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Research Article

Radiological Imagining for Prognosis and Staging of Hilar Cholangiocarcinoma

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Abstract

Background: Hilar cholangiocarcinoma or Klatskin tumor is a rare form of cancer occurring near the bifurcation of the right and left hepatic bile ducts. Surgery remains the only potential treatment for patients with perihilar cholangiocarcinoma yet radical resection requires aggressive surgical strategies that should be specially designed with respect to the location, size and vascular invasion of the tumors. Thus, it became very critical to accurately diagnose and stage such tumors for prognosis and treatment optimization. Computed tomography (MDCT), magnetic resonance imaging (MRI) and positron emission tomography (PET/CT) are useful tools, both to diagnose and stage hilar cholangiocarcinoma.

Objective of the Study: Objective of the Study was to evaluate the diagnostic performance values of computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography/computer tomography (PET/CT) in determining the resectability of HCC

Methods: A Systematic search in the scientific database (Medline, Scopus, EMBASE, and Cochrane databases) from 1980 to 2016 was conducted for all relevant studies that fulfilled the inclusion criteria. Study quality was assessed with the quality assessment of diagnostic accuracy studies tool.

Results: An overall of eleven Publications were included. 5 studies were retrospective; 4 were prospective and 2 was a semi - prospective study. CT had the highest pooled sensitivity at 95% (95% CI: 91 - 97), whereas PET/CT had the highest pooled specificity at 81% (95% CI: 69 - 90). The area under the curve (AUC) of CT, MRI, and PET/CT was 0.9269, 0.9194, and 0.9218, respectively

Conclusion: CT is the most frequently used imaging modality to assess HCC resectability with a good sensitivity and specificity. MRI was generally comparable with that of CT and can be used as an alternative imaging technique. PET/CT appears to be the best technique in detecting lymph node and distant metastasis in HCC but has no clear role in helping to evaluate issues of local resectability.

Keywords: *Cholangiocarcinoma; Hilar; Biliary Neoplasm; Radiological Staging; Magnetic Resonance Imaging; Computed Tomography; Hepatic Resection*

Introduction

Cholangiocarcinoma (CCA) is an adenocarcinoma that arises from the bile duct epithelium and is observed in the entire biliary tree (intrahepatic, hilum, and extrahepatic distal) [1]. They are commonly known as hilar cholangiocarcinoma (HCCA), Klatskin tumors or perihilar cholangiocarcinomas, are rare malignancies that account for up to 3% of all gastrointestinal cancers. With an incidence rate of 0.5 - 2.0 cases per 100000, it is estimated that there are between 2500 and 4000 new cases per year in the United States [2].

Hilar CCA may potentially affect any location of the biliary tree, it usually involves the biliary confluence, left - hand drive (LHD) and right - hand drive (RHD) (true Klatskin tumors) which are the most common (40% - 60%)of all cases. Around 2/3 of cholangiocarcinomas are hilar or extrahepatic and originate from the bile duct epithelium at the level of confluence of the right and left ducts, whereas 30% are distal or intrapancreatic and 5% - 10% are intrahepatic [3].

Clinical Presentation

The majority of patients with HCCA present with severe painless jaundice as the initial clinical presentation. However, not every patient with jaundice and biliary obstruction at the hepatic hilus will eventually be confirmed as HCCA. In fact, almost 25% of cases turn out to have other benign conditions (such as lymphoplasmacytic cholangitis or Mirizzi syndrome) or other malignant disease (such as gallbladder cancer or nodal metastasis) that has obstructed the hepatic confluence [4].

The physical findings are often nonspecific but may provide some useful information. Jaundice will usually be obvious. Patients with pruritus often have multiple excoriations of the skin. The liver may be enlarged and firm as a result of biliary tract obstruction. The gallbladder is usually decompressed and nonpalpable with hilar obstruction. Thus, a palpable gallbladder suggests a more distal obstruction or an alternative diagnosis. Rarely, patients with long - standing biliary obstruction and/or portal vein involvement may have findings consistent with portal hypertension [5].

Diagnostic Evaluation

Over 80% of proximal biliary obstructions are secondary to HC [6]. The remaining 15 - 20% are caused by benign strictures secondary to inflammatory disease, sclerosing cholangitis, stone disease, and gallbladder cancer invading the hepatoduodenal ligament [7]. Both benign and malignant biliary strictures present with similar clinical features [8]. Moreover, bilirubin and serum tumor marker levels do not reliably distinguish malignant and benign biliary strictures [8,9]. Preoperative identification of benign biliary strictures remains uncertain therefore resection remains most appropriate.

Less than one half of HC are resectable [10]. Accurate radiological staging of these lesions is difficult secondary to the complexity of the hilar region, proximity to major vessels, and small tumor sizes [11]. Computed topography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)/CT and ultrasound (US) are used to characterize suspicious biliary lesions. Initial radiographic assessment is usually transabdominal US due to its low cost and accessibility. It is sensitive for detecting biliary duct dilatation, but less sensitive in localizing the exact site of obstruction [12]. Typically, any HC mass appears hypoechoic relative to surrounding liver parenchyma. US can be also used yet is unable to accurately determine the type of obstruction or extent of tumor involvement.

Materials and Methods

Literature search

The present Systematic Review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta - Analyses (PRISMA) guidelines.

Data Sources: Electronic databases were searched: Scopus, EMBASE, and Google Scholar), PubMed/MEDLINE, Scopus, The Cochrane Library, and Web of Science. Econlit from 1980 to 2016.

Search terms included "resectability," and "diagnosis" "CT" or "computed tomography," "Magnetic Resonance Imaging" or "MRI," "positron emission tomography/computer tomography" or "PET/CT," "hilar cholangiocarcinoma," "Klatskin tumour," "Bile Duct Neoplasms,"

Study Selection

Search results were screened by scanning abstracts for the following:

Inclusion Criteria

1. CT, MRI, or PET/CT was used to evaluate the resectability of HCC
2. Patient count > 10
3. For per - patient statistics, sufficient data were presented to calculate the true - positive (TP), false - negative (FN), false - positive (FP), and true - negative (TN) values;
4. When data or subsets of data were presented in more than one article, the article with the most detail or the most recent article was chosen
5. Articles were published in English

Exclusion Criteria

1. Non - English language studies
2. Book chapters, and case reports

Quality Assessment

The quality assessment scores of 11 studies showed high quality ranging from 11 to 12 (table 1), with a mean study quality score of 11. The imaging findings were probably known during surgery and therefore the reference standard was generally not blinded to the results of the index test (QUADAS item 11). Inclusion and exclusion criteria were clearly mentioned in all studies.

Results

The initial search was broad, accepting any article related to ensure a comprehensive view of available work. Searches identified 1944 publications in addition to another 9 publications that were found through manual research. After removal of duplicates, abstracts and titles 798 publications were assessed as identified from title and abstract, and 350 papers were excluded. 79 papers full text could not be retrieved and another 85 papers with the same cohort. There were also 245 papers excluded because they did not have the same endpoint (didn't conclude or touch base on the outcome of decompression surgery on Spinal metastasis).

Finally, 12 eligible articles met the inclusion and exclusion criteria and detailed as the focus for the present study.

We followed the Preferred Reporting Items for Systematic Reviews and Meta - Analyses (PRISMA) guidelines in reporting the results [17] (Figure 1).

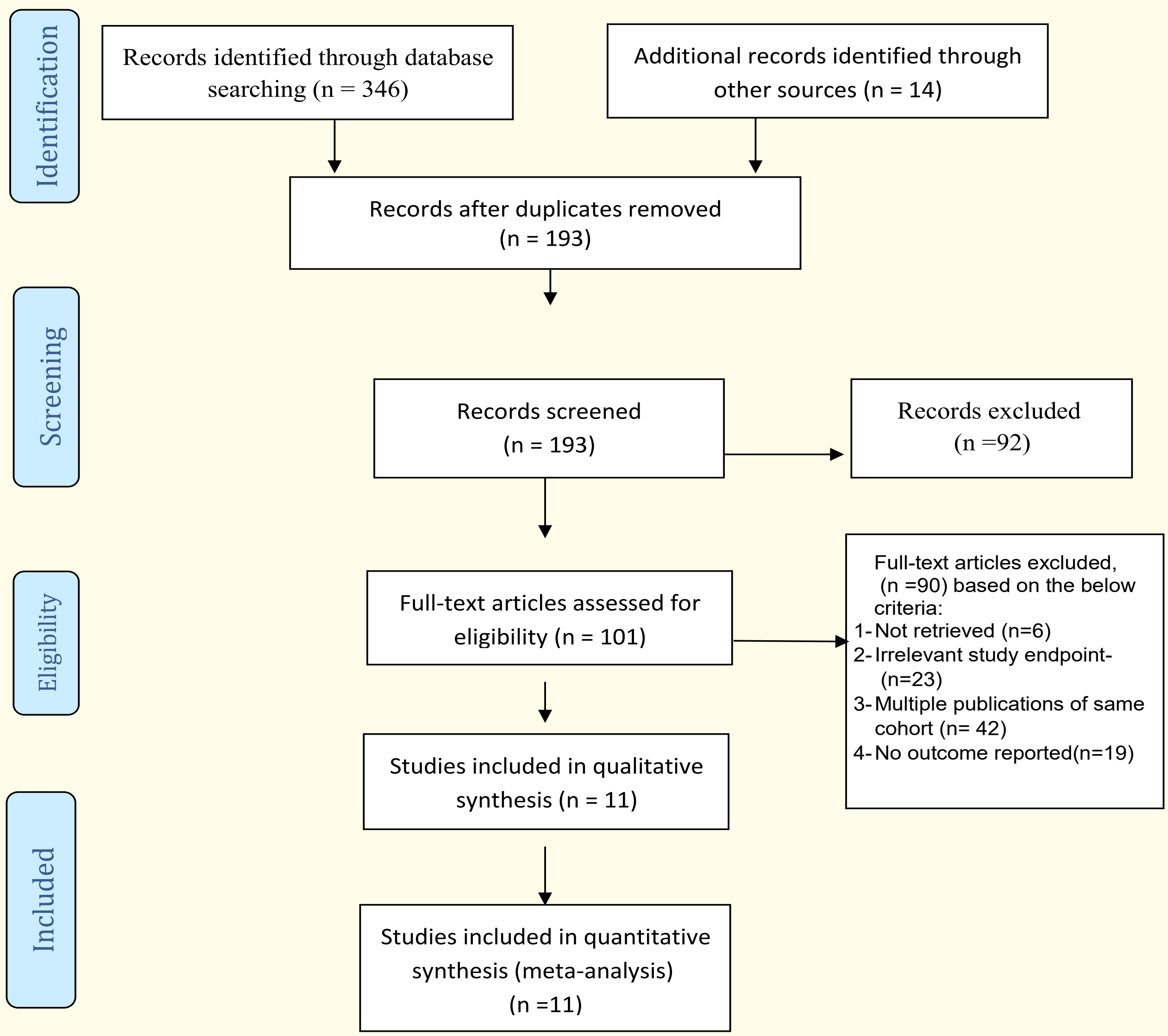

Figure 1: *PRISMA flow diagram showing the selection criteria of assessed the studies [17].*

Study Characteristics

The characteristics of the included studies can be shown in Table 1. They represent a total of 521 eligible patients (median 41 patients). Age range was from 21 to 88 years, and the proportion of male patients was 51% to 82%. 6 articles studied the performance of CT [14-16,21,23,24], 4 MRI [17,18,20,22], and 2 PET/CT [19,20]. The TP, FN, FP, and TN results and diagnostic performance of imaging in each study are shown in Tables 2, 3 and 4.

Study	Study design	Number of patients	Age, mean (range)	Patients selection	QUADAS Score	Modality		
						CT	MRI	PET/CT
Cha., *et al.* 2000 Korea [14]	Retrospective	21	56 (34 - 69)	Consecutive	11	X		
Aloia., *et al.* 2007 USA [15]	Prospective	32	67	Consecutive	11	X		
Unno., *et al.* 2007 Japan [16]	Retrospective	24	64	Consecutive	11	X		
Yin., *et al.* 2007 China [17]	NA	31	53 (21 - 74)	Consecutive	12		X	
Masselli., *et al.* 2008 Italy [18]	Retrospective	15	58 (49 - 74)	NA	12		X	
Li., *et al.* 2008 Germany [19]	Prospective	17	62	NA	11			X
Kim., *et al.* 2008 Korea [20]	Prospective	123	60 (28 - 78)	Consecutive	12		X	X
Chen., *et al.* 2009 China [21]	Prospective	75	60	Consecutive	12	X		
Ryoo., *et al.* 2010 Korea [22]	Retrospective	60	66 (45 - 77)	Consecutive	12		X	
Cannon., *et al.* 2012 USA [23]	Retrospective	110	64 (21 - 88)	Consecutive	11	X		
Nagakawa., *et al.* 2014 Japan [24]	NA	13	65 (39 - 83)	NA	11	X		

***Table 1:** Study.*

X= covering the imaging technology in the headline.

Author	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Cha., *et al.* 2000 Korea	6	6	0	9	100	60	50	100	71.4
Aloia., *et al.* 2007 USA	17	1	3	11	85	91.7	94.4	78.6	87.5
Unno., *et al.* 2007 Japan	15	4	0	5	100	55.6	78.9	100	83
Chen., *et al.* 2009 China	45	5	2	23	95.7	82.1	90	92	91
Cannon., *et al.* 2012 USA	37	22	0	51	100	69.9	62.7	100	80
Nagakawa., *et al.* 2014 Japan	10	2	0	1	100	33.3	83.3	100	85

***Table 2**: Diagnostic performance of CT.*

Study	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Li., *et al.* 2008 Germany	8	2	1	6	88.9	75	80	85.7	82
Kim., *et al.* 2008 Korea	76	5	6	36	92.7	87.8	93.8	85.7	91.1

***Table 3:** Diagnostic performance of PET/CT.*

Study	TP	FP	FN	TN	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Yin., *et al.* 2007 China	16	3	0	12	100	80	84.2	100	90.3
Masselli., *et al.* 2008 Italy	11	1	0	3	100	75	91.7	100	93.3
Kim., *et al.* 2008 Korea	74	12	8	29	90.2	70.7	86	78.4	83.7
Ryoo., *et al.* 2010 Korea	51	2	2	5	96.2	71.5	96.2	71.4	93.3

***Table 4**: Diagnostic performance of MRI.*

Discussion

The present study comprehensively reviews the literature on Radiological Imaging for Assessing the Respectability of Hilar Cholangiocarcinoma. Included studies were classified according to the outcomes reported.

A variety of risk factors have been associated with HC including advanced age, male gender, cirrhosis, inflammatory bowel disease, and chronic pancreatitis. Moreover, resectability is defined by factors specific for HCC, including invasion of the portal vein and hepatic artery, lymph node status, and proximal ingrowth into the segmental bile ducts. Although imaging modalities cannot become the determinants of resectability in patients with HCC, accurate preoperative assessment of tumor extent and resectability with an appropriate imaging study is one of the most important steps in treatment planning.

Computed Topography (CT)

CT was the most well studied imaging modality and demonstrated an acceptable accuracy (> 80%) in assessing ductal, portal vein and hepatic artery involvement although it was unable to accurately assess lymph node involvement [25]. Thinly sliced (2 - 5 mm) multidetector CT (MDCT) correlates well (greater than 90%) with local tumor extension when compared with operative and pathological findings [10]. Moreover, peritoneal metastases are generally underestimated [26]. Therefore, despite reported high sensitivity and specificity for HC with CT imaging, metastatic involvement and spread to contiguous organs and vascular structures remains a possibility at the time of surgery even One systematic review of HCC imaging techniques demonstrated an acceptable accuracy (86%) of CT in assessing ductal extent of HCC [27] and showed that the sensitivity and specificity estimates of CT were 89% and 92% for evaluation of portal vein involvement and 83% and 93% for hepatic artery involvement, respectively. However, it has been reported that CT may underestimate lymph node involvement and peritoneal metastases. In the series by Cha., *et al*. [28], among 21 patients with HCC, CT correctly detected the unresectable tumor in 9 cases with a 100% NPV. However, in 12 patients with suspected resectable disease by CT, 6 cases turned out to be unresectable (PPV: 50%). Besides, CT failed to detect small hepatic metastasis (n = 1), lymph node metastasis (n = 1), extensive tumor (n = 2), and variation of bile duct (n = 2), which precluded surgical resection. if undetected on CT.

This meta - analysis of CT, MRI, and PET/CT revealed that CT with the highest pooled sensitivity of 95% was able to accurately estimate the resectability of HCC. Nevertheless, CT is limited in detecting small hepatic or lymph node metastasis. Tumor spread to normal - sized lymph nodes and hepatic metastases smaller than 1 cm size seem to be beyond the power of current imaging techniques.

Magnetic Resonance Imaging (MRI)

MRI has increasingly gained favor in assessing biliary tumors. HC appears as a hypointense signal on T1 weighted images and high signal intensity of T2 imaging. The tumor generally appears hypovascular in relation to adjacent hepatic parenchyma and may be characterized by irregular thickening of the bile duct wall with upstream dilation of intrahepatic bile ducts [29]. The combination of MRI with MRCP is about 80% accurate in predicting HC resectability [30]. However, in a comparison of MRI combined with MRCP versus MDCT with direct cholangiography, Park and colleagues demonstrated no difference between the two groups in assessing HC resectability [31]. Currently, the combination of MRCP and CT is favored over direct cholangiography. Unfortunately, MRCP does not allow for invasive procedures such as biopsy, biliary drainage and stent insertion therefore direct cholangiography is still necessary in the study by Masselli., *et al* [32]. MRI correctly predicted vascular involvement in 73% and liver involvement in 80% of the cases. The number of overall correctly assessed patients with regard to resectability was 11 true positive, 1 false positive, and 3 true negative. In a comparison of MRI/MRCP versus MDCT with direct cholangiography, Park and colleagues [33] demonstrated no difference between the two groups in assessing HCC resectability. The overall accuracy meta - analysis showed that MRI had a pooled sensitivity of 94% and specificity of 71%, generally comparable to CT in the evaluation of the resectability of HCC. Therefore, MRI/MRCP can be used as an alternative imaging technique to establish the diagnosis of HCC due to the additional benefits of having a shorter preoperative diagnostic time, being a noninvasive procedure, and not exposing patients to radiation as 77.8% for both MRI and MRCP necessary in these instances.

PET/CT

The role of PET/CT in HC remains less clear. PET/CT has a reported specificity of over 80% to detect lymph node and distant metastases, but it seemingly does not have much utility in assessing local resectability [19]. Since malignant tumor cells often show increased glucose metabolism, whole body PET/CT imaging with the tracer fluoro - 2 - deoxy - D - glucose (FDG) has been used as a functional imaging to evaluate the metastasis of HCC [34]. PET/CT, which combines a full - ring detector clinical PET scanner and multidetector computed tomography (MDCT) scanner, acquires both metabolic and anatomic imaging data with a single device during a single diagnostic session. It has the advantage of surveying the entire body and becomes more valuable than CT and MRI in detecting lymph node and distant metastases. Unnecessary surgery can be avoided if patients with advanced disease are defined by PET/CT [35]. For 123 patients with suspected cholangiocarcinoma enrolled in Kim., *et al.'s* study [14], the overall values for sensitivity, specificity, and accuracy of PET/CT in primary tumor detection were 84.0%, 79.3%, and 82.9%, respectively. PET/CT demonstrated no statistically significant advantage over CT and MRI/MRCP in the diagnosis of primary tumor. However, PET/CT revealed significantly higher accuracy than CT and MRI in the diagnosis of regional lymph nodes metastases (75.9% versus 60.9%, p = 0.004) and distant metastases (88.3% versus 78.7%, p = 0.004). Additionally, PET/CT corrected resectability in 15 (15.9%) cases of cholangiocarcinoma who had been falsely recognized by CT and MRI. In those 15 patients, the stage was upgraded from resectable to unresectable in 7 and downgraded from unresectable to resectable in 8. In our study, PET/CT showed the highest pooled specificity of 81%, compared to 71% for MRI and 69% for CT. A high specificity assures surgeons resectability determined by the findings of PET/CT with a great deal of certainty. A 91% pooled sensitivity of PET/CT also indicated that PET/CT had a good power to define the settings of unresectability. Nevertheless, the small number of patients included in some studies of this meta - analysis may have influence on the results. Although this molecular imaging technique is becoming increasingly available, PET/CT remains an expensive imaging tool which necessitates ionizing radiation exposure. Furthermore, FDG is not a tumor - specific substance. Increased FDG accumulation may be observed in a variety of benign entities and in some physiologic conditions, which may yield false - positive findings, and the limited spatial resolution may also reduce the accuracy of the technique. More studies on the application of PET/CTs are needed to further investigate the benefits of this imaging modality in HCC.

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Conclusion

CT is the most frequently used imaging modality to assess HCC resectability with a good sensitivity and specificity. MRI was generally comparable with that of CT and can be used as an alternative imaging technique. PET/CT appears to be the best technique in detecting lymph node and distant metastasis in HCC but has no clear role in helping to evaluate issues of local resectability. Future researches with a bigger sample size, a more reasonable design, are required to yield more efficient diagnostic strategy. Furthermore, cost - effectiveness analyses of MRI and PET/CT in patients with HCC are also needed.

Diagnostic accuracy studies of CT, MRI, ultrasound or PET/CT for staging of hilar cholangiocarcinoma are sparse and have moderate methodological quality. Data primarily concern CT, which has an acceptable accuracy for assessment of ductal extent, portal vein and hepatic artery involvement, but low sensitivity for nodal status.

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