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ORIGINAL ARTICLE

Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination

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Abstract

Background: Hilar cholangiocarcinoma presents both diagnostic and therapeutic challenges. While establishing a diagnosis is important for patients considering aggressive treatment, a transperitoneal fine needle aspiration (FNA) may lead to seeding of the tumour. The aim of the present study was to determine whether patients who have undergone transperitoneal FNA of the primary tumour have a higher incidence of metastases.

Patients and Methods: Outcomes of 191 patients enrolled in a neoadjuvant chemoradiotherapy followed by liver transplantation (LT) from 1 October 1992 to 1 January 2010 were analysed. The incidence of metastases was compared between those who did or did not undergo a transperitoneal FNA biopsy of the primary tumour.

Results: A total of 16 patients underwent FNA biopsy. There were six patients with biopsies positive for adenocarcinoma and 5/6 (83%) had peritoneal metastases at operative staging. Nine patients had biopsies, which did not demonstrate a tumour, and had no evidence of metastasis. One patient had an equivocal biopsy. Of those who did not undergo a transperitoneal biopsy, the incidence of peritoneal metastasis was 8% (14/175), $P = 0.0097$ vs. positive staging (83%) in those with a diagnostic transperitoneal FNA. Survival at 5 years for those who underwent LT was 74%.

Conclusion: Transperitoneal biopsy of hilar cholangiocarcinoma is associated with a higher rate of peritoneal metastases, and it should not be performed if a curative approach such as LT is available.

Keywords

cholangiocarcinoma < liver, radiological imaging/intervention < cholangiocarcinoma, outcomes < transplant, outcomes < cholangiocarcinoma

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Introduction

Hilar cholangiocarcinoma (CCA) is a malignant neoplasm arising from biliary epithelium which has a poor prognosis. The incidence in the US population is approximately 1.2 in 100 000 although it is much higher in Eastern Europe and Asia, and overall, appears to be increasing.[1–3] Standard therapy for hilar CCA is resection; however, the majority of patients present with unresectable tumours due either to involvement of bilateral hilar structures or the presence of underlying primary sclerosing cholangitis, a primary risk factor for the development of hilar CCA. A protocol for patients with unresectable hilar CCA involving neoadjuvant chemoradiotherapy followed by liver transplantation has been developed and has been demonstrated to be effective, with reported 5-year survival rates of approximately 75%.[4,5]

In spite of advances in therapeutic options, establishing the diagnosis of CCA remains a considerable challenge. The use of imaging modalities such ultrasound, high-resolution computed tomography (CT) and magnetic resonance imaging (MRI) remains the mainstay of CCA diagnosis. While MRI with ferumoxides (Feridex) and magnetic resonance cholangiopancreatography (MRCP) have improved the diagnostic sensitivity and specificity of cross-sectional imaging for both diagnostic and staging purposes,[6–8] as a result of the biological characteristics of the tumour, early definitive radiographic diagnosis remains problematic. Cholangiocarcinoma is a desmoplastic lesion with a tropism for bile which leads to extension along the bile duct rather

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than growth in a radial diameter. While they have a high specificity, endoscopic brushings and biopsies may remain negative even with well-established disease.[9]

Because patients may be candidates for very aggressive therapy including major surgical resection or chemoradiotherapy followed by liver transplantation, the importance of a definitive diagnosis has led some to consider the use of transperitoneal fine-needle aspiration (FNA) either using a percutaneous or transluminal endoscopic ultrasound (EUS)-guided approach.[10–13] While these techniques may improve the diagnostic yield when compared with biopsies and brushing obtained with endoscopic retrograde cholangiopancreatography (ERCP), there are few studies which have directly compared these techniques, as typically, EUS is performed only after ERCP fails to make the diagnosis. In addition, the risk of tumour seeding from exposure of the peritoneum to the needle containing the biopsy specimen is unknown. Tumour seeding from or extension along percutaneous transhepatic cholangiogram (PTC) tracts has been described in several prior reports,[14–16] although the incidence of peritoneal metastasis after transperitoneal biopsies has not been reported. The purpose of the present study was to determine whether patients who have undergone FNA biopsy of hilar CCA either via a percutaneous or transluminal EUS-guided approach are at higher risk of subsequent peritoneal metastasis.

Methods

Clinical data for all patients with hilar CCA enrolled in the liver transplant protocol at the Mayo Clinic Rochester between 1 October 1992 and 1 January 2010 were reviewed. The protocol for combined neoadjuvant chemoradiotherapy followed by liver transplantation (LT) has been previously described.[17,18] Inclusion criteria included the presence of localised, unresectable hilar CCA. All patients are evaluated for potential resectability by an experienced hepatobiliary surgeon and only those with advanced underlying PSC or bilobar involvement that would preclude resection are considered for the neoadjuvant protocol. The diagnosis is established by endoluminal brushing or biopsy obtained at the time of ERCP or PTC. Patients with a malignant appearing dominant stricture and with an associated mass lesion and/or a Ca 19–9 > 100 and/or FISH polysomy are also candidates for enrolment. We do not perform FNA biopsies at our centre because of the risk, thus all patients with a FNA biopsy had this performed at an outside facility. Exclusion criteria are attempted resection with violation of the tumour plane, prior malignancy within 5 years, or prior abdominal radiation. After neoadjuvant therapy and before LT all patients underwent a staging laparotomy which involved abdominal exploration with routine biopsy of perihilar lymph nodes as well as any lymph nodes or nodules suspicious for tumour. Only patients with negative staging operations remained eligible for transplantation.

During the study period, 191 patients enrolled in the LT protocol were analysed. The incidence of metastatic disease found at operative staging was compared between those who underwent a transperitoneal FNA biopsy of the primary tumour vs. those who did not undergo an FNA biopsy. The site of disease metastasis within the groups was also compared. In addition, the incidence of disease recurrence after LT was assessed. Results were compared using Fisher's exact test. Five-year survival for patients enrolled in the combined neoadjuvant chemoradiotherapy followed by LT was determined by Kaplan–Meier analysis.

Results

Of the 191 patients enrolled in the neoadjuvant chemoradiotherapy followed by LT protocol, a total of 16 underwent transperitoneal FNA biopsy of the primary tumour (13 percutaneous and 3 EUS). Six patients had a biopsy of the primary tumour which was positive for adenocarcinoma and nine patients with hilar CCA underwent transperitoneal biopsies which did not demonstrate a tumour. One additional patient had equivocal findings on his trans-peritoneal biopsy ('glandular cells'). He also developed peritoneal metastasis demonstrated on staging, but he is not included in the analysis in the FNA (+) group as a result of his equivocal biopsy result. The demographics of the groups were similar (see Table 1). In particular, the time from enrolment to staging was similar in those who underwent a positive or non-diagnostic FNA biopsy as well as those without an FNA biopsy. Additionally, there were no identifiable differences between the tumour characteristics such as the presenting Ca 19-9 level, the frequency of a mass or size of a mass lesion when present or the histology. Information such as tumour differentiation or perineural invasion was not known at enrolment given the limited amount of diagnostic tissue.

Of the six patients whose biopsies demonstrated malignancy, 5/6 (83%) were found to have disease spread directly into the peritoneum at operative staging, whereas the remaining patient had a negative staging operation but died in the peri-operative period of technical complications related to transplantation (see Table 2). All nine patients with transperitoneal biopsies which did not demonstrate a tumour underwent negative operative staging and underwent subsequent LT, with one death from recurrent CCA and one death from post-transplant lymphoproliferative disorder (PTLD) in this group.

Of the remaining 175 patients who did not undergo transperitoneal biopsy, the incidence of peritoneal metastasis at operative staging was 8% (14/175), $P = 0.0097$ vs. those found at operative staging with metastatic disease in those with a positive percutaneous FNA by Ficher's exact test. Overall there were 36 patients with staging demonstrating metastatic disease of which 14 had had peritoneal metastasis, 14 had lymph node metastasis, 4 had direct extension and 4 had intra-hepatic metastasis.

Outcomes for patients who underwent LT after neoadjuvant treatment for hilar CCA during this time period demonstrated a

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Table 1 Demographics for patients enrolled in a protocol for chemoradiotherapy followed by liver transplantation (LT) for hilar cholangiocarcinoma (CCA) from 1993 to January 2010

	No biopsy	Positive transperitoneal biopsy	Negative transperitoneal biopsy
Number of patients	175	6	9
Mean age	50 (SD ± 10.8, range 26–69)	57 (±9.9, range 39–69)	55 (±6.27, range 44–67)
Gender male/female	121 : 54	5 : 1	8 : 1
PSC	70	1	4
Mass lesion present	63 (36%)	1 (16%)	6 (66%)
Mean size of mass, if present	2.9 cm (1.0–4.9 cm)	3.9 cm	2.1 (1.4–3.1)
Ca 19-9 at presentation	Mean 878 (0–28,750)	293 (118–522)	519.9 (4–2840)
Positive/suspicious histology by endoscopic brushing/biopsy	128 (73%)	Brushing not performed (FNA biopsy+)	4 (44%)
Interval from enrolment to staging (days)	Median 92 (–39[a]–408) Mean 121.3	Median 76 (54–249) Mean 121	Median 89 (77–366) Mean 150

P = NS for demographics, tumour characteristics and interval from enrolment to staging.
[a]Negative value as a result of staging performed before enrolment in two cases.

Table 2 Incidence of peritoneal metastasis in patients who underwent a diagnostic transperitoneal fine needle aspiration (FNA) biopsy of hilar cholangiocarcinoma (CCA)

	No biopsy	Positive transperitoneal biopsy	Negative transperitoneal biopsy
Peritoneal metastasis at staging	14/175 (8%)	5/6 (83%)[a]	0/9

[a]*P* = 0.0001 using Fisher's exact test.

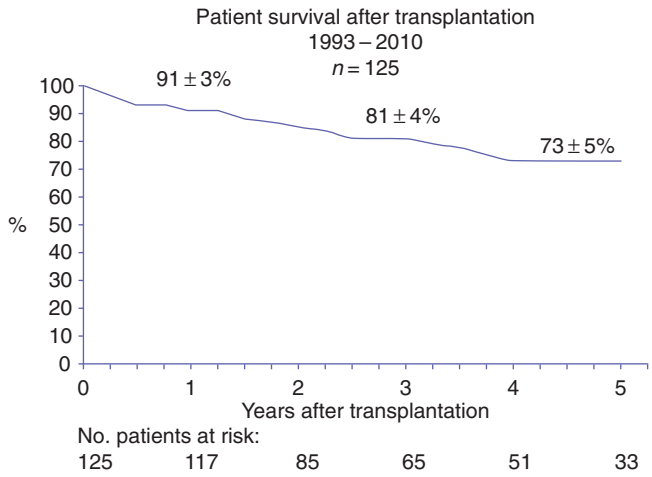

Figure 1 Outcomes for patients who undergo neoadjuvant chemoradiotherapy followed by liver transplantation (LT) for hilar cholangiocarcinoma (CCA)

5-year survival of 73% using Kaplan–Meier analysis (see Fig. 1). There were 125 patients who underwent LT during this period, with 17 patients who died of recurrent disease and an additional 12 who died of other causes.

Discussion

Establishing the diagnosis of hilar CCA is particularly challenging because of the biological characteristics of the disease including tumour location, pauci-cellular nature and longitudinal rather than radial growth pattern. Percutaneous biopsy and, more recently, transluminal endoscopic biopsy via EUS guidance both have been proposed as procedures which may improve the diagnostic sensitivity. The current analysis demonstrates a markedly higher incidence of peritoneal metastasis in patients who undergo percutaneous or *trans*-luminal endoscopic FNA biopsy of hilar CCA, when compared with those who did not undergo a transperitoneal approach. Given the interval from enrolment to staging and identifiable tumour characteristics were similar in all groups, this difference does not appear to be related to more aggressive or advanced tumours in those with a diagnostic FNA biopsy.

The benefits of a definitive tissue diagnosis go beyond a prognostic role when potentially curative but highly invasive therapy is available. While hilar cholangiocarcinoma is associated with poor survival overall, 5-year survival for patients who are candidates for surgical resection ranges from 20–40%, depending on the stage of the tumour.[19–24] More recently, neoadjuvant chemoradiotherapy followed by liver transplantation has proved beneficial for those with unresectable hilar lesions (those who are not candidates for surgical resection either because of bilobar involvement or underlying liver disease) with a 5-year survival approaching 75%. Resection and in particular neoadjuvant chemoradiotherapy followed by LT are associated with significant morbidity. An additional consideration for patients being considered for LT is the extreme shortage of available organs. The implications for undergoing non-beneficial highly invasive therapy, or missing a potentially curable yet highly lethal malignancy, are considerable. Thus, the motivation to expand our current diagnostic capabilities is clear.

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The use of percutaneous or more recently trans-luminal biopsies using EUS guidance have been described as a way to improve the diagnostic yield. A recent report by Fritscher-Ravens *et al.* on EUS-guided FNA of hilar lesions found a definitive diagnosis in 43/44 of patients with hilar strictures which were suspicious, but not diagnostic of hilar CCA.[10] In this series, 31/44 patients were found to have malignancy whereas 12 were found to have benign disease (4 of which were later found on clinical or autopsy follow-up to have been malignant.) The authors reported the results changed the pre-planned management in about half of the cases. A second prospective study of 24 patients with suspected hilar CCA who underwent EUS-guided FNA found a sensitivity of 77%, specificity of 100% and a negative predictive value of 29%.[11] In addition to the potential to falsely conclude a benign diagnosis when a malignancy exists, the primary concern with this approach is the potential for disease metastasis to the peritoneum as a result of seeding of tumour cells along the needle tract.

Peritoneal seeding after trans-peritoneal biopsy of hilar CCA either by percutaneous methods or trans-luminal endoscopic methods has thus far not been reported. However, peritoneal spread of hilar CCA after percutaneous biliary drainage has been reported in multiple case series. A recent case series of 67 patients with hilar CCA found the incidence of PTC site seeding to be 6%.[15] Additionally, peritoneal seeding of hepatocellular carcinoma after percutaneous FNA or core needle biopsy has also been reported.[25–28] A recent meta-analysis by Silva *et al.* which is worth highlighting analysed eight published series and determined the risk of needle-tract seeding of HCC to be 2.7%.[27] Although the incidence of needle-tract seeding appears to be low, the general recommendation is to avoid pre-operative percutaneous drainage of the biliary tree unless it is necessary to relieve obstructive jaundice, and to avoid biopsy of potential HCC due to the risk of complications such a tumour seeding or bleeding and because the diagnosis can typically be established by radiographic criteria.

The present study demonstrates a high rate of peritoneal metastasis (83%) in patients who underwent percutaneous or trans-luminal FNA biopsy of the primary hilar tumour mass. Although the overall numbers of patients undergoing *trans*-peritoneal FNA biopsy is small ($n = 6$), all were candidates for a potentially curative therapy. The rate of disease metastasis in those who did not undergo a percutaneous FNA biopsy was low (20% overall, with an 11% incidence of peritoneal metastasis.) A primary weakness of the present study is that patients were non-randomised, although there were no remarkable demographic differences between the groups. The present study is also limited by the retrospective nature; however, it is unlikely that a prospective randomised controlled trial comparing transperitoneal FNA biopsy with other diagnostic methods could be performed. This is because of the relative infrequency of this diagnosis, as well as the high mortality for patients not eligible for potentially curable therapy which would make it difficult to demonstrate peritoneal seeding as patients may succumb before this becoming clinically evident.

The incidence of peritoneal seeding of hilar CCA in the current analysis appears higher than that reported after PTC for hilar CCA and also higher than that after FNA for HCC. The reasons for this are unknown. The amount of peritoneal exposure for FNA biopsy for CCA may be greater than of the peritoneal exposure for PTC or HCC as in both of the later cases the liver is adjacent to the abdominal wall which limits peritoneal exposure. It may also be that after chemoradiotherapy, patients are more susceptible to peritoneal spread because of relative immunosuppression or other changes to the peritoneal surfaces, although this seems unlikely as the transperitoneal biopsy preceded the neoadjuvant therapy by weeks to months in all cases.

Neoadjuvant chemoradiotherapy followed by liver transplantation offers excellent survival benefit for patients with early stage yet unresectable disease. Patients with resectable disease have 5-year survival rates which are approximately 20–40% depending on the stage of disease. Based on the current analysis, the risk of peritoneal seeding is prohibitively high and therefore percutaneous or trans-luminal endoscopic FNA of hilar CCA should be avoided in patients who may be candidates for potentially curative therapies.

Conflict of interests

None declared.

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