

Malignant mediastinal lymphadenopathy detected by endoscopic ultrasound and guided fine needle aspiration in patients with resectable pancreaticobiliary cancer

Praveer Rai¹ · Vinod Kumar¹ · Ram Naval Rao²

Received: 19 October 2016 / Accepted: 24 April 2017 / Published online: 29 May 2017
© Indian Society of Gastroenterology 2017

Abstract

Background Resection surgery for pancreaticobiliary malignancies carries significant morbidity and mortality. Hence, preoperative assessment to exclude unresectable disease is mandatory. CT abdomen is the primary modality for staging of pancreaticobiliary cancers. However, some patients have malignant mediastinal lymphadenopathy (MML), which may be detected on endoscopic ultrasound (EUS) but not on CT scan. **Methods** We prospectively evaluated 75 consecutive patients (median age 54 years: 44 men) with a diagnosis of resectable pancreaticobiliary cancer (carcinoma gallbladder, carcinoma pancreas, cholangiocarcinoma, or periampullary carcinoma) for the presence of MML using EUS by an experienced endosonographer. If a lymph node had one or more features suggestive of malignancy, i.e. size exceeding 1 cm, hypoechoic appearance, a round shape, and regular margins, it was subjected to EUS-FNA.

Results In seven (9.3%; 95% confidence intervals: 3.8% to 18.2%) of the 75 patients, EUS revealed enlarged mediastinal lymph nodes. The location of these lymph nodes was subcarinal in three, paraesophageal in two, and paratracheal in one patient; another patient had lymph nodes at two sites, i.e. the subcarinal and aortopulmonary window. In four of these seven patients, FNA documented the presence of MML. The overall rate of pathologically proven MML was 4/75 (5.3%; 95% CI [1.4% to 13%]).

Conclusion EUS-FNA diagnosed MML in 5.3% of patients with pancreaticobiliary cancer. It may be useful to consider EUS assessment in patients with otherwise resectable pancreaticobiliary malignancy.

Keywords EUS-FNA · Malignant mediastinal lymph nodes · Pancreaticobiliary cancer

Introduction

The term “pancreaticobiliary cancers” includes cancers of various parts of the biliary tree, i.e. the gallbladder, bile duct, and surrounding structures such as the pancreas and ampulla of Vater. Among patients with cancers of the biliary tree, lymph node involvement is common and only a small proportion of patients have resectable disease [1]. In patients with resectable disease, surgery is the mainstay of treatment but carries significant morbidity and mortality [2].

In patients with pancreaticobiliary cancers, surgery is beneficial only if R0 resection is achieved [3–5]. Hence, in these, preoperative staging is extremely important. The presence of malignant mediastinal lymphadenopathy (MML) would preclude surgery. Hence, there is a need to identify MML in patients considered to have resectable disease by CT angiography. Endoscopic ultrasound (EUS) is highly sensitive and specific to determine MML and is relatively noninvasive; hence, it is well suited for this purpose [6–10].

Some studies have looked at the role of EUS of the mediastinum in the detection of MML in patients with pancreaticobiliary malignancies. In a study by Hahn and Faigel, mediastinal lymph nodes were positive for malignancy in 6.1% of patients with pancreaticobiliary masses, i.e. masses arising from cancers of the pancreas, bile duct, or gallbladder. More specifically, these were present in 7.0% of masses of pancreatic origin, the

✉ Praveer Rai
praveer_rai@yahoo.com

¹ Department of Gastroenterology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226 014, India

² Department of Pathology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226 014, India

most common type of pancreatobiliary masses among their patients [11].

Agarwal et al. retrospectively reviewed the presence of MML at EUS-guided FNA (EUS-FNA) in consecutive patients with pancreatobiliary cancer and found it in 5% of their patients. Based on this, they recommended that staging EUS for pancreatobiliary malignancy should also include assessment of the mediastinum [12].

All the available studies on MML are from Western countries, where pancreatic malignancy is more common. There have been no studies on MML in pancreatobiliary cancers from Asia and, in particular, India, where a large proportion of pancreatobiliary malignancy is carcinoma gallbladder. We thus looked for the presence of MML in our patients with pancreatobiliary cancer.

Methods

This was a prospective, cross-sectional study in which 75 consecutive adult patients with pancreatobiliary malignancy whose disease was considered to be resectable at computed tomography (CT) angiography of the abdomen were included. The diagnosis of malignancy was based on typical clinical picture, imaging features on CT, and, where possible, by fine needle aspiration cytology, endoscopic biopsy, or endobiliary biopsy. These patients underwent EUS by an experienced endosonographer (PR) between February 2014 and February 2016 to look for mediastinal lymphadenopathy. Pregnant women, patients who declined to give consent, and those at high risk for sedation as judged by the anesthesiologist were excluded. A CT scan of the mediastinum had not been done in any of the patients.

For EUS, a curved linear scanning echoendoscope with frequencies of 7.5–10 MHz was used. Representative digital images were captured and archived for subsequent review. If a lymph node had one or more features suggestive of malignancy, i.e. size exceeding 1 cm, hypoechoic appearance, a round shape, and regular margins, it was subjected to FNA. Multiple (up to seven) needle passes were made using a 22-gauge FNA needle until adequate material was obtained as assessed by an on-site pathologist.

The study was approved by our institution's ethics committee. Statistical analysis was performed using SPSS software, version 21. For proportions, 95% confidence intervals were calculated using a binomial exact method.

Results

During the study period, we enrolled 78 patients. Three patients were subsequently excluded (denied consent: one, high risk for anesthesia: two). Thus, finally, 75 patients (31 women,

44 men) with resectable pancreatobiliary cancer were included. The clinical characteristics and investigation data for these patients are shown in Table 1. Twenty-eight patients (37.3%) had periampullary carcinoma, 19 (25.3%) had carcinoma gallbladder, 17 (22.7%) had carcinoma pancreas, and 11 (14.7%) had cholangiocarcinoma.

On CT, five patients had paraaortic abdominal lymph nodes and one patient had inter-aortocaval lymph nodes which were smaller than 1 cm in diameter. In all these patients, FNA from the abdominal lymph nodes was negative for malignancy.

On EUS, seven patients had mediastinal lymph nodes with imaging features suggestive of malignancy. Of these, three had subcarinal lymph nodes, two had paraesophageal lymph nodes, and one had paratracheal nodes. An additional patient had suspicious lymph nodes at two locations (subcarinal and aortopulmonary window) (Table 2). All these seven patients underwent EUS-guided FNA from mediastinal lymph nodes.

In four of seven patients with suspicious malignant mediastinal lymph nodes, FNA documented a malignancy (5.3%; 95% CI [1.4% to 13%]). Of the four patients who had MML, two had periampullary carcinoma, one had gallbladder carcinoma, and one had pancreatic carcinoma. Two of the 11 patients with cholangiocarcinoma had suspicious mediastinal lymph nodes on EUS, which tested negative for malignancy on FNA (Table 3).

Overall, EUS detected enlarged mediastinal lymph nodes in 9.3% (95% CI [3.8%, 18.2%]) of our patients with

Table 1 Characteristics of study subjects

Characteristics	Patients (n=75)
Men, number (%)	44 (58.6)
Median age, (range)	54 (30–72)
Jaundice, number (%)	58 (77)
Pain abdomen, number (%)	58 (77)
Fever, number (%)	45 (60)
Site of cancer ^a	
Periampullary	28 (37.3)
Gallbladder	19 (25.3)
Pancreas	17 (22.7)
Bile duct	11 (14.7)
Laboratory values ^b	
Total bilirubin (mg/dL)	10±9.3
Direct bilirubin (mg/dL)	6.6±6.1
SGOT (U/L)	98.6±77.1
SGPT (U/L)	79.3±77.9
Alkaline phosphatase (U/L)	420±371
Prothrombin time (international normalized ratio)	1.18±0.3

^a Data are shown as number (%)

^b Laboratory data are shown as mean±standard deviation

Table 2 Mediastinal lymphadenopathy identified by endosonography in patients with pancreaticobiliary cancer

Mediastinal lymph node group	Number
Subcarinal	3
Paraesophageal	2
Paratracheal	1
Subcarinal and subaortic (aortopulmonary window)	1

resectable pancreaticobiliary malignancy, and FNA confirmed the presence of MML in 5.3% (95% CI [1.4%, 13%]) of patients.

Discussion

In this prospective study of 75 patients with resectable pancreaticobiliary cancer who underwent EUS examination, we found that seven (9.3%) patients had mediastinal lymph nodes on EUS that were suspicious for malignant infiltration using the morphologic criteria, and four of these patients had positive cytology on EUS-FNA. Our study subjects included 28 (37.3%) patients with periampullary carcinoma, 19 (25.3%) with carcinoma gallbladder, 17 (23%) with carcinoma pancreas, and 11 (14.7%) with cholangiocarcinoma. MML was roughly equally distributed among the patients with cancers of different sites.

Some previous studies have assessed the frequency of involvement of mediastinal lymph nodes in patients with biliary neoplasms, using EUS. In an initial study, Fritscher-Ravens et al. found metastasis in mediastinal lymph nodes in one of 153 patients with pancreatic cancer [13]. Thereafter, Hahn and Faigel found enlarged mediastinal lymph nodes suspicious for malignancy in 11 of their

Table 3 Location of the primary tumor, location of the enlarged mediastinal lymph nodes, and results of fine needle aspiration in patients with enlarged mediastinal lymph nodes

No.	Location of primary tumor	Location of lymph node	FNA result for malignancy
1	Periampullary	Paraesophageal	Positive
2	Periampullary	Subcarinal	Positive
3	Periampullary	Subcarinal	Negative
4	Periampullary	Paraesophageal	Negative
5	Gallbladder	Subaortic (aortopulmonary window)	Positive
6	Pancreas	Paratracheal	Positive
7	Cholangiocarcinoma	Subcarinal	Negative

FNA fine needle aspiration

66 patients (16.6%: 95% CI [7.7%, 25.6%]) with pancreatobiliary masses (57 pancreatic; 5 ampullary; 4 cholangiocarcinoma), including four patients (6.1%: 95% CI [0.3%, 11.9%]) in whom EUS-guided FNA revealed metastatic adenocarcinoma [11]. However, only 38 of their 66 patients had biopsy-proven adenocarcinoma; thus, it is possible that some of their remaining patients had a nonmalignant disease and that their study underestimated the frequency of MML. Also, their study did not include any patient with gallbladder carcinoma. In another study, Agarwal et al. retrospectively reviewed the data from their 160 patients with pancreatic cancer and found mediastinal lymph nodes with morphologic features suspicious for malignancy in 14 patients [12]. On FNA of mediastinal lymph nodes, metastatic disease was found in eight (5%: 95% CI [2%, 8%]) patients, including one who had distant metastases at another site on CT and/or positron emission tomography.

Our study differs from the previous studies in having a different profile of pancreaticobiliary cancers, in that the study included many patients with gallbladder cancer. However, despite this difference, the prevalence of MML in our patients was similar to that reported in the previous studies.

Preoperative identification of MML using EUS-FNA in patients with pancreaticobiliary cancer may be useful, since it helps obviate unnecessary surgery. In recent years, advances in surgical techniques and preoperative chemoradiation have made it possible to undertake resection of pancreatic tumors with early venous involvement [14–16]. Thus, now, a larger proportion of patients with locally advanced tumors are considered for potentially curative treatments. The presence of malignant mediastinal lymph nodes carries a prognostic implication similar to that of distant metastases, and hence, constitutes a disqualification for resection surgery. Besides the inherent medical advantages, such an approach also has major financial implications, particularly for the patients in developing countries.

It may be argued that one could assess the mediastinum using CT. There are no data to compare the utility of CT and EUS in detecting MML. Also, EUS could particularly be useful in patients who may not be candidates for CT, e.g. in pregnancy and in persons with contrast allergy. Also, in our practice, many patients have had pancreaticobiliary cancers diagnosed at abdominal CT; in them, chest CT would mean another procedure, which may be avoided by EUS.

In our study, as per the usual practice, chest CT was not done which is a limitation. Thus, it cannot answer the question whether prior chest CT can help select patients in whom EUS-FNA is more likely to be useful and to avoid EUS in others.

To conclude, our study confirms the finding that EUS-FNA detects MML in a small percentage of patients with pancreaticobiliary (including gallbladder) cancers who are being considered for resection surgery.

Compliance with ethical standards

Conflict of interest PR, VK, and RNR declare that they have no conflict of interest.

Ethics statement The authors affirm that the study was performed in a manner complying with the Helsinki Declaration of 1975, as revised in 2000 and 2008 concerning Human and Animal Rights, and that the authors followed the policy concerning Informed Consent as shown in Springer.com.

References

- Lazcano-Ponce EC, Miquel JF, Muñoz N, et al. Epidemiology and molecular pathology of gallbladder cancer. *CA Cancer J Clin*. 2001;51:349–64.
- Sperti C, Pasquali C, Piccoli A, Pedrazzoli S. Survival after resection for ductal adenocarcinoma of pancreas. *Br J Surg*. 1996;83:625–31.
- Bouvet M, Gamagami RA, Gilpin E, et al. Factors influencing survival after resection for periampullary neoplasms. *Am J Surg*. 2000;180:13–7.
- Nitecki SS, Sarr MG, Colby TV, Heerden JAV. Long term survival after resection for ductal adenocarcinoma of the pancreas. *Ann Surg*. 1995;221:59–66.
- Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas. *Ann Surg*. 1996;221:721–33.
- Chang KJ, Nguyen P, Erikson RA, Durbin TE, Katz KD. The clinical utility of endoscopic ultrasound-guided FNA in the diagnosis and staging of pancreatic carcinoma. *Gastrointest Endosc*. 1997;45:387–93.
- Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology*. 1997;112:1087–95.
- Faigel DO, Ginsberg GG, Bentz JS, Gupta PK, Smith DB, Kochman ML. Endoscopic ultrasound-guided real-time fine-needle aspiration biopsy of the pancreas in cancer patients with pancreatic lesions. *J Clin Oncol*. 1997;15:1439–43.
- Buscail L, Pages P, Berthelemy P, Fourtanier G, Frexinos J, Escourrou J. Role of EUS in the management of pancreatic and ampullary carcinoma: a prospective study assessing resectability and prognosis. *Gastrointest Endosc*. 1999;50:34–40.
- Gress FG, Hawes RH, Savides TJ, et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center experience. *Gastrointest Endosc*. 1999;50:786–91.
- Hahn M, Faigel DO. Frequency of mediastinal lymph node metastases in patients undergoing EUS of pancreatico-biliary masses. *Gastrointest Endosc*. 2001;54:331–5.
- Agarwal B, Gogia S, Eloubeidi MA, Correa AM, Ho L, Collins BT. Malignant mediastinal lymphadenopathy detected by staging EUS in patients with pancreaticobiliary cancer. *Gastrointest Endosc*. 2005;61:849–53.
- Fritscher-Ravens A, Sriram PVJ, Bobrowski C, et al. Mediastinal lymphadenopathy in patients with or without previous malignancy. EUS-FNA based differential cytodagnosis in 153 patients. *Am J Gastroenterol*. 2000;95:2278–84.
- Bold RJ, Charnsangavej C, Cleary KR, et al. Major vascular resection as part of the pancreatoduodenectomy for cancer: radiologic, intraoperative and pathologic analysis. *J Gastrointest Surg*. 1999;3:233–43.
- Leach SD, Lee JE, Charnsangavej C, et al. Survival following pancreatoduodenectomy with resection of the superior mesenteric-portal vein confluence for adenocarcinoma of the pancreatic head. *Br J Surg*. 1998;85:611–7.
- Evans DB. Preoperative chemoradiation for resectable and locally advanced adenocarcinoma of the pancreas. *J Gastrointest Surg*. 2001;5:2–5.