Consideration of a Biliary Tract Cancer diagnosis in liver-involved Cancer of Unknown Primary

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Abstract

Biliary Tract Cancer (BTC) is one of the gastrointestinal (GI) cancers associated with poor outcomes, 80% of patients present with advanced, unresectable disease[1]. Intrahepatic cholangiocarcinoma(CCA), a sub type of BTC is difficult to differentiate pathologically from other tumour types such as pancreatic and upper gastrointestinal (Upper GI) cancers.[2] This potentially leads to misdiagnosis of cancer of unknown primary (CUP).[2,3,4] Establishing the correct diagnosis in these patients if they are BTC, changes the treatment algorithm, which may impact on survival. This study aims to investigate the consideration of BTC in patients with liver-involved CUP.

Introduction

- CUP is defined as a metastatic malignant disease without an identifiable primary despite standardised diagnostic work-up.[5,6]
- Patients usually arrive into the pathway with a diagnosis of provisional CUP (pCUP) and through further diagnostic work-up either have their primary diagnosis elicited or become confirmed CUP (cCUP).[5]
- There are around 8,600 new cases of CUP in the UK every year, which accounts for 2% of all new cancer cases and it is the 6th most common cause of cancer death, with around 9,500 deaths a year.[7]
- Patients diagnosed with confirmed CUP (cCUP) are disadvantaged in many ways such as; absence of standardised referral guidelines, uncertainty around appropriate diagnostic tests, insufficient specialist oncology expertise, inappropriate onwards referral and optimal treatment uncertainty.[5]
- Intrahepatic cholangiocarcinoma (iCCA), a subtype of BTC, is difficult to diagnose and some of these patients will therefore enter the CUP pathway.[2]
- A retrospective study on a single cancer-centre in the UK identified 34% of patients with liver-involved pCUP fulfilled the radiological criteria for an iCCA diagnosis.[2]
- Therefore, consideration of iCCA in those patients with liver involved CUP, could optimise diagnosis of this subtype of BTC and potentially offer management specific to the primary diagnosis. Hence having a better understanding of the journey that patients undergo within the CUP pathway will begin to offer opportunities for improvement.

Method

We spoke to seven CUP Lead oncologists and one CUP research oncologist from eight UK centres of which seven were from academic/ teaching hospitals and one from a district general hospital. Each oncologist undertook an interview with a Medical Science Liaison Manager from October to December 2022 (see fig. 1). Pre-planned questions focused on patient referral routes, CUP multidisciplinary Team (MDT) operations, and their influence on diagnosis and treatment decisions. Their responses were collected on Google Forms and analysed.

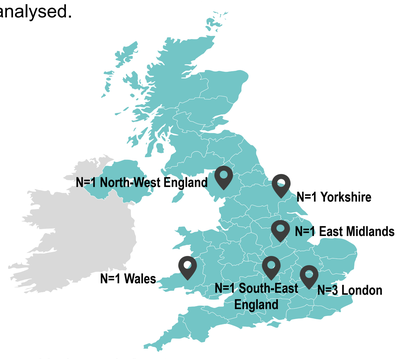

Figure 1 Geographical spread of centres

Results

Referral pathway

- There were two distinct routes identified for patients presenting to the CUP MDT, two centres accept confirmed CUP patients only - referral pathway A, while six accept those with pCUP, conducting further tests before referral to a tumour specific MDT- referral pathway B.
- Five centres noted suspicious liver metastases or single liver lesions as the main reason for referral from the CUP MDT to the Hepato-Pancreato-Biliary Multi-Disciplinary Team (HPB MDT)†.

Experience of CUP lead/members of the CUP MDT

- Seven oncologists acknowledged they were aware of data suggesting BTC misdiagnosis as CUP; five integrate this awareness into their practices.
- Two centres highlighted the importance of a senior pathologist and radiologist at the CUP MDT.
- One CUP lead highlighted that the experience of the CUP lead oncologist in treating BTC was essential in steering the pathologist or radiologist towards considering BTC in their investigations CUP patients.

A sample of the relevant questions asked at interview	Range	Median, (n)
What number/proportion of patients who enter the CUP pathway have their primary cancer successfully identified?	10-60%	34.7%, (4)
What proportion of patients that have their primary confirmed, end up being HCC/BTC?	1-30%	10%, (5)
How long is the typical pCUP patient in the CUP pathway before cCUP or primary diagnosis is made?	2-4weeks	3 weeks, (4)
What proportion of patients entering the CUP pathway via referral into the CUP MDT have multiple liver lesions?	30-36%	37% (4)
What proportion of patients are referred from the CUP MDT to the HPB/ upper GI MDT?	25%	25%, (1)

Table 1: Results given as ranges from the 8 centres
† Reasons patients are referred out of the CUP MDT into the HPB/Upper GI MDT: Suspicious liver metastases by radiology, Distribution of disease is consistent with HCC/ BTC as per histology, Genomic tests consistent with BTC i.e. FGFR2

Discussion

Liver metastases represent the most prevalent manifestation in patients with CUP.[6] Distinguishing between primary BTC subtypes with or without liver metastases and non-liver primary tumours with accompanying liver metastases presents an ongoing challenge. This difficulty complicates the process of directing these patients to the appropriate MDT for site-specific management. While the majority of the centres interviewed confirmed that they refer patients with suspicious liver metastases or solitary liver lesions that are consistent with BTC or HCC as confirmed by imaging or histopathology to the HPB MDT, histological findings can be nonspecific and radiological imaging may be inconclusive. Given that BTC is a rare cancer requiring specialized expertise for accurate diagnosis, prior experience and/or exposure to BTC of the oncologists, pathologists or radiologists could influence the consideration of BTC as a potential primary and subsequent referral to the appropriate MDT. The importance of having a senior pathologist or radiologist at the CUP MDT was noted by two CUP leads who believe their senior level will be reflected on their experience in managing BTC.

Referral decisions are guided by local protocols, NICE[5] and ESMO[6] CUP clinical guidelines. Recent updates to the ESMO CUP clinical guideline have included diagnostic criteria to assist in differentiating CUP with liver metastases from intrahepatic cholangiocarcinoma (iCCA).[6] The interviews for this publication were carried out prior to this ESMO update, however national guidelines remain the same.

Among the interviewed oncologists, seven acknowledged awareness of data suggesting BTC misdiagnosis as CUP, and five confirmed integrating this knowledge into their practice. The other two oncologists who are aware, can't apply this knowledge to their CUP MDT, because this CUP MDT is pathway A where patients who already have a diagnosis of cCUP are referred for management. Notably, these oncologists in referral pathway A also treat BTC and therefore would be part of the MDT where patients with liver involved pCUP are directly referred, therefore their knowledge of this data could still be utilised at their HPB MDT.

The timeframe for diagnosing the primary site or confirming CUP status ranged from 2 to 4 weeks, with significant variability across centres in the proportion of patients whose primary was successfully identified (see Table1). Despite this variability, the overarching goal of the CUP MDT remains to ensure that patients, once diagnosed, are deemed fit for active treatment. This is consistent with NICE clinical guidelines[5], which advise against further investigations for patients deemed unfit for treatment, emphasizing the need to balance diagnostic investigations with treatment initiation timelines.

CUP patients, even after identifying the primary site, experience poorer outcomes compared to those with metastatic known primaries. The reasons for this disparity remain uncertain, with some studies suggesting that dysregulated immunity may contribute to unusual presentations, rendering standard chemotherapy less effective.[6]

Limitations

- There was a wide range for the proportion of patients whose primary was confirmed as BTC or HCC that was seen across centres. This variation is potentially attributed to differences in data collection practices. Direct referrals to the HPB MDT for BTC diagnosis may not be captured in the CUP MDT audit, contributing to lower reported proportions. This could impact the comparability of results across centres.

Conclusion

- If a patient with a BTC remains as cCUP then, if fit, they will receive treatment for CUP which is different to that for BTC.
- One out of eight of the oncologists was not aware of any data suggesting BTC misdiagnosis as CUP. This offers an opportunity for education.
- Since liver metastases are common in CUP patients, adopting the ESMO guidelines could enable timely identification of potential CCA/ BTC diagnosis.
- Analysis of the eight centres indicates two distinct referral routes into the CUP MDT, further exploration is necessary to unpick the different referral routes and the impact on diagnosis and treatment.

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