



The dark side of the guidelines
2nd Interventional Radiologist under 40 Meeting



Interventional Oncology

8-10 Maggio 2017

Bologna

Società Medica Chirurgica - Palazzo dell'Archiginnasio

Pancreas

Il ruolo del trapianto di isole pancreatiche

Claudio Sallemi

Unità operativa di Radiologia

Ospedale Sant'anna

Como



OSPEDALE SAN RAFFAELE

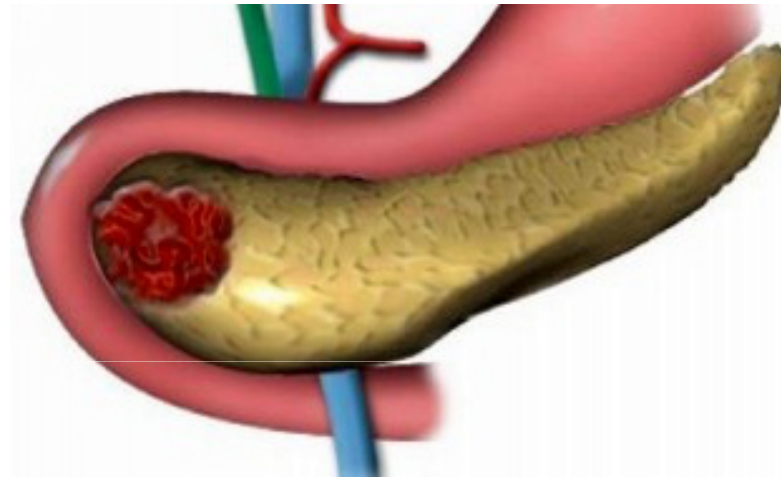
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Diabete pancreaticogenico

Aumento dei Pazienti sottoposti a chirurgia pancreatica:

- diagnosi precoce di lesioni premaligne ¹;
- sempre maggiore rinvio di pazienti affetti da malattie pancreatiche di pertinenza chirurgica nei centri ad alto volume ².



Maggiore aspettativa di vita di Pazienti (mediana di sopravvivenza libera da malattia di 23 mesi se trattamento chirurgico+ cht adiuvante ³) esposti al rischio di diabete post-chirurgico.

1 Lahat G, Ben Haim M, Nachmany I, et al. Pancreatic incidentalomas: high rate of potentially malignant tumors. J Am Coll Surg. 2009;209: 313–319.

2 Balzano G, Zerbi A, Capretti G, et al. Effect of hospital volume on outcome of pancreaticoduodenectomy in Italy. Br J Surg. 2008;95:357–362.

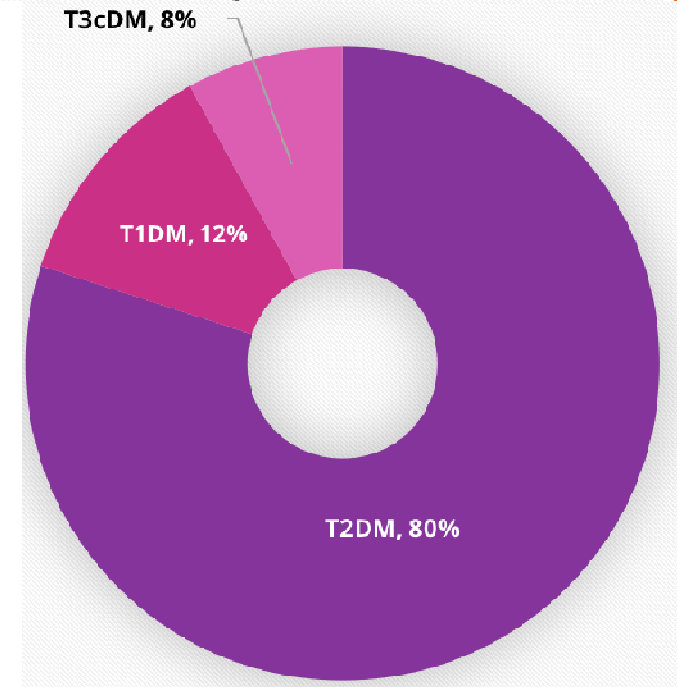
3 Neoptolemos JP, Stocken DD, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. JAMA. 2010;304: 1073–81.

Diabete pancreaticogenico

Perdita di parenchima dopo resezione pancreatica →

- significativo disturbo dell'omeostasi glucidica ⁴⁻⁵ caratterizzato da gravi episodi di iperglicemia o ipoglicemia ³⁻⁴ ("brittle diabetes").
- conseguente aumento di morbidità e mortalità ⁶⁻⁷ e danneggiamento degli organi target⁴.

Distribution of T1DM, T2DM and T3cDM



Cui Y & Andersen DK 2011 Pancreatogenic diabetes: special considerations for management. *Pancreatology*

4 Maeda H, Hanazaki K. Pancreatogenic diabetes after pancreatic resection. *Pancreatology*. 2011;11:268–276.

5. Dresler CM, Fortner JG, McDermott K, et al. Metabolic consequences of (regional) total pancreatectomy. *Ann Surg*. 1991;214:131–140.

6 Cui Y, Andersen DK. Pancreatogenic diabetes: special considerations for management. *Pancreatology*. 2011;11:279–294.

7 Parsaik AK, Murad MH, Sathananthan A, et al. Metabolic and target organ outcomes after total pancreatectomy: Mayo Clinic experience and meta-analysis of the literature. *Clin Endocrinol (Oxf)*. 2010;73:723–731.

Diabete pancreaticogenico

- Incidenza compresa tra 4 e 73 %⁸⁻¹⁰ a seconda del tipo di resezione e del volume pancreatico resecato.
- Aumento aspettativa di vita → mortalità e complicanze ipoglicemia-correlate (nefropatia, neuropatia e retinopatia) simili a T1DM e T2DM¹¹⁻¹².



→ **impatto significativo su qualità e aspettativa di vita**

10 Sohn TA, Campbell KA, et al. Quality of life and long-term survival after surgery for chronic pancreatitis. J Gastrointest Surg. 2000;4(4):355,64

11 Couet C, Genton P, et al. The prevalence of retinopathy is similar in diabetes mellitus secondary to chronic pancreatitis with or without pancreatectomy and in idiopathic diabetes mellitus. Diabetes Care. 1985;8(4):323–328.

12 The prevalence and severity of microvascular complications in pancreatic diabetes and IDDM. Diabetes Care 1995; 18: 971–974.

Il trapianto di isole pancreatiche

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

N Engl J Med 2004;350:694-705.

MEDICAL PROGRESS

Islet Transplantation as a Treatment for Diabetes — A Work in Progress

- Pancreas digerito con collagenasi per liberare le isole dal tessuto esocrino circostante.
- Le isole liberate vengono purificate mediante centrifugazione a gradiente di densità per rimuovere i residui cellulari esocrini rimasti.
- Le isole purificate vengono infuse attraverso un catetere posizionato per via percutanea transepatica nella vena porta, attraverso la quale giungono sino ai sinusoidi epatici.

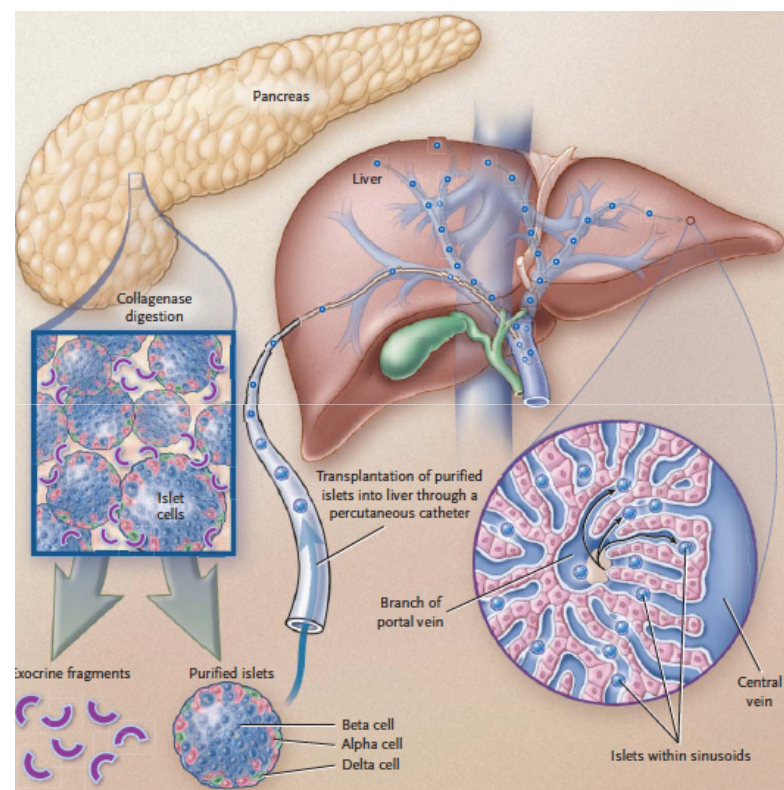


Table 1. Synopsis of Reports of Successful Islet Transplantation in Patients with Type 1 Diabetes.*

Study	Year of Report	No. of Recipients and Size of Transplant	Outcome
Largiader et al. ¹⁹	1980	1 Recipient of pancreas microfragments containing 200,000 islets	Insulin-independent with normal glucose level at 9½ mo

Allotrapianto di isole pancreatiche

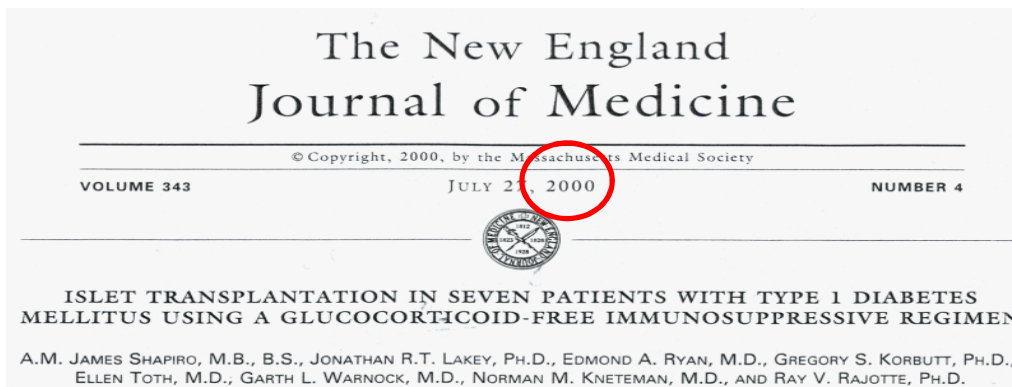
Reprinted from DIABETES, VOL. 38, SUPPLEMENT 1, JANUARY 1989
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Automated Islet Isolation From Human Pancreas

CAMILLO RICORDI, PAUL E. LACY, AND DAVID W. SCHARP

ISLET AFTER KIDNEY (IAK) TRANSPLANTATION

Diabete tipo 1 “long-term” + insufficienza renale cronica
Riceventi già obbligati a terapia immunosoppressiva a vita



ISLET TRANSPLANTATION ALONE (ITA)

Diabete tipo 1 “short-term type” + conservata funzionalità renale
Edmonton protocol → regime immunosoppressivo “steroid-free”

Allotrapianto di isole pancreatiche

→ Diabete Tipo 1 scompensato

Goals:

- Insulino-indipendenza
- Riduzione della richiesta di insulina esogena
- Riduzione degli episodi di ipoglicemia
- Prevenzione delle complicanze del diabete
- Miglioramento qualità della vita

Vantaggi vs TX di pancreas:

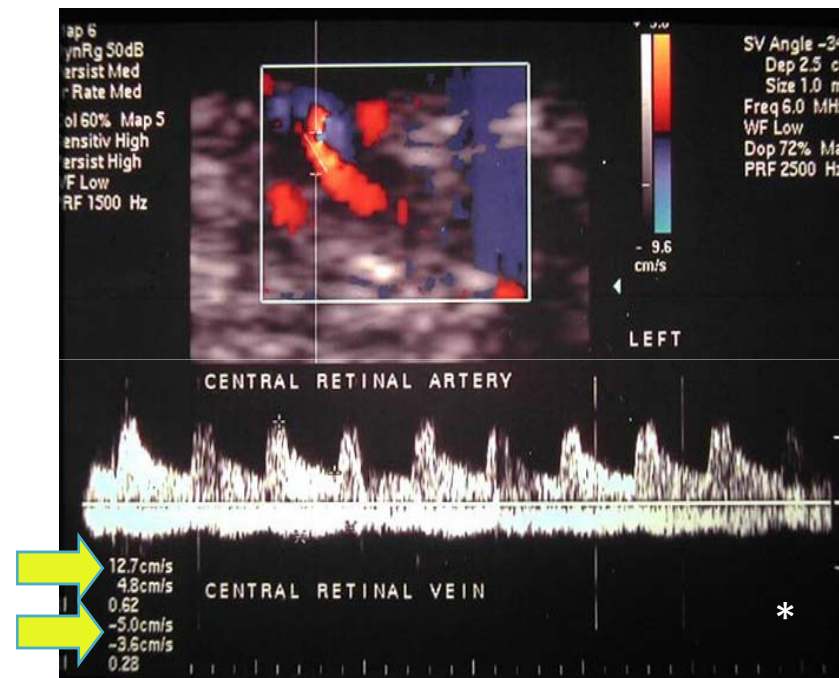
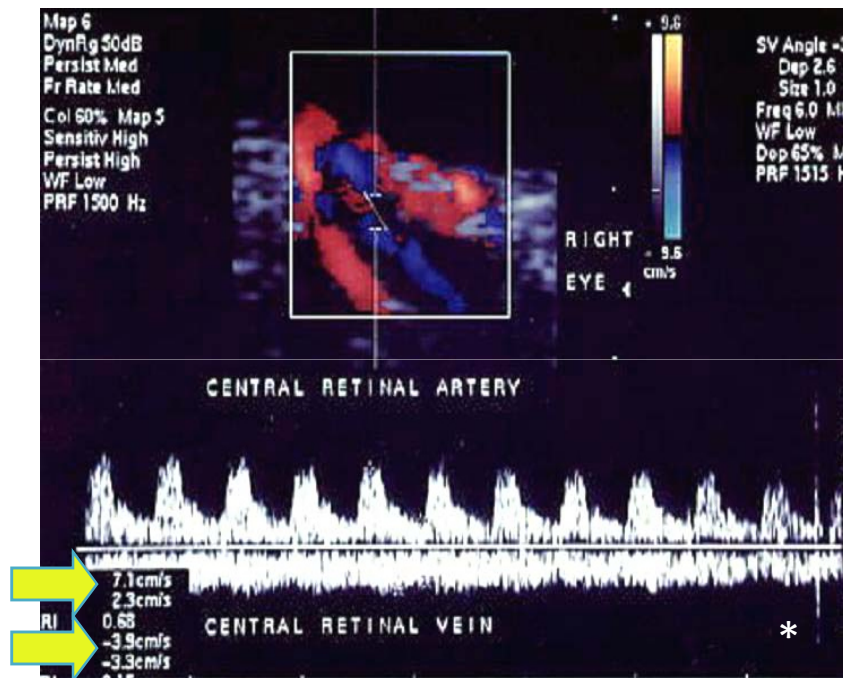
- Minore invasività
- Sicuro
- Ripetibile



ONE
PANCREAS
PLEASE

Trapianto di isole pancreatiche

effetti sulla vasculopatia periferica (→ **miglioramento flusso retinico**)



Early Increase of Retinal Arterial and Venous Blood Flow Velocities at Color Doppler Imaging in Brittle Type 1 Diabetes after Islet Transplant Alone

Massimo Venturini,¹⁻³ Paolo Fiorina,² Paola Maffi,² Claudio Losio,¹ Andrea Vergani,² Antonio Secchi,²

Autotrapianto di isole pancreatiche

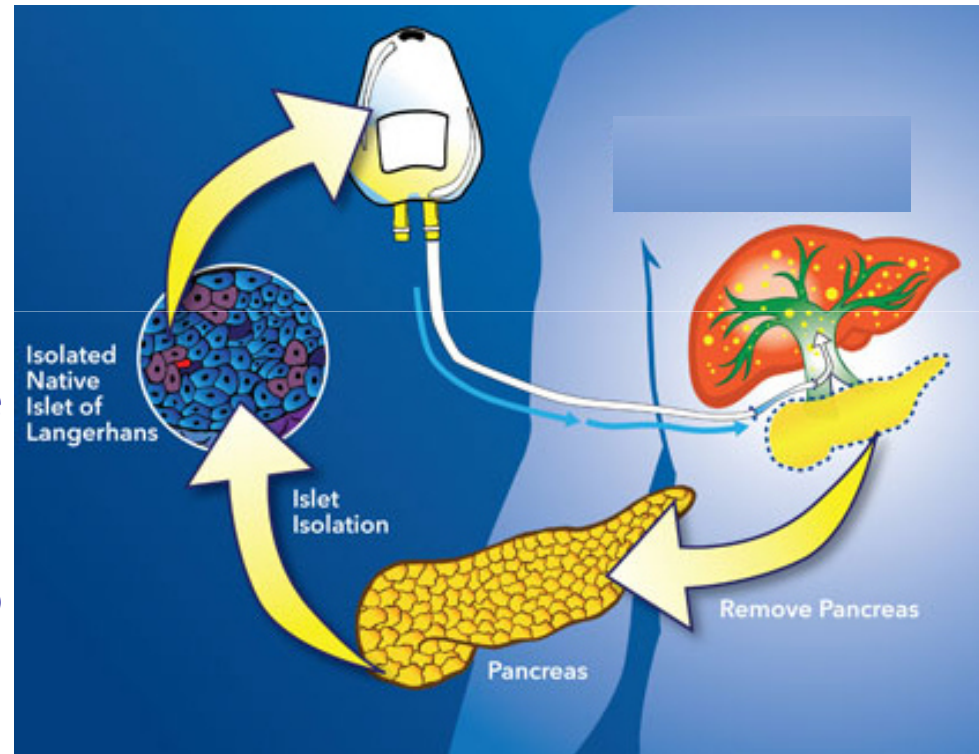
→ Diabete pancreaticogenico

Prevenzione del diabete post pancreasectomia:

- Richiesta di iniezione giornaliera di insulina esogena
- Relativamente difficile da controllare

Vantaggi vs allotrapianto:

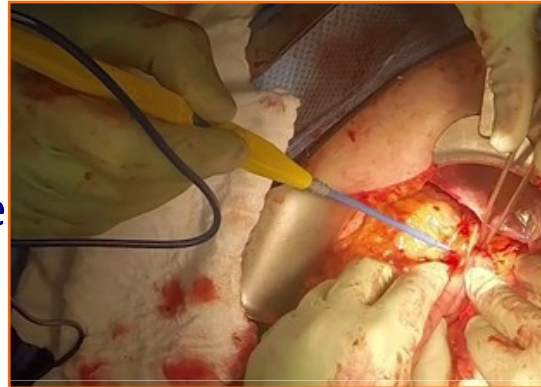
- Buona conservazione del pancreas nativo
- No terapia immunosoppressiva
- No rigetto



Autotrapianto di isole pancreatiche

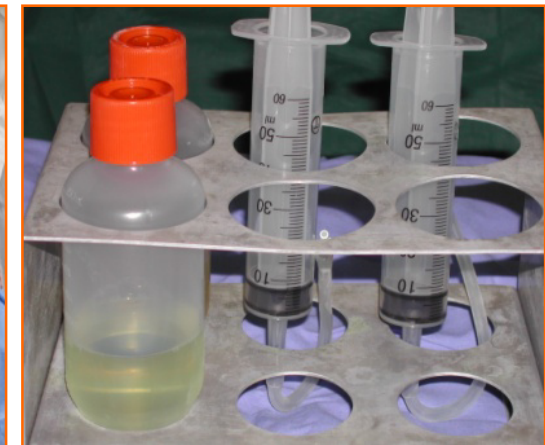
Dalla sala operatoria:

- Raccolta del segmento pancreatico da trapiantare



Al laboratorio:

- Purificazione delle isole¹³

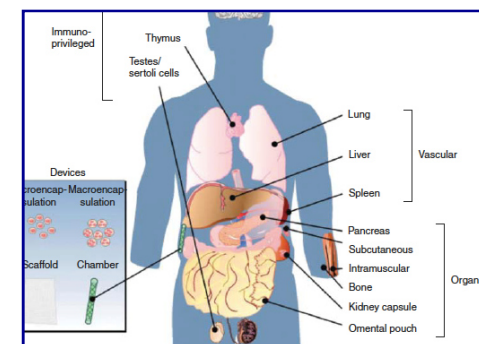
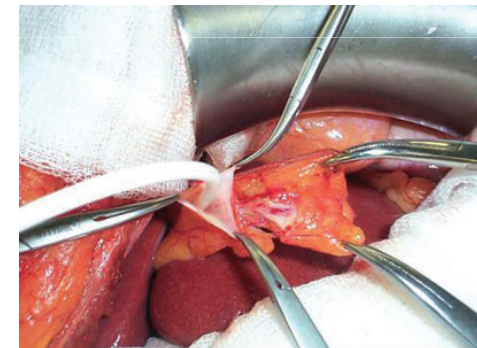
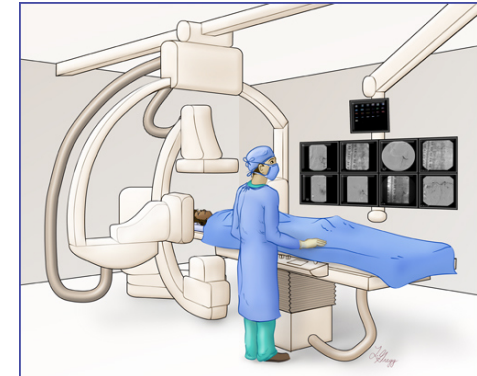


13 Melzi R, Mercalli A, Sordi V, et al. Role of CCL2/MCP-1 in islet transplantation. Cell Transplant. 2010

Autotrapianto di isole pancreatiche

Al trapianto → 3 metodi:

- Angiografico (cateterizzazione transepatica della vena porta e infusione lenta per gravità delle isole).
- Intraoperatorio (le isole purificate tornano in sala operatoria e, dopo incannulamento della vena porta con cannula 18G, vengono infuse lentamente nel flusso portale).
- Altri siti privilegiati (in pazienti dove l'infusione intraportale non è indicata, si utilizzano altri siti come il midollo osseo della cresta iliaca).

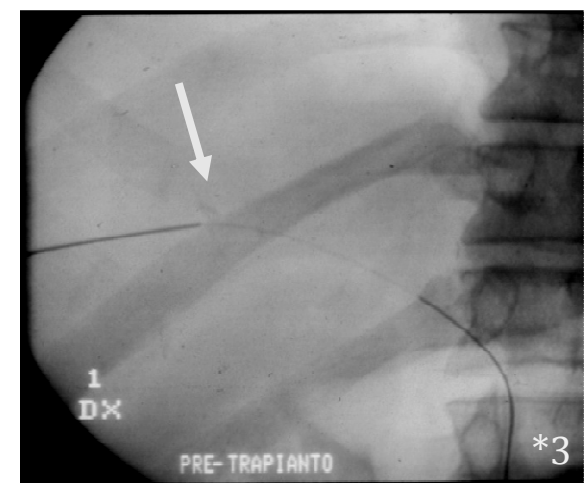


Autotrapianto di isole pancreatiche

Alla sala angiografica:

➤ Infusione delle isole*

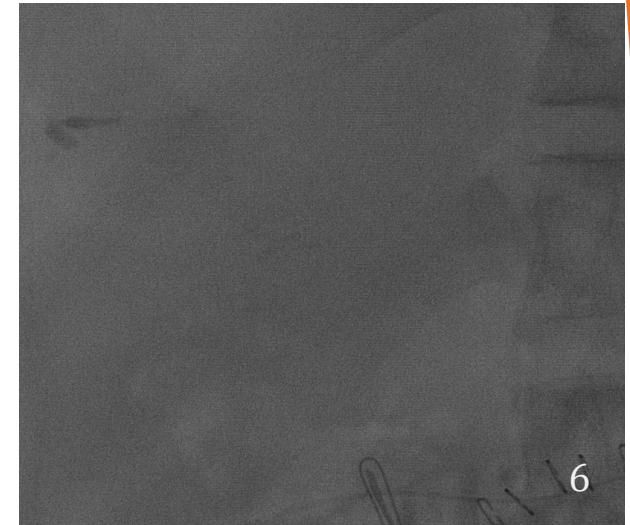
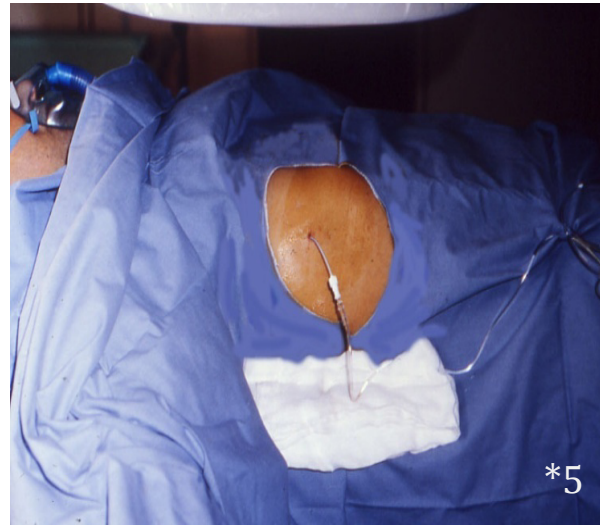
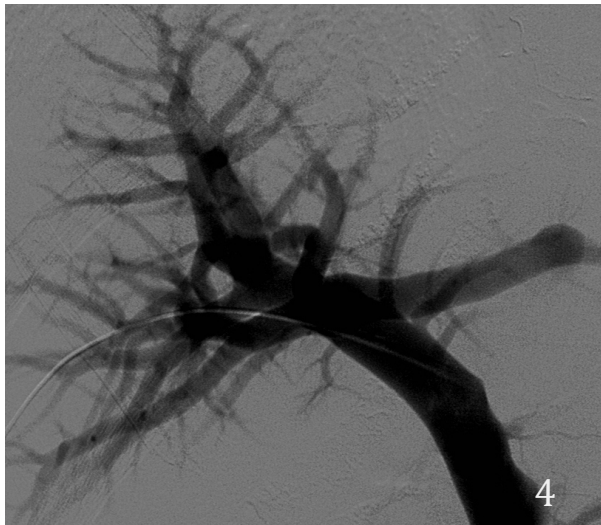
1. Valutazione colorDoppler del flusso portale.
1. Puntura ecoguidata con ago di chiba (21 G) del ramo portale destro.
1. Cateterizzazione fluoroguidata (4 Fr) del tronco portale principale



*Venturini M., Angeli E., et al. Technique, Complications, and Therapeutic Efficacy of Percutaneous Transplantation of Human Pancreatic Islet Cells in Type 1 Diabetes: The Role of US. Radiology 2003;
2nd Interventional Radiologist under 40 Meeting
Interventional Oncology

Autotrapianto di isole pancreatiche

4. Portografia + misurazione delle pressioni portalì (pre e post trapianto)
5. Infusione lenta delle isole pancreatiche (20')
6. Embolizzazione del tramite → spongostan



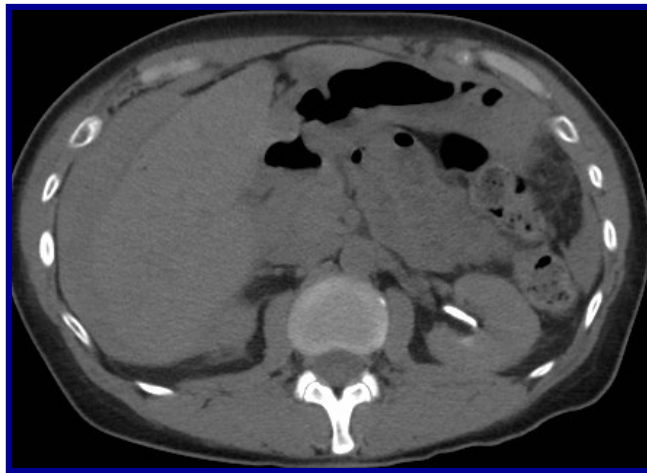
*Venturini M., Angeli E., Maffi P., et al. Technique, Complications, and Therapeutic Efficacy of Percutaneous Transplantation of Human Pancreatic Islet Cells in Type 1 Diabetes: The Role of US. Radiology 2003;
2nd Interventional Radiologist under 40 Meeting
Interventional Oncology

Complicanze post-procedurali

Comprese tra il 19 e il 23,5%¹⁻²:

Complicanze maggiori (sanguinamento, trombosi portale): 12 - 9%¹⁴⁻¹⁵.

Sanguinamento (rapida riduzione dei valori di emoglobina maggiore di 25 g/L o la necessità di trasfusioni/chirurgia): 6-12%⁴⁻¹⁵.

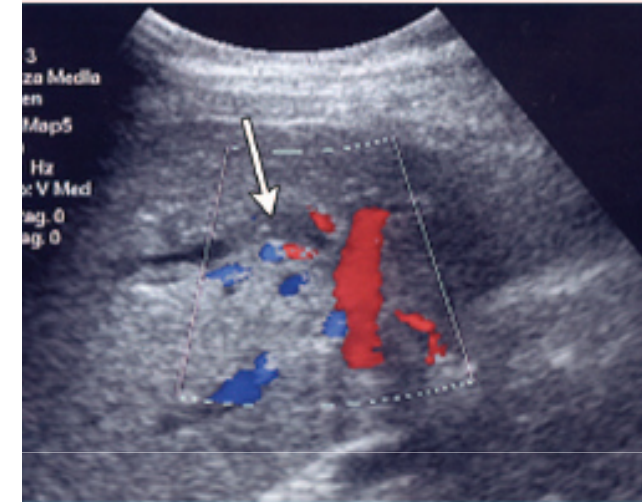


14 Owen R.J.T., Edmond A.R., et al. Percutaneous Transhepatic Pancreatic Islet Cell Transplantation in Type 1 Diabetes Mellitus: Radiologic Aspects. Radiology 2003

15 Venturini M., Sallemi C., et al. Single-centre experience of extending indications for percutaneous intraportal islet autotransplantation (PIPIAT) after pancreatic surgery to prevent diabetes: feasibility, radiological aspects, complications and clinical outcome. Br J Radiol; 2016

Complicanze post-procedurali

Trombosi portale: 2-5% ⁴⁻¹⁵ → prevalentemente segmentaria e generalmente con risoluzione completa dopo terapia anticoagulante entro 6 mesi.



DOI:10.1111/j.1477-2574.2011.00332.x

ORIGINAL ARTICLE

Percutaneous transhepatic islet cell autotransplantation after pancreatectomy for chronic pancreatitis: a novel approach

Katherine A. Morgan¹, Michael Nishimura¹, Renan Uflacker² & David B. Adams¹

HPB

prolonged ventilation. Complications related specifically to IAT included partial portal vein thrombosis (PVT), which occurred in two patients, in both of whom portal venous pressures during infusion rose to >30 mmHg. One patient was diagnosed during her completion portal venogram after transplant, was treated with systemic heparin i.v. and thrombosis resolved within 24 h without clinical consequence. The other was diagnosed remotely,

Il ruolo dell'ecografia

166 • Radiology • October 2003

Vascular and Interventional Radiology

Radiology

Richard J. T. Owen, MB
Edmond A. Ryan, MD
Kevin O'Kelly, MB
Jonathan R. T. Lakey, PhD
Malrin C. McCarthy, MB
Breay W. Paty, MD
David L. Bigam, MD
Norman M. Kneteman, MD
Gregory S. Korbutt, PhD
Ray V. Rajotte, PhD
A. M. James Shapiro, MD,
PhD

Percutaneous Transhepatic Pancreatic Islet Cell Transplantation in Type 1 Diabetes Mellitus: Radiologic Aspects¹

PURPOSE: To report our experience with percutaneous transhepatic pancreatic islet

51/68 pz → guida fluoroscopica:
4 punture non target delle vie biliari (1 dotto
biliare intraepatico, 3 punture della
colecisti) → trattamento conservativo.
17/68 pz → guida ecografica: nessuna
puntura non target.

Vascular and Interventional Radiology

Radiology

Massimo Venturini, MD
Enzo Angeli, MD
Paola Maffi, MD
Paolo Fiorina, MD
Federico Bertuzzi, MD
Marco Salvioni, MD
Francesco De Cobelli, MD
Carlo Socci, MD
Luca Aldrighetti, MD
Claudio Losio, MD
Valerio Di Carlo, MD
Antonio Secchi, MD
Alessandro Del Maschio,
MD

Technique, Complications, and Therapeutic Efficacy of Percutaneous Transplantation of Human Pancreatic Islet Cells in Type 1 Diabetes: The Role of US¹

PURPOSE: To retrospectively evaluate the role of ultrasonography (US) with regard

51/58 pz (89%): unica puntura monoparete
7/58 pz (11%): max.3 punture

Nessuna puntura non target

Complicanze: 3/58 pz (5%)

→ 1 ematoma sottocapsulare

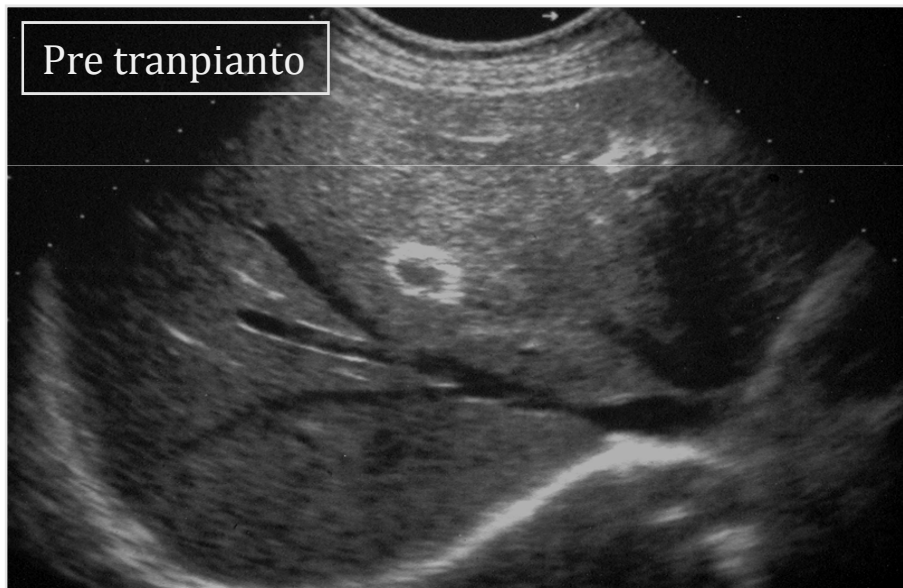
→ 1 emotorace

→ Trombosi portale subsegmentaria

Il ruolo dell'ecografia

Follow-up post-trapianto:

- ✓ Precoce 1-3-7 giorni (complicanze vascolari → **trombosi portale**)
- ✓ A lungo termine (ogni 6 mesi)



Attecchimento delle isole pancreatiche → **steatosi epatica** post trapianto¹⁵

¹⁵ Venturini M., Angeli E., et al. Technique, Complications, and Therapeutic Efficacy of Percutaneous Transplantation of Human Pancreatic Islet Cells in Type 1 Diabetes: The Role of US. Radiology 2005;
2nd Interventional Radiologist under 40 Meeting
Interventional Oncology

Steatosi epatica post trapianto

Magnetic Resonance–Defined Periportal Steatosis Following Intraportal Islet Transplantation A Functional Footprint of Islet Graft Survival?

James F. Markmann,¹ Mark Rosen,² Evan S. Siegelman,² Michael C. Soulen,² Shaoping Deng,¹ Clyde F. Barker,¹ and Ali Naji¹

DIABETES, VOL. 52, JULY 2003

DIABETICMedicine

DOI: 10.1111/j.1464-5491.2010.03035.x

Short Report

Liver focal fatty changes at ultrasound after islet transplantation: an early sign of altered graft function?

M. Venturini*, E. Angeli*, P. Maffi†, C. Losio*, P. Pozzi†, C. Paties†, M. Cellina*, F. De Cobelli*¶, P. Fiorina†§, A. Secchi*¶ and A. Del Maschio*¶



Contents lists available at ScienceDirect

Pharmacological Research

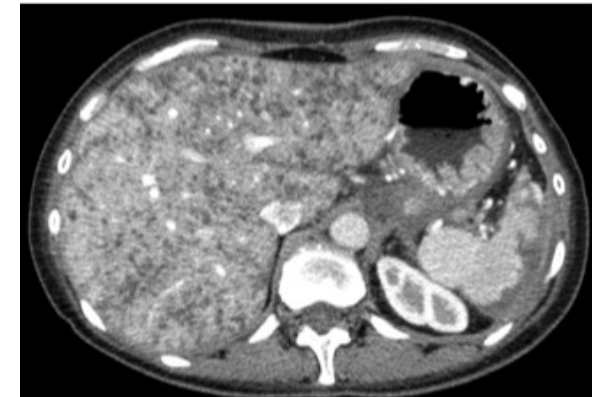
Journal homepage: www.elsevier.com/locate/yphrs



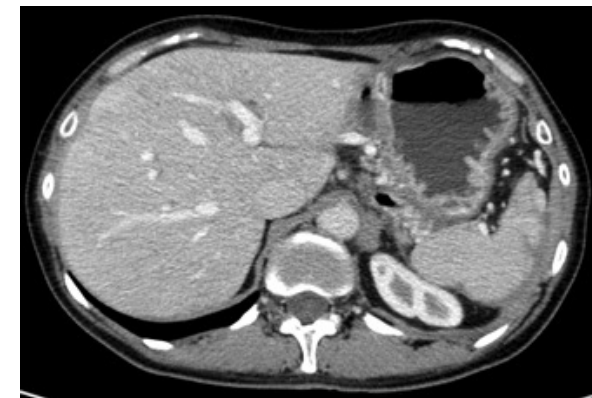
Hepatic steatosis after islet transplantation: Can ultrasound predict the clinical outcome? A longitudinal study in 108 patients



Massimo Venturini^{a,*}, Paola Maffi^b, Giulia Querques^c, Giulia Agostini^a, Lorenzo Piemonti^b, Sandro Sironi^c, Francesco De Cobelli^{a,d}, Paolo Fiorina^e, Antonio Secchi^{b,d}, Alessandro Del Maschio^{a,d}



6 mesi post trapianto



12 mesi post trapianto

Segno precoce di perdita di funzione del graft?

ORIGINAL ARTICLE

Total Pancreatectomy With and Without Islet Cell Transplantation for Chronic Pancreatitis

A Series of 85 Consecutive Patients

Giuseppe Garcea, MD, MRCS, James Weaver, MBChB, John Phillips, MBChB, Cristina A. Pollard, BA, Severine C. Ilouz, PhD, M'Balu A. Webb, BSc, David P. Berry, MD, FRCS, and Ashley R. Dennison, MD, FRCS

Studio monocentrico prospettico – 85 pz sottoposti a pancreatectomia (50 con associato IAT).
Follow up da 6 a 10 anni (mediana 8 anni).

- 12 pz insulino indipendenti per un periodo significativo.
- 5 pz insulino indipendenti per tutto il follow up.

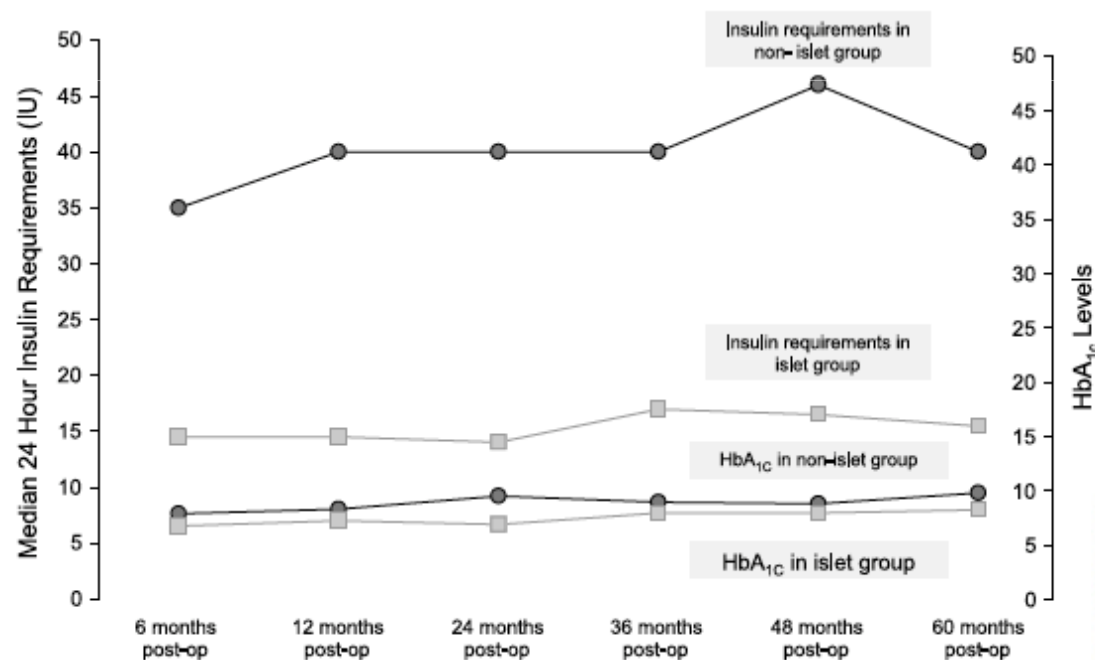
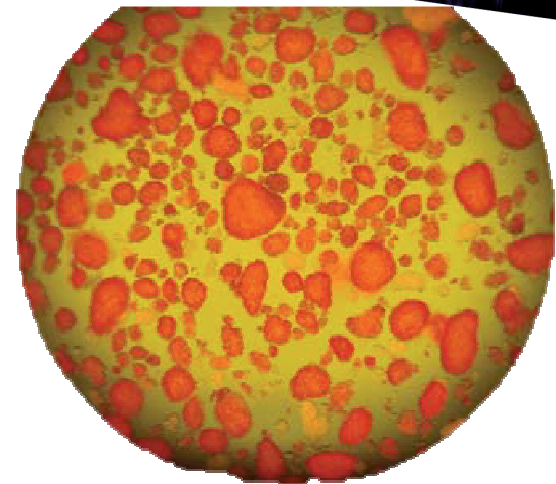


FIGURE 6. Median 24-hour insulin requirements and HbA_{1c} levels in islet cell recipients and non-islet cell recipients.

Criticità: il numero di isole

CRITICAL ISLET MASS IN ISLET AUTOTRANSPLANTATION(IaTx) AFTER PANCREAS(Px) RESECTION. Raja Kandaswamy,¹ Bernhard Hering,¹ David E.R. Sutherland.¹

	Insulin ind.	Mean IEQ/ kg (SD)	Mean Px wt(g) (SD)	Mean pt wt(kg) (SD)
IEQ/kg>2500 (n=10)	80% (8)	4692(1213)	67(7)	60(7)
IEQ/kg<2500 (n=4)	0%	1002(777)	38(23)	63(21)
p value	0.02	0.00002	0.04	0.83
Prev Px surg (n=5)	20%(1)	1995 (1877)	38(20)	54(10)
No prev Px surg (n=9)	78%(7)	4214(1491)	57(26)	65(22)
p value	0.49	0.04	0.16	0.2



Pancreas Resection and Islet Autotransplantation for End-Stage Chronic Pancreatitis

Ann. Surg. • March 2001

Steven A. White, MD,† Joanne E. Davies, PhD,* Cris Pollard, BA,* Sue M. Swift, PhD,† Heather A. Clayton, PhD,* Chris D. Sutton, FRCS,* Simon Weymss-Holden, DM,* Patrick P. Musto, FRCA,* David P. Berry, MD,* and Ashley R. Dennison, MD*

I pazienti che hanno ricevuto meno di 2500 IEQ/kg → 35% insulino indipendenza.

Associazione significativa tra insulino indipendenza e numero di isole trapiantate

REVIEW

Endocrine Journal 2015, 62 (3), 227-234

Systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients

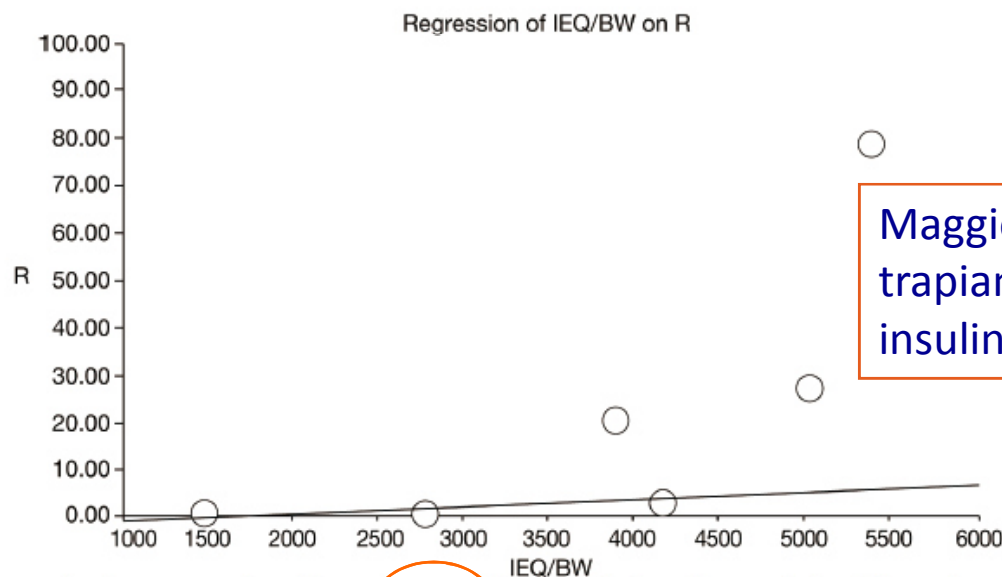
Qian Wu¹⁾, Mei Zhang¹⁾, Yao Qin¹⁾, Ruimei Jiang¹⁾, Heng Chen¹⁾, Xinyu Xu¹⁾, Tao Yang¹⁾,
Kuirong Jiang²⁾ and Yi Miao²⁾

Criteri di inclusione: pazienti con pancreatite cronica sottoposti a TP+IAT

Criteri di esclusione: **pazienti con tumori maligni**; case report e follow up <6 mesi

Single-centre case series

Follow up range: da 1 210 mesi



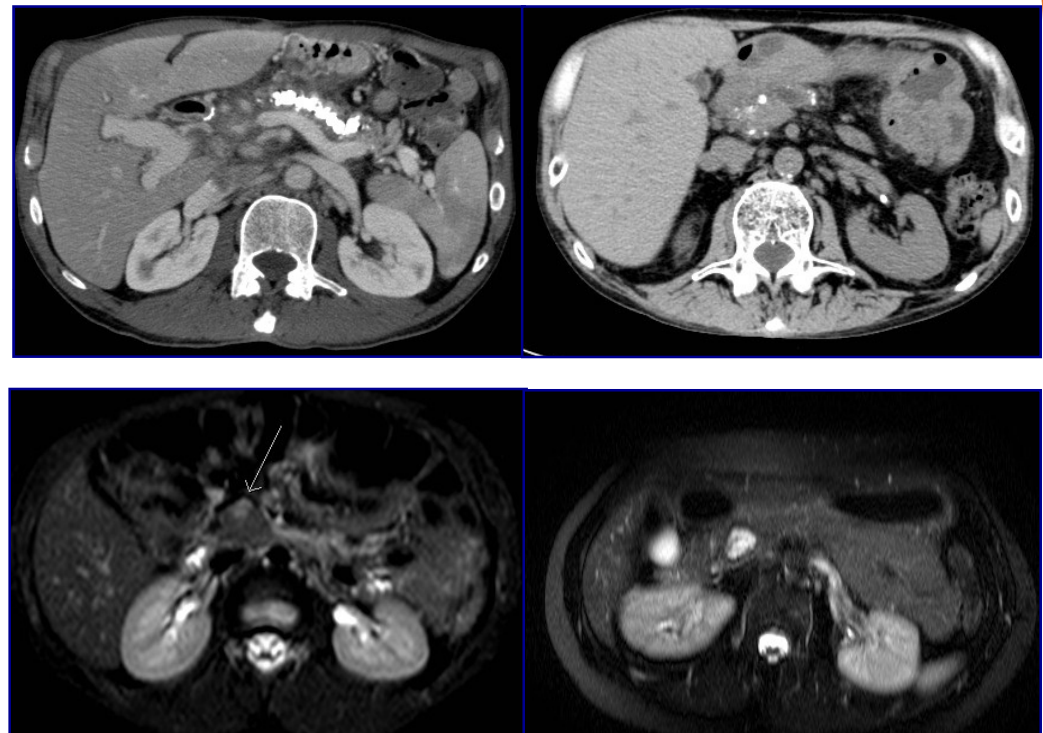
Maggior è il numero di IEQ/kgBW trapiantate, più alto sarà il grado di insulino indipendenza

Fig. 3 Meta-regression between R and IEQ/kgBW ($P=0.026$) (R, insulin independence at the last follow up)

Autotrapianto di isole pancreatiche

Pancreasectomia + autotrapianto di isole: indicazioni

- Pancreatite cronica¹⁶⁻¹⁷
- Chirurgia pancreatica (tumori benigni del corpo-coda)¹⁸
- Pancreasectomia totale per trauma addominale severo¹⁹



¹⁶ Dong M, et al. Systematic review and meta-analysis: islet autotransplantation after pancreatectomy for minimizing diabetes. Clin Endocrinol (Oxf). 2011;

¹⁷ Sutherland DE, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg. 2012;214:409–424;

¹⁸ Ris F, et al. Islet autotransplantation after extended pancreatectomy for focal benign disease of the pancreas. Transplantation. 2011;91:895–901.

¹⁹ Jindal RM, et al. Autologous pancreatic islet transplantation for severe trauma. N Engl J Med. 2010;362:1550.

REVIEW

Endocrine Journal 2015, 62 (3), 227-234

Systematic review and meta-analysis of islet autotransplantation after total pancreatectomy in chronic pancreatitis patients

Qian Wu¹⁾, Mei Zhang¹⁾, Yao Qin¹⁾, Ruimei Jiang¹⁾, Heng Chen¹⁾, Xinyu Xu¹⁾, Tao Yang¹⁾,
Kuirong Jiang²⁾ and Yi Miao²⁾

Studies	Period of inclusion	Islet isolation Institution	No. of patients	Female %	Age (years)	Duration of CP(years)	Baseline DM%	Alcoholic %	Length of follow-up (months)	Transplanted IEQ/kg body weight
Cameron <i>et al.</i> [7]	1978-1980	Johns Hopkins	8	13	43.1±10.9	6.7(1-20)	0	75	NR	NR
Hinshaw <i>et al.</i> [8]	1979-1980	California	5	20	42.4±5.7	5.6±3.8	20	80	13±5.2	NR
Rastellini C <i>et al.</i> [9]	1990-1996	Pittsburgh Centre	5	NR	NR	NR	0	NR	3-64	NR
Oberholzer <i>et al.</i> [10]	1992-1999	Geneva	6	NR	NR	NR	NR	NR	45.7±17.5	2785 (386-3223)
Ahmad <i>et al.</i> [11]	2000-2004	Cincinnati	45	67	39(16-62)	NR	NR	4	18(1-46)	4933±520
Argo <i>et al.</i> [12]	2005-2007	UAB	21	40	43.5±2.4	NR	100	30	6.7±1.7	1551 ± 368
Dixon <i>et al.</i> [13]	1998-2008	South Carolina	7	57	M:29,F:40	NR	0	NR	NR	NR
Takita <i>et al.</i> [14]	2006-2009	Baylor	17	76	40.1	7.0	6	12	7.3±2.6	5279±571
Sutherland <i>et al.</i> [15]	1977-2011	Minnesota	409	74	35.3(5-69)	6.6±0.3	8	7	NR	NR
Walsh <i>et al.</i> [16]	2007-2010	Cleveland Clinic	20	40	43±13.3	NR	0	25	12(6.75-24)	3846(3063-5430)
Dorlon <i>et al.</i> [17]	2009-2012	South Carolina	74	80	42(16-69)	8(1-28)	14	8	NR	4114
Garcea <i>et al.</i> [18]	1990-2013	Leicester	60	NR	43(21-65)	5(0.5-35)	NR	31.7	138(6-210)	NR

Mortalità a 30 gg : 0-1,2%¹⁶⁻¹⁷.

Insulino indipendenza a 2 aa fino al 32%¹⁷.

¹⁶ Dong M, et al. Systematic review and meta-analysis: islet autotransplantation after pancreatectomy for minimizing diabetes. Clin Endocrinol (Oxf). 2011;

¹⁷ Sutherland DE, et al. Total pancreatectomy and islet autotransplantation for chronic pancreatitis. J Am Coll Surg. 2012;214:409-424;

¹⁸ Ris F, et al. Islet autotransplantation after extended pancreatectomy for focal benign disease of the pancreas. Transplantation. 2011;91:895-901.

Autotrapianto di isole pancreatiche

Pancreasectomia + autotrapianto di isole: indicazioni

- Chirurgia pancreatica (tumori benigni del corpo-coda)³



Lee et.(2005)→ 10 pazienti con pancreasectomia parziale + IAT : no mortalità, basso grado di complicanze (sospetta PVT in 1 paziente) e 70% di insulino indipendenza a 1 anno.

Ris et al (2011)→ 15 pazienti pancreasectomia parziale + IAT: no mortalità e basso grado di morbidità (batteriemia in 1 paziente)e grado di insulino indipendenza del 94% a 10 anni.

Can J Diabetes 37 (2013) S94–S96



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www.canadianjournalofdiabetes.com



Clinical Practice Guidelines

Pancreas and Islet Transplantation

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

RECOMMENDATIONS

1. Individuals with type 1 diabetes and ESRD who are being considered for kidney transplantation should also be considered for simultaneous pancreas transplantation [Grade D, Level 4 (12,14)].
2. Individuals with type 1 diabetes with preserved renal function, or who have undergone successful kidney transplantation but have persistent metabolic instability characterized by severe glycemic lability and/or severe hypoglycemia despite best efforts to optimize glycemic control, may be considered for pancreas or islet allotransplantation [Grade D, Consensus].
3. Individuals undergoing total pancreatectomy for benign pancreatic disease may be considered for islet autotransplantation but only in the context of an experienced islet transplantation centre [Grade D, Consensus].

Abbreviation:

ESRD, end stage renal disease.

Review Article

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Clinical Transplantation

Current principles and practice in autologous intraportal islet transplantation: a meta-analysis of the technical considerations

Table 1. Overview of the world literature series – indications for pancreatectomy with IAT

Author, IAT center, level of evidence	No. of cohort	Etiology	Total (TP)/segmental pancreatectomy (SP)	Islet yield (IEQ/kg)
Ahmad et al., Cincinnati Level III Retrospective	45	CP	TP	4933
Argo et al., Alabama Level III Prospective	6	CP	SP	1317 ± 692
Argo et al., Alabama Level III Prospective	21	CP	TP	3145 ± 692
Cameron et al., Baltimore Level III Prospective	8	CP	SP	NR
Oberholzer et al., Geneva Level III Prospective	6	CP	TP	2785 (285–4362)
Berney et al., Geneva Level III Prospective	7	Benign tumors	SP	4190 ± 3960
Ris et al., Geneva group Level III Prospective	15	Benign tumor and trauma	SP (Distal)	Total 222 367
Dixon et al., South Carolina Level III Prospective	7	CP	TP	NR
Hinshaw et al., California (1980) Level III Prospective	5	CP	TP	NR
Jindal et al., Indianapolis Level III Prospective	6	CP	TP	3229 (1630–6290)
Fontana et al., Genoa Level III Prospective	24	CP	TP	NR
Webb et al., Leicester Level III Prospective	46	CP	TP	2245 (405–20 385)
Garraway et al., British Columbia Level III Retrospective	2	Trauma	SP (distal in both cases)	Total 88 000 & 32 5000
Sakata et al., Sedai, Japan Level III Retrospective	3	Pancreatic arterio-venous malformation	TP	310,238, 244 758, 355 270
Gala-Lopez et al., Alberta, Canada Level III Retrospective	1	Multifocal metastasis from renal cell cancer	TP	4400
Jindal et al., Miami/Washington Level III Retrospective	1	Severe gunshot trauma to pancreas	TP and remote center processing of pancreas for islet cells and infusion within 24 h	3000
Liu et al., Rostock, Germany Level III Retrospective	1	Adeno-carcinoma leakage	TP	Total 116 000
Kobayashi et al., Nagaoka, Japan Level III Retrospective	1	Recurrent pancreas cancer in the remnant pancreas	TP (i.e., completion)	NR

TRANSPLANTATION PROCEEDINGS

May 2004

Volume 36, Issue 4, Pages 1125–1126

Islet autotransplantation combined with pancreatectomy for treatment of pancreatic adenocarcinoma: a case report

S Förster, X Liu, U Adam, W.D Schareck, U.T Hopt

DOI:10.1111/hpb.12062

HPB

ORIGINAL ARTICLE

Relaparotomy for a pancreatic fistula after a pancreaticoduodenectomy: a comparison of different surgical strategies

Gianpaolo Balzano¹, Nicolò Pecorelli¹, Lorenzo Piemonti², Riccardo Ariotti¹, Michele Carvello¹, Rita Nano², Marco Braga¹
& Carlo Staudacher¹

¹Pancreatic Surgery Unit, Department of Surgery and ²Islet Producing Facility, San Raffaele Scientific Institute, Milan, Italy

Abstract

Introduction: A relaparotomy for a pancreatic fistula (PF) after a pancreaticoduodenectomy (PD) is a formidable operation, and the appropriate treatment of anastomotic leakage is under debate. The objective of this study was to compare the outcomes of different strategies in managing the pancreatic remnant during a relaparotomy for PF after a PD.

Methods: In this retrospective study on prospectively collected data, 669 PD were performed between 2004 and 2011. The study group comprised 31 patients requiring a relaparotomy, because of delayed haemorrhage ($n = 19$) or sepsis ($n = 12$). The pancreatic stump was treated either using pancreas-preserving techniques (simple drainage or duct occlusion) or completion of a pancreatectomy (CP). In 2008, autologous islet transplantation (AIT) was introduced for endocrine tissue rescue of CP.

Results: The mortality rate, blood loss and transfusion requirement were similar for all techniques. Patients undergoing a CP required a further relaparotomy less frequently than patients with pancreas preservation (7% versus 59%, $P < 0.01$), and the intensive care unit (ICU) stay was reduced after CP ($P = 0.058$). PF persisted at discharge in 66% of patients after pancreas-preserving techniques. AIT was associated with CP in 7 patients, of whom one died post-operatively. Long-term graft function was maintained in four out of six surviving patients, with one insulin-independent patient at 36 months after transplantation.

Conclusions: When a PF requires a relaparotomy, CP has become our favoured technique. AIT can reduce the metabolic impact of the procedure.

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Extending Indications for Islet Autotransplantation in Pancreatic Surgery

Milan protocol (2008)

Gianpaolo Balzano, MD,* Paola Maffi, MD,† Rita Nano, MChem,‡ Alessandro Zerbi, MD,§ Massimo Venturini, MD,¶ Raffaella Melzi, MBiol,‡ Alessia Mercalli, MBiol,‡ Paola Magistretti, MBiol,† Marina Scavini, MD,|| Renato Castoldi, MD,* Michele Carvello, MD,* Marco Braga, MD,*†† Alessandro Del Maschio, MD,§†† Antonio Secchi, MD,*†† Carlo Staudacher, MD,*†† and Lorenzo Piemonti, MD‡

Table 1: Indications for IAT according to the Milan Protocol¹

- I. Clinical indications for IAT (must have either of the followings, A to D)
 - A Pancreatitis
 - Chronic pancreatitis: cases of nondilated duct without any cephalic mass when subtotal or total pancreatectomy is indicated (refractory pain in patients in whom medical therapy has failed)
 - Acute pancreatitis: in cases of recurrent disease (≥3 episodes over 6 months without evidence of current gallstone or other correctable aetiology)
 - B High-risk pancreatic stump
Patients undergoing pancreaticoduodenectomy in whom pancreatic anastomosis was deemed at high risk for leakage (according to the judgment of the chief surgeon), based on a combination of narrow duct and soft and/or frail pancreatic texture (NCT01346098)
 - C Extensive distal pancreatectomy
For benign/borderline neoplasm located at the pancreatic body neck (as an alternative to median pancreatectomy)
 - D Severe complications after pancreatic surgery
Grade C pancreatic fistula, according to the definition of the International Study Group on Pancreatic Fistula, requiring relaparotomy with completion pancreatectomy or left pancreatectomy
- II. General indications for IAT (must have each of the followings, 1–4)
 - (1) Age >18 years
 - (2) Fasting glycaemia <126 mg/dL without glucose-lowering medications
 - (3) Ability to provide written informed consent
 - (4) Mental stability and ability to comply with study procedures

Contraindications

The presence of a pancreatic malignant disease was not an exclusion criterion *per se*, although patients who met any of the following criteria were not eligible:

- (1) Presence of any multifocal pancreatic neoplasm at preoperative imaging or intraoperative evaluation
- (2) Diagnosis of intraductal papillary mucinous neoplasm, unless the absence of multifocal lesion is demonstrated by endoscopic ultrasound
- (3) Involvement of the pathologic pancreatic transection margin, including any degree of dysplasia or ductal disepithelialization. If a malignant disease is the reason for the surgery, 1 cm of the pancreatic remnant close to the pancreatic margin will be resected and sent for immediate pathology to confirm margin negativity and to rule out multifocal tumor.
- (4) Diagnosis (suspected or ascertained) of multiple endocrine neoplasm
- (5) Any medical condition that, in the opinion of the investigator, might interfere with the safe completion of IAT

¹To be considered for IAT, patients must meet criteria in sections I and II, without contraindications.

Extending Indications for Islet Autotransplantation in Pancreatic Surgery

Gianpaolo Balzano, MD,* Paola Maffi, MD,† Rita Nano, MChem,‡ Alessandro Zerbi, MD,§
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508 Pz sottoposti a chirurgia pancreatica 41 cadidati a resezione
 +IAT → 8 esclusi per isole inadeguate o contaminazione batterica

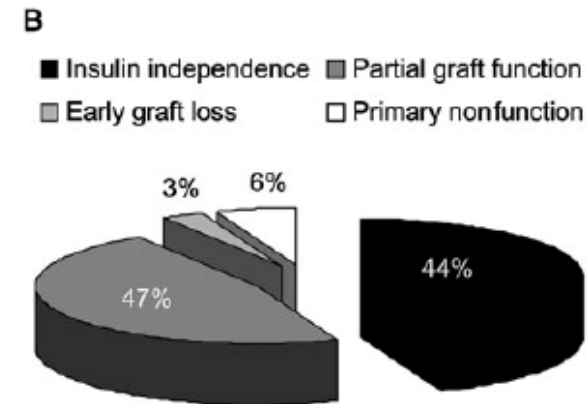
	Subtotal Pan- createctomy for Chronic Pancreatitis	Pancreatic Resection Because of Postoperative Complications	Predicted High-Risk Anastomosis During PD	Extensive Distal Pancreatectomy for Benign Neoplasm	TOT
N	2	15	16	8	41
Age	42 ± 11	55 ± 4	63 ± 3	58 ± 4	58 ± 2.1
Sex (M/F)	2/0	11/4	11/5	2/6	26/15
Body mass index	22.8 ± 3.6	25.7 ± 0.92	25.2 ± 1	26.8 ± 1.3	25.5 ± 0.59
Diagnosis					
Periampullary tumors*	—	#1, #9, #11, #12, #24, #32	#4, #20, #22, #26, #35, #40	—	12
Pancreatic ductal adenocarcinoma	—	#6, #33, #34,	#7, #14, #15, #25, #30, #36	—	9
Pancreatic cystic neoplasm†	—	#16, #18	#19, #39	#23, #28, #29, #31	8
Neuroendocrine neoplasm	—	#27, #3	#13, #17	#2, #10, #21	7
Chronic pancreatitis	#8, #38	#5	—	—	3
Others‡	—	#37	—	#41	2
Disease localization					
Head	—	13	16	—	29
Neck/Body	—	2	—	8	10
Diffuse	2	—	—	—	2

*Adenocarcinoma of the ampulla of Vater (n = 4), adenocarcinoma of the distal bile duct (n = 3), adenocarcinoma of the duodenum (n = 2), adenoma of the duodenum and papilla of Vater (n = 2), and duodenal gangliocytic paraganglioma (n = 1).

†Serous cystoadenomas (n = 3), mucinous cystoadenomas (n = 3), intraductal papillary mucinous neoplasms (n = 1), and solid-pseudopapillary neoplasm (n = 1).

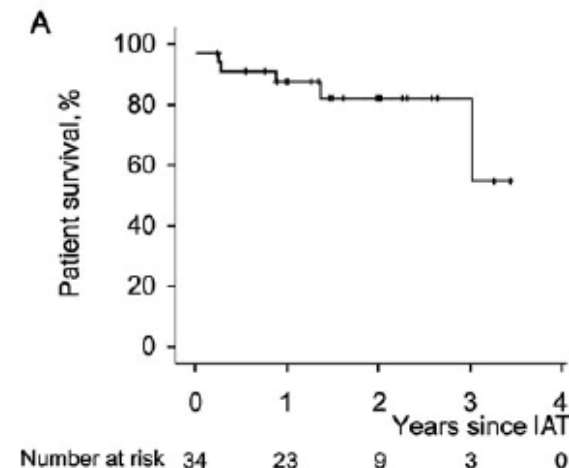
‡Gastrointestinal stromal tumor (n = 1) and sequelae after iatrogenic duodenal perforation (n = 1).

Insulino indipendenza: 15/34 pts (44%)
 Funzione parziale del graft: 16/34 pts (47%)
 Disfunzione primaria del graft : 2/34 pts (6%)
 Perdita precoce del graft: 1/34 pt (3%)



Mediana IEQ trapiantate di
 2032 IEQ/kg (553–5018 IEQ/kg).

Mediana follow up 491 giorni
 Tutti i pz con npl benigna/basso grado
 di malignità liberi da malattia



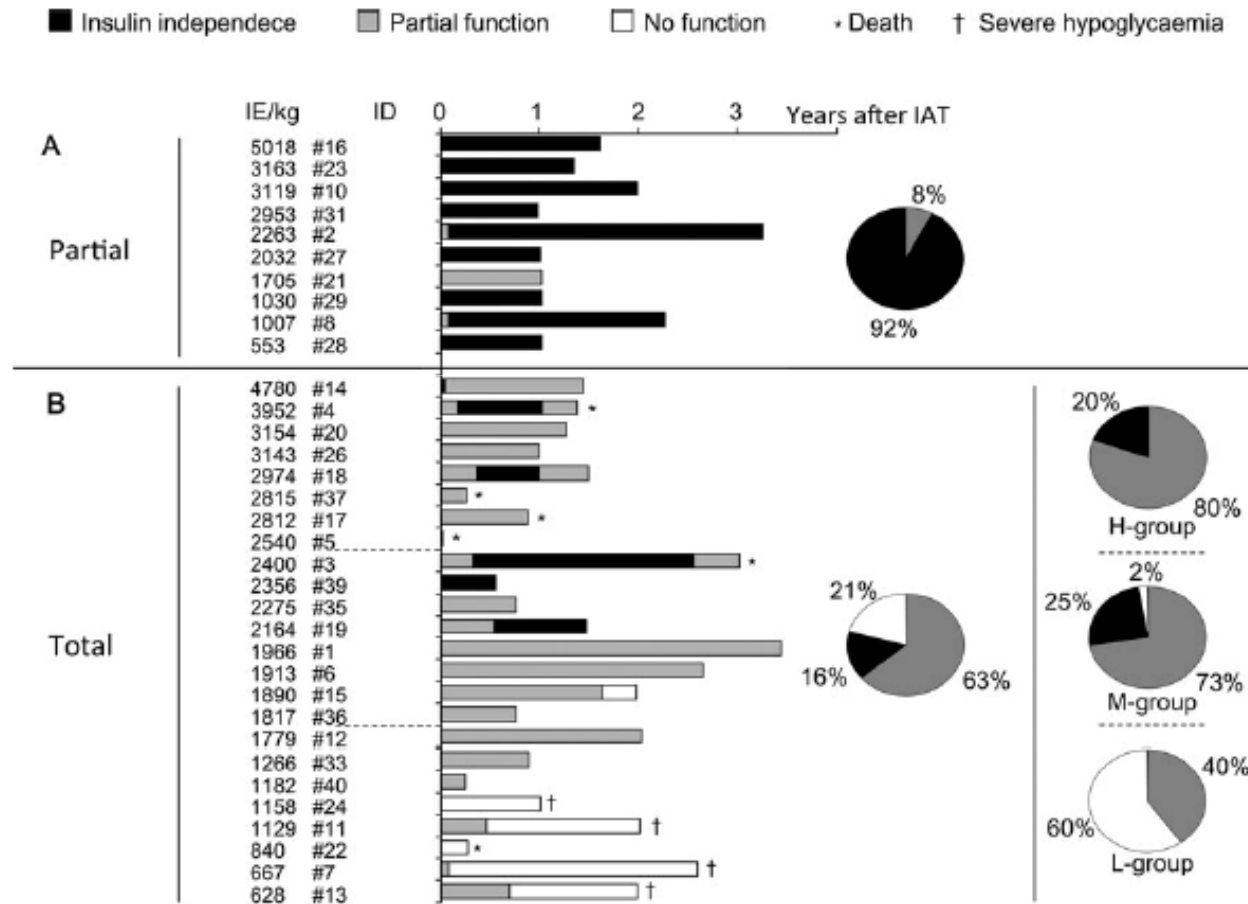
Pazienti con tumore maligno

- 13/17 pz (71%) disease free (mediana follow up, 725 gg);.
- 4/17 hanno sviluppato metastasi a distanza (peritoneo e polmone).

TABLE 3. Oncologic Characteristics: TNM, Stage, Follow-up

Total Pancreatectomy With IAT										PD Without IAT*		
ID	pT	pN	pM	R†	G	Stage UICC-TNM	CT/RT	Disease-Free Survival and Recurrence Site	Death	n	Disease-Free Survival	Overall Survival
Pancreatic ductal adenocarcinoma												
#6	3	0	0	0	2	IIA	Yes	Local + Lung (738d)	No	32	386d (330–441)	> 750d
#33	3	0	0	0	2	IIA	Yes	Disease-free (32.5d)	No			
#36	3	0	0	1	2	IIA	Yes	Disease-free (27.9d)	No			
#14	3	0	0	0	3	IIA	Yes	Disease-free (843d)	No			
#7	3	1	0	1	3	IIB	Yes	Disease-free (944d)	No	99	350d (226–473)	578d (465–690)
#15	3	1	0	1	2	IIB	Yes	Disease-free (722d)	No			
Adenocarcinoma of the ampulla of Vater												
#1	2	0	0	0	2	II	No	Disease-free (1254d)	No	14	265d (68–461)	564 d (0–1254)
#26	2	0	0	0	2	II	No	Disease-free (364d)	No			
#40	2	0	0	0	1	II	No	Disease-free (89d)	No			
#12	2	1	0	0	2	III	Yes	Disease-free (73.9d)	No	11	247d (191–302)	505d (225–603)
Carcinoma of the distal bile duct												
#24	3	0	0	0	1	IIA	No	Disease-free (368d)	No	4	IN	IN
#11	3	1	0	0	2	IIB	Yes	Disease-free (733d)	No	5	IN	IN
Adenocarcinoma of the duodenum												
#22	4	1	0	0	3	III	No	Peritoneum (87d)	Yes (102d)	1	IN	IN
#4	3	0	1	2	2	IV	Yes	Already liver metastases at the time of surgery	Yes (501 d)	1	IN	IN
Neuroendocrine carcinoma												
#3	4	1	0	0	1	III	Yes	Disease-free (1102d).	Yes (1102)	0	IN	IN
#17	3	1	1	2	3	IV	Yes	Already liver metastases at the time of surgery	Yes (322 d)	3	IN	IN
Duodenal gangliocytic paraganglioma												
#20	2	1	0	0	1	—	No	Disease-free (421d)	No	0	IN	IN

Numero di isole e pancreasectomia parziale vs. totale sono fattori di rischio indipendenti di insulino-indipendenza



Br J Radiol;89:20160246

Single-centre experience of extending indications for percutaneous intraportal islet autotransplantation (PIPIAT) after pancreatic surgery to prevent diabetes: feasibility, radiological aspects, complications and clinical outcome

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²GIANPAOLO BALZANO, MD, ^{1,3}ANTONIO ESPOSITO, MD, ^{3,4}ANTONIO SECCHI, MD, ^{1,3}FRANCESCO DE COBELLI, MD,
^{2,3}MASSIMO FALCONI, MD, ⁵LORENZO PIEMONTE, MD, ⁴PAOLA MAFFI, MD and ^{1,3}ALESSANDRO DEL MASCHIO, MD

Legate alla procedura: 8/34 pazienti (23.5%), maggiori in 4/8 (14.7%) (TCAE score ≥ 3):

Trombosi portale in 3/84:

- 1/3 branca sinistra e 2/3 segmentarie → risoluzione dopo terapia anticoagulante con eparina a basso peso molecolare.

Sanguinamento da accesso transepatico in 4/34 pz:

- 2/4 (ematoma periepatico), trattamento conservativo;
- in 1/4 solo trasfusioni;
- 1/4 ha richiesto trasfusioni+intervento chirurgico.

Complicanze non maggiori rispetto a quanto riportato in letteratura

Pancreatology 2014 ;

Original article

Total pancreatectomy and islet autotransplantation in chronic pancreatitis: Recommendations from *PancreasFest*

Melena D. Bellin^{a,**,1}, Martin L. Freeman^{b,1}, Andres Gelrud^{c,1}, Adam Slivka^{d,1}, Alfred Clavel^e, Abhinav Humar^{f,1}, Sarah J. Schwarzenberg^a, Mark E. Lowe^{g,h,1}, Michael R. Rickelsⁱ, David C. Whitcomb^{d,*}, Jeffrey B. Matthews^{j,1}, for the PancreasFest Recommendation Conference Participants²

International Association of Pancreatology and European Pancreatic Club.

7. Clinical recommendations

Discussion Question 1: What are the indications for considering TPIAT to manage chronic pancreatitis?

Guidance Statement 1: The primary indication for TPIAT is to treat intractable pain in patients with impaired quality of life due to CP or RAP in whom medical, endoscopic, or prior surgical therapy have failed.

Evidence Level: 2a.

Grade of recommendation: B.

Level of Agreement: A 76%; B 19%; C 5%; D 0

Q2.2: What are the medical contraindications for TPIAT?

Guidance Statement 2.2: TPIAT should not be performed in patients with specific medical conditions, including: C-peptide negative diabetes, type 1 diabetes, portal vein thrombosis, portal hypertension, significant liver disease, high-risk cardiopulmonary disease, or known pancreatic cancer.

Evidence Level: 5.

Grade of recommendation: D.

Level of Agreement: A 68%; B 29%; C 3%; D 0%; E 0%

American Journal of Transplantation 2016; 16: 1812–1826

Autologous Islet Transplantation in Patients Requiring Pancreatectomy: A Broader Spectrum of Indications Beyond Chronic Pancreatitis

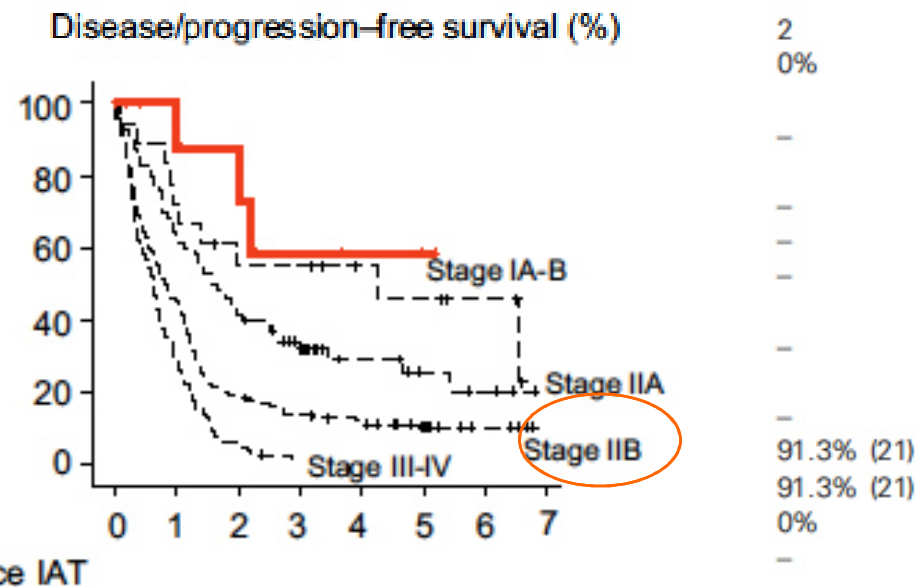
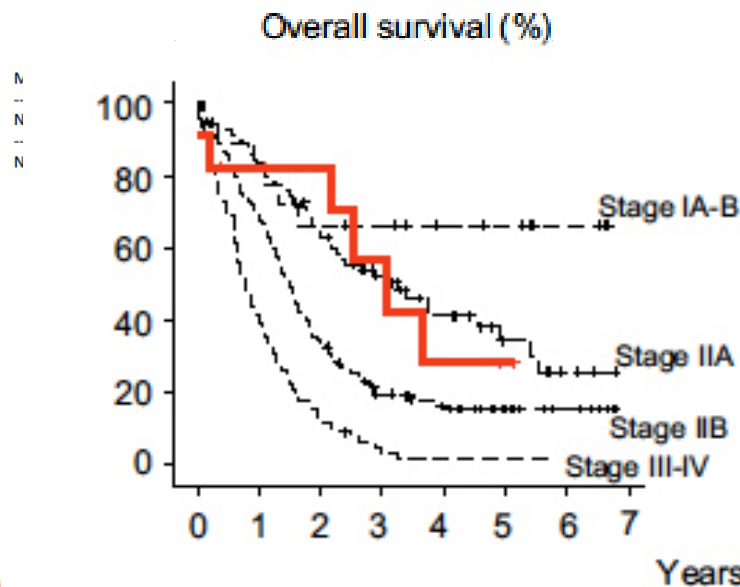
G. Balzano¹, P. Maffi², R. Nano², A. Mercalli², R. Melzi², F. Aleotti¹, A. Zerbi³, F. De Cobelli⁴, F. Gavazzi³, P. Magistretti², M. Scavini², J. Peccatori⁵, A. Secchi^{6,7}, F. Ciceri⁵, A. Del Maschio^{4,7}, M. Falconi^{1,7} and

Table 6: Oncologic follow-up

	Malignant	No/low malignant
Percent (n)	100% (31)	100% (23)
Median follow-up	914 ± 382	1460 ± 62
Died	29% (9)	8.7% (2)
Disease-free death	9.7% (3)	8.7% (2)
Surgical death	2	—
...	—	—

72 pz

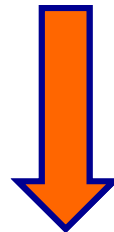
	Simultaneous IAT after total pancreatectomy	Salvage IAT after relaparotomy	Simultaneous IAT after extended distal pancreatectomy
Candidates	32	21	19
Transplanted	28	13	17



I pazienti sottoposti a pancreatectomia sono destinati a sviluppare il diabete pancreaticogenico. L' **autotrapianto di isole pancreatiche** offre loro la possibilità di rimanere insulino-indipendenti o di evitare le complicanze metaboliche del diabete pancreaticogenico, mantenendo l'euglicemia.

L'unica indicazione attuale all'autotrapianto di isole è il trattamento del dolore nella pancreatite cronica in pazienti che non rispondono alla terapia medica. Sono state estese le indicazioni a Pazienti con tumori benigni e dopo trauma pancreatico severo.

Ad oggi, non ci sono evidenze di contaminazione neoplastica nelle isole trapiantate dopo chirurgia per patologia pancreaticata maligna → estensione delle indicazioni a pazienti con tumori maligni?



necessità di trial clinici randomizzati (protocollo PAN-IT).

Grazie per l'attenzione



Gaspare Traversi. L'operazione chirurgica, olio su tela cm. 77,5 × 103,5, Staatsgalerie.

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