A Tumour of Uncertain Origin: A Balanced Approach
Kok Hing Lim1, Chen Xiu Fen1, Tan Gek San1, Tony Kiat Hon Lim1.
1Department of Anatomical Pathology, Division of Pathology, Singapore General Hospital, Singapore.

INTRODUCTION
Tumours of uncertain origin are not an uncommon situation in routine pathological practice. This is especially the case in the upper gastrointestinal tract, where adenocarcinomas of different sites often resemble one another by histomorphology and immunohistochemistry. We present an example of such a case, and steps we took to resolve it.

CASE PRESENTATION
A 51 year old Chinese male with a background of alcohol-related cirrhosis and pancreatitis with pancreatic pseudocysts presented with an enlarging segment 4 liver mass. A wedge resection was performed, revealing a 2.5cm tumour, the histology of which was determined at the time to be an intrahepatic cholangiocarcinoma (ICC; Fig 1A). The immunohistochemical profile of the tumour was CK7 positive, with patchy CK20 and CDX2 positivity.

Shortly after, a follow-up positron emission tomography-computerised tomography (PET-CT) scan revealed an area of increased metabolic activity in a pancreatic tail pseudocyst that had otherwise been relatively stable in size on prior follow-up with magnetic resonance imaging (MRI), and thus had never been previously sampled, having been assumed to be benign (there had even been a decrease in its size over the past year, with a reduction in surrounding parenchymal hypoenhancement). Fine needle aspiration (FNA) of this pancreatic lesion was done, with cytological analysis revealing the presence of atypical glandular cells with an immunohistochemical profile similar to that of the liver tumour (Fig 2). A subtotal pancreatectomy was performed, the histology of which confirmed the FNA result (Fig 1B).

Mutational analysis on material from both sites showed a common PTEN gene mutation, namely a T to C substitution in Exon 1 of the translation initiation codon Met1. Following a discussion at a multi-disciplinary team meeting, it was decided to manage the patient as per a pancreatic ductal adenocarcinoma (PDAC), with a metastasis to the liver, rather than vice versa or as synchronous PDAC and ICC.

DISCUSSION
The factors supporting the two tumours as being related include:
1) Both demonstrated identical morphology, with similar architectural and nuclear grades.
2) Both demonstrated a common specific PTEN mutation, and the molecular analysis overall did not reveal any discordancies in terms of mutational profile.
3) Both demonstrated an identical immunohistochemical profile.

The factors supporting the pancreatic tumour as the primary tumour include:
1) The presence of pre-cancerous changes in the pancreas in the form of PanIN (Fig 1B).
2) The pancreatic mass was larger than the liver deposit (3.5cm).
3) While the liver is one of the most common metastatic sites for PDAC (1), ICC metastasising to the pancreas appears to be an exceedingly rare event, with only one definite documented report (2) in our literature search, in which the patient in question also had concurrent lung metastases (no evidence of metastatic disease elsewhere was found in our case).

While none of the above factors would individually be absolutely decisive, altogether their cumulative weight, together with the lack of any clear-cut opposing features, make a convincing argument. This thus highlights the utility of a balanced, multi-disciplinary approach to arrive at the most rational conclusion to a case where an immediate clear-cut solution is not evident. The advent of emerging molecular techniques will be of great aid in facilitating such processes, and their robustness and accuracy will be best tested by incorporating their usage in the multidisciplinary process.

REFERENCES