. Horneland[1,*], V. Paulsen[2], J. P. Lindahl[3], K. Grzyb[4], T. J. Eide[4], K. Lundin[2], L. Aabakken[2], T. Jenssen[3,5], E. M. Aandahl[1,6,7], A. Foss[1] and O. Øyen[1]

remained an independent predictor of patient death in multivariate analysis. PTx-DD showed a higher rate of thrombosis and inferior results, but facilitated a protocol biopsy program by EUS that was feasible and safe. Given that technical difficulties can be solved,

Horneland et al., Am J Transpl, 2015

DD vs DJ - inital experience

# (%) / Mean (range) / Mean ± SD	**PTx-DD Sep 2012 – Sep 2013 *n=40***	**PTx-DJ (Control) Feb 2011 – Sep 2012 *n=40***	**p** t-test/ Fisher exact
Reoperations (# patients) **- Bleeding/Thrombosis/Exocrine Leakage / Kidney related/Other**	19 (**47,5%**) 8 / 4 / 0 / 2 / 6	12 (**30%**) 6 / 2 / 2 / 0 / 2	0.168
Pancreas venous thrombosis rate **- Graft loss due to v. thrombosis**	9 (**22,5%**) - 5 (12,5%)	2 (5%) - 2 (5%)	**0.048*** 0.432
Rejection rate; biopsy-verif. (# pts) **- Total # of rejections treated**	9 (22,5%) - 14	10 (25%) - 11	1.000
Pancreas Graft loss	8 (**20%**)	5 (12,5%)	0.546
Kidney Graft loss (SPK)	1 (2,5%)	1 (3,3%)	1.000
Patient death	1 (2,5%)	3 (7,5%)	0.615


a
Graft Survival PTx DD vs DJ
Percent survival
100
80
60
40
20
0
0
500
1000
GS PTx DD (n=40)
GS PTx DJ (n=40)
p=0,073
b
Graft Survival S-PTx DJ+DD vs SPK DJ+DD
GS S-PTx DJ+DD (n=30)
GS SPK DJ+DD (n=50)
p=0,099
c
Graft Survival S-PTx DD vs DJ
GS S-PTx DD (n=20)
GS S-PTx DJ (n=10)
p=0,38
Days
d
Graft Survival SPK DD vs DJ
GS SPK DD (n=20)
GS SPK DJ (n=30)
p=0,31
Days

Horneland et al., Am J Transpl, 2015

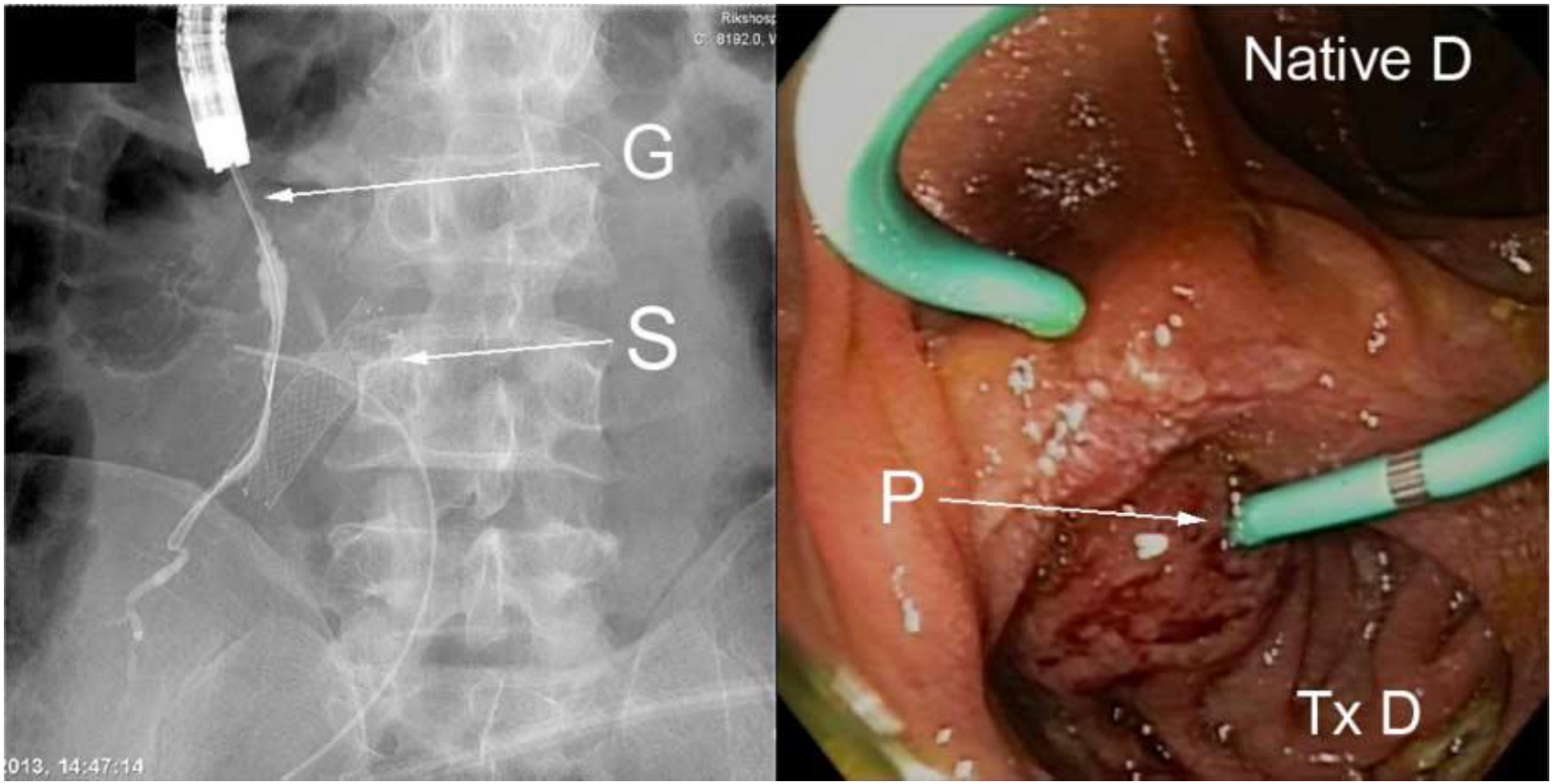
Risc factor analysis

Cox regression **Dependent var.:**	**Independent covar. w/ statistical significance at p < 0.15 included**	**Univariate analysis**		**Multivariate analysis**	
		p	**Hazard Ratio (95% CI)**	**p**	**Hazard Ratio (95% CI)**
Pancreas graft loss	**Time on waiting list**	**0.007***	1.00 (1.00-1.00)	0.493	1.00 (1.00-.1.00)
	HLA -A+B mismatches **- DR mismatches**	**0.038*** 0.549	0.51 (0.27-0.96) 0.76 (0.31-1.87)	0.323	0.69 (0.34-1.43) -
Patient death	**Recipient age**	**0.009***	1.21 (1.05-1.41)	**0.066***	1.24 (0.99-1.56)
	Time on waiting list	**0.008***	1.00 (1.00-1.00)	0.906	1.00 (1.00-1.01)
	HLA -A+B mismatches **- DR mismatches**	**0.038*** 0.211	0.33 (0.11-0.94) 0.36 (0.07-1.79)	0.437 -	0.51 (0.09-2.79) -
Binary logistic Regression **Dependent var.:**	**Independent variables w/ statistical significance at p < 0.15 included**	**Univariate analysis**		**Multivariate analysis**	
		p	**Odds Ratio (95% CI)**	**p**	**Odds Ratio (95% CI)**
Reoperation Per patient; (one or more reop.)	**Recipient BMI**	**0.040***	1.17 (1.01-1.36)	**0.039***	1.30 (1.01-1.67)
	Donor age: - Continous var. - <50 vs > 50 - <45 vs > 45 - <40 vs > 40	**0.028*** 0.035* 0.005* 0.042*	1.04 (1.00-1.08) 3.41 (1.09-10.66) 4.16 (1.55-11.19) 2.61 (1.03-6.57)	**0.021***	1.08 (1.01-1.14)
Rejection	-	-	-	-	-

Horneland et al., Am J Transpl, 2015
Biopsies

# Biopsies performed / # Rejections detected	PTx-DD Sep 2012 – Sep 2013 *n=40*	PTx-DJ (Control) Feb 2011 – Sep 2012 *n=40*
Scheduled biopsies total	61	78
Endoscopic biopsies of Duodenum/Pancreas	45 / 39	30 / 0
Percutaneous Kidney biopsies 6/52wks (SPK)	16 / 1 (n=20)	23 / 25 (n=30)
Rejections detected by sched. biopsies alone D/P/K	0 / 3 / 0	0 / - / 0
Indication biopsies total	35	31
Endoscopic biopsies Duodenum/Pancreas	11 / 3	1 / 0
Percutaneous Pancreas biopsies	15	3
Percutaneous Kidney biopsies	7	27
Rejections detected by indication biopsies D/P/K	2 / 6 / 0	0 / 1 / 10

The duodenoduodenostomy: Stenting the pancreatic duct



CONCLUSIONS II (Horneland et al.)

- A huge increase in PTx during recent years
  - A very high rate of Sol-PTx
  - Releasing on donor criteria (age etc) is dangerous
- (Still a high rate of reoperations (30-50%))
- (A high rate of thrombosis – initially - in DD's)
- Solitary PTx results are still poorer than SPK!
- Duodeno-duodenostomi is safe and offers improved access for biopsies and ductal stenting
  - Value of scheduled EUS biopsies still not proven!

FUTURE STUDIES
Questions to be adressed

- Prospective PTx study started in Oct. 2013
- The value of endoscopic/scheduled biopsies ??
  - Duodenal segment biopsies ? Pancreas biopsies ?
- Reasons for poorer Solitary PTx results ??
  - Impeded rejection monitoring due to lack of reporter-kidney?
  - Immunologically protection due to TX-kidney? (SPK>PAK>PTA)
  - Still to weak immunosuppression ?
- Non-invasive rejection monitoring ?
  - **C-peptide** - CRP - Amylase - Lipase?
  - Advanced immunologic markers?

Preliminary data ongoing PTx-study 09-2013 ->

- N = 65 (per 08.12.15) 35 S-PTx, 30 SPK
- Patient survival 64/65 = 99%
- Graft survival 60/65 =92%
  - Graft loss 2 thrombosis, 3 rejection (PTA, AMR), 1 bleeding
- Thrombosis 5/65 cases (8%)
  - 2 Graftectomy. 3 underwent successful perc. trhombectomy
- Lower rate of intervention due to bleeding. Still higher rate of thrombosis than before DD-era.
- Rejection rate is higher in PTA
  - DSA and AMR predicts very poor outcome in PTA