Liver Transplant Pathology – a general view

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Addenbrooke's Hospital
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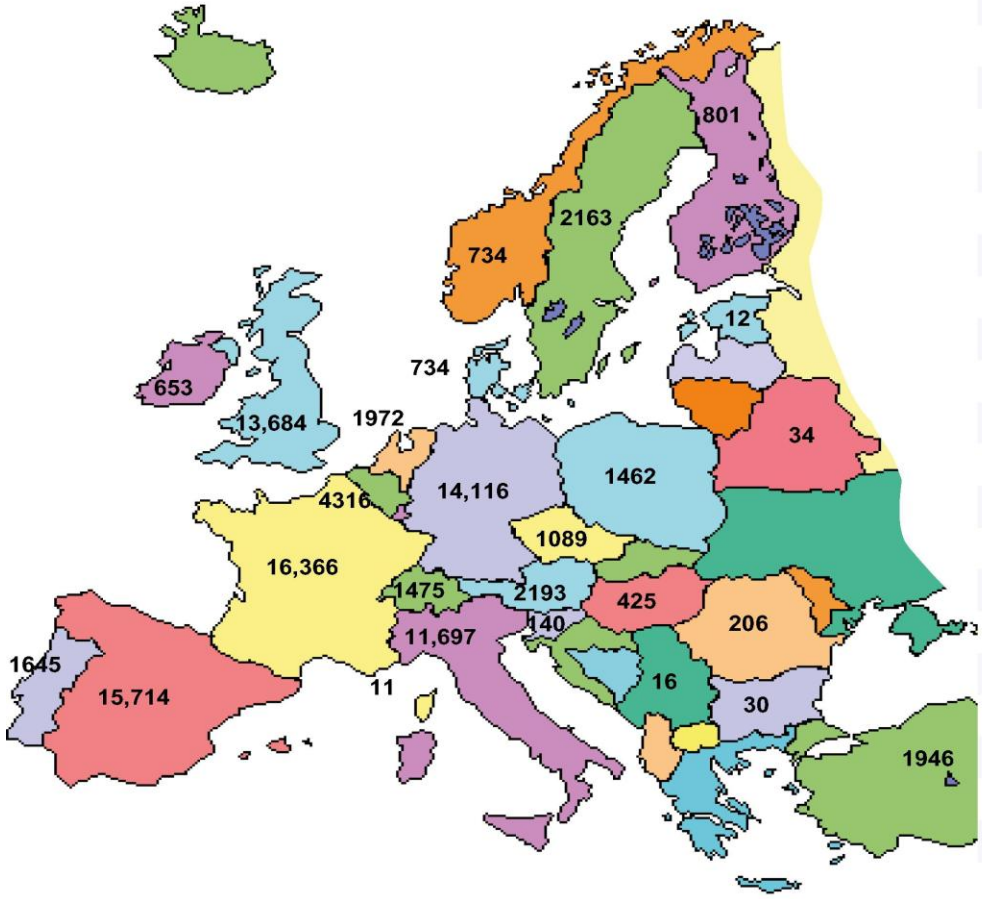
ACP/BSG Meeting Leeds 2012

Liver transplantation

- When and where?
- Who and why?
- How?

- Then what…

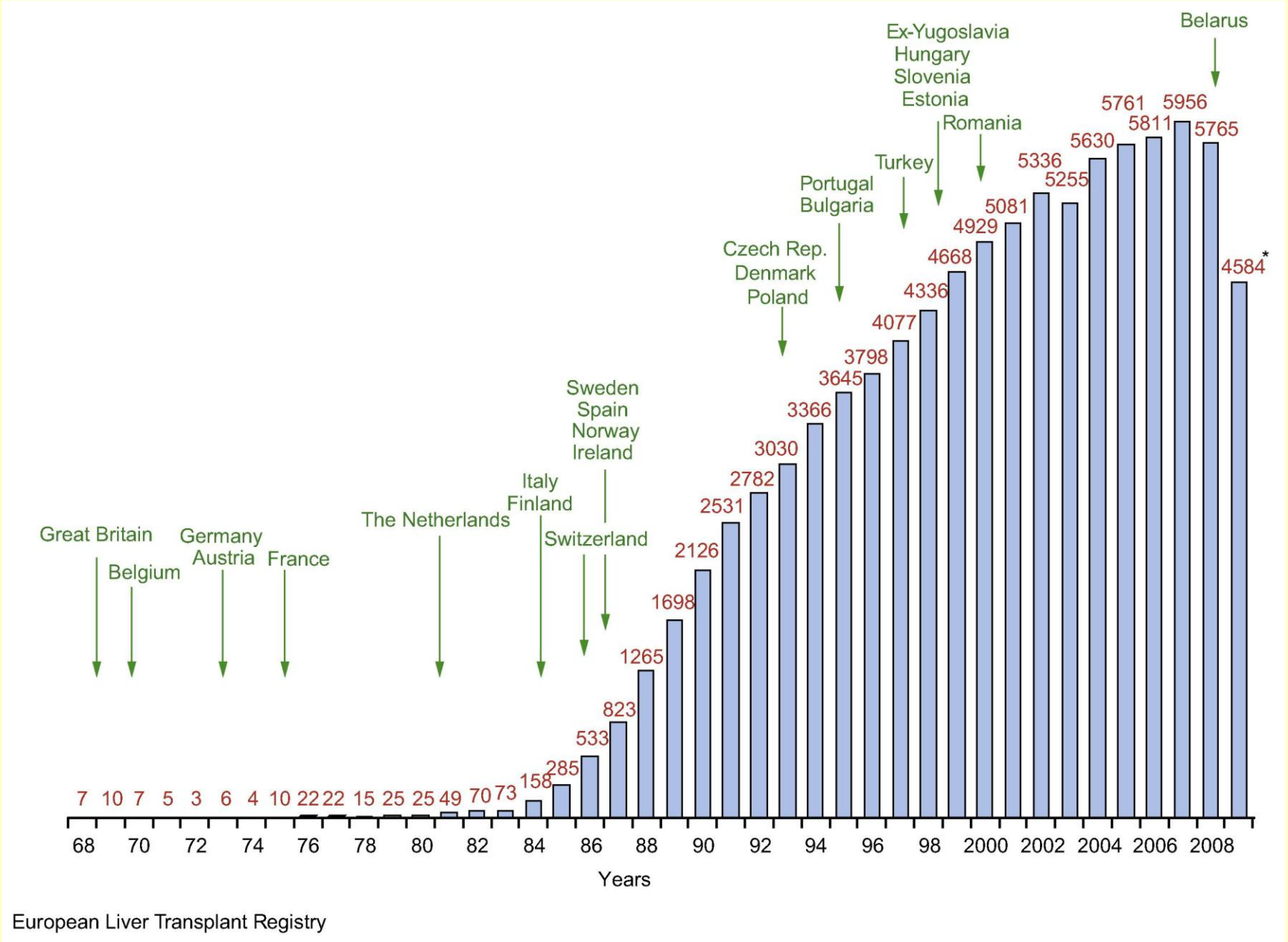


	Overall	LRLT
AUSTRIA	2193	38
BELARUS	34	0
BELGIUM	4316	341
BULGARIA	30	15
CZECH REPUBLIC	1089	1
DENMARK	734	8
ESTONIA	12	0
FINLAND	801	0
FRANCE	16,366	409
GERMANY	14,116	715
GREAT BRITAIN	13,684	138
HUNGARY	425	3
IRELAND	653	0
ITALY	11,697	212
MONACO	11	0
NORWAY	734	1
POLAND	1462	135
PORTUGAL	1645	26
ROMANIA	206	47
SLOVENIA	140	0
SPAIN	15,714	189
SWEDEN	2163	54
SWITZERLAND	1475	59
THE NETHERLANDS	1972	14
TURKEY	1946	1217
EX-YUGOSLAVIA	16	1
TOTAL	93,634	3622

ELSEVIER

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

Fig. 2



Journal of Hepatology 2012; 57:675-688

Indications for LT

European Registry 1988-2009 (80,347)

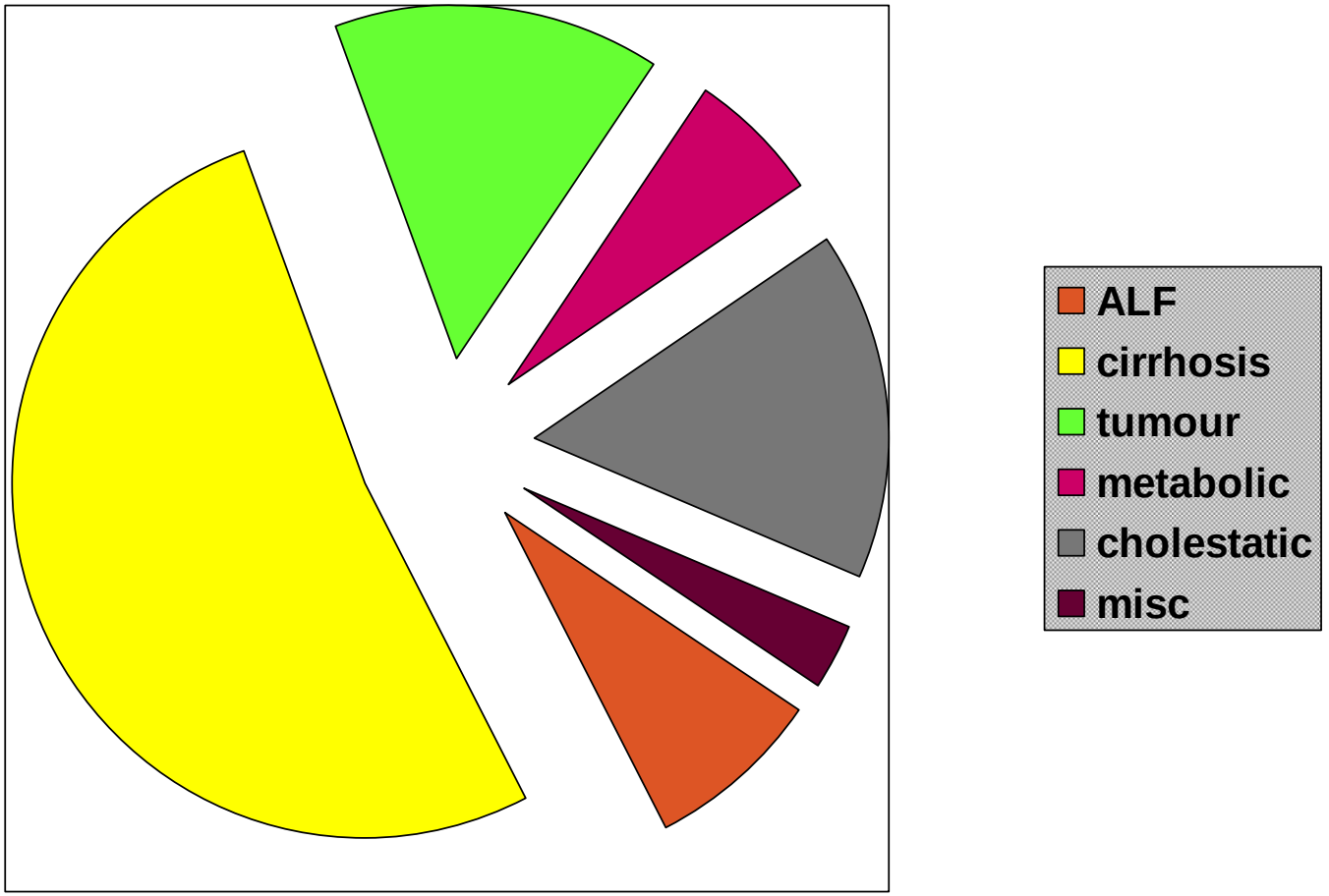
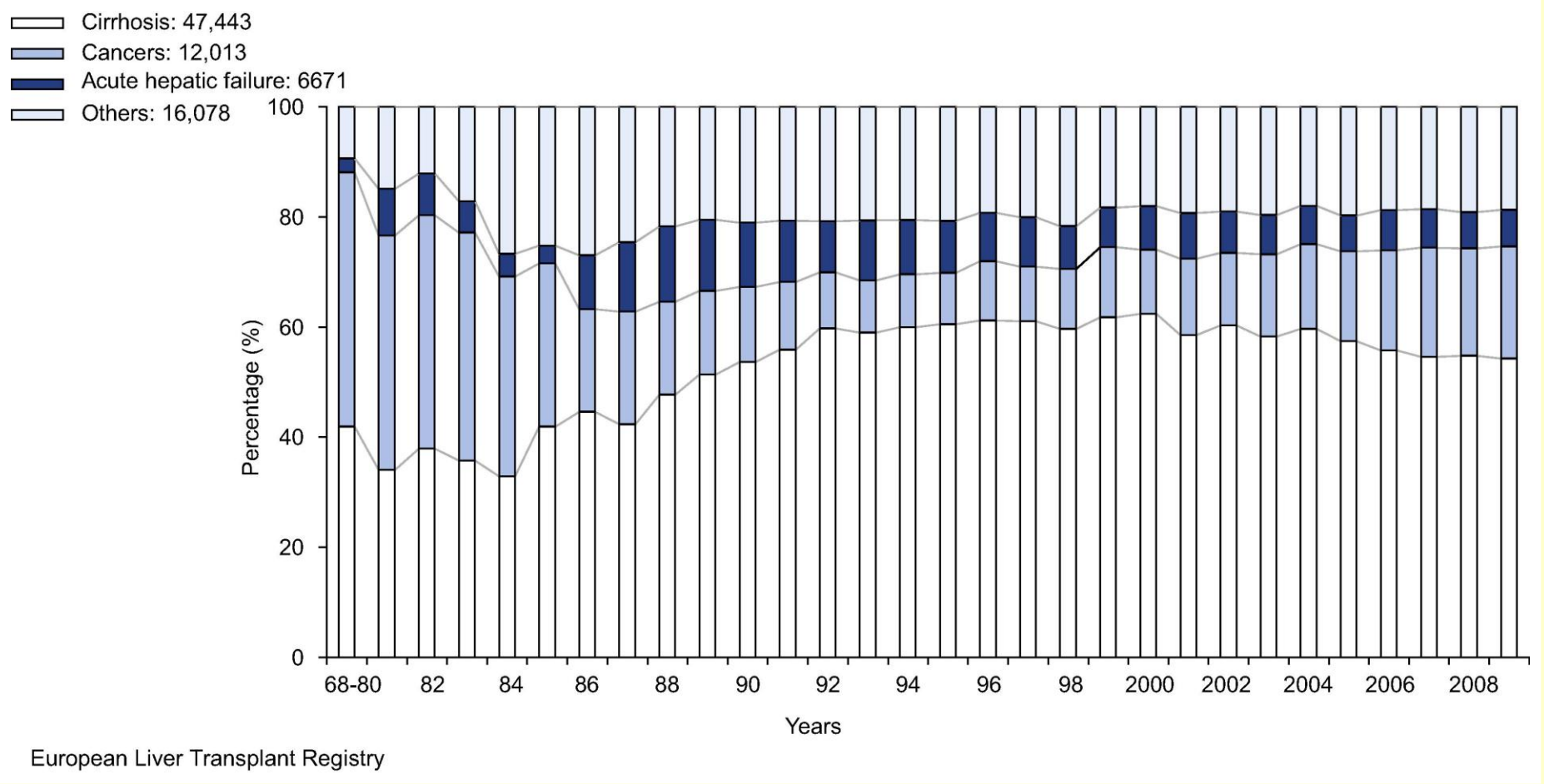


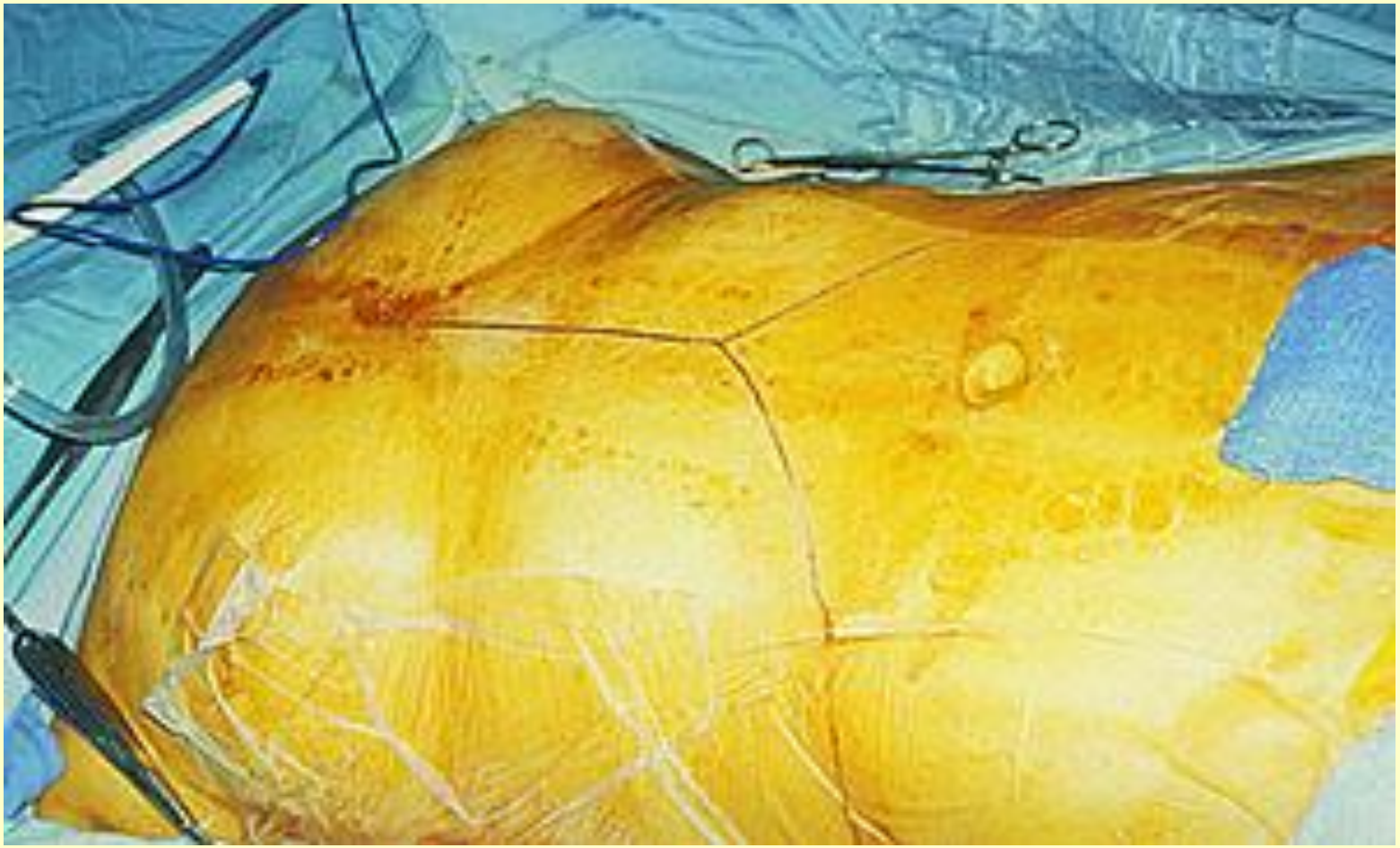
Fig. 3

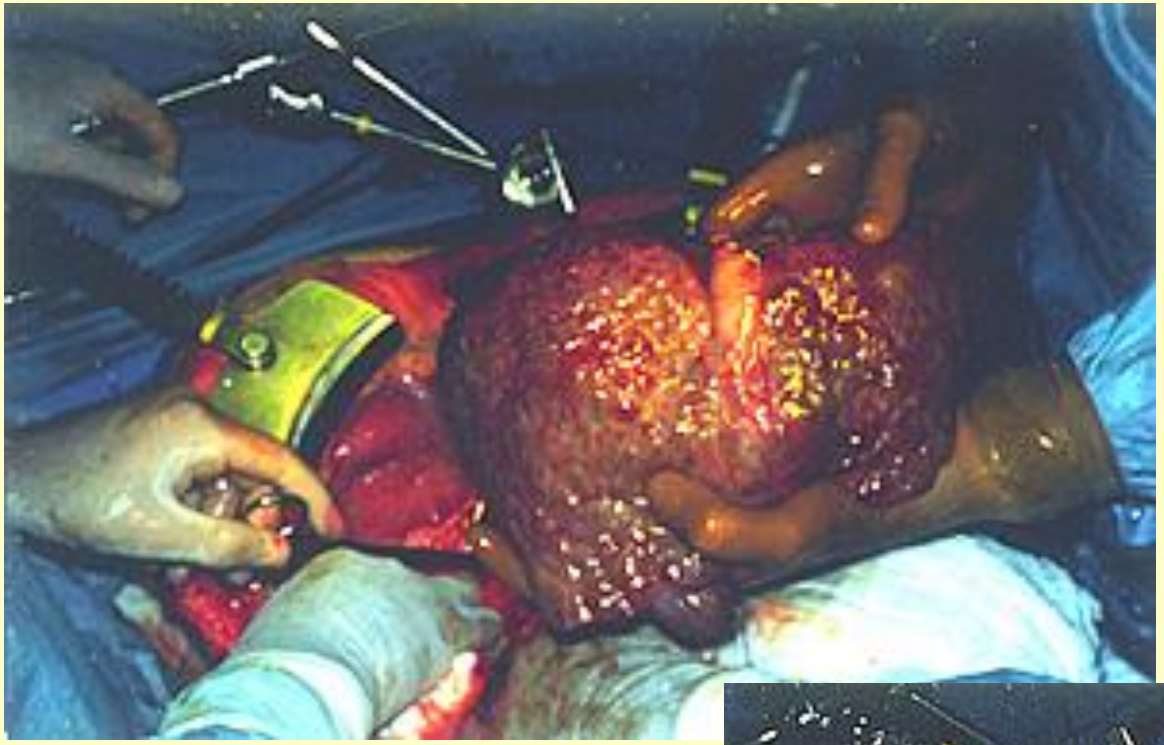
Indications over time



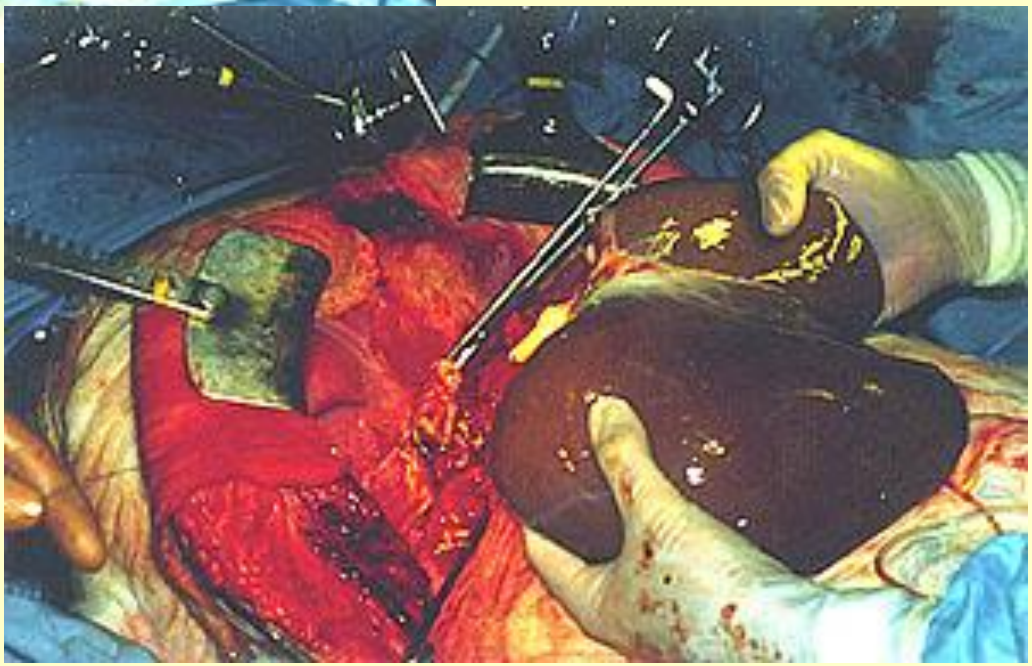
Source: Journal of Hepatology 2012; 57:675-688 (DOI:10.1016/j.jhep.2012.04.015)

How - Incision



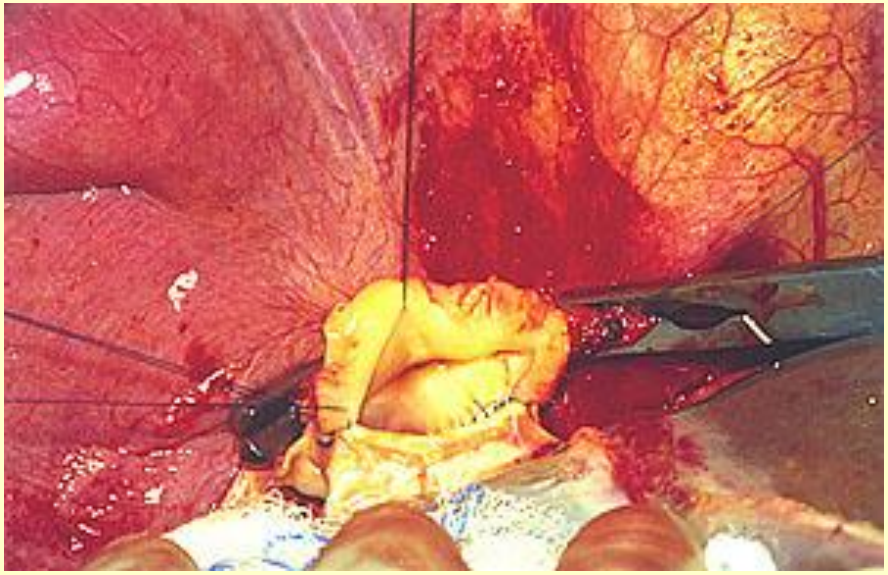


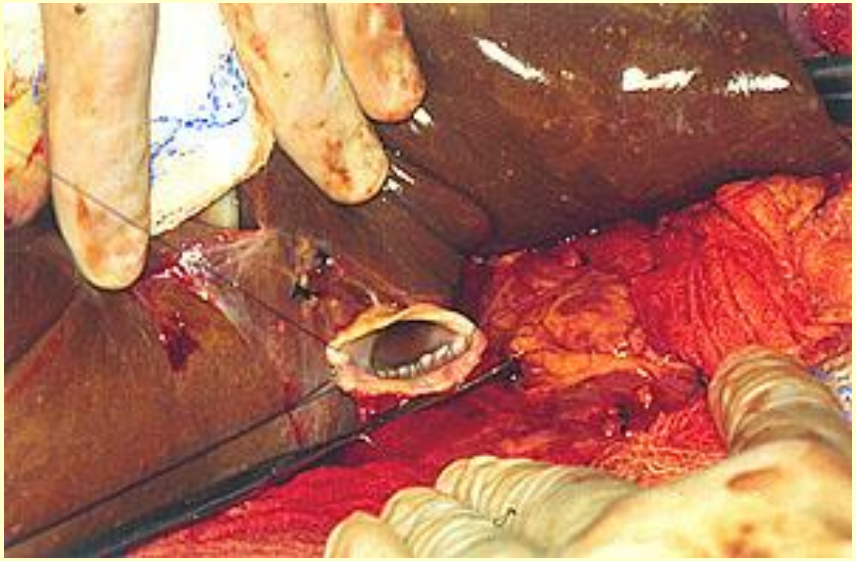
Recipient
Hepatectomy

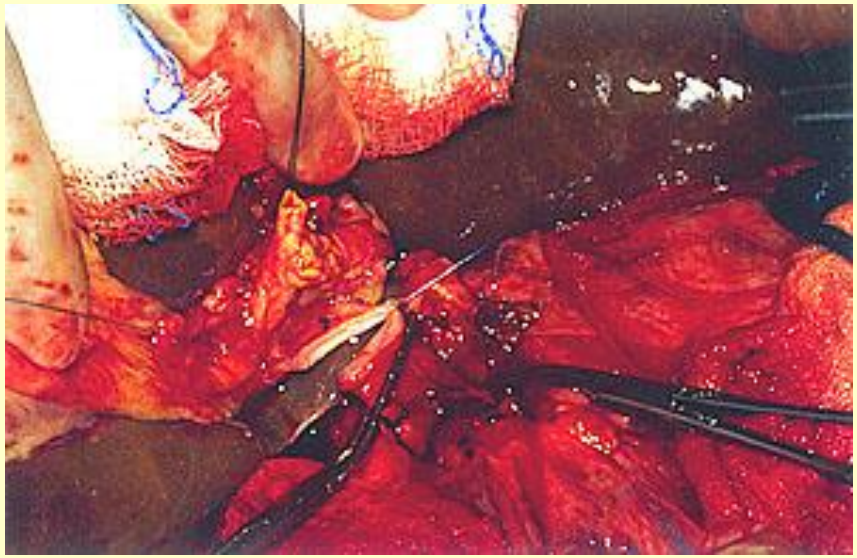


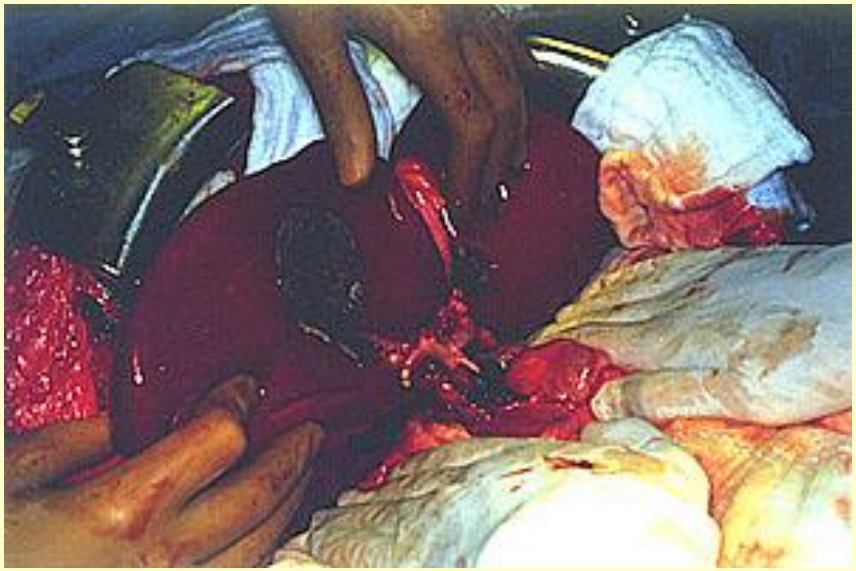
Implantation

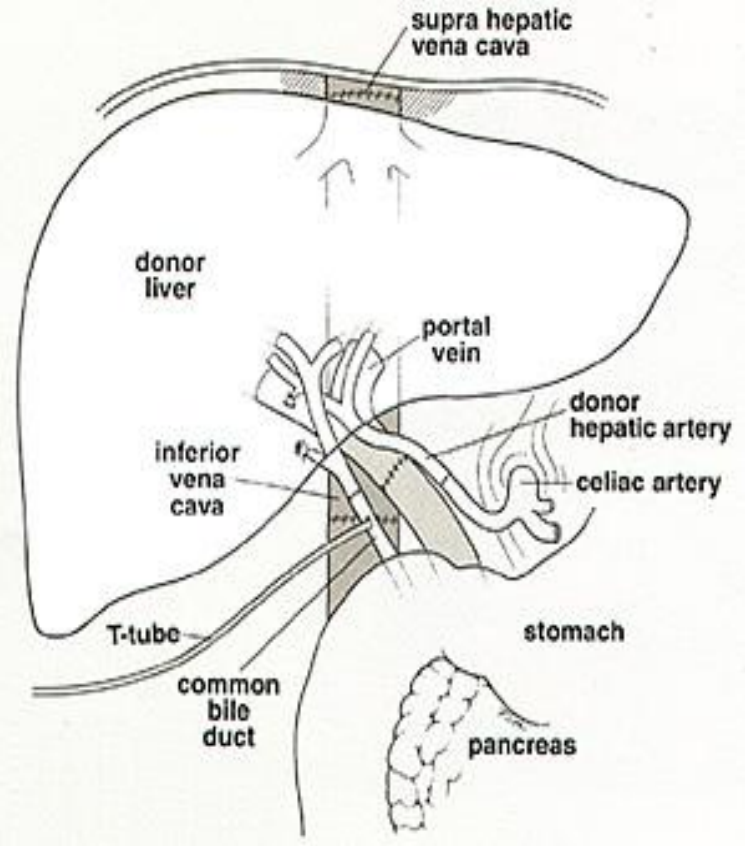
Anastomoses

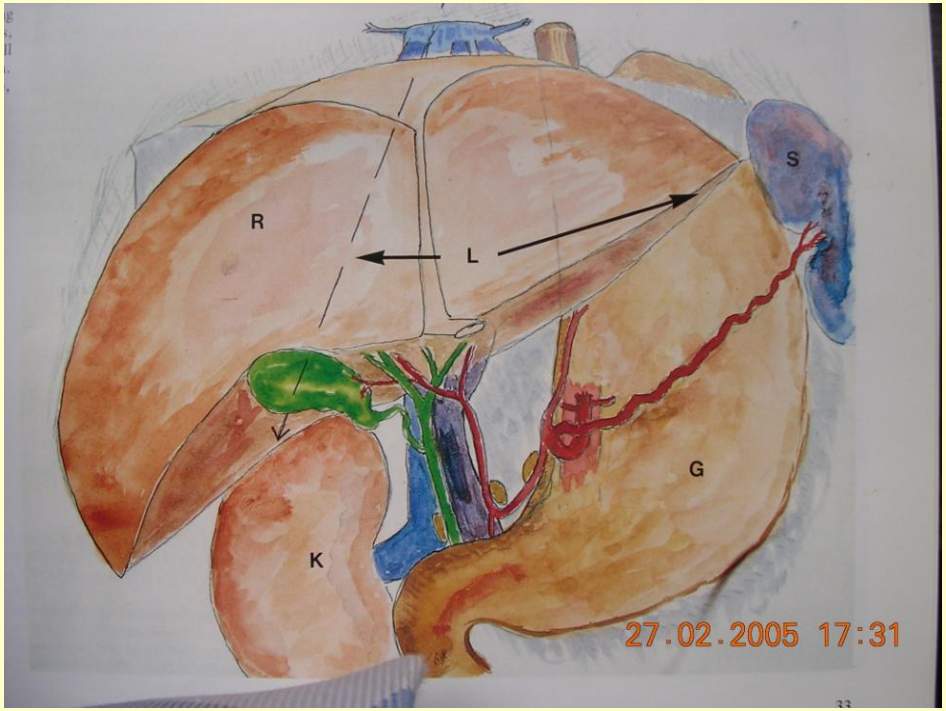









supra hepatic
vena cava
donor
liver
portal
vein
donor
hepatic artery
inferior
vena
cava
celiac artery
T-tube
stomach
common
bile
duct
pancreas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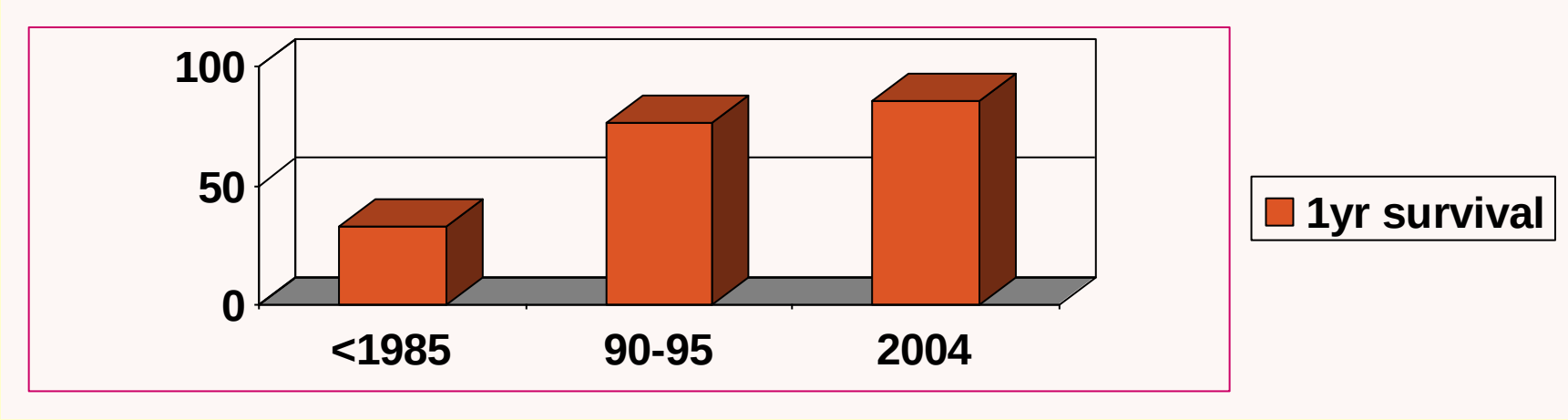
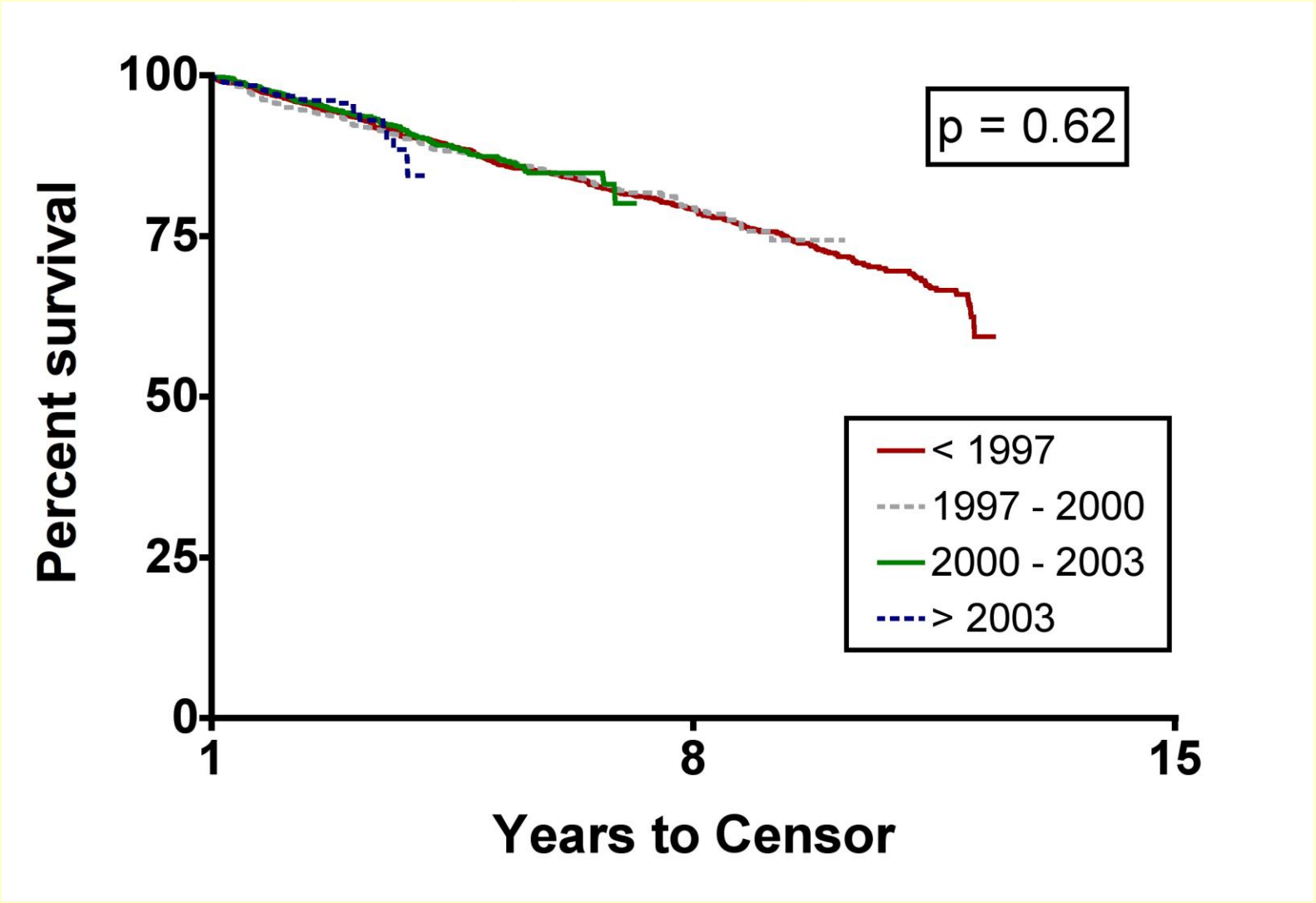
Survival…

- Critical period is 1st 6 months, with 46% of deaths and 65% of re-transplants; technical, vascular, primary non-function, MOF, sepsis, rejection
- 1,3 and 6 months survival all rapidly increased; 94%, 91% and 88% now in 2000s
- One year survival also improved



Late OLT Survival in the UK (n = 4483)



Why this plateauing?

- ☹
- Stalemate
- Powerful immunosupression exacerbates HCV, other recurrent diseases, including HCC recurrence
- Extending liver donation with unexpected consequences

- ☺
- Stopped a decrease!
- Donors and recipients older, patients sicker and cases with HCV and HCC more numerous
- Good surgery, immunospupressants, antibiotics etc

Causes of mortality beyond year-1 in the UK

Year post OLTx:	**1 – 3**	**3 – 5**	**5 – 10**	**>10**
Number dying:	241	189	208	25
Number in group:	4,483	3,151	2,081	409
Proportion dying:	5.4%	6.0%	10.0%	6.1%
Cause of death:				
Recurrent malignancy (13.7%)		Non-lymphoid malignancy (19.6%)	Non-lymphoid malignancy (19.7%)	Graft failure (20.0%)
Non-lymphoid malignancy (12.4%)		Graft failure (13.2%)	Other (13.5%)	Cardiac (12.0%)
Multisystem failure (12.4%)		Unknown (11.1%)	Unknown (12.0%)	Multisystem failure (12.0%)
Other (11.2%)		Infectious (10.6%)	Multisystem failure (10.6%)	CVA (8.0%)
Infectious (10.8%)		Other (10.1%)	Cardiac (9.6%)	Lymphoid malignancy (8.0%)
Graft failure (10.0%)		Cardiac (9.5%)	Infectious (8.7%)	Non-lymphoid malignancy (8.0%)
Cardiac (7.1%)		Recurrent malignancy (7.4%)	Lymphoid malignancy (6.3%)	Renal failure (8.0%)
Lymphoid malignancy (7.1%)		Multisystem failure (5.8%)	Graft failure (5.3%)	GI bleed (4.0%)
Unknown (4.1%)		GI bleed (3.7%)	CVA (3.8%)	Haemorrhage (4.0%)
Accidental (2.5%)		Lymphoid malignancy (3.2%)	Recurrent malignancy (3.4%)	Infectious (4.0%)
Renal failure (2.5%)		CVA (2.1%)	GI bleed (2.4%)	Recurrent malignancy (4.0%)
GI bleed (2.1%)		Renal failure (1.6%)	Renal failure (2.4%)	Other (4.0%)
CVA (1.7%)		Haemorrhage (1.1%)	Suicide (1.0%)	Unknown (4.0%)
Haemorrhage (0.8%)		Suicide (1.1%)	Accidental (0.5%)	Accidental (0%)
PE (0.8%)		Accidental (0%)	Haemorrhage (0.5%)	PE (0%)
Suicide (0.8%)		PE (0%)	PE (0.5%)	Suicide (0%)

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PE (0.8%)		Accidental (0%)	Haemorrhage (0.5%)	PE (0%)
Suicide (0.8%)		PE (0%)	PE (0.5%)	Suicide (0%)

Then what…

- Long-term patient survival is not improving in UK liver transplant recipients.
- The major causes of death after year-1 in the UK Transplant cohort were malignancy, infection, multi-system failure, graft failure and cardiac events.
- Positive associations with death were various aetiologies ALD, AIH or cryptogenic, HCV and HCC
- Worse outcome with use of prednisolone, compared with all other IS

Huge number of factors at play

Initial disease – genotype, viral load

Age of donor, age of recipient

State of donor liver, ischaemia time (12 hours)

Complications of anastomoses

Immunosuppressants altering natural history

Co-factors – iron, alcohol, fatty metabolism

Episodes of rejection

Immunosupressant-related complications

Post Transplant Lymphoproliferative Disorder

Other tumours

Opportunistic infections

Decreased immunosupression, intentional or otherwise leading to rejection episodes

Acceleration of recurrent disease processes and atypical forms – viral and NAFLD

Renal damage

Metabolic effects

THE PROBLEM

Cardiovascular disease

Renal

Infections

Blood pressure

Obesity

Cancer

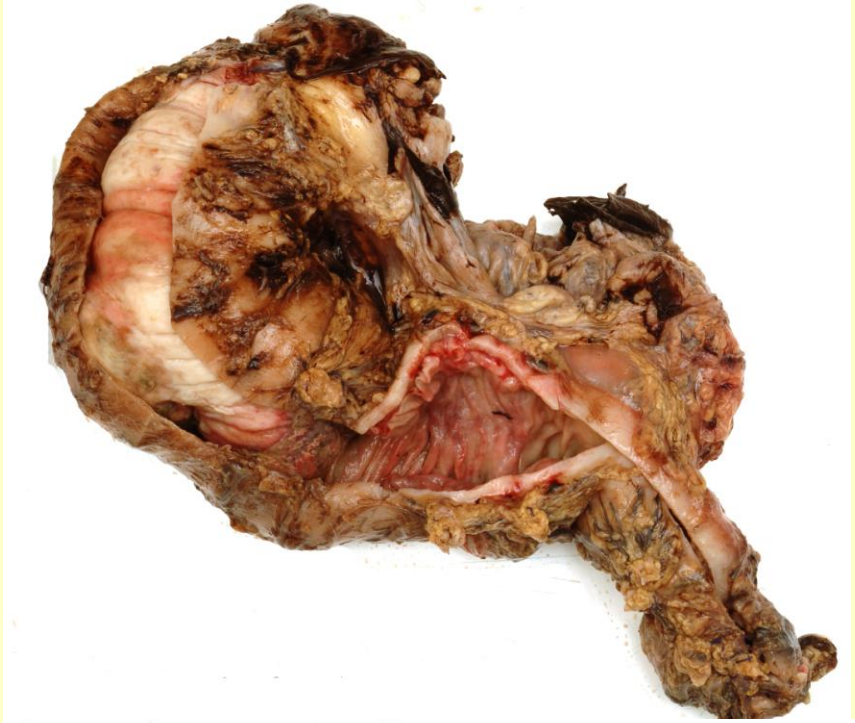
DM

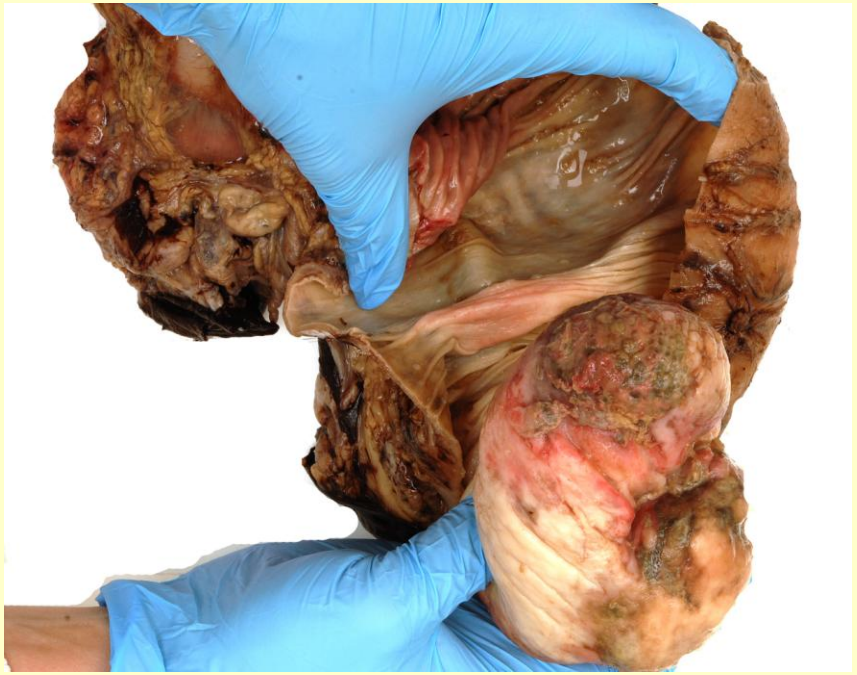
Tolerability

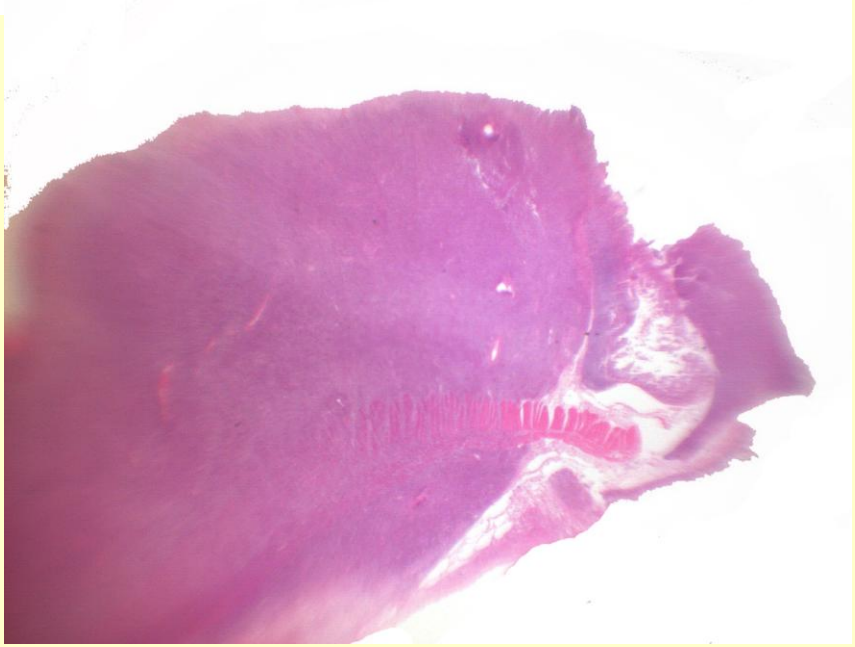
REJECTION

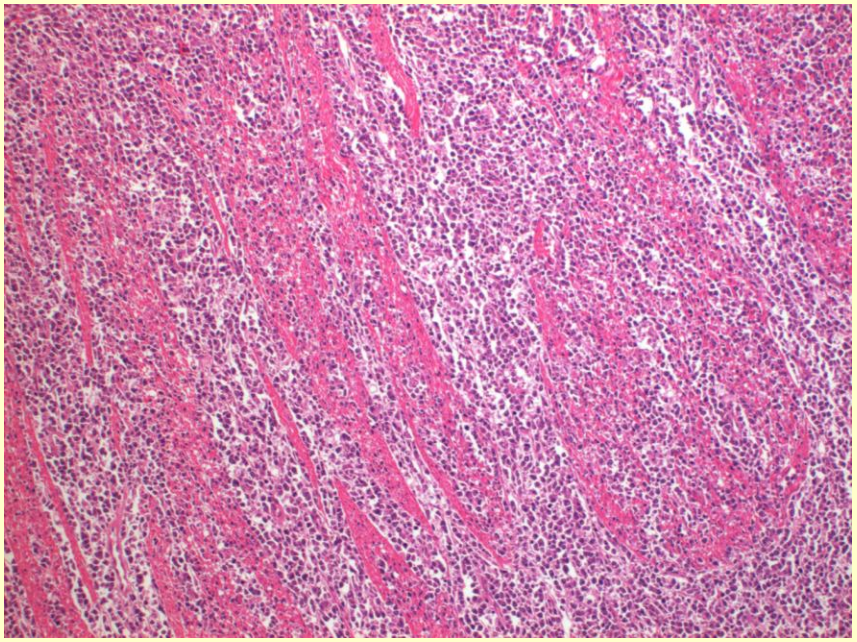
Post Transplant Lymphoproliferative Disorder

- Range of Lymphoid hyperplasia and neoplasia
- Affects 2-5% of solid organ recipients; graft or extra-nodal & multiple
- EBV infection implicated in the majority,
- Commonly early – within 1st 1-2 years
- Variable clinical manifestations, prognosis depends on type.

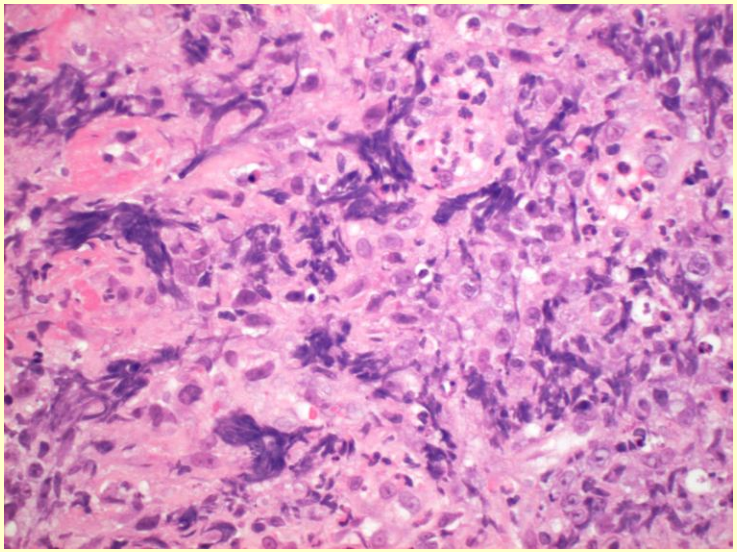


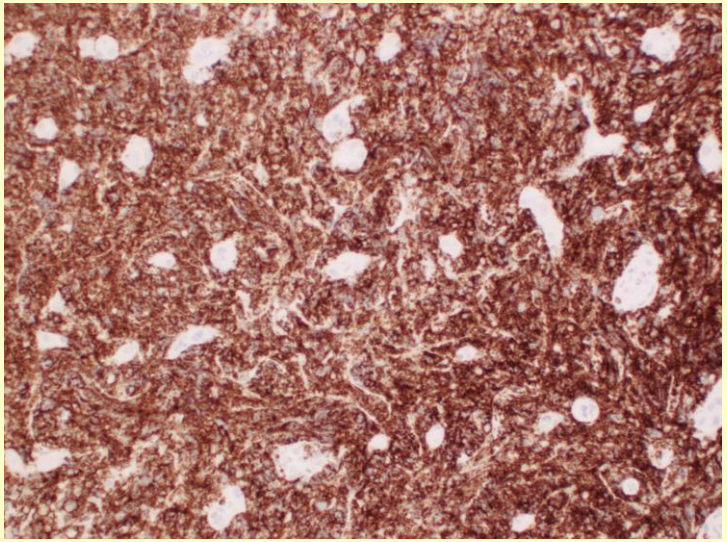






Burkitt's like, non EBV





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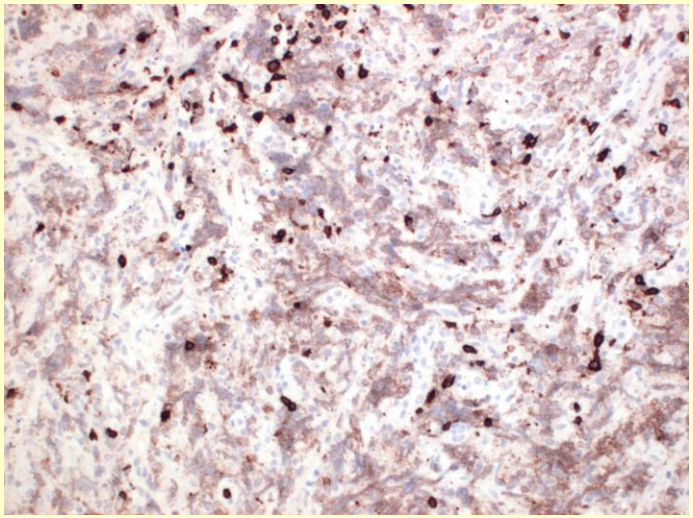

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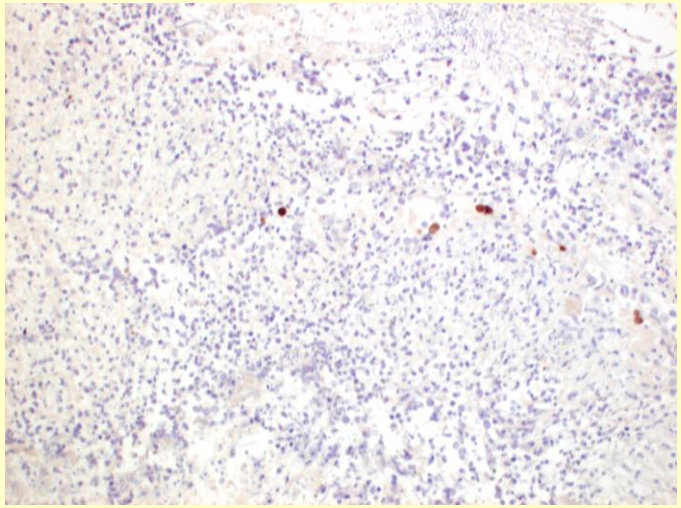
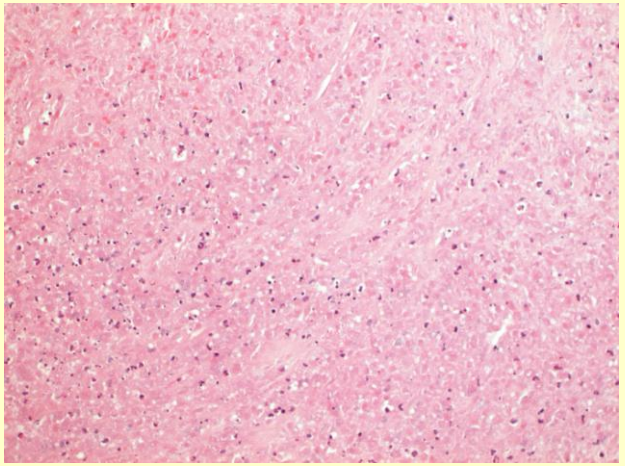
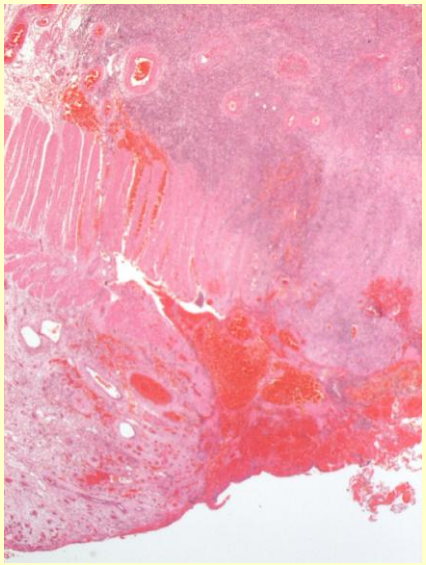


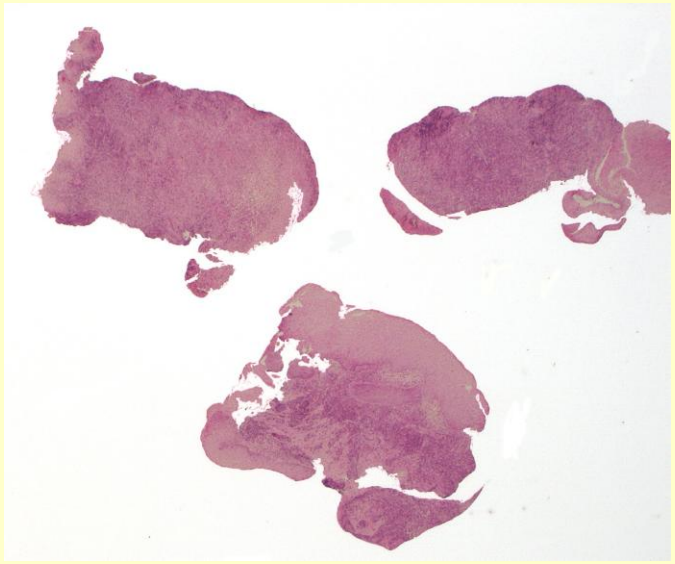
EBV

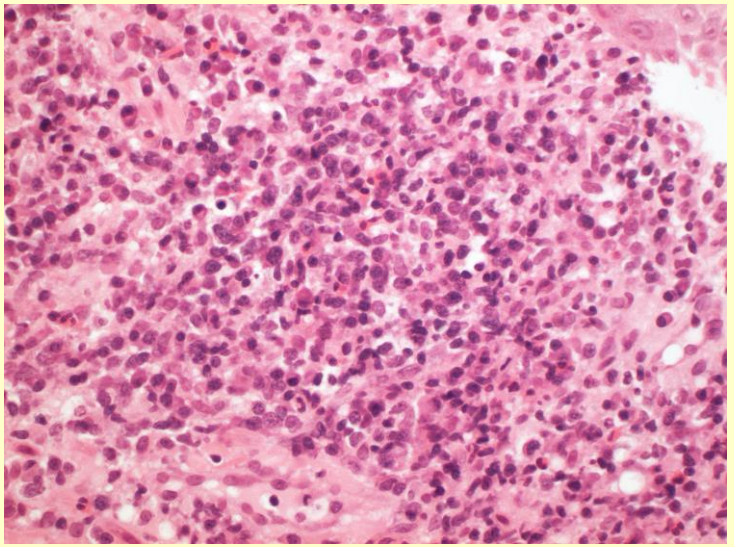
Another case – perforation post treatment

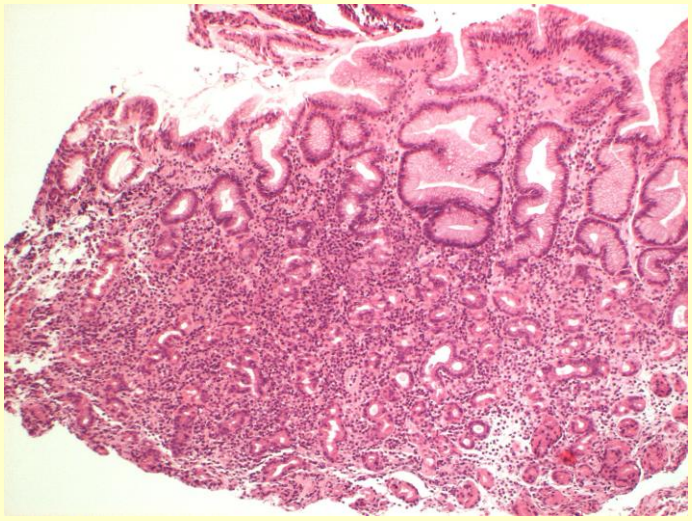


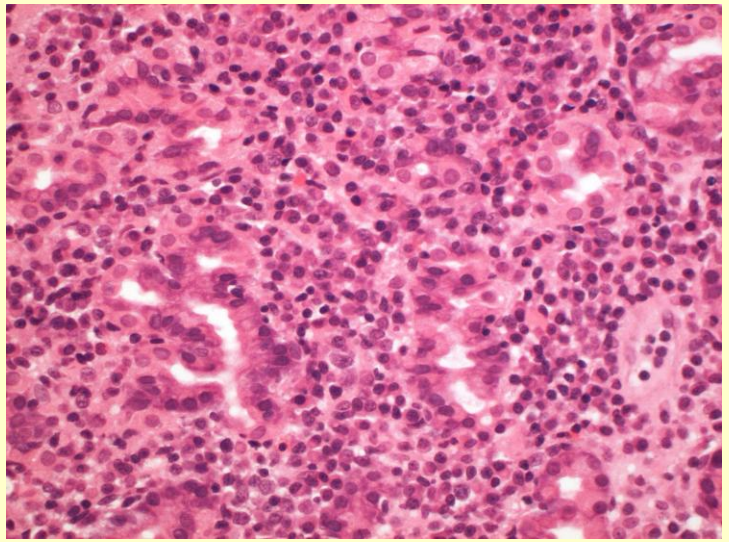


Multifocal disease

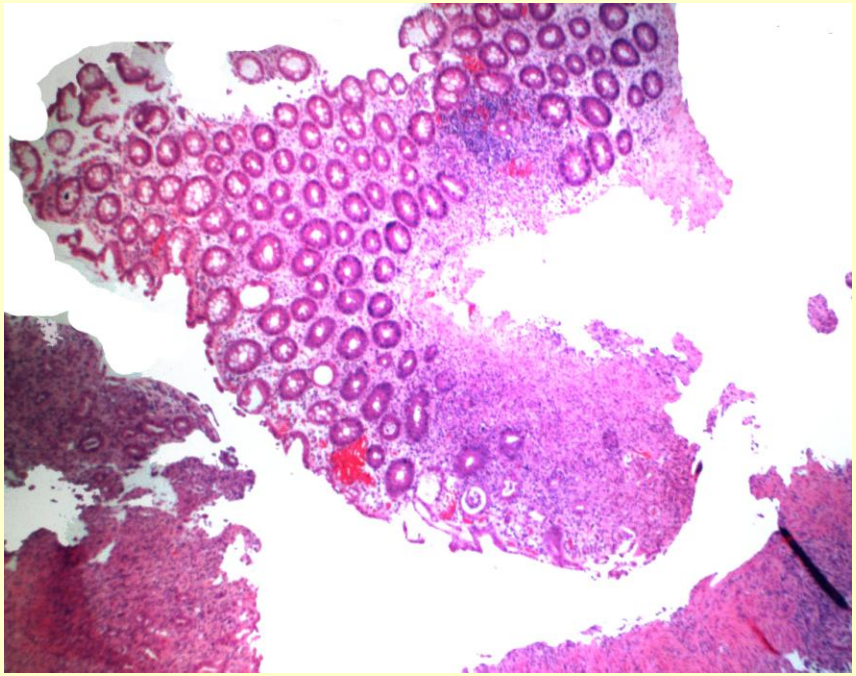


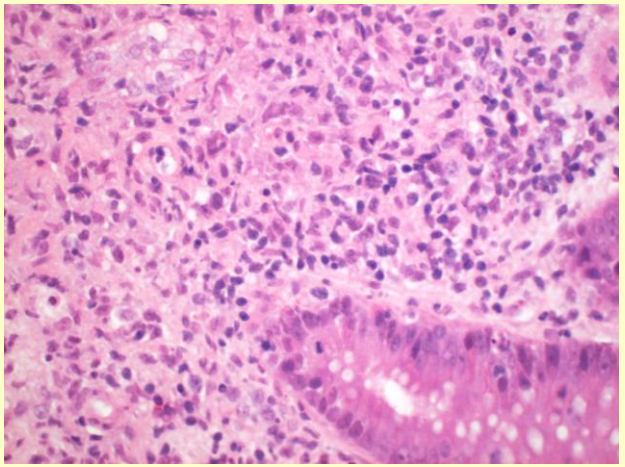


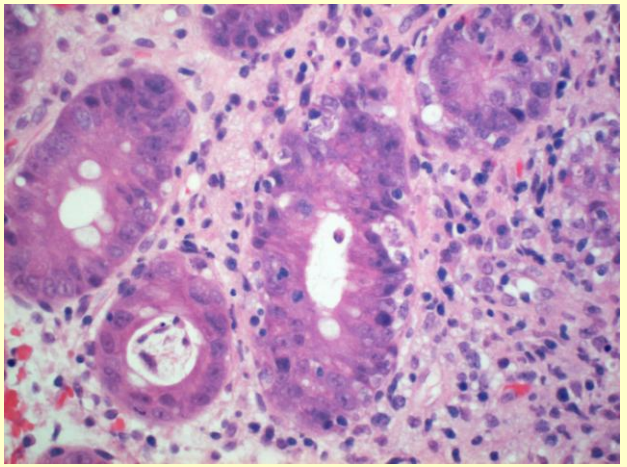


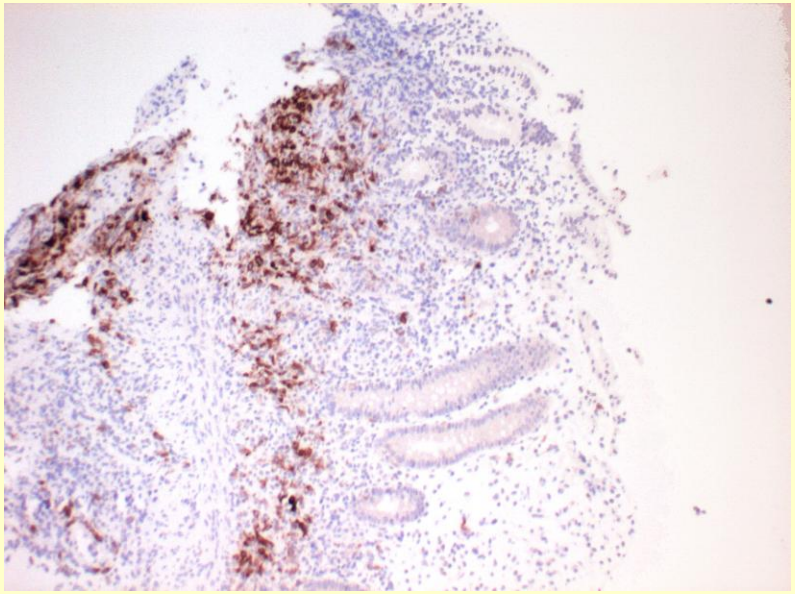


Referred as infective colitis









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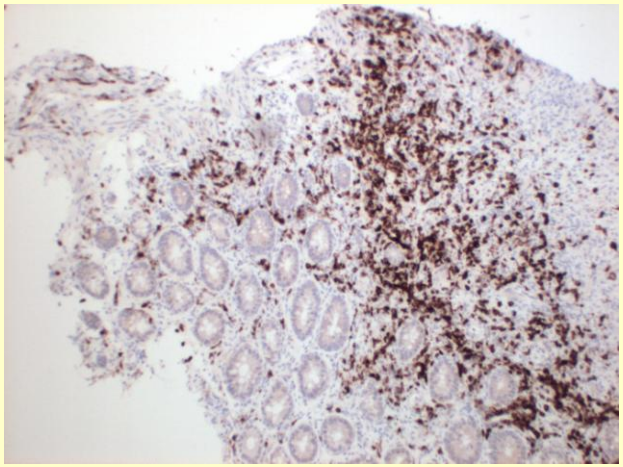
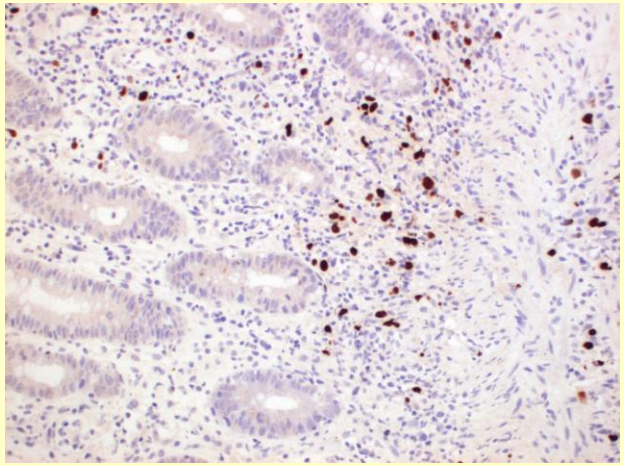


CD20



EBER

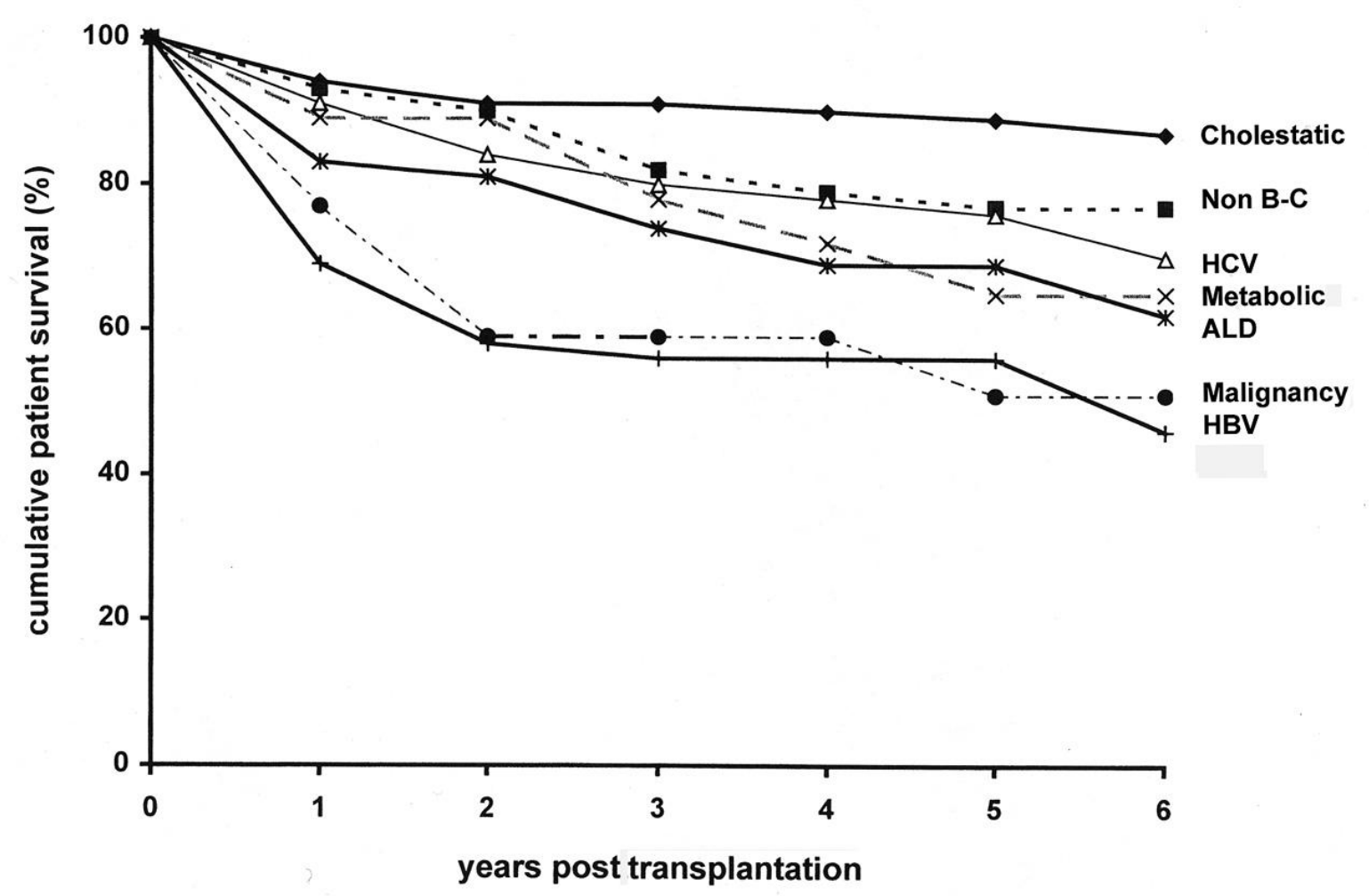
Hodgkins like, EBV assoc

PTLD Classification WHO

1. **Early Lesions;** plasmacytic hyperplasia, Infectious mononucleosis-like lesion
2. **Polymorphic PTLD**
3. **Monomorphic PTLD2**
   B-cell neoplasms; diffuse large B-cell lymphoma, Burkitt lymphoma, plasma cell myeloma, plasmacytoma-like lesion, other

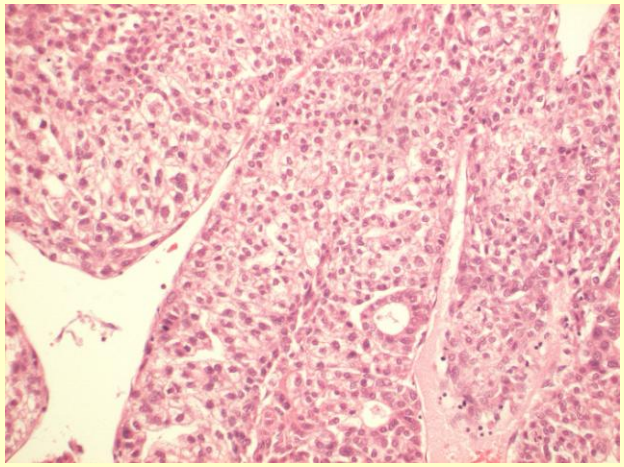
   T-cell neoplasms; peripheral T-cell lymphoma, NOS, Hepatosplenic T-cell lymphoma, other<SUP3< sup>
4. **Classical Hodgkin lymphoma-type PTLD**

OLT for HCC - Eurohep group, >700 patients, 1984-95

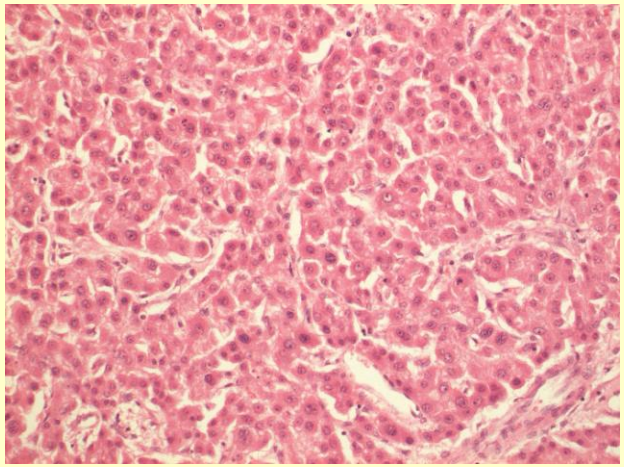


But…

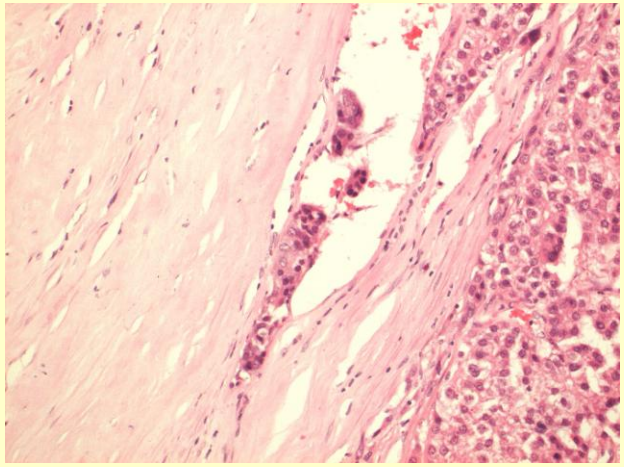
OLT for WD; x 2 HCCs, 8.5 + 2cm ; T3



Grade 2



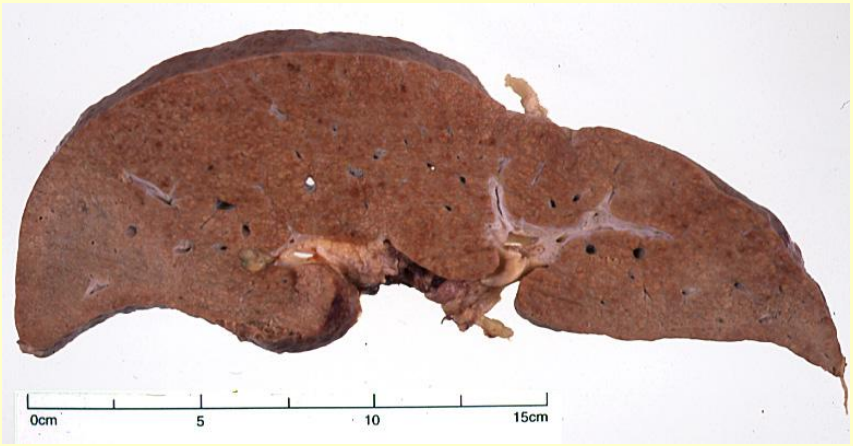
Grade 1

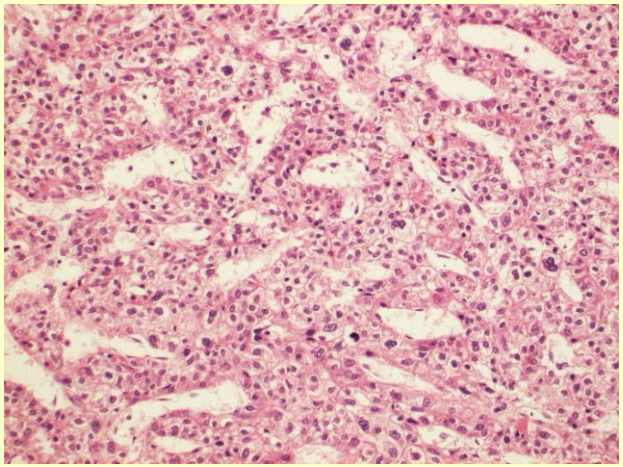


Vascular invasion

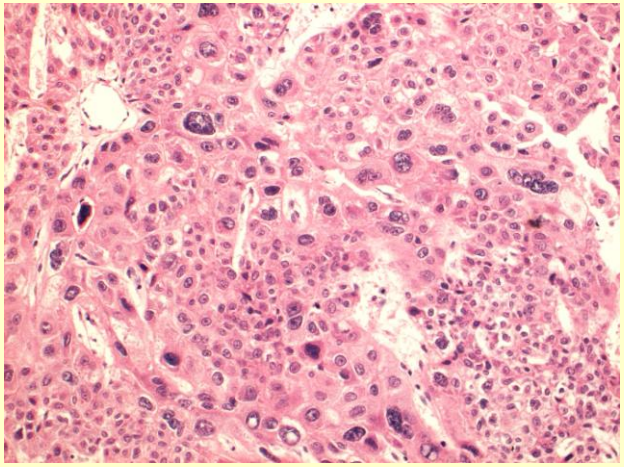
And Another..

OLT HCV and HCC
1.4cm, T2



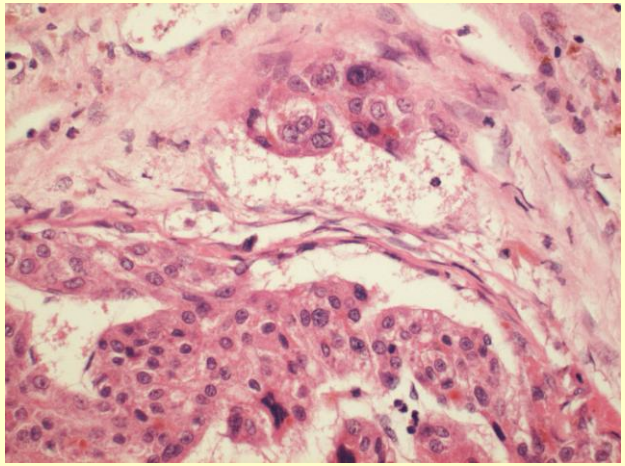


Grade 2



Grade 3

Vascular
invasion

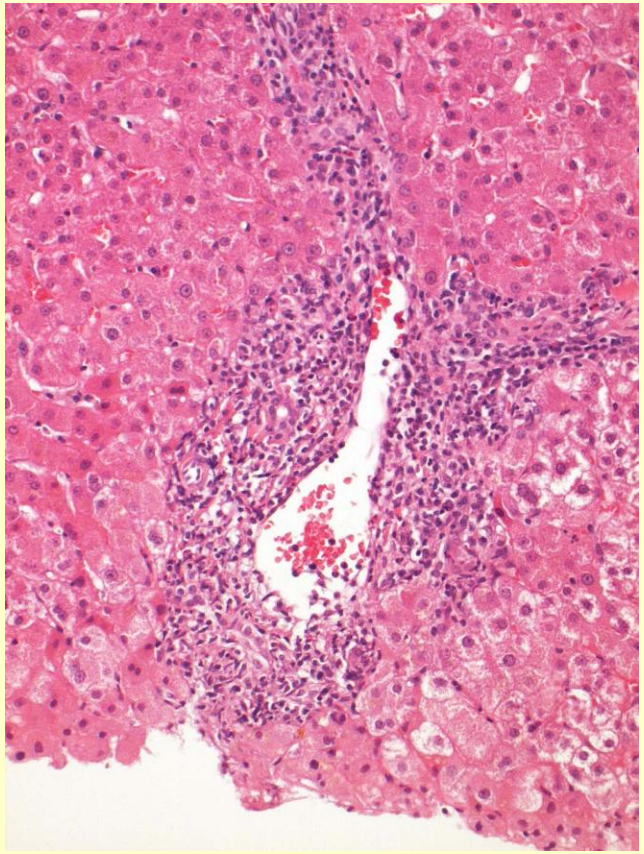


Late Graft problems

- Disease recurrence,
- Problems with immunosupression; infections, neoplasia
- New diseases – rejection, hepatitis, biliary
- Drug complications

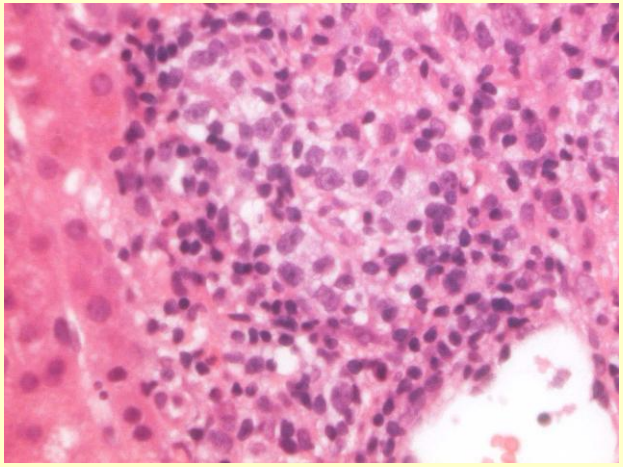
- More than one process!

Typical triad of acute rejection in 1st few weeks.

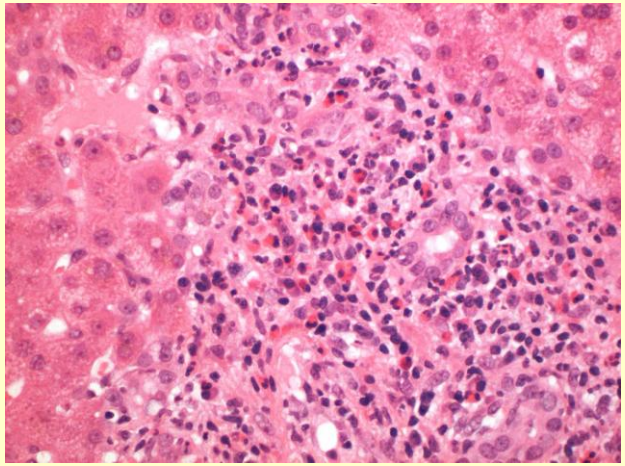


Classic triad

blasts

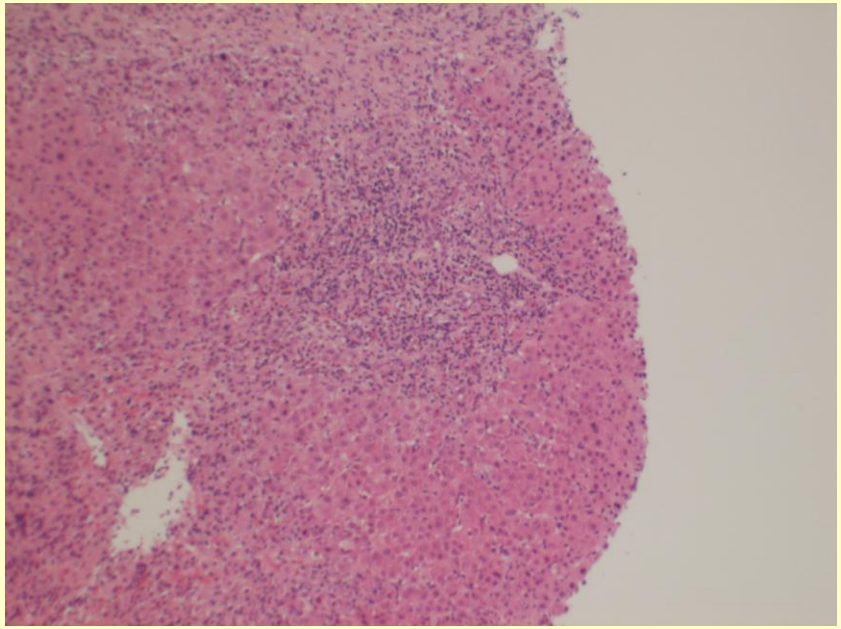


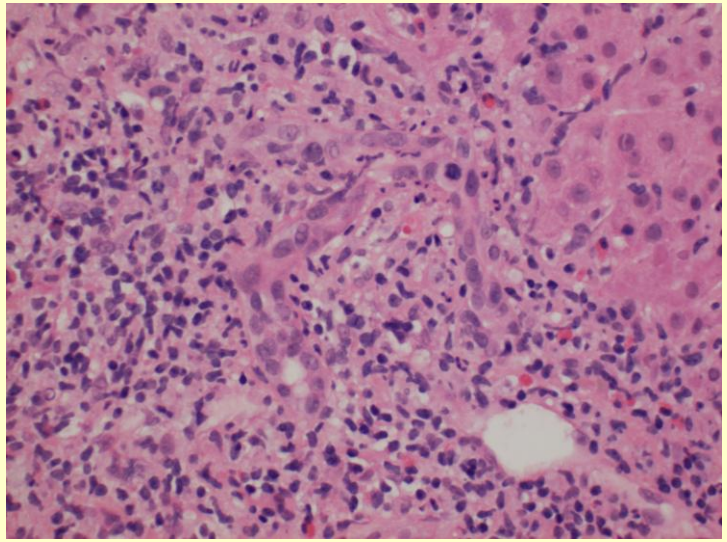
Eosinophils & duct involvement



Patient stopped immuno at 8 months

Often less portal involvement with less blasts and endothelialitis

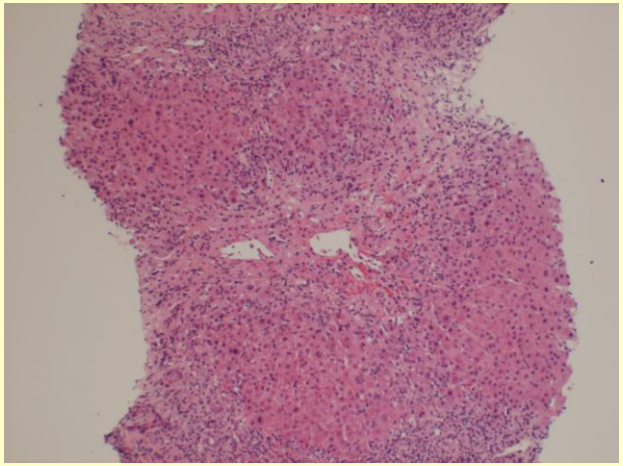


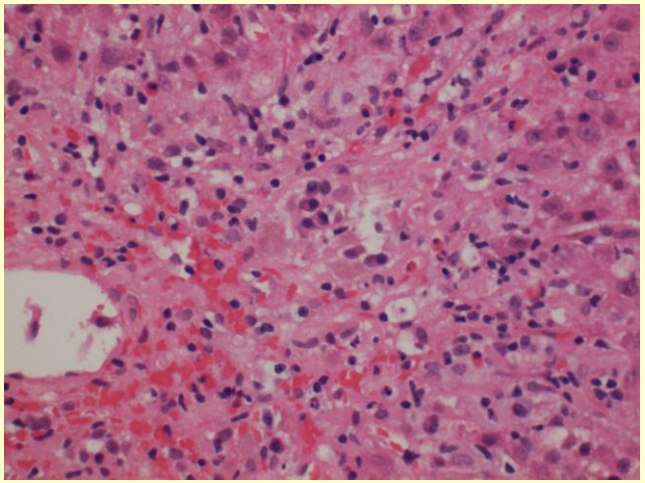


Marked perivenulitis

Centro-central bridging

Plasma cell prominent





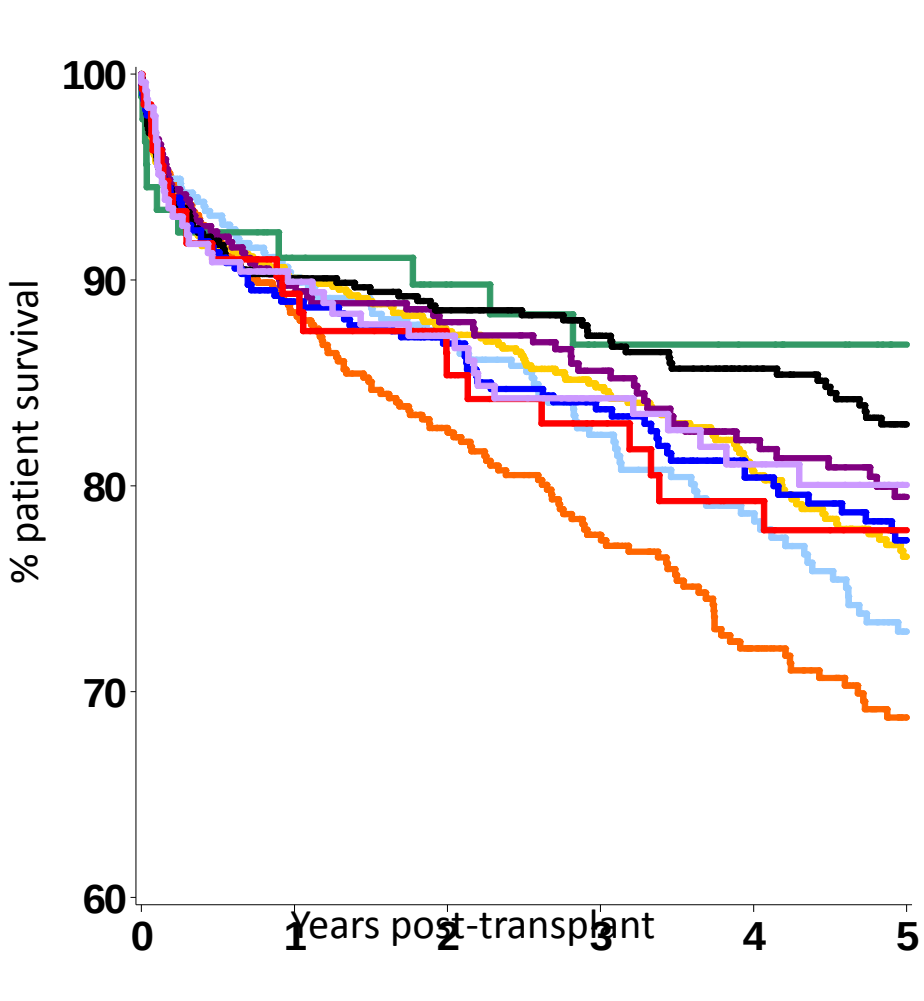
Significance of late acute rejection?

- May not be recognized, may be only perivenular
- May get further episodes of acute rejection
- Transition to Chronic rejection with duct loss
- Development of de novo autoimmune hepatitis/ idiopathic hepatitis
- Chronic progressive fibrosis

HCV and liver transplantation

- The commonest indication for transplantation in many units
- Near universal recurrence of viraemia and associated with inflammation
- But wide variations in outcome
- Atypical forms and more rapid fibrosis progression (x5-x10) than in non-transplant setting
- Although short term survival for HCV negative and positive similar, now decreased patient and graft survival

Five-year unadjusted patient survival by liver disease (2000-2010)



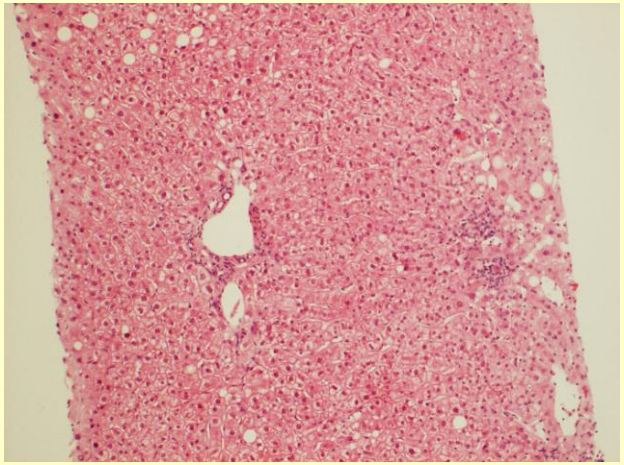
	% survival	(95% CI)	N
Cancer	68.7	(64.0 – 73.0)	666
HCV	72.9	(67.7 – 77.4)	471
ALD	76.6	(72.9 – 79.8)	864
HBV	86.9	(77.4 – 92.5)	91
PSC	79.5	(74.5 – 83.5)	411
PBC	83.0	(79.1 – 86.2)	524
AID	77.4	(72.3 – 81.6)	400
Metabolic	77.8	(68.3 – 84.8)	135
Other	80.0	(73.3 – 85.3)	246

Log-rank p-value=0.001

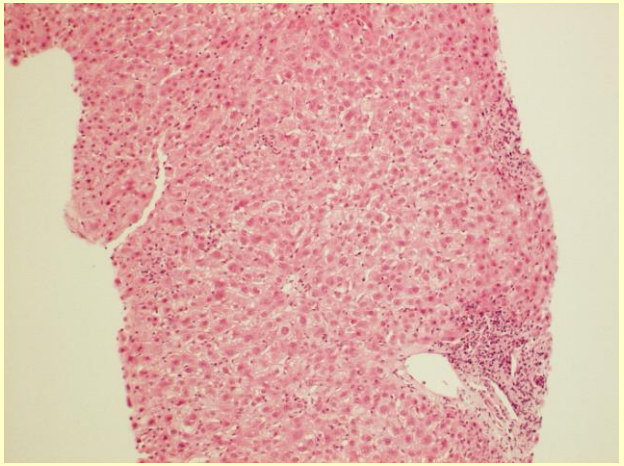
Factors implicated in rapid progression

- Donor age
- Lack of pre-transplant alcohol abuse
- Viral load pre-transplant, genotype 1
- Inflammatoray activity in recipient's explant
- Warm ischaemia time
- Immunosupression; treble & double agents
- Number of episodes of rejection- treated
- Severity of hepatitis at recurrence
- Degree of fibrosis at 1 year

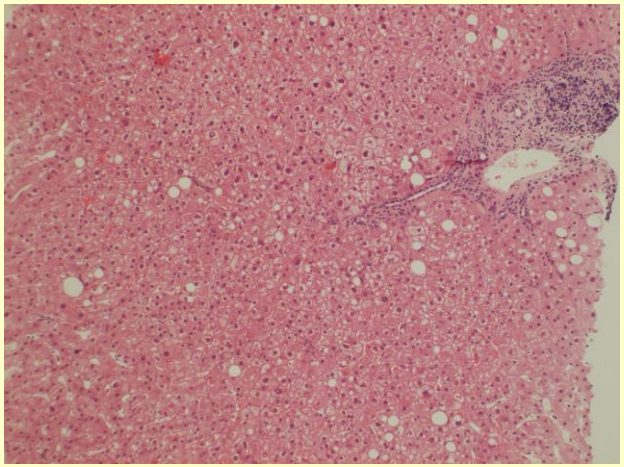
Neither of these had ACR treated, donors > 60yrs, nor different immunosupression….



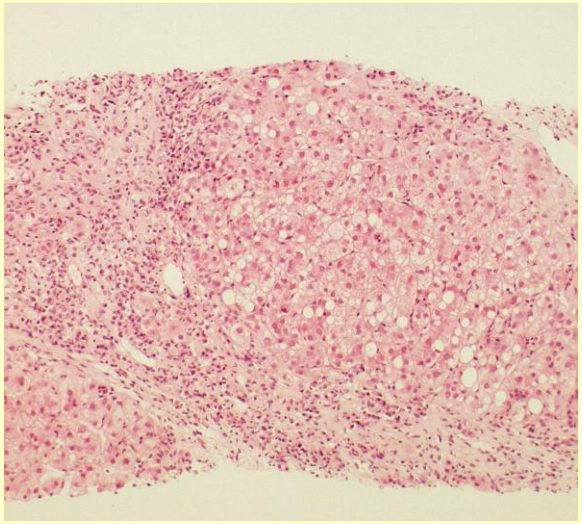
8 months



5 months



5 years



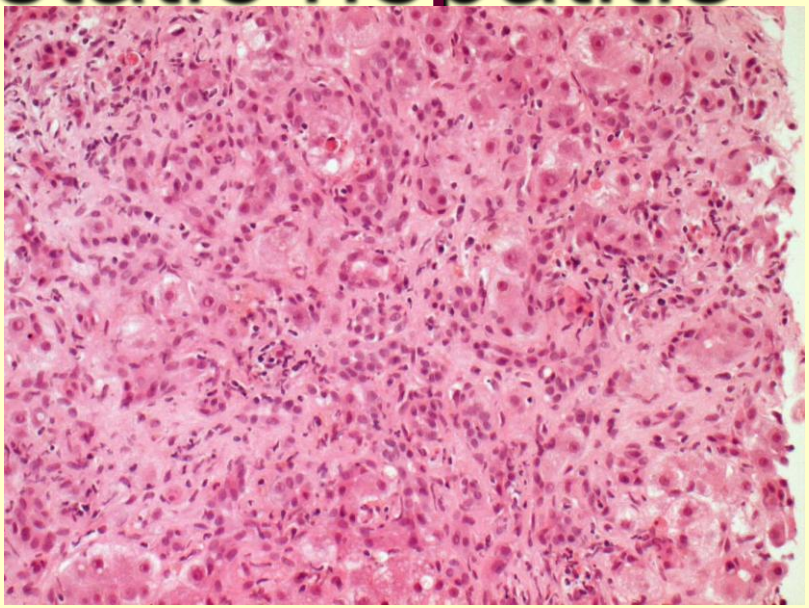
20 months

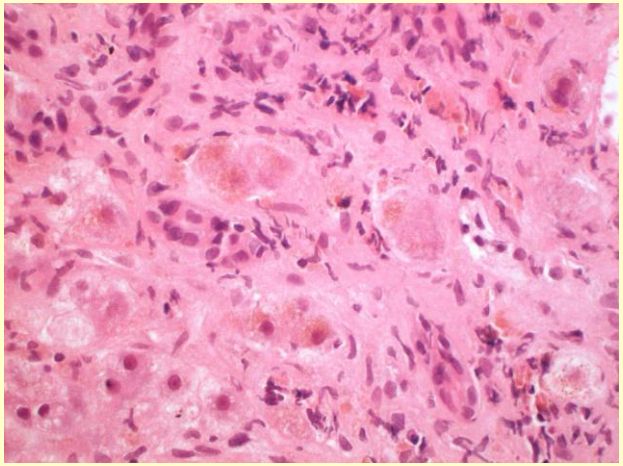
Case 1

Case 2

Fibrosing cholestatic hepatitis

- Less than 10%
- Very high viral loads
- Cytopathic
- Only seen with immunosupression



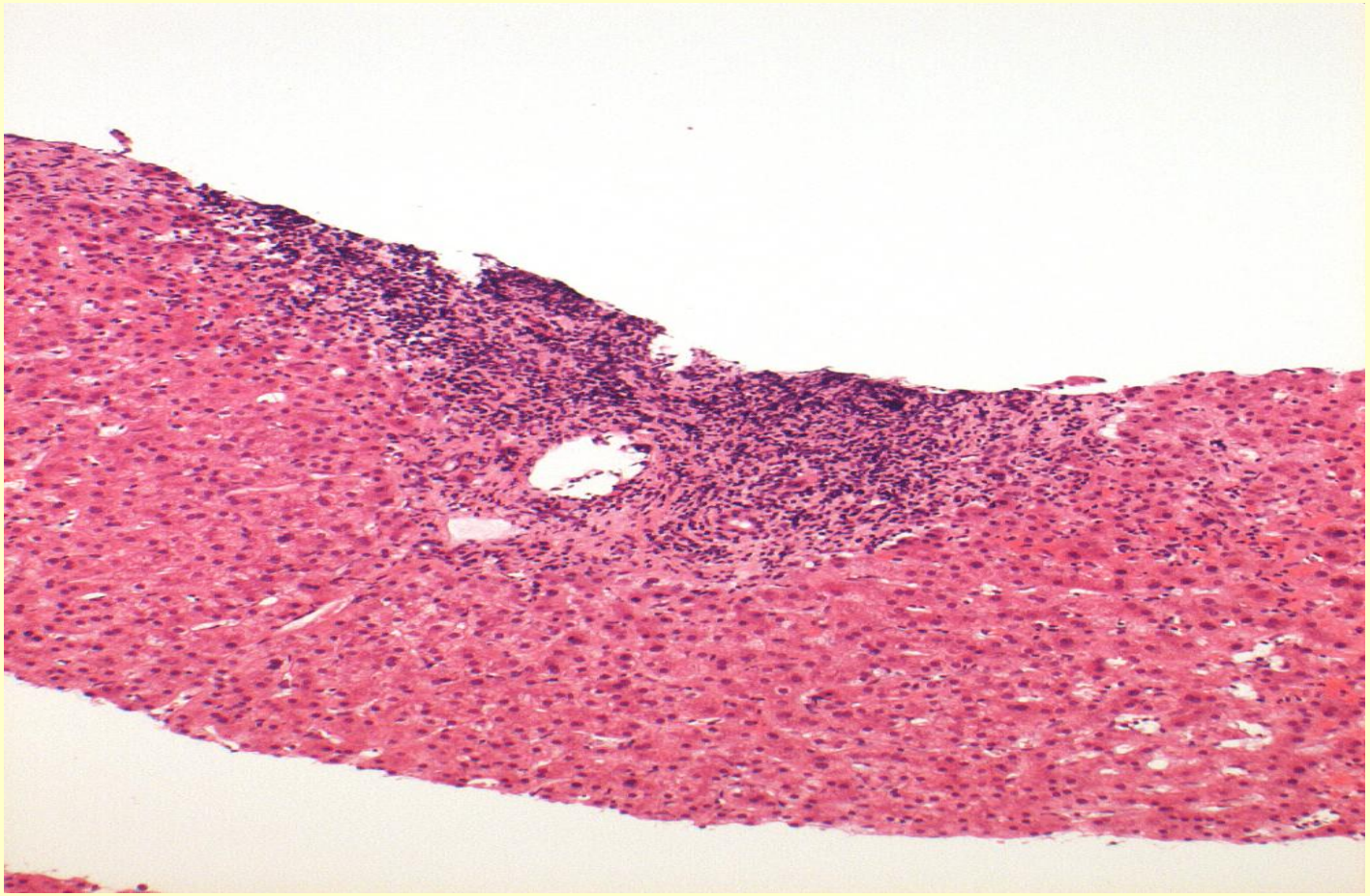


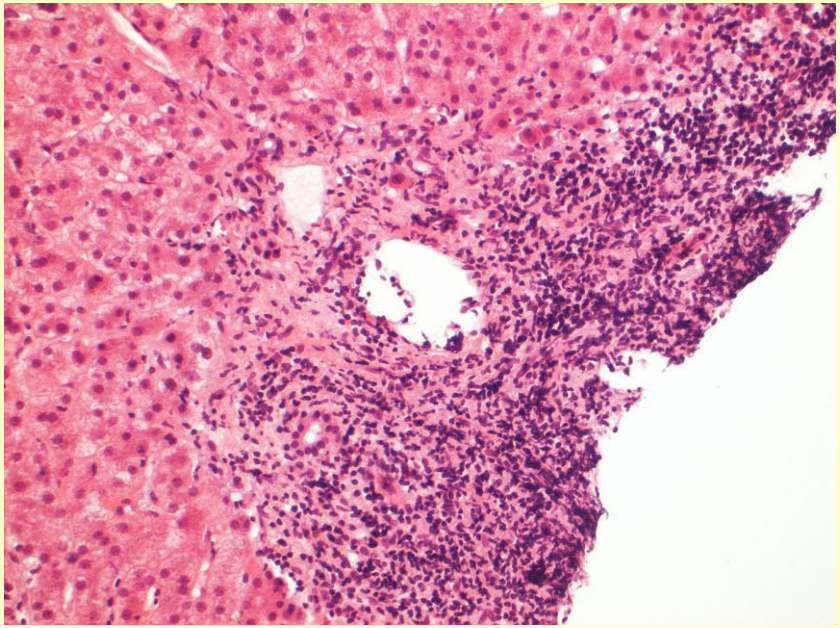
Is it chronic HCV or ACR?

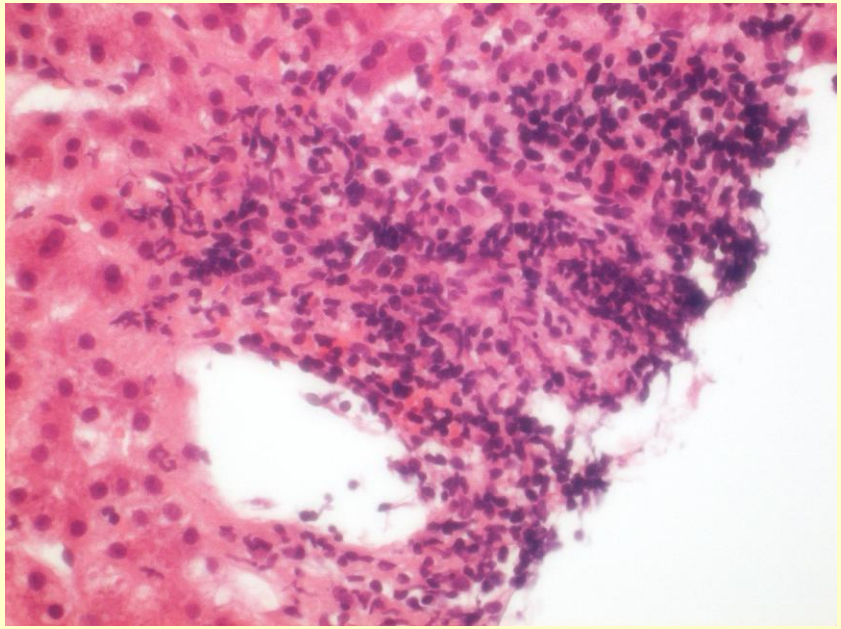
(and so avoid inappropriate corticosteroids in graft infection with HCV)?

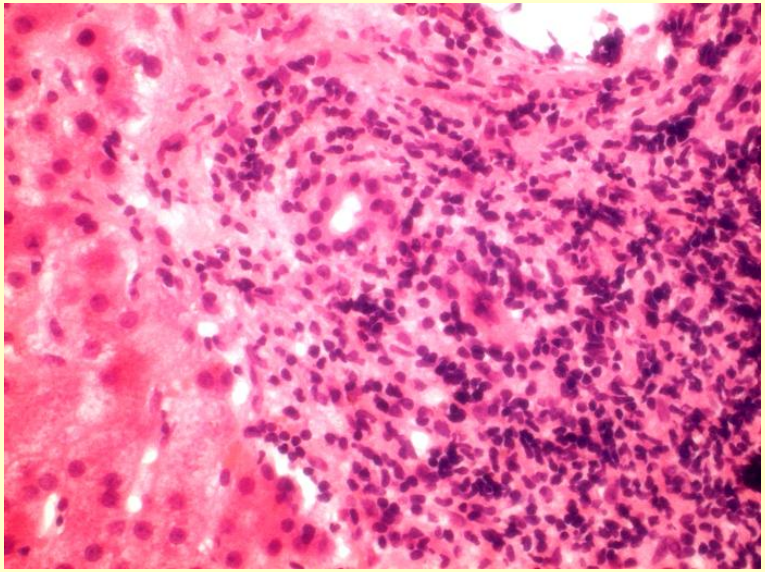
- Usually not a problem in first few weeks when ACR most common
- But definite overlapping features – centred on the portal tract
- What about later…?

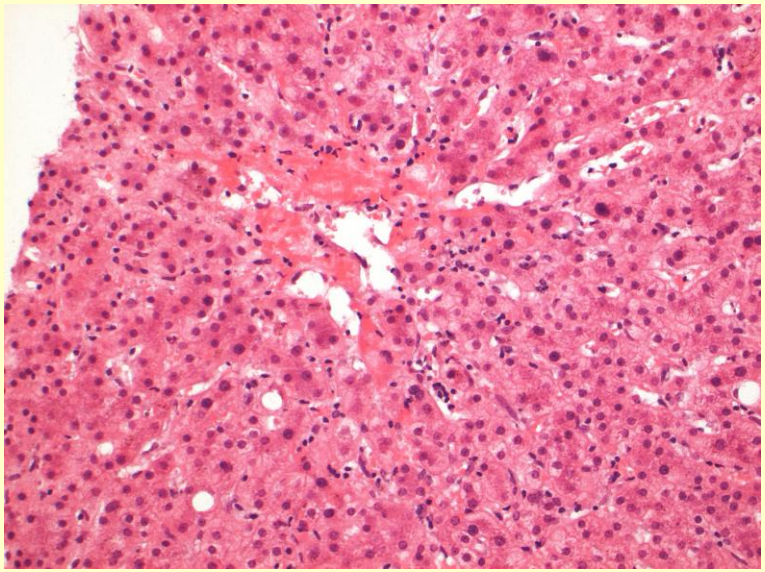
- 52yr female, HCV, Bx at 14 mo











What is de novo AIH? Is it alloimmune?

- Histology and clinically indistinguishable from classic AIH, auto Abs, ↑
- Seen following transplantation for non-AIH diseases, mimics AIH
- Initially in paediatric but also adults
- Histology; prominent portal lymphoplasmacytic infiltrate, interface activity with rossetting, lobular inflammation with **perivenular necrosis**, occ bridging.
- ? A form of rejection, Plasma cell hepatitis in HCV? – immunoresponsive!

Are things ever normal?

'Routine' histology – 55 liver biopsies, >3yrs

Normal	**8**	
Unsuspected acute rejection	**2**	
Unsuspected recurrent disease	**15**	**7/11 PBC; 2/8 PSC; sarcoid**
Expected recurrence	**4**	**4 HCV**
Mild non-specific hepatitis	**25**	**IPTH**
Steatosis alone	**6**	
siderosis	**4**	**1 recipient HFE heterozygote**
A1AT globules	**1**	**Donor SZ**

Idiopathic Post Transplant Hepatitis

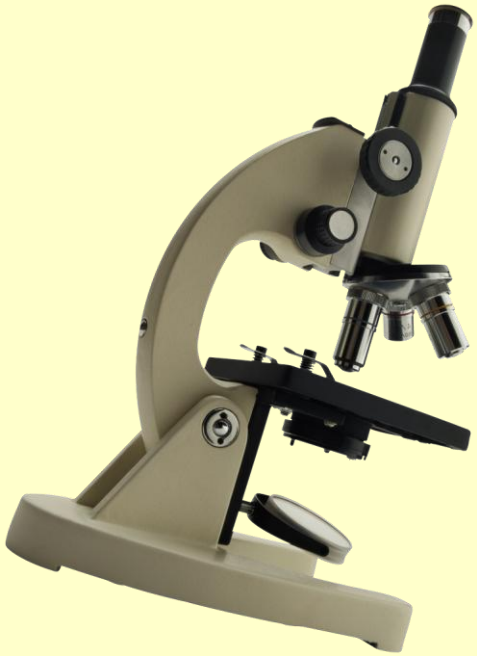
- Chronic hepatitis without cause
- ~40% of adult grafts after 1 year
- Seen more clearly in children, up to 60% at 10yrs
- Can see zone 3 fibrosis and cirrhosis
- Associated with **perivenulitis** (may be called de novo AIH if antibodies)
- Can respond to immunosupression

What causes late graft dysfunction?

Diagnosis	Incidence 5yrs	comment
Auto Immune H	30%	Need higher IS, HLA assoc
De novo AIH	<5%	Adults & children
HBV	100%	If replication
HCV	~100%	Hi viral load, rapid progression, atypical
PBC	20-30%	Us asymptomatic, ~AIH like
PSC	20-30%	M, intact colon
Acute rejection	<30%	Less common than early
Chronic rejection	~3%	
Idiopathic Post T Hepatitis	5-60%	Variation but upto 15% progressive

Demetris et al (Banff), Hepatology 2006; 44:489-501

…the generalist



…the solution

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What next?

- The key to increase survival in LT needs altering the natural history of diseases impacting on graft – HCV and HCC.
- New treatments – anti-proteases in HCV, molecular targeted therapies in HCC, pre-transplant interventions
- Better patient selection – predicting natural history of HCCs, immunogenetics
- Stopping immunosupressants in tolerant recipients
- Managing the risk factors for other systemic diseases

Acknowledgements

- Raaj Praseedom
- Will Gelson
- Graeme Alexander
- Rebecca Brais
- All the patients and staff involved in the Liver transplant programme at CUH

References

- *Demetris et al (Banff), Liver Biopsy Interpretation for causes of late liver allograft dysfunction. Hepatology 2006; 44:489-501*
- *Adeyi et al. Liver allograft pathology:approach to interpretation of needle biopsies with clinicopathological correlation. J Clin Path 2010; 63: 47-74*
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