

CHAPTER 3

RESEARCH DESIGN AND METHODOLOGY

RESEARCH QUESTIONS

Primary question:

How good is MRCP as an instrument for preoperative diagnosis and in the assessment of hilar CHCA?

Secondary question:

How good is MRCP as an instrument for preoperative diagnosis and in the assessment of CHCA at the common duct?

RESEARCH OBJECTIVES

Primary objective:

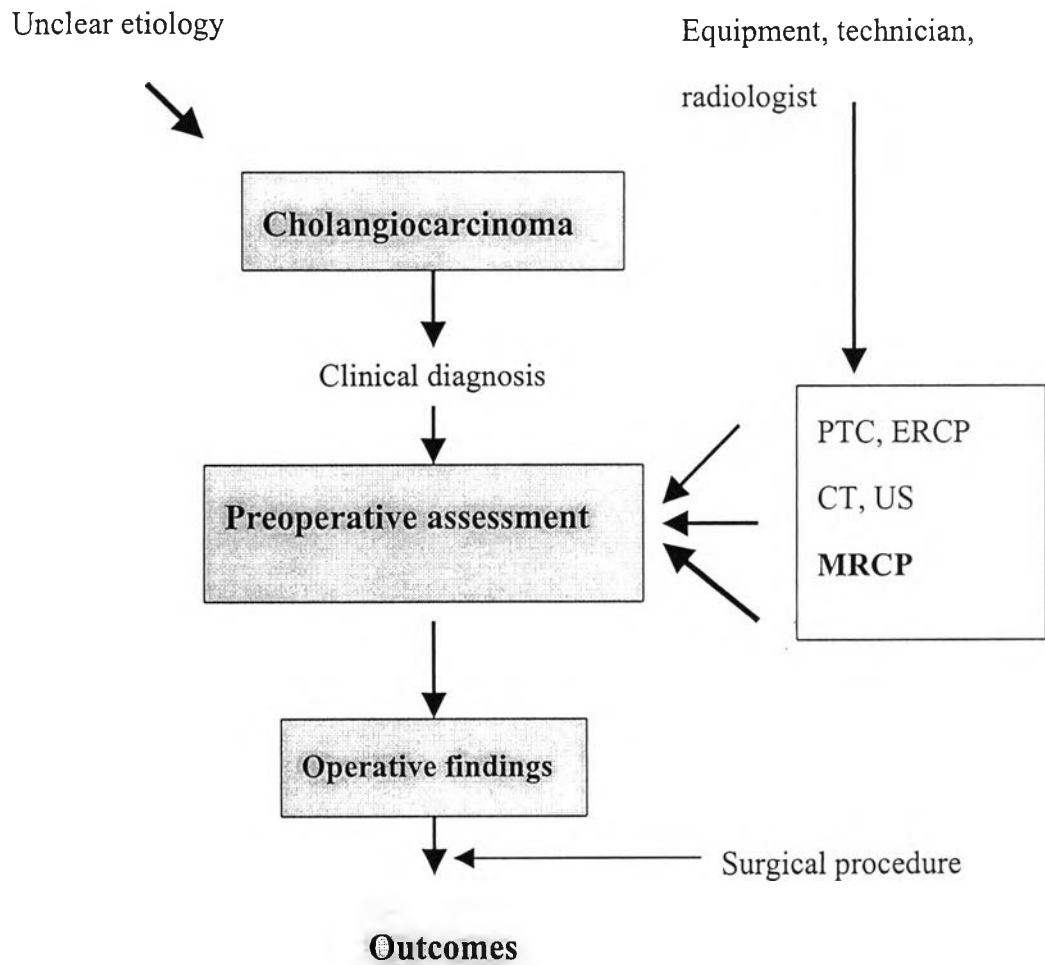
To determine the diagnostic performance of MRCP as a preoperative diagnosis of patients with hilar CHCA.

Secondary objective:

To determine the diagnostic performance of MRCP as a preoperative diagnosis of patients with common duct CHCA.

To evaluate the agreement between MRCP and operative findings for assessing the biliary tree in hilar CHCA and common duct CHCA.

Figure 4. Conceptual framework: This study focuses on preoperative diagnosis and assessment of patients with CHCA



KEY WORDS

Hilar CHCA (cholangiocarcinoma)

MRCP (magnetic resonance cholangiopancreatography)

Preoperative diagnosis

Preoperative assessment

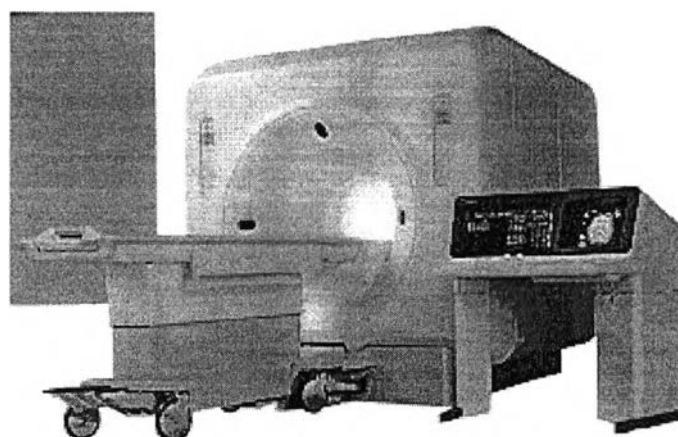
Diagnostic test

OPERATIONAL DEFINITION

MRCP: a special MR imaging technique used to image biliary ducts including the gallbladder and pancreatic duct. MRCP is performed with on MR machine and special software. The technologist conducts the imaging. The radiologist assesses the imaging and interprets the result of the imaging.

MRCP machine: All MRCP were performed with a 1.5-T system (Signa Horizon; GE medical System) using a body coil.

Figure 5. MRI machine



Our MRCP technique: The 2D cholangigram was performed using coronal heavily T2 weighted images. We used a body coil. The following parameters were used 12,000-15,000/200-260 : TR/TE (repetition time msec/effective echo time msec), FSE (fast spin echoes) section thickness of 3 mm with no intersection gap, field of view (FOV) 30x30 cm, 3 nex phase, 220x224 matrixs, flow com sat SI, fat sat, extended dynamic with respiratory trigger. Following the use of MIP (maximum intensity projection), the imaging was obtained and interpreted.

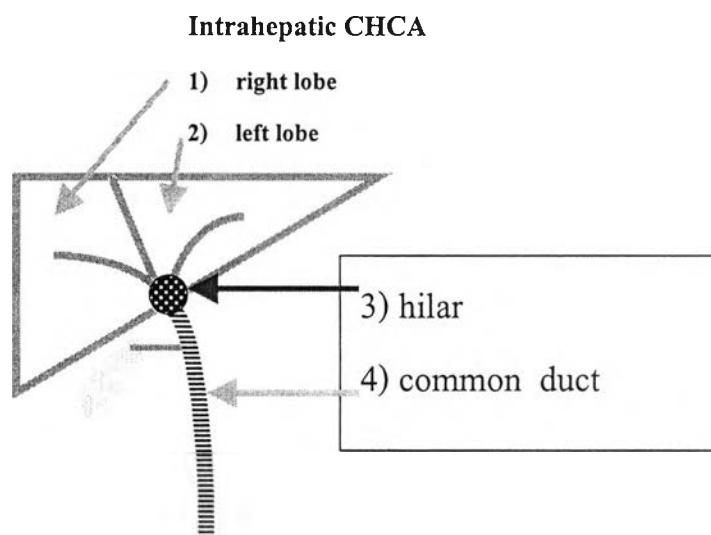
Figure 6. Normal finding of MRCP



Operative findings: Findings of lesions caused by CHCA as seen intra-operatively. Surgeons assessed and interpreted operative findings.

Hilar CHCA: CHCA originates at the hilar region as seen in Figure 7.

Figure 7. Location of CHCA



RESEARCH DESIGN

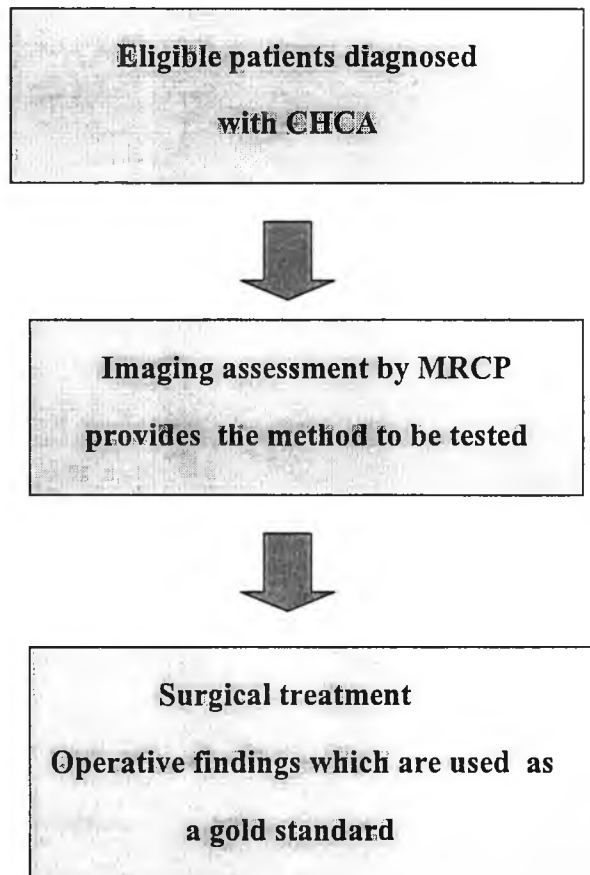
The study was conducted as a descriptive, diagnostic test study. This study aimed to determine the performance of MRCP as a preoperative diagnosis in patients with hilar CHCA and common bile duct CHCA. The overview design is shown in Figure 8.

SCOPE OF THE STUDY

The scope of this study focused on hilar CHCA for the following reasons.

- 1) Hilar CHCA is a common location of CHCA in Northeast Thailand, and represents a major health problem in this region.
- 2) The hilar location is easily visualized in the operative field by the surgeon. Therefore operative findings of the hilar CHCA can be used as an efficient gold standard (reference standard) in this study.
- 3) Hilar CHCA patients need more aggressive surgical treatment and differently planned surgical therapeutic procedures for satisfactory long term survival.

Figure 8. Design overview of the study.



Imaging of hilar CHCA provides information relevant to deciding whether a tumor is resectable, and identifies which patients may benefit from aggressive surgery.

CHCA of the common bile duct was also included in this study as a secondary objective. In addition, CHCA of the common bile duct was easily seen in the operative field. The study did not involve intrahepatic CHCA, despite this being a major problem in Northeast Thailand. The intrahepatic location of CHCA is in a deep area in the liver parenchyma, which is usually difficult or impossible

to visualize in the operative field. Therefore, operative findings of the intrahepatic CHCA are unable to be used as a gold standard.

JUSTIFICATION

The study was conducted to determine the performance of MRCP as a preoperative diagnostic procedure in patients with hilar CHCA. To achieve the stated study objective, a diagnostic test was decided upon as the most suitable study design.

TARGET POPULATION

The target population consists of patients with CHCA who are potential candidates for surgical treatment.

STUDY POPULATION

The study population consisted of patients with CHCA in Srinagarind hospital, Khon Kaen University, Khon Kaen, Thailand.

INCLUSION CRITERIA:

1) Patients with CHCA who were diagnosed by clinical or other imaging modalities including US or CT.

1.1) Patients who had one of the following clinical presentations being proposed by Uttaravichien T, et al(74, 75) were included.

Jaundice :

1.1.1) Jaundice patients with no fever may have an enlarged liver, hydrop gallbladder, ascites, or serum bilirubin of more than 15 mg %.

1.1.2) Jaundice patients with fever and abdominal pain which may be accompanied by have intermittent fever, fever with chill, right upper abdominal pain, or tenderness of the gallbladder.

1.1.3) Jaundice patients with fever and septic shock may also show symptoms of clinical manifestation of ascending cholangitis, serum bilirubin may be higher than 20 mg % - 40 mg %, renal failure, or liver failure.

No jaundice:

1.1.4) Patients with chronic abdominal pain may have an enlarged liver with a have consistency, or hydrop gallbladder.

1.1.5) The patients who had clinical manifestation of cholecystitis, acalculus, or cholecystitis.

1.2) **For imaging criteria**(41), we included clinically suspected patients who recorded one of the following imaging findings,

1.2.1) Liver mass, nodular, particularly ill defined boundary or infiltrative mass and minimal peripheral enhancement on CT scan.

1.2.2) Dilatation of the biliary tree; peritumoral bile ductdilatation, tortuosity and irregular dilatation.

Other imaging findings that assisted with patient inclusion were regional lymph node enlargement and atrophy of obstructed lobe of the liver.

2) Patients who were investigated by MRCP.

3) Patients who recieved surgical treatment and in whom diagnosis of CHCA was previously confirmed.

EXCLUSION CRITERIA:

1) Preoperative diagnosis showed CHCA but operative findings revealed other abnormal pathology such as the presence of stone, or carcinoma of adjacent regions.

- 2) Patients with MRI contraindications such as patient with a cardiac pace maker, cochlea implantation, intracranial aneurysm clip or claustrophobia.

SAMPLE SIZE

With the expected sensitivity of the MRCP in the diagnosis of hilar CHCA at 90%, and a study precision of 10% at 95% CI, the sample of subjects with operative findings of hilar CHCA is

$$\begin{aligned} n &= (Z_{0.975})^2 p(1-p) / d^2 \\ &= (1.96)^2 (0.9)(1-0.9) / d^2 = 35 \end{aligned}$$

The prevalence of hilar CHCA among all patients with CHCA in our hospital was 65%. Therefore the sample size is $35 \times 100 / 65 = 54$ patients with CHCA

VARIABLES TO BE MEASURED

- 1) General characteristics of CHCA patients which made up the baseline data: age, gender, address.
- 2) Information of other imaging modalities.
- 3) MRCP findings assessed a radiologist.
- 4) Operative findings assessed by surgeons who were blinded to the MRCP findings.

MEASUREMENT

Operative findings: The method for giving the gold standard. ERCP and the pathological findings of surgical specimens were used to provide additional information in some cases.

MRCP: The method used to determine the performance of identifying patients with hilar CHCA and common duct CHCA and particularly the location. MRCP is a special MRI technique used to image the cholangiogram. The MRCP in this study were conducted using the MR machine, a 1.5 T GE medical system. Necessary software, special parameter and well trained technologists are needed to image of the biliary tree.

Radiologists interpret the results of the imagings.

VALIDITY AND RELIABILITY OF MRCP

For validity:

Content validity: There were many reports showing that MRCP is valid to diagnose and assess the biliary system in both human and phantoms. Experts in medical imaging accept MRCP as one method to assess the biliary tract.

Calibration: The machine has a routine calibration program to make its performance comply with international standards.

For reliability:

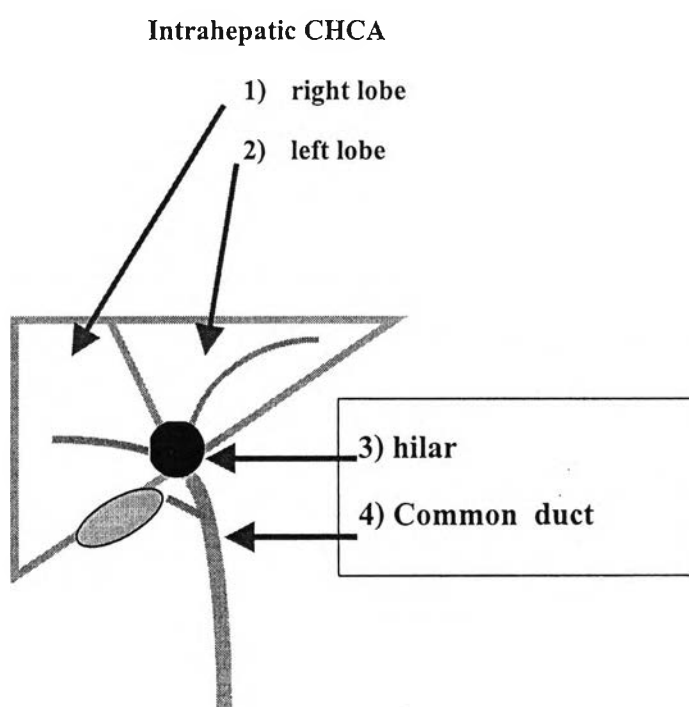
Interpreters: The radiologist interpreted the MRCP imaging.

Inter-rater and intra-rater reliability tests for the interpretation of radiologists were conducted in 30 patients before the main study was performed, in order to assess their standard in the interpretation of MRCP. We found the Kappa value of inter-rater reliability test was 0.91 and Kappa values of intra-rater reliability tests were 0.94 and 0.92 for the first and second radiologists respectively.

OUTCOMES MEASUREMENT

For the primary research question: Each CHCA patient will be assessed using the **MRCP** and **Operative findings** for hilar CHCA (lesion in location 3) as seen in Figure 9.

Figure 9. The location of the interest hilar(3) and common duct (4)



The **MRCP** finding of hilar CHCA was interpreted as

- positive (+ve) when the hilar lesion caused by a tumor was seen on the MRCP by the radiologist.
- negative (-ve) when no hilar lesion caused by a tumor was seen on the MRCP by the radiologist.

The **operative finding** of hilar CHCA was assessed and interpreted as

- positive (+ve) when surgeons found hilar CHCA in the operative field.
- negative (-ve) when surgeons did not find hilar CHCA in the operative field.

For secondary research question:

The common duct location was assessed using an MRCP and the operative findings in the same manner as hilar CHCA.

DATA COLLECTION

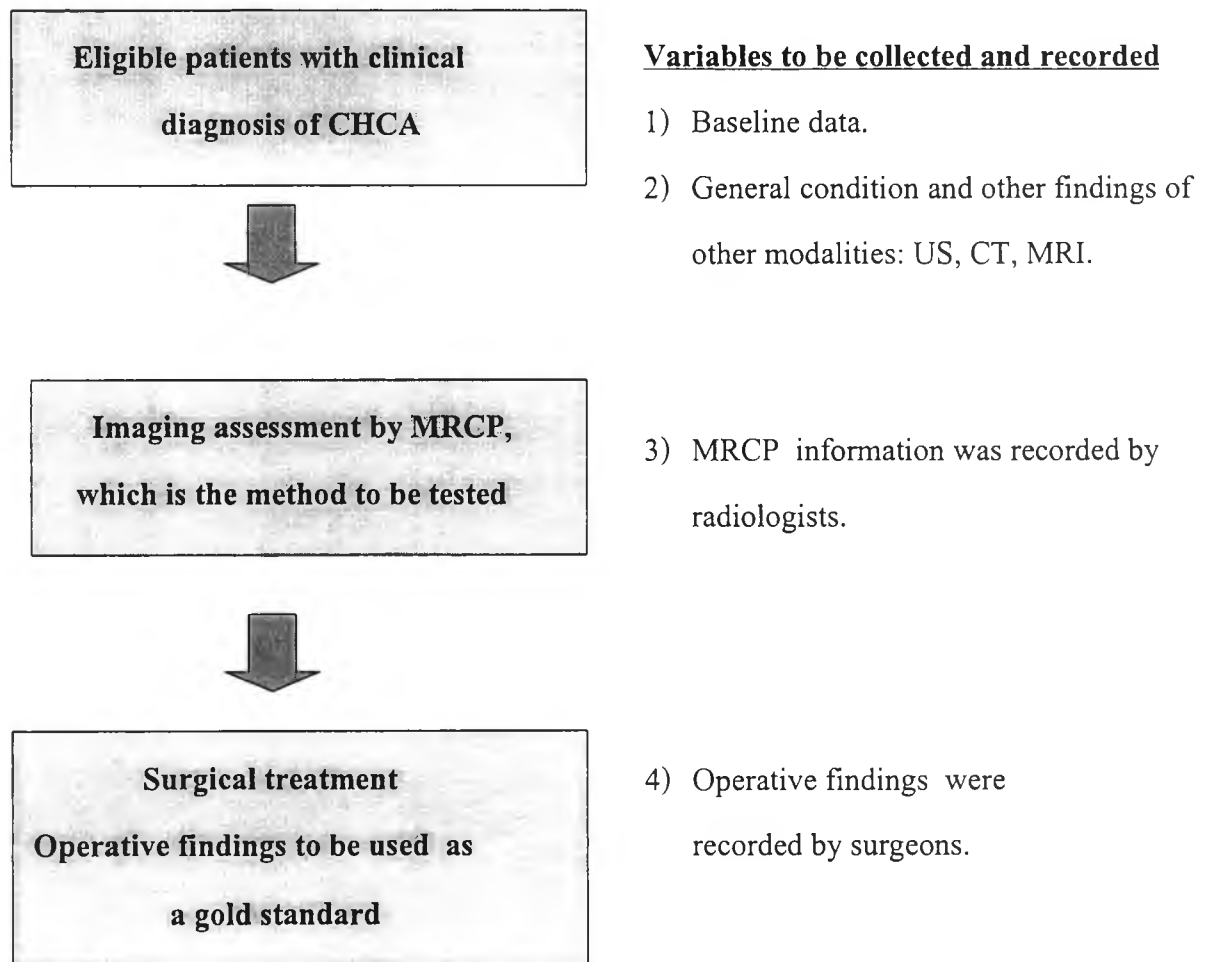
Method of data collection: prospective data collection. Information of CHCA patients who were diagnosed by an MRCP and underwent an operation between January 2000 to February 2001 was collected and recorded.

The **variables** which were measured and collected are as follows:

- 1) Base line data: age, gender and address.
- 2) General condition including other imaging modality information such as US, CT and MRI.
- 3) MRCP findings: assessed, interpreted and recorded by radiologists.
- 4) Operative findings: assessed and recorded by surgeons.

Overview of the data collection method is shown in Figure 10

Figure 10. Overview of the method of data collection



DATA ANALYSIS

1) Base line variables of patients were described as percentages for categorical data, mean (SD) and median (range).

2) For the primary research question:

MRCP findings of hilar CHCA were compared to the operative findings in a 2x2 table. The sensitivity (sen), specificity (spec), accuracy (acc), positive predictive value (PV+), negative predictive value (PV-), post-test likelihood if

the test was negative, likelihood ratio and correlation of variables were calculated to measure the MRCP performance.

A 95% confidence interval (CI) of the expected sensitivity was calculated.

Table 1. MRCP findings versus the operative findings of hilar CHCA patients, dummy table

MRCP	Operative findings		Total
	+	-	
+	a	b	a+b
--	c	d	c+d
Total	a+c	b+d	a+b+c+d

- a** = operative + (hilar CHCA was seen on operation) and MRCP + (visualized hilar CHCA on MRCP)
- b** = operative - (no hilar CHCA was seen on operation) and MRCP + (visualized hilar CHCA on MRCP)
- c** = operative - (hilar CHCA was seen on operation) and MRCP - (no visualized hilar CHCA on MRCP)
- d** = operative - (no hilar CHCA was seen on operation) and MRCP - (no visualized hilar CHCA on MRCP)

Statistical tests were calculated as follows:

$$\begin{aligned}
 \text{Sensitivity} &= a/a+c \\
 \text{Specificity} &= d/b+d \\
 \text{Accuracy (total corrected prediction)} &= a+d/(a+b+c+d) \times 100 \\
 \text{Positive predictive value (PV+) or post-test probability or} & \\
 \text{Post-test likelihood if the test was positive} &= a/a+b \\
 \text{Negative predictive value (PV-)} &= d/c+d \\
 \text{Post-test likelihood if the test was negative} &= c/c+d \text{ or } 1- (PV-) \\
 \text{Likelihood ratio} &= \frac{a/a+c}{b/b+d} \\
 &= \frac{a(b+d)}{b(a+c)}
 \end{aligned}$$

For the secondary research question:

We calculated statistics for the manifestation of the common duct location by using the same methods as for the hilar location.

An agreement test between the MRCP findings and the operative findings of hilar CHCA and common duct CHCA was conducted by using the Kappa statistic (K) follows.

$$K = \frac{Po - Pe}{1 - Pe}$$

ETHICAL CONSIDERATION

This research involved operative procedures and special investigation. Therefore the proposal of thesis research was sent to and approved by both the ethical committee of the Faculty of Medicine at Khon Kaen University, and the ethical committee of the Faculty of Medicine at Chulalongkorn university.

MRI and special techniques such as MRCP and MRA are accepted as safe techniques for human investigation worldwide, and are also approved by the FDA in the USA.

The researchers were not involved in the decision making process of patients to participate in the research.

LIMITATION

The study included operative procedures, which may include aggressive surgery. Some patients refused to undergo surgical treatment.

BENEFITS OF THE STUDY

MRCP, as a non-invasive cholangiographic method to assess the biliary tree, may replace invasive direct cholangiography such as ERCP or PTC, to provide a preoperative diagnosis and assessment of the biliary tract obstruction in relation to hilar CHCA.

MRCP requires neither a contrast agent nor other forms of intervention. It is therefore a safe method to assess biliary tract obstruction, and particularly hilar CHCA.

Recent reports between 1998 and 2000 reported an increasing trend in the use of aggressive surgical treatment for hilar CHCA. MRCP may be the best adjunctive imaging technique to provide information for operative planning and for making a decision as to whether a tumor is resectable or not. It may also help in the selection of patients who might benefit from extensive surgery.

The results of MRCP may be beneficial in planning surgical treatment, type of operation, and selection of patients that may benefit from the operation. This will affect the outcome and quality of life of patients.

CONSIDERATION FOR RELIABILITY, VALIDITY AND CONTROL OF BIAS

We considered the reliability and validity of the results of the MRCP findings as interpreted by the radiologists. Inter-observer and intra-observer reliability tests were performed before the main research started. An MRCP findings assessment form was created because of the need to ensure the interpretation of MRCP findings used the same pattern and were easy to interpret. An operative findings assessment form was also developed for the same purpose. We also considered the interval between the MRCP and the operation date. Change in the tumor, such as size or extension of the tumor, was a focal point for researchers. The mean (\pm S.D.) interval was 13.6 (\pm 8) days. We assumed that the pathology, which was seen on the MRCP and in the operative field, was of the same status. We were concerned about the operative assessment bias of the surgeon. The MRCP information was blinded to the surgeon during the process of prospective data collection in order to control potential bias. We selected the operative finding of the hilar CHCA and common bile duct CHCA as the gold standard because these areas are clearly visible in the operative field. It is therefore believed to be a genuine gold standard.

SUMMARY OF RESEARCH DESIGN AND METHODOLOGY

RESEARCH QUESTIONS

Primary question: How effective is MRCP in the diagnosis of hilar CHCA ?

Secondary question: How effective is MRCP in the diagnosis of CHCA of the common bile duct?

RESEARCH OBJECTIVES

Primary objective:

To determine the diagnostic performance of MRCP in patients with hilar CHCA.

Secondary objectives:

To determine the diagnostic performance of MRCP in patients with common bile duct CHCA.

To evaluate the agreement between MRCP and the operative findings in the diagnosis of hilar CHCA and common bile duct CHCA.

RESEARCH DESIGN

Descriptive study, diagnostic test.

TARGET POPULATION

Patients with CHCA requiring preoperative assessment.

STUDY POPULATION

Patients with CHCA in Srinagarind Hospital, Khon Kaen University.

Inclusion criteria: Patients with CHCA who were assessed by MRCP and underwent surgery.

Exclusion criteria: Patients with unconfirmed CHCA.

SAMPLE SIZE

With the requirement 90% sensitivity and 10% precision at a 95% CI and with 65% prevalence of hilar CHCA, the sample size was estimated to be 54 patients with CHCA.

OUTCOME MEASUREMENT

MRCP findings : assessed, interpreted and recorded by radiologists.

Operative findings: assessed and recorded by surgeons.

DATA COLLECTION

Prospective data collected between January 2000 and February 2001.

DATA ANALYSIS

MRCP and operative findings were compared in a 2x2 table. Statistics for diagnostic test, including sensitivity, specificity, accuracy and likelihood ratio were calculated.