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Research Article,

"Diagnostic-Therapeutic Management in Patients with Extrahepatic Bile Duct Cancer"

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Abstract:

Introduction: Biliary tract tumors, or cholangiocarcinomas (CCAs), comprise a heterogeneous group of malignant tumors that can affect any part of the biliary tree, from the interlobular canals of Hering to the primary biliary duct. In the last 20-30 years, the incidence of these tumours has increased especially after the introduction of the new imaging techniques endoscopic retrograde cholangiopancreatography (ERCP, percutaneous transhepatic cholangiography) and the increased interest for this pathology.
Objective: To evaluate the diagnostic methods and therapeutical results in patients with extrahepatic bile duct cancer.
Material and Method: This cross-sectional study was conducted in the Department of Surgery, Mymensingh Medical College Hospital, Mymensingh, Bangladesh from Jun-2018 to July-2021. We included 124 consecutive patients with suspected bile duct cancer who underwent endoscopic retrograde cholangiopancreatography (ERCP). Every patient underwent an ultrasound (US) examination before ERCP. ERCP was considered as the "gold standard" for diagnosis. The therapy applied consisted of endoscopic stenting, US guided biliary drainage or surgery. The sensitivity, specificity and accuracy were calculated for every tumour localisation and also globally for all tumours.
Results. The sensitivity, specificity and accuracy of US were 85.9%, 76.9% and 84.4% for hilar localization, 59.1%, 50% and 57.1% for the mid common bile duct (CBD) and 33.3%, 42.8% and 36.8% for the distal CBD tumours. The global performances for US in diagnosing extrahepatic chlonagiocarcinoma were 73.5%, 61.5% and 70.9%. In 73 cases (74.5%) an endoscopic stent was placed. In 11 cases (11.2%) we performed an US guided biliary drainage and in 14 cases (14.2%) surgery was recommended.
Conclusion: Ultrasonography proved to be a reliable method for the diagnosis of bile duct cancer in spite of its low accuracy for distal localization. The combination of the two investigations (US and ERCP) was very efficient in the management of these patients. Endoscopic stenting for hilar localization is a good therapeutical option.

Keywords: Bile Duct Cancer, Abdominal Ultrasound, Biliary Stenting, Endoscopic Retrograde Cholangiopancreatography.

Introduction:

Biliary tract tumors, or cholangiocarcinomas (CCAs), comprise a heterogeneous group of malignant tumors that can affect any part of the biliary tree, from the interlobular canals of Hering to the primary biliary duct. Depending on their anatomic location, the tumors are classified as intrahepatic CCA (iCCA) (20% of cases), which originate in the biliary tree within the liver, and extrahepatic CCA (eCCA), which originate outside the liver parenchyma; the latter is further subdivided into perihilar cho-langiocarcinoma (pCCA or Klatskin tumor, 50-60% of cases) and distal cholangi-ocarcinoma (dCCA, 20% of

cases). CCA affects multiple sites in 5% of cases [1, 2]. Taken together, these tumors constitute the second most frequent type of primary liver cancer and approximately 3% of all gastrointestinal neoplasms. The tumor is unusual in most countries, with an incidence of fewer than 6 cases per 100000 persons. Extrahepatic bile duct cancer is classified depending its localization into: hilar (60-80%) known as Klatskin tumour, mid-common bile duct (CBD) (10-20%), respectively distal (10-20%) [2,3]. In the last 20-30 years, the incidence of these tumours has increased especially after the introduction of the new imaging techniques endoscopic retrograde cholangiopancreatography (ERCP, percutaneous transhepatic cholangiography) and the increased interest for this pathology [2]. For the diagnosis, the first examination is abdominal computed tomography ultrasound (US) [4-6]. The accuracy of US (21-47%) depends on the operator experience and on the anatomic conditions [7-9]. In a previous study performed in our department, the global sensitivity of the method was 72% but there were differences depending on tumour localization: hilar 85%, mid-CBD 80% and distal 55% [10]. Magnetic resonance cholangiopancreatography (MRCP) has become recently a very frequently used method in the diagnosis of cholangiocarcinoma [11-14]. Ultrasound endoscopy (EUS) is a new technique, which provides excellent information, comparable with ERCP, and is helpful in determining the tumour extension, especially in mid-CBD and distal localizations [15, 17]. The "gold standard" in the diagnosis of cholangiocarcinoma is considered to be ERCP, which also allows interventional procedures [18-19]. The only curative method is surgical resection. None of the unoperated patients will survive. No matter the therapy applied, the survival rate at 5 years is 0-3.6% [20, 21]. For palliation, endoscopic stenting, biliary drainage or surgical intervention can be performed, but the survival rate does not exceed 6 months [1]. The aim of our study was to evaluate the diagnostic methods and therapeutical results in patients with extrahepatic bile duct cancer the efficacy of various imaging methods.

Material and Methods:

This cross-sectional study was conducted in the Department of Surgery, Mymensingh Medical College Hospital, Mymensingh, Bangladesh from Jun-2018 to July-2021. We included 124 consecutive patients admitted among them 72 men and 52 women, mean age 63.8 years (ranges 38-87) for men and 63.1 years (ranges 30-83) for women with suspected bile duct cancer who underwent ERCP. All patients gave their informed consent for inclusion into the study. The examinations performed in these patients before admission were also taken into consideration. Every patient underwent an US examination before ERCP. ERCP was considered as the "gold standard" for diagnosis. The therapy applied consisted of endoscopic stenting, US guided biliary drainage or surgery. The efficacy of endoscopic stenting was evaluated at 24 and 72 hours by abdominal US (presence of aerobilia, size of the bile ducts) and serum levels of bilirubin, alkaline phosphatase (ALP) and gamma glutamyl transpeptidase (GGT).

Treatment: CCA should be managed in hospital with a multidisciplinary team experienced in endoscopic, percutaneous, and surgical approaches. Management depends on the classification of the tumor. Thus, patients with early-stage disease could benefit from surgery, with complete surgical resection being the cornerstone of cure. However, only a minority of patients are diagnosed in the early stages and are suitable candidates for resection [22]. In the subset of patients diagnosed with locally advanced or metastatic disease, chemotherapy has been used to improve outcome and delay progression [23]. There is a subgroup of patients who, owing to their comorbid conditions, will only be candidates for symptomatic/palliative treatment [24].

Statistical analysis: The sensitivity, specificity and accuracy were calculated for every tumour localisation and also globally for all tumours. We also calculated the positive predictive value (PPV) and the negative predictive value (NPV) for US in diagnosis of bile duct cancer.

Results:

ERCP confirmed the existence of extraheptic cholangiocarcinoma in 98 out of 124 cases. We included 124 consecutive patients admitted among them 72 male and 52 female, mean age 63.8 years (ranges 38-87) for men and 63.1 years (ranges 30-

83) for women with suspected bile duct cancer who underwent ERCP. The level of the tumour was hilar 64 (65.3%), mid-CBD in 22 (22.4%) and distal in 12 patients (12.2%). US revealed a tumour in 72 cases (55/13/4) and in 26 cases (9/9/8) it was false negative. In 10 cases (3/ 3/4), the suspected bile duct cancer was excluded by ERCP and in 16 cases (10/3/3) the absence of the tumour was confirmed by ERCP. The sensitivity, specificity and accuracy of US examination are shown in (Table 1). In 73 cases (74.5%) an endoscopic stent was placed. The mean values of cholestasis tests before and after stenting were: 14.1/9.2 mg/dl for bilirubin, 892/582 U/l for ALP and 287/189 U/l for GGT. Normal values were considered < 1mg/ dl for bilirubin, <300 U/l for ALP and <50 U/l for GGT. In 11 cases (11.2%) we performed an US guided biliary drainage. We noticed a slow decrease of bilirubin, ALP and GGT levels during the follow-up. No major complications after endoscopic stenting were noticed. The stent was replaced successively at 3.2 months (42 patients), 2.3 months (23 patients) and 2.1 months (14 patients) then the follow-up was ended. The biliary drainage was performed only in case of hilar localization after failure to insert a stent. In 14 cases (14.2%) surgery was recommended. In 11 cases (78.5%) a stent was placed before surgery in order to improve the jaundice. In 11 cases (78.5%) a pancreaticoduodenectomy was performed: 5 for distal and 3 for mid-CBD localization. In 4 cases (28.5%) with mid-CBD localization we performed only palliation and in 2 cases the patients were lost from follow-up (Table-2). None of the hilar tumours could be operated, especially due to the tumour extension (30 type Bismuth II, 24 type Bismuth III and 10 type Bismuth IV). We noticed in 24 cases hepatic metastases and in 18 vascular invasions.

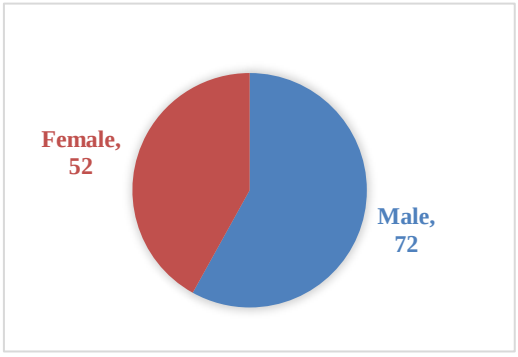

Figure-1: Sex distribution of patients.

Table 1: US diagnostic performance in the patients with extrahepatic holangiocarcinoma for different localization in the common bile duct.

	Hilum	Mid-CBD	Distal	Total
Sensitivity	85.9%	59.1%	33.3%	73.5%
Specificity	76.9%	50%	42.8%	61.5%
Accuracy	84.4%	57.1%	36.8%	70.9%
PPV	94.8%	81.2%	50%	87.8%
NPV	52.6%	50%	42.8%	38.1%

Table-2: Therapeutic procedures applied in patients withextrahepatic cholangiocarcinom (bile duct cancer).

Method	Tota (98 cases)	Hilar localization (64 cases)	Medium localization (22 cases)	Distal localization (12 cases)
Endoscopic stenting	73 (74.5%)	53 (84%)	14 (63.6%)	6 (50%)
PercutaneousUS guidedbi-liary drainage	11 (11.2%)	11 (15.9%)		
Surgery	14 (14.2%)	-	8 (36.4%)	6 (50%)

Discussion:

Ultrasound is a reliable method for the diagnosis of extrahepatic bile duct cancer with better performance in hilar localization. Our results are similar to those of other studies, which showed a better performance for hilar localization [25-27]. Unfortunately, this localization has a poor resectability rate. Stenting was possible only in 53 of 64 patients (82.8%). In the remaining 11 cases, a biliary drainage under US guidance could be realized. The US accuracy decreased for the more distal localizations and an additional investigation was necessary, in our study ERCP. A distal localization allows a better resectability and we recommended surgical intervention in 14 cases, but pancreaticoduodenectomy was possible only in 8 cases due to the tumour extension. The utility of preoperative stenting is also controversial as it has certain benefits (it decreases jaundice, increases visualisation of biliary tract and allows possibility of endobiopsy), but also can lead to complications such as infection, hemobilia, fistulas and pancreatitis [28]. We performed endoscopic stenting in all possible cases, with good results and no major complications. The endoscopic stenting as a palliative therapy proved to be successful. The 3 days follow-up after stenting showed a significant decrease in the diameter of the bile ducts; serum bilirubin, AP and

GGT decreased with approximately 35% from the value before stenting, proving the efficacy of palliation. We performed percutaneous biliary drainage only in case of stenting failure, with good results: serum bilirubin, AP and GGT decreased. The diagnosis suspected following the first laboratory investigations performed in the patients with extrahepatic bile duct cancer before admittance was that of acute hepatitis in 62 patients (63.2%), which caused a delay in diagnosis. US should be recommended early by the family doctor in a patient with jaundice and may have an essential contribution to earlier diagnosis. Ultrasound still remains the only screening method in patients with jaundice, due to its low costs and good accessibility.Resection is the only option that provides a real possibility of long-term survival in patients diagnosed with CCA. Improved staging of these tumors and a more aggressive surgical approach have improved the outcome of surgery. Even so, in most series, only 30%-65% of patients with CCA have potentially resectable tumors. The possibility of a radical resection increases if hepatectomy is routinely combined with resection of the biliary tract. Similarly, resection of the caudate lobe helps to reduce the number of patients with affected surgical margins [29]. Morbidity and mortality are high after resection of CCA. The risk increases somewhat if the patient has both cholestasis and hypoalbuminemia during the preoperative period. Therefore, preoperative optimization is essential in such cases. The indication and extension of surgery depends on the clinical status of the patient, functional liver reserve, and the location and extension of the tumor, which includes the association with vascular structures and negative metastatic disease. Block resection with macroscopically and microscopically negative margins (R0) is the main prognostic factor [30].

Conclusion:

In extrahepatic bile duct cancer the prognosis depends on tumor localization and extension. Patients with hilar localization have a bad prognosis, as they are usually diagnosed in advanced stages, when the tumour is large and metastases are present. Ultrasound is a very useful method for diagnosis in these patients, even if the accuracy is lower for distal localization. The combination US-ERCP was successful in the management of these patients. Endoscopic stenting proved to be a good palliation in the majority of patients with perihilar localization, without procedure-related mortality or major complications.

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