

UNIVERSITY OF MEDICINE AND PHARMACY OF CRAIOVA
PhD SCHOOL

PhD THESIS

**MODERN MEDICAL IMAGING TECHNIQUES
USED IN DIAGNOSING THE ETIOLOGY OF THE
BILIARY TRACT OBSTRUCTION**

-ABSTRACT-

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I. CURRENT STATE OF KNOWLEDGE

INTRODUCTION

Jaundice is represented by a yellow colouring of the skin, sclera and mucous membranes due to the appearance of bilirubin tissue deposits at these levels. Usually, jaundice is associated with liver or bile tract damage.

Obstructive jaundice is a plurietiological disease and can be encountered in both genders, at any age. Some of the most common causes known to determine obstructive jaundice are: cholelithiasis, inflammatory, infectious or neoplastic processes developed in the biliary tract, the presence of parasites inside the biliary tract, pancreatic cancer, acute pancreatitis, chronic pseudotumoral pancreatitis and large periportal lymphadenopathies.

The use of medical imaging techniques is essential to establish the etiological diagnosis of the obstructive jaundice. Numerous imaging methods such as ultrasonography, computed tomography, magnetic resonance imaging with magnetic resonance imaging colangiopancreatography, endoscopic retrograde colangiopancreatography, percutaneous transhepatic colangiography and ecoendoscopy can be used in this regard.

At the time of writing, parameters such as minimal age, mean age, maximum diameter and mean diameter of the common bile duct in patients with diseases that generate biliary tract obstruction have not been fully studied in Romania. Assessing these parameters can significantly contribute to establishing the etiologic diagnosis of biliary tract obstruction.

Key words: obstructive jaundice, biliary lithiasis, cholangiocarcinoma, chronic pancreatitis, pancreatic cancer, ampullary carcinoma.

I.1. OBSTRUCTIVE JAUNDICE

In adults, the normal total bilirubin serum value is up to 1 mg/dl, with a higher recorded value for unconjugated bilirubin. A slight increase in total serum bilirubin may not be associated with jaundice. Usually, jaundice becomes clinically obvious at bilirubin concentrations that exceed 3 mg/dl [1].

Obstructive jaundice is a plurietiological disease and can be encountered in both genders, at any age. Obstructive jaundice may be generated by benign (acute pancreatitis, chronic pseudotumoral pancreatitis, choledocholithiasis, hepato-biliary parasitosis) or malignant diseases (pancreatic cancer, hepatocellular carcinoma, cholangiocarcinoma, ampullary carcinoma).

I.2. IMAGING DIAGNOSIS OF THE OBSTRUCTIVE JAUNDICE

The use of medical imaging techniques is essential to establish the etiological diagnosis of the obstructive jaundice. Numerous imaging methods such as ultrasonography, computed tomography, magnetic resonance imaging with magnetic resonance imaging colangiopancreatography, endoscopic retrograde colangiopancreatography, percutaneous transhepatic colangiography and ecoendoscopy can be used in this regard.

I.3. BILIARY LITHIASIS

Biliary lithiasis is a plurietiological disease that involves interactions between multiple risk factors, including age and gender, diet, pregnancy, rapid weight loss, complete parenteral nutrition, drugs, serum lipid values and genetic factors.

Most patients with biliary lithiasis are asymptomatic. Biliary colic is the dominant symptom among symptomatic patients and is characterized by pain with sudden onset located in the epigastrium or right hypochondrium, radiating posteriorly. Symptoms usually occur after ingesting food containing a large amount of fat. The painful crisis can last up to 4 hours. If its duration exceeds 6 hours, a complication (acute cholecystitis or acute pancreatitis) is taken into consideration. Also, patients may experience nausea and vomiting that do not relieve pain intensity.

Medical imaging diagnosis plays a central role in detecting biliary lithiasis and other related changes. Each of the imaging methods used to explore the biliary tract presents several advantages and disadvantages [2, 3, 4].

The therapeutic management of patients with symptomatic biliary lithiasis was significantly improved by developing endoscopic and radiological techniques. However, surgery is still the most important therapeutic option.

I.4. CHOLANGIOCARCINOMA

The etiology of cholangiocarcinomas is not fully elucidated. Studies evaluating the involvement of risk factors in cholangiocarcinomas are limited by the large variability among populations, as well as due to the fact that many studies group cholangiocarcinomas together with hepatocellular carcinomas.

Primary sclerosing cholangitis is one of the most frequently involved risk factors in cholangiocarcinogenesis. Numerous studies have pointed out that the carcinogenetic process usually begins in the first 3 years after diagnosing primitive sclerosing cholangitis. Patients diagnosed with Caroli disease or choledochal cysts have an incidence rate of

cholangiocarcinomas between 6% and 30%. The surgical removal of these cysts reduces the risk of cholangiocarcinogenesis but does not eliminate it.

Depending on the location, three types of cholangiocarcinoma can be encountered: intrahepatic, perihilar and distal. In the past, perihilar and distal cholangiocarcinomas were grouped up together under extrahepatic cholangiocarcinomas [5, 6].

Diagnosing cholangiocarcinoma is often difficult and requires a multidisciplinary approach. This disease has a silent evolution until it reaches advanced stages. Pain located in the epigastrium and right hypochondrium, night sweats, weight loss and fatigue are nonspecific signs and symptoms encountered in the late stages of this disease. Extrahepatic cholangiocarcinoma is associated with painless jaundice in advanced stages.

Surgical intervention is the only therapeutic method with curative intent in cholangiocarcinomas. More than half of the patients have unresectable tumors at the time of diagnosis. Approximately one-third of patients with tumors initially considered resectable found to be unresectable during surgery. If they can be resected, surgery for single intrahepatic cholangiocarcinomas consists of hepatic segmentectomy or hepatic lobectomy. In over 60% of patients, negative resection margins are obtained, where patients have a survival rate of up to 63% at 5 years [7, 8, 9].

I.5. CHRONIC PANCREATITIS

Chronic pancreatitis is a plurietiological disease resulting from the interaction of many risk factors: alcohol consumption, smoking, genetic factors, autoimmune pancreatitis, recurrent acute pancreatitis, obstructive causes and chronic idiopathic pancreatitis.

In most cases, chronic pancreatitis is associated with pain frequently located in the epigastrium, radiating posteriorly, which can be diminished by various antalgic positions. The intense epigastric pain experienced by these patients limits their food consumption and contributes to malnutrition and weight loss. Also, it significantly affects the patients' quality of life and makes them vulnerable to using excessive amounts of medication with analgesic effect. Jaundice may be present in patients with chronic pancreatitis and is mainly determined by cholestasis due to a pancreatic head pseudocyst. Similarly, an increased pancreatic volume during acute phases can lead to choledochal obstruction, associated with jaundice.

In advanced stages, patients with chronic pancreatitis exhibit exocrine (maldigestion, malabsorption and steatorrhea) and endocrine pancreatic insufficiency (diabetes). Biological explorations usually reveal normal values of serum amylase and amylazuria, except acute phases. Serum lipase has increased values over time in patients with chronic pancreatitis. Serum trypsinogen has very low levels in advanced stages.

The quality of life of patients diagnosed with chronic pancreatitis is mainly affected by intense abdominal pain experienced in the epigastrium and, more rarely, in the right or left hypochondrium. Thus, therapeutic means aim to remove or diminish pain intensity. This goal can

be achieved by administering analgesic drugs. Generally, the use of non-steroidal anti-inflammatory drugs is avoided in these patients. Opioid analgesia addiction occurs in approximately one third of patients [10].

I.6. PANCREATIC CANCER

Smoking is the most important risk factor involved in the carcinogenetic process in the pancreatic tissue. Around 20-25% of all cases of pancreatic cancer are caused by smoking [11]. A diet with an increased fat content and an increased consumption of red or processed meat is associated with an increased risk of developing pancreatic cancer, while fruit and vegetable consumption has a protective but limited effect [12, 13]. Pancreatic cancer has a high incidence among patients diagnosed with chronic pancreatitis. Also, the heredo-collateral history of pancreatic cancer significantly influences the individual risk [14].

Pancreatic cancer can be located in the head (65%), body (15%) or caudal region (15%) or it can diffusely affect the entire pancreas (5%) [15].

Pancreatic head cancer determines the obstruction of the common bile duct, relatively fast in its evolution, followed by the installation of unremitting jaundice in about 50-80% of patients. Also, the obstruction of the distal common bile duct is followed, in 30% of cases, by an increased volume of the gallbladder, unaccompanied by pain through palpation (the Courvoisier-Terrier sign). Patients with pancreatic cancer located in the corporeal or caudal region present continuous epigastric pain in advanced phases, which progressively accentuates and can radiate to the left hypochondrium. The mechanism of pain in these patients is represented by the invasion of the celiac plexus and the upper mesenteric plexus [16].

Regarding pancreatic cancer, the surgical resection of the malignant tumor is the only therapeutic option with potentially curative intent, available at the time of writing. Unfortunately, due to the onset and silent evolution of this disorder, most patients are diagnosed in advanced stages of this disease, when only 15-20% can be subjected to surgery [17, 18]. In case of pancreatic head cancers, cephalic duodenopancreatectomy is performed. Tumors developed in the pancreatic body and caudal regions are surgically treated through removal of body and/or caudal regions of the pancreas associated with splenectomy. Unresectable pancreatic cancers benefit from various palliative therapeutic methods.

I.7. AMPULLARY CARCINOMA

Ampullary carcinoma is part of the periampullary carcinomas group that includes duodenal carcinomas, ampullary and pancreatic cancers and cancers affecting the distal portion of the common bile duct.

Familial adenomatous polyposis represents an important risk factor for the development of ampullary carcinoma [19]. For patients with familial adenomatous polyposis, periampullary carcinomas represent the second most common cause of death after colorectal cancer.

Approximately 70-80% of patients diagnosed with ampullary carcinoma develop obstructive jaundice. It differs from the one encountered in pancreatic head carcinoma because of its fluctuating character and early onset. Other signs and symptoms among these patients include weight loss, pruritus, abdominal pain predominantly located in the epigastrium.

Surgical resection is the only treatment with a curative intent in case of ampullary carcinoma and consists in performing a cephalic duodenopancreatectomy. This disease is associated with an increased rate of resection (80-90%) at the time of diagnosis [20, 21].

II. PERSONAL CONTRIBUTION

II.1. OBJECTIVES OF THE PhD THESIS

Regarding my PhD thesis, my main objective was to evaluate the magnitude of the common bile duct diameter changes according to the etiological factor that generated biliary tract obstruction. Also, in the current study, I wanted to identify possible connections between the minimum and mean age of the patients involved in the study and the conditions that caused obstructive jaundice.

Due to an extremely varied etiology regarding biliary tract obstruction, I considered that the present study should include patients with the following conditions: biliary lithiasis, pancreatic cancer, chronic pancreatitis, cholangiocarcinoma and ampullary carcinoma.

The results and conclusions of this study can prove useful both locally and globally by expanding the current level of knowledge.

II.2. MATERIALS AND METHODS

The study included 133 patients diagnosed with one of the five aforementioned conditions: biliary lithiasis, pancreatic cancer, chronic pancreatitis, cholangiocarcinoma and ampullary carcinoma. The current study was performed in a prospective manner. Patients enrolled in the study were investigated through medical imaging methods and diagnosed with biliary lithiasis, pancreatic cancer, chronic pancreatitis, cholangiocarcinoma or ampullary carcinoma during 01.10.2016-01.10.2018 at the Department of Radiology and Medical Imaging of the Clinical Emergency County Hospital Craiova and in the Department of Medical Imaging of the University of Medicine and Pharmacy of Craiova, respectively. The patients enrolled in

the study belonged to the Department of Gastroenterology and Surgery I and II of the Clinical Emergency County Hospital Craiova. All patients have been subject to rigorous inclusion and exclusion criterias.

Regarding the imaging diagnostic protocol, all patients included in the study were initially examined through an abdominal ultrasound examination. Subsequently, they were subjected to an abdominal (patients with biliary lithiasis or chronic pancreatitis) or thoraco-abdomino-pelvic computed tomography scan (patients with pancreatic cancer, colangiocarcinoma or ampullary carcinoma) using a iodine contrast agent, followed by an abdominal MRI examination using additional MRCP sequences and a paramagnetic contrast agent.

The initial group of 133 patients was divided according to the etiological factor involved. Thus, we obtained 5 lots of patients:

- the group of patients diagnosed with biliary lithiasis (63 patients);
- the group of patients diagnosed with pancreatic cancer (32 patients);
- the group of patients diagnosed with chronic pancreatitis (17 patients);
- the group of patients diagnosed with cholangiocarcinoma (12 patients);
- the group of patients diagnosed with ampullary carcinoma (9 patients).

STATISTICAL PROCESSING OF DATA

Regarding the statistical processing of data obtained from the patients included in the study, we turned to applications such as Excel 2010 (developed by Microsoft) and SPSS Statistics version 20 (developed by IBM).

The Excel 2010 application allowed me to calculate mean, minimum and maximum values in a numeric string using the "AVERAGE", "MIN" and "MAX" functions. This approach facilitated the calculation of parameters such as the mean, minimum and maximum values of the age or diameter of the common bile duct. Also, using this application, I was able to make many "pie chart" two-dimensional graphics.

The SPSS Statistics version 20 application was used to determine whether or not there are correlations between the various studied parameters. In this regard, we used the One-Way ANOVA test, which can be accessed from the menu ("Analyze" - "Compare Means" - "One-Way ANOVA"). In the present study, the value of p and the accuracy of the graphs were of interest. p values lower than 0.05 indicated a significant association between the parameters.

II.3. RESULTS

RESULTS OBTAINED IN THE GROUP OF PATIENTS DIAGNOSED WITH BILIARY LITHIASIS

This study included a total of 63 patients (36 women, 27 men) diagnosed with biliary lithiasis.

Among all patients diagnosed with biliary lithiasis, the minimum age was 29 years, the maximum age was 84 years and the mean age was 64.09 years.

Among all patients diagnosed with biliary lithiasis, the diameter of the common bile duct recorded the following minimum, maximum and average values:

- minimum – 4 mm;
- maximum – 20 mm;
- mean – 11,47 mm.

Depending on the number of gallstones discovered inside the gallbladder, the patients diagnosed with biliary lithiasis were classified as follows:

- no gallstones: 12 patients;
- 1 gallstone: 15 patients;
- 2 gallstones: 3 patients;
- 3 gallstones: 3 patients;
- >3 gallstones: 30 patients.

Depending on the number of gallstones discovered inside the common bile duct, the patients diagnosed with biliary lithiasis were classified as follows:

- no gallstones: 39 patients;
- 1 gallstone: 9 patients;
- 2 gallstones: 0 patients;
- 3 gallstones: 12 patients;
- >3 gallstones: 3 patients.

Among all patients diagnosed with biliary lithiasis, the minimum, maximum and mean size of the largest gallstones discovered inside the gallbladder was:

- minimum – 4 mm;
- maximum – 47 mm;
- mean – 16,47 mm.

Among all patients diagnosed with biliary lithiasis, the minimum, maximum and mean size of the largest gallstones discovered inside the common bile duct was:

- minimum – 4 mm;
- maximum – 15 mm;
- mean – 9,91mm.

Among all patients diagnosed with choledocholithiasis, the diameter of the common bile duct recorded the following minimum, maximum and mean values:

- minimum – 6 mm;
- maximum – 20 mm;
- mean – 14,25 mm.

We highlighted a significant association between the diameter of the common bile duct and the maximum size of the gallstones discovered inside the common bile duct ($p = 0.000$).

RESULTS OBTAINED IN THE GROUP OF PATIENTS DIAGNOSED WITH PANCREATIC CANCER

This study included a total of 32 patients (19 men, 13 women) diagnosed with pancreatic cancer.

Among all patients diagnosed with pancreatic head cancer, the minimum age was 51 years, the maximum age was 78 years and the mean age was 63.25 years.

Among all patients diagnosed with pancreatic head cancer, the following minimum, maximum, and mean values regarding tumor dimensions were recorded:

- minimum – 22 mm;
- maximum – 52 mm;
- mean – 33,53 mm.

Among all patients diagnosed with pancreatic head cancer, the diameter of the common bile duct recorded the following minimum, maximum and mean values:

- minimum – 5 mm;
- maximum – 20 mm;
- mean – 13,4 mm.

Among all patients diagnosed with pancreatic head cancer, the diameter of the Wirsung duct recorded the following minimum, maximum and mean values:

- minimum – 3 mm;
- maximum – 12 mm;
- mean – 5,75 mm.

Depending on the TNM stage, patients with pancreatic head cancer included in the study were classified as follows:

- stage 0: 0 patients;
- stage IA: 0 patients;
- stage IB: 10 patients;
- stage IIA: 3 patients;
- stage IIB: 13 patients;
- stage III: 4 patients;
- stage IV: 2 patients.

This study showed a significant association between the size of the pancreatic head tumor and the diameter of the Wirsung duct ($p = 0.018$). However, the size of the pancreatic head tumor did not correlate with the diameter of the common bile duct ($p = 0.102$).

RESULTS OBTAINED IN THE GROUP OF PATIENTS DIAGNOSED WITH CHRONIC PANCREATITIS

This study included a total of 17 patients, all males, diagnosed with chronic pancreatitis.

Among all patients diagnosed with chronic pancreatitis, the minimum age was 48 years, the maximum age was 73 years and the mean age was 60.35 years.

Among patients diagnosed with chronic pancreatitis, the common bile duct diameter recorded the following minimum, maximum and mean values:

- minimum – 6 mm;
- maximum – 20 mm;
- mean – 10.05 mm.

Among patients diagnosed with chronic pancreatitis, the diameter of the Wirsung duct recorded the following minimum, maximum and mean values:

- minimum – 4 mm;
- maximum – 20 mm;
- mean – 8.70 mm.

Among patients diagnosed with chronic pancreatitis, the antero-posterior diameter of the pancreatic head recorded the following minimum, maximum and mean values:

- minimum – 35 mm;
- maximum – 55 mm;
- mean – 40.82 mm.

Pseudocysts developed within the pancreatic head had a minimum size of 11 mm, a maximum size of 35 mm and a mean size of 20.93 mm.

RESULTS OBTAINED IN THE GROUP OF PATIENTS DIAGNOSED WITH CHOLANGIOCARCINOMA

This study included a total of 12 patients (10 men, 2 women) diagnosed with various forms of cholangiocarcinoma.

Among all patients diagnosed with cholangiocarcinoma, the minimum age was 60 years, the maximum age was 76 years and the mean age was 68.75 years.

Among patients diagnosed with an extrahepatic form of cholangiocarcinoma, the common bile duct diameter recorded the following minimum, maximum and mean values:

- minimum – 14 mm;

- maximum – 27 mm;
- mean – 20.6 mm.

RESULTS OBTAINED IN THE GROUP OF PATIENTS DIAGNOSED WITH AMPULLARY CARCINOMA

This study included a total of 19 patients, all males, diagnosed with ampullary carcinoma. Among all patients diagnosed with ampullary carcinoma, the minimum age was 60 years, the maximum age was 68 years and the mean age was 63.88 years.

Among patients diagnosed with ampullary carcinoma, the common bile duct diameter recorded the following minimum, maximum and mean values:

- minimum – 10 mm;
- maximum – 18 mm;
- mean – 15.33 mm.

Among patients diagnosed with ampullary carcinoma, the diameter of the Wirsung duct recorded the following minimum, maximum and mean values:

- minimum – 7 mm;
- maximum – 17 mm;
- mean – 11.66 mm.

Depending on the TNM stage, patients with ampullary carcinoma included in the study were classified as follows:

- stage 0: 0 patients;
- stage IA: 2 patients;
- stage IB: 1 patients;
- stage IIA: 1 patients;
- stage IIB: 5 patients;
- stage III: 0 patients;
- stage IV: 0 patients.

II.4. DISCUSSIONS

After calculating the minimum and mean age for each of the five pathologies mentioned above (biliary lithiasis, pancreatic cancer, chronic pancreatitis, colangiocarcinoma, ampullary carcinoma), I developed several graphs indicating the minimum and mean age of the patients included in the study based on the disease that caused biliary tract obstruction. Furthermore, the data obtained from the study allowed me to calculate the mean diameter of the common bile duct of the patients included in the study based on the disease that caused biliary tract obstruction.

FUTURE RESEARCH OBJECTIVES

After completing my PhD thesis, I set the following goals:

- to continue the current study on biliary tract obstruction;
- to collaborate with other medical centers in Romania - the possibility of carrying out a multicentric national study;
- to study additional pathologies involved in biliary tract obstruction;
- to present the results of my PhD thesis to national and international scientific events;
- to elaborate a BDI or ISI original paper in which I will present the results of my study.

II.5. CONCLUSIONS

- The use of medical imaging techniques is essential to establish the etiological diagnosis of the obstructive jaundice. Numerous imaging methods such as ultrasonography, computed tomography, magnetic resonance imaging with magnetic resonance imaging colangiopancreatography, endoscopic retrograde colangiopancreatography, percutaneous transhepatic colangiography and ecoendoscopy can be used in this regard.
- Patients diagnosed with chronic pancreatitis had the lowest mean age (60.35 years), while patients diagnosed with various forms of cholangiocarcinoma recorded the highest mean age (68.75 years).
- Depending on the average age of men included in the study, three stages are identified: 60 years - chronic pancreatitis; 63-64 years old – ampullary carcinoma and pancreatic head cancer; 70-71 years - cholangiocarcinoma and biliary lithiasis.
- We highlighted a significant association between the size of the common bile duct and the maximum size of the gallstones located inside the common bile duct ($p = 0.000$) in patients with biliary lithiasis.
- The current study did not reveal a significant association between the size of the common bile duct and the number of gallstones located inside the common bile duct ($p = 0.111$) in patients with biliary lithiasis.
- In the Romanian population included in the study, most of the patients with pancreatic head cancer were diagnosed in stages IB and IIB.
- The current study indicated a significant association between the pancreatic head tumor size and the diameter of the Wirsung duct ($p = 0.018$) in patients with pancreatic head carcinoma.
- Out of 32 patients diagnosed with pancreatic head cancer included in the study, 25 patients (78,125%) had jaundice (15 males – 78.95%, 10 women – 76.92%).
- The size of the pancreatic head tumor did not correlate with the common bile duct diameter ($p = 0.102$) in patients with pancreatic head cancer.

- Approximately 55% of patients with ampullary carcinoma were initially diagnosed in stage IIB.
- The mean diameter of the common bile duct according to the disease oscillated between 10.05 mm and 20.6 mm. The minimum value was recorded in patients with chronic pancreatitis, while the maximum value was recorded in patients with extrahepatic cholangiocarcinoma. Patients diagnosed with pancreatic head cancer, biliary lithiasis and ampullary carcinoma had an average diameter of the common bile duct ranging between 13.4 mm and 15.33 mm.
- The mean diameter of the common bile duct according to the disease in male patients oscillated between 10.05 mm and 21.5 mm. The minimum value was recorded in men with chronic pancreatitis, while the maximum value was recorded in men with extrahepatic cholangiocarcinoma. Men diagnosed with pancreatic head cancer, biliary lithiasis and ampullary carcinoma had an average diameter of the common bile duct ranging between 13.73 mm and 15.4 mm.

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