Surgical update in Cholangiocarcinoma

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Consultant Hepatobiliary Surgeon
Classification

Intrahepatic
- Peripheral: 5%

Extrahepatic
- Hilar (Klatskin tumour): 65%
- Distal: 30%

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
- 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
- Nihilism in West
Contraindications for resection

- Metastatic disease including distant lymph node spread
- Frail patient
Patient journey
• Cholangiocarcinoma UK survey

• We received 36 responses including most of the surgical centers
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.
• 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
The Multi-Disciplinary Team (MDT) Meeting in Liverpool
The Multi-Disciplinary Team (MDT) across the UK
“The MDT is a Decision Making Machine”
Elements of Decision Making

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

Flin et al (2009)
55yr Male presents with jaundice. CT shows a mass in liver with intra-hepatic biliary dilatation.
Diagnosis and staging

- A: FDG-PET
- B: Staging lap
- C: Liver MRI with contrast
- D: All of the above
- E: Other (please...)

Cholangiocarcinoma UK survey
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
- ERCP
- PTC
- Not required
- Combined procedure
Biliary drainage – What modality is used?

- A: ERCP
- B: PTC
- C: Equal use depending on...
- D: Other (please...)

Cholangiocarcinoma UK survey
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- MRI liver
- MRCP
- Tumour markers
- PET
- Biopsy
- EUS

Node 2:
Treatment of jaundice
- ERCP
- PTC
- Not required
- Combined procedure

MDT input:
- Diagnostic Radiology
- Interventional radiology
- Gastroenterology
- HPB surgeon
- Oncology
Biliary drainage – Is this performed at the tertiary Hepatobiliary centre?

- A: Always
- B: Majority of times
- C: Roughly equal split
- D: Occasionally

Cholangiocarcinoma UK survey
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

MDT input:
- Diagnostic Radiology
- Interventional radiology
- Gastroenterology
- HPB surgeon
- Oncology

Node 2: Treatment of jaundice
- ERCP
- PTC
- Combined procedure
- Not required

Node 3: Decision upon intervention
- Patient choice
- Patient fitness
- Staging laparoscopy*
- Holistic needs
- Liver volume
- Vascular resection
- Palliative chemotherapy
- Targeted treatment
- Clinical trials
- SIRT
- SBRT
- Peri-op chemo
- Surgery

Generating Options based on additional data
Select and Implement an option
Outcome Review
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

Bismuth-Corlette classification of perihilar cholangiocarcinomas

1  2  3A  3B  4
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

<table>
<thead>
<tr>
<th>Label</th>
<th>Side/Location*</th>
<th>Description</th>
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<tbody>
<tr>
<td>Bile duct (B*)</td>
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<td>Common bile duct</td>
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<tr>
<td>B2</td>
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<td>Hepatic duct confluence</td>
</tr>
<tr>
<td>B3</td>
<td>R</td>
<td>Right hepatic duct</td>
</tr>
<tr>
<td>B3</td>
<td>L</td>
<td>Left hepatic duct</td>
</tr>
<tr>
<td>B4</td>
<td></td>
<td>Right and left hepatic duct</td>
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<tr>
<td>Tumor size (T)</td>
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<td></td>
</tr>
<tr>
<td>T1</td>
<td></td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>T2</td>
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<td>1-3 cm</td>
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<tr>
<td>T3</td>
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<td>2-3 cm</td>
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<td>Tumor form (F)</td>
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<td>Sclerosing</td>
<td></td>
<td>Sclerosing (or periductal)</td>
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<td>Mass</td>
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<td>Mass-forming (or nodular)</td>
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<td>Mixed</td>
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<td>Sclerosing and mass-forming</td>
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<td>Polypoid</td>
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<td>Polypoid (or intraductal)</td>
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<td>Involvement (&gt;100°) of the portal vein (PV)</td>
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<td>PV1</td>
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<td>Main portal vein</td>
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<td>PV3</td>
<td>R</td>
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<td>PV4</td>
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<td>Involvement (&gt;100°) of the hepatic artery (HA)</td>
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<td>No arterial involvement</td>
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<tr>
<td>HA1</td>
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<td>Proper hepatic artery</td>
</tr>
<tr>
<td>HA2</td>
<td></td>
<td>Hepatic artery bifurcation</td>
</tr>
<tr>
<td>HA3</td>
<td>R</td>
<td>Right hepatic artery</td>
</tr>
<tr>
<td>HA4</td>
<td>L</td>
<td>Left hepatic artery</td>
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<tr>
<td>Liver remnant volume (Vr)</td>
<td></td>
<td></td>
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<tr>
<td>Vr</td>
<td></td>
<td>No information on the volume needed (liver reactions not foreseen)</td>
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<tr>
<td>V%</td>
<td></td>
<td>Percentage of the total volume of a putative remnant liver after resection</td>
</tr>
<tr>
<td>Nodal disease (N*)</td>
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<td></td>
<td>No nodal node involvement</td>
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<td>N1</td>
<td></td>
<td>HI+ or hepatic artery</td>
</tr>
<tr>
<td>N2</td>
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<td>Peritoneal nodal node involvement</td>
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<td>Metastasis (M*)</td>
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</tr>
<tr>
<td>M0</td>
<td></td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td></td>
<td>Distant metastasis (including liver and peritoneal metastases)</td>
</tr>
</tbody>
</table>

*“R” indicates right, and “L” indicates left.
†Based on the Bismuth classification. **Based on the Japanese Society of Biliary Surgery classification. ††Based on the TNM classification.
Defining resectability

Fig. 4. Anatomical conditions for hepatic resection. A: Portal vein involvement (PV3-L) and (or) main portal vein involvement (PV4). B: The bile duct is involved by the tumor (B3-L). C: The common bile duct is involved (B3-R). D: The main portal vein is involved (PV3-L). E: The right portal vein is involved (PV3). F: The left portal vein is involved (PV4). G: The main hepatic artery is involved (HA1). H: The right hepatic artery is involved (HA2). I: The left hepatic artery is involved (HA3-L). J: The middle hepatic artery is involved (HA3-R). K: The common bile duct is involved (B3-L). L: The main portal vein is involved (PV3-L).
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
ERAS

Pre-admission counseling

Audit

No bowel prep

Carbo load

No premed

No NG

Epidural

Short-acting anesthetics

No fluid overload

Short-lap incision & no drain

Early oral diet

Early removal of lines/catheters

PONV prevention

Avoid opioids

Early mobilization

Normo-thermia

Early removal of lines/catheters

PONV prevention

Avoid opioids

Early mobilization

Normo-thermia
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No NG

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Epidural

Avoid opioids
Short-acting anesthetics

Early mobilization
No fluid overload

Normo-thermia
No fluid overload

Short-lap incision & no drain
No fluid overload
Systematic review of the literature for HPB ERAS programmes

All ERAS series to date exclude CCA
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

6 weeks later

? Radioembolization

6 weeks later
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

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%
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

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

Meta-analysis of 4786 resected peri-hilar cholangiocarcinoma

Bird et al, BJS 2018
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 et 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 Gastroenterological Surgery 2017
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
• 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
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 Radiochemotherapy-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.
Cholangiocarcinoma: A tumour of unmet need?
Cholangiocarcinoma: a tumour of unmet need?

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%

Median survival 1.4 yrs

P<0.001
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

P=0.093
Surgical practice across the UK

Average Numbers of liver resections/yr over past 5 years

- A: <80
- B: 80-160
- C: >160

Cholangiocarcinoma UK survey
Surgical practice across the UK

Average Numbers of Peri-hilar CCA/yr over past 5 years

- A: 1-4
- B: 5-10
- C: >10 - please specify
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

<table>
<thead>
<tr>
<th>Type</th>
<th>Period</th>
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<tbody>
<tr>
<td>(All)</td>
<td>(Multiple values)</td>
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**Trust Activity Breakdown**

The bar charts below show the volume of activity broken down by categories relevant to the chosen pathway. Click a bar to filter the other graphics on the dashboard to drill down into indicators.

### Operation Type

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<tr>
<th>Type</th>
<th>Count</th>
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<td>Major</td>
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### Admission

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### Sex

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<td>264</td>
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<tr>
<td>Male</td>
<td>232</td>
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</table>

**Coding errors?**

**Undertreated patients?**
**SWORD: 2013-19**

**In-hospital mortality**

<table>
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<tr>
<th>Type</th>
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<th>Period</th>
<th>(Multiple values)</th>
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**Open / Lap**

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</tr>
</tbody>
</table>
Variation in healthcare

Variations in health care
The good, the bad and the inexplicable

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

(A) Rates of textbook outcome across years

(B) Hospital variation in textbook outcome

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

Centres of expertise

- Clinical outcomes
- Research and innovation
- Education and training

The Team
Conclusion

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

- Cholangiocarcinoma is a rare and aggressive disease
- Radical resection in select patients can achieve long term survival
- Role of transplantation is currently unproven
- Start the conversation: development of centres of expertise