Review

The Importance of Imaging Techniques in the Assessment of Biliary Tract Cancer

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ABSTRACT: Biliary tract cancer is reported to be uncommon among most countries in Europe. On the other hand, higher incidence values were recorded in Southeast Asia due to various local hepatobiliary flukes and other risk factors. The malignant process can develop anywhere along the biliary tract and it can be divided into three different types according to their anatomic location: cholangiocarcinoma, carcinoma of the ampulla of Vater and gallbladder cancer. The biggest problem that we are currently facing with this type of malignancy is that patients are usually diagnosed in late stages with few alternatives regarding therapy. Due to its silent, yet fatal evolution, clinicians require additional help from imaging techniques. Initial evaluation of the biliary tract is usually performed with the help of ultrasonography (US) which can determine if an additional imaging procedure will be required next for further evaluation. Some of these imaging techniques include magnetic resonance imaging (MRI), computed tomography (CT), percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP) and MRI with magnetic resonance cholangiopancreatography (MRCP). The purpose of this Review is to evaluate the advantages and disadvantages of various imaging procedures for the assessment in this type of malignancy.

KEYWORDS: *biliary tract cancer, computed tomography, magnetic resonance imaging, ultrasonography*

Introduction

Biliary tract malignancy is the second most common primary hepatic cancer and it includes three different entities, each affecting a different anatomic location: cholangiocarcinoma, carcinoma of the ampulla of Vater and gallbladder cancers [1]. Therefore, the malignant process can occur anywhere along the biliary tract.

Cholangiocarcinoma is further divided into three subtypes as follows: distal, perihilar and intrahepatic [2].

Considering that most of the biliary tree is lined with a simple columnar epithelium, malignant changes that occur at this level will often generate adenocarcinomas [3].

In order to become a carcinoma, it must first follow an evolutionary sequence that starts with metaplasia, which is then followed by dysplasia, carcinoma being the next and final step of this process [4,5].

Biliary tract cancers are often diagnosed late and have poor prognosis due to the silent, yet fatal evolution. Non-specific signs and symptoms can sometimes be discovered in patients when the malignant process is in an advanced stage.

The debate that arises at this point concerns the improvement of the diagnostic algorithm in this type of malignancy, in order to detect this disease in initial stages. This could imply the initiation of early treatment which can increase survival rates. The advances in imaging technology over the past few decades have played a crucial part in helping clinicians diagnose this type of malignancy in its early days.

The most useful imaging techniques that provide valuable information for clinicians are magnetic resonance imaging (MRI), computed tomography (CT), percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP) and MRI with magnetic resonance cholangiopancreatography (MRCP).

The information obtained through imaging techniques, combined with data related to the patients like patient's age, gender, risk factors, clinical history, is used to characterize this type of malignancy in a more accurate way than before and can also prove its efficiency in providing the most appropiate therapy [6].

Epidemiology

Although it is considered to be the most common biliary malignancy, the incidence of cholangiocarcinoma is not as high as other types of cancer [7].

Therefore, only 2% of all cancers are considered to be cholangiocarcinomas [8].

In most parts of the world, this type of malignancy is considered uncommon. For example, USA and Europe have incidence values for this disease ranging around 1-2 per 100.000 [9].

However, this isn't the case for Southeast Asia, which has recorded the highest prevalence for this malignancy [10].

Various studies in this area have shown a strong connection between multiple hepatobiliary flukes like Clonorchis sinensis or Opisthorchis viverrini and development of biliary tree cancer [11,12,13].

There are some obvious regional differences like risk factors, culture, personal beliefs and individual habits that lead to such different numbers between countries throughout the world. However, these numbers might not reflect the real situation, considering this is a disease often misdiagnosed or diagnosed in late stages. Considering the low incidence of this malignancy, there is a chance that clinicians either do not take into account this pathology when examining the patient or some of them might not have even encountered such cases before in their entire career.

Usually, patients who develop biliary tract cancer have no identifiable risk factors [14].

However, a strong association has been discovered between primary sclerosing cholangitis and the development of cholangiocarcinoma. Recent studies report that primary sclerosing cholangitis leads to an increased risk of cholangiocarcinogenesis of up to 15% [15]. In the same matter, Caroli's disease is responsible for an increased risk of developing cholangiocarcinoma of up to 30% [16].

In 2005, Shaib YH performed a study on a total of 625 patients with intrahepatic cholangiocarcinoma. The study also included 90834 controls who were basically randomly selected individuals without any form of cancer. The results of the study have proven a potential link between cholangiocarcinoma and human immunodeficiency virus, hepatitis C virus, liver cirrhosis and diabetes [17].

Normal histology and histopathological aspects

The biliary tree starts inside the liver with bile canaliculi which carry the exocrine bile from the hepatocytes to the interlobular ducts. These small intrahepatic bile ducts group up into two larger ducts called the left and right hepatic ducts which further reunite to form the common hepatic duct. The cystic duct, which connects the gallbladder to the extrahepatic bile duct, joins the common hepatic duct in order to form the common bile duct. The pancreatic duct joins the common bile duct on its distal segment in order to form the ampulla of Vater. At this point, the passage of bile and pancreatic juice into the second part of the duodenum is controlled by the sphincter of Oddi through various cycles of contraction and relaxation. The smallest intrahepatic bile ductules are lined with a simple cuboidal epithelium, while larger bile ducts contain a simple columnar epithelium. The latter type is also found in the gallbladder wall along with three additional layers represented by: muscular, perimuscular connective tissue and serosa.

Cholangiocarcinogenesis is a complex process that develops in time and goes through multiple evolutionary stages (metaplasia, dysplasia, carcinoma).

In 85% of all cases, gallbladder cancer has proven to be an adenocarcinoma with the following subtypes: papillary, tubular and mucinous. Other histological types include: squamous cell carcinoma, small cell carcinoma and carcinosarcoma.

Regarding immunohistochemistry, this type of cancer was positive for carcinoembryonic antigen (CEA) and keratin.

In the same matter, cholangiocarcinoma was also considered to be an adenocarcinoma in up to 95% of all cases [14,18].

Some of the proteins that are usually expressed in hepatocellular carcinoma (CK7, CK19) are found quite often in cholangiocarcinoma as well [19].

Considering the macroscopic growth pattern, intrahepatic cholangiocarcinoma can also be divided into intraductal growing, periductal infiltrative, mass-forming and superficial spreading types [20,21].

In the same matter, extrahepatic cholangiocarcinoma can be separated into intraductal and mass-forming types [13].

Diagnosis and staging of cholangiocarcinoma

The diagnosis of cholangiocarcinoma can prove to be difficult most of the time due to its silent, yet fatal evolution. Considering that unspecific signs and symptoms like pain located in the right hipocondrum, night sweats, weight loss, fatigue and jaundice can often be found in late stages, clinicians often rely on the information obtained through imaging techniques and will also need to maintain a high degree of clinical suspicion regarding patients with known risk factors [6].

According to its anatomic location, there are three types of cholangiocarcinoma: distal, perihilar and intrahepatic [2].

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In the past, distal and perihilar types were grouped as extrahepatic cholangiocarcinomas. Distal cholangiocarcinoma is the most frequently encountered type with up to 40-60% of all cholangiocarcinomas, while the perihilar type represents a total of 30-50% of all cases. Intrahepatic cholangiocarcinoma accounts for only 10%, therefore being the least frequently encountered type [22].

The results of an italian study published in 2010 by Alvaro D et al. indicated that men were more frequently affected by this disease compared to women. Also, the authors of the study have noticed an increasing trend regarding the incidence of this type of malignancy in Italy in the past two decades [23].

A national survey performed by the same author one year later indicated that 70% of all patients diagnosed with cholangiocarcinoma were assessed with at least three different imaging techniques, therefore suggesting the importance of imaging procedures and the need to link the data offered by each technique in order to provide a more accurate diagnosis of this disease [24] (Fig. 1).

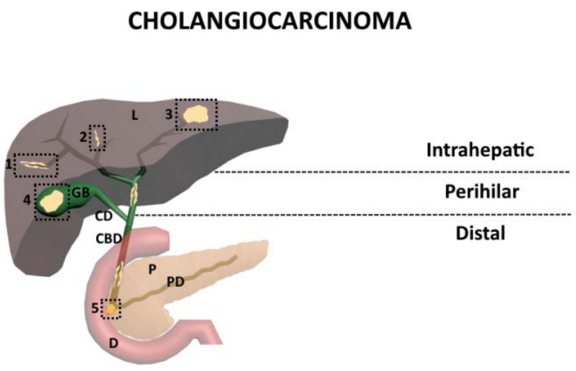

Fig. 1. Types of cholangiocarcinoma. 1. Periductal infiltrative; 2. Intraductal; 3. Mass-forming; 4. Carcinoma of the gallbladder; 5. Ampullary carcinoma; L-Liver; GB-Gallbladder; CD-Cystic duct; CBD-Common bile duct; P-Pancreas; PD-Pancreatic duct; D-Duodenum

Staging systems basically take into account different parameters and assign each patient affected by biliary tract cancer to the appropriate stage. In practice, this has proven to be extremely useful for clinicians because it allows them to understand how advanced the disease is and therefore provide a more accurate prognosis and therapy regarding each patient. However, none of the staging systems that are currently available for cholangiocarcinoma actually meet all of these requirements simultaneously [19].

Regarding distal cholangiocarcinoma, the only staging system that is currently used is the seventh edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) [17]. Like most of the other staging systems, this one also has a few limitations. Hong SM et al. published a study in August 2009 which included 147 patients diagnosed with distal cholangiocarcinoma. The results of their study indicated that the AJCC T classification cannot be considered an accurate method for predicting prognosis [25].

Two staging systems are used for perihilar cholangiocarcinoma: the Memorial Sloan-Kettering Cancer Center (MSKCC) and the AJCC/UICC staging systems. According to Deoliveira ML et al., new staging systems are under development and await validation [26].

Intrahepatic cholangiocarcinoma currently has three staging systems available: the National Cancer Center of Japan (NCCN), the Liver Cancer Study Group of Japan (LCSGJ) and the AJCC/UICC staging systems. Various studies published between 2013-2014 indicate the superiority of LCSGJ staging system over the seventh edition of AJCC/UICC staging system [27,28].

Imaging of biliary tract cancer

Like in every aspect of our lives, advances in technology in the past few decades have also played an important part in the development of imaging procedures, which aided in an early discovery of cholangiocarcinoma.

Therefore, it comes like a helping hand for clinicians who mostly rely on non-specific symptomatology that is often an advanced stage diagnosis, with poor therapy results and low survival rates.

Some of the most useful imaging techniques that provide valuable data for clinicians are ultrasonography (US), magnetic resonance imaging (MRI), computed tomography (CT), percutaneous transhepatic cholangiography (PTC), endoscopic retrograde cholangiopancreatography (ERCP) and MRI with magnetic resonance cholangiopancreatography (MRCP).

The information obtained through imaging techniques, combined with data related to patients like age, gender, risk factors, clinical history, is used to characterize this type of malignancy in a more accurate way than before and can also provide some useful hints regarding the most appropiate therapy [6] (Fig. 2).

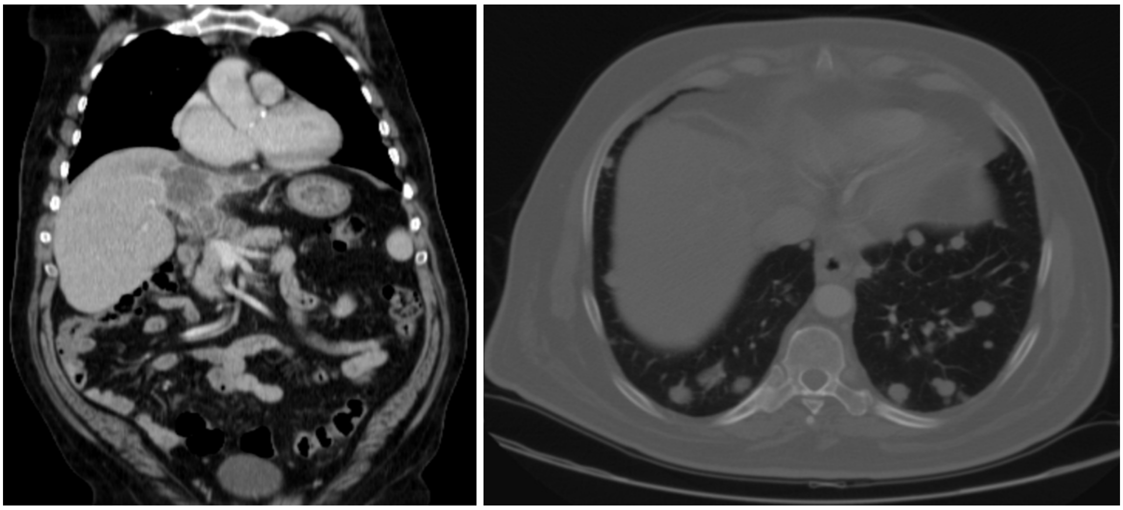

Fig. 2. A 64-Slice CT scanner was used to perform an abdominal CT examination of a 59 year old male pacient and revealed a hypoattenuating area showing low contrast enhancement, mostly peripheral, located in the right hepatic lobe, suggesting an intrahepatic form of cholangiocarcinoma. The pacient also had multiple pulmonary metastases

The initial evaluation of the biliary tract is usually done with the help of US which can exclude the presence of gallbladder stones inside the biliary tract and can also detect any dilatation that occurs along the biliary duct. The vascular involvement and tumor extension can also be evaluated with the help of US. Therefore, US can determine if an additional imaging procedure will be used next for further evaluation [29].

CT utilizes X-rays in order to identify bile duct wall thickening or a tumor mass. Compared to MRCP, CT is largely available worldwide and it implies lower costs [30] (Fig. 3).

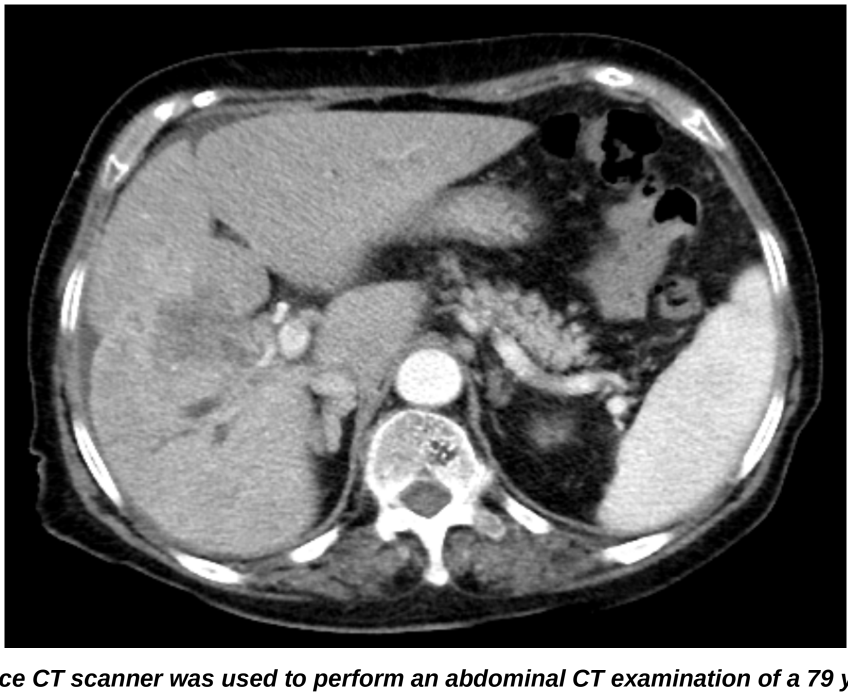

Fig. 3. A 64-Slice CT scanner was used to perform an abdominal CT examination of a 79 year old female pacient and revealed a hypoattenuating area showing low contrast enhancement located in the right hepatic lobe, just above the gallbladder, suggesting a perihilar cholangiocarcinoma

MRCP is considered to be one of the most advanced imaging procedures available and is usually found within the diagnostic algorithm due to its capability to evaluate vascular, parenchymal and biliary extension. In order to perform a better evaluation of the biliary tract strictures, MRCP will require an additional unenhanced and contrast enhanced MRI [31] (Fig. 4).

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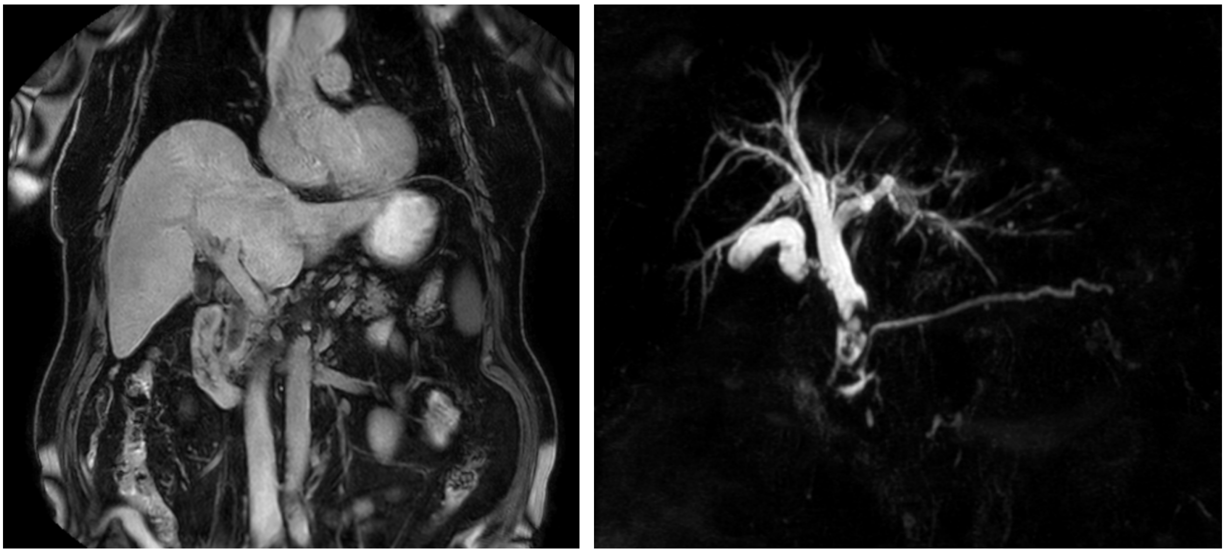

Fig. 4. A 3 Tesla MRI examination with MRCP sequences performed on a 72 year old male patient revealed choledochal lithiasis accompanied by an extrahepatic cholangiocarcinoma that extended towards the common bile duct, just before the emergence of the cystic duct

On the other hand, because of their invasive nature, imaging techniques like ERCP or PTC tend to become replaced by CT or MRCP. However, ERCP can yield extremely valuable information due to the possibility to provide tissue samples through various methods like fine needle aspiration or brush cytology. Obtaining all this data requires experienced personnel and an increased duration of the procedure [30,32].

An American study published by Kim JY et al. enrolled 123 patients suspected of biliary tract malignancy, who underwent positron emission computed tomography (PET-CT), following an initial CT and MRI/MRCP scan. The results reported by the authors of the study regarding sensitivity and specificity of PET-CT were 84% and 79.3%, respectively. According to the authors, PET-CT showed no significant advantages over CT and MRI/MRCP regarding detection of the primary tumor [33].

In March 2014, Singh A et al. published a prospective study which included 50 patients with various symptoms suggesting a biliary obstructive disease. Patients with less than 12 years of age, prehepatic or hepatic jaundice and contraindications to MRI were excluded from the study. They were initially tested using ultrasonography, which was then followed by CT and MRCP. Out of 50 biliary tract strictures, 24 proved to be of malignant nature, being mainly caused by periampullary carcinoma (29.2%), closely followed by cholangiocarcinoma (25%) and gallbladder carcinoma (25%), while the rest of 20.8% of the patients were affected by pancreas head carcinomas.

Regarding periampullary carcinoma, MRCP proved to be superior to CT scan and ultrasonography, reaching 100% sensibility and 100% specificity, compared to CT scan which recorded values of 85.71% sensibility and 100% specificity.

Ultrasonography was far behind with 57.14% sensibility and 100% specificity.

In the same matter, MRCP and CT scan proved to be superior once again to ultrasonography when used for the diagnosis of cholangiocarcinoma, both reaching values of 83.33% sensibility and 100% specificity.

The sensibility and specificity of ultrasonography were 66.67% and 100%, respectively.

The authors of the study were confronted with a few limitations which mainly affected the image quality on the MRCP sequences due to patients being unable to hold their breath for the amount of time required. At the end of the study, the authors concluded MRI-MRCP was superior to CT scan and ultrasonography regarding diagnosis of both benign and malignant lesions [34] (Fig. 5).

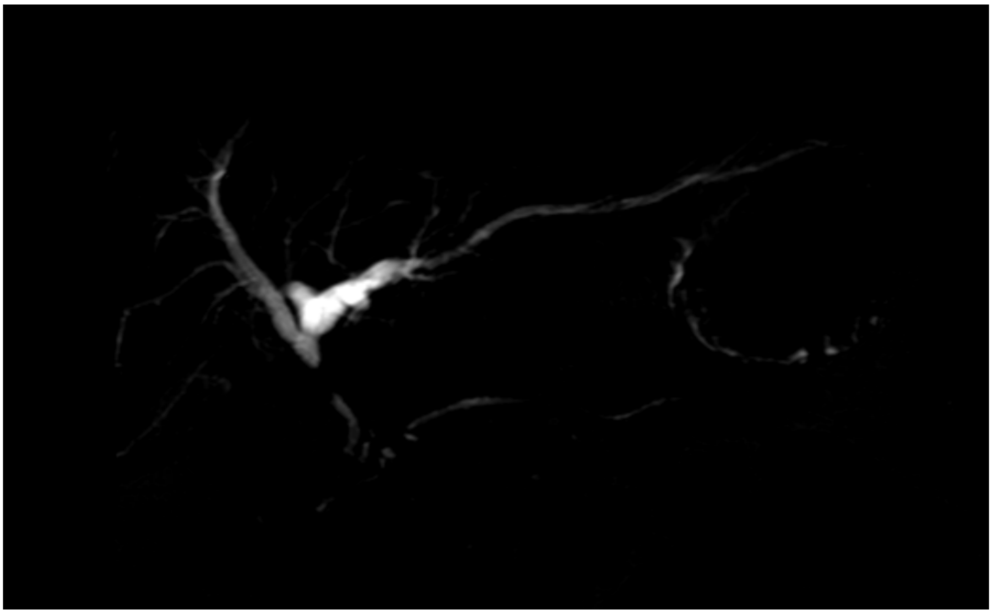

Fig. 5. A 3 Tesla MRI examination with MRCP sequences performed on a 69 year old male pacient revealed complete obstruction of the common bile duct on 12,7 mm length, accompanied by superjacent dilatation of the biliary tract, suggesting an extrahepatic form of cholangiocarcinoma

Several months later, in November 2014, Seung June Lee et al. assessed 168 patients with biliary strictures suspected to be of malignant nature who were explored with the help of ERCP and tissue sampling procedures like aspiration cytology, biopsy and brush cytology. Patients with postoperative biliary strictures and previous histological confirmation of malignancy were excluded from the study. The patients were divided into two groups as follows: the first group included 121 patients (79 males and 42 females) and underwent double-tissue sampling, while the second group analyzed 47 patients (33 males and 14 females) with the help of triple-tissue sampling. Double-tissue sampling proved that 77 out of 121 patients were suffering from a malignant biliary stricture (63.6% of the analyzed patients), compared to 85.1% in the triple-tissue sampling group, with 40 out of 47 patients being affected by biliary tract cancer. In both groups, the most common cause was represented by cholangiocarcinoma, with pancreatic cancer coming up on second place. Regarding single-tissue sampling, aspiration cytology reached 42.1% sensitivity and 100% specificity, while brush cytology and biopsy recorded sensitivity values of 58.4% and 63.5%, respectively. Higher values for sensitivity (64.9%) and specificity (100%) were obtained with the help of double-tissue sampling, while triple-tissue sampling reached values of 85% for sensitivity and 100% specificity, therefore proving its superiority compared to the other methods when used for the diagnosis of malignant biliary strictures, especially for cholangiocarcinoma [35].

In the same matter, a study performed in 2015 by Aydelotte JD et al. evaluated the utility and accuracy of MRCP regarding biliary tract pathology. A total of 81 patients were included in the study and they underwent MRCP followed by ERCP, out of which 14 patients had positive findings on both procedures for masses and strictures of the biliary tract. The authors of the study reported a sensitivity and specificity for MRCP of 80% and 94%, respectively and pointed out that MRCP should no longer be a reliable option when it comes to the diagnosis of biliary tract pathology and that it should be abandoned [36].

Hongchen Zhang et al. collected data from various studies in order to notice the general tendencies regarding the importance of CT, MRI and PET-CT in diagnosing hilar cholangiocarcinoma and evaluating resectability. The meta-analysis reported similar values between CT and MRI regarding pooled sensitivity (95% vs. 94%) and specificity (69% vs. 71%). Highest pooled specificity values were recorded by PET-CT (81%). The authors concluded that CT is the most frequently used imaging procedure in order to diagnose and evaluate resectability of hilar cholangiocarcinoma, with MRI being a reliable alternative. PET-CT proved useful in detecting lymph nodes but with little to no use in evaluating the resectability [37] (Fig. 6).

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Fig. 6. A 16-Slice CT scanner was used to perform a CT examination of a 59 year old female pacient and revealed mixed gallstones and lack of visualization of the retropancreatic choledoch duct. The pacient was diagnosed with an extrahepatic form of cholangiocarcinoma

Conclusion

Biliary tract cancer remains a major health burden due to the silent evolution and advanced stage symptomatology. These unspecific signs and symptoms include weight loss, jaundice, abdominal pain, night sweats and they are often ignored by either the patient or the clinician. Luckily, with advances in technology, we are able to benefit from imaging procedures like US, MRI, CT, PTC, ERCP and MRCP. Right now, US is used for initial evaluation of the biliary tract and determines if additional imaging techniques are required for diagnosis. At this point, MRCP is considered to be the technique of choice when it comes to diagnosing cholangiocarcinoma. Each of these imaging methods still has certain limitations. However, all of these procedures can provide altogether an accurate and early stage diagnosis with multiple therapeutic options.

Conflict of interest

No conflict of interest to declare.

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