Intestinal and Multivisceral Transplantation

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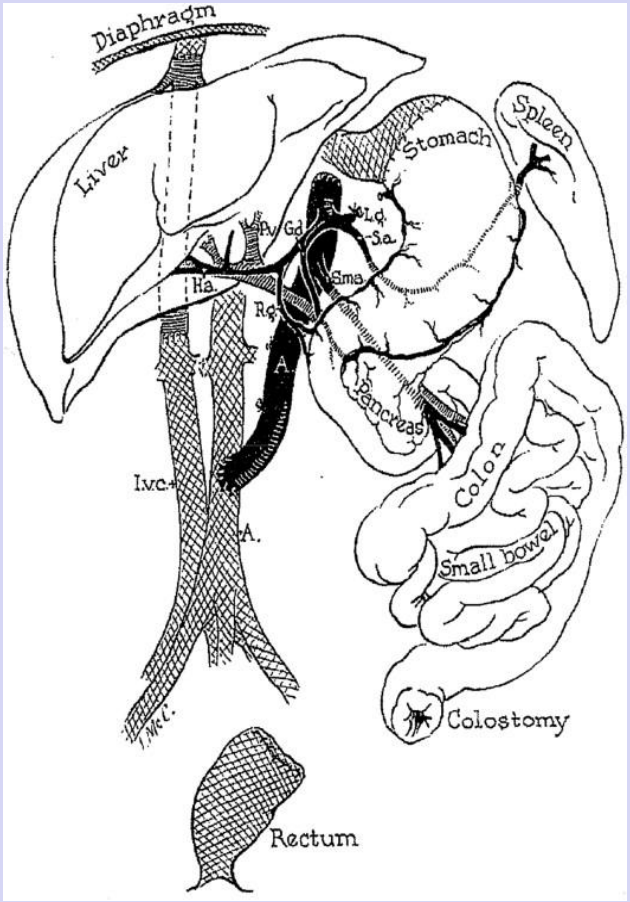
Summary

- History and its lessons
- Intestine transplantation at Pittsburgh
- Intestine transplantation worldwide
- What is new

T.E. Starzl, H.A. Kaupp Jr

1960: Mass homotransplantation of abdominal organs in dogs

Surg Forum, 11 **(1960),** pp. 28–30

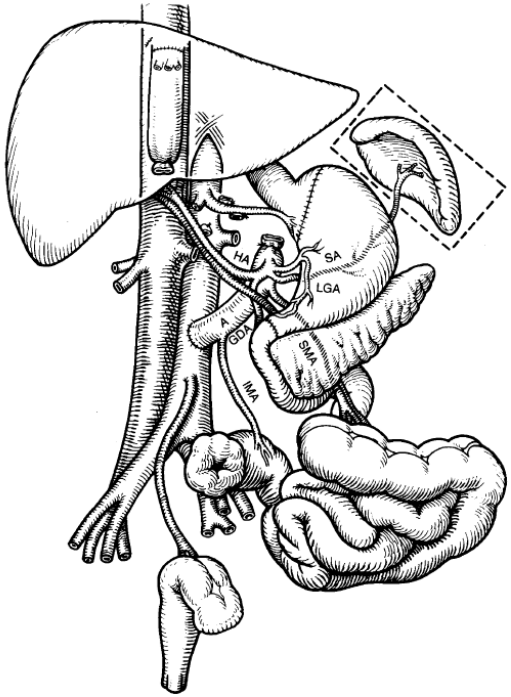


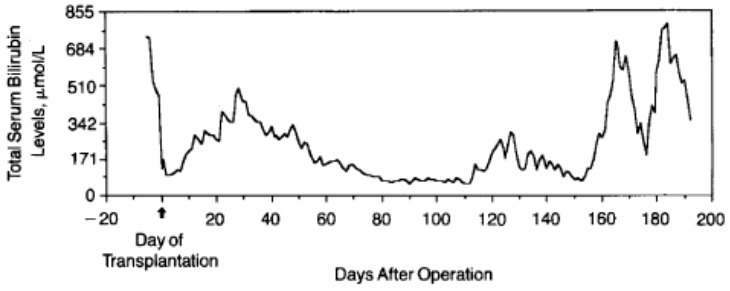
R.C. Lillehei, B. Goott, F.A. Miller: Homografts of the small bowel Surg Forum, 10 (1960), pp. 197–201

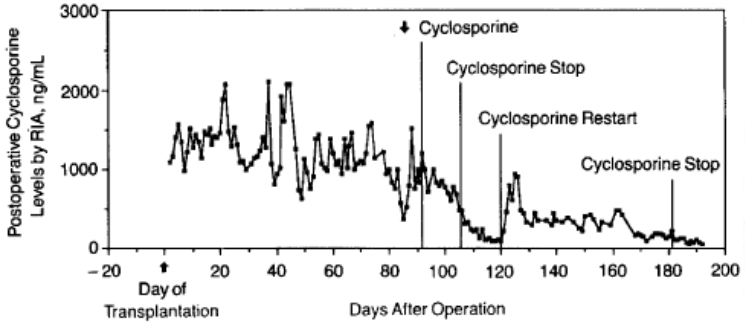
Transplantation of Multiple Abdominal Viscera

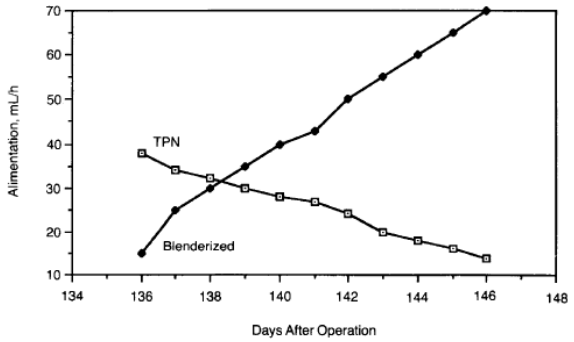
1989

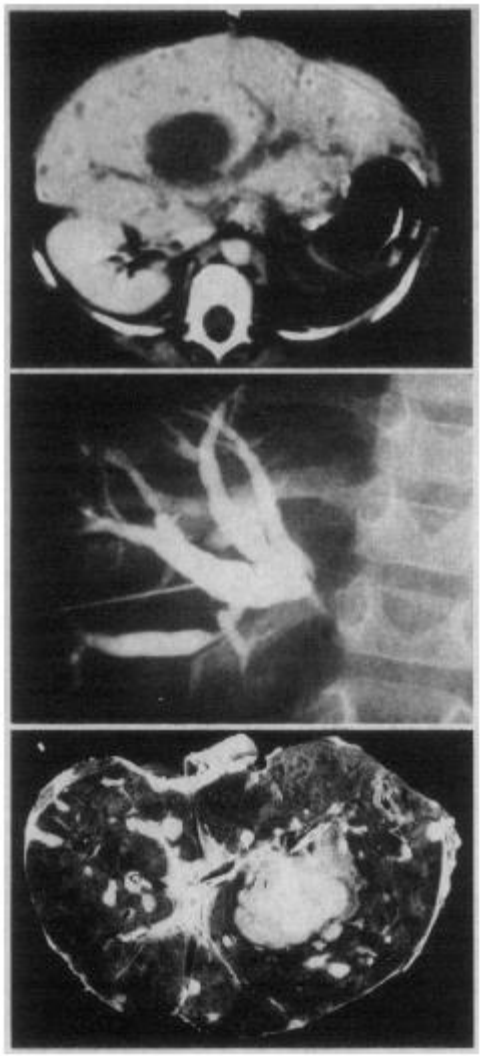
Thomas E. Starzl, MD, PhD; Marc I. Rowe, MD; Satoru Todo, MD; Ronald Jaffe, MB, BCh; Andreas Tzakis, MD; Allen L. Hoffman, MD; Carlos Esquivel, MD, PhD; Kendrick A. Porter, MD, DSc; Raman Venkataramanan, PhD; Leonard Makowka, MD, PhD; Rene Duquesnoy, PhD











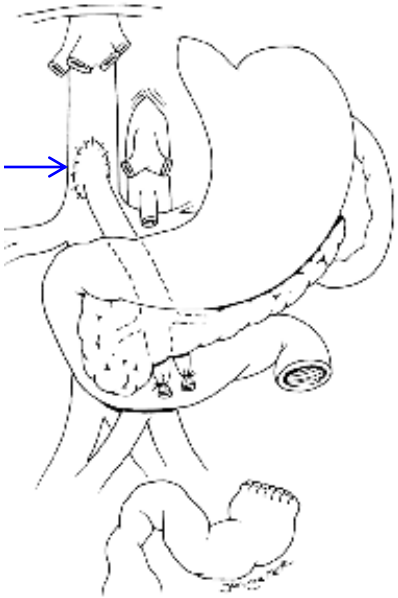
(*JAMA*. 1989;261:1449-1457)

(*JAMA*. 1989;261:1458-1462)

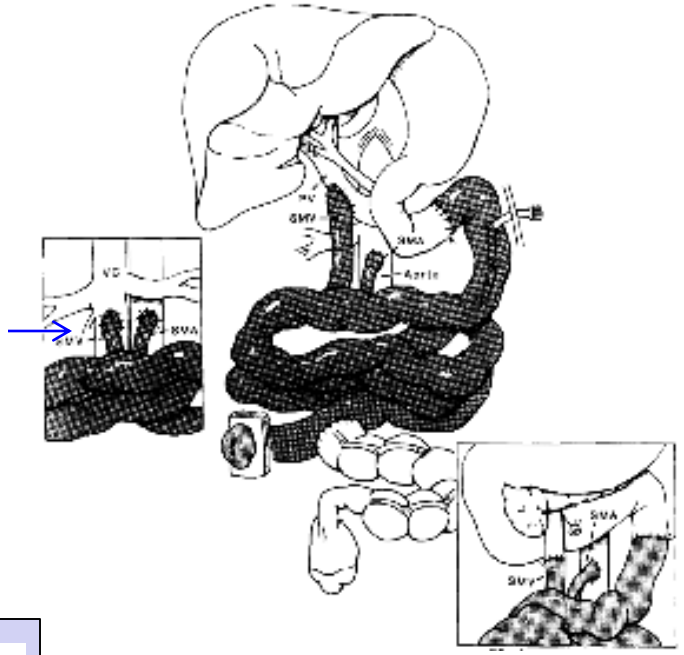
Small Bowel and Liver/Small Bowel Transplantation in Children

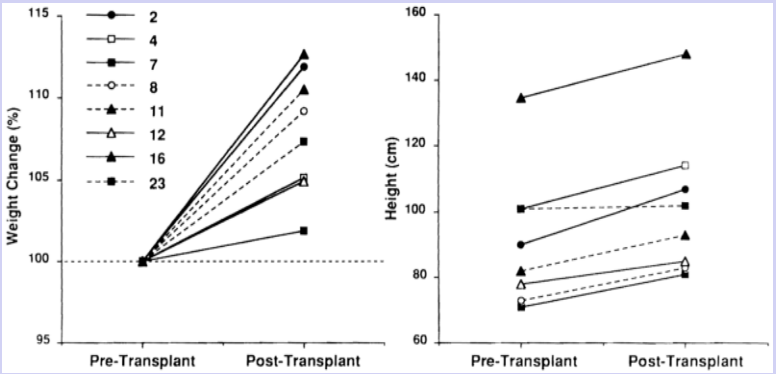
1993

Jorge Reyes, **Andreas G. Tzakis**, **Satoru Todo**, **Bakr Nour**, and **Thomas E. Starzl**
Department of Surgery, University Health Center of Pittsburgh, University of Pittsburgh; and the Veterans Administration Medical Center, Pittsburgh, PA



N=11
M:F 4:7
0.5-10.2 years
L-ITx: ITx 8:3
Alive 8, off TPN
Dead: 3, GVHD, PTLD, Bile leak





Semin Pediatr Surg. 1993 November ; 2(4): 289–300.

1990-1995

Between May 1990 and February 1995, 71 intestinal transplantations were performed in 66 patients using tacrolimus and low-dose steroids. The first 63 patients, all but one treated 1 to 5 years ago, received either isolated grafts (n = 22), liver and intestinal grafts (n = 30), or multivisceral grafts (n = 11). Three more recipients of allografts who recently underwent surgery and one undergoing retransplantation were given unaltered donor bone marrow cells perioperatively as a biologic adjuvant.

Results

Of the first 63 recipients, 32 are alive: 28 have functioning primary grafts and 4 have resumed total parenteral nutrition after graft enterectomy. Thirty-five primary grafts were lost to technical and

- N=71 grafts in 67 recipients, 63 with one year follow-up
- 28 fuctioning grafts, 4 on TPN after enterectomy
- 35 graft losses-technical 10, rejection-6, infection-19
- **Infection:** Lymphoma-8, CMV-5, bacterial-6
- **Contributors to graft loss:** rejection, OKT3, steroid use, high FK levels, graft colon, CMV+ donor

difficult to pinpoint because of multiple interlocking factors (Fig. 6). The principal diagnosis was rejection in only 6 cases, whereas an infectious complication attributable to antirejection therapy was the major diagnosis in 19. The responsible microorganisms included bacteria and fungi (n = 6), but among the viruses, cytomegalovirus (CMV) alone accounted for nearly as many losses (n = 5). Moreover, Epstein–Barr virus (EBV) associated B-cell lymphomas occurred in 12 (19%) of the 63 patients, of whom 8 lost their grafts and died of this complication. Eleven of the 12 patients who developed the lymphomas had been treated with OKT3.

Retransplantation

Four patients underwent retransplantation on the same day as primary graft removal (two liver–intestine) or 1 to 2 months later (two intestine only). They died 47

ative donor was used, but only 14% with a CMV-positive donor (Fig. 7). As recently reported in detail,[38] therapy that can regularly control this infection in other kinds of allograft recipients was only marginally effective in the intestinal recipient. Once the clinical diagnosis of CMV was made, the predominant target in essentially all cases was the intestinal allograft itself. The resulting ulcerations were associated with bacterial translocation.

Inclusion of a colonic segment in 29 patients was a significant risk factor. Significantly better graft survival was observed in 34 patients without the colon than with it (Fig. 8). Although the negative colon influence was more pronounced in adults, it also was identified in the

History

- **1989**: First successful isolated intestine transplant: *Deltz, 1989; Goulet, 1990; Starzl, 1991.*

- **1990**: First successful liver-small bowel Tx, *Grant et al*
- **1995:** 71 consecutive intestine transplant procedures, 32 survivors, 28 off TPN, *Todo and Starzl et al*
- **2001:** Medicare coverage for intestine Tx in the U.S.

- **2015:** 500 consecutive intestine transplants at Pittsburgh, *Abu-Elmagd et al.*

- **2016:** Intestine transplant registry reports 3174 transplants from 29 centers representing 90% of international activity

History Lessons

- Technically feasible: limit anastomotic leaks with duodenal-sparing liver-small bowel composite graft
- Rejection, infection, lymphoma and GVHD common occurrences: avoid colon, avoid CMV+donors
- One-year survival roughly 50%
- Need for more effective less toxic immunosuppression

Intestine Transplantation today

- Multidisciplinary evaluation
- The procedure
- Expected challenges and adverse events
- Survival outcomes
- Growth

MULTIDISCIPLINARY Intestine transplant evaluation

Does clinical need exist, If so, which operation

- Short gut (TPN >50% calories) with complications: growth failure, liver failure, access failure
- Liver involved: biopsy, TPN cholestasis vs cirrhosis
- GI contrast studies: ? residual bowel, gut rehab procedures
- Motility studies: connect vs end-ileostomy, include stomach

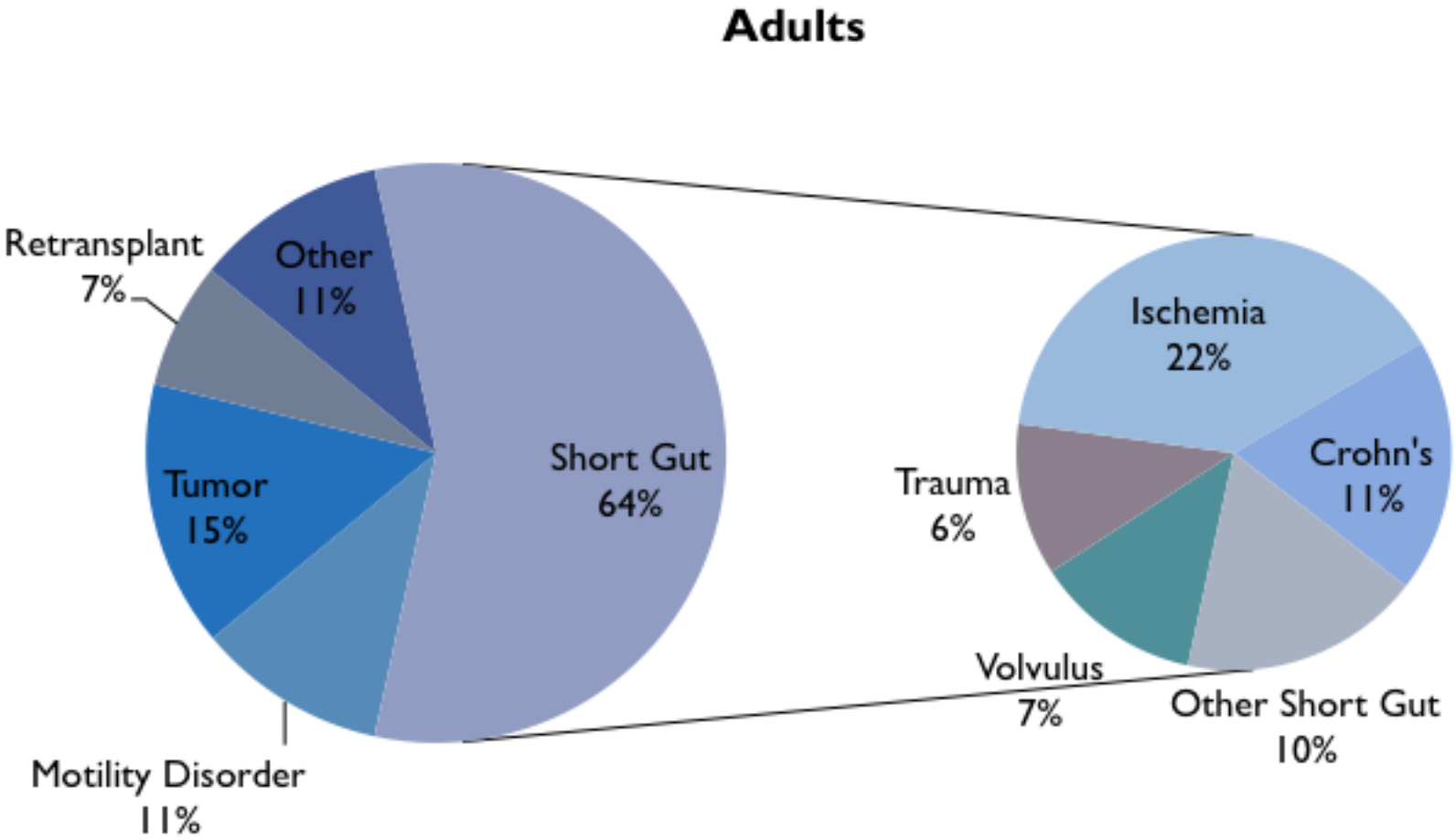
Can the recipient undergo ITx safely, and make good use of organ

- Comorbidities: prematurity sequelae-bronchopulmonary dysplasia, irreversible CNS damage, mitochondrial disease

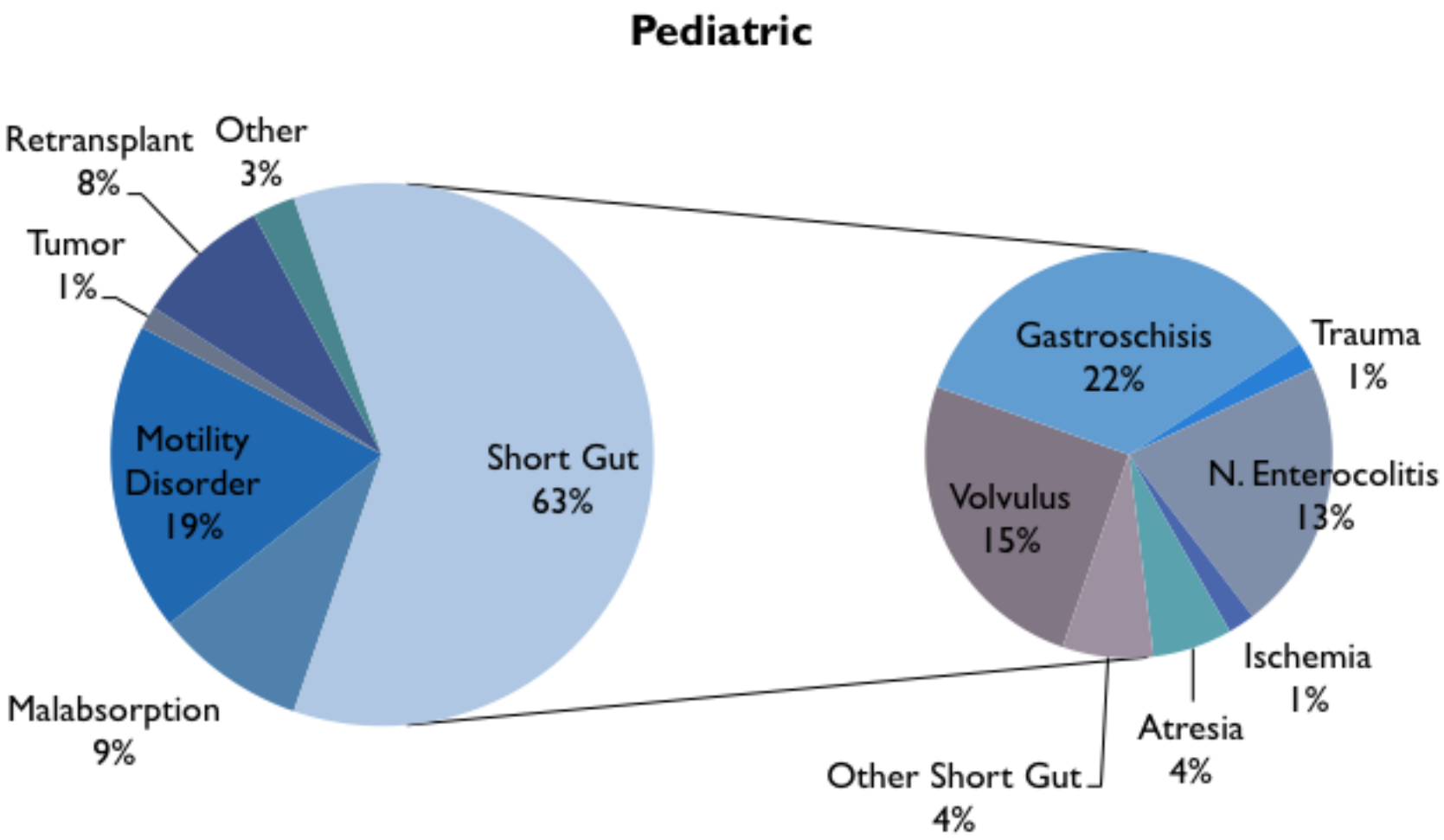
Is Psychosocial support adequate to handle

- Meds, compliance, surveillance requirements

Indications



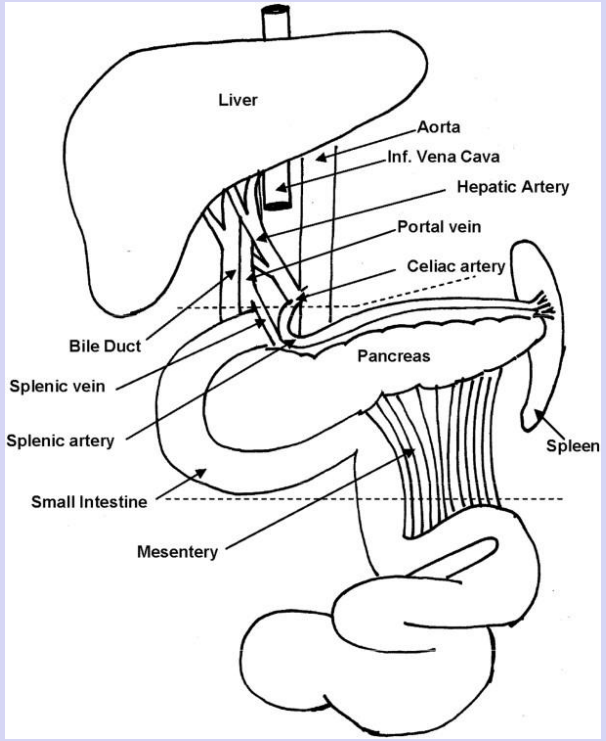
Indications

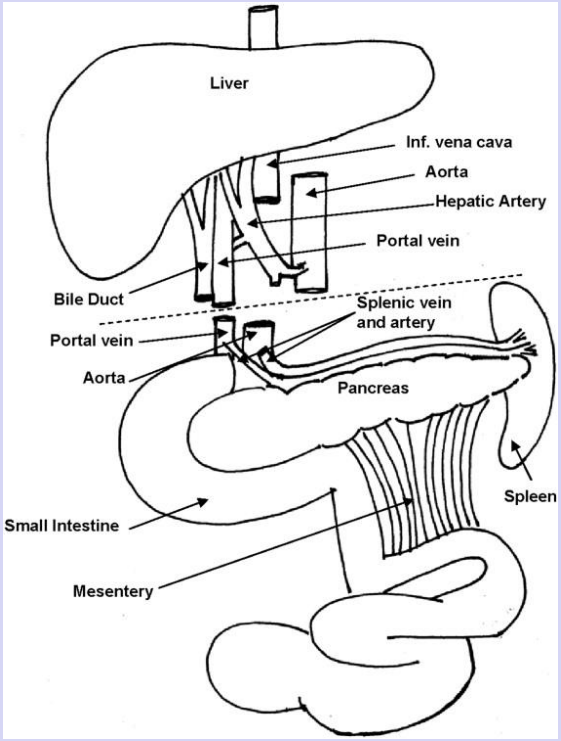


The multivisceral donor and Intestine grafts

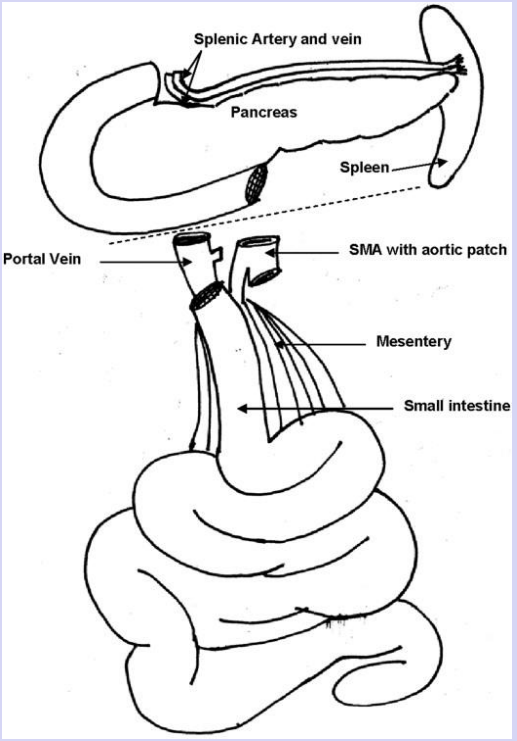
Sindhi, Transplantation, 1995

Liver-intestine allograft





Isolated Intestine Allograft



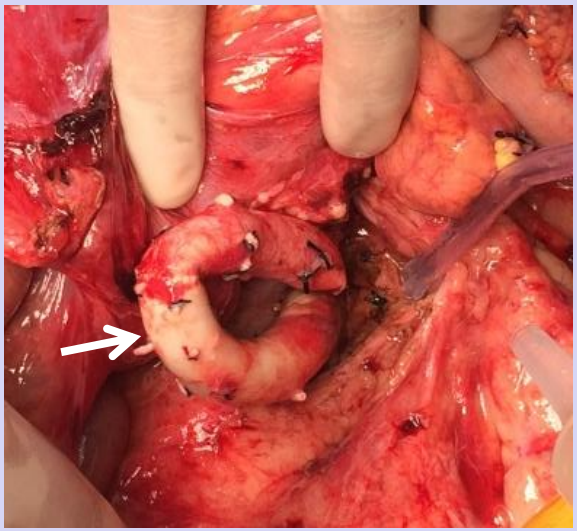
+ stomach = multivisceral

+ stomach = modified multivisceral

Intestine transplantation: procedure

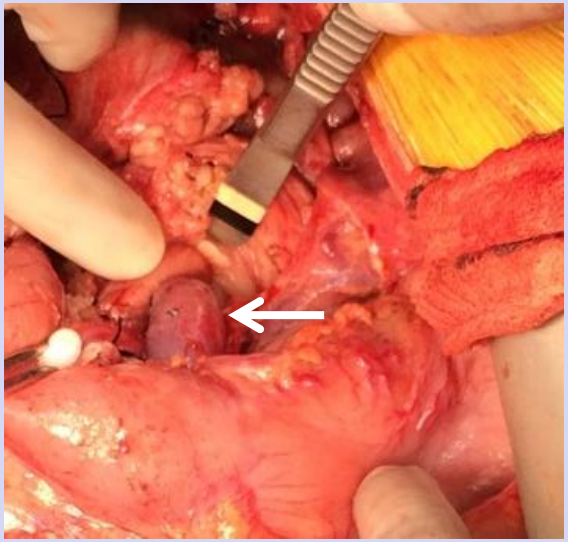
Mazariegos, Celik et al 2016

Arterial conduit on Infrarenal aorta



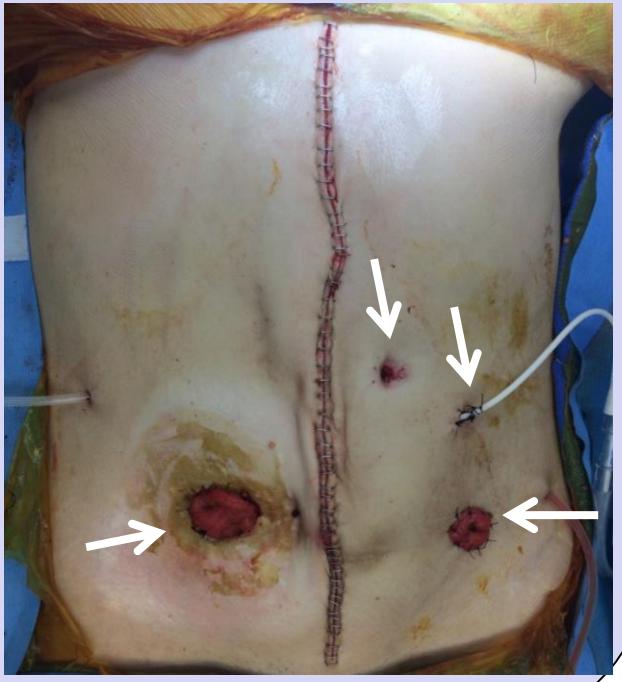
Same for isolated and Liver-intestine Tx

SMV extension graft on infrarenal cava for Isolated intestine Tx



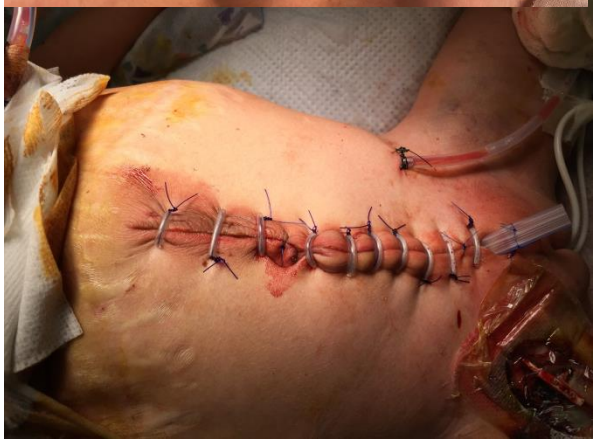
Upper caval venous outflow for Liver-intestine and MVTx

Loop ileostomy, end colostomy, G-tube, J tube



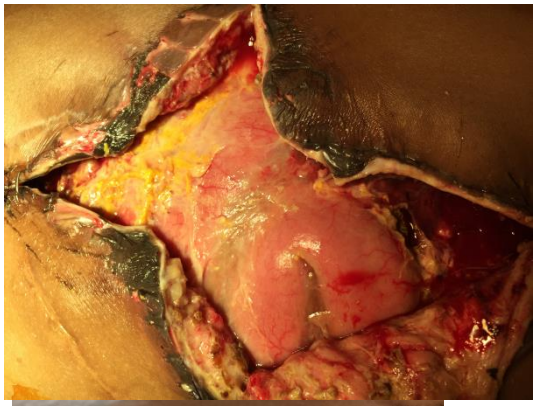
Avoid J-tube if bowel caliber is small

Abdominal domain and Wound management



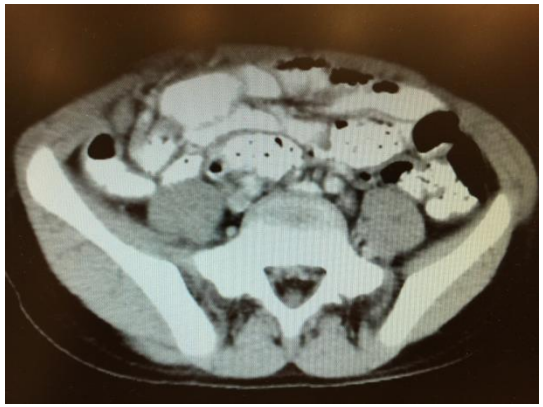
Skin closure

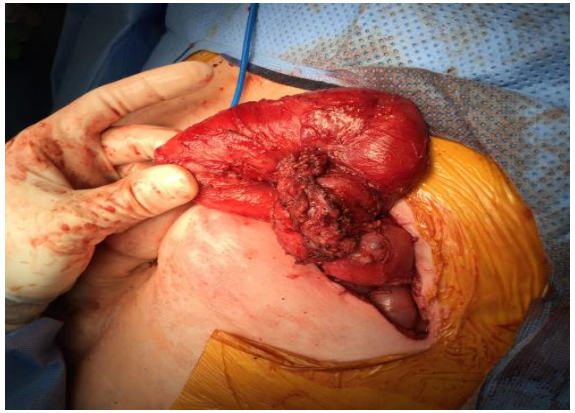
- Prevent abdominal compartment syndrome, silastic mesh
- Delayed closure: skin or biologic
- Avoid tension and excessive debridement
- **NUTRITION**



Skin + biologic

Challenge: Stomas





Early

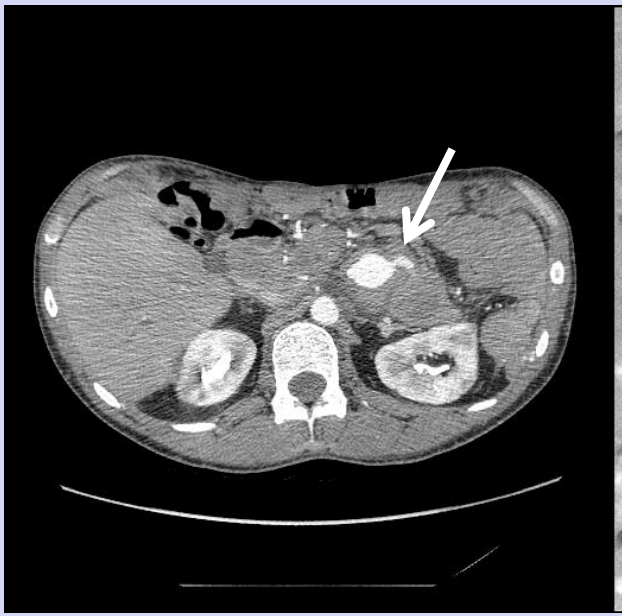
- Avulsion: Vac dressing
- Prolapse: prevention fix mesentry, fix to peritoneal surface

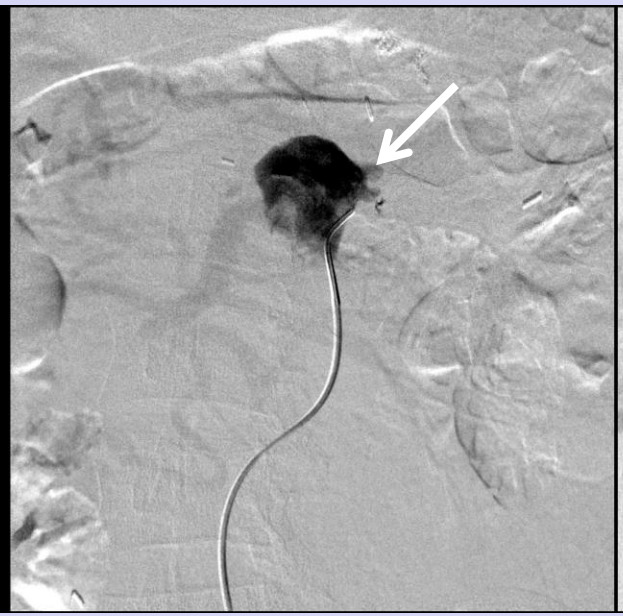
Post-closure

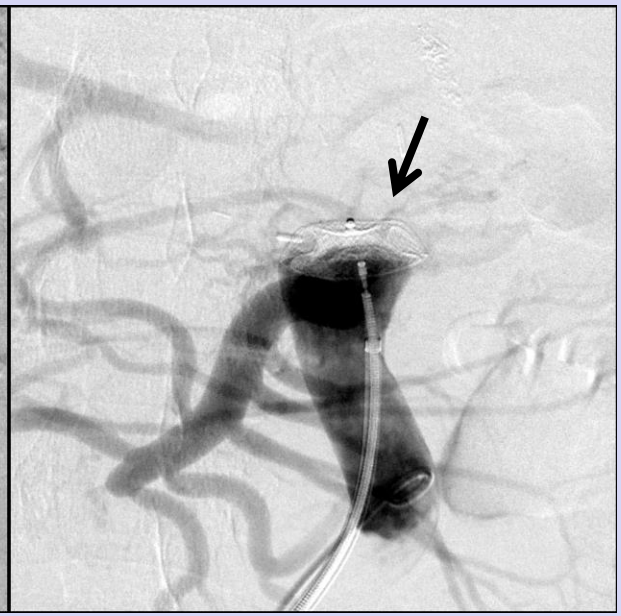
- obstruction, recheck distal motility, reverse if needed
- Enterocutaneous fistula after closure

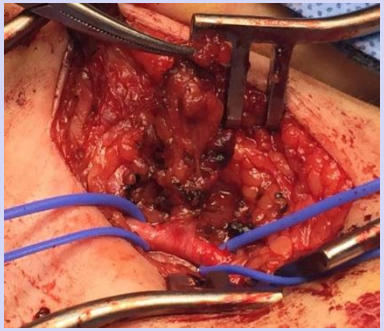
- **NUTRITION**

Challenge: Vessels









Pseudoaneurysm

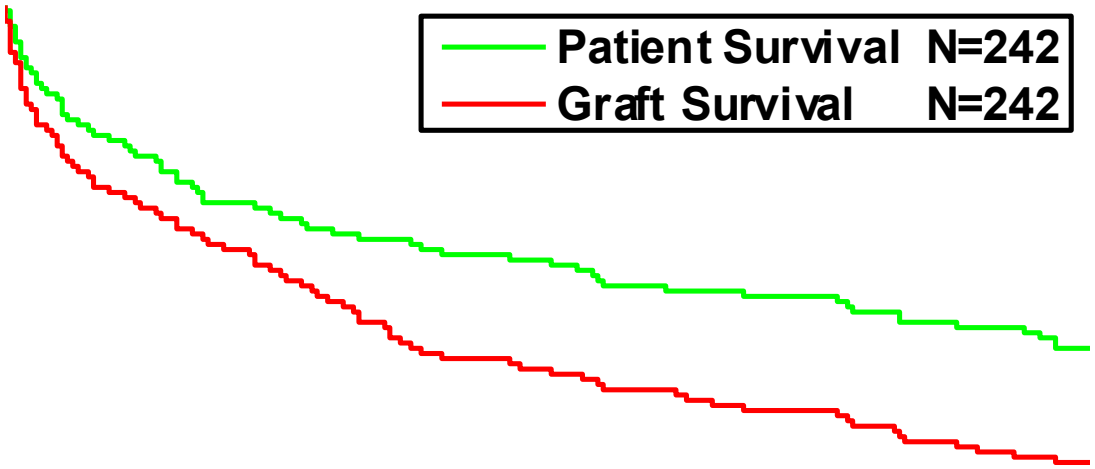
- Prevention: generous bites during anastomosis, meticulous hemostasis of suture line
- Treatment: surgical if accessible, interventional radiology if intra-abdominal

Technical challenges and complications

- Abdominal compartment syndrome: delayed closure
- Bleeding
- **Volvulus:** isolated ITx, long vascular conduits to aorta and IVC, failure to fix mesentry
- **Paraplegia** (suprarenal conduit grafts)
- Pseudoaneurysm: aorto-aortic, tip of aortic conduit
- **Ureteric injury** in reTx or enterectomy or prior extensive surgery-stents
- Venous outflow stenosis-growth factor
- Stomal prolapse-fix mesentry, fix to peritoneal surface
- Enterocutaneous fistula

OVERALL PATIENT AND PRIMARY GRAFT SURVIVAL

(n=244, 2016, Soltys, Celik, Mazariegos et al, 2016)



Survival: Induction vs no induction

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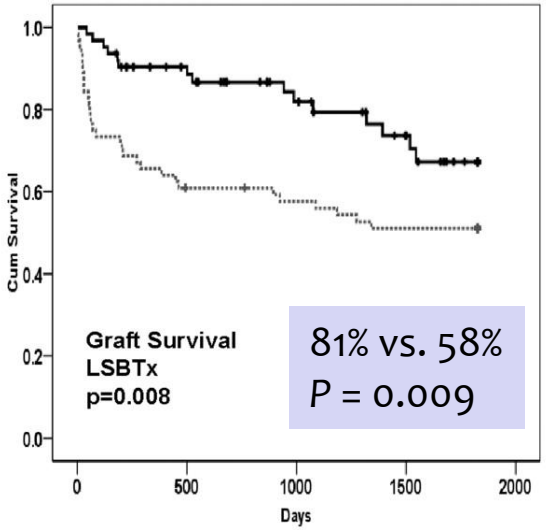
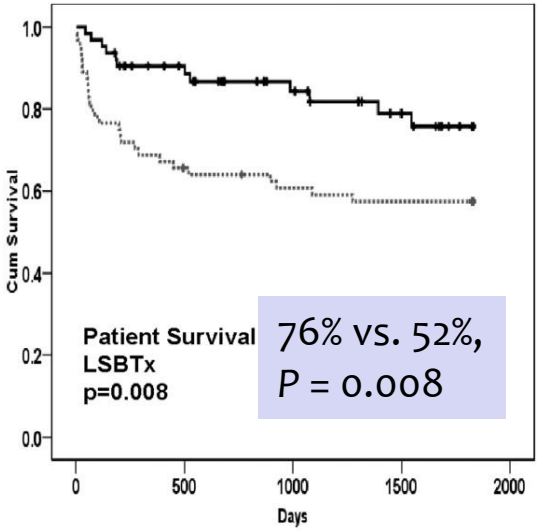
Combined Liver-intestine



81% vs. 58%
P = 0.009



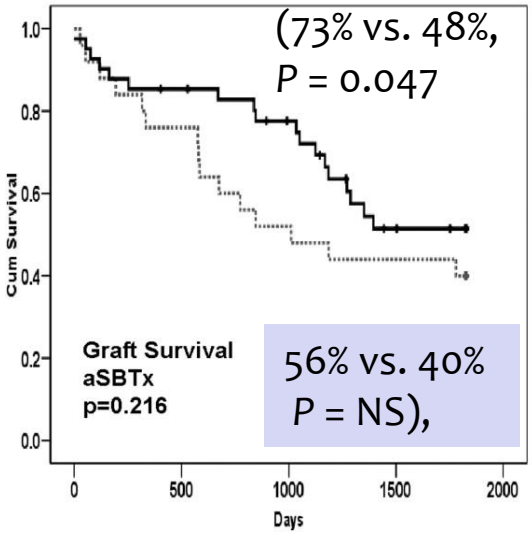
76% vs. 52%,
P = 0.008

Graft

rATG
Pre- rATG

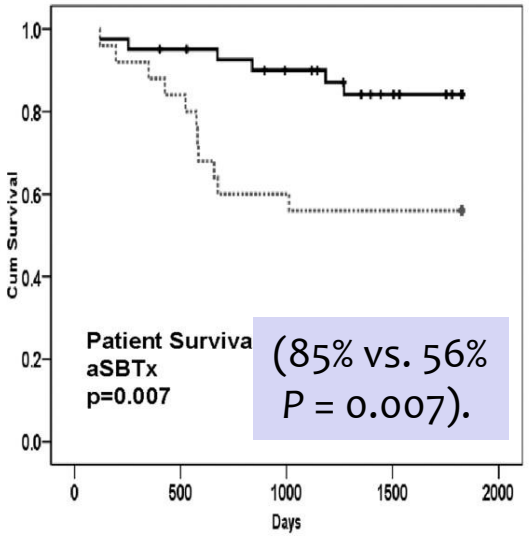
Patient

Intestine



(73% vs. 48%,
P = 0.047

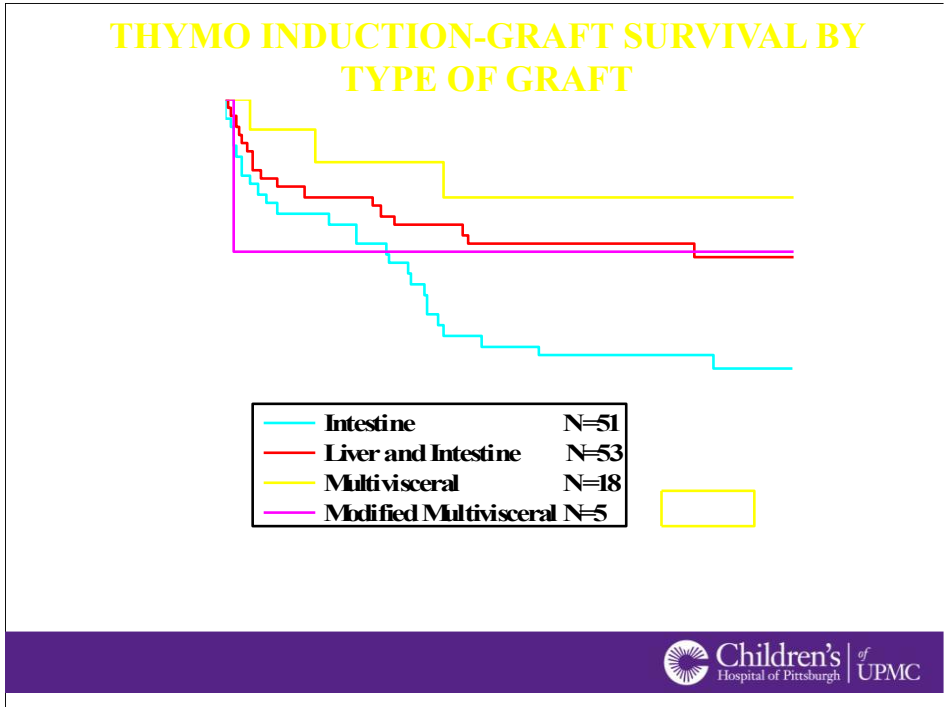
56% vs. 40%
P = NS),

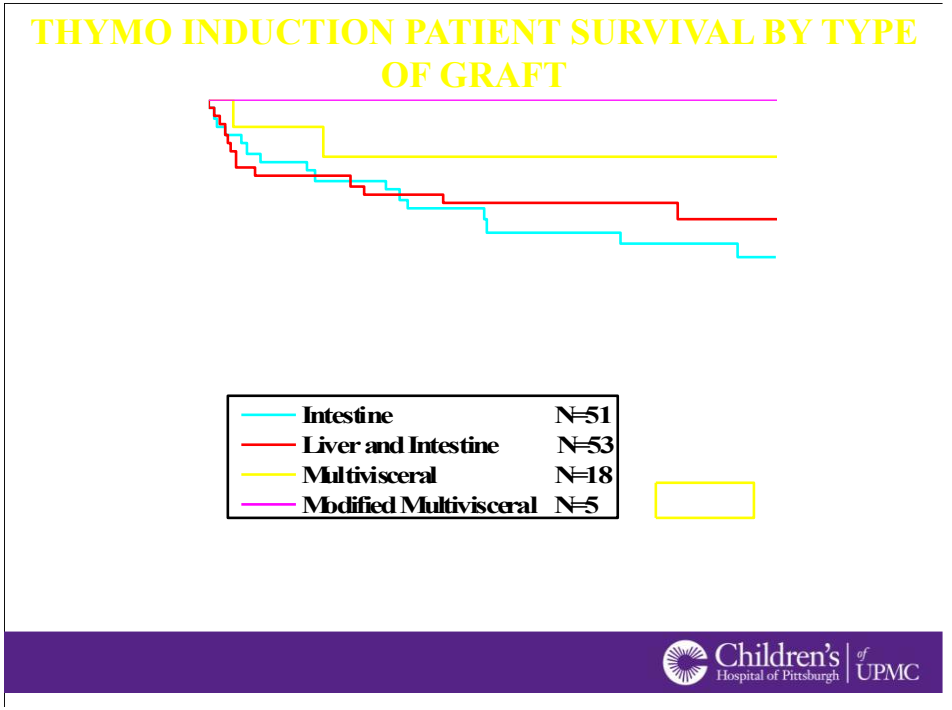


(85% vs. 56%
P = 0.007).

Survival: Liver-containing allografts do better

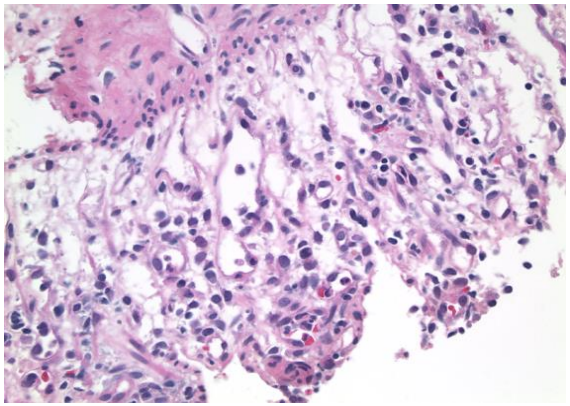
Soltys, Celik, Mazariegos et al, 2016



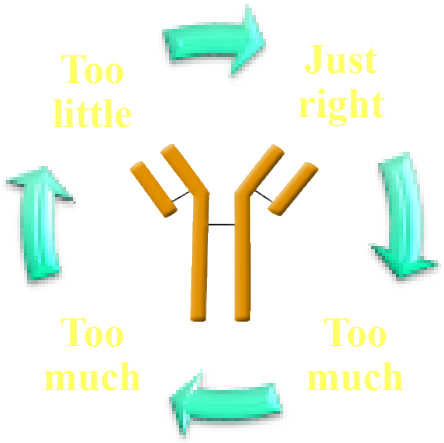


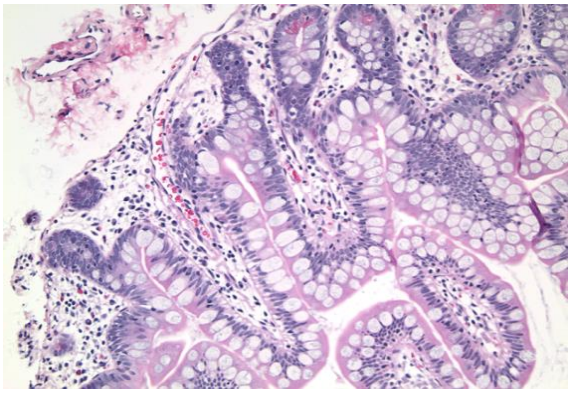
Problem?

Failure?

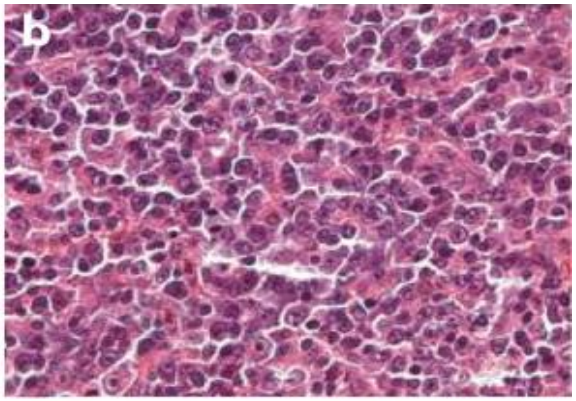


Acute cellular Rejection (30-60%)





Normal (Rejection-free)



PTLD (10-12%)

PTLD	11/103 = 11%
CMV	13/103 = 13%
GVHD	15/103 = 15%

GVHD (10-12%)

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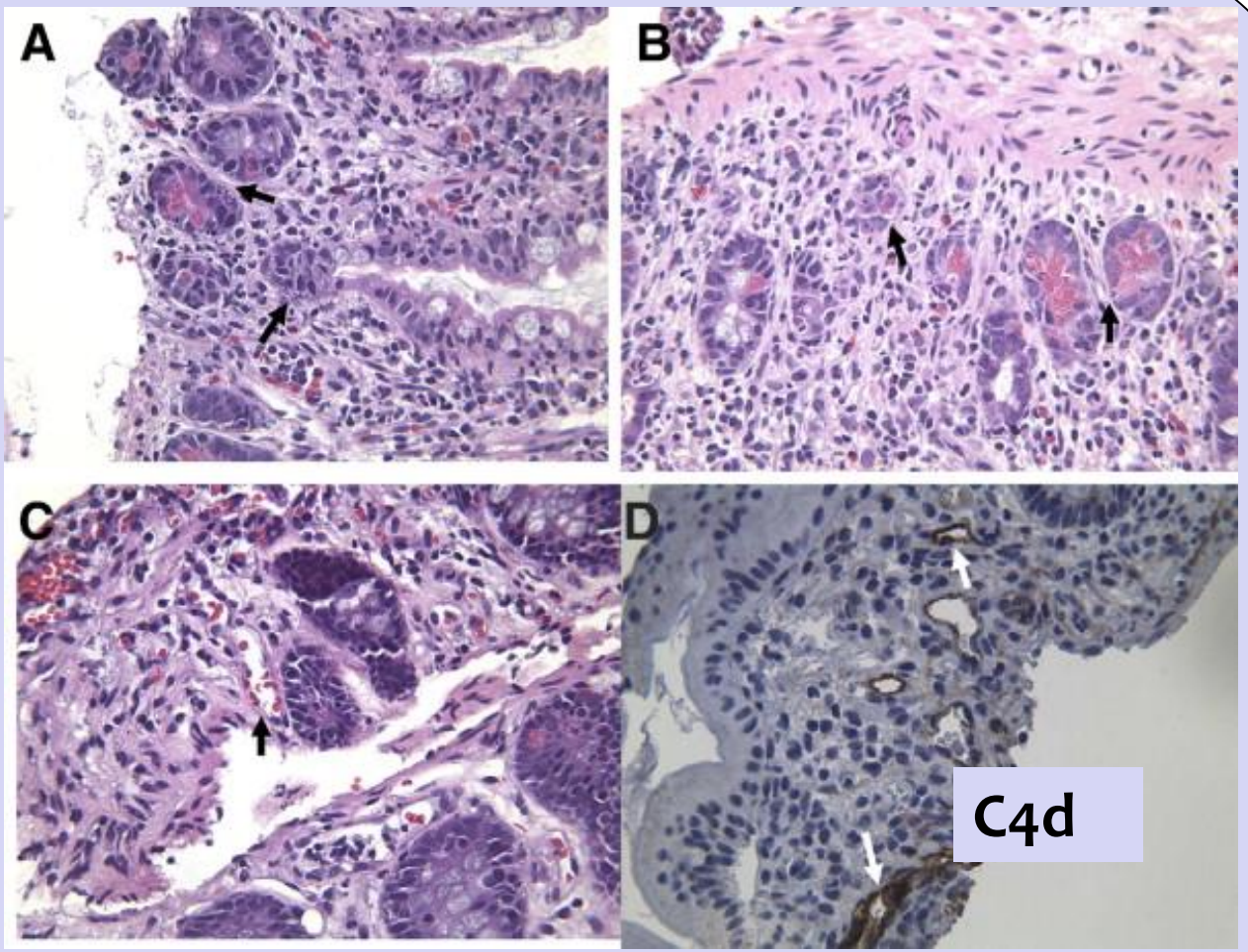
Rejection

Cellular
30-60%
50% resistant
Rejection-free
12-24% at 2 to 5y

Antibody-mediated
10%



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Late sequelae

Chronic rejection

- Median time — 39 months (22-67)
- ITx : Liver-intestine Tx — 8/38, **21.05%** vs. 2/65, **4.6%**, *p*=0.017

Renal Failure

- Incidence — 5/103, 4.6%
- Prior renal insufficiency — 3/5, 60%

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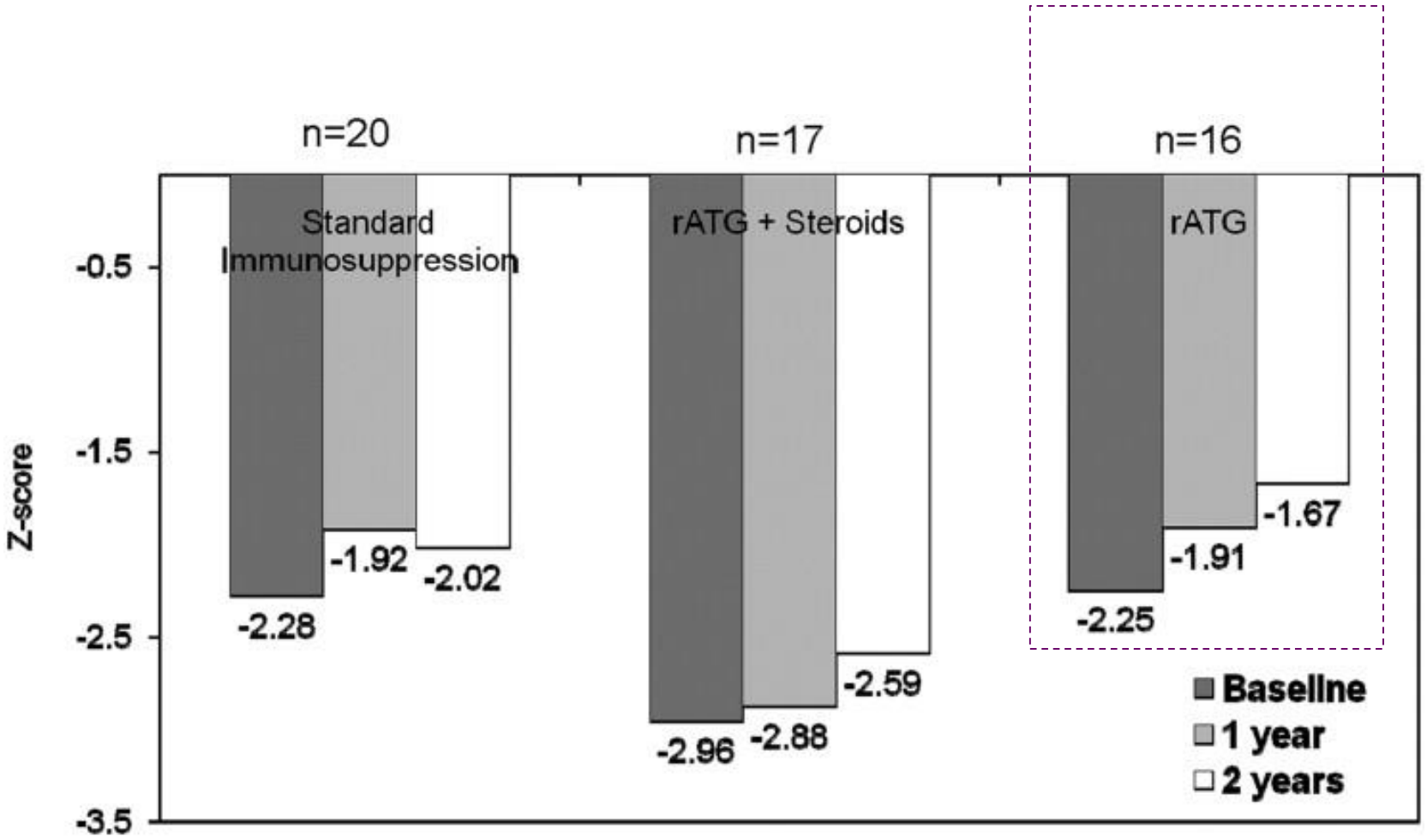
Steroid avoidance favors growth



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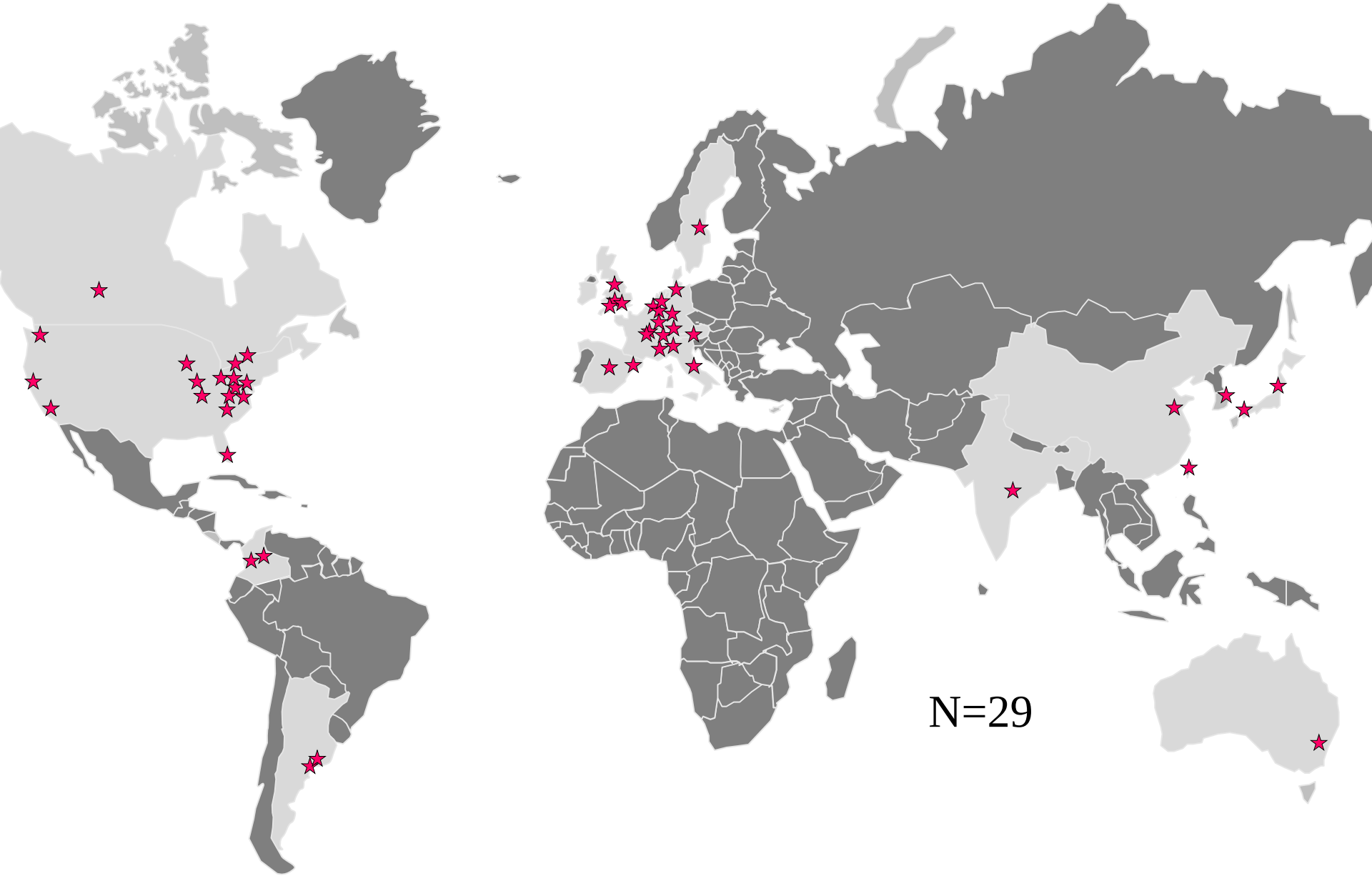
The state of Intestine Transplantation Internationally

- International Transplant Registry
- 90% of active centers report to the Registry
- Survival trends are improving
- Colon increasingly included in the allograft

Active Centres



Global Clinical Experience with ITx

(All recipients transplanted between Jan 1985-Jan 2016)

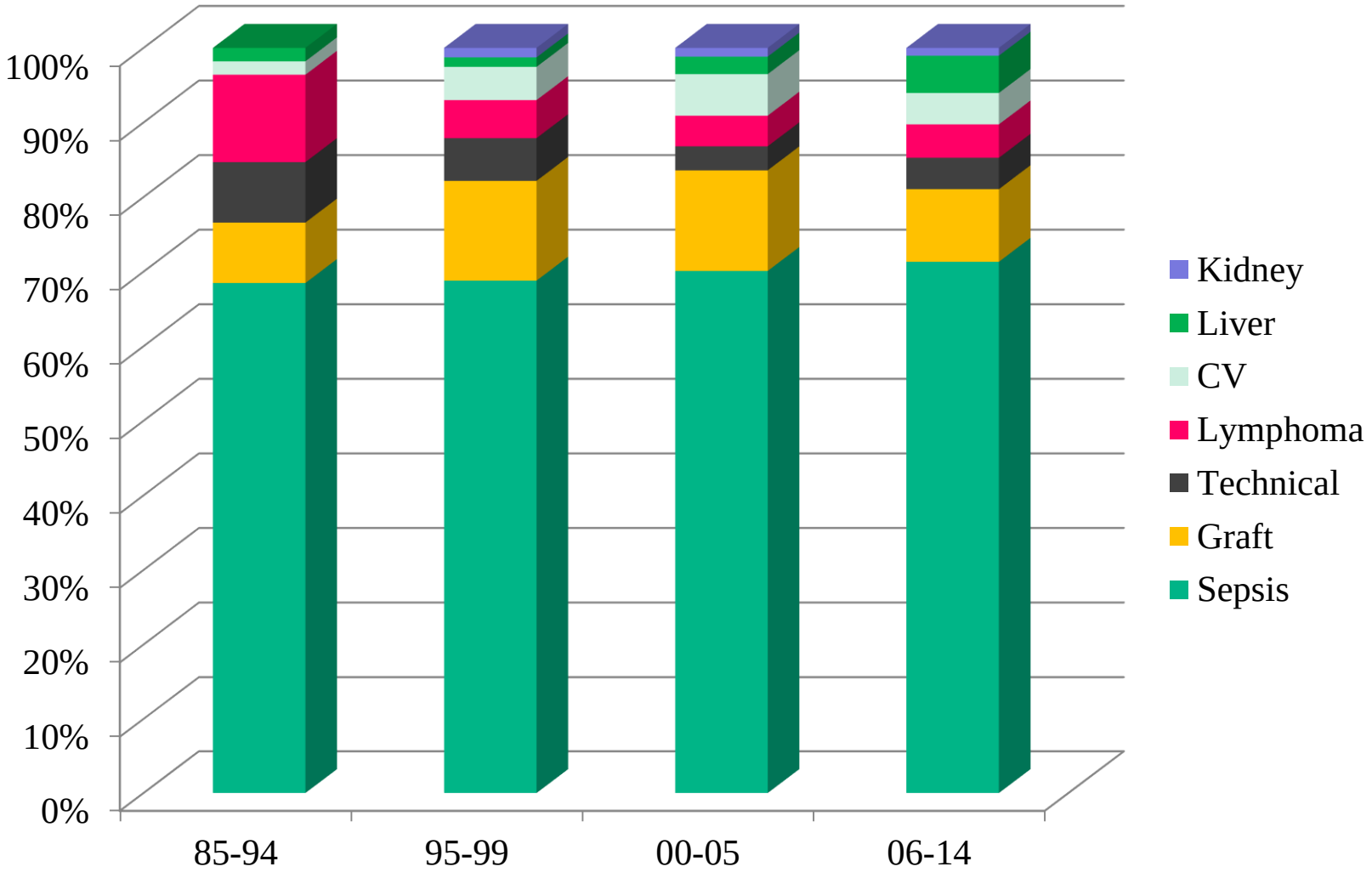
	Total	**Pediatric**
Number of Transplants	**3194**	**1731**
Center count	85	64
Active Centers	**29**	**22**
ITx alone	1429 (44.7%)	622 (35.9%)
Intestine+Liver	949 (29.7%)	767 (44.3%)
MVT+Modified MVT	656+160 (25.5%)	299+43 (19.8%)
Current survivors	**1651**	**883**

Multiple Variable Regression Analysis: Preliminary Results

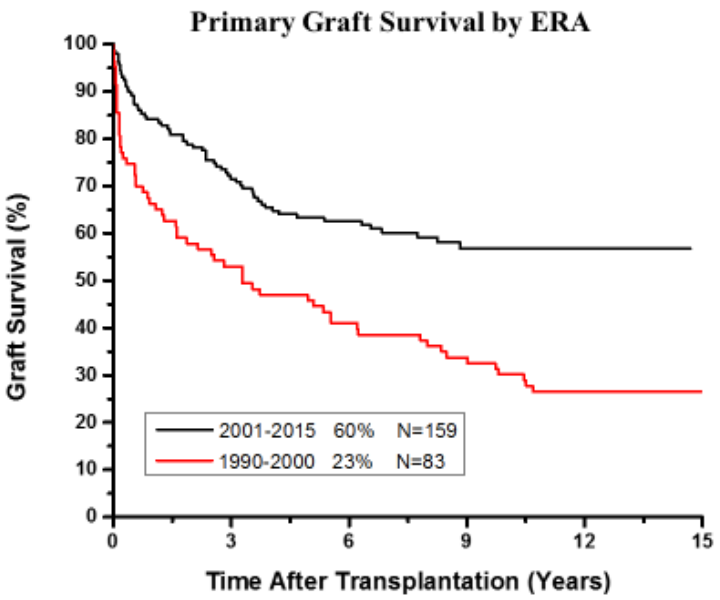
2001 - 2014 Cases	Overall*		1 Yr Conditional	
Predictor	HR*	P value	HR*	p-v
Infant (0-2 Years)	0.84	**0.005**	0.71	**0.001**
Pediatric (3-6 Years)	0.75	**0.037**	0.79	**0.049**
Regraft vs. Primary	1.85	0.08	1.26	0.06
Called in from home for IT	0.55	**0.01**	0.87	0.23
+ Liver component	0.78	**0.031**	0.68	**0.005**
Rapamycin Maintenance	0.87	**0.023**	0.77	**0.05**

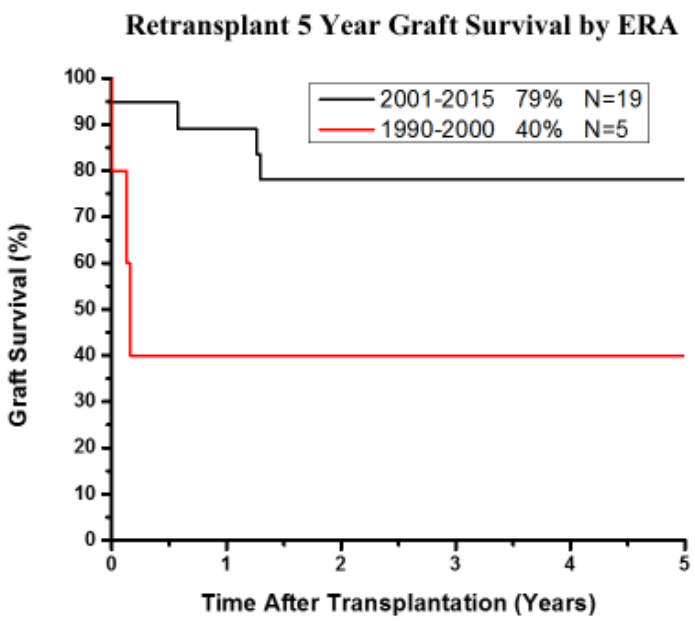
** Lower ratio = improved survival*

Causes of Death

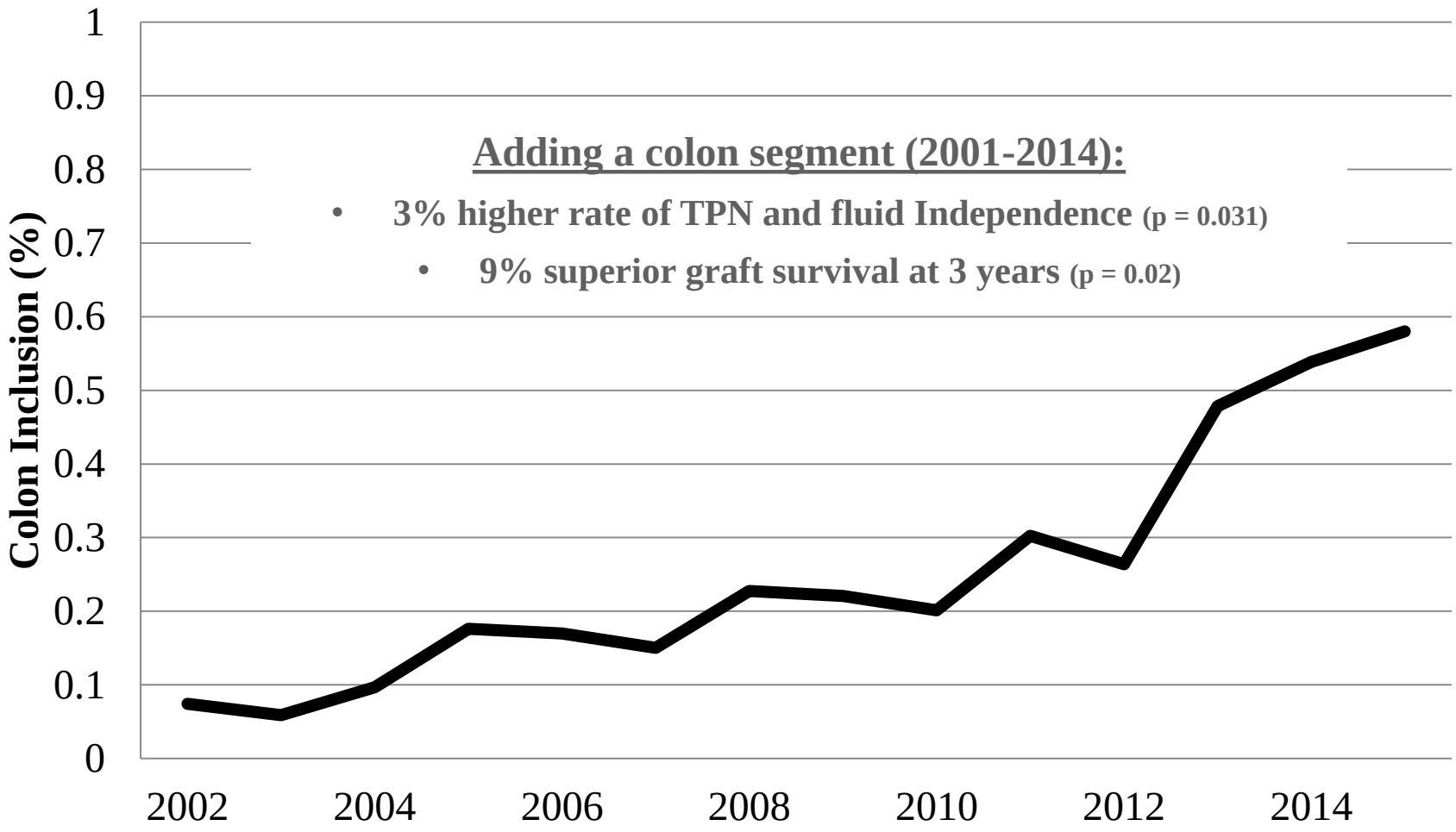


Survival by era: Before and after 2000



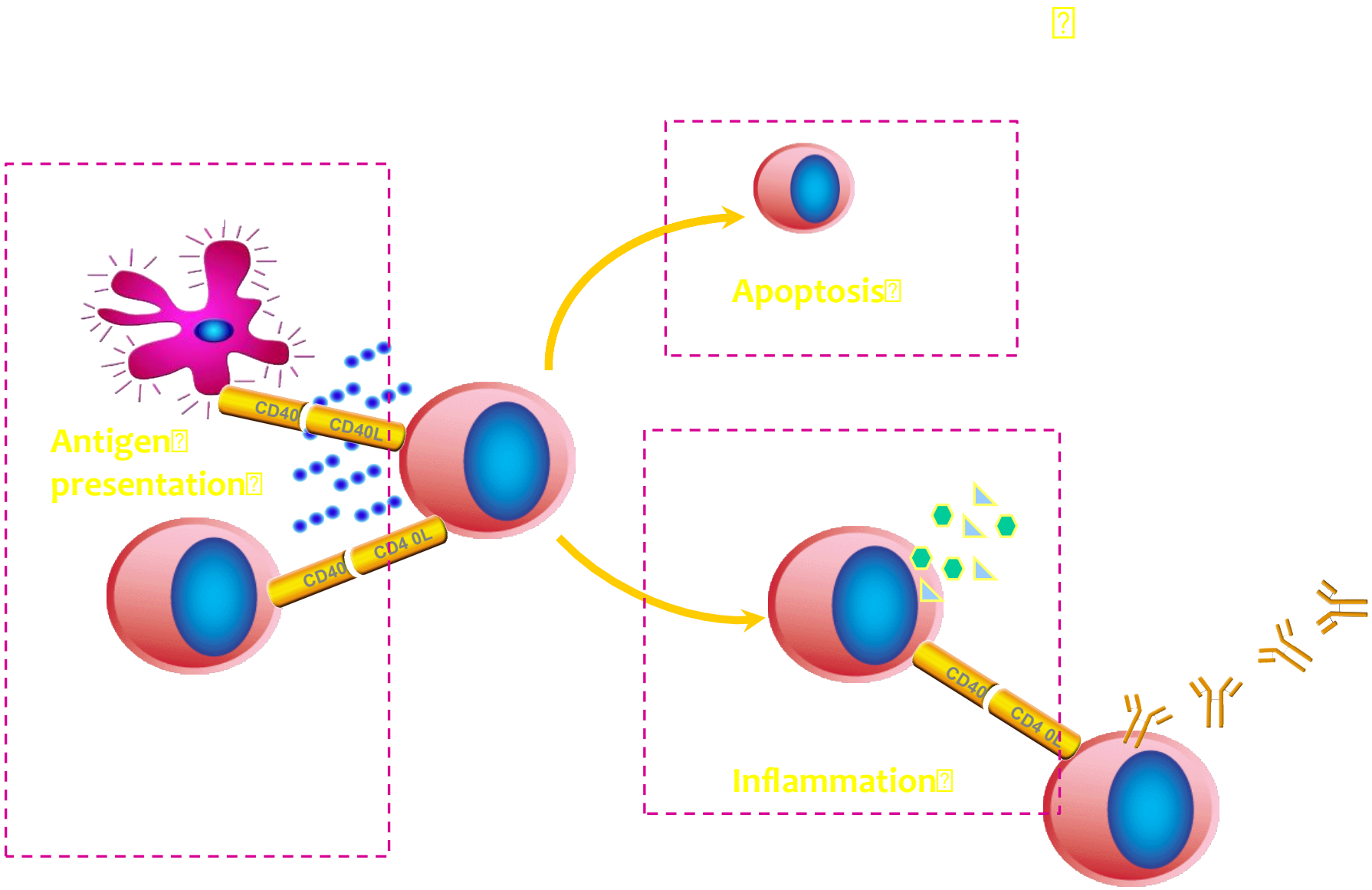


Colon Inclusion Over Time



What is New

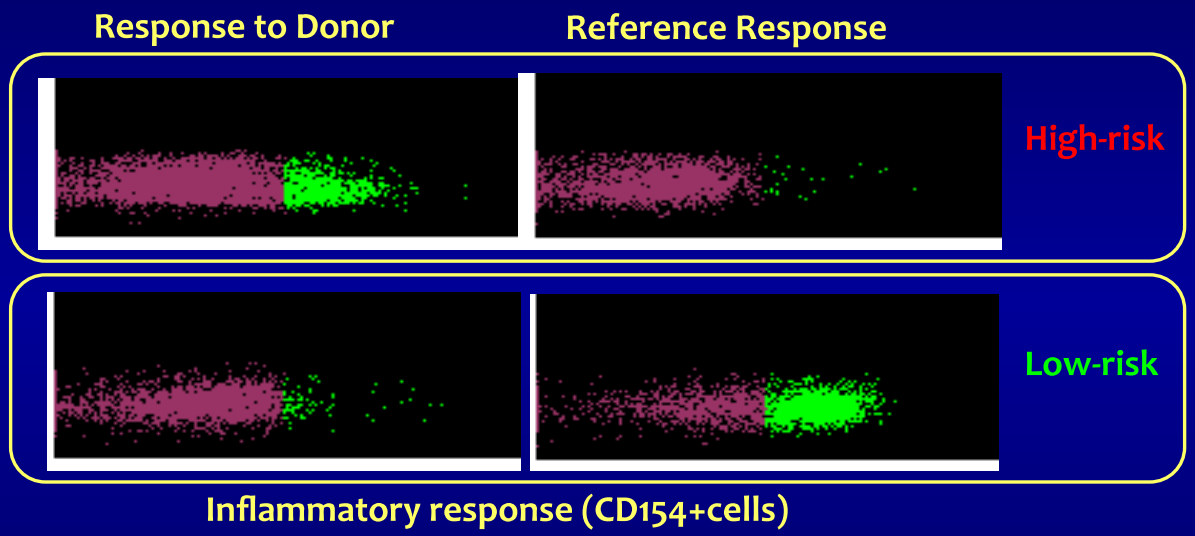
- Inclusion of colon
- FDA-approved test to predict cellular rejection
- GVHD: failure to repopulate donor allograft mucosa
- Gut microbiome and metabolome as biomarkers


Apoptosis
Antigen
presentation
CD40
CD40L
CD40
CD4 0L
CD40
CD4 0L
Inflammation

Allospecific CD154+T-cytotoxic memory cells (CD154+TcM)

FDA-approved, August 2014

- Overnite
- Disease-specific
- Personalized
- **Rejection-risk index ≥ 1.1**

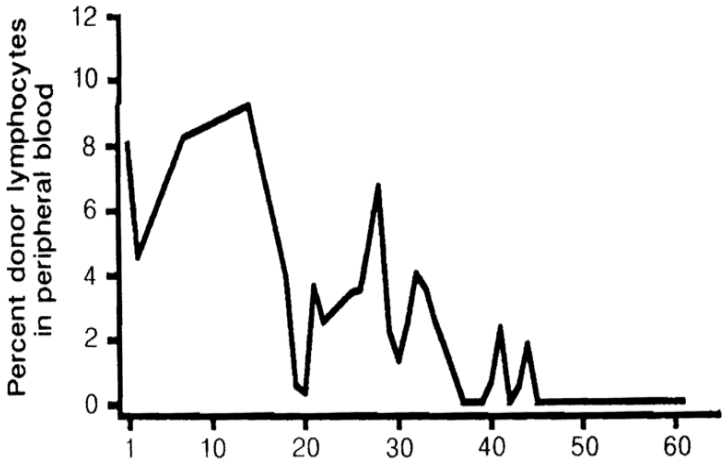


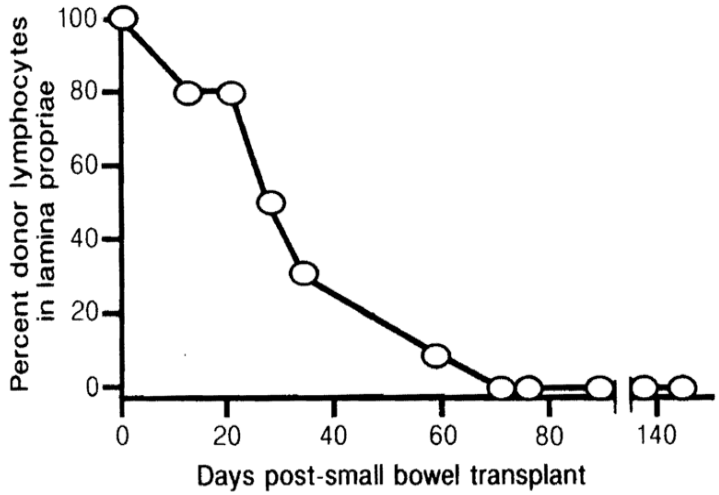
Organ	N	Sensitivity	Specificity	Reference
Liver	58	92%	85%	Am J Transplant, 2009
Intestine	32	93%	88%	Surgery, 2009
Kidney	43	88%	88%	Transplantation, 2011

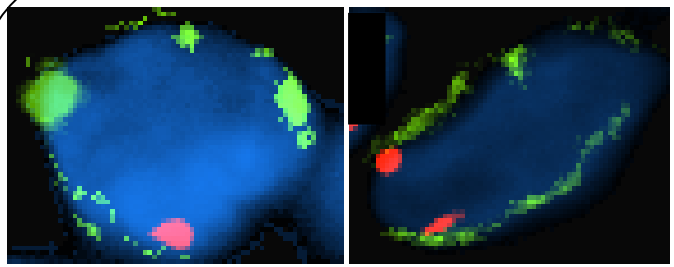
Replacement of donor lymphoid tissue in small-bowel transplants

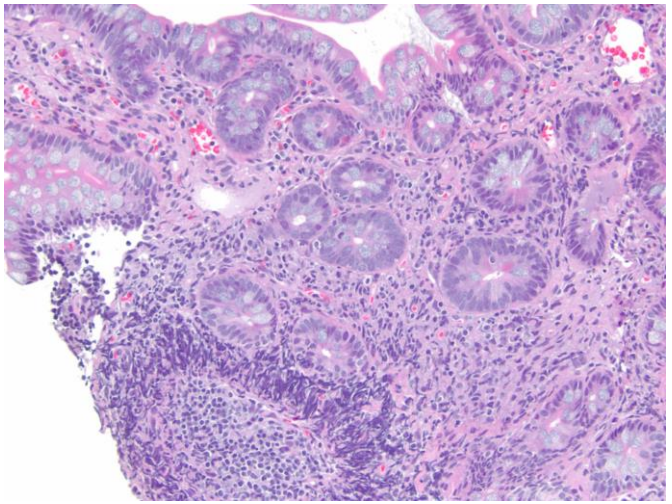
Prof Yuichi Iwaki, MD, PhD, Prof Thomas E. Starzl, MD, PhD, Atsuhito Yagihashi, MD, PhD, Satoshi Taniwaki, MD, Kareem Abu-Elmagd, MD, Andreas Tzakis, MD, John Fung, MD, PhD, and **Satoru Todo, MD, PhD**
Departments of Surgery (Prof Y. Iwaki, MD, PhD, Prof T. E. Starzl, MD, PhD, A. Yagihashi, MD, PhD, S. Taniwaki, MD, K. Abu-Elmagd, MD, A. Tzakis, MD, J. Fung, MD, PhD, S. Todo, MD, PhD) and Pathology (Y. Iwaki), University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

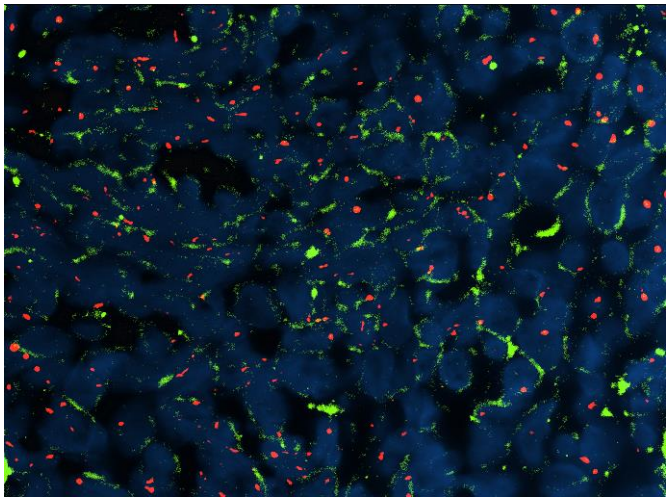
Lancet. 1991 April 6; 337(8745): 818–819.





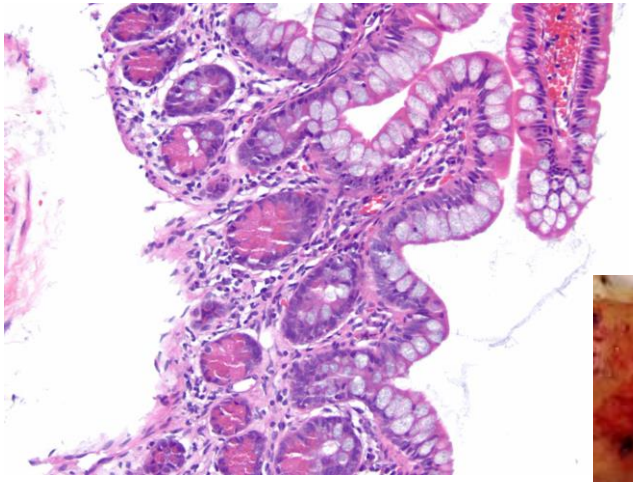




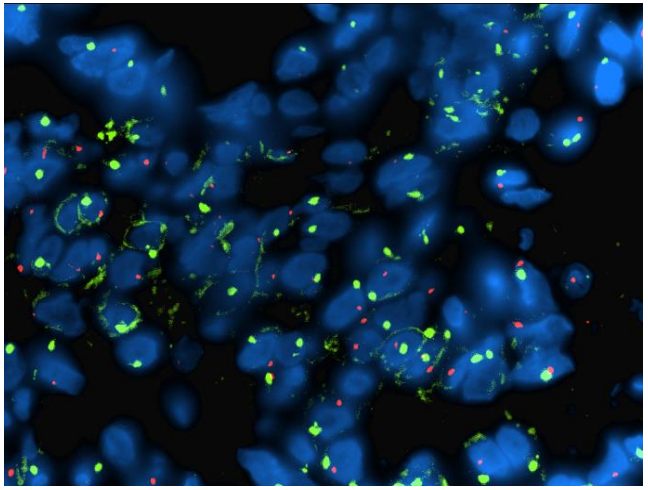


Non-rejector: HE x20 and FISH for XY and CD45 with 100% female (XX) population of graft

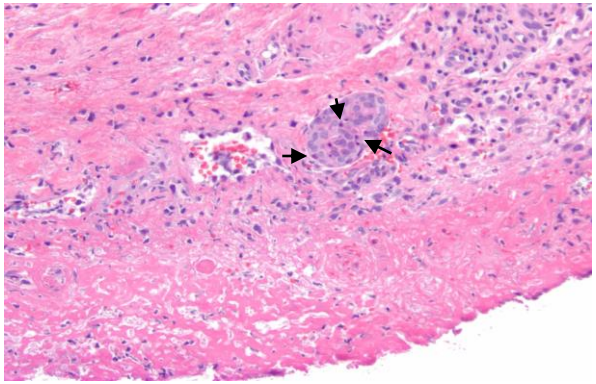
Refractory GVHD: failed repopulation of lamina propria with recipient immune cells



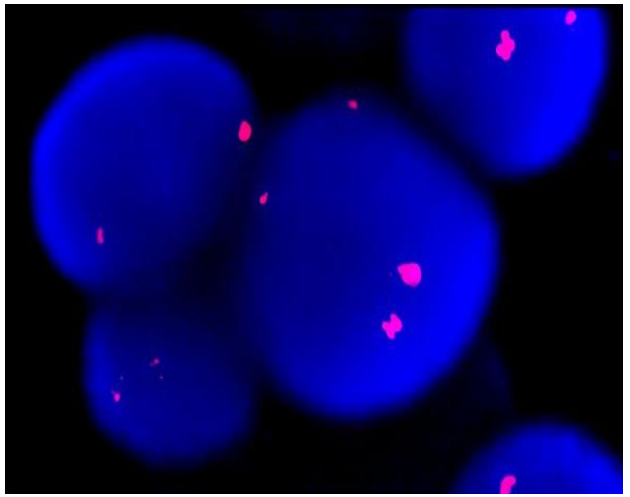
Allograft biopsy no ACR



Allograft lamina propria 97% CD45+cells (green outline) are XY+ in girl with GVHD

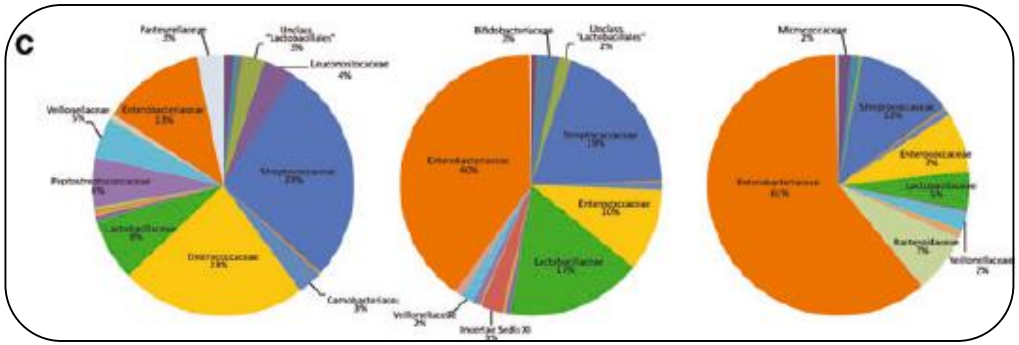


Skin GVHD: Ulcerated skin, loss of keratinocytes (lower edge), adnexal gland with frequent apoptoses (black arrows)

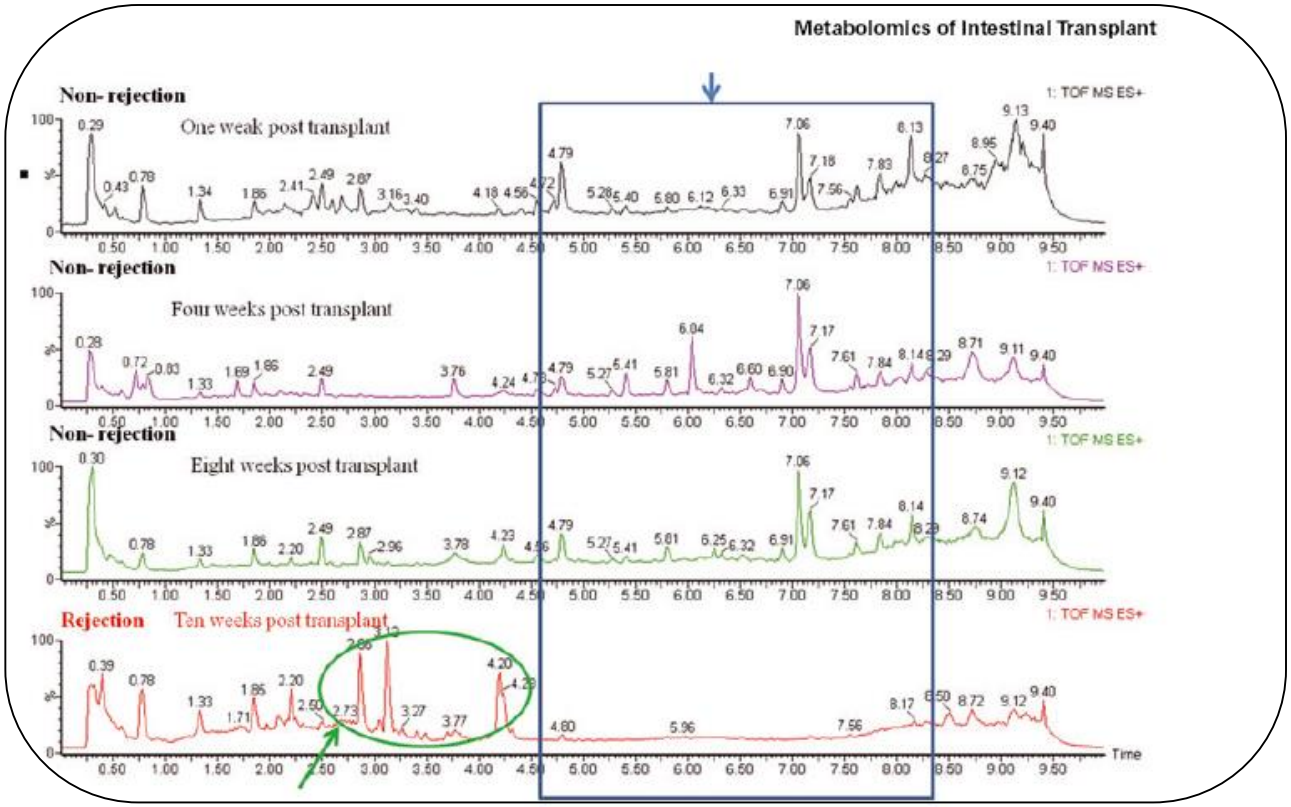


Bone marrow biopsy shows 100% XX cells in girl with GVHD

The gut microbiome and metabolome



Oh et al. *American Journal of Transplantation* 2012; 12: 753–762



Girlanda et al.

American Journal of Transplantation
doi: 10.1111/j.1600-6143.2012.04183.x

Summary

- Intestine Tx is a viable option for refractory short gut syndrome.
- Survival continues to improve, except isolated ITx with 50% median 5-year graft survival
- Surveillance of rejection and infection has been critical
- Cohesive team which includes intestinal rehab services
- Complex management needs requires multidisciplinary team including interventional radiology, advanced GI imaging, pharmacology, nutritional support
- INSTITUTIONAL SUPPORT

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- Szalay family foundation.
- Hillman Foundation of Pittsburgh
- Plexision, Pittsburgh, PA.

Summary

Viable option for refractory short gut
Survival continues to improve, except isolated ITx which lag its peers with 50% median 5-year graft survival
High incidence of rejection and complexity requires multidisciplinary team including interventional radiology, avanced GI imaging

Immunological

11/103=107%