Retrospective identification of patients with Intrahepatic Cholangiocarcinoma (iCCA) initially diagnosed with Carcinoma of Unknown Primary (CUP)

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Carcinoma of Unknown Primary (CUP)

- **CUP** means there is cancer spread (secondary cancer), but it is **unclear where the cancer started** (primary cancer)
- **2% of all cancer** diagnoses[1] and uses the National Institute for Health & Care Excellence (NICE) CUP Pathway
- Detection of tissue of origin is now a key area of research, and is thought to be possible in 98% of samples[3]
- Studies show that up to 21% of CUP may originate in the biliary tract2, suggesting potential for misdiagnosis of patients with CUP

Intrahepatic cholangiocarcinoma (iCCA)

- Cholangiocarcinoma is a tumour that arises from the biliary tree; classified according to anatomy into 3 types (**Figure 1**)
- Cholangiocarcinoma is the second most common liver malignancy[4], with iCCA being the most common of the 3 types[5]
- Most individuals present with advanced disease[6,7,8] and prognosis is usually poor on presentation
- Diagnosis involves use of Ultrasound, Computerised Tomography (CT) and Magnetic Resonance Imaging (MRI) scanning[9,10,11], with blood and tissue sample markers still a focus of research
- Few patients are suitable for curative surgery, so the current gold standard chemotherapy regimen in the first-line advanced setting is cisplatin and gemcitabine[12]
- **Genomic testing** allows identification of changes such as Isocitrate Dehydrogenase (IDH) mutations and Fibroblast Growth Factor Receptor (FGFR) fusions. Treatments targeting these changes have shown good clinical response in trials, with pemigatinib (an FGFR inhibitor) recently receiving FDA approval for use as a targeted second-line treatment for adults with unresectable advanced cholangiocarcinoma[13]

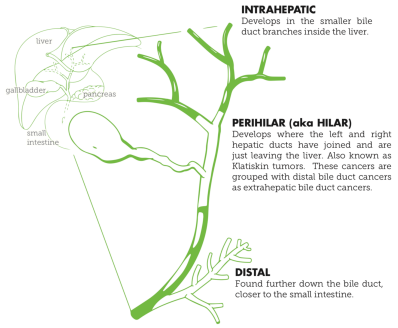

Figure 1. Anatomical classification of cholangiocarcinoma[3]

Study objectives & methods

This study aimed to describe the **frequency of potential iCCA diagnoses within patients with CUP** (both in the whole group and after excluding patients with no disease in the liver)

Methods

- Study registered as Clinical Audit Project at the Christie NHS Foundation Trust (Ref 2515)
- Patients were identified between January 2017 and April 2020 and then classified according to **Figure 2**
- Demographics, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and Multi-Disciplinary Team (MDT) discussions were collected for each patient

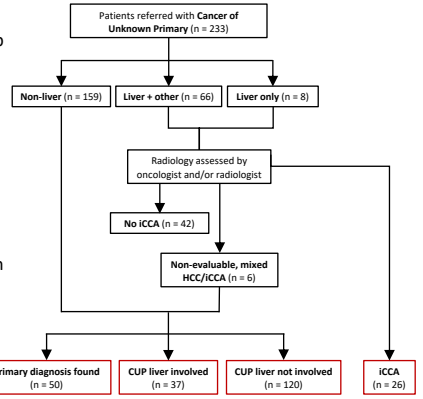

Figure 2. Patient group classification flow diagram

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- Patients with liver involvement (Liver + Other and Liver Only groups) had their radiology reviewed according to the criteria shown in **Table 1**
- Patients with iCCA + Possible iCCA were pooled for detailed pathology analysis and genomic testing

Table 1. Classification of radiological findings

Classification	Definition
Non-Evaluable	No scan available for patient
iCCA	Hypodense liver lesion with irregular margins, rim enhancement, biliary obstruction, capsular retraction or hepatic atrophy (**Figure 3a**)
Non-iCCA	Small lesions within the lobes of liver in keeping with metastatic process (**Figure 3b**)
Possible iCCA	Review equivocal- unable to strictly classify as iCCA or non-iCCA

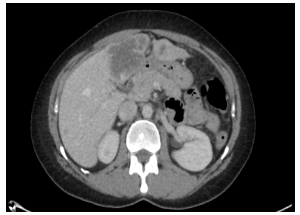

Figure 3a. iCCA; typical appearance with dominant mass-forming lesion and capsular retraction

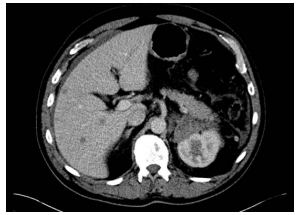

Figure 3b. non-iCCA; multiple liver metastases distributed throughout the liver

Results

- Patient demographics are shown in **Table 2**

Table 2. Comparative demographics between entire group and iCCA group

Demographic	Entire Group (N = 233)	iCCA Group (N = 26)
Age at diagnosis (years)	**Mean:** 68, **Median:** 70 **Range:** 26-93	**Mean:** 63, **Median:** 65 **Range:** 31-79
Gender	**Male:** 51%, **Female:** 49%	**Male:** 23%, **Female:** 77%
ECOG PS ≤2	73%	65%

Key findings

- **iCCA accounts for 11% of entire group** (n = 26/233) and **35% of liver-inclusive patients** (n = 26/74)
- **65% of iCCA patients** demonstrate an ECOG **performance status of ≤2 (Figure 4)**

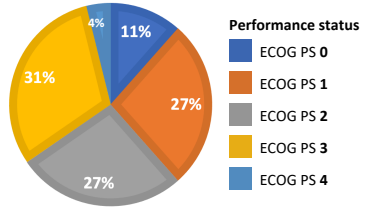

Figure 4. Performance status for iCCA group

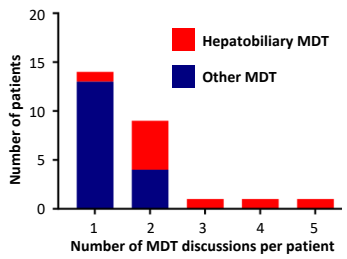

Figure 5. Total MDT discussions for a patient with a focus on Hepatobiliary MDT

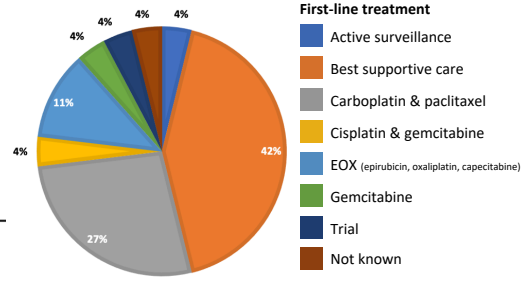

Figure 6. First-line treatment decisions for iCCA group (n = 26)

Multidisciplinary team meeting (MDT) discussions

- Patients were discussed on average (median) at 1 MDT meeting (range 1-5). **Figure 5** demonstrates that 9/26 patients were discussed at a hepatobiliary MDT meeting

iCCA treatment decisions

Figure 6 shows that 50% of patients received chemotherapy. Of these:

- One patient received gold-standard cisplatin-gemcitabine chemotherapy first-line
- 54% received carboplatin paclitaxel regimen

Genomic testing

- Two patients were enrolled in trials involving molecular profiling of tumour tissue; all findings were consistent with common molecular alterations of iCCA: one with IDH-1 mutation and one with FGFR fusion

Conclusions

- **iCCA accounted for 11% of the entire CUP population and 35% of patients with liver-inclusive disease**
- **65%** (n = 17) patients in the iCCA group had **no record of review in a HPB MDT**
- Patients with iCCA were on average **younger and more often female**, which may explain the increased use of carboplatin-paclitaxel therapy in this group
- **65% of the iCCA group had a performance status ≤2 and therefore may have been eligible for treatment** with gold standard **cisplatin-gemcitabine** and other therapies
- Even in the case of a **cancer of unknown primary suspected to be an iCCA**, cisplatin-gemcitabine **can be used in place of other regimens**
- Two patients had mutational analysis performed; all had **molecular alterations commonly seen in iCCA tumours** which are now **potentially targetable with newer therapies** such as FDA-approved **pemigatinib**

Next steps

- **Alterations to the CUP pathway** are proposed to detail an **iCCA-specific subgroup**, provide **guidance in terms of radiology** features for CUP MDT meetings and to **introduce genomic testing as standard** practice for identifying potential therapeutic targets. This should allow for an **improved appreciation of the epidemiology of iCCA**, as well as making care and treatment the **best it can be for these patients**

References; [1]Hainsworth *et al* 2018. ASCO Educational Book, 20, [2]Hainsworth *et al* 2013. J Clin Oncol 31(2), 217, [3]https://cholangiocarcinoma.org/wp-content/uploads/2018/11/2018-Infographic-1.pdf, accessed 08.06.2019, [4]Everhart *et al* 2009. J Gastro 136(4), 1134, [5]Genus *et al* 2019. Ann Oncol 30 (4), 155, [6]Banales *et al* 2016. Nat Rev Gastroenterol Hepatol 13(5), 261, [7]Doherty *et al* 2017. Curr Gastroenterol Rep 19(1), 2, [8]Gibilino *et al* 2017. Eur Rev Med Pharmacol Sci 21, 730, [9]Bridgewater *et al* 2014. J Hepatol 60(6), 1268, [10]Rizvi *et al* 2018. Nat Rev Clin Oncol 15(2), 95, [11]Bartella *et al* 2015. J Gastrointest Liver Dis 24(4), 481, [12]Valle *et al* 2010. N Engl J Med 362(14), 1273, [13]https://investor.incyte.com/news-releases/news-release-details/fda-approves-incytes-pemazyretm-pemigatinib-first-targeted, accessed 14.05.2020