Liverpool Hepatobiliary Centre

Aintree University Hospital

NHS Foundation Trust

UNIVERSITY OF LIVERPOOL

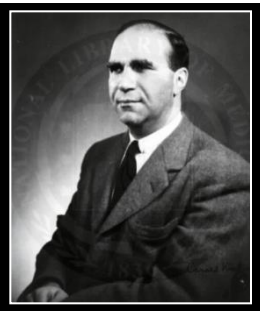
NHS

Surgical update in Cholangiocarcinoma

Hassan Z Malik MD, FRCS

Consultant Hepatobiliary Surgeon

Classification



Gerald Klatskin

Intrahepatic

- ***Peripheral*** **5% ↑**

Extrahepatic

- ***Hilar (Klatskin tumour)*** **65 %**
- ***Distal*** **30 %**

Nakeeb, 1996. Reding, 1991. National Library of Medicine

Cholangiocarcinoma

Challenges for the surgeon

- Complexity of Liver Hilar anatomy
- Assessment of tumour extent
- Pathophysiology of jaundice and functional assessment
- Technical demands of surgery
  - Ro resections
  - Extended Liver resection
  - Vascular resections
  - PSC
- Neoadjuvant and adjuvant therapies

Cholangiocarcinoma

Challenges for the surgeon

- Complexity of Liver Hilar anatomy
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  - Ro resections
  - Extended Liver resection
  - Vascular resections
  - PSC
- Neoadjuvant and adjuvant therapies
- Nihilism in West

Contraindications for resection

- Metastatic disease including distant lymph node spread
- Frail patient

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Patient journey

Practice across the across the UK?

- Cholangiocarcinoma UK survey
- We received 36 responses including most of the surgical centers

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Patient journey

- Patients may present with mild, non specific symptoms often with deranged liver function tests or jaundice.
- They are often referred after basic investigations by GP to the local hospital.
- An initial diagnosis of a liver tumour is made after further tests, usually a CT scan.

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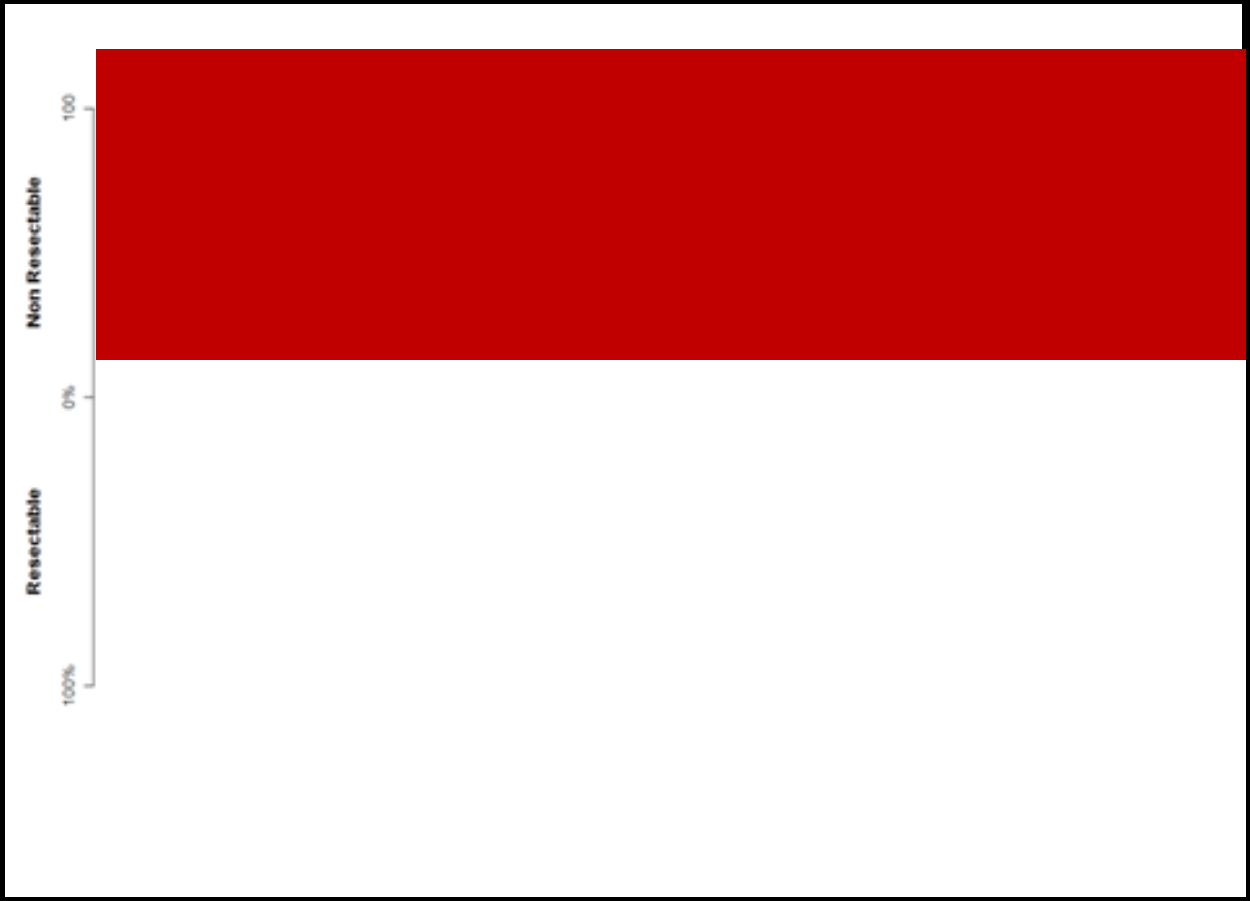
Patient journey

- Patients may present with mild, non specific symptoms often with deranged liver function tests or jaundice.
- They are often referred after basic investigations by GP to the local hospital.
- An initial diagnosis of liver tumour is made after further tests, usually a CT scan.
- Some may be referred on for a specialist Hepatobiliary Multidisciplinary tumour board opinion.

Variation between specialist and non-specialist assessment

Colorectal liver metastases



Jones et al BJS 2012

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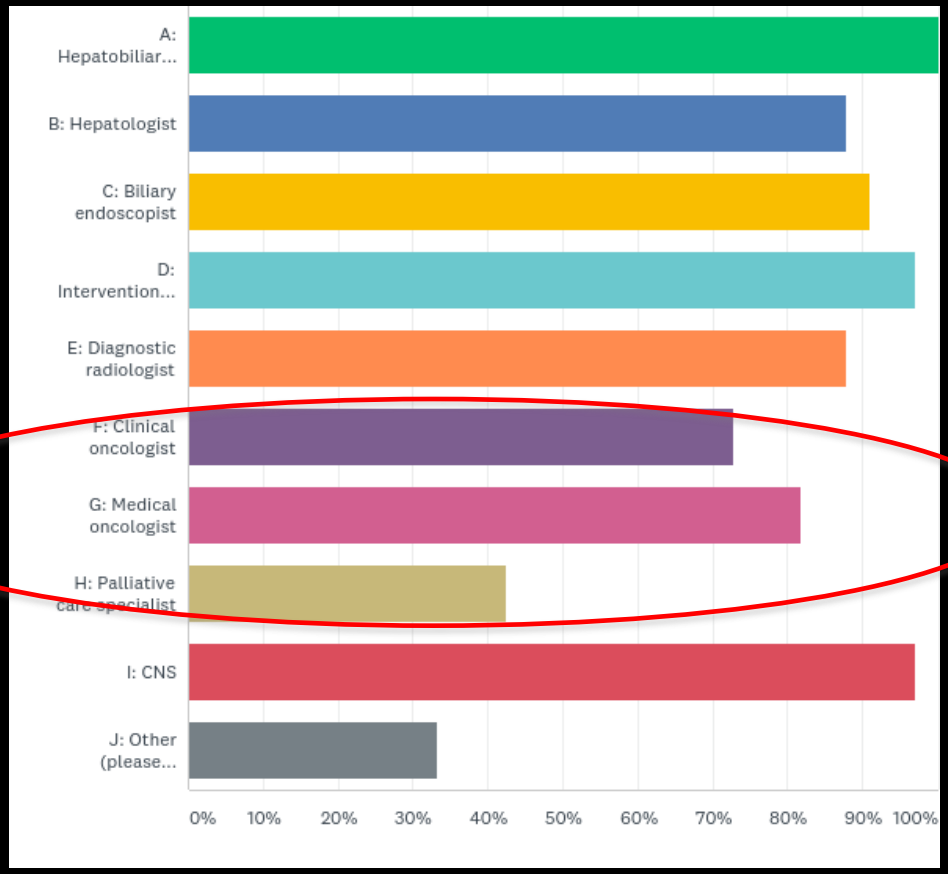
The Multi-Disciplinary Team (MDT) Meeting in Liverpool

The Multi-Disciplinary Team (MDT) across the UK



Cholangiocarcinoma UK survey

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Decision Making

"The MDT is a Decision Making Machine"

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Elements of Decision Making

- Situation Assessment
- Generating Options
- Selecting and implementing an option
- Outcome Review

Flin et al (2009)

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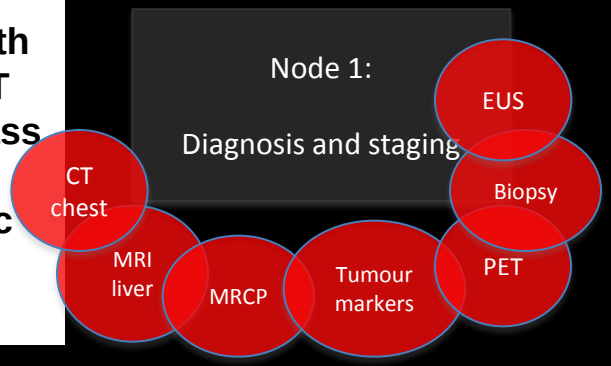
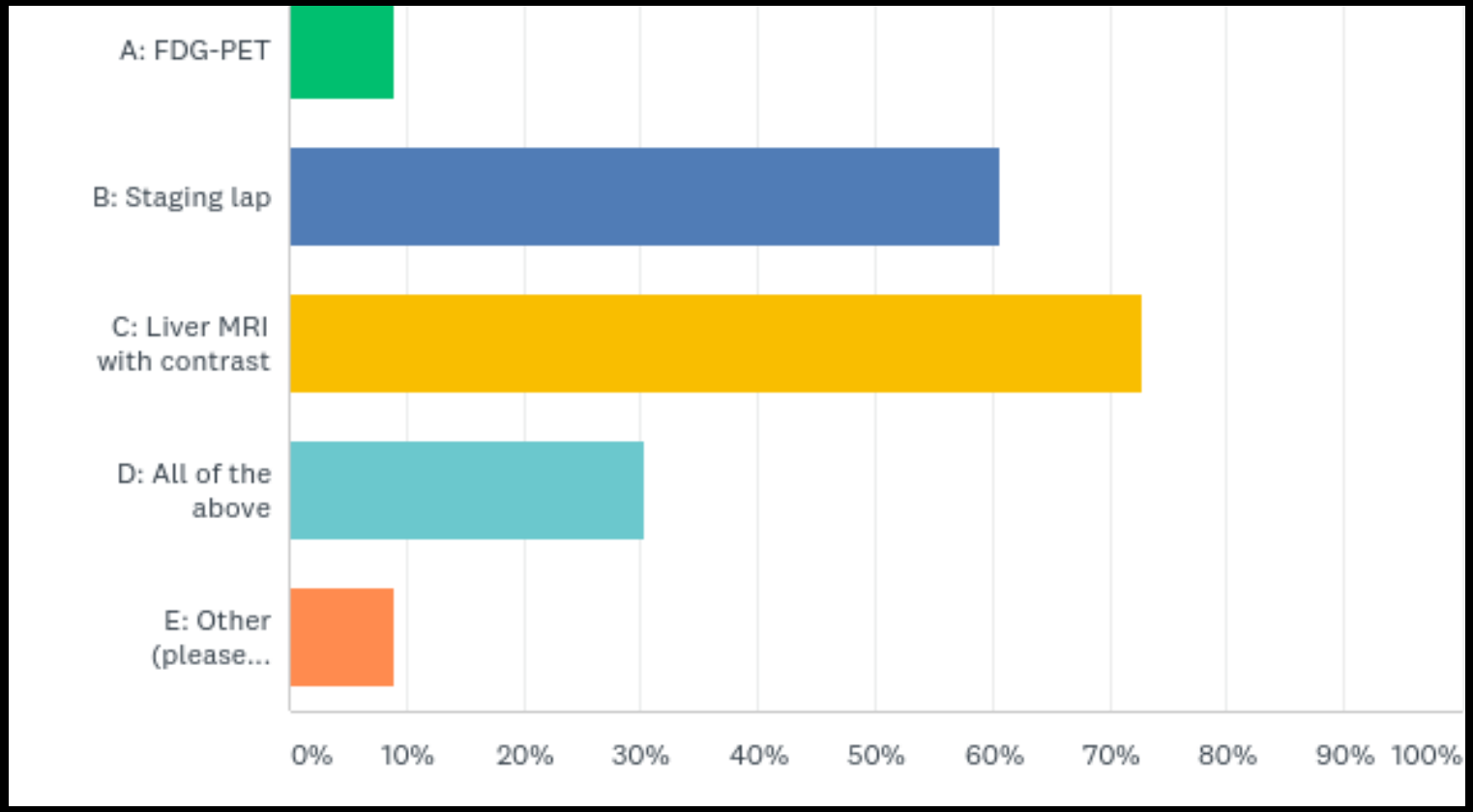
55yr Male presents with jaundice. CT shows a mass in liver with intra-hepatic biliary dilatation.



Diagnosis and staging



Cholangiocarcinoma UK survey

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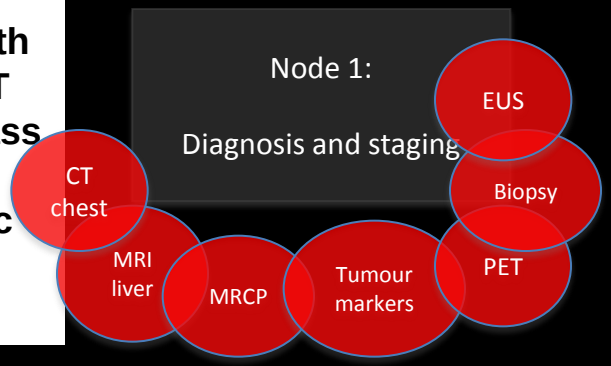
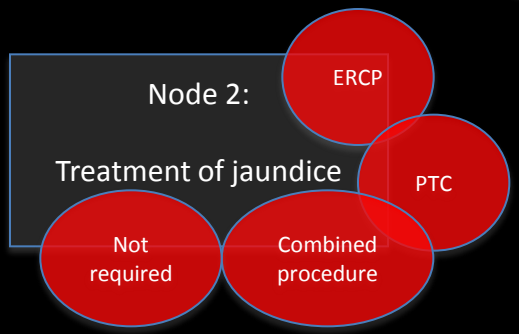
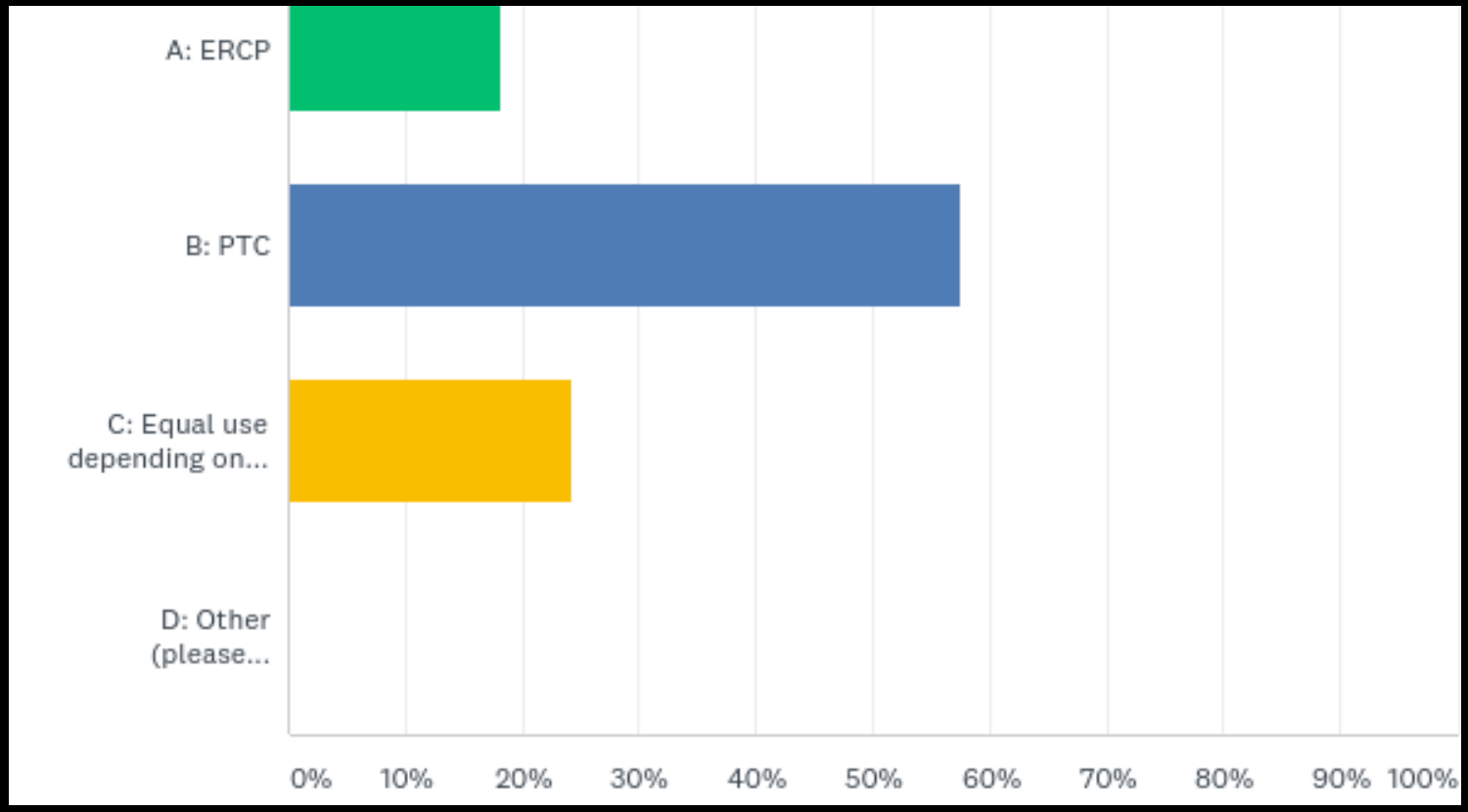




Biliary drainage – What modality is used?



Cholangiocarcinoma UK survey

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55yr Male presents with jaundice. CT shows a mass in liver with intra-hepatic biliary dilatation.

Node 1:

Diagnosis and staging

- CT chest
- MRI liver
- MRCP
- Tumour markers
- PET
- Biopsy
- EUS

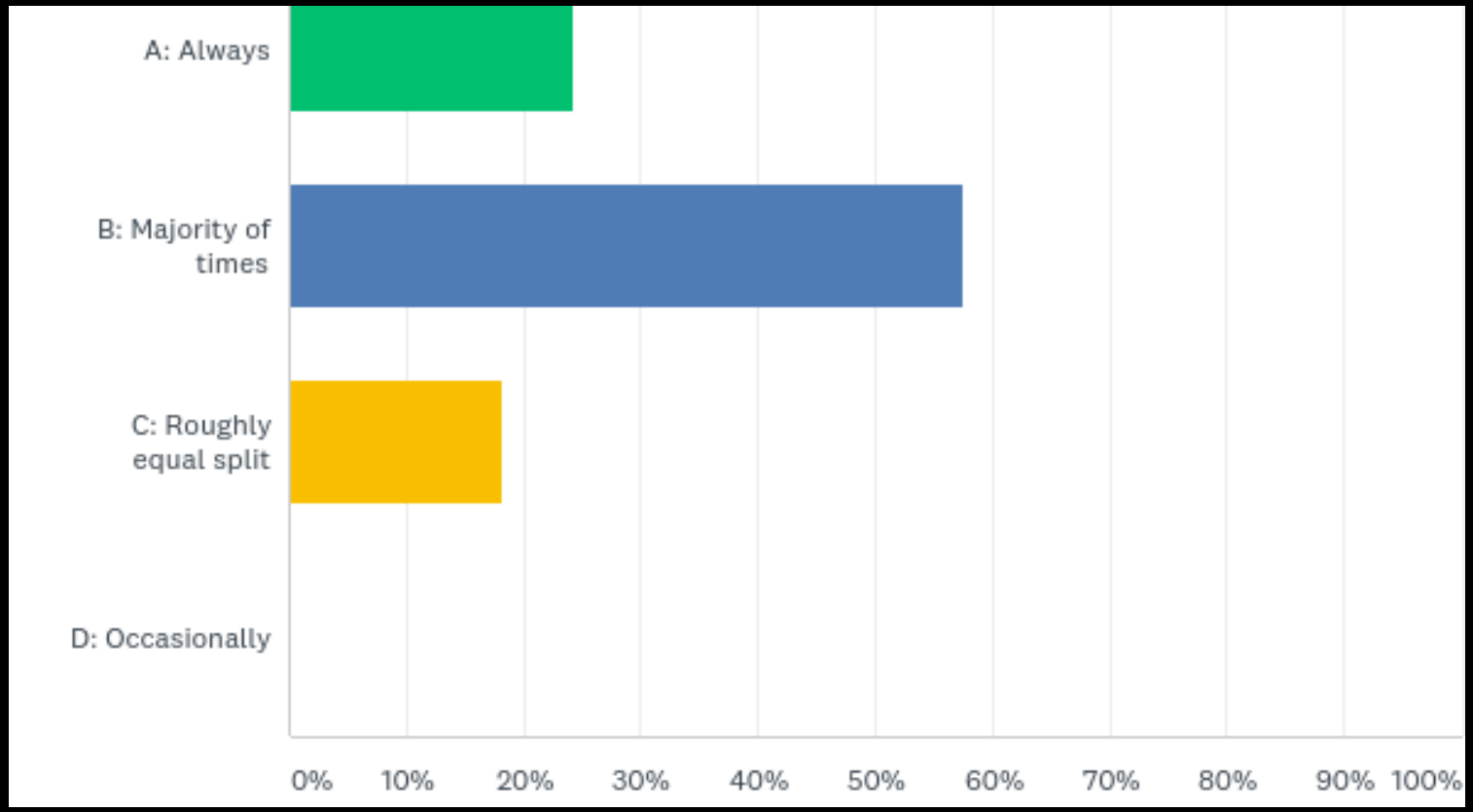
Node 2:

Treatment of jaundice

- Not required
- Combined procedure
- PTC
- ERCP

MDT input:
Diagnostic Radiology
Interventional radiology
Gastroenterology
HPB surgeon
Oncology

Biliary drainage – Is this performed at the tertiary Hepatobiliary centre?



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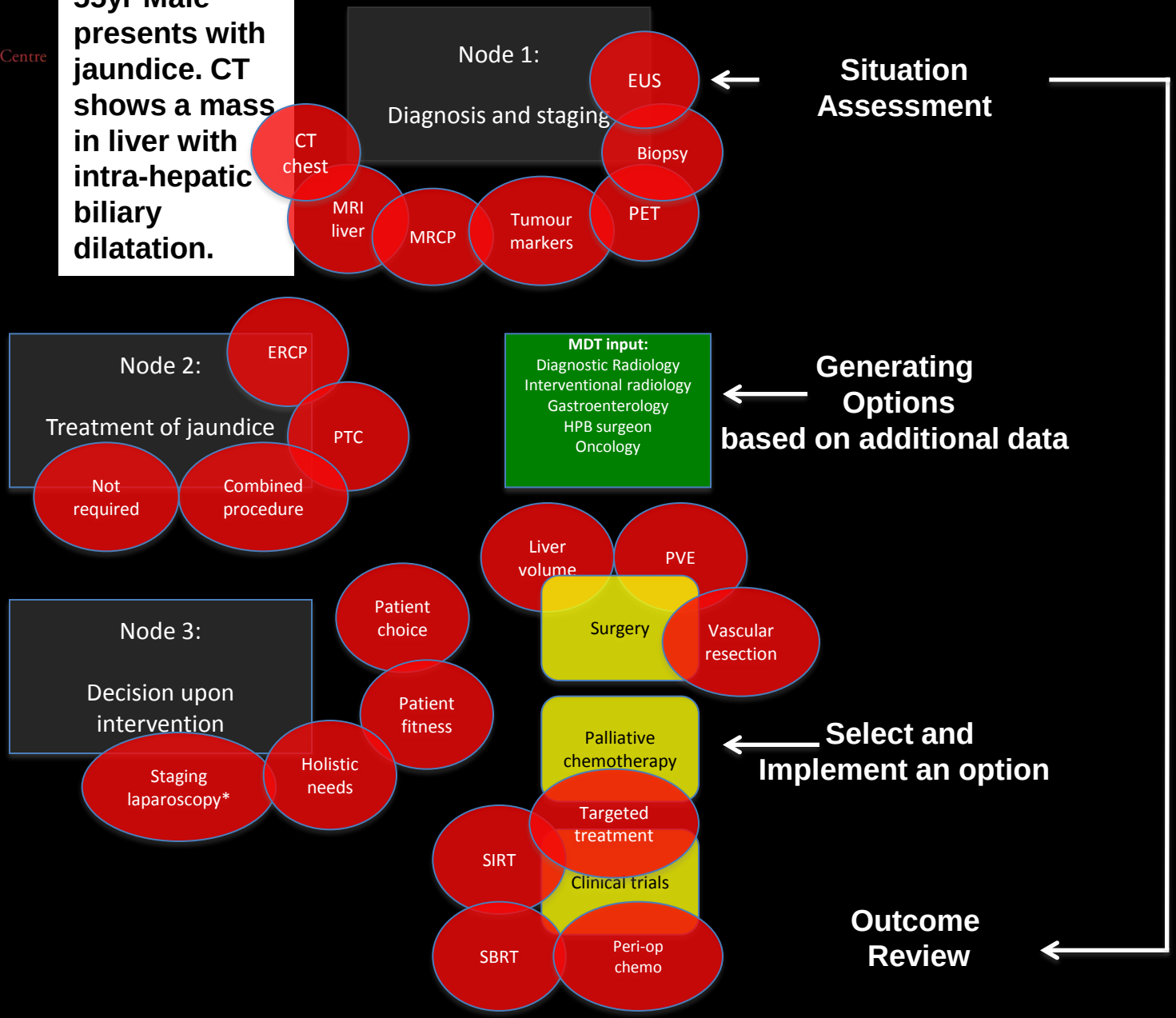

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How to decide upon which patients are operable?

What factors to consider when planning surgery

Prognostic factors

Size of tumour

Vascular invasion

Nodal status

Patient co-morbidity/unit outcomes

Medical risk of resection

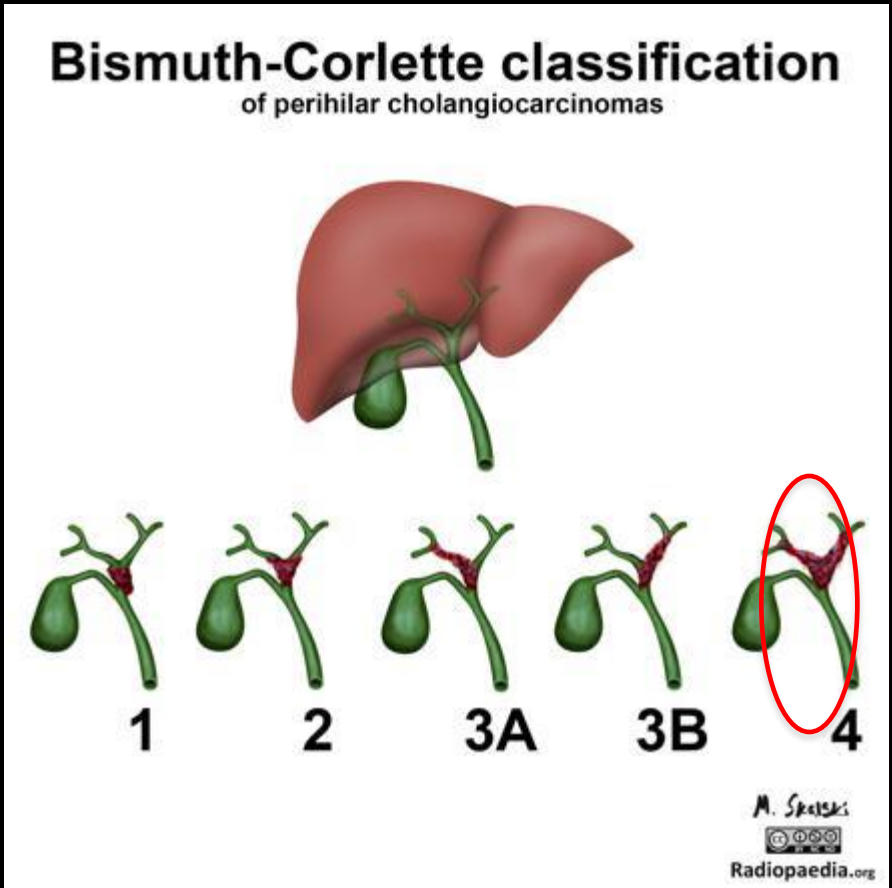
in YOUR unit

Resectability

Remaining functional liver tissue

Invaded structures/segments

Defining resectability



Defining resectability

Number of different staging systems have now combined into proposed new staging system by "International study group" incorporating –

Tumour type

Biliary involvement

Arterial involvement

Venous involvement

Nodal disease

Underlying liver disease

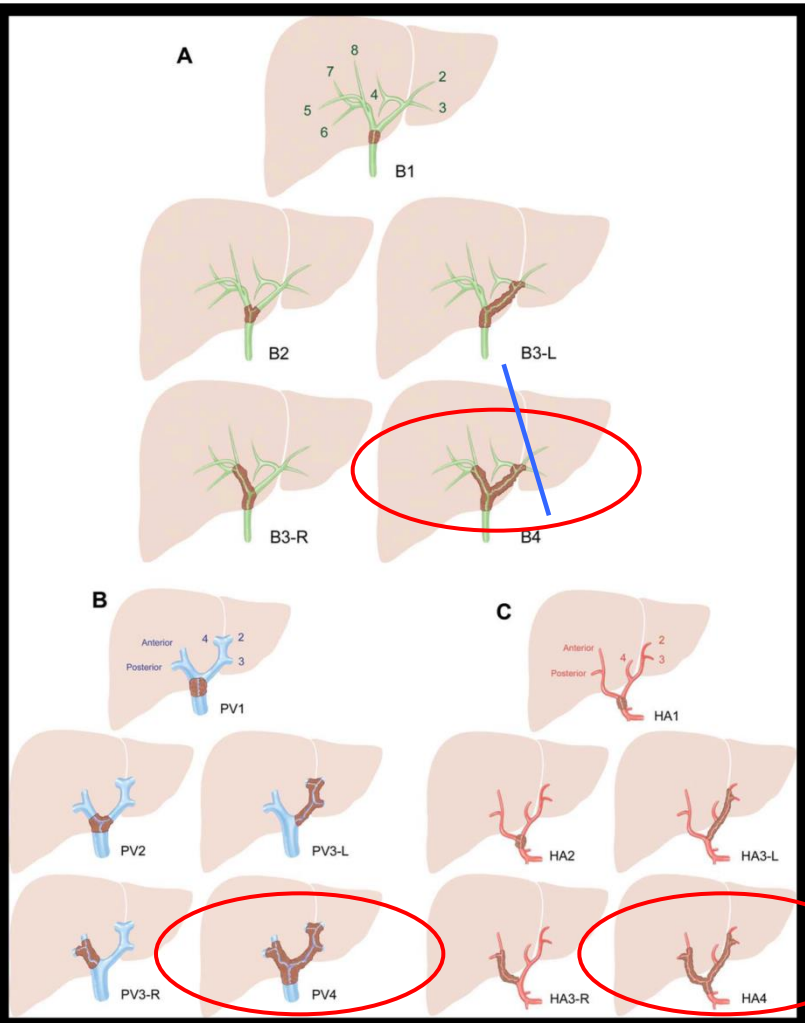
Table 4. Proposed Classification System

Label	Side/Location*	Description
Bile duct (B)†		
B1		Common bile duct
B2		Hepatic duct confluence
B3	R	Right hepatic duct
B3	L	Left hepatic duct
B4		Right and left hepatic duct
Tumor size (T)		
T1		<1 cm
T2		1-3 cm
T3		2:3 cm
Tumor form (F)		
Sclerosing		Sclerosing (or periductal)
Mass		Mass-forming (or nodular)
Mixed		Sclerosing and mass-forming
Polypoid		Polypoid (or intraductal)
Involvement (>180°) of the portal vein (PV)		
PV0		No portal involvement
PV1		Main portal vein
PV2		Portal vein bifurcation
PV3	R	Right portal vein
PV3	L	Left portal vein
PV4		Right and left portal veins
Involvement (>180°) of the hepatic artery (HA)		
HA0		No arterial involvement
HA1		Proper hepatic artery
HA2		Hepatic artery bifurcation
HA3	R	Right hepatic artery
HA3	L	Left hepatic artery
HA4		Right and left hepatic artery
Liver remnant volume (V)		
V0		No information on the volume needed (liver resection not foreseen)
V%	Indicate segments	Percentage of the total volume of a putative remnant liver after resection
Underlying liver disease (D)		Fibrosis Nonalcoholic steatohepatitis Primary sclerosing cholangitis
Lymph nodes (N)‡		
N0		No lymph node involvement
N1		Hilar and/or hepatic artery lymph node involvement
N2		Periaortic lymph node involvement
Metastases (M)§		
M0		No distant metastases
M1		Distant metastases (including liver and peritoneal metastases)

*"R" indicates right, and "L" indicates left.
†Based on the Bismuth classification.[19,20]
‡Based on the Japanese Society of Biliary Surgery classification.[48]
§Based on the TNM classification.[21]

DeOlivera et al Hepatology 2011

Defining resectability



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Surgical work-up

Enhanced recovery after surgery (ERAS) concept

AIM: streamline peri-operative pathways resulting in improvements in patient outcomes; efficiency and reduction in costs

Multimodal process with four main elements

Improved preoperative assessment
Reducing the physical stress of surgery
Improved perioperative management
Early mobilisation and discharge

Kehlet BJA 1997; 78: 606-17
Kehlet The Lancet; 2003: 362

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ERAS

- Audit
- Pre-admission counseling
- No bowel prep
- Carbo load
- No premed
- No NG
- Epidural
- Short-acting anesthetics
- No fluid overload
- Short-lap incision & no drain
- Normo-thermia
- Early mobilization
- Avoid opioids
- PONV prevention
- Early removal of lines/catheters
- Early oral diet

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ERAS

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Systematic review of the literature for HPB ERAS programmes

All ERAS series to date exclude CCA

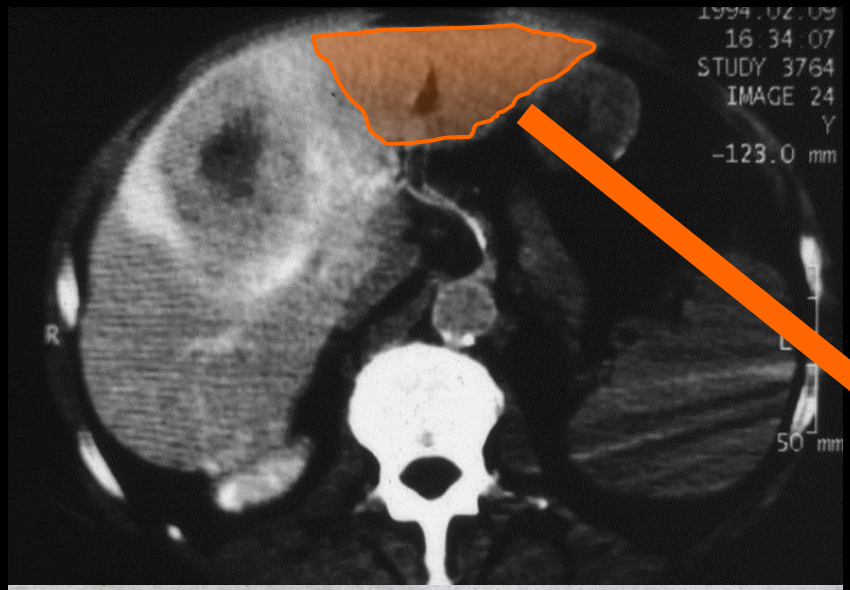
Clavian et al World J Surg 2016

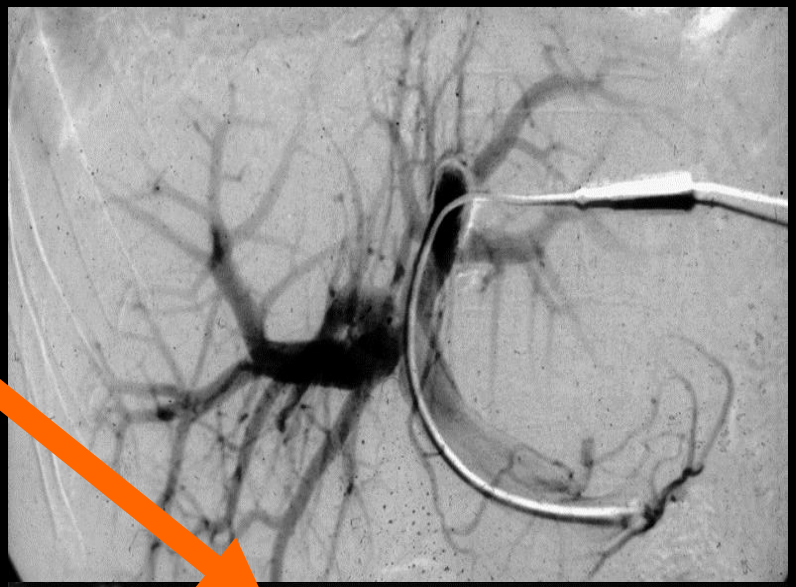
Liverpool ERAS experience – Peri-hilar Cholangiocarcinoma

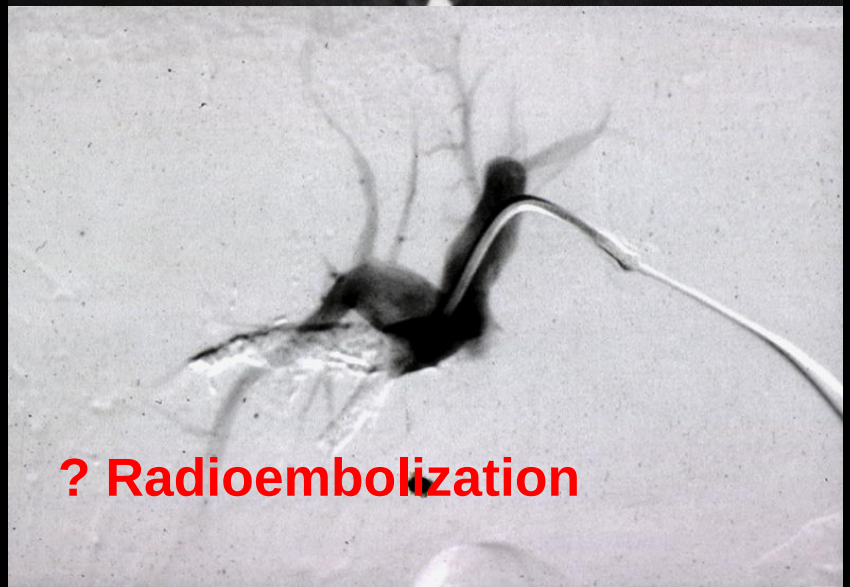
Pre-habilitation: all patients have pre-op CPET test; biliary drainage and optimisation of nutritional, medical co-morbidity and anaemia.

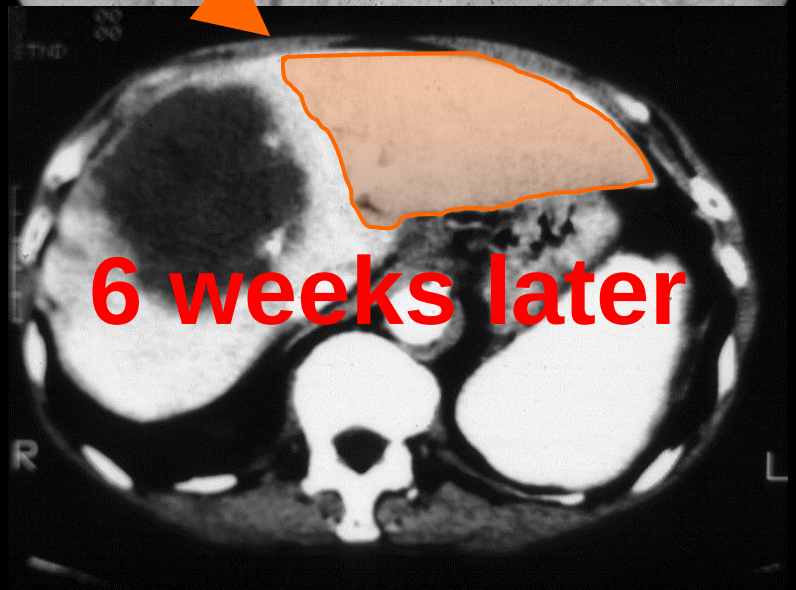
If Future Liver Remnant <40% consider PVE

Increasing resectability: Portal vein embolisation









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If Future Liver Remnant <40% consider PVE

Intra-op: epidural, PICCO monitoring with goal directed fluid management

Post-op: extubation in theatre, HDU, 48hrs antibiotics (extended as per medical microbiology cultures), epidural analgesia, early mobilisation and establishment of enteral nutrition

Liverpool ERAS experience – Peri-hilar Cholangiocarcinoma

- Median Length of Stay in hospital is 11 day (range 5-59): standard liver resection median is 6 days
- Median numbers of complications

  (Clavien Dindo 2-4) = 1 (range 0 -10)
- Post-operative mortality is 13%

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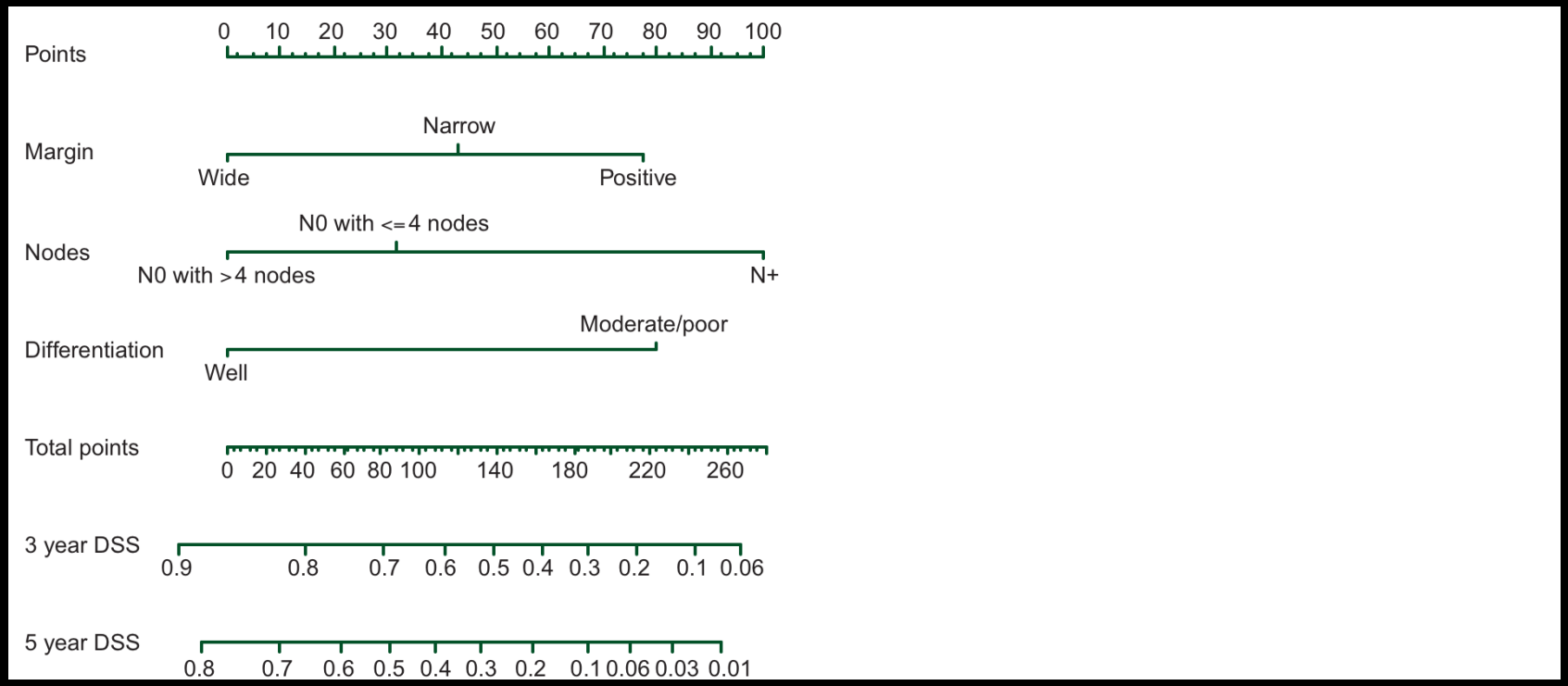
Prognosis following surgery

Hilar cholangiocarcinoma
Prognostic factors



306 resections from MSKCC & AMC

Concordance Index 0.72 for validation dataset, compared to 0.60 for 7th Edition of AJCC system

Koerkamp et al, Ann Oncol 2015

Hilar cholangiocarcinoma
Prognostic factors Meta-analysis

Variable (default)	N*	Heterogeneity		Random effects	
		I^2	p	ln (HR) (95% CI)	HR (95% CI)
Tumour size (small)	5	36.4%	0.178	0.19(-0.10,0.48)	1.21(0.90,1.62)
Age (young)	10	0.3%	0.435	0.11(0.00,0.22)	1.12(1.00,1.25)
LN involvement (-ve)	17	22.9%	0.188	0.62(0.51,0.72)	1.86(1.67,2.05)
Microvascular invasion (-ve)	7	0.0%	0.470	0.38(0.24,0.52)	1.46(1.27,1.68)
Peri-neural invasion (-ve)	12	0.0%	0.656	0.41(0.30,0.51)	1.51(1.35,1.67)
Portal vein resection (none)	8	58.7%	0.018	0.31(0.07,0.55)	1.36(1.07,1.73)
Resection margin status (-ve)	17	57.1%	0.002	0.63(0.47,0.78)	1.88(1.60,2.18)
Gender (male)	9	29.1%	0.187	0.06(-0.09,0.21)	1.06(0.91,1.23)
Tumour status (T1-T2)	5	54.9%	0.065	0.43(0.18,0.68)	1.54(1.20,1.97)
Tumour differentiation (well differentiation)	10	0.0%	0.505	0.43(0.32,0.54)	1.54(1.38,1.72)

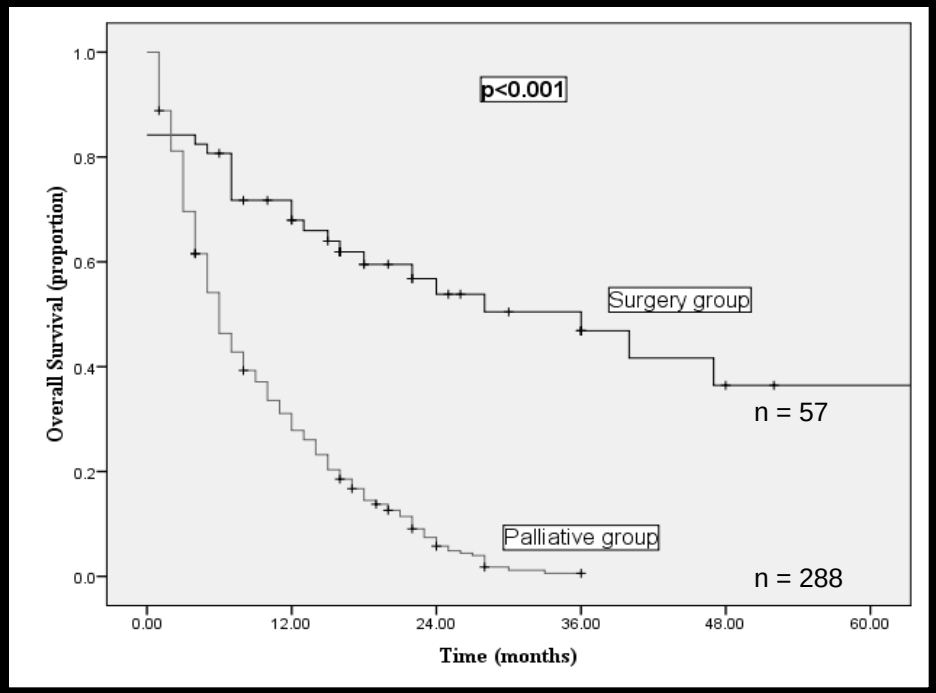
Meta-analysis of 4786 resected peri-hilar cholangiocarcinoma

Bird et al, BJS 2018

Long term outcomes

Impact of specialized multi-disciplinary approach and an integrated pathway on outcomes in hilar cholangiocarcinoma

D. Gomez [a], P.B. Patel [a], C. Lacasia-Purroy [b], C. Byrne [a], R.P. Sturgess [d], D. Palmer [c], S. Fenwick [a], G.J. Poston [a], H.Z. Malik [a,*]



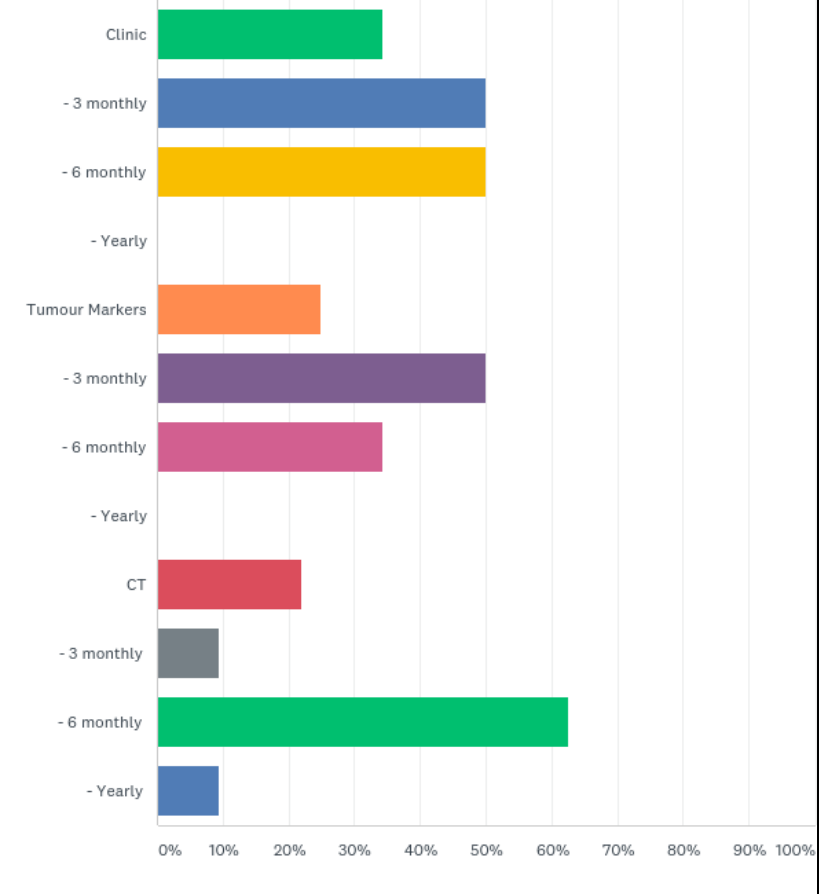
Consecutive peri-hilar CCC resections 2000-2011

Gomez at al EJSO 2013

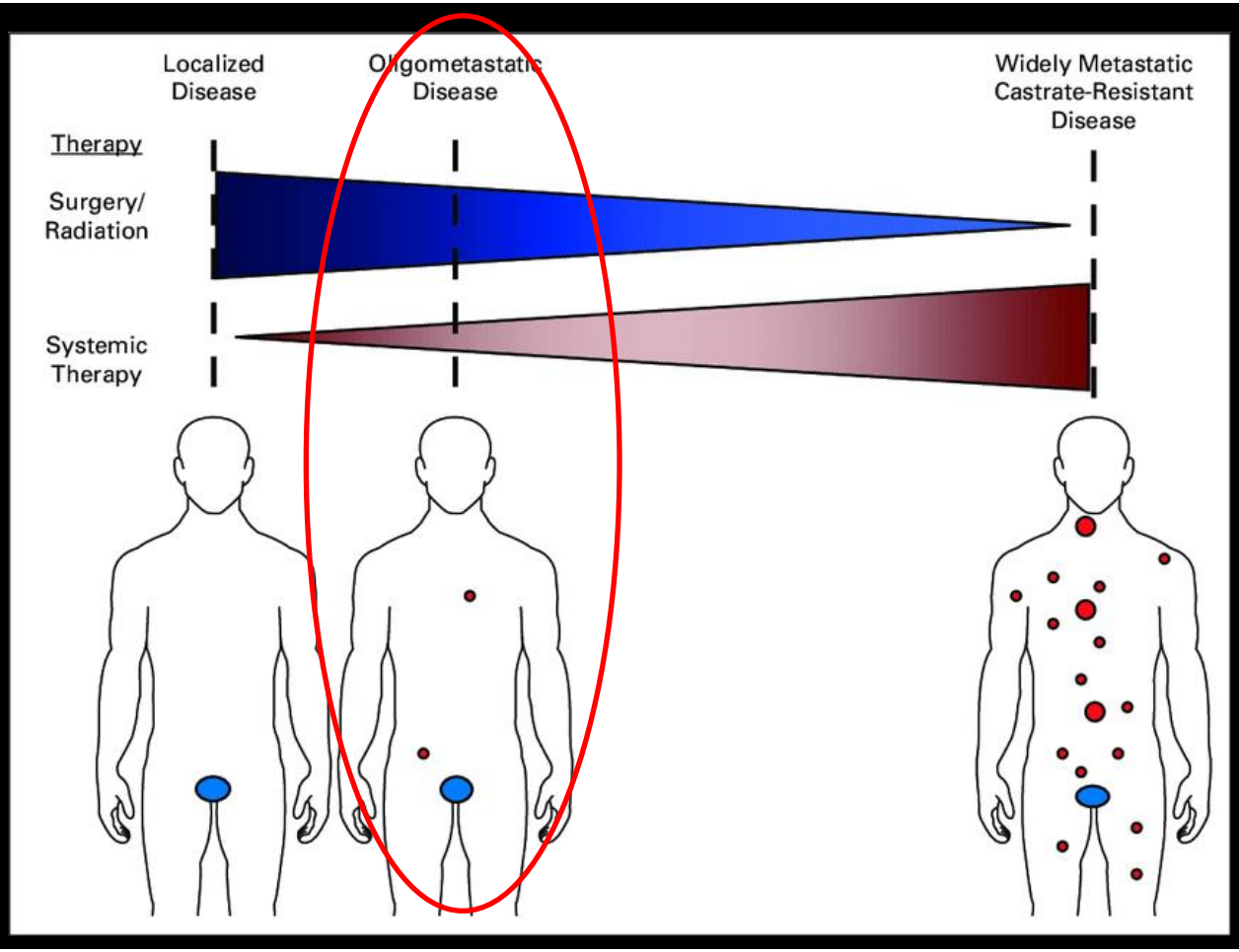
Liverpool post resection follow-up

- Initial clinic visit **4-6 weeks** to check on recovery and discuss histology and referral to HPB oncology team.
- Clinical review with bloods (including CA19-9) every **3 months**.
- CT scans Chest, Abdomen and Pelvis **every 6 months for 5 years** and then annually for 10 years.

UK post resection follow-up unit protocols



Why follow patients up after resection?



Biliary oligo-metastatic disease

Intra Hepatic Cholangiocarcinoma

107 liver re-resections for recurrent IHC

Largest single series of 41 cases with median survival of 26 months

Extra-hepatic (inc gallbladder cancer)

Small series with variable outcomes

Miyazaki et al Ann Gasteroenterological Surgery 2017

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Other options?

Hilar cholangiocarcinoma Transplantation

Mayo clinic protocol

External beam radiation therapy (45 Gy in 30 fractions, 1.5 Gy twice daily) and continuous infusion 5-FU – administered over 3 weeks

↓

Brachytherapy (20 Gy at 1 cm in approximately 20–25 hours) – administered 2 weeks following completion of external beam radiation therapy

↓

Capecitabine – administered until the time of transplantation, held during perioperative period for staging

↓

Abdominal exploration for staging – as time nears for deceased donor transplantation or day prior to living donor transplantation

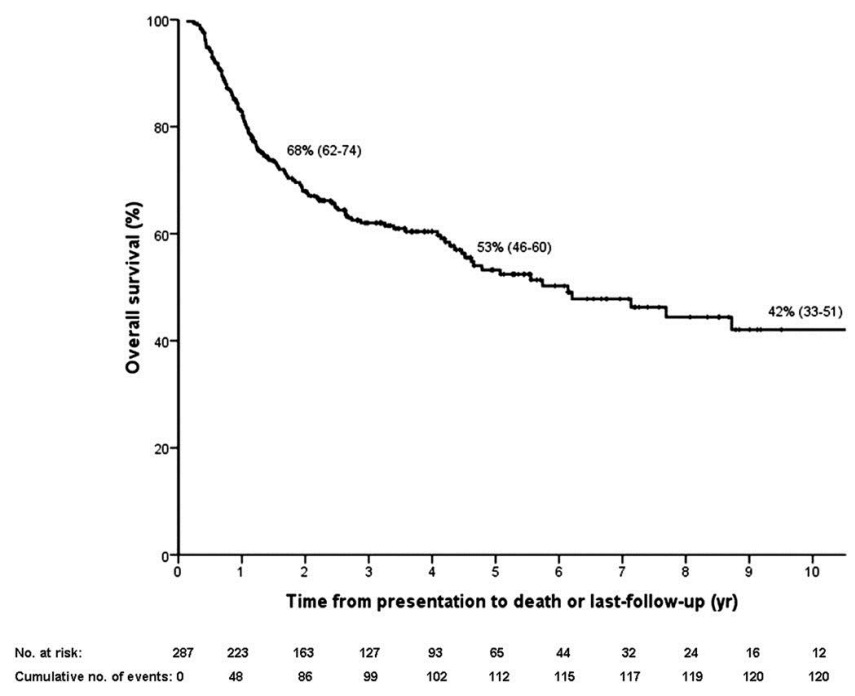
↓

Liver transplantation

Murad et al Gastroenterology 2012

Hilar cholangiocarcinoma Transplantation

- Intention to treat 5-yr survival 53%
- 30% patients never had confirmation of malignancy on pre-tissue acquisition



- Multicenter US series did however demonstrate a 5-year OS with OLT in proven CCA of 54% compared to 29% with resection for tumours staged pre-operatively as <3cm/N0

Murad et al Gastroenterology 2012
Ethun et al Ann surg 2017

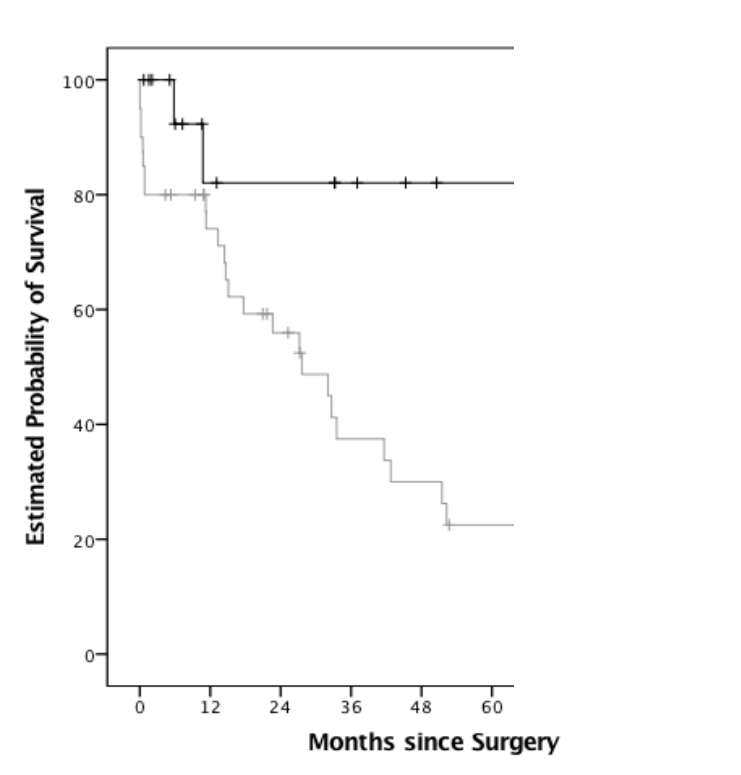
Hilar cholangiocarcinoma Transplantation

Comparing Apples with Oranges?

- 57 peri-hilar CCA resected in Liverpool 2009-17
- 5-yr OS 38.5%

  However

- 17 patients with <3cm, N0 tumours
- Survival in this group is 82% at 5 years



- Results from RCT: Liver Resection Versus Radio-chemotherapy-Transplantation for Hilar Cholangiocarcinoma (TRANSPHIL) awaited

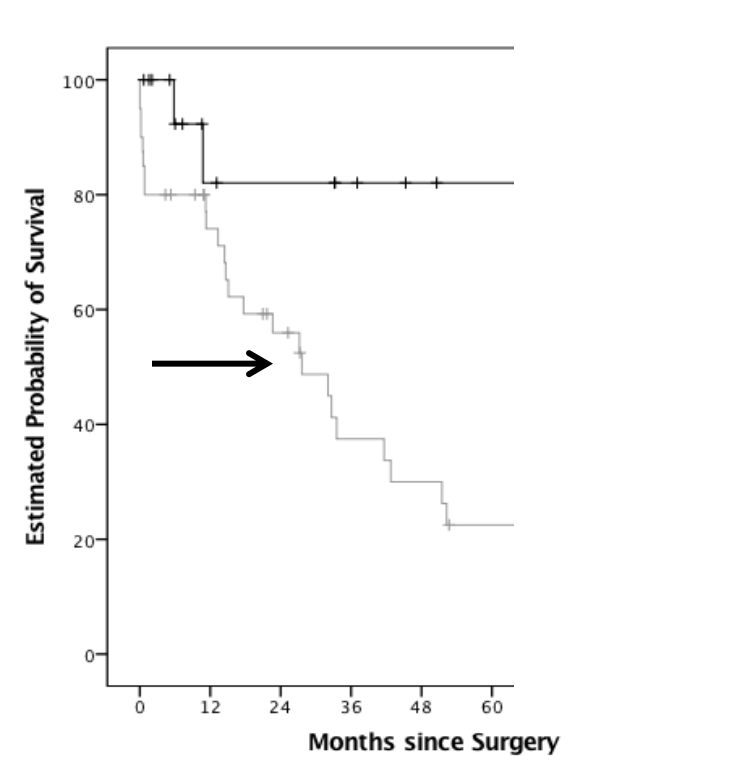
Stremitzer et al EJSO 2019

Hilar cholangiocarcinoma

Role of multimodal treatment

Comparing Apples with Oranges?

- **Prognosis determined by tumour biology**
- **Adjuvant chemotherapy beneficial (BILCAP)**
- **Role for neo-adjuvant chemotherapy as well as adjuvant radiotherapy is being investigated.**



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Cholangiocarcinoma: A tumour of unmet need?

Cholangiocarcinoma: a tumour of unmet need?

Public Health England

cancer52
the common voice for less common cancers

Protecting and improving the nation's health

National Cancer Intelligence Network
Rare and less common cancers

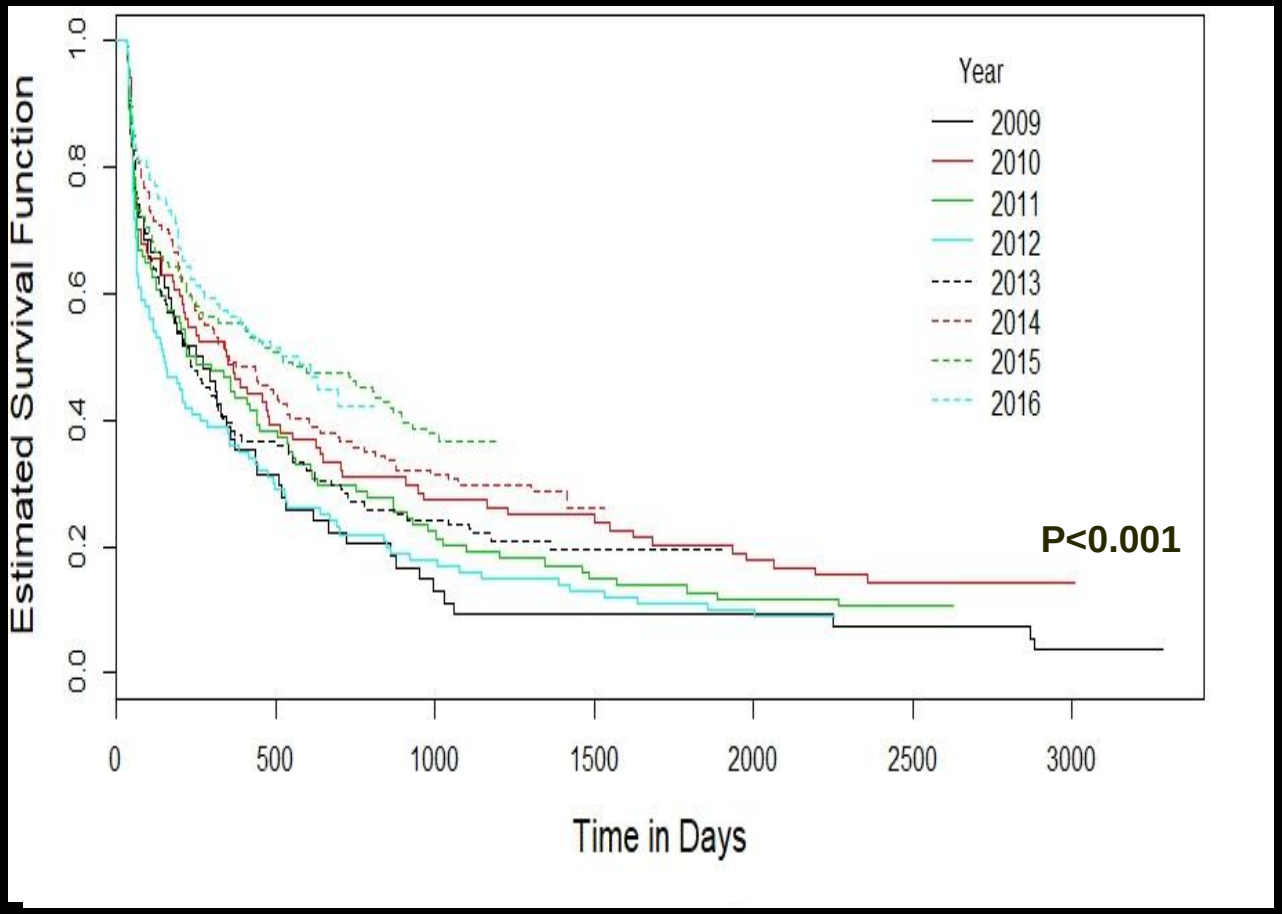
Incidence and Mortality in England, 2010 to 2013

Table 1.15 Upper Gastro-Intestinal (UGI) cancer incidence, 2010 to 2013, England

	Cancer site 2010 to 2013	Number of incident cases	Incidence rate per 100, 000 population
Upper GI	Ampulla of Vater	1,569	0.74
	Biliary tract cancer (or cholangiocarcinoma or bile duct cancer (intra- or extrahepatic))	7,606	3.58
	Duodenal cancer	1,700	0.80
	Gallbladder cancer	2,714	1.28
	Pancreas	29,892	14.05
	Primary liver (excluding intrahepatic bile duct cancer)	9,902	4.66

All are ***rare*** except pancreas which is ***less common***

Cholangiocarcinoma: a tumour of unmet need?



Liverpool 2009-16

HCC

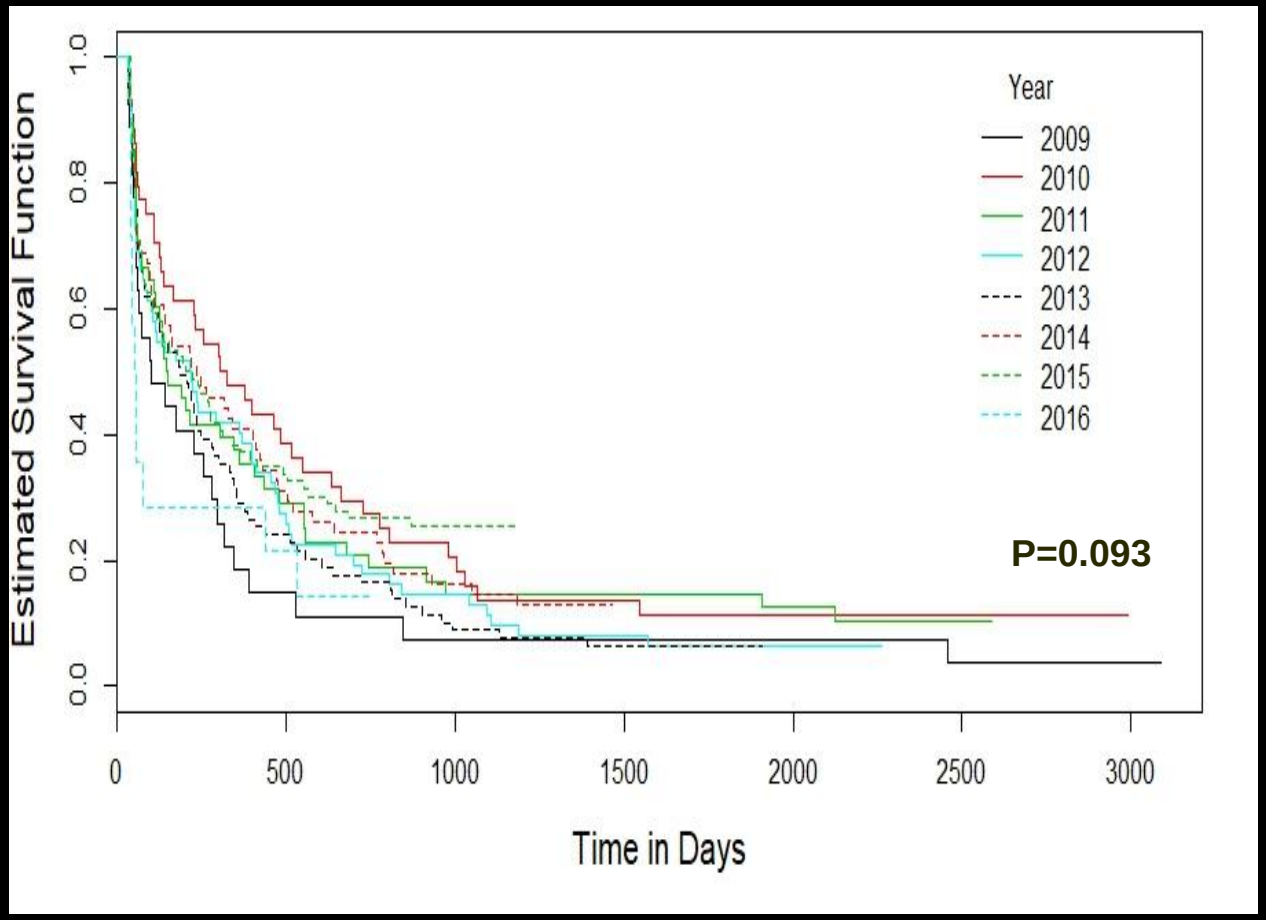
837 patients

Curative intent treatment in 27%

Additional 27% received active intervention: TACE and clinical trials

Best supportive care 46%

Cholangiocarcinoma: a tumour of unmet need?



Liverpool 2009-16

CCA

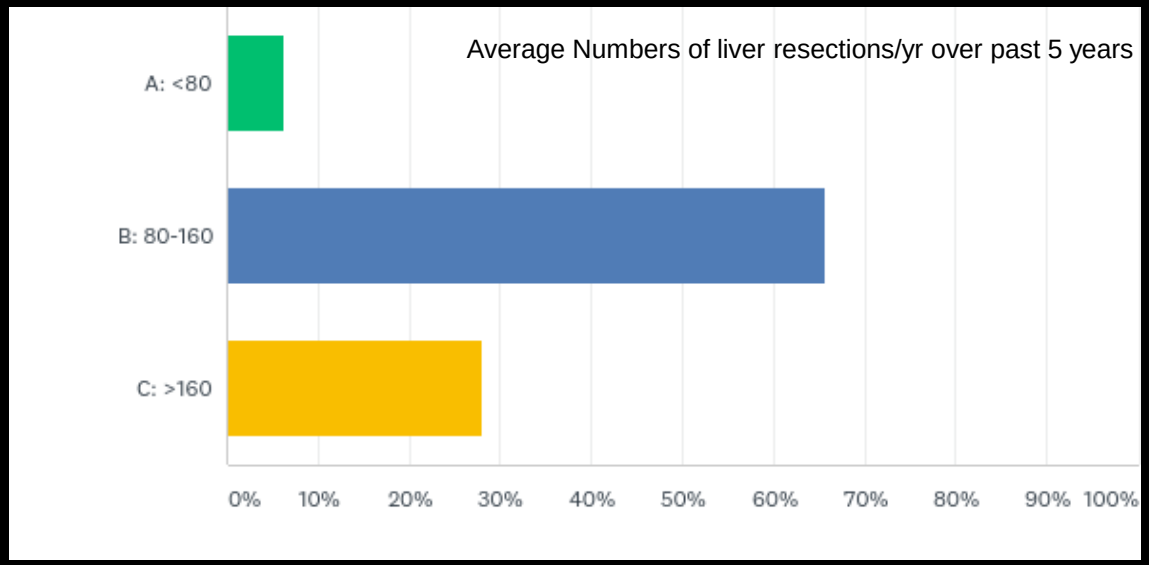
393 hilar CCA patients

Curative intent treatment in 19%

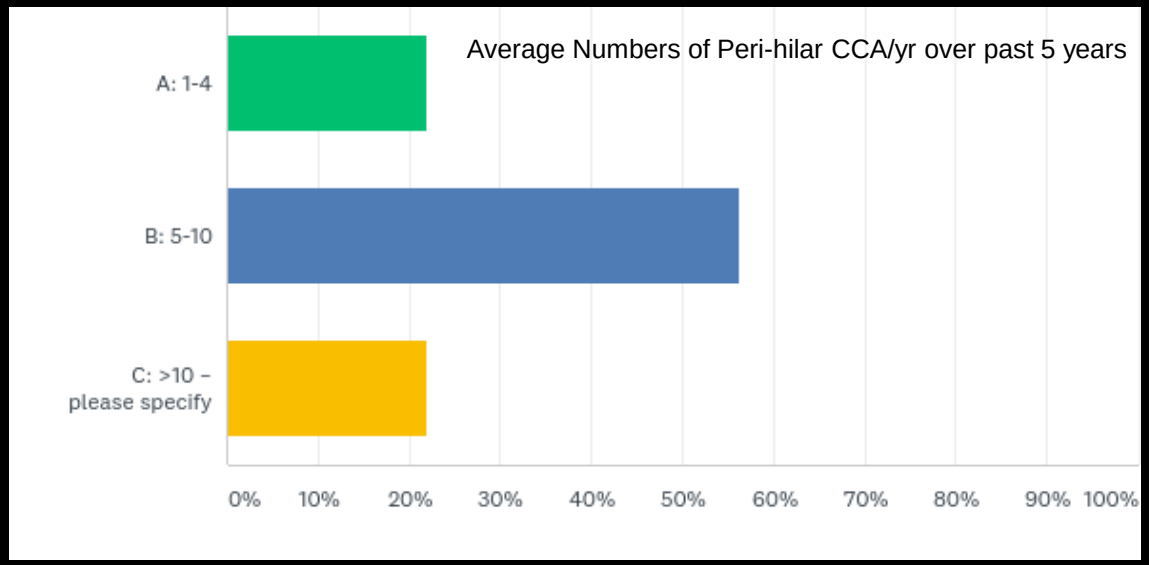
Additional 24% of patients received active intervention:
Palliative chemo with active stent management and clinical trials

57% Best supportive care

Surgical practice across the UK



Surgical practice across the UK



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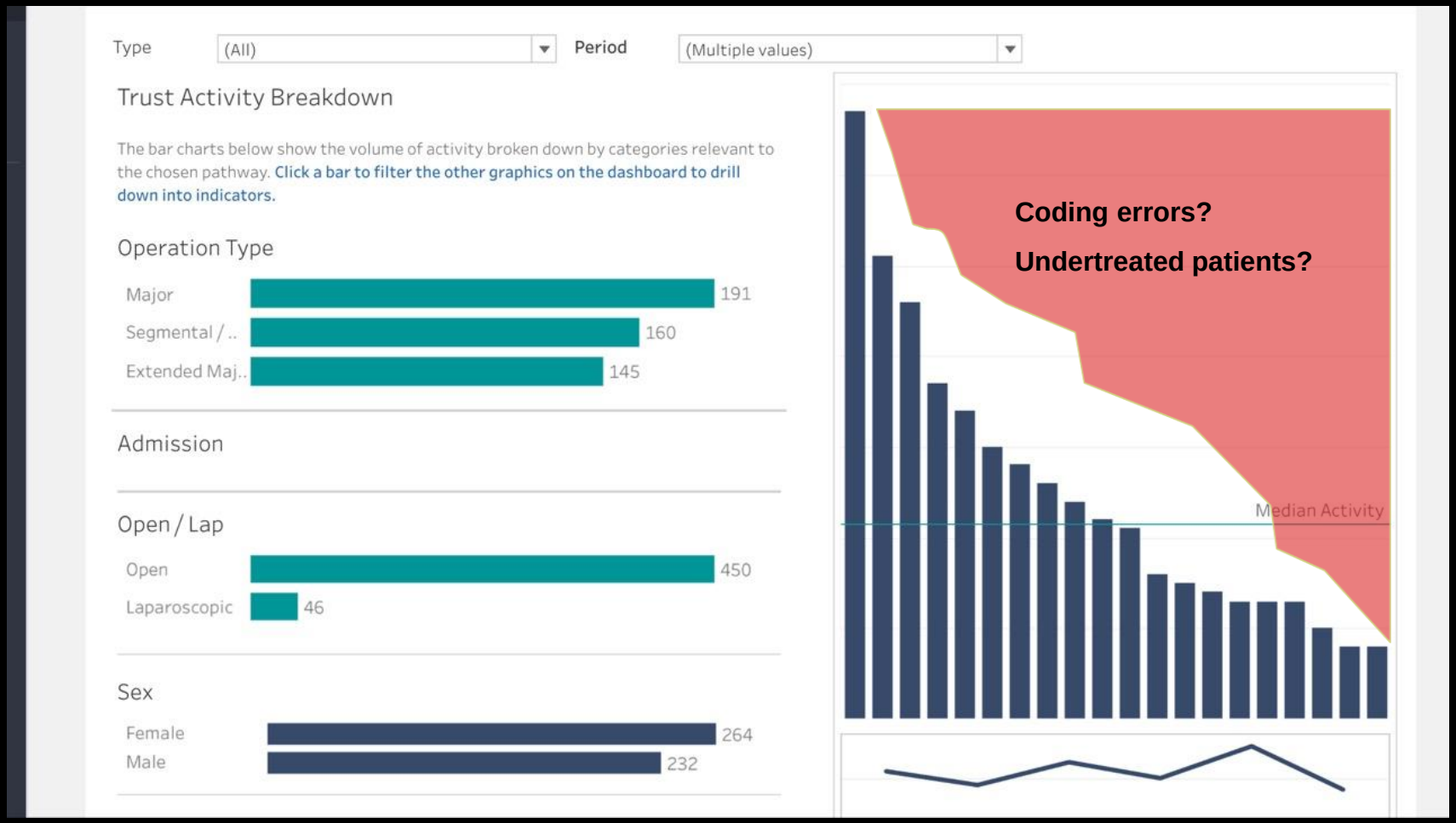
SWORD

- The Surgical Workload Outcomes Audit Database (SWORD)
- Uses Hospital Episode Statistics (HES) and Summary Hospital-level Mortality Indicator (SHMI) to track outcomes for procedures by individual treating hospitals
- Identification of CCA activity challenging as split between liver, bile duct and pancreatic resections

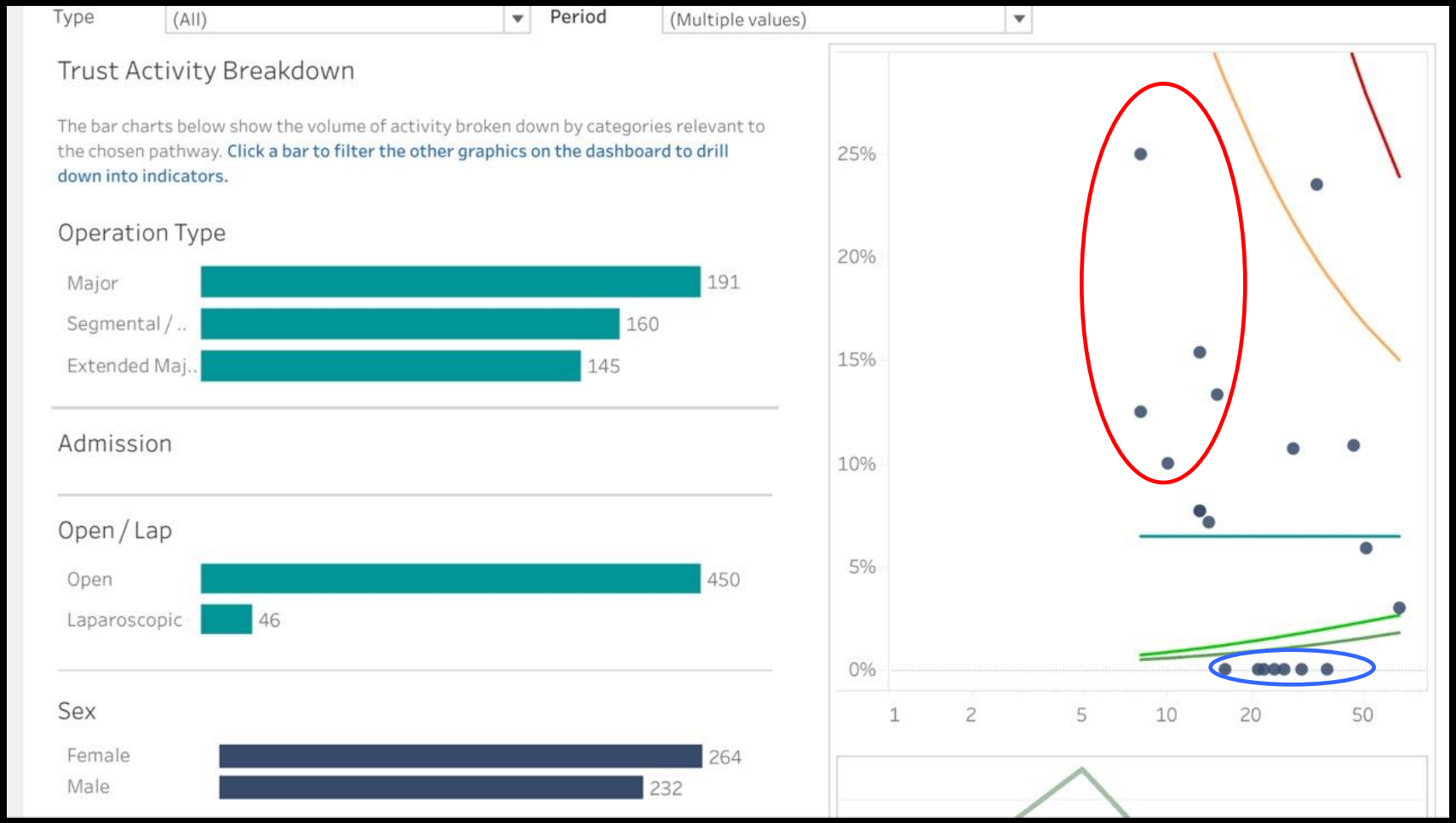
SWORD: 2013-19

CCA liver resection volume by unit

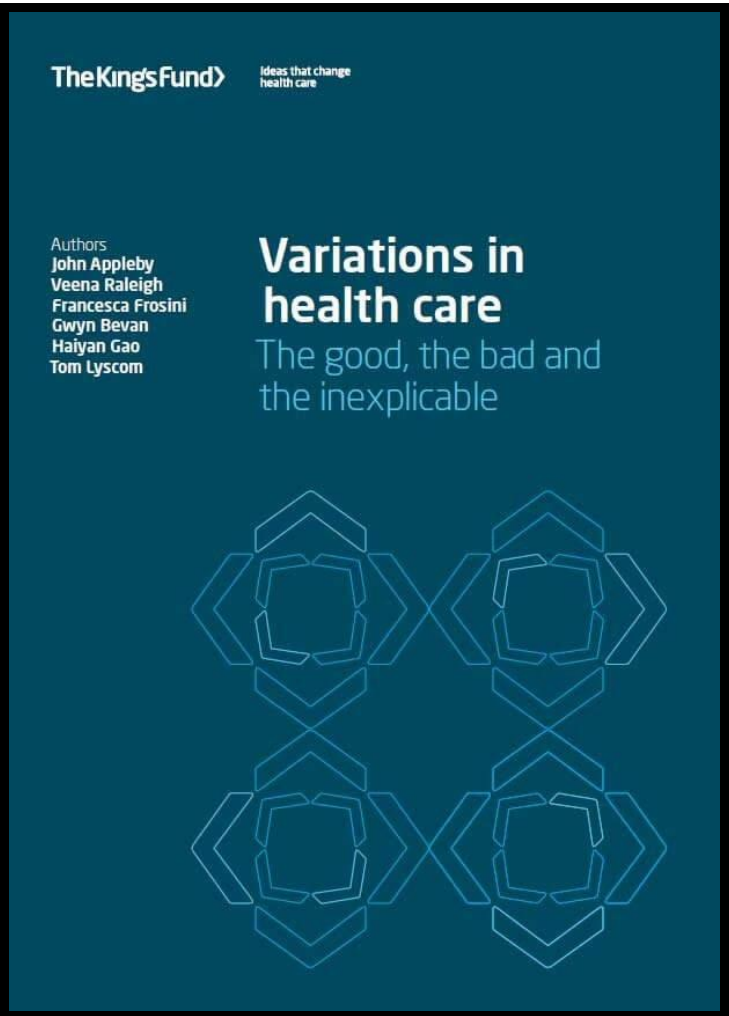


SWORD: 2013-19

In-hospital mortality



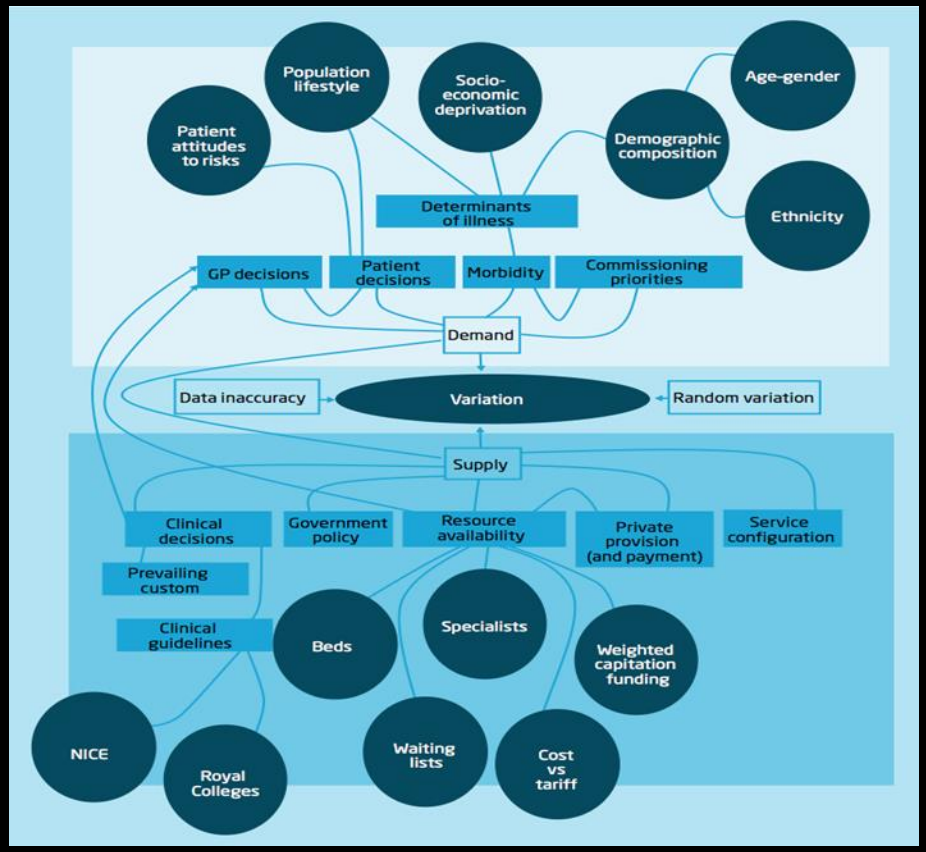
Variation in healthcare



If all variation were bad, solutions would be easy. The difficulty is in reducing the bad variation, which reflects the limits of professional knowledge and failures in its application, while preserving the good variation that makes care patient centred. When we fail, we provide services to patients who don't need or wouldn't choose them while we withhold the same services from people who do or would, generally making far more costly errors of overuse than of underuse.

(Mulley 2010)

Variation in healthcare



Variation in healthcare

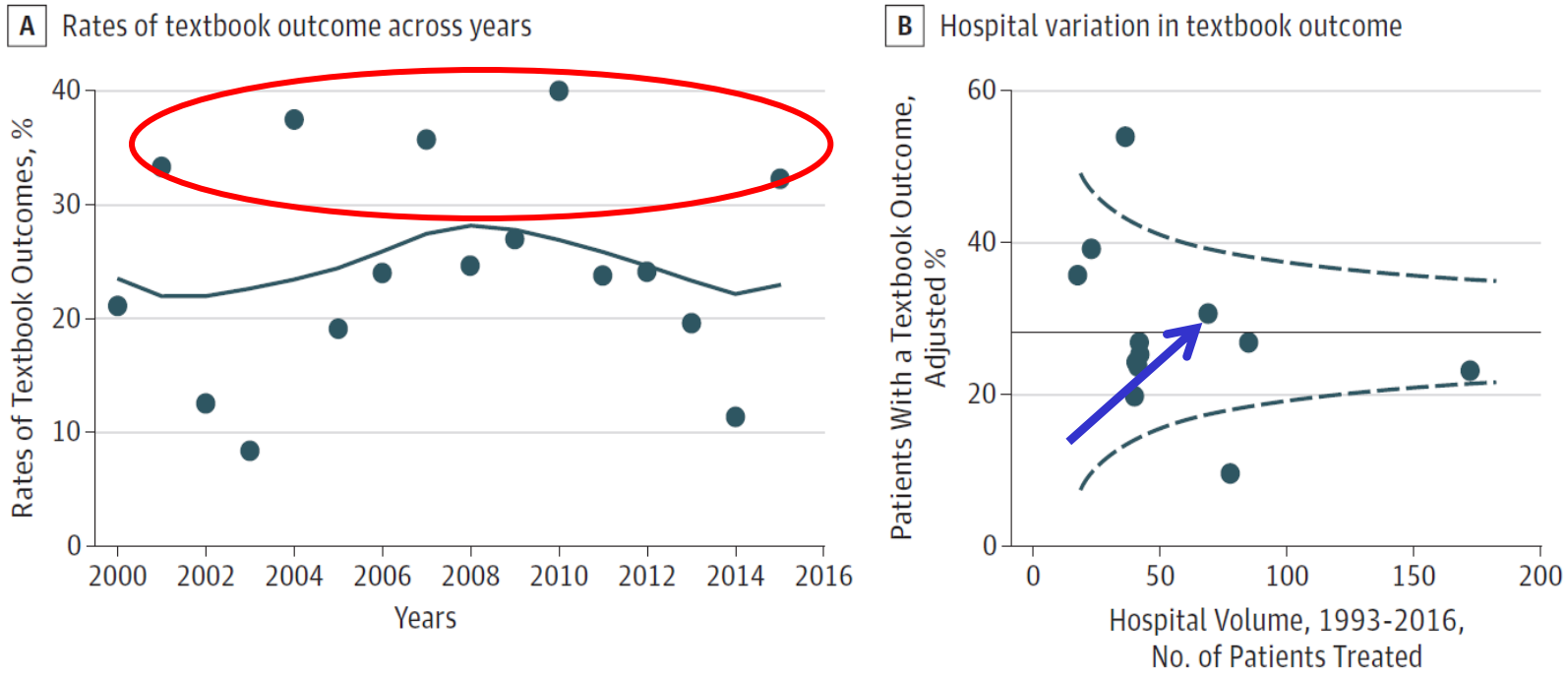
15 major centers in USA, Europe, Australia and Asia.

687 Intra-hepatic CCA resections reviewed

Composite end point of textbook outcome, defined as negative margins, no perioperative transfusion, no postoperative surgical complications, no prolonged length of stay, no 30-day readmissions, and no 30-day mortality

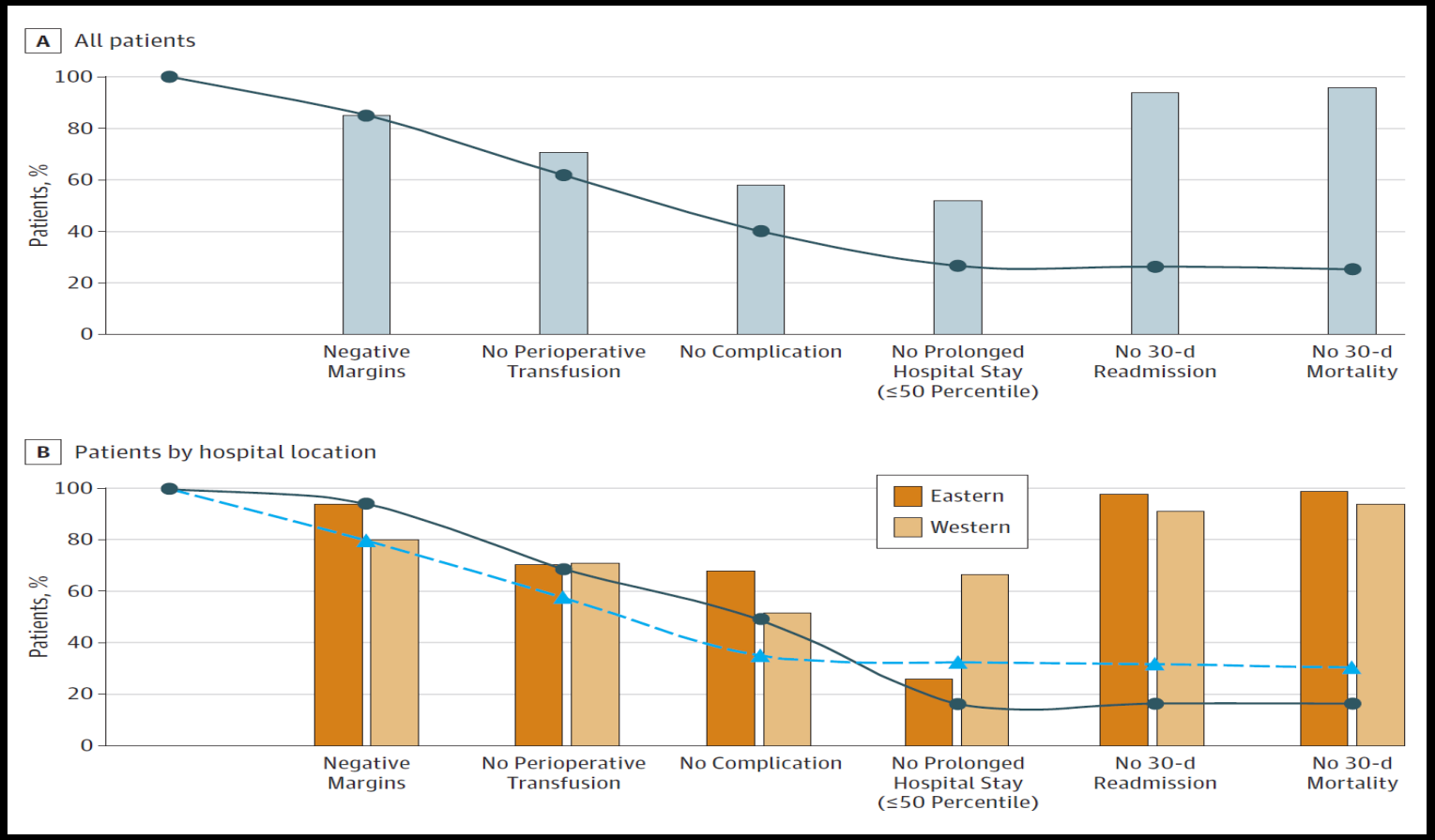
Merath et al JAMA 2019

Variation in healthcare



Merath et al JAMA 2019

Variation in healthcare



Merath et al JAMA 2019

Centres of expertise

Clinical outcomes

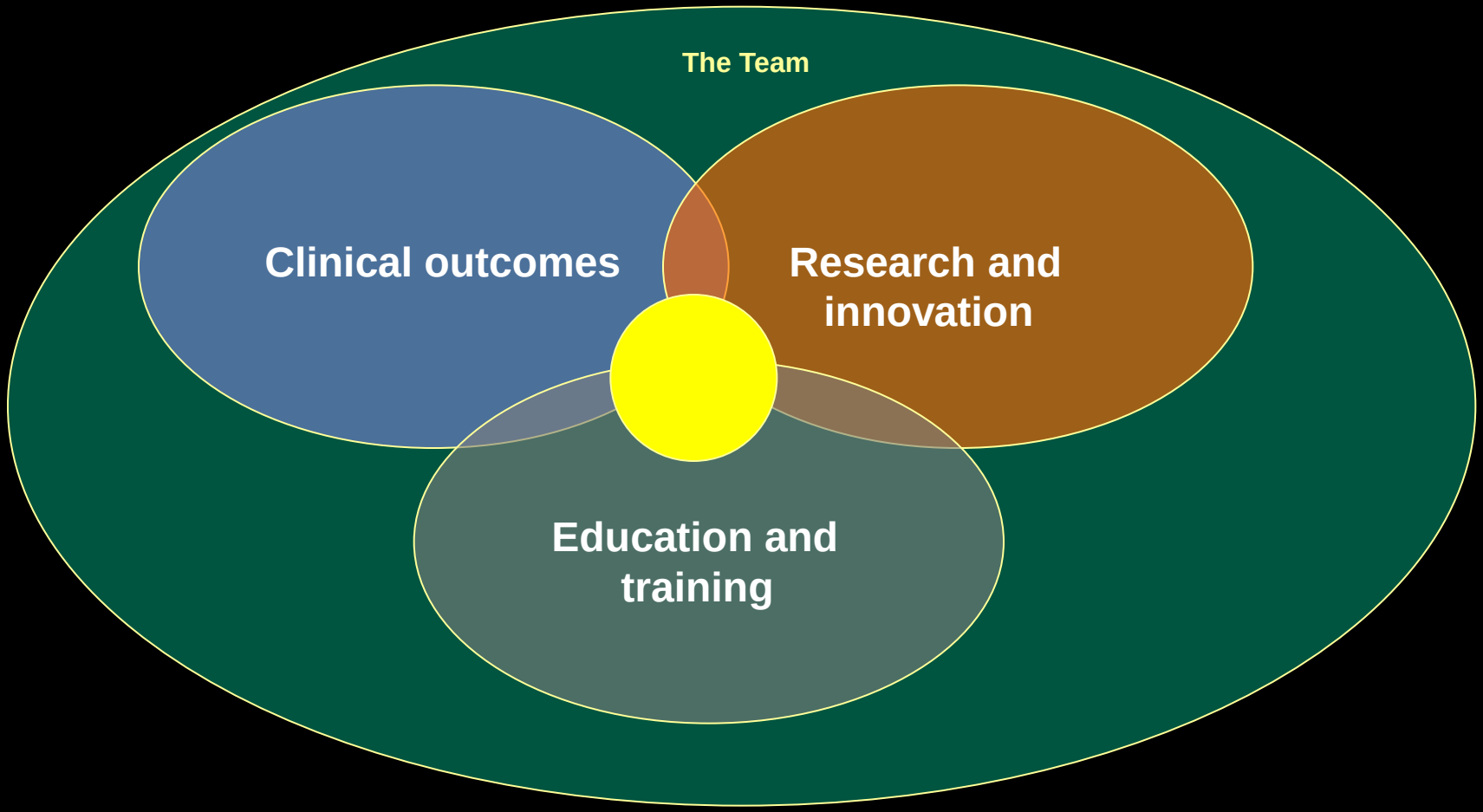
HPB commissioning group NHS England
Quality metrics dashboard 2018/19

28 Quality metrics for HPB Cancer Services

0 refer to Peri-hilar/intra-hepatic Cholangiocarcinoma

https://www.england.nhs.uk/wp-content/uploads/2018/03/hepatobiliary-and-pancreas-metric definitions-2018-19.pdf

Centres of expertise



Liverpool Hepatobiliary Centre

Conclusion

- Cholangiocarcinoma is a rare and aggressive disease
- Radical resection in select patients can achieve long term survival
- Role of transplantation is currently unproven

Liverpool Hepatobiliary Centre

Conclusion

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- **Start the conversation: development of centres of expertise**