Pathology

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Introduction

- **Histopathological review is necessary when**:

  a) A suspicion of malignancy identified in a donor
     i. ‘lump’ in a potentially transplantable organ
     ii. Suspected ‘cancer’ in a hollow viscus

  b) Further assessment of organ quality is required
     i. Liver (fat)
     ii. Kidney (glomerulosclerosis)

- Urgent histopathological analysis can enable the utilisation of donor organs that would otherwise have been discarded

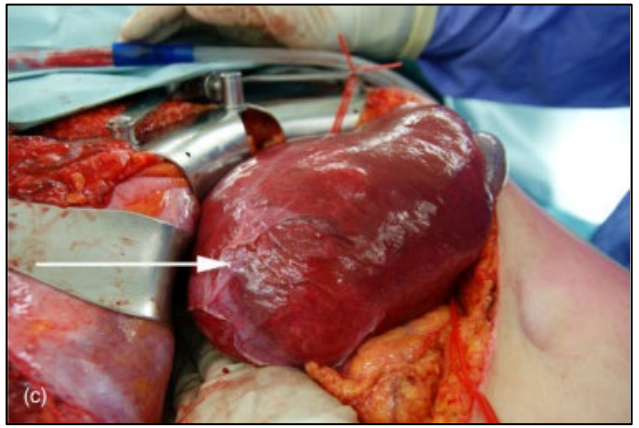
Case 1

- 42 year old male
- ‘liked a drink’
- RTA
  - Head injury
  - DBD donor
    - LFTs – Normal
    - U+E – Normal
- 6 Organs accepted:
  - 2 kidneys
  - Heart and lungs
  - Pancreas
  - Liver

Creatinine	73
Amylase	40
Glucose	8
Bilirubin	18
ALT	17
GGT	78
PT	12
U Output	3400mls

Case 1

- Retrieval
  - All organs retrieved
  - Heart and Lungs – dispatched
  - Abdominal organs were retrieved ‘En-bloc’
  - On the back table – lesion was noted posteriorly in the Right lobe of the liver
  - WHAT NEXT?

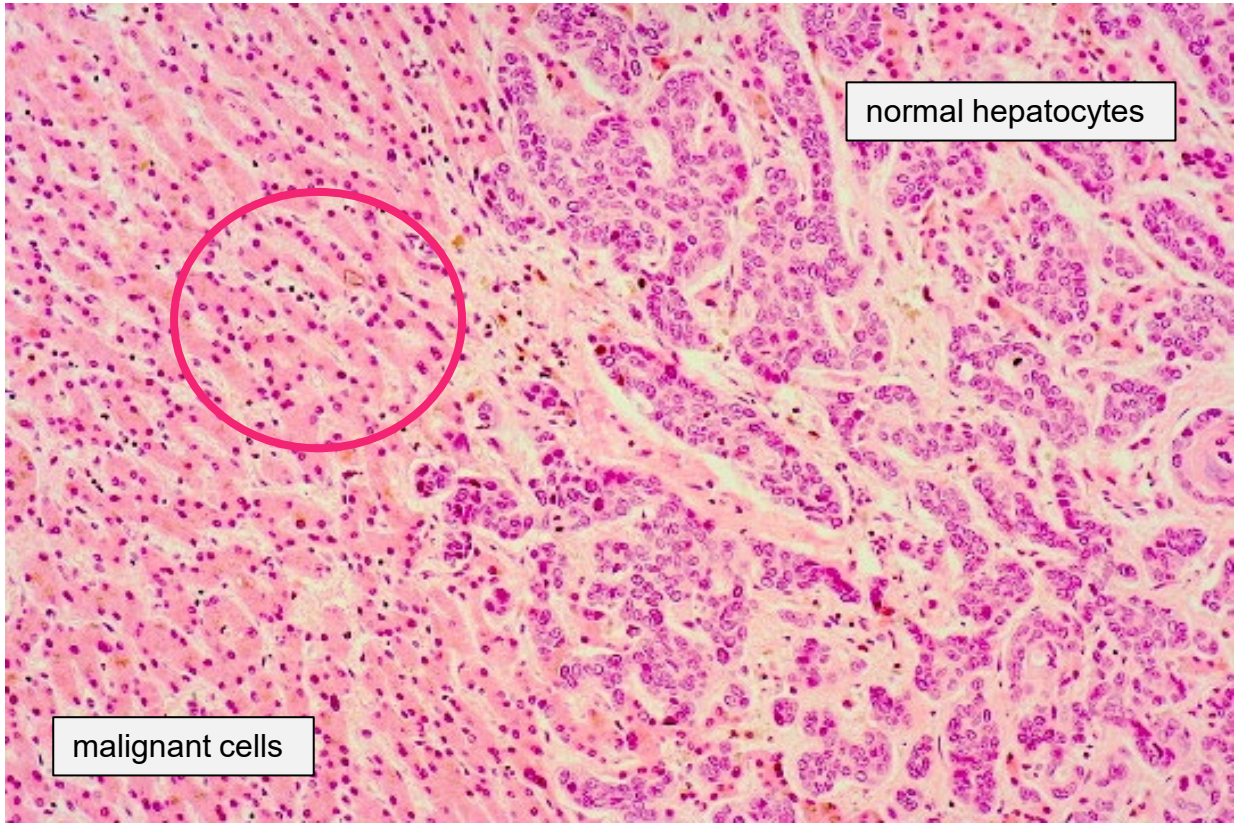


Case 1

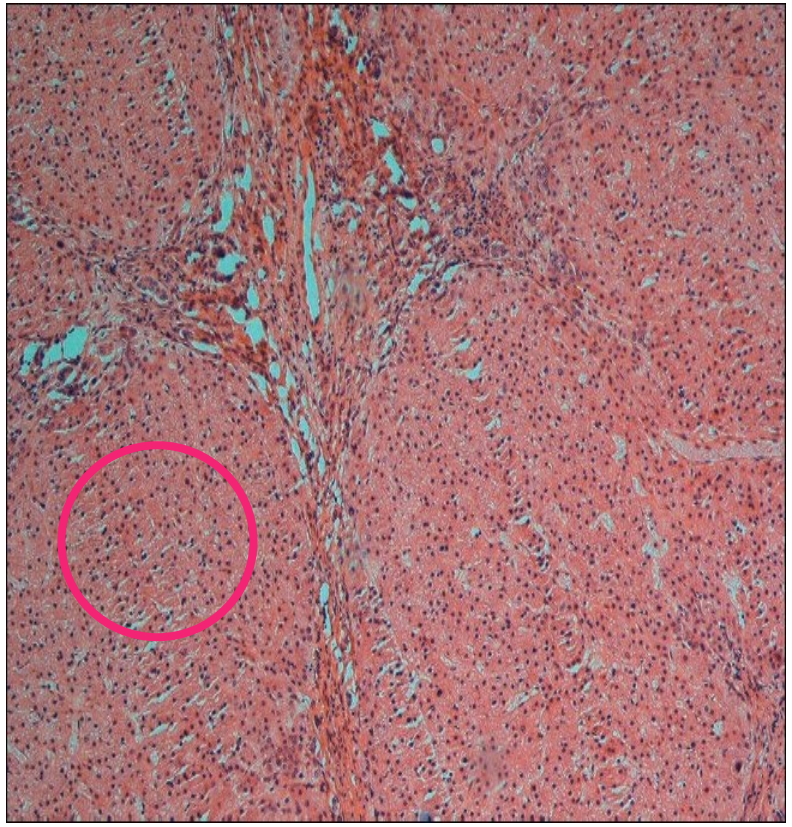
- Options:
  - Ignore – surgeon says its benign
  - Discard all organs
  - Biopsy

- The pathologist on call that night could not decide if it was malignant or not

Case 1



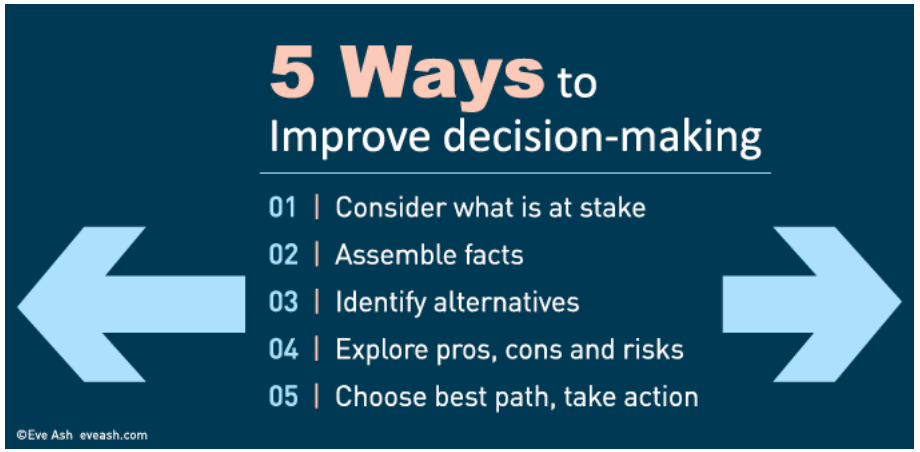
Hepatocellular Carcinoma



Focal Nodular Hyperplasia

Case 1

- Options:
  - Ignore – surgeon says its benign
  - Discard all organs
  - Biopsy results awaited. . . .



- What about the heart and lungs – already dispatched?

Case 1: FNH (benign)

- FNH is the second most common hepatic lesion and is found at autopsy
  - prevalence of 0.3 – 3 %
- Clinically relevant cases of FNH are rare
  - reported prevalence in US studies of 0.03 %
- Caused by an injury to the portal tract resulting in the formation and enlargement of arterial to venous shunts
  - This causes hyper-perfusion in local arteries resulting in oxidative stress that triggers a response from hepatic stellate cells to produce the **central scar typically seen in cases of FNH**

Buscarini L et al, 1993; Wanless IR et al, 2006

Types of FNH lesions

- **Traditional**
  - those containing abnormal nodular architecture, malformed appearing vessels and cholangiolar proliferation)
  - most likely to be associated with symptoms.

- **Telangiectatic**
- **Mixed**
- **Atypical forms**
  - less likely to be associated with symptoms.

Hsee LC et al, 2005

RC pathology guidelines

The Royal College of Pathologists
Pathology: the science behind the cure

Clarification of the use of the College publication 'Guidelines on staffing and workload for histopathology and cytopathology departments' in limiting the workload of pathologists

Professor Peter Furness, Director of Professional Standards

In recent months the College and RCPath Consulting have undertaken invited reviews of a number of cellular pathology departments and have become aware that the College workload guidance may, on occasions, be misinterpreted and used in an unintended and rigid manner in discussions on working practices between medical staff and managers. The national consultant contract is time-based (programmed activities) and the intention of the College guidance is to indicate an appropriate workload for a period of time. The College acknowledges that there will normally be variations in the amount of work that can be safely delivered by pathologists depending on their experience and the types of work being performed. It is therefore appropriate to be flexible in interpreting the guidance in the interests of good patient care, and not limiting work by a rigid interpretation of a fixed number of points per day.

The College is concerned to be told that its guidance could be used in this unintended and rigid manner. As a result, this clarification is being published and the matter will be emphasised in the next full update of the guidance.

The guidance document states that it is intended to:

a) support departments of pathology in balancing staffing with the anticipated workload, so as to ensure that a sustainable, high-quality service is provided for the benefit of patients

b) facilitate equitable distribution of work among pathologists within a department

c) provide information for job planning.

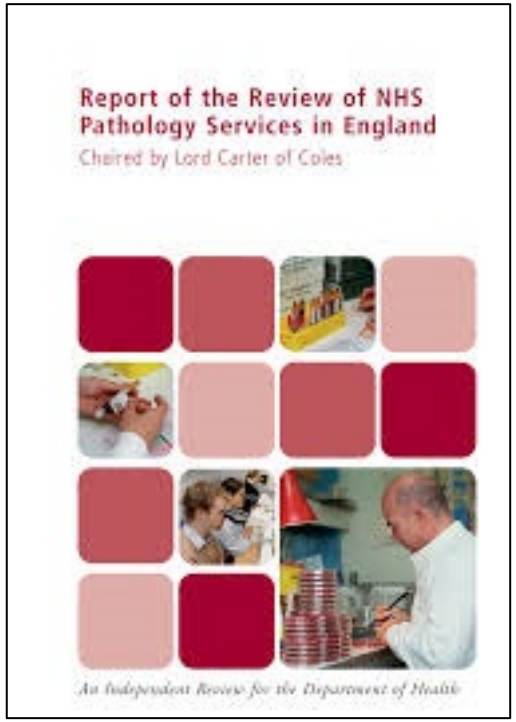
It goes on to add:

"It is expected that service users and commissioners will find this guidance helpful in predicting the resource implications of changes in demand."

It also states:

"These guidelines are not intended to provide a basis for a 'fee per case' system of payment."

Nothing in these guidelines is intended to alter the nationally agreed terms and conditions of service of consultants or associate specialists, in which time is the basis of remuneration.



Specialist On-call Rota's

Case 2

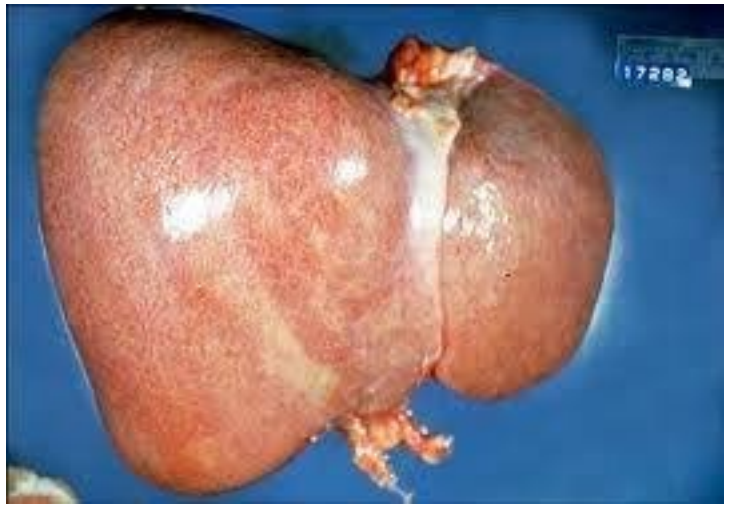
- 42 year old male
- ‘liked a drink’
- BMI - 36
- RTA
  - Head injury
  - DBD donor
    - LFTs – Abnormal
    - U+E – Normal
- 6 Organs accepted:
  - 2 kidneys
  - Heart and lungs
  - Pancreas
  - Liver

Creatinine	73
Amylase	40
Glucose	8
Bilirubin	**28**
ALT	**17**
GGT	**378**
PT	**17**
U Output	3400mls

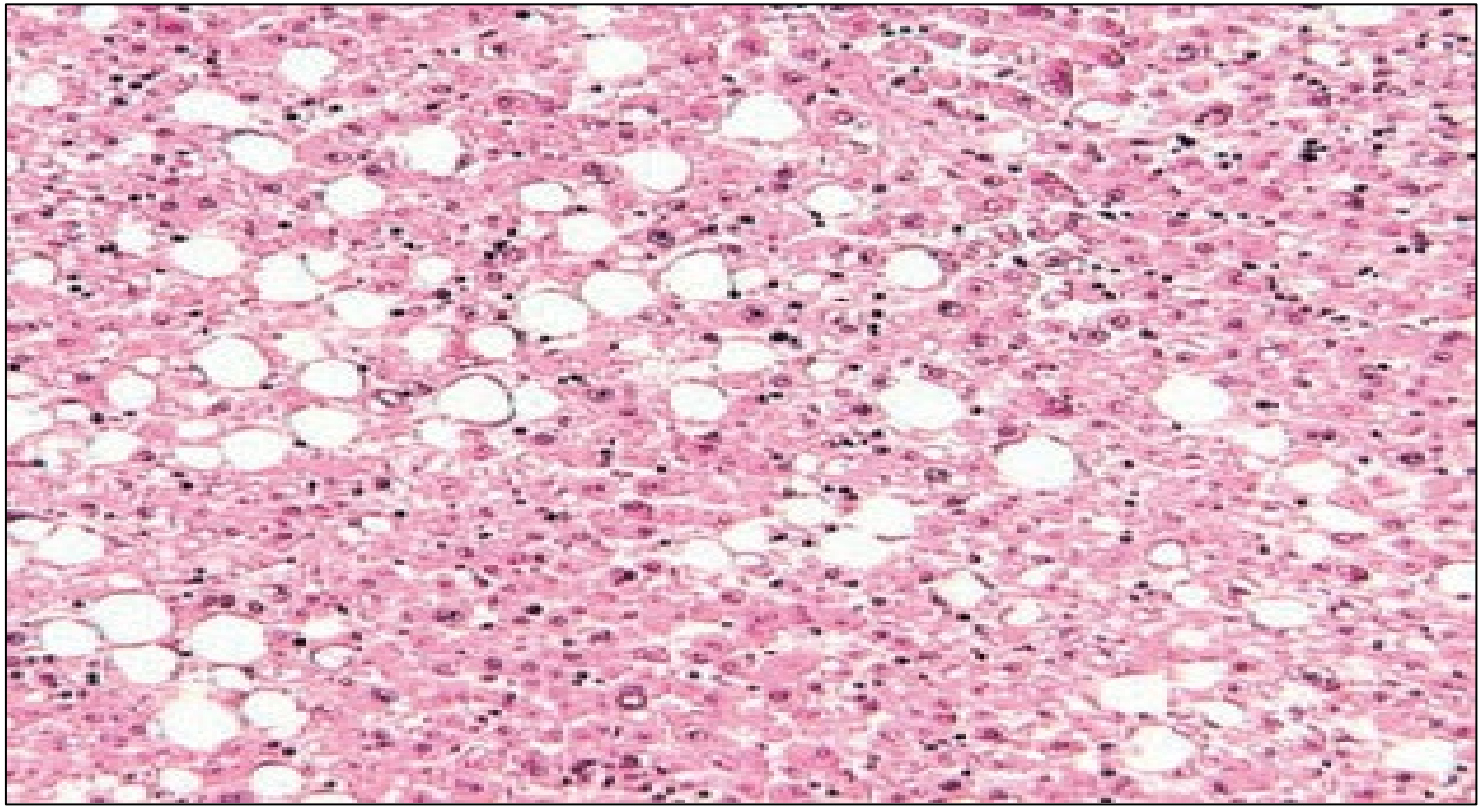
Case 2

- At retrieval:
  - Liver noted to be ’moderately fatty’

- What next:
  - Ignore
  - Biopsy
  - Contact recipient Centre



Case 2: 16% to 20% Macrovesicular steatosis

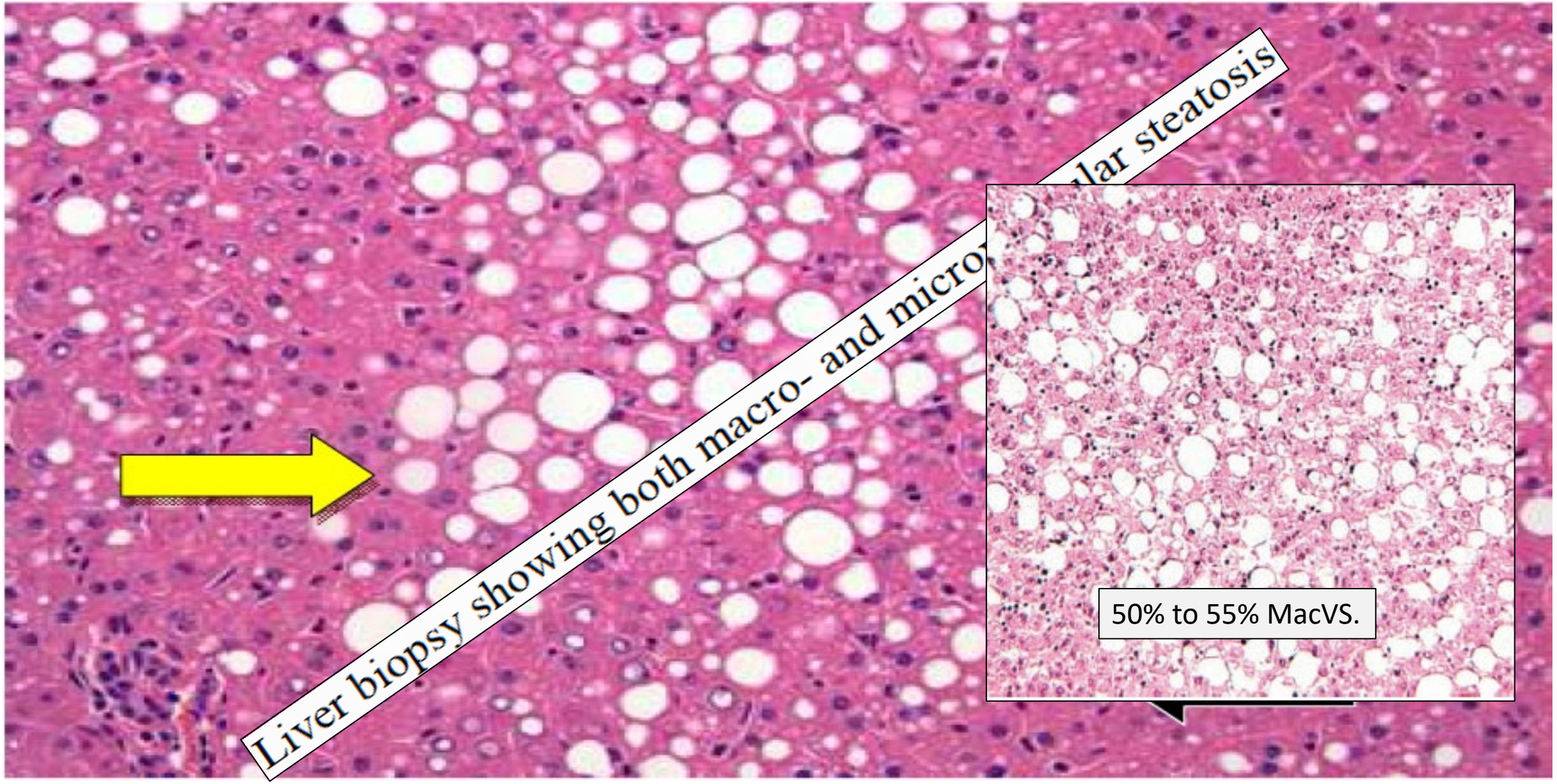


There are two forms of Liver ‘Graft–Steatosis’

- **Macrovesicular steatosis**
  - fat vacuoles occupy most of the hepatocytes cytoplasm and displaces the nucleus peripherally
    - associated with ***excessive alcohol, obesity, diabetes and hyperlipidaemia***

- **Microvesicular steatosis**
  - fat vacuoles are smaller and have a centrilobular distribution
    - associated *with* ***mitochondrial injury such as acute viral or drug induced injury, sepsis and some metabolic disorders***

Angele MK et al, Am J Surg 2008; 195: 214.



Large droplet Macro-VS, small droplet Macro-VS, Micro-VS

Hepatic Steatosis – Outcome after LT

Definition

- < 30% **Mild**
- 30% - 60% **Moderate**
- > 60% **Severe**

D'Alessandro A. Transplantation 1991

Impact of a 'fatty' graft

- Primary non-function
  - No steatosis: < 5%
  - Mild steatosis: 5 %
  - Moderate steatosis: 10-15%
  - Severe steatosis: > 50%

Strasberg SM, Hepatology, 1994
Ploeg R, Transplantation, 1993

MORE SPECIFIC: LARGE DROPLET MacVS, SMALL DROPLET MacVS, MicVS, TOTAL STEATOSIS

Case 2: best utilisation?

- **Recipient**
  - 40 year old ALD
    - Abstinent for 2 years
  - 5 cm HCC
    - Previously 6.2 cm
    - Down-sized with TACE and RFA
    - Meeting the ‘new criteria’
  - Been waiting 100 days
    - First offer of a liver

Case 3

- Female donor:
  - 63 years old
  - SAH
  - BMI - 32
  - History of
    - Hypertension and MODM
    - Smoker for 20 years
    - ‘liked a drink’
    - Previous breast cancer – stage I – 10yrs before
      - Given the ‘all clear’
  - DBD
    - Offer of liver and kidneys

Creatinine	**92**
Amylase	**40**
Glucose	14
Bilirubin	18
ALT	**47**
GGT	118
ICU stay	**3days**
U Output	**1400mls**
Po2	10

Case 3

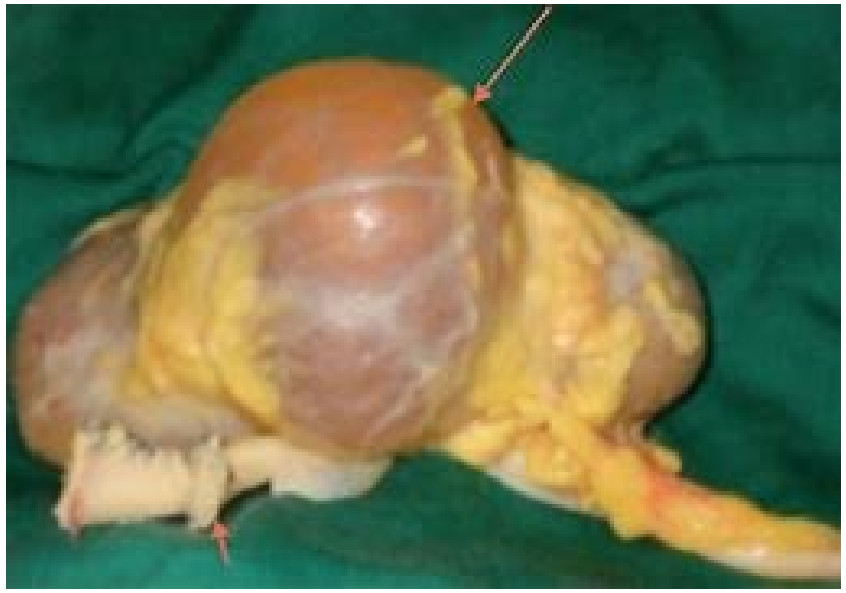
- At retrieval:
  - L kidney was noted to have multiple cysts

  - What next:
    - Ignore
    - Biopsy
    - ‘De-roof’
    - Contact the recipient Centre

Case 3

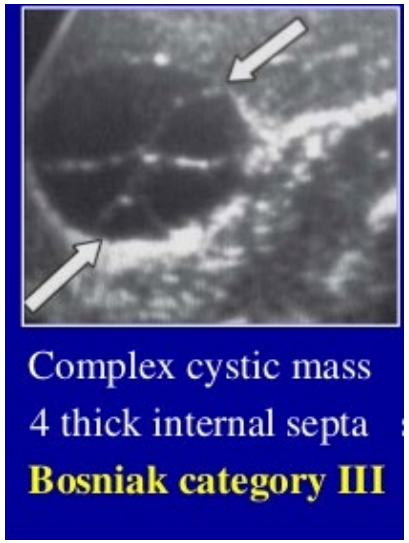
- What if the cyst was more complex

- What next:
  - Ignore
  - Biopsy
  - Contact the recipient Centre

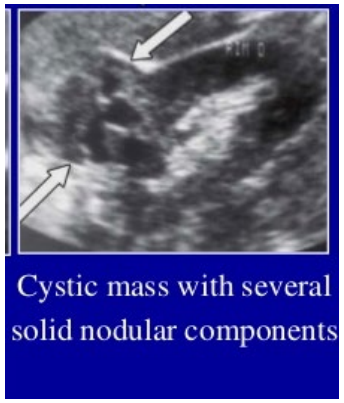


Renal cysts

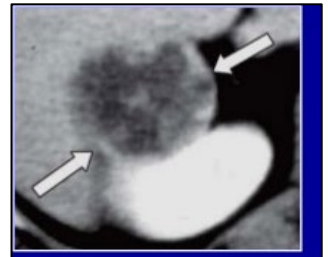
Category	CT features	Significance
Class I	Water density homogenous Noncalcified, smooth margin No enhancing component	Benign
Class II	Thin septae (<1 mm) Thin calcification (<1 mm) Hemorrhagic cyst	Benign
Class IIF		Likely benign Follow-up imaging indicated
Class III	Thick septa Thick calcification Thick wall Multilocular +/− enhancement	≈ 50% malignant
Class IV	Criteria of category III Enhancing solid mass of wall or septa	Definitely malignant



Complex cystic mass
4 thick internal septa
Bosniak category III



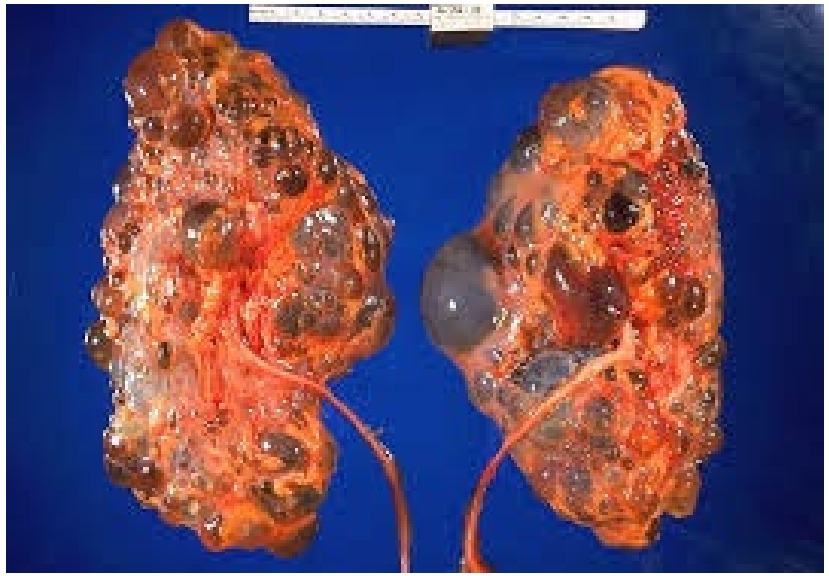
Cystic mass with several solid nodular components

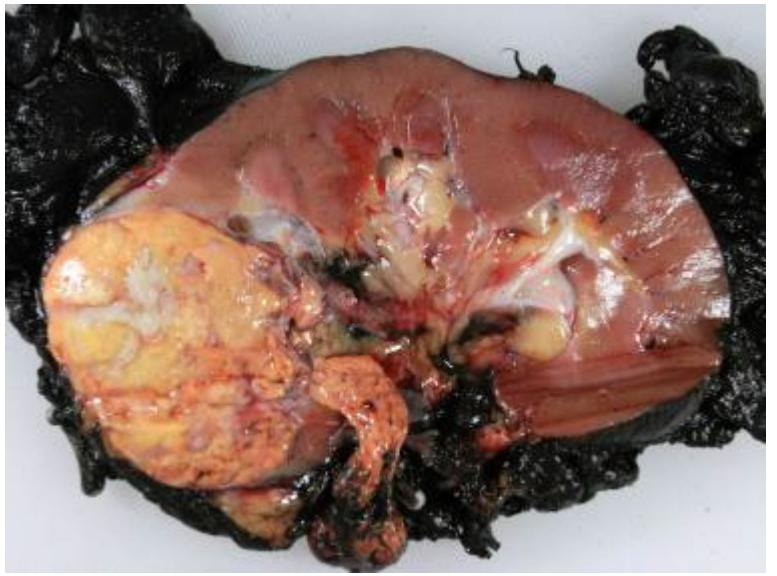


Enhancing soft-tissue components within cyst
Bosniak category IV

Chapple et al, 2011

Which one should be biopsied?





Case 4

- 72 year old man
  - Hypertension
  - Diabetes
- Sudden collapse
- Plan to withdraw treatment
- Offered kidneys as a DCD
- NORS surgeon noted significant scarring
  - Both kidneys

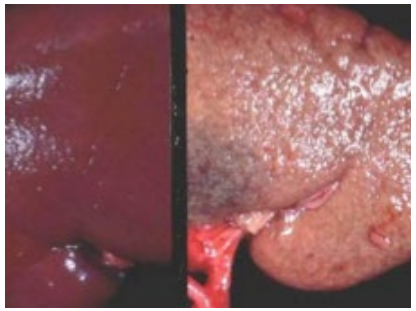
Creatinine	**102**
Amylase	**24**
Glucose	14
Bilirubin	18
ALT	**27**
GGT	78
ICU stay	**3days**
U Output	**400mls**
Po2	12

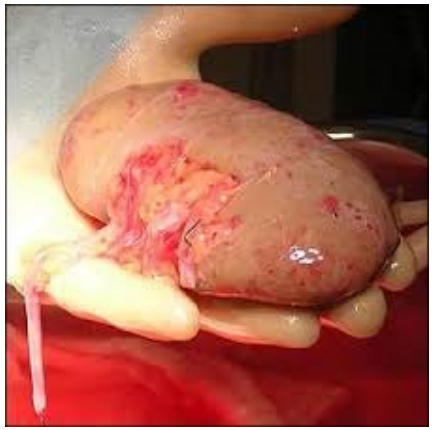
Case 4

- At the implanting Centre there were concerns

- Options:
  - Ignore and implant
  - NMP
  - Discard
  - Biopsy

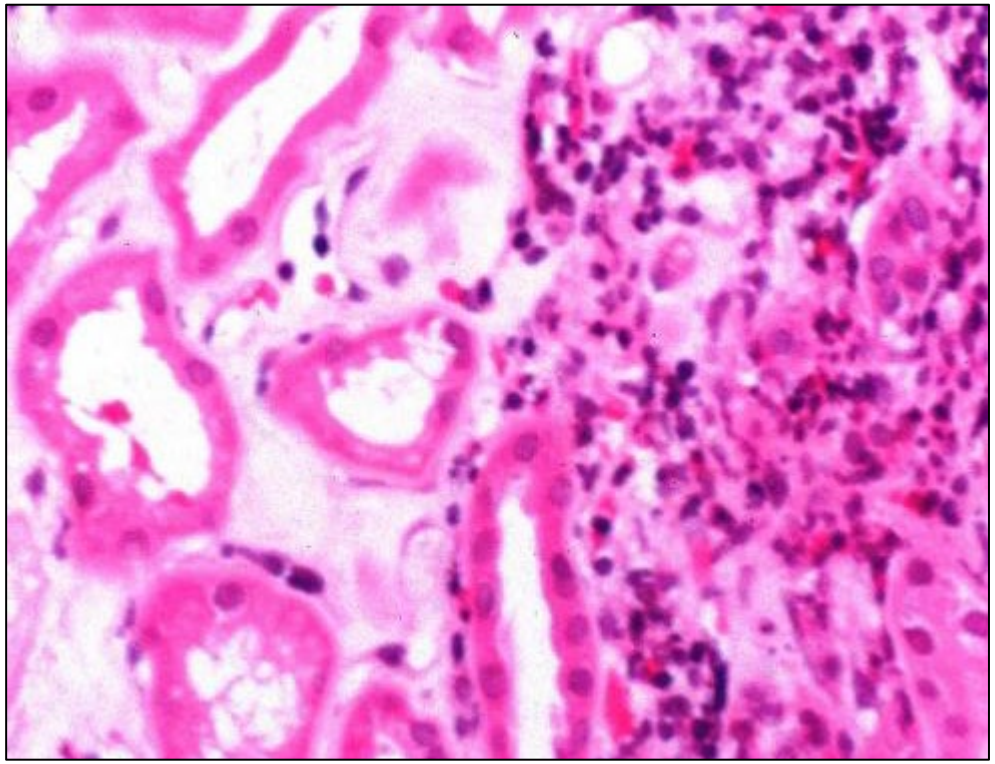
REMUZZI SCORE: 8



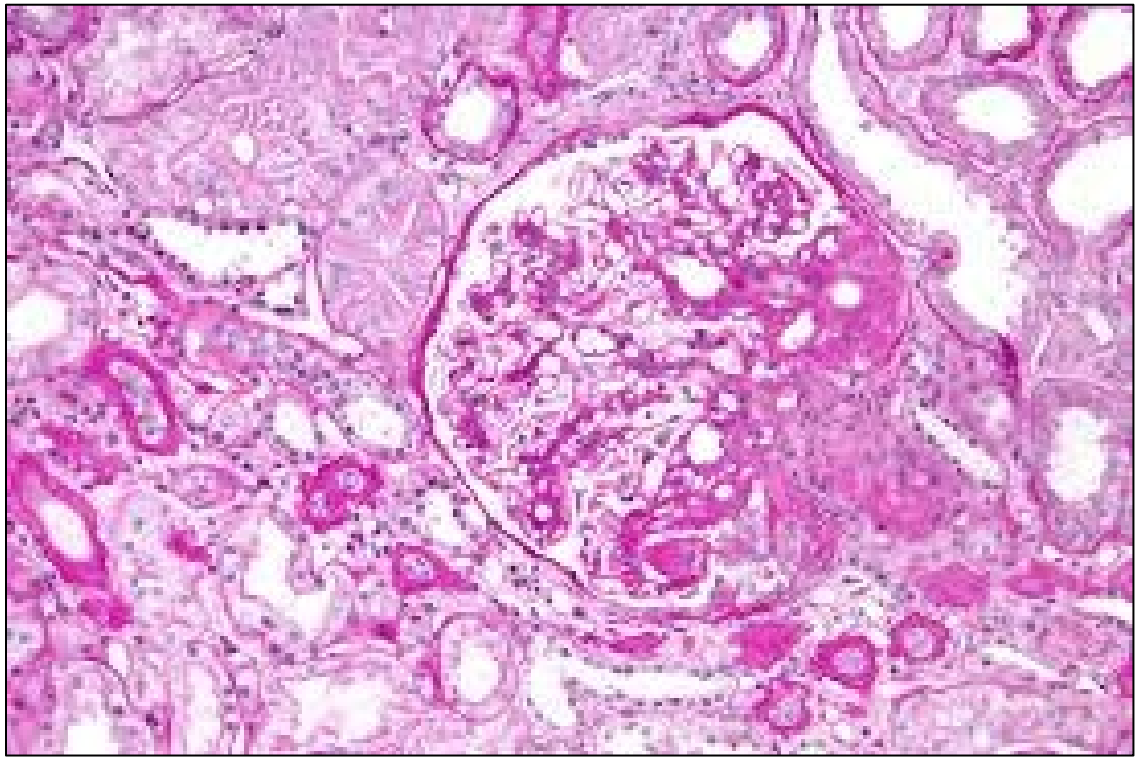


Case 4

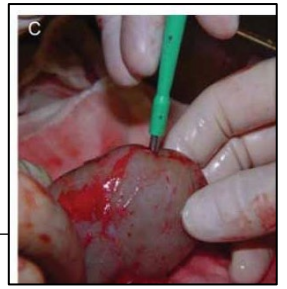
Tubulointerstitial fibrosis



Glomerulosclerosis



Scarred kidney. . .



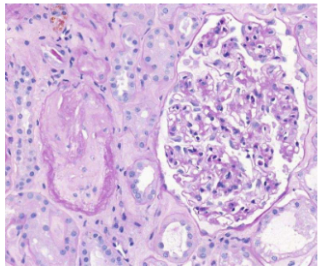
- With **increasing age** there is an increase in chronic vascular changes, tubulointerstitial scarring and glomerulosclerosis in kidneys
  - The histological extent does not correlate with the serum creatinine
- The only reliable way to determine the extent of scarring is by an **adequately sized biopsy**, that takes in the full thickness of the cortex:
  - to prevent over representation of subcapsular accentuation of glomerulosclerosis
  - includes arcuate arteries more likely to show hypertensive type intimal changes impacting the luminal area
- The use of a biopsy has been shown to increase the utilization of elderly donors with good outcomes

Mallon DH et al, 2015; Remuzzi G et al, 2006

Remuzzi Score (Cambridge modification)

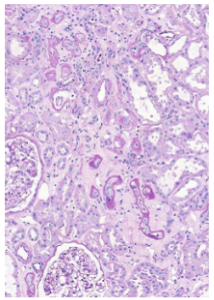
Glomerular sclerosis

- >25 gloms (Karpinski >20) – should be 50-75
- G0 no sclerosed gloms
- G1 1% - <20%
- G2 20% - 50%
- G3 >50%
- If 100 gloms
- G1 1GS to 19GS



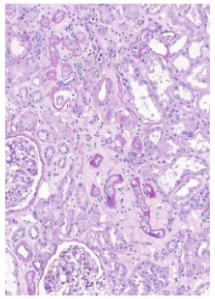
Tubular atrophy

- We are defining tubular atrophy as < 50% diameter of normal tubule (Banff)
- Percent of cortex involved
- TA0 no atrophic tubules
- TA1 >0 - <20%
- TA2 20%-50% Banff cut off 25%
- TA3 >50%



Interstitial fibrosis

- % cortex scarred
- IF0 no fibrosis
- IF1 >0 - <20% Banff IF0 (ci0) up to 5%
- IF2 20%-50% Banff cut off 25%
- IF3 >50%

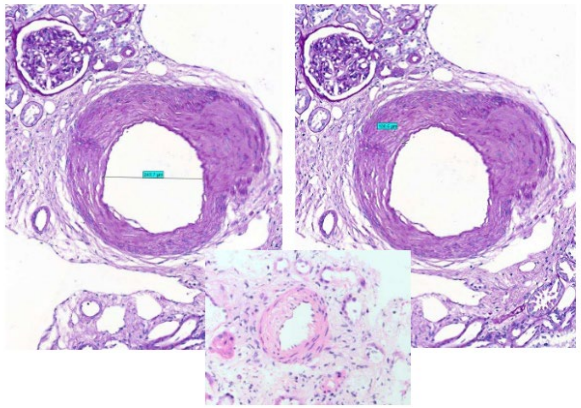


Vessels

- Cambridge modification
- Do not score arterioles
- Original Remuzzi – worst of artery and arteriole
- If arterioles bad – they will mention in comments and discuss with the surgeon – but not is score.
- WORST ARTERY IN BIOPSY SCORED
- A0 normal artery
- A1 wall thickness < lumen diameter
- A2 wall thickness = ~~or slightly >~~ lumen diameter
- A3 wall thickness >> lumen diameter Cambridge modification

Remuzzi – wall thickness far exceeds with severe luminal narrowing

REMUZZI VASCULAR 1: wall thickness <lumen diameter
wall thickness 108.6 &lumen diameter 243.7



REMUZZI SCORE (Cambridge modification)

(G + TA + IF + A)
0 1 2 3 **4** 5 6 7 8 9

ADEQUACY

Is the biopsy adequate (≥ 25 glomeruli AND ≥ 3 arteries)
Yes No

OTHER COMMENTS:

REPORTING PATHOLOGIST: Desley Neil
DATE: 22/9/17 **TIME:** 2.30 PM

Remuzzi score

- G +TA +IF + A (0-12)

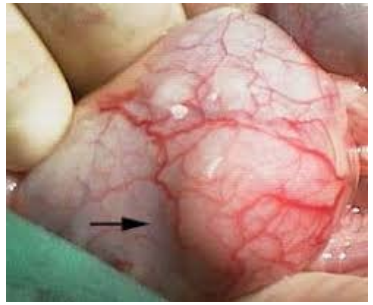
CURRENT PRACTICE IN CAMBRIDGE WITH REMUZZI SCORE (CAMBRIDGE MOD)

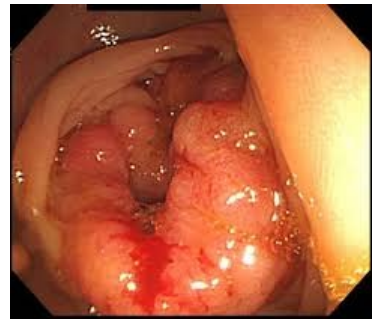
≤4 Single transplant
5-6 Dual transplant*
≥7 Discard

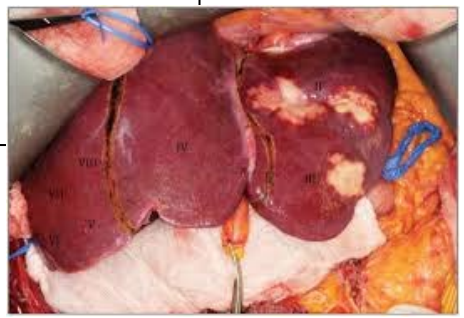
* "good 5s" with minimal (<5%) glomerular sclerosis, tubular atrophy and interstitial fibrosis

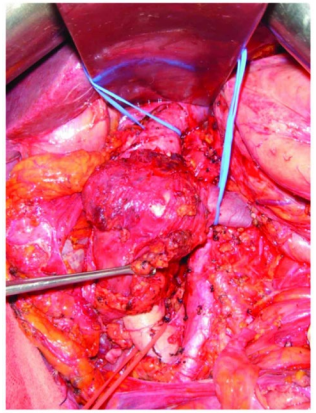
the need

- For those unexpected lesions identified during organ retrieval or at the time of examination of the organ/s at the implanting centre.
  - Histopathological analysis becomes necessary before safe transplantation can proceed.
    - Once its biopsied all is put on hold until there is an outcome
  - At present there is NO FORMAL 'JOINED-UP' process across TRANSPLANTING CENTRES IN THE UK for obtaining 'out-of-hours' histopathological review of retrieved organs
    - Some centers have an on-call
    - Some centers – 'good-will'
    - Some centers have no service





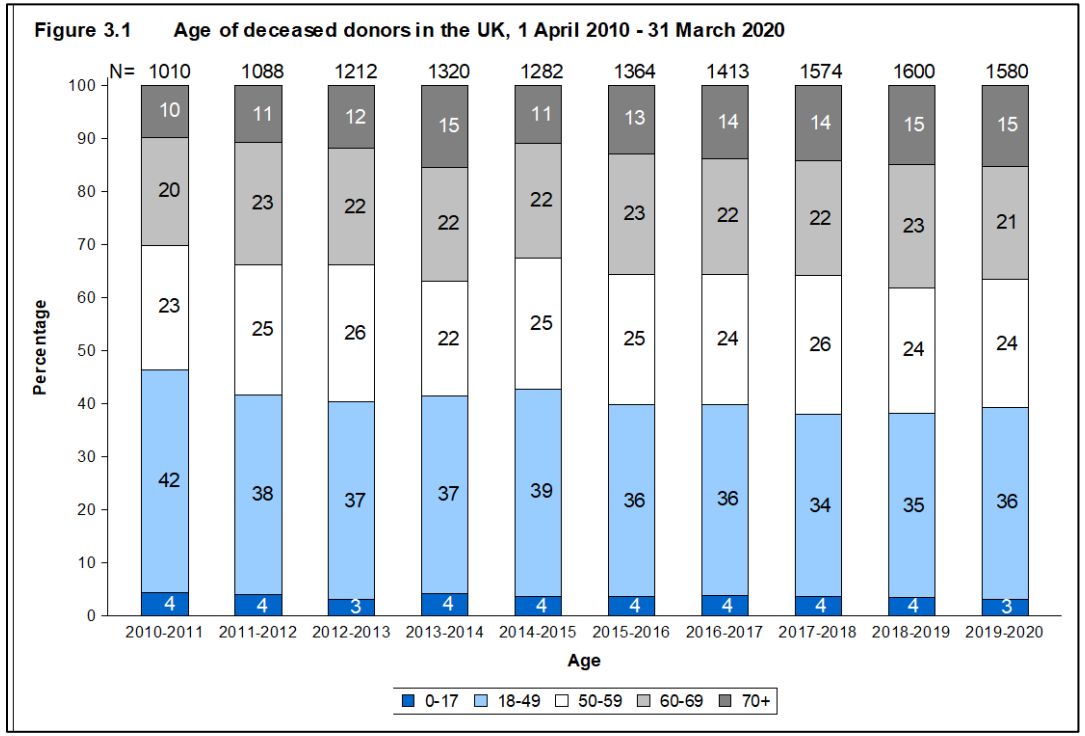




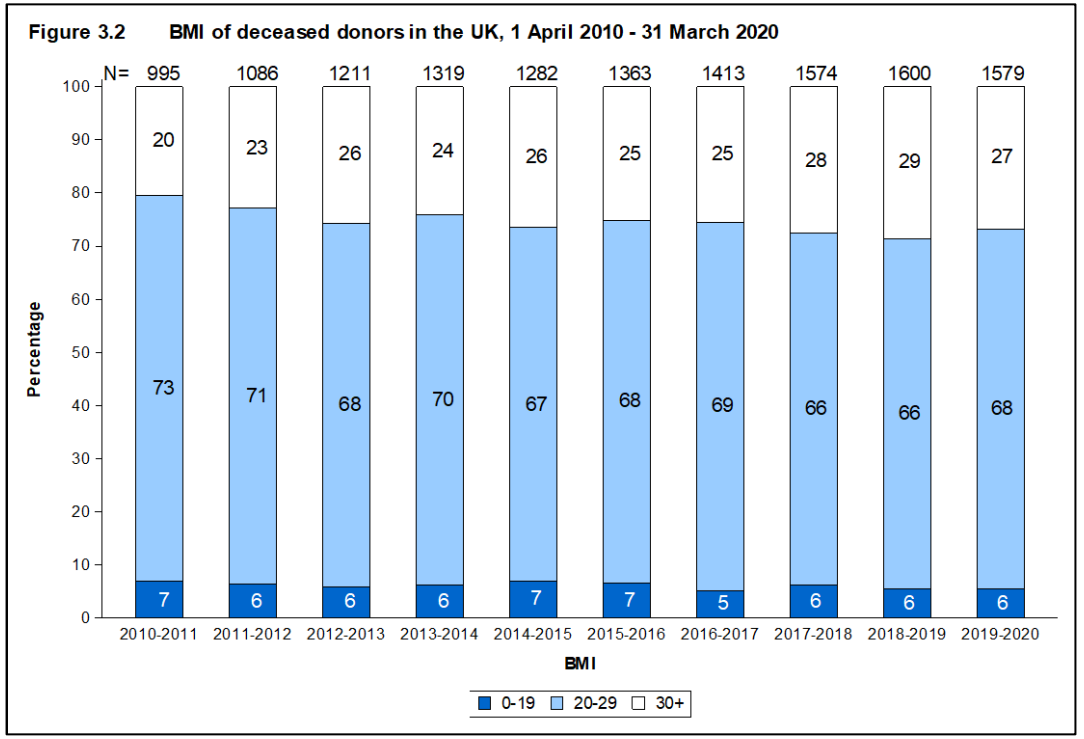
Why is pathological analysis important?

- Risk of malignant lesions is increased with:
  - Increasing age
  - Obesity
  - Excess alcohol
  - Smoking
  - History of previous malignancy (metastases to liver and lungs)
- Further assessment of organ quality is required
  - enable the better utilization of donor organs

Age and BMI



37% > 60



30% > 30

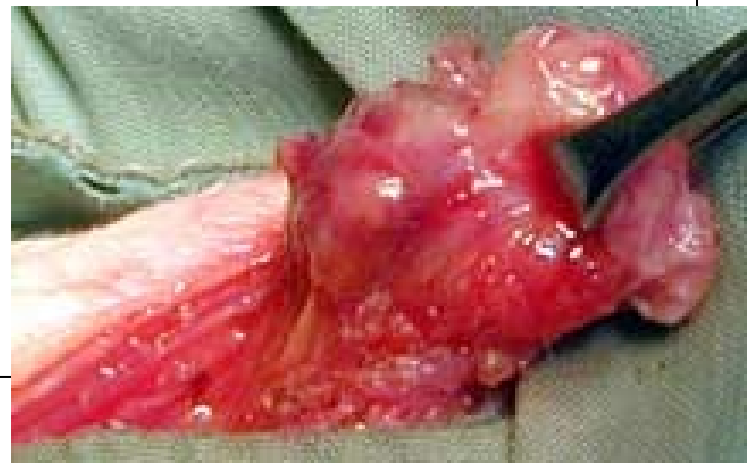
Case 5

- Male donor:
  - 18yrs old
  - Attempted suicide by hanging
  - Was found by friends and cut down
    - ‘hanging-time’ unknown
      - ??? WIT
  - Resuscitated by paramedics
  - No past medical history
  - All his organs offered as a DBD

Creatinine	**375 → 101**
Amylase	**300 → 88**
Glucose	4
Bilirubin	18
ALT	**702 → 204**
Po2	18
ICU stay	**5days**
U Output	**800mls**

Case 5

- At retrieval a large para-aortic lymph node mass (2.5 cms) was found
- SNOD attempted to get a histology assessment @ 2am
- No pathologist was available
- NORS surgeon assessed it as benign



Case 5

- What next:
  - Cardiac patient was asleep
  - R kidney was allocated to a recipient for a beneficial match (waited 3 years)
  - Liver was allocated to a Sero-negative hepatitis 27 year old female
  - Pancreas was allocated to an islet patient with severe hypoglycemic unawareness

  - 6 organs were discarded and 6 patients missed out
    - 2 died

The National Histopathology Audit (2013/14)

Aim of the audit

1. Define the incidence of ‘urgent’ histopathological analysis requests
    1. *Urgent biopsies were defined as those biopsies where the report was awaited in order to proceed either for retrieval or for transplantation*
2. Define numbers of retrieved organs utilised following histology

3. Identify impact of an out-of-hours histopathology service on:
    - Donor/organ utilisation
    - Recipient safety

What was done. . .

- **Prospective audit** over a 6 month period
- All NORS team retrievals and All Transplant Centers were involved

- 654 Retrievals
- 2322 Organs Retrieved
  - Utilized: **2064 (88%)**
  - Taken, Accepted and Not Utilized: **258 (12%)**
- *100% Data Returned*

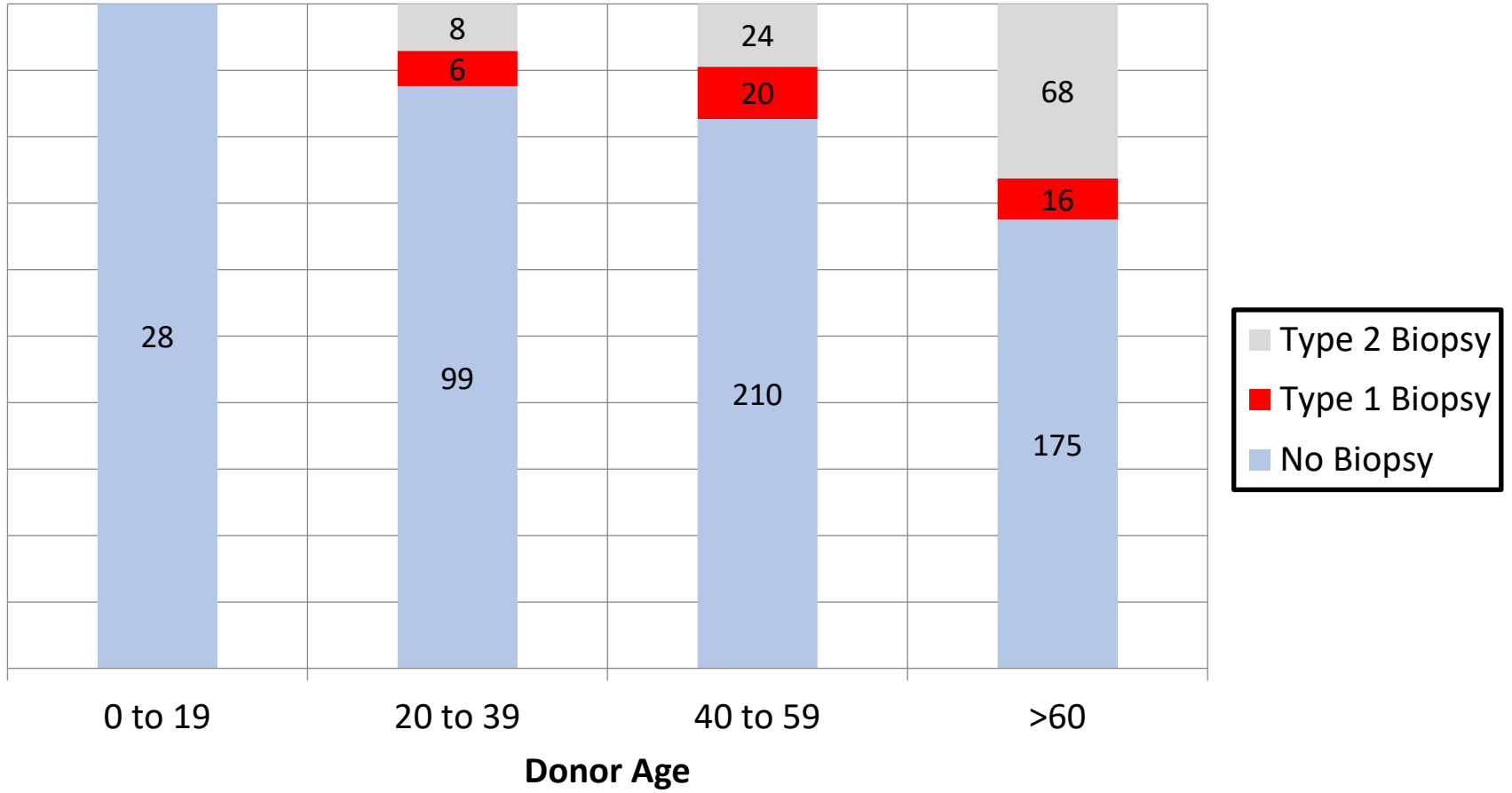
Number of biopsies requested

- **142 urgent biopsies in 654 retrievals (21.7%)**
  - 42 (29.6%) - Suspected Malignancy (Type 1)
  - 100 (70.4%) – Quality (Type 2)

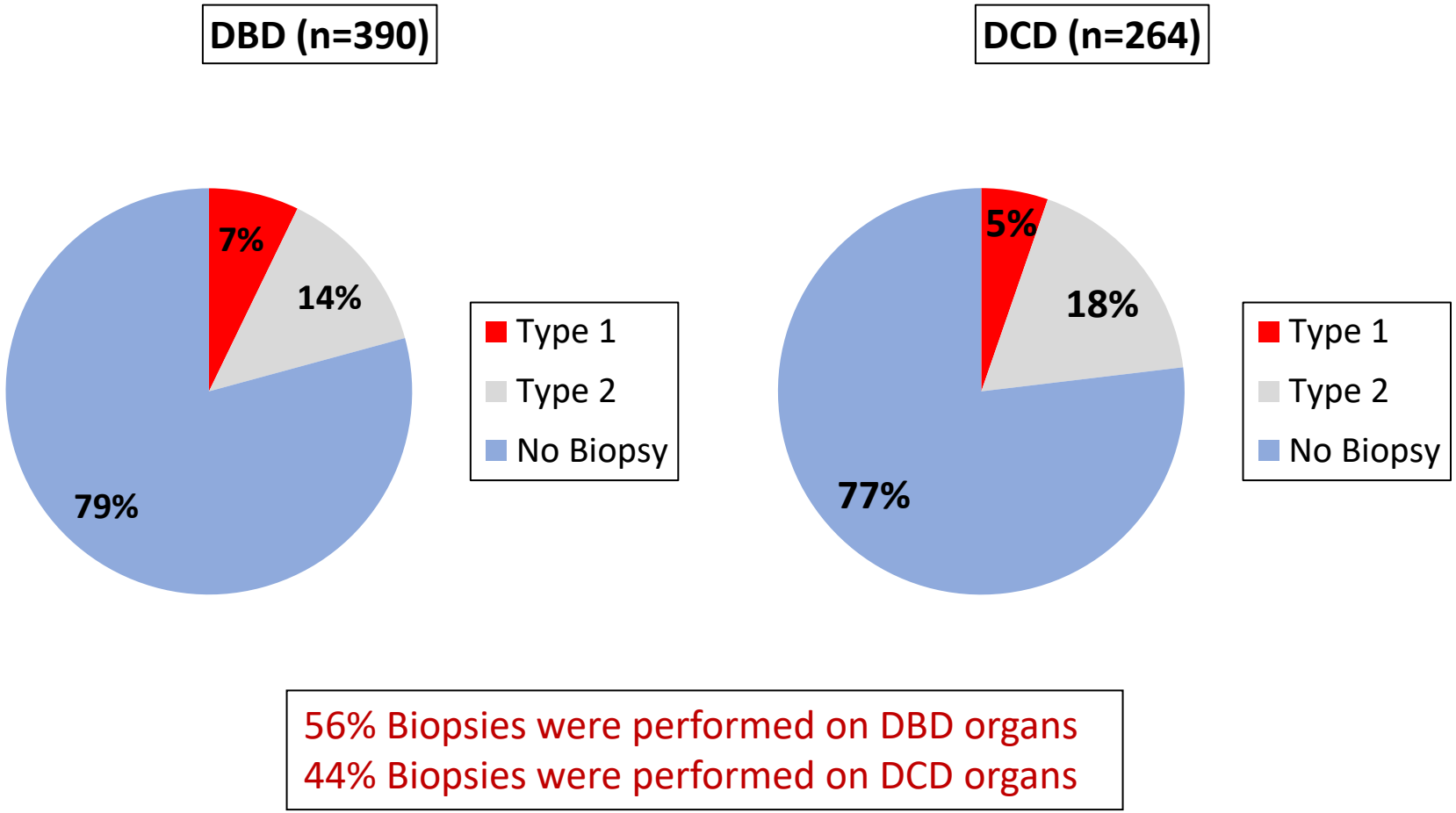
- **51% out-of-hours (1900 to 0700 and weekends)**

- 95% biopsies sent to pathology services at NORS centers
- The organs biopsied at Transplanting Centres were mostly **Livers and Kidneys**
- There was only **one biopsy taken at CT Transplant Centre**
- **NO** biopsies from **Pancreases**

Results – biopsy incidence by age



Results – biopsy incidence by donor type



56% Biopsies were performed on DBD organs
44% Biopsies were performed on DCD organs

Results – Type 1 (potential malignancy) Biopsies

- 42/654 Biopsies for suspected malignancy (6.4%)
  - 3/654 Malignancies identified (0.45%)
  - 3/42 Biopsies confirmed malignancy (7%)
- There were **119 organs** safely transplanted thanks to negative Biopsy report

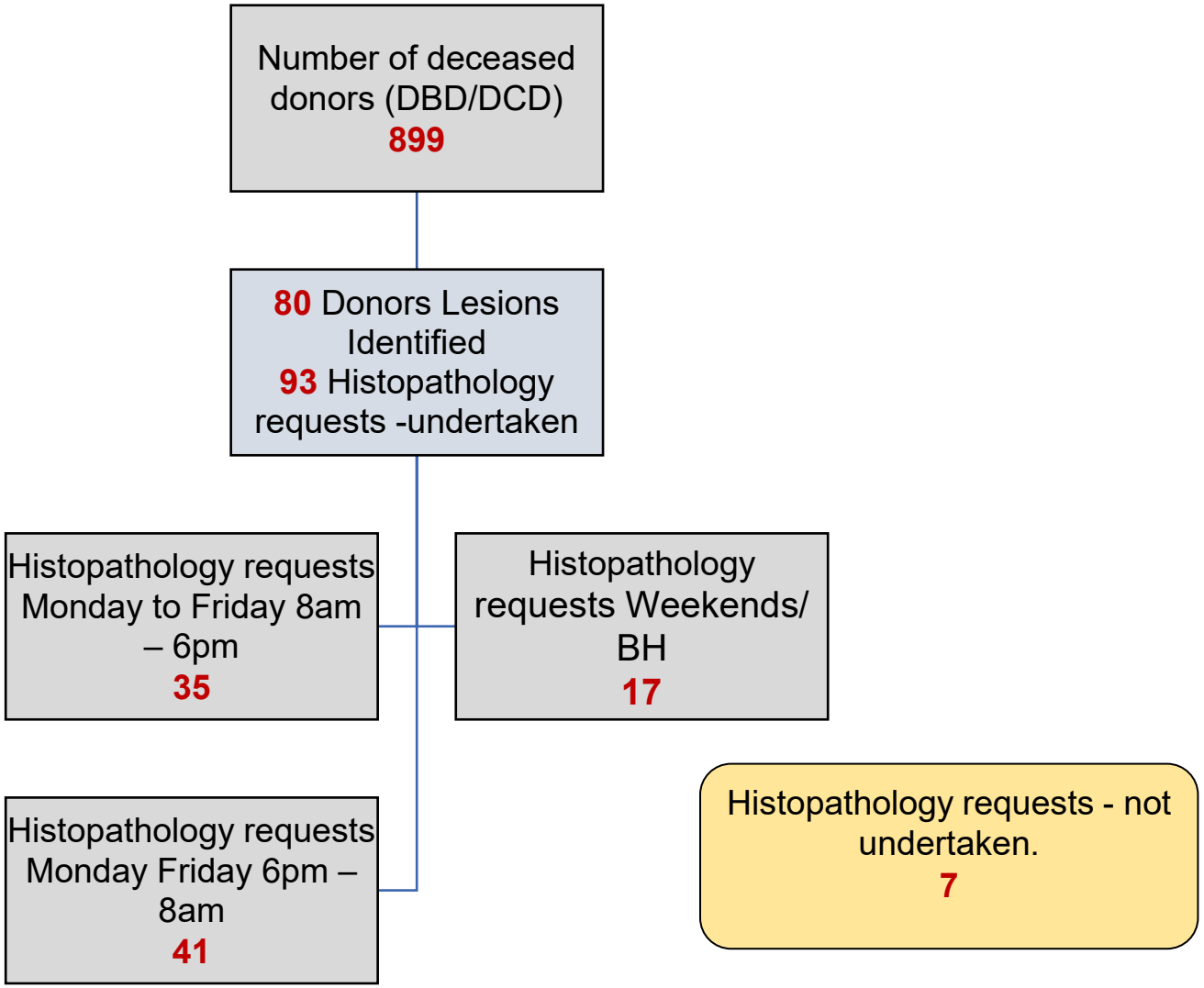
Results – Type 2 Biopsy

- 100 Type 2 Biopsies
  - 22 liver
  - 78 kidney
- Unsuitable organ quality in 5% (4 kidneys;1 liver)
- 21 Livers and 74 Kidneys utilised following Type 2 Biopsy

Impact of Biopsies (All Donors)

	Number of Organs Retrieved	Number of Organs Used WITHOUT ANY Biopsy (%)	Number of Organs used after Type 1 Bx (%)	Number of Organs used after Type 2 Bx (%)	Total N. Organs Used	Increase Utilisation %
Kidneys	1220	980 (80.3)	69 (5.6)	73 (6)	1122 (92)	**11.7**
Whole Livers	481	384 (80)	25 (5.2)	19 (4)	428 (89)	**9**
Pancreases	166	102 (61.4)	5 (3)	N/A	107 (64.4)	**3**
Hearts	97	87 (89.7)	5 (5.1)	N/A	92 (95)	**5.3**
Lungs	229	199 (87)	13 (5.6)	N/A	212 (92.5)	**5.5**
Total	**2193**	**1752 (79.9)**	**117 (5.5)**	**92 (4.2)**	**1961 (89.4)**	**9.6**

Retrospective audit for suspected malignancy: 1/9/19 – 1/3/20



Retrospective audit 19/20: Histopathology undertaken

Organ type	Number
Liver	16
Kidney	15
Pancreas	12
Lung	10
Lymph nodes	8
Ovary	7
Uterus	5
Other	20

Retrospective audit 19/20: Where were they performed

Abdominal NORS centres undertaking histopathology	Number
Leeds	19
Cambridge	15
Kings College	14
Newcastle	11
Royal Free	8
Birmingham	7
Edinburgh	4
Cardiff	2
Non NORS centres	13

Increased vulnerability of 'out of hours' Histopathology from October 2020

Abdominal NORS	24/7 Histopathology Service- Current	Histopathology undertaken September 1st – February 28th	24/7 Histopathology Service - October	Additional Info
Birmingham	Yes	7	Yes	No formal rota, 2 pathologists will undertake out of hours histopathology, not contracted or paid to do so
Cambridge	Yes	15	Yes	Will only process their own histopathology
Cardiff	Yes	2	Yes	
Edinburgh	No	4	No	Stopped 2 years ago
King's College	Yes	14	Yes	Only Liver and related specimens. No BMS/lab staff on call just Pathologists
Manchester	No	0	No	
Leeds	Yes	19	No	Likely to cease in October 2020 although not confirmed
Newcastle	Yes	11	No	Will cease in October 2020
Royal Free	Yes	8	Yes	
Oxford	No	0	No	

The current process: ‘vulnerable’

Specimen to Laboratory

Biomedical Scientist

Histopathology Processing

Frozen Section

Glass Slide

Pathologist

Histopathology Assessment

Glass slide

Provisional histopathology report emailed to HUB operations

Glass Slide - Histopathology Processing/ Histopathology Assessment

Advent of digital technology

Journal of Entomology and Zoology Studies 2019; 7(2): 43-49

Journal of Entomology and Zoology Studies

Available online at www.entomoljournal.com

E-ISSN: 2320-7078
P-ISSN: 2349-6800
JEZS 2019; 7(2): 43-49

Received: 22-01-2019
Accepted: 26-02-2019

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The advent of digital pathology: A depth review

Sandeep Dwivedi, Madhu Swamy, Amita Dubey and Yamini Verma

Abstract
Digital pathology is an image based information environment which is enabled by computer technology that allows for the management of information generated from a digital slide. Digital pathology is enabled in part by virtual microscopy, which is the practice of converting glass slides into digital slides that can be viewed, managed, shared and analyzed on a computer monitor. Growing demand for accurate and reliable diagnosis along with issues of patient safety is pushing traditional diagnosis towards an update. Over the last two-three decades the field of optics has made great advancements in the form of ever-improving optics and digital cameras. Persistent gains in computer processing power, data transfer speeds, advances in software and cloud storage solutions have enabled the use of digital images for a wide variety of purposes in pathology. High-resolution images are generated from whole glass slides which can be analyzed and managed using software. Digital Pathology has become a useful and valuable tool in clinical and research pathology. A fully digital workflow would mean that image analysis could be performed on any pathology image without the need for specific image preparation. Image analysis software is already widely available, and has FDA regulatory approval. The digital decade will likely redefine how pathology is practiced and the role of the pathologist.

Keywords: Whole slide image, scanner, Z- stacking, virtual microscopy, image analysis

1. Introduction
Pathology, as with most medical specialties, is currently facing a growing demand to improve quality, patient safety and diagnostic accuracy because there is an increased emphasis on sub-specialization. The ever advancing practice of histology and cytology is demanding the wide use of human perceptual and cognitive processes. The changing diagnostic scenario coupled with factor like economic pressure to consolidate and centralize diagnostic services is driving the development of systems that can optimize access to expert opinion and highly specialized pathology services [1].
The field of optics has made great advancements over the last two-three decades in the form of advance optics and digital cameras. Since the 1990s, persistent gains in computer processing power, data transfer speeds, advances in software and cloud storage solutions have enabled the use of digital images for a wide variety of purposes in pathology [2].
High-resolution images are generated from whole glass slides which can be analyzed and managed using software [3]. Hence, these digitized slides or virtual slides can significantly optimize the workflow of the pathologist [4]. The still or dynamic images captured with microscope mounted cameras are transferred by the means of network connections to remote sites to be assessed by another pathologist, commonly called telepathology as second opinion and frozen section consultations.
Digital pathology has the potential to transform the practice of diagnostic pathology. However the way radiology has been revolutionized by the introduction of digital imaging over the past 30 years, despite the promise of digital pathology to offer similar benefits, its uptake for diagnostic pathology has been slow [5]. The present review attempts to analyze the present scenario, scope and limitations of Digital Pathology.

2. The Digital Pathology workflow
Standard Digital Pathology workflow begins with the procedure performed on the patient, most commonly a biopsy or a resection. The material is then sent to a pathology division associated by an order (ideally in a digital way), along with appropriate clinical information.
Once received, samples are registered in the local laboratory information system on or before undergoing the necessary procedure in order to be managed to glass slides. Then, the glass slides are observed under a light microscope in order to create report.

Scanner

Histopathology

Histopathology 2015 DOI: 10.1111/his.12879

Validation of digital pathology imaging for primary histopathological diagnosis

David R J Snead,[1,2] Yee-Wah Tsang,[1,2] Aisha Meskiri,[2] Peter K Kimani,[3] Richard Crossman,[3] Nasir M Rajpoot,[2,4] Elaine Blessing,[1] Klaus Chen,[1] Kishore Gopalakrishnan,[1] Paul Matthews,[1] Navid Momtahan,[1,5] Sarah Read-Jones,[1] Shatrughan Sah,[1] Emma Simmons,[1] Bidisa Sinha,[1] Sari Suortamo,[1] Yen Yeo,[1] Hesham El Daly[1] & Ian A Cree[1,2]
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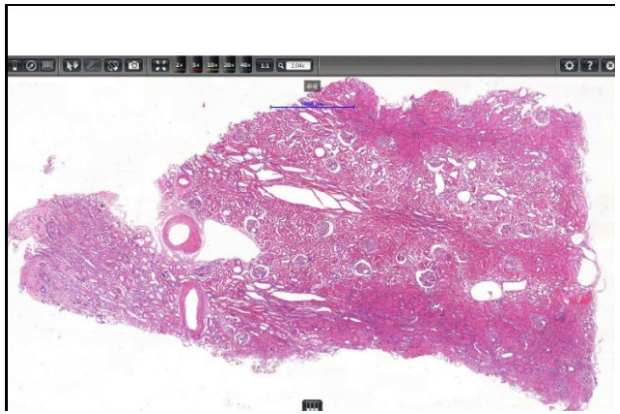
High resolution scanner chosen 0.137µm/pixel (60x)
Best for renal and liver for diagnosis

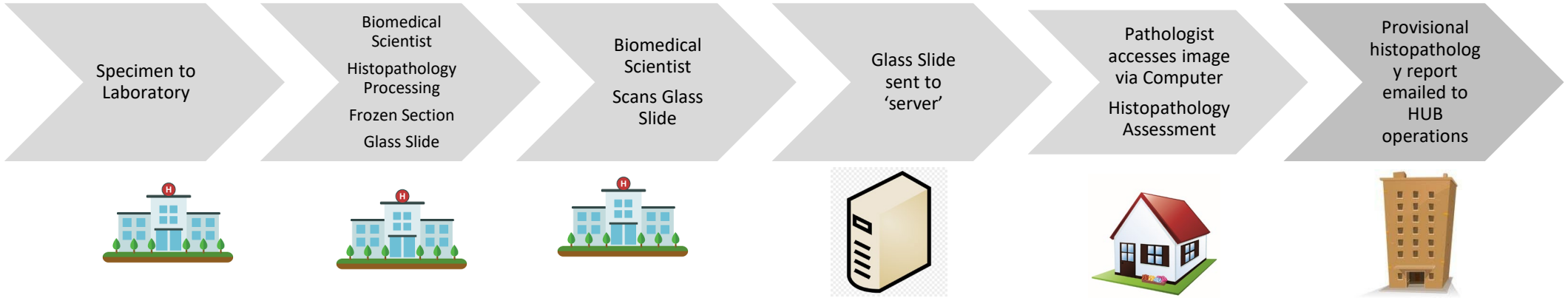
Digital Pathology

3DHistech scanner

Pannoramic DESK



Slide Scanner - Histopathology Processing/ Histopathology Assessment



PITHIA TRIAL: Slides Scanners currently in 6 centres

- 6 Scanner Centres

- Cambridge
- Royal Free
- Birmingham
- Leeds
- Newcastle
- Edinburgh

Option 1. National Histopathology Assessment Centre/ NORS Histopathology Processing Centre (With Slide Scanner)

Single National Histopathology Assessment Centre

BMS on call at 6 Scanner Centres

6 subspecialty pathologists on call

- Urothelial Kidney
- Liver and Hepatobiliary
- Gynaecology
- Lung
- Gastrointestinal
- Haematological

Single National Histopathology Assessment Centre

BMS on call at 6 Scanner Centres

4 subspecialty pathologists on call

- Urothelial Kidney
- Liver and Hepatobiliary
- Gynaecology
- Lung

Option 2. NORS Histopathology Assessment Centre/ NORS Histopathology Processing Centre (With Slide Scanner)

6 Histopathology Assessment Centres

BMS on call at 6 Scanner Centres

6 subspecialty pathologists on call

- Urothelial Kidney
- Liver and Hepatobiliary
- Gynaecology
- Lung
- Gastrointestinal
- Haematological

6 Histopathology Assessment Centres

BMS on call at 6 Scanner Centres

4 subspecialty pathologists on call

- Urothelial Kidney
- Liver and Hepatobiliary
- Gynaecology
- Lung

Option 3. National Histopathology Assessment Centre/ NORS Histopathology Processing Centre (Slide Scanner) – Informal Rota (Histopathology rota leads)

Single National Histopathology Assessment Centre

BMS on call at 6 Scanner Centres

6 subspecialty pathologists – Informal Rota

- Urothelial Kidney
- Liver and Hepatobiliary
- Gynaecology
- Lung
- Gastrointestinal
- Haematological

Single National Histopathology Assessment Centre

BMS on call at 6 Scanner Centres

4 subspecialty pathologists – Informal Rota

- Urothelial Kidney
- Liver and Hepatobiliary
- Gynaecology
- Lung

Next steps

- Workforce (Staffing/ standby/ call out)
- Transport requirements
- Distance of travel for samples
- Impact on SNODs/ HUB/ BMS/ Pathologists
- Cost of equipment (initial, recurring)

History of cancer in a potential organ donor

Original article

Estimated risk of cancer transmission from organ donor to graft recipient in a national transplantation registry

R. Desai[1], D. Collett[1], C. J. E. Watson[2], P. Johnson[3], T. Evans[4] and J. Neuberger[1]

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Correspondence to: Dr R. Desai, NHS Blood and Transplant, Fox Den Road, Stoke Gifford, Bristol BS34 8RR, UK (e-mail: rajeev.desai@nhs.net)

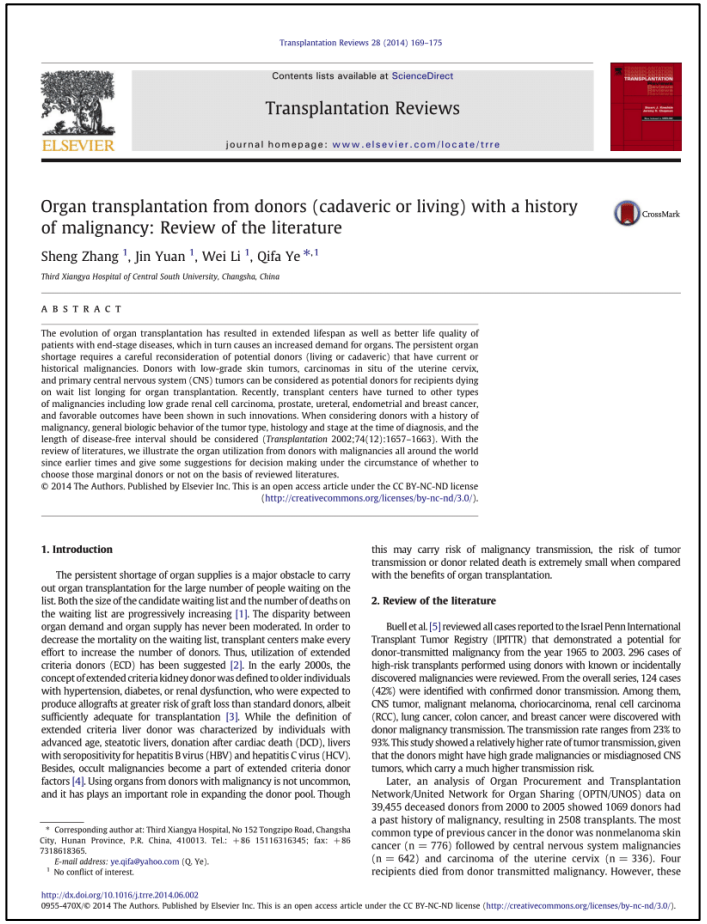
Background: Transplanted organs carry the risk of inadvertent donor cancer transmission. Some cancers in organ donors have been classified as being associated with a high or unacceptable risk, but the evidence for such recommendations is scanty.

Methods: The risk of cancer transmission from donors characterized as high or unacceptable risk was studied by analysing transplant and cancer registry data. Donors and recipients from England (1990–2008) were identified from the UK Transplant Registry. Cancer details were obtained from cancer registries and classified using guidelines from the Council of Europe and Organ Procurement and Transplantation Network/United Network for Organ Sharing.

Results: Of 17 639 donors, 202 (1·1 per cent) had a history of cancer, including 61 donors with cancers classed as having an unacceptable/high risk of transmission. No cancer transmission was noted in 133 recipients of organs from these 61 donors. At 10 years after transplantation, the additional survival benefit gained by transplanting organs from donors with unacceptable/high-risk cancer was 944 (95 per cent confidence interval (c.i.) 851 to 1037) life-years, with a mean survival of 7·1 (95 per cent c.i. 6·4 to 7·8) years per recipient.

Conclusion: Strict implementation of present guidelines is likely to result in overestimation of cancer transmission risk in some donors. Organs from some donors with cancers defined as unacceptable/high risk can be used safely.

Paper accepted 16 January 2014
Published online 28 April 2014 in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.9460



Transplantation Reviews 28 (2014) 169–175

Contents lists available at ScienceDirect

Transplantation Reviews

journal homepage: www.elsevier.com/locate/trre

Organ transplantation from donors (cadaveric or living) with a history of malignancy: Review of the literature

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A B S T R A C T

The evolution of organ transplantation has resulted in extended lifespan as well as better life quality of patients with end-stage diseases, which in turn causes an increased demand for organs. The persistent organ shortage requires a careful reconsideration of potential donors (living or cadaveric) that have current or historical malignancies. Donors with low-grade skin tumors, carcinomas in situ of the uterine cervix, and primary central nervous system (CNS) tumors can be considered as potential donors for recipients dying on wait list longing for organ transplantation. Recently, transplant centers have turned to other types of malignancies including low grade renal cell carcinoma, prostate, ureteral, endometrial and breast cancer, and favorable outcomes have been shown in such innovations. When considering donors with a history of malignancy, general biologic behavior of the tumor type, histology and stage at the time of diagnosis, and the length of disease-free interval should be considered (*Transplantation* 2002;74(12):1657–1663). With the review of literatures, we illustrate the organ utilization from donors with malignancies all around the world since earlier times and give some suggestions for decision making under the circumstance of whether to choose those marginal donors or not on the basis of reviewed literatures.

1. Introduction

The persistent shortage of organ supplies is a major obstacle to carry out organ transplantation for the large number of people waiting on the list. Both the size of the candidate waiting list and the number of deaths on the waiting list are progressively increasing [1]. The disparity between organ demand and organ supply has never been moderated. In order to decrease the mortality on the waiting list, transplant centers make every effort to increase the number of donors. Thus, utilization of extended criteria donors (ECD) has been suggested [2]. In the early 2000s, the concept of extended criteria kidney donor was defined to older individuals with hypertension, diabetes, or renal dysfunction, who were expected to produce allografts at greater risk of graft loss than standard donors, albeit sufficiently adequate for transplantation [3]. While the definition of extended criteria liver donor was characterized by individuals with advanced age, steatotic livers, donation after cardiac death (DCD), livers with seropositivity for hepatitis B virus (HBV) and hepatitis C virus (HCV). Besides, occult malignancies become a part of extended criteria donor factors [4]. Using organs from donors with malignancy is not uncommon, and it has plays an important role in expanding the donor pool. Though this may carry risk of malignancy transmission, the risk of tumor transmission or donor related death is extremely small when compared with the benefits of organ transplantation.

2. Review of the literature

Buell et al. [5] reviewed all cases reported to the Israel Penn International Transplant Tumor Registry (IPITTR) that demonstrated a potential for donor-transmitted malignancy from the year 1965 to 2003. 296 cases of high-risk transplants performed using donors with known or incidentally discovered malignancies were reviewed. From the overall series, 124 cases (42%) were identified with confirmed donor transmission. Among them, CNS tumor, malignant melanoma, choriocarcinoma, renal cell carcinoma (RCC), lung cancer, colon cancer, and breast cancer were discovered with donor malignancy transmission. The transmission rate ranges from 23% to 93%. This study showed a relatively higher rate of tumor transmission, given that the donors might have high grade malignancies or misdiagnosed CNS tumors, which carry a much higher transmission risk.

Later, an analysis of Organ Procurement and Transplantation Network/United Network for Organ Sharing (OPTN/UNOS) data on 39,455 deceased donors from 2000 to 2005 showed 1069 donors had a past history of malignancy, resulting in 2508 transplants. The most common type of previous cancer in the donor was nonmelanoma skin cancer (n = 776) followed by central nervous system malignancies (n = 642) and carcinoma of the uterine cervix (n = 336). Four recipients died from donor transmitted malignancy. However, these

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[1] No conflict of interest.

http://dx.doi.org/10.1016/j.trre.2014.06.002
0955-470X/

History of cancer in a potential organ donor

- 61 donors donated 140 organs
- 133 recipients, comprising a total of
  - 86 Kidneys
  - 22 Livers
  - 10 Hearts
  - 8 Lungs
  - 7 multiple organs
    - (4 kidney–pancreas, 2 heart–lung and 1 kidney–heart).
- Comparison of the survival of recipients of single organs from donors with an unacceptable/high risk and standard/non-standard risk of cancer transmission revealed no significant difference in unadjusted survival or risk-adjusted hazard of death

- At 10 years after transplantation, the additional survival benefit of transplanting the organs from donors with an unacceptable/high risk of cancer transmission was 944 (95 per cent C.I. 851 to 1037) life-years, with a mean survival of 7·1 (95 per cent C.I. 6·4to7·8) years per recipient.
- 8 of these recipients developed post-transplant cancers, but none had the same cancer type as their donor, indicating these were likely to be de novo cancers

	Transplants from donors with an unacceptable/high risk of cancer transmission			Transplants from donors with a standard/non-standard risk of cancer transmission				Risk-adjusted hazard of death for recipients from donors with unacceptable/high risk‡	
Recipient group	*n*	Mean age (years)	Recipient survival (years)	*n*	Mean age (years)	Recipient survival (years)	*P*†	Hazard ratio	*P*
Kidney	86	47·4 (43·7, 51·0)	8·79 (3·80, –)*	23 994	42·6 (42·4, 42·8)	10·96 (10·69, 11·27)	0·522	0·87 (0·55, 1·39)	0·566
Liver	22	41·2 (32·6, 49·9)	5·37 (0·11, –)*	6560	39·4 (39·0, 39·8)	4·86 (4·43, 5·42)	0·807	1·07 (0·43, 2·64)	0·884
Heart	10	34·3 (22·8, 45·8)	3·75 (0·01, –)*	2720	32·2 (31·7, 32·7)	3·56 (2·72, 4·17)	0·686	0·73 (0·17, 3·18)	0·670
Lung	8	39·0 (28·1, 49·9)	0·43 (0·04, 5·94)	1245	36·6 (35·8, 37·3)	0·94 (0·70, 1·29)	0·400	2·85 (0·94, 8·62)	0·063
Pancreas	0	–	–	149	32·7 (30·7, 34·6)	6·20 (5·84, 10·32)	–	–	–

Desai R et al, 2014

Bad for transplantation. . .

Soldier died after being given smoker's lungs in transplant

Cancer developed and drugs prescribed by
Papworth hospital served to speed up disease, coroner hears

The Guardian, Monday 12 October 2009

Transplant patients given kidneys from donor with cancer

Investigation under way into how two transplant patients
were given kidneys from a donor with a rare form of lymphoma

•The Guardian, Tuesday 22 March 2011

A kidney operation changed Robert's life. He got cancer

Father of four was assured stringent tests
had been carried out on the organ he was receiving – but there was one vital flaw

•The Guardian, Tuesday 22 March 2011

Cancer Spreads from Organ Donor to 4 People in 'Extraordinary' Case

By Rachael Rettner September 15, 2018

(Image: © Shutterstock)

It's well known that organ transplants can pass infectious diseases from donors to recipients in rare cases. But even more rarely, transplants can transmit cancer, as a new case shows.

Donor Malignancy Transmission Risk Assessment

Table 2: Suggested risk categorizations for specific tumor types[1]

Risk category	Tumors
No significant risk	Benign tumors in which malignancy is excluded (see Table 3 and Supporting Table S4)
Minimal risk (<0.1% transmission)	Basal cell carcinoma, skin
	Squamous cell carcinoma, skin without metastases
	Carcinoma *in situ*, skin (nonmelanoma)
	In situ cervical carcinoma
	In situ vocal cord carcinoma
	Superficial (noninvasive) papillary carcinoma of bladder (T0N0M0 by TNM stage) (nonrenal transplant only)[5]
	Solitary papillary thyroid carcinoma, ≤0.5 cm
	Minimally invasive follicular carcinoma, thyroid, ≤ 1.0 cm
	(Resected) solitary renal cell carcinoma, ≤1.0 cm, well differentiated (Fuhrman 1–2)[4]
Low risk (0.1–1% transmission)	(Resected) solitary renal cell carcinoma, >1.0 cm ≤2.5 cm, well differentiated (Fuhrman 1–2)[4]
	Low grade CNS tumor (WHO grade I or II)
	Primary CNS mature teratoma
	Solitary papillary thyroid carcinoma, 0.5–2.0 cm
	Minimally invasive follicular carcinoma, thyroid, 1.0–2.0 cm
	History of treated non-CNS malignancy (≥5 years prior) with >99% probability of cure
Intermediate risk (1–10% transmission)	Breast carcinoma (stage 0 i.e. carcinoma *in situ*)
	Colon carcinoma (stage 0 i.e. carcinoma *in situ*)
	(Resected) solitary renal cell carcinoma T1b (4–7 cm) well differentiated (Fuhrman 1–2) stage I [4,6]
	History of treated non-CNS malignancy (≥5 years prior) with probability of cure between 90–99%
High risk (>10% transmission)	Malignant melanoma
	Breast carcinoma >stage 0 (active)[2]
	Colon carcinoma >stage 0 (active)[2]
	Choriocarcinoma
	CNS tumor (any) with ventriculoperitoneal or ventriculoatrial shunt, surgery (other than uncomplicated biopsy), irradiation or extra-CNS metastasis
	CNS Tumor WHO grade III or IV (see Supporting Table S3)[7]
	Leukemia or lymphoma
	History of melanoma, leukemia or lymphoma, small cell lung/neuroendocrine carcinoma
	Any other history of treated non-CNS malignancy either (a) insufficient follow-up to predict behavior, (b) considered incurable or (c) with probability of cure <90%
	Metastatic carcinoma
	Sarcoma
	Lung cancer (stages I–IV)[6]
	Renal cell carcinoma >7 cm or stage II–IV[6]
	Small cell/neuroendocrine carcinoma, any site of origin
	Active cancer not listed elsewhere[3]

Nalesnik MA et al, 2011

Discussion

- Histopathology is vital to improve donor characterization
- Donors are now much older and the risk of malignancy is significantly higher
- Risk averse practices can be reduced when histopathology analysis is available
- Organ utilization can be improved

- There is a recognition that there is a need for organ specific pathological analysis
- Need for sustainability
- Need for a robust service