Monitoring trends in Cholangiocarcinoma
Why Coding is Important

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Cholangiocarcinoma (CCA)

- Malignancy arising in the biliary tree
- Durand-Fardel 1840
- Second commonest primary liver tumour after HCC
- 5-10% all primary liver cancers
- Peak age seventh decade
- Slight male preponderance
- Overall 5 year survival 5%
Worldwide Epidemiology of CCA

Incidence reflects geographical risk factors ("Exposome") & genetic differences.
Cholangiocarcinoma (CCA) sub-types: Intrahepatic/ Perihilar/ Extrahepatic

- **Intrahepatic CCA**: 20–30% arise in intrahepatic ducts, \textit{iCCA}
- **Perihilar CCA**: 50–60% “Perihilar”: arise at bifurcation of main ducts, \textit{pCCA}
- **Extrahepatic CCA**: 10–20% distal CBD, \textit{dCCA}

\textit{pCCA}, \textit{dCCA}, and \textit{iCCA} represent the subtypes of CCA based on their anatomical sites of origin.
ASMR of all parenchymal tumours, HCC, unspecified tumours & intra + extrahepatic CCA, Eng & Wales, 1968-1996 (Men)

Taylor-Robinson et al., Gut 2001
Internationally increasing age standardized mortality rates (ASMR) for intrahepatic CCA in men

Khan et al. J Hepatol 2002
Global mean estimated annual % change (EAPC) in ASMR from
- IHBT (top)
and
- gall bladder + EHBT (bottom)

*Patel, BMC Cancer 2002*
Joinpoint analysis: primary liver cancer (PLC) ASMR in 12 European countries, USA, Japan, Australia, 1990 - 2010

2002 to 2007, PLC rates in European Union fell:
3.9 to 3.6/100,000
0.4%/year in M;
& to 0.8/100,00;
2%/year in F

Intrahepatic CCA ASMR increased 9% in M & F, 1990-2008 to:

1.1/100,000 M
0.75/100,000 F

Highest rates in UK, Germany, and France (1.2–1.5/100,000 M, 0.8–1.1/100,000 F)

International trends in liver cancer incidence rates (men),

Ci5 Database

per 100,000 person-yrs,

age-adjusted to world standard population,


Petrick et al. Int J Ca 2016

Petrick et al. Int J Ca 2016
- HCC and iCCA have some common risk factors, but geographic areas of increasing iCCA rates do not entirely correspond with those of increasing HCC rates

- Likely other potential differences in liver cancer aetiology

Limitations

- Some countries (e.g. China) did not have histology information in Ci5

- Ci5 only histologically classifies microscopically verified tumours, and HCC Dx often radiological (or AFP)

- Little African data - historic lack of inclusion in Ci5
Taiwan

Age-standardized incidence rates of iCCA, eCCA, unspecified CCA;
1998 to 2008

Lee TY et al. Hepatol Int 2013
Intrahepatic CCA rates are increasing

Extrahepatic CCA rates are decreasing

Overall, CCA is increasing

Is it really iCCA that’s increasing? Or pCCA? Or dCCA?

Better diagnosis? Awareness? Coding changes?
Coding of (Peri)Hilar (Klatskin) CCA: Intrahepatic or Extrahepatic?

Hilar/Klatskin CCA are extrahepatic but are not specifically differentiated in routine data

ICD-O-1:
- Klatskin CCA not assigned specific morphology/histology code & could be classed as intra (C22.1) or extrahepatic (C24.0)

ICD-O-2:
- Klatskin CCA given unique histology code, 8162/3, BUT this was cross referenced to topography code for intra- NOT extrahepatic CCA
- ICD-O-2 adopted in USA 1991; Eng & Wales 1995

ICD-O-3:
- Klatskin CCA (8162/3) cross referenced to intra or extrahepatic
- ICD-0-3 adopted in USA 2001; UK 2008

So, perihilar CCA may have been misclassified in ALL versions of ICD-O, esp to intrahepatic during ICD-O2

50-60% of CCA are, pCCA
20-30% are distal CBD, dCCA
10-20% are intrahepatic iCCA
Relative percentages of perihilar (Klatskin) CCA classified as C22.1 (iCCA) or C24.0 (eCCA)/year in England & Wales, 1995-2004. (UK ONS);

ICD-O-2 in use throughout this period

<table>
<thead>
<tr>
<th>Year</th>
<th>C22.1 (IHBD) (%)</th>
<th>C24.0 (EHBD)</th>
</tr>
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<tbody>
<tr>
<td>1995</td>
<td>100%</td>
<td>0%</td>
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<tr>
<td>1996</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>1997</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>1998</td>
<td>92%</td>
<td>8%</td>
</tr>
<tr>
<td>1999</td>
<td>100%</td>
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</tr>
<tr>
<td>2000</td>
<td>86%</td>
<td>14%</td>
</tr>
<tr>
<td>2001</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>2002</td>
<td>91%</td>
<td>9%</td>
</tr>
<tr>
<td>2003</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>2004</td>
<td>86%</td>
<td>14%</td>
</tr>
</tbody>
</table>

SEER database (USA), 1995-2007: ICD-O-2 in use until 2001, then ICD-O-3 adopted

<table>
<thead>
<tr>
<th>Year</th>
<th>C22.1 (IHBD) Total number (%)</th>
<th>C24.0 (EHBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>88%</td>
<td>12%</td>
</tr>
<tr>
<td>1996</td>
<td>92%</td>
<td>8%</td>
</tr>
<tr>
<td>1997</td>
<td>97%</td>
<td>3%</td>
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<tr>
<td>1998</td>
<td>94%</td>
<td>6%</td>
</tr>
<tr>
<td>1999</td>
<td>78%</td>
<td>22%</td>
</tr>
<tr>
<td>2000</td>
<td>88%</td>
<td>12%</td>
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<tr>
<td>2001</td>
<td>45%</td>
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<tr>
<td>2002</td>
<td>62%</td>
<td>38%</td>
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<td>2003</td>
<td>43%</td>
<td>57%</td>
</tr>
<tr>
<td>2004</td>
<td>38%</td>
<td>62%</td>
</tr>
<tr>
<td>2005</td>
<td>48%</td>
<td>52%</td>
</tr>
<tr>
<td>2006</td>
<td>35%</td>
<td>65%</td>
</tr>
<tr>
<td>2007</td>
<td>42%</td>
<td>58%</td>
</tr>
</tbody>
</table>

Khan...& Toledano 2012, J Hepatol
Trends in ASIR for tumours coded to **C22.1 (iCCA) & C24.0 (eCCA) 1990-2007** & when ICD-O-2 & ICD-O-3 were introduced in **USA** (SEER Data)

**Figure 3.**
CCA Epidemiology – problems with the data

- Studies do not differentiate between types of eCCA, namely pCCA, dCCA and GBC
- Most cases present at an advanced stage and differentiating between iCCA and pCCA may be clinically difficult
- ICD editions change every few years and are adopted by countries at different times
- UK Cancer registries reported that if a tumour site is unspecified, most would classify as intrahepatic
CCA Epidemiology – problems with the data

- Study of concordance between cancer registries and the patient register: systematic underreporting of Biliary tract cancers (Kilander 2014)

- Sweden: most liver cancer deaths are classified by the Cancer Register as “unspecified” and hepatocellular carcinoma is likely underreported (Duberg 2017)

- Misclassification between HCC and iCCA may be confounding
  - Not discrete entities/heterogeneity and overlap
CCA Epidemiology – demographic trends that could be impacting the true incidence of Cholangiocarcinoma subtypes

- Rising obesity rates & changing burden of chronic viral hepatitis
  - both recognised risk factors for iCCA AND HCC

- Population migration between different risk areas

- PSC rates?

- Improvements in accuracy and availability of diagnostic tools?
CCA Epidemiology: Conclusions

• We need international consistency in topographical classification of CCA to allow accurate monitoring of epidemiology

• Bile duct cancers should be sub-classified as Intrahepatic, Perihilar or Distal

• These have different epidemiology, pathobiology, clinical presentations and management

• Cholangiocarcinoma/Biliary Tract Cancer trends need to be interpreted with caution

• Data needs to be recorded uniformly and accurately

• The responsibility to do so lies with clinicians > cancer registries

However Cholangiocarcinoma is classified, its incidence seems to be rising. Urgent studies into its causes & effective therapies are needed

AMMF have been at the forefront of driving this for many years
CCA Epidemiology: Ongoing work

National Cancer Registration and Analysis Service (NCRAS)
• run by Public Health England (PHE)

• responsible for cancer registration in England to support cancer epidemiology, public health, service monitoring and research

• information is collected through the process of cancer registration - systematic collection of data about cancers

• collects information on > 300,000 cancer cases, including patient details (inc name, address, age, sex, date of birth)

• & detailed data about the type of cancer, its stage and treatments
CCA Epidemiology: Ongoing work

NCRAS uses a wide range of data sources

- histopathology and haematology services
- medical records
- radiotherapy departments
- hospices
- independent hospitals
- screening services
- death certificates
- GPs
- UK cancer registries

Data from multiple sources matched & merged to build a complete picture of incidence of cancer in England, plus understanding how cancer patients are diagnosed, treated and their outcomes
CCA Epidemiology: Ongoing work

- AMMF, SK, Dr Mireille Toledano (Dept Epidemiology, Imperial College): project proposal to National Cancer Registration & Analysis Service (NCRAS) of Public Health England

Questions:
- Is CCA truly increasing in England? If so, which age groups/gender(s)?
- Which type(s) of CCA is rising/falling?
- Has adoption of new ICD-codes affected incidence rates?
- Is the basis of diagnosis for CCA appropriate?
- Has the route to diagnosis changed over recent years?
- If the rise in CCA is due to better diagnosis, is the stage of disease at time of diagnosis changing?
- Are there regional variations in mortality which might reflect variation in referral practices?
- Are there common co-morbidities in CCA patients and are there regional variations in incidence/case clustering, which may indicate potential underlying risk factors?
CCA Epidemiology: Ongoing work

• We need to have an accurate picture to ensure appropriate resources are allocated to CCA research and management is consistently the best it can be across all areas of the country

• Project proposal accepted by NCRAS

• AMMF to fund an analyst to undertake this project (one year)

• Currently AMMF are working with NCRAS to employ a suitably qualified analyst
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