



Endosonographic Features of Cholangiocarcinoma and Comparison with Computed Tomography and Endoscopic Retrograde Cholangiography Findings

Kolanjiokarsinomun Endosonografik Özellikleri ve Bilgisayarlı Tomografi ve Endoskopik Retrograd Kolanjiyografi Bulguları ile Karşılaştırılması

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ABSTRACT

Objective: Endosonographic (EUS) features of cholangiocarcinoma (CC) have not been clearly described in the literature. The aim of our study was to determine the EUS features of CC and to compare them to computed tomography (CT) and endoscopic retrograde cholangiography (ERCP) findings.

Material and Methods: Thirty-five patients who were diagnosed with CC between January 2008 and January 2011 were recruited in the study. Their EUS, CT, and ERCP findings were retrospectively evaluated.

Results: EUS showed a hypoechoic mass lesion in 33 (95%) patients. CT and ERCP findings were concordant with EUS findings in terms of localization of the tumor. The margin and contour of the mass lesions were regular and well defined in 15 patients; however, they were irregular and ill defined in 20. Considering these features, we identified 2 patterns of CC on EUS: 1) a hypoechoic lesion with an irregular and ill-defined border without a clear relationship with the bile ducts and 2) a hypoechoic lesion with a regular and well-defined border, with the relationship to the bile ducts clearly demonstrated.

Conclusion: In this retrospective study, EUS revealed mass lesions in all the patients with CC. CC may exhibit two distinct patterns on EUS.

Key Words: Cholangiocarcinoma, Endosonography, Computed tomography, Endoscopic retrograde cholangiopancreatography

ÖZ

Amaç: Literatürde kolanjiokarsinomun (CC) endosonografik (EUS) özellikleri açık bir şekilde tanımlanmamıştır. Çalışmamızın amacı, CC'nin EUS özelliklerini belirlemek ve bunları bilgisayarlı tomografi (BT) ve endoskopik retrograd kolanjiyografi (ERCP) bulgularıyla karşılaştırmaktır.

Gereç ve Yöntemler: Çalışmaya Ocak 2008-Ocak 2011 tarihleri arasında KK tanısı konan 35 hasta alındı. EUS, BT ve ERCP bulguları retrospektif olarak değerlendirildi.

Bulgular: EUS, 33 (% 95) hastada hipoeoik kitle lezyonu gösterdi. BT ve ERCP bulguları, tümörün lokalizasyonu açısından EUS bulguları ile uyumluydu. Kitle lezyonlarının kenar ve konturları 15 hastada düzenli ve iyi tanımlanmış, ancak 20 hastada düzensiz ve kötü tanımlanmıştır. Bu özellikleri göz önünde bulundurarak, EUS üzerinde 2 adet CC paterni belirledik: 1) safra kanalları ile net bir ilişkisi olmayan, düzensiz ve kötü sınır ile tanımlı hipoeoik bir lezyon 2) safra kanalları ile ilişkisi açıkça görülen, düzenli ve iyi bir sınır ile tanımlı hipoeoik bir lezyon.

Sonuç: Bu retrospektif çalışmada EUS, CC'li tüm hastalarda kitle lezyonlarını ortaya koydu. CC, EUS üzerinde iki ayrı paten sergileyebilir.

Anahtar Sözcükler: Kolanjiokarsinoma, Endosonografi, Bilgisayarlı tomografi, Endoskopik retrograd kolanjiyopankreatografi

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INTRODUCTION

Cholangiocarcinoma (CC) is an aggressive type of cancer that comprises 10–15% of malignancies that arise from the bile duct epithelium (1). Despite recent developments of diagnostic techniques, the diagnosis of CC and its preoperative assessment is quite difficult. Transabdominal ultrasonography, computed tomography (CT), endoscopic ultrasound (EUS), magnetic resonance cholangiopancreatography, and endoscopic retrograde cholangiography (ERCP) are the most widely used methods for assessing CC (2,3).

EUS has recently become one of the preferred methods for the diagnosis and staging of CC (4). The sensitivity and specificity of EUS has been reported as 79% and 62%, respectively, in a prospective study of patients with suspected CC (5). A meta-analysis of 9 studies reported the sensitivity and specificity of EUS as 78% and 84%, respectively (6). There are, however, few published studies that have assessed the findings of CC with EUS, and therefore, the criteria for diagnosis are not clearly established. The purpose of this retrospective study was to assessment of EUS features of CC and compare these features with CT, and ERCP findings.

MATERIALS and METHODS

Patients: Thirty-five patients who were diagnosed with CC by clinical, laboratory, and imaging methods, and by surgery or EUS-guided biopsy with thin needle aspiration and/or brush cytology with ERCP at the Suleyman Demirel University Faculty of Medicine between January 2008 and January 2011 were recruited in this study. EUS reports and images, CT results, and ERCP reports and images of the patients were assessed and compared retrospectively. In our study, we accept the principle of compliance with the Helsinki Declaration Principles.

EUS protocol: All of the EUS examinations of patients were performed by one endoscopist by using a radial video echoendoscope (EG-3670 URK, Pentax Europe, Hamburg, Germany) or a linear video echoendoscope (EG-3830 UT, Pentax Europe) and a Hitachi EUB 6500 ultrasound processor (Hitachi Co. Ltd., Tokyo, Japan).

Localization in the biliary system, complexity, and echogenicity of the tumor with diffusion to the surrounding tissues and the presence of lymphadenopathy (LAP) were assessed and recorded separately. Tumors in the intrapancreatic section of the common bile duct (CBD) were defined as distal CC, and the others as proximal CC. The following criteria were used to distinguish distal CC from pancreatic adenocarcinoma:

- 1) On EUS, the tumors were limited to within the biliary tract, and the pancreatic tract was normal.

- 2) Malignant forms were limited to the CBD. Pancreatographic findings were normal, as assessed by using cholangiography (if necessary).
- 3) CC was diagnosed on the basis of cytological examination (3).

Preoperative inoperability criteria for CC by using EUS: Patients who had the following were accepted as inoperable:

- 1) Metastasis: Sonographic or histopathological appearance of metastasis with metastatic nodules in the liver and/or ascites
- 2) LAP: Presence of non-regional lymph nodes that had malignant appearances when viewed by sonography or cytopathology
- 3) Vascular invasion: Involvement of tumor with the main portal vein, any portal vein, or the hepatic artery with the following criteria:
 - a- Loss of 5-mm “interface echo” between the tumor and the vascular structure
 - b- Irregular tumor and vessel interface
 - c- Appearance of tumor in the vessel lumen (finding of “tumor in the vessel”)
 - d- Completely blocked vessel that did not exhibit blood flow on Doppler examination
 - e- The presence of collateral circulation in the tumoral region (3).

General inoperability criteria for CC: Patients who met 1 of the following criteria were accepted as inoperable:

- 1) A tumor that was determined to be inoperable during laparoscopy or laparotomy
- 2) Presence of malignant non-regional lymph nodes detected by using fine-needle aspiration (FNA) biopsy (e.g., aortocaval and celiac), presence of malignant ascites, or presence of distant metastasis (7).

RESULTS

Twelve of the 35 patients (34%) were female. The average age was 68.8 years (range, 43–85). Fifteen (42.8%) were diagnosed as distal CC, and 20 (57%) as proximal CC.

EUS findings: Mass lesions were detected in all patients by using EUS. Thirty-three of the mass lesions (95%) were hypoechoic; however, 2 of them had isoechoic patterns. Clear and regular mass borders were observed in 15 cases; however, mass lesions with irregular and unclear borders were observed in 20. Four of the masses with well-defined margins (26%) were formed as polypoid structures that filled the lumen, seven (46.6%) were formed as fusiform thickening of the wall without exceeding the borders of

CBD, 2 (13.3%) had a cystic appearance, and 2 had wall thickness of CBD and formed as a mass filling the lumen.

The main pancreatic ducts were normal in all these cases. There were pathological LAPs in 14 cases (40%, periportal LAP in 10 and celiac in 4), other organ involvement in 5 cases (14.2%, duodenal invasion in 3 and invasion of the pancreas in 2), ascites in 4 cases (11.4%), and vascular invasion in 11 cases (31.4%, portal vein adhesion in 5 and portal vein invasion in 6). Inoperability criteria were met in 17 cases. The assessment of these findings revealed 2 different endosonographic appearances (Table I):

Type 1: A lesion with an irregular border, hypoechoic, and the relationship with the biliary duct could not be detected (Figure 1).

Type 2: A lesion with regular borders, hypoechoic (rarely isoechoic), and the relationship with the biliary duct could be detected (Figure 2A,B). In this type, the lesion

could appear as a polypoid bulge and/or diffuse fusiform thickening in the CBD.



Figure 1: A hypoechoic mass lesion with irregular and comparatively unclear borders in the biliary tracts on linear EUS imaging (white arrows).

Table 1: Features of type 1 and type 2 lesions on endoscopic ultrasonography.

	Type 1	Type 2
Number of patients	20	15
Lesion features (number)	Irregular borders, relationship with the biliary tract could not be seen clearly (20)	Regular borders, relationship with the biliary tract visible. <ul style="list-style-type: none"> • Polypoid structure that fills the CBD lumen (4) • Fusiform wall thickening that does not exceed the CBD wall (7). • Cystic appearance (2) • Both wall thickening and mass that fills the lumen (2)
Echogenicity (number)	Hypoechoic (20)	Hypoechoic (13) Isoechoic (2)
Localization (number)	Distal (9) Proximal (11)	Distal (6) Proximal (9)

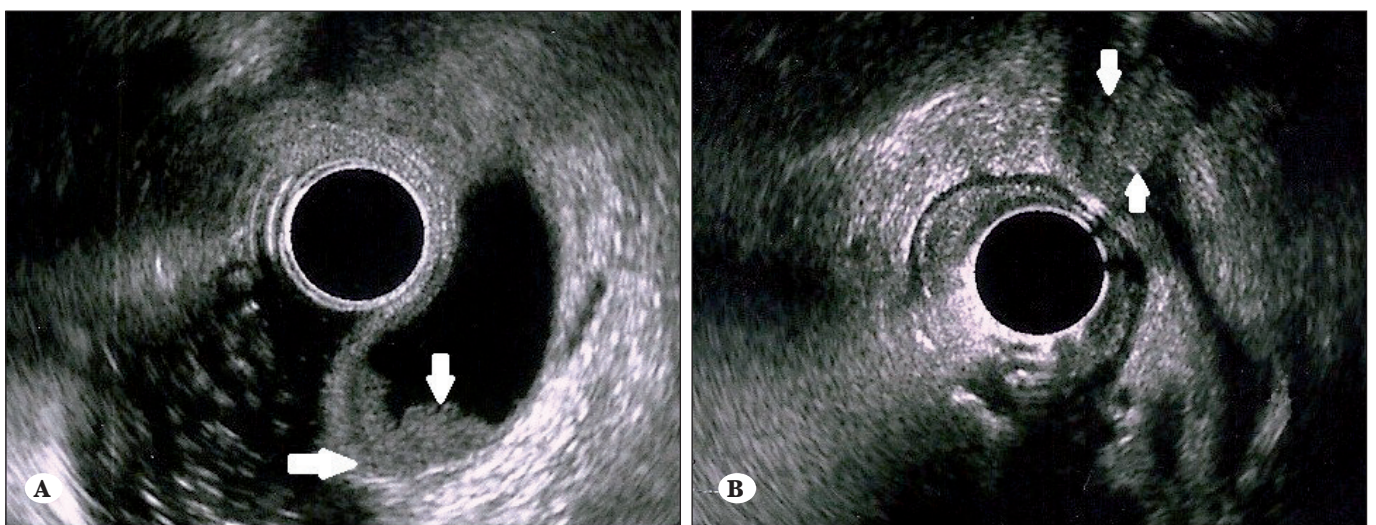


Figure 2: **A**) An isoechoic mass lesion with clear borders at the distal part of CBD (white arrows) and dilatation at the proximal part of CBD. The tumor did not exceed the borders of CBD and the main pancreas tract is normal. **B**) A mass with clear borders at the proximal part of CBD (white arrows). The diameter of the CBD at the distal to the mass is normal, but proximal dilatation is present.

CT findings: Of the 35 patients, 22 underwent CT before endosonographic examination, and the mass was detected in 10 (45.4%). A distal hypodense mass lesion was identified in 5 of the 10 cases, and a proximal hypodense mass lesion was defined in the other 5. While both the intrahepatic and extrahepatic biliary tract were wide in the patients with distal mass lesions, only the intrahepatic biliary tract was wide in the patients with proximal mass lesions. Periportal pathological LAP was found in a patient who had a hypodense mass in the proximal part of CBD. Metastases to the liver was observed in 2 patients who had distal hypodense mass lesions and in another 2 patients who had no mass lesions detected on CT. There were also vascular invasion findings for 2 cases with no mass lesions. Six patients were reported to meet the inoperability criteria.

ERCP findings: ERCP procedure was performed on 33 patients; 2 did not undergo an ERCP procedure and 5 did not undergo cannulation for choledocholithiasis. After the procedure, 16 cases were diagnosed as proximal CC, 11 as distal CC, and 1 as diffused CC. There was no difference between the ERCP and EUS diagnosis for tumor localization in 26 of the 28 patients. However, a mass image and diffuse thickness of the CBD were detected with EUS in 1 patient; widening and narrowing in the CBD was monitored at the ERCP in this case and it was accepted as a diffuse CC enhanced on a sclerosing cholangitis background. Further, 10% of the proximal CC patients were diagnosed with Klatskin tumors on the basis of ERCP.

DISCUSSION

CC is a malignant tumor arising from the biliary tract and categorized as intrahepatic cholangiocarcinoma or extrahepatic cholangiocarcinoma (EHCC) according to anatomical localization (8). The mortality rate due to CC is high because it is generally diagnosed in advanced stages, is difficult to monitor with radiology, and do not respond to any treatment other than surgery (9). Despite the highly developed imaging methods, diagnosis of CC is still difficult. EUS is a useful method for assessing the biliary tract and its sensitivity and specificity for the diagnosis of CC were reported as 78% and 84%, respectively (6). Applying FNA during EUS can increase the diagnostic accuracy (10). However, there are few studies that have reported the EUS findings of CC.

EUS is an important method for evaluation of biliary strictures and has an advantages of tissue sampling by FNA. It is also superior to other imaging modalities in determining vascular invasion and resectability of tumor. CC generally appears as hypoechoic and less frequently heterogenous mass lesion on EUS (11). There are two types of EUS systems. Radial EUS imaging provides 360 degree

view and usefull for diagnosis and staging of cancer. Linear EUS imaging also usefull for examination and provides tissue sampling by FNA. Both EUS probes were used for examination in the literature about the role of EUS in the diagnosis of CC. However, there is not any comperative study between the two methods in terms of visualization of tumor. Only in one study by Hara et al., they suggest that linear EUS system is very usefull for not only EUS-FNA also screening and close examination of cancer with vascular invasion, and it has similar or even better diagnostic accuracy for pancreaticobiliary disaeses than radial EUS imaging (12). In our study we also used both radial and linear EUS methods for examination There are no differences in terms of visualization of lesion and detecting vascular invasion and pathological LAPs.

In a study performed by De Witt et al, masses were found in 23 of 24 patients (96%), and it was reported that 19 of 23 masses had a hypoechoic structure and the other 4 had a heterogeneous structure; in this study, 18 masses had irregular borders and 5 had clear and regular borders (13). In another study by Mohamednejad et al., which evaluated the preoperative assessment of CC cases, masses were detected in 76 of 81 patients (94%). Seventy-three patients (96%) had masses with a hypoechoic pattern and 3 (4%) had a heterogeneous pattern. Fifty-two of these cases had irregular borders (68%) and 24 (32%) had regular borders (3). According to a recent study by Alper et al. that analyzed the radial EUS findings for the prediction of CC diagnosis in cases with distal biliary tract obstruction, the highest sensitivity and specificity of EUS were determined as 75.8% and 88.1%, respectively, for a hypoechoic mass lesion that causes total occlusion (14). Additionally, in this study, hypoechoic irregular wall thickness, sudden interruption of the distal choledochal lumen, or having short segment reduction were estimated to be CC findings with variable sensitivity and specificity rates.

EUS-FNA may be technically difficult for diagnosis of CC, especially in proximal tumors, however it has several advantages such as high sensitivity for diagnosis in patinets with prior negative imaging and negative brush cytology during ERCP, ability to determine regional and distant lymph nodes metastasis, avoid unnecessary surgery due to diagnosing metastatic spreading and diagnosing benign and alternative pathologies (15). In a recent study by Weilert et al reported that, the overall sensitivity and accuracy of EUS-FNA in suspected malignant biliary obstruction were 94% and 94 %, respectively. In this study EUS-FNA was found to superior to ERCP-based tissue sampling for pancreatic masses (sensitivity, 100% vs 38%, $p < 0.0001$) and comparable for biliary masses (79% sensitivity for both) (16). In a recent meta-analysis, which include 20 studies involving 957 patients, sensitivity and specificity of EUS-

FNA for the diagnosis of malignant biliary obstruction were reported as 80% and 97%, respectively. In this meta-analysis, only four adverse events were reported (Mild self-controlled bleeding in three patients, and biliary peritonitis and procedure related death in one patient). Although EUS-FNA is a safe procedure, some authors suggest that it may not be done in cases available for surgical resection and contraindicated in cases candidates for liver transplantation (17).

The current study defined the EUS findings of cases diagnosed as CC. Fifteen of the lesions (42.8%) were distal and 20 (57.2%) of them were proximal CC. Thirty-three of the masses (95%) had hypoechoic pattern and 2 had isoechoic pattern. The borders of the masses were clear and regular in 15 cases and irregular and unclear in 20 cases. Masses with regular borders had a polypoid structure that filled the CBD lumen. Masses with well-defined margins were seen as polypoid structures that filled the lumen, or fusiform wall thickness that did not exceed the borders of CBD, or cystic appearance, or both wall thickness of CBD and masses that filled the lumen. Briefly, 2 types of CC were obtained in endosonographic examination. There was a hypoechoic irregular mass lesion in the first image pattern (Type 1), that the borders were not clearly demonstrated and the CBD lumen could not be determined clearly. Nine of the 15 distal CC cases (60%) and 11 of 29 proximal CC cases (55%) had this lesion pattern. The second pattern was mostly hypoechoic (rarely isoechoic), with clear borders, and could be discriminated from surrounding tissue; a relationship with the biliary duct could be observed (Type 2). Most of the cases in this group had wall thickness of CBD as oval, fusiform, or diffused forms. Isoechoic echogenicity was observed in a single case that had both proximal and distal CCs.

EHCC appears as a focal wall thickness with different image patterns (18). EHCC is diagnosed with 78.6–92.3% accuracy with modern contrast-enhanced multidetector CT. However, it cannot be detected in many cases because of the small size of lesion (18-20). Triphasic helical CT detects 90–100% of CC cases (19, 21). Sensitivity for the assessment of the resectability of the tumors is less than 60% for CT (22). CT monitoring before EUS occurred in 22 of our 35 cases. Conventional contrast-enhanced CT was used in all of these cases. Masses were detected in 10 of 22 cases (45.4%). Hypodense lesions were observed in 5 distal cases and 5 proximal cases. The masses were detected at the same location on endosonographic examination. CCs were detected with EUS in 12 cases that were not detected on

CT. Therefore, the diagnostic sensitivity of CT in our study was much lower than that reported in other recent studies. We suppose the difference is related to the technique used for performing the CT. Additionally, the referral of cases to our clinic after performing CT in different health centers may have contributed to the lower sensitivity.

CT is useful to evaluate vascular invasion and lymph node involvement in CC. In a study of 55 patients with CC, the rate of accurate detection of portal vein invasion, arterial invasion, and lymph node invasion was 86%, 93%, and 84%, respectively (23). In another study using a 4-channel multidetector CT, hepatic arterial invasion was detected with 100% sensitivity and 90% specificity, and portal invasion with 92.3% sensitivity and 90.2% specificity (24). Seven of our cases (31%) were deemed inoperable by using CT, and 17 of 35 cases (49%, 8 distal CC, 9 proximal CC) were deemed inoperable by using EUS. Five cases assessed as inoperable with CT were assessed as inoperable by EUS as well, but an additional 2 cases were assessed as inoperable with EUS. Liver metastases were observed in these cases using CT. These metastases were not detected with EUS. The left lobe of the liver can be assessed with EUS, but the right lobe cannot. Therefore, CT has an advantage over EUS for assessing distant metastasis.

Asymmetrical irregular narrowing in the biliary tract on ERCP is an indication of malignancy (2). The sensitivity of cholangiography was 75–85%; specificity, 70–75%; and accuracy rate, 95% for CC diagnosis (25, 26). Eleven of our cases were diagnosed as distal CC and 16 as proximal CC. Mass localizations determined by ERCP were the same as all of the cases' images obtained endosonographically. Three cases were diagnosed as distal CC and 9 cases as proximal CC by using ERCP; these cases were not identified by using CT.

Our study showed that, EUS can detect the mass lesion in all CC cases and there were 2 different endosonographic patterns. The diagnosis was supported by ERCP findings in the cases that were diagnosed as CC with EUS. Lesions were not visible on CT in more than half of the cases. However, CT could detect organ metastasis that could not be detected on EUS. Assessment of these endosonographic patterns in patients suspected to have biliary tract malignancy could be helpful to direct them to a CC diagnosis. In our opinion, joint evaluation of the findings of EUS, multidetector helical CT, and ERCP can increase the diagnostic accuracy.

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