DOI:10.1111/j.1477-2574.2010.00254.x HPB

ORIGINAL ARTICLE

Endoscopic ultrasound may be unnecessary in the preoperative evaluation of intraductal papillary mucinous neoplasm

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Abstract

Objectives: Several imaging modalities are commonly performed during work-up of intraductal papillary mucinous neoplasm (IPMN), but guidelines do not suggest any one technique. The aim of this study was to evaluate tumour and duct measurements by computed tomography (CT) and endoscopic ultrasound (EUS) and their ability to predict high-grade dysplasia (HGD) and cancer within pancreatic IPMN.

Methods: Patients with IPMN who underwent preoperative CT and EUS between 2001 and 2009 were selected. Data were gathered retrospectively from medical records.

Results: The study group was comprised of 52 patients, 33% (17/52) of whom had HGD or cancer. On fine needle aspirate (FNA), neither carcinoembryonic antigen (CEA) >200 nor cytological analysis correlated with malignancy. In multivariate analysis, duct size ≥1.0 cm ($P = 0.034$) was a significant predictor of HGD or cancer, and diameter on CT scan ($P = 0.056$) approached significance. Lesion diameter of ≥ 2.5 cm on CT scan identified malignancy in 71% (12/17) of patients ($P = 0.037$). When analysed, all patients with HGD or cancer had a lesion diameter ≥2.5 cm and/or a duct diameter ≥1.0 cm by CT scan.

Conclusions: The use of radiographic criteria on CT including lesion size ≥2.5 cm and/or pancreatic duct diameter ≥1.0 cm appears to reliably identify patients with either HGD or invasive cancer. High-resolution CT scanning may obviate the need for EUS and FNA in patients with suspected IPMN.

Keywords

intraductal papillary mucinous neoplasm, endoscopic ultrasound, computed tomography, malignancy, pancreas

Received 26 April 2010; accepted 19 September 2010

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Introduction

Pancreatic resection remains a complex and potentially morbid operation which is associated with overall rates of in-hospital mortality and perioperative complications as high as 6.5% and 35.6%, respectively.[1,2] Appropriate patient selection remains paramount in surgical decision making. Unlike other surgical diseases of the pancreas, the definitive preoperative diagnosis of malignant intraductal papillary mucinous neoplasm (IPMN) remains elusive in diagnostic testing. While some patients continue to undergo pancreatic resection for benign disease, an unknown number remain under clinical observation and are harbouring malignancy. Computed tomography (CT), used broadly as an initial diagnostic imaging technique, was not useful for distinguishing benign from malignant disease until the advent of multidetector scanning technology.[3] Endoscopic ultrasound (EUS) has substantially improved diagnostic accuracy and staging in a number of gastrointestinal malignancies, including oesophageal and rectal cancer.[4–7] This modality has also been applied in IPMN in efforts to improve the determination of benign vs. malignant disease.[8–13] However, a growing body of evidence suggests the sensitivity and accuracy of EUS in the preoperative diagnosis of malignant IPMN are low.[3,14–16]

The published international consensus guidelines for the management of IPMN[17] suggest resection of IPMN if it is main duct type or if it is branch duct type with a lesion size of ≥3.0 cm, or if symptoms, mural nodules or positive cytology are present.

This paper was presented at the International Hepato-Pancreato-Biliary Association Meeting, 18–22 April 2010, Buenos Aires, Argentina.

However, these guidelines do not suggest any particular imaging modality. A year after these guidelines were published, a study from the Mayo Clinic demonstrated that no malignancies were missed using these criteria, but only 15% of patients who underwent resection had cancer.[18] This suggests that there is room for improvement in patient selection as many patients undergo resection for benign disease. The current study aims to examine the accuracy of preoperative diagnostic techniques in patients with a histopathological diagnosis of IPMN with high-grade dysplasia (HGD) or invasive cancer, specifically focusing on the utility of CT and EUS.

Materials and methods

The Oregon Health & Science University Institutional Review Board approved this study. All patients with a surgical pathology specimen demonstrating IPMN and dated between January 2001 and July 2009 were identified. Data were then gathered from their electronic medical records in a retrospective fashion. Information was collected on demographics, presentation, work-up, procedures, pathology, hospital course and longterm follow-up. Sixty patients were initially identified, but, for reasons including incomplete work-up and evaluation, eight were eliminated. The remaining 52 patients were evaluated using SPSS PASW Version 18 (SPSS, Inc., Chicago, IL, USA) statistical software for means and frequencies. Contingency tables were constructed to look at the correlation between individual tumour and patient characteristics including HGD, invasive cancer, carcinoembryonic antigen (CEA) value, gender, symptoms, size of tumour on both CT and EUS, and size of main pancreatic duct on CT. Because IPMN is felt to represent a disease progression along the adenoma–carcinoma continuum, HGD was included with the invasive cancer group for analysis as both HGD and invasive cancer are indications for resection. Associations between variables were assessed using chi-squared and Fisher's exact tests as appropriate. Further analysis was conducted with a multivariate logistic regression model in an attempt to isolate characteristics that were independently predictive of HGD or invasive cancer. We also looked at gender, age, duct size ≥1.0 cm and the maximum diameter of the lesions using CT and EUS measurements. Computed tomography scans were performed using a high-resolution, multi-detector 16- or 64-row scanner.

Results

Fifty-two patients were identified, slightly more of whom (54%, $n = 28$) were female. Their average age was 65 years. Final pathology revealed that six (12%) patients had HGD and 11 (21%) had invasive cancer. A total of 25% (13/52) had pancreatic duct dilation of ≥1.0 cm as measured on the CT scan.

Endoscopic ultrasound with fine needle aspiration (FNA) was performed in all but two patients, allowing for the comparison of cytological findings. In lesions identified in final pathology as IPMNs, the FNA detected mucin in only 32 (64%). Among the 17 patients with HGD or invasive cancer, cytology was read as 'negative' in five, as 'positive' in another five, and 'atypical' in seven. One 'positive' result referred to a patient who was found not to have HGD or invasive cancer on final pathology, and 12 of 19 patients with 'atypical' cells did not have HGD or invasive cancer. Levels of CEA were measured in the cyst fluid in 26 patients. Ten of the 26 had a CEA value >200, but only two of these patients had HGD or invasive cancer. Table 1 shows positive and negative predictive values of EUS FNA for HGD or invasive cancer.

The diameters of the lesion and duct were also evaluated. Numerical measurements of the lesion were obtained by both EUS and CT in 47 of the 52 patients. The maximum diameter of the lesion measured larger on EUS than on CT in 34 of the 47 patients. The accuracy of measurement criteria was compared with the chi-squared test for diameters of both 2.5 cm and 3.0 cm. Applying a CT scan diameter of ≥2.5 cm identified 12 of 17 patients with HGD or invasive cancer ($P = 0.037$), compared with nine of 17 when using a CT scan diameter of ≥3.0 cm ($P = 0.118$). Applying an EUS diameter of ≥2.5 cm identified 12 of the 17 cases ($P = 0.346$), and using an EUS diameter of ≥3.0 cm identified 10 ($P = 0.032$). In a multivariate model, the maximum diameter as a continuous variable on CT approached significance as a predictor of HGD or invasive cancer ($P = 0.056$) (Table 2). The addition of the diameter in EUS did not help in predicting HGD or invasive cancer. Next we evaluated the duct size by CT scan. Thirteen ducts were found to be ≥1.0 cm in diameter and eight of these 13 came from patients with HGD or invasive cancer. On multivariate analysis, duct size ≥1.0 cm was found to be an independent predictor of HGD or invasive cancer ($P = 0.034$) (Table 3). The positive and negative predictive values of duct size ≥1.0 cm, as well as lesion size ≥2.5 cm, were calculated individually. We then combined the two CT measurement criteria and calculated predictive values using the criteria of duct size ≥1.0 cm or lesion size ≥2.5 cm and found the negative predictive value to

Table 1 Endoscopic ultrasound with fine needle aspiration: positive (PPV) and negative (NPV) predictive values for malignancy

	PPV	NPV
Positive cytology	83%	72%
Negative cytology	21%	52%
Mucin	30%	58%
CEA > 200	20%	75%

Table 2 Multivariate logistic regression model with diameter as a continuous variable

Variable	OR	95% CI	*P*-value
CT lesion diameter (continuous)	1.44	0.99–2.094	0.056
Female gender	0.28	0.072–1.107	0.070
Age	0.99	0.923–1.073	0.892

OR, odds ratio; 95% CI, 95% confidence interval; CT, computed tomography

Table 3 Multivariate logistic regression model with a dichotomized diameter of ≥2.5 cm

Variable	OR	95% CI	*P*-value
CT duct ≥ 1.0 cm	27.2	1.28–580	0.034
CT lesion ≥ 2.5 cm	3.00	0.32–28.3	0.338
Age	0.92	0.80–1.07	0.279
Female gender	2.72	0.21–34.8	0.442

OR, odds ratio; 95% CI, 95% confidence interval; CT, computed tomography

Table 4 Positive and negative predictive values for malignancy using duct size, lesion size and the combination

CT criteria	PPV	NPV
Duct ≥ 1.0 cm	62%	90%
Lesion ≥ 2.5 cm	48%	80%
Duct ≥ 1.0 cm or lesion ≥ 2.5 cm	52%	100%

CT, computed tomography; PPV, positive predictive value; NPV, negative predictive value; CT, computed tomography

be 100% (Table 4). Of the 52 patients in our cohort, 17 had HGD or invasive cancer, and all 17 would have been resected using CT guidelines of lesion diameter ≥2.5 cm or duct size ≥1.0 cm.

Discussion

There remains great uncertainty about the accurate identification of malignancy arising in IPMN. The purpose of this study was to evaluate the two primary preoperative imaging techniques used at this institution and their ability to predict HGD or invasive cancer. In patients with pathology-proven IPMN, measurements obtained with CT were smaller than those obtained with EUS, and FNA cytological information was not helpful when differentiating malignant from benign lesions. The use of CT criteria of lesion size ≥2.5 cm or duct size ≥1.0 cm would have resulted in the resection of all cases of IPMN with HGD or invasive cancer.

When to operate in IPMN has been the topic of a multitude of papers.[19–27] Most agree that main duct lesions should be removed, but there are varying criteria for what differentiates main from branch duct lesions. The international consensus guidelines state that dilation of the main duct ≥1.0 cm strongly suggests main duct IPMN.[17] Bassi *et al.* asserts that main duct IPMN is characterized by involvement of the duct of Wirsung, dilated to >1.0 cm in diameter.[28] Several other studies impose a cut-off at 5 mm or 6 mm.[22,29,30] To determine when to resect the branch duct type, they include other characteristics such as lesion size, with the cut-off in the range of 3.0–4.0 cm,[17,22,25,31,32] presence of mural nodules,[9,17] and protrusion of the nodule.[3,33] Although the criteria and risk for future malignancy in main and branch duct IPMN differ, the focus of the present study was to evaluate duct and lesion characteristics of IPMN as a whole that might predict the presence of HGD or invasive cancer at the time of patient encounter with non-invasive imaging. Simplifying the criteria might help clinicians to decide whether or not to resect and help them to counsel patients on the risk that cancer or HGD is present in their IPMN.

The primary imaging modality for the initial detection of pancreatic lesions is CT scan.[11] Whether this is the most appropriate diagnostic modality is a current topic of debate.[3,11,16,34] Fisher *et al.* looked at the accuracy of CT for predicting malignancy of all cystic pancreatic lesions and found CT alone to be 61% accurate.[34] However, only 11 of 48 patients had IPMN. Another study by Cellier *et al.* looked at only IPMN patients and found CT to have an accuracy of 76% to distinguish malignant features.[16] This study used conventional CT technology, not the high-resolution, multi-detector CT scanners used in the present study. The introduction of multi-detector CT technology has led to considerable improvement in CT imaging quality. Higher-resolution CT can better detect smaller lesions and associated masses, and delineate main from branch duct IPMN.[35] The results from the present study's cohort show that using the appropriate criteria, including duct diameter ≥1.0 cm and/or mass ≥2.5 cm, achieves a sensitivity and negative predictive value of 100%. Thus, in the population studied, no lesions with HGD or invasive cancer would have been missed. Some argue that EUS is a better test for malignant IPMN. Mural nodules, a criteria for resection according to the international guidelines,[17] is one tumour characteristic best seen by EUS. This was studied by Ohno *et al.*, who found that the presence of papillary or invasive mural nodules had an accuracy of 75%.[9] However, because of the operator-dependent nature of EUS, mural nodules may or may not be detected or reported. In the present study, only one report found a mural nodule. The overall accuracy of EUS has been quoted at 63%[13] and at 86% with the addition of FNA.[10]

The utility of FNA analysis has also been questioned. It adds another element of invasive testing to the already invasive EUS. Complications, including injury to adjacent organs, haemorrhage, and the seeding of malignant cells into the peritoneum have been reported.[11] It also requires deep sedation, increases cost, is operator-dependent and is not widely available. Maker *et al.* report that over 60% of FNA cytology is non-diagnostic, carrying a false negative rate of 72%.[14] Another study found the accuracy to be 56.5%.[32] The data in the present study show that only 29% of patients with malignancy had positive cytology. Although the number of patients with measured fluid CEA was smaller, there was no correlation between CEA values >200 and malignancy, as has been suggested in the past.[12] This is in agreement with Pais *et al.*, who found no difference in cyst fluid CEA between benign and malignant IPMN.[10]

Lesion diameter has been shown to correlate with increased risk for malignancy.[17,22,25,31,32] Many of these measurements were determined using EUS. There are few data on how well CT and EUS measurements correlate. In the present study, CT consistently measured smaller than EUS (72%). This is very important when considering pancreatic lesions. Most guidelines use measurements of >3.0 cm as one of the criteria for increased malignant potential

but do not specify by which imaging modality the measurement should be obtained. Values of both 2.5 cm and 3.0 cm were tested for differentiating HGD or invasive cancer from benign IPMN and results showed that using a cut-off of 3.0 cm according to CT scan would have caused several malignant lesions to be missed. Applying this cut-off in combination with the resection criterion of a duct diameter of ≥1.0 cm would still have allowed two cancers to be undiagnosed.

This study has various limitations, including its retrospective design. It only examined those patients with IPMN who were surgically resected. Patients who may have been observed, gone on to develop cancer and undergone resection at another institution would not have been included in this database. There may also have been other variables predictive of HGD or invasive cancer that were not identified by this study. This study does not include patients with cystic neoplasms that proved to have different pathologic diagnoses. Neither does it include patients with cystic lesions suspicious for IPMN who did not undergo resection. The patient sample is gathered from a single university hospital, which is often, but not always, the referral site for uncommon lesions such as IPMN. The data depend on the accuracy of the medical record and the study lacks a control group.

In conclusion, IPMN is an uncommon but well-known lesion of the pancreas that has the potential to harbour malignancy. Diagnostic assessment has historically included cross-sectional imaging and endoscopic evaluation. In this study's cohort of patients, EUS with or without FNA was unnecessary. Using measurements of lesion size ≥2.5 cm and/or pancreatic duct diameter ≥1.0 cm, obtained in CT imaging, would have led to the resection of all tumours with HGD or cancer. This finding has substantial applications for clinical practice, especially for settings in which high-resolution CT is available but an experienced endosonographer is not.

Conflicts of interest

None declared.

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