



Teleconsultation ultrasonography: a new weapon to combat cholangiocarcinoma

Nittaya Chamadol,^{1,2,3} Vallop Laopaiboon,¹ Jiraporn Srinakarin,¹ Watcharin Loilome,^{2,3,4} Puangrat Yongvanit,^{2,3,4} Bandit Thinkhamrop,^{2,3,5} Narong Khuntikeo^{2,3,6}

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ABSTRACT

Although cholangiocarcinoma (CCA) is usually a rare cancer, in northeast Thailand it kills 20 000 or more people every year. The prognosis is very poor owing to late stage diagnosis, with palliative treatment often representing the only option. In this area of predominantly rural Thailand, CCA is associated with infection with the liver fluke, *Opisthorchis viverrini*, which is classified as a group 1 carcinogen. Up to 6 million Thais are infected with this fluke. The Cholangiocarcinoma Screening and Care Program (CASCAP) was initiated in 2014 with the aim of detecting early stage CCA, allowing curative surgery, by using ultrasound (US) screening of prospectively 500 000 at risk individuals. In order to assess the massive number of radiological images, a teleconsultation system was set-up. This allows US images to be sent to a dedicated server where they can be viewed by an expert radiologist who then provides a provisional diagnosis, recommending more advanced diagnostic techniques (CT and MRI) for suspected cases. To date, 250 000 people have been screened, and 2000 cases of CCA diagnosed. This innovative information transfer procedure will also be made available to Laos, Cambodia and Vietnam, where *O. viverrini* infection is also common.

INTRODUCTION

Cholangiocarcinoma (CCA) is a highly malignant epithelial tumour of the biliary system. It is the second most common primary liver cancer worldwide after hepatocellular carcinoma.¹ CCA is the most common liver cancer in northeast Thailand^{2,3} where the highest incidence worldwide is significantly correlated with the presence of the liver fluke *Opisthorchis viverrini*, which is classified as a group 1 carcinogen.⁴ Infection with this trematode occurs when raw or undercooked fish is consumed, something common in the traditional nutrition pattern of this part of Thailand.⁵ If untreated, *O. viverrini* can survive for years in humans where it progressively accumulates in the biliary system, leading to a chronic inflammatory response and eventually periductal fibrosis (PDF). This facilitates the development of CCA.⁶ PDF

has been documented in the non-tumorous area of the liver parenchyma in patients with CCA.^{7,8}

In addition to the liver fluke, other risk factors include primary sclerosing cholangitis, biliary duct cysts, hepatolithiasis, toxins, inflammatory bowel disease, hepatitis C virus, hepatitis B virus, cirrhosis, obesity, alcohol consumption, smoking and a genetic predisposition 1. Once the disease manifests, surgery is the only hope for cure.^{9,10} To achieve a better survival outcome, focus should centre on the detection of patients with early stage cancer followed by radical surgery.¹¹

CCA arises in the intrahepatic duct or the extrahepatic duct epithelium. The tumour is classified based on its anatomical location as intrahepatic CCA if it occurs at or above the level of second order branches of the bile duct or extrahepatic (E-CCA) if it occurs below the level of second order branches of the bile duct down through the distal part of the common bile duct. E-CCA is further divided into perihilar (P-CCA) if it occurs above the level of cystic duct junction and distal (D-CCA) if it occurs below the level of cystic duct junction.¹²

Based on its morphology, CCA is classified into three types by the Liver Cancer Study Group of Japan.¹³

1. Mass-forming CCA (MF-CCA) originates in the mucosa of the duct and appears as mass lesion.
2. Periductal infiltrating CCA (PI-CCA) in which the tumour originates in the mucosa and involves the submucosa and serosa of the duct wall.
3. Intraductal CCA (ID-CCA) in which the tumour originates in the mucosa of the bile duct along which it spreads. The tumour may be small in size intraductally and may be associated with mucin formation.¹⁴

¹Department of Radiology, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
²Cholangiocarcinoma Screening and Care Program (CASCAP), Khon Kaen University, Khon Kaen, Thailand
³Multidisciplinary team, Cholangiocarcinoma Research Institute, Khon Kaen University, Khon Kaen, Thailand
⁴Department of Biochemistry, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand
⁵Department of Epidemiology and Biostatistics, Faculty of Public Health, Khon Kaen University, Khon Kaen, Thailand
⁶Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand

Correspondence to
Professer Nittaya Chamadol;
nittayachamadol@yahoo.com

Combinations of these types are possible as the growth of PI-CCA may lead to invasion of the liver parenchyma.

According to its anatomical location and tumour morphology, clinical presentation may also vary, including a non-specific clinical presentation in the early stages of the disease. For patients presenting in the advance stage of the disease, the prognosis is very poor.^{15,16}

Using ultrasonography, CCA may appear as liver mass (MF-CCA) and bile duct dilatation (PI-CCA and ID-CCA) caused by biliary obstruction or by mucin production by the tumour. This technique represents the most effective means of screening, as no definite tumour marker is available for reliable tumour screening or surveillance. It allows an acceptable initial imaging modality for liver and hepatobiliary diseases.¹⁷ It is non-invasive, readily available, repeatable and portable. It also has high sensitivity for the detection of liver mass^{18,19} and is accurate for the detection of bile duct dilatation.¹⁷ It can be used for the detection of parenchymal liver disease,¹⁹ and a recent report shows its potential role in the detection of PDF in an endemic area for CCA by which the carcinoma can be detected in situ.⁷

The main disadvantage of ultrasonography is that it is operator dependent.^{7,17-19} The reliability of the examination is directly related to the operator's experience; therefore, training and the availability of an expert for consultation are of critical importance.

THE CASCAP STUDY

The risk group of CCA in the northeast Thai endemic area of *O. viverrini* is estimated to be approximately 21 million from 20 provinces covering an area of approximately 160 000 km². Ultrasonography is the critical screening method used by the Cholangiocarcinoma Screening and Care Program (CASCAP) of the Medical Faculty of Khon Kaen University in northeast Thailand^{20,21}. This study has initial funding for 4 years starting 2014. The aims of surveillance and screening for CCA by CASCAP are the following: (1) detection of PDF with close follow-up by ultrasonography and (2) detection of liver mass or bile duct dilatation or a combination of these to be considered for immediate additional diagnostic investigation. This will provide increased primary prevention for tumours by allowing early estimates of individual risk of developing CCA and facilitate the early diagnosis of the disease at a time when resection is still a treatment option. The process for patient transfer to a proper management scheme after diagnosis has been negotiated with the Thai Ministry of Health.

In order to reach as many of the at risk population as possible, without requiring extensive travel to a diagnostic hospital facility, a training course based at Khon Kaen University Hospital was established in order to increase the number of doctors and general practitioners who can perform ultrasound (US) examinations in rural northeast Thailand. The 2-day training course for CCA surveillance includes both theoretical and practical aspects with

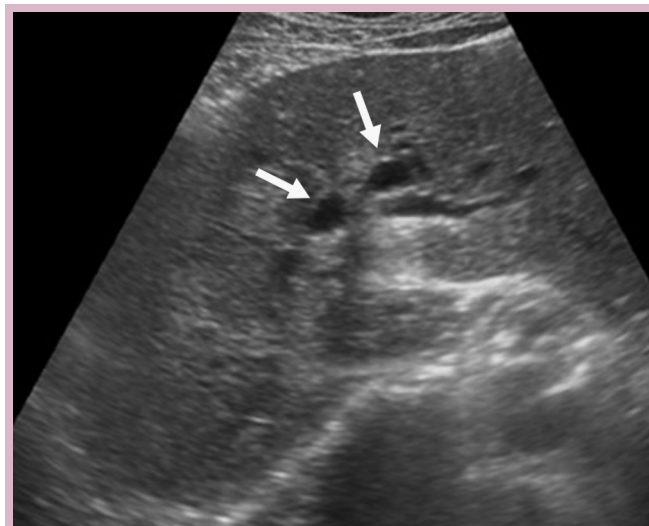


Figure 1 Periductal infiltrating cholangiocarcinoma (PI-CCA). Ultrasonographic image showing dilatation of the intrahepatic duct in the left liver lobe (arrows) of a 71-year-old man. Further imaging showed dilatation of the bile duct in keeping with PI-CCA in the left lobe liver.

emphasis on PDF and CCA detection. The first day of training provides the trainees with an overview of CCA imaging: gallbladder and biliary tree diseases and normal sonographic findings of the hepatobiliary system, US imaging of other organs including the pancreas, kidney and spleen and US features of hepatobiliary diseases such as liver mass and parenchymal liver diseases. The second day is devoted to hands-on US practising. This is being carried out with the aim of establishing online consultation and diagnosis of ultrasonographic images (figure 1).

Online consultation assists less experienced medical workers with interpreting the ultrasonographic findings. The expert and rural health worker can then communicate for the proper management of each patient via an online software application. For patients with PDF, a follow-up US is recommended, and if there is a mass lesion or dilatation of the bile duct, the expert radiologist will confirm the finding via online consultation and aid in making a decision on further diagnostic measures.

This online consultation, called CASCAP MD KKU Solution (figure 2), is part of a larger scheme called CASCAP Tools that is located at <http://www.cascap.in.th>. This solution system comprises an application installed in a workstation computer connected to the US machine (Hitachi Aloka, Japan), software at the picture archiving and communication system (PACS) server and a web application in CASCAP Tools. The application at the workstation is to manage the digital communication in medicine (DICOM) file using an electronic imaging format to be stored systematically in PACS. The CASCAP MD KKU Solution performs the following tasks: (1) It sets up the US machine with DICOM so that it can store the images according to the designated worklist; (2) The workstation retrieves the worklist, which lists the risk group to be screened. This has been prepared

CASCAP – MD KKU Solution

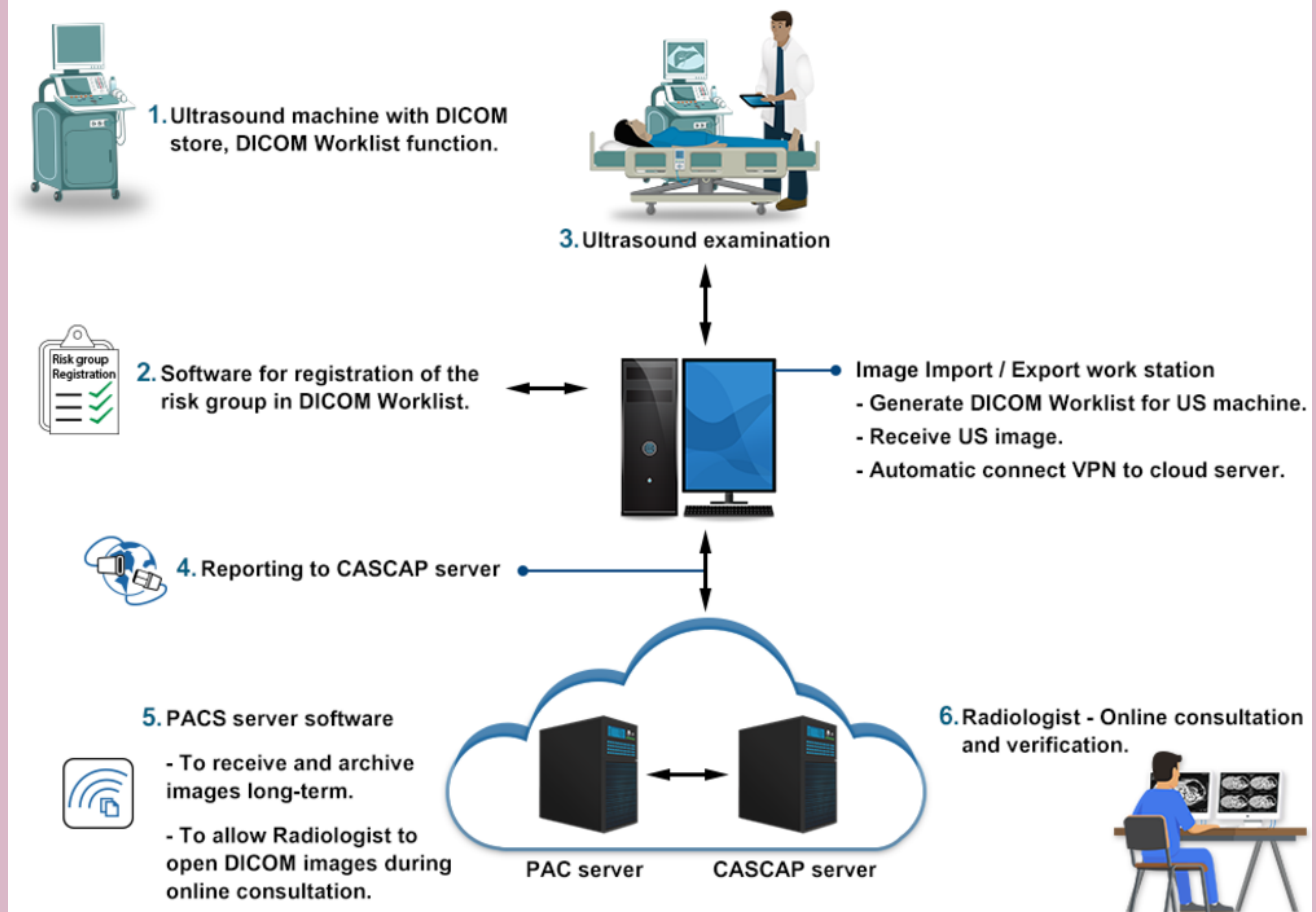


Figure 2 Diagram showing the CASCAP MD KKU Solution workflow for ultrasound image collection and teleconsultation. CASCAP, Cholangiocarcinoma Screening and Care Program; DICOM, digital communication in medicine; PACS, picture archiving and communication system; US, ultrasound; VPN, virtual private network.

by the local health workers using CASCAP Tools. This is then used to generate the worklist for the US machine; (3) Medical workers perform the US examination; (4) The workstation receives the US images and reports to CASCAP Tools via a virtual private network (VPN); (5) The PACS server archives all images for long-term use, as well as allowing a radiologist to open the DICOM images for online consultation and (6) The radiologist provides online consultation and verification of the diagnosis.

CASCAP Tools is accessible to public and private hospitals, as well as to other health facilities, for their own use free of charge. To be able to download CASCAP Tools, the system administrator will be verified and requested to sign an agreement according to Thai regulations. Once activated, the administrator can then add members to the system including data managers, physicians who will provide services in ultrasonography and other healthcare personnel. On logging into the system with user identification and password, the healthcare personnel can enrol risk groups to receive ultrasonography for CCA screening using a unique identification, the 13-digit Thai citizen identification number (CID) and the hospital code forming an

18-digit personal identification (PID) number. This can be done anywhere, at any time prior to or at the same time as the ultrasonographic examination. At the appointment date for ultrasonography, the healthcare worker only needs to enter the PID into the ultrasonography device before performing the examination. The healthcare worker can then store each image, followed by entering information regarding the diagnosis. All of this information will be transferred to the CASCAP server located at a secured location and operated by the programmers of the Cholangiocarcinoma Foundation of Thailand.

Between 5 and 15 ultrasonographic images are stored for each individual per examination. Each image is stored in DICOM format with a size of less than 300 KB per image. Based on this image size, the current CASCAP Tools server can accommodate data for the whole country with a population size of 67 million for more than 5 years. The DICOM file can also be viewed on most computer screens without any loss of image quality, hence, allowing validation of the diagnosis at any computer that is connected to the Internet. The system also allows each diagnosis to be made by a radiologist. This enhances quality assurance of

the diagnosis, as well as promoting continuing medical education efficiently. Most importantly, there are tools to help suspected cases of CCA to receive appropriate care and management. All securely stored data can be retrieved and viewed by authorised health personnel responsible for the healthcare services using the CID. Thus, all participating institutions, no matter where they are, can recognise and provide medical care to the same client or patient when appropriate. By using the CID, it is possible to detect and track changes in the ultrasonographic findings with time. This will facilitate the early detection of CCA, which is critical for the success in combating this usually fatal disease.

Three years after the launch of CASCAP Tools, there were more than 549 800 individuals enrolled in the risk group for further screening. More than 282 800 have received an ultrasonography examination, and there are more than 3270 healthcare facilities that have activated CASCAP Tools. All of these were done on a voluntary basis.

Teleconsultation provides a means for screening by physicians in consultation with expert radiologists, thus allowing treatment and curative surgery if necessary, in a usually fatal disease. Teleconsultation is not confined by country borders, and this service can be provided throughout the Greater Mekong Subregion where CCA is common and 90 million people are at risk²², including populations in poorly accessible county areas, without the need for the patient to be transported to a major hospital for screening.

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