Spectrum of periampullary lesions and the role of endoscopic retrograde cholangiopancreatography in their diagnosis

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Context
The periampullary area is a hot spot for neoplasia and lesions arising there often obstruct the biliopancreatic stream, so drainage and tissue diagnosis of any suspicious lesion are very important.

Aims
The aims were to estimate the frequency of different types of periampullary lesions, and assess the diagnostic accuracy of biopsy and brush cytology taken by endoscopic retrograde cholangiopancreatography (ERCP).

Patients and methods
A prospective study conducted at Assiut University Hospital over a period of 1 year starting from June 2017. The authors enrolled patients presented with clinical and radiological suspicion of periampullary lesions indicating ERCP. Physical, laboratory, and imaging data were recorded and data of ERCP examination as well as results of endoscopic biopsies were studied and compared with the final diagnosis after definitive surgical intervention and/or sufficient follow-up. Statistical Package for the Social Sciences, version 20, IBM.

Results
During the 1 year, periampullary lesions represented 18.8% of all cases who underwent ERCP (154 out of 818), including 25 cases with distal common bile duct (CBD) stone/s, 40 inflammatory, 15 benign, and 74 malignant lesions. The sensitivity and specificity of grasp biopsy were 67.5 and 70% when any dysplasia was regarded as a malignant lesion and they were 54 and 90% when only high-grade dysplasia was considered malignant. Sensitivity and specificity of brush cytology was 33 and 100%.

Conclusion
Periampullary area has a high potentiality for neoplastic changes and ERCP-guided biopsy has a reasonable diagnostic yield.

Keywords:
endoscopic retrograde cholangiopancreatography, endoscopic retrograde cholangiopancreatography-guided biopsy, periampullary lesions

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Introduction

In 1720, the German anatomist Abraham Vater coined the term 'ampulla of Vater' to describe that flask-shaped structure, which provides a conduit for biliopancreatic fluids to the gastrointestinal tract (GIT) and regulates its drainage by a sphincter called the sphincter of Oddi. The periampullary region is an area located within 2 cm around Vater's ampulla, including it and the surrounding duodenal mucosa, the distal common bile duct, and the adjacent pancreatic tissue [1,2].

Pathological conditions occurring in this region easily obstruct the biliopancreatic ductal system leading to obstructive jaundice and/or pancreatitis [3]. The transition between three different types of epithelium and the direct contact with powerful digestive enzymes make this area a hot spot for dysplasia and malignant changes [4]. The spectrum of periampullary lesions is wide so that their management widely varies. Defining the exact nature of some lesions may be challenging for the surgeon and the radiologist due to the great similarity between some inflammatory and some malignant lesions [5,6].

In 1968, the surgeon McCune and his colleagues first reported on the endoscopic visualization of the ampullary area and the common bile duct. With improvements in technology, ERCP becomes indispensable in the diagnosis of diseases of the biliopancreatic tree [7]. ERCP also allows some therapeutic procedures and permits sampling of pancreatic juice, bile, and brush cytology or grasp biopsy from any doubtful lesion [7].

ERCP is often the method of choice for definitive diagnosis and management of distal common bile duct stones and strictures, and for palliative management of malignant biliary obstruction in unfit or inoperable patients [8]. Our study aim was to determine the spectrum of periampullary lesions and the diagnostic accuracy of biopsy and brush cytology taken by ERCP in our hospital.

Patients and methods

This prospective study was conducted over a period of 1 year starting from June 2017 and included 154 patients.

Ethical consideration

The study was carried out at Assiut University Hospital after taking approval from the Medical Ethics Committee of Faculty of Medicine under no: 17100192.

Informed consent was taken from each case. Identifiable data were kept securely.

Inclusion criteria

(1) Cases presented to our hospital with clinical and radiological suspicion to have periampullary lesions
(2) The patient must be eligible for ERCP.

Exclusion criteria

(1) Cases with periampullary lesions managed without ERCP
(2) Cases with insufficient follow-up
(3) Cases with cause of obstruction outside the periampullary region.

Patients were subjected to the following:

(1) Complete history taking and thorough physical examination
(2) Imaging studies including abdominal ultrasound and magnetic resonance cholangiopancreatography as a standard
(3) Routine laboratory investigation and tumor markers when malignancy was suspected
(4) ERCP was performed by standard techniques (by Pentax ED-3490TK 4.2 duodenoscope), routinely in the left lateral position under general anesthesia (intravenous propofol). Endoscopic features of the periampullary region were recorded. Endoscopic sphincterotomy was routinely performed (using Cook DASH-480 Howell DASH Direct Access System, Wilson-cook medical inc. 4900 bethania station road Winston-salem NC 27105, USA). Once biliary access was available with the guide wire, cholangiography was done and recorded. Grasp biopsy (Radial Jaw 4 biopsy forceps: Boston Scientific- 2546 first streat Propark, COYOL, Alajuela, COSTA RICA (DLB 3-3.5 ;COOK medical, Bloomington, Monroe, USA) was performed when indicated and possible
(5) Follow-up was done for 8–12 months including clinical, laboratory, radiological, and/or endoscopic follow-up. Data of any surgical intervention were recorded including results of surgical biopsies to be compared with corresponding endoscopic biopsies.

The final diagnosis in each case was based on the following:

(1) Histopathological studies of surgical specimens when available
(2) Follow-up imaging studies (computed tomography or MRI)
(3) Disease course consisting of signs of clinical or radiological deterioration or improvement and/or appearance of changes in lesions on follow-up ERCP.

Data collection and processing

Data were prospectively collected with a close follow-up and telephone communication with patients/families and their respective referring doctors. Additional information was collected by reviewing hospital files and records. Statistical analysis was performed using the SPSS (Statistical Package for the Social Sciences, version 20; IBM, Armonk, New York, USA). Continuous data were expressed in the form of mean ± SD, while nominal data were expressed in the form of frequency and percentage. Receiver operating characteristic curve was used for the diagnostic performance of endoscopic biopsies.

Results

Out of 818 cases that underwent ERCP at our gastrointestinal endoscopy center during this year, 154 (18.8%) patients had periampullary lesions and were included in our study. The mean age of studied cases was 51.27 ± 12.46 years, with 79 (51.3%) male patients and 75 (48.7%) female patients.

Summary of laboratory data

The main presentation of patients was obstructive jaundice (83.8%). The remaining (16.2%) were

Table 1 Baseline laboratory data of studied patients

Variables	Malignant group	Nonmalignant group	General values
Liver function tests			
Bilirubin (μmol/l)	223.7±115.1	131.9±119.3	192.5±135.5
Direct (μmol/l)	189.5±104.6	121.8±122.7	163.1±119.5
Aspartate transaminase (U/l)	112.82±12.8	85.3±60.2	117.5±70.3
Alanine transaminase (U/l)	165.76±17.98	102.9±57.4	123.1±78.8
Alkaline phosphatase (U/l)	487.6±56.78	302.4±273.5	469.3±318.2
CEA (U/l)	3.18±1.41	2.11±2.2	2.63±2.6
CA 19-9 (U/l)	354.1±58.98	35.9±44.5	188.8±73.9

Data were expressed in the form of mean±SD. Grouping was done during analysis after reaching the final diagnosis. CEA, carcinoemberionic antigen, was raised in 45.9% of cases in the malignant group and not raised in 73.7% of cases in the nonmalignant group; CA19-9, carbohydrate antigen 19-9 was raised in 72.7% of cases in the malignant group, but it was also raised in 47.8% of cases in the nonmalignant group.

presented with vague symptoms including abdominal pain, fever, or vomiting. The abdominal ultrasound showed biliary dilatation before appearance of jaundice. Table 1 summarizes baseline laboratory data.

Provisional imaging diagnosis

Based on imaging data including abdominal ultrasound and magnetic resonance cholangiopancreatography in addition to abdominal MSCT in 62 cases, the provisional diagnosis for the cause of obstructive jaundice was suggested as illustrated in Fig. 1. Abdominal ultrasound was the only imaging study available in 18 cases (distal CBD stone was correctly diagnosed in 11 of them).

Endoscopic features of periampullary region in studied cases

During ERCP, the endoscopic views of the ampullary and juxta-ampullary duodenal mucosa, and cholangiographic features were as categorized in Tables 2 and 3, respectively. Fig. 2 shows the endoscopic view and cholangiography of a case of malignant periampullary lesion.

Results of ERCP-guided biopsy and brush cytology

(1) Histopathological diagnoses of ERCP-guided biopsy done in 57 cases were:
   (a) Nonspecific inflammatory lesion in 20 cases and benign adenoma in six cases,
   (b) Inflammatory with mild focal dysplasia in five cases.
   (c) Adenomatous lesion with high-grade dysplasia in eight cases and moderate-grade dysplasia in four cases,
   (d) Adenocarcinoma in 14 cases (one of them was mucinous carcinoma).

(2) Brush cytology was done for only 75 cases and was positive for malignancy in 17 cases and negative in 58 cases.

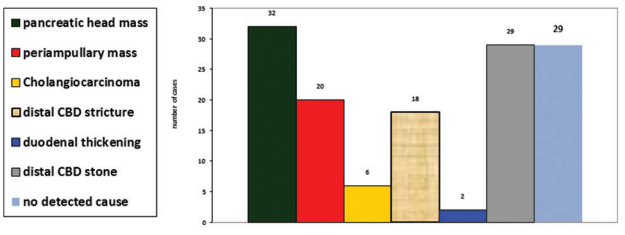
Table 2 Endoscopic features in studied patients

	n (%)
Malignant duodenal infiltration	8 (5.2)
Duodenal diverticulum	16 (10.4)
Duodenal papilomatosis	2 (1.3)
Malignant ampullary infiltration	10 (6.5)
Periampullary duodenal mass	10 (6.5)
Ampullary mass	15 (9.7)
Swollen papilla	11 (7.1)
Swollen papilla with endopapillary growth	2 (1.3)
Papilitis	8 (5.2)
Periampullary ulceration	14 (9.1)
Normal findings	58 (37.7)
Total	154 (100)

Table 3 Cholangiographic features in studied cases

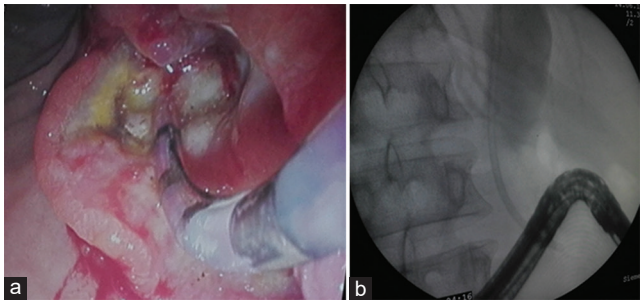
	n (%)
Ampullary mass	11 (7.1)
Distal CBD strictures with	
Smooth outline	49 (31.8)
Irregular outline	19 (12.3)
Shouldering	7 (4.5)
Tight strictures	4 (2.6)
Distal CBD stones	
Stone only	16 (10.4)
With low inserted cystic duct	2 (1.3)
Stricture + stone	7 (4.5)
Fasciola infestation	2 (1.3)
Papillary stenosis	9 (5.8)
Normal finding	12 (7.8)
Failed cannulation	16 (10.4)
Total	154 (100)

Figure 1



Provisional diagnosis for the cause of biliary dilatation based on imaging data.

Figure 2



A 46-years-old male patient with malignant periampullary mass: (a) endoscopic view showing ulceration and fungation; (b) cholangiography showing distal CBD stricture with shouldering, 'original pictures.'

Final diagnosis in studied patients

Follow-up was done for 8–12 months and the final diagnosis in each case was based on:

(1) Histopathological studies of surgical specimens when available
(2) Follow-up imaging studies (computed tomography or MRI)
(3) Disease course consisting of signs of deterioration or improvement and/or appearance of changes on follow-up ERCP.

Twenty-five (16.2%) patients were diagnosed to have distal CBD stone/s revealed by cholangiography with successful stone extraction in 23 (92%) of them. Forty (26%) patients had inflammatory stricture and were improved by stenting and medical treatment, 15 (9.7%) patients had benign lesions that showed a stationary course with no changes on follow-up.

Seventy-four (48.1%) patients were diagnosed to have malignant periampullary lesions; among patients with malignant lesions 37 cases had a resectable mass and underwent Whipple operation, and nine cases had unresectable mass and underwent triple shunt operation. Palliative ERCP stenting was done for 22 inoperable or unfit cases. Percutaneous tubal drainage was done in six cases.

To relieve CBD obstruction, stent was inserted in 97 cases, 51 of them was in malignant lesions. Stent insertion failed in 16 cases. Overall successful cannulation rate was 89.6% in general and 97.5% in nonmalignant cases.

Regarding surgical biopsies of 37 Whipple operations plus two lymph node biopsies during triple-shunt operations, the final histopathological diagnosis was pancreatic adenocarcinoma in 19 cases, ampullary adenocarcinoma in six cases, distal cholangiocarcinoma in four cases, moderately differentiated duodenal adenocarcinoma in three cases, neuroendocrine tumors in two cases, and poorly differentiated adenocarcinoma in five cases.

Table 4 Cross-tabulation between results of endoscopic retrograde cholangiopancreatography-guided biopsy and final diagnosis

ERCP-guided biopsy	Final diagnosis	
	Malignant lesion	Nonmalignant lesion
If any dysplasia regarded as malignant		
Malignant	25	6
Nonmalignant	12	14
If moderate dysplasia regarded as malignant		
Malignant	22	4
Nonmalignant	15	16
If high-grade dysplasia regarded as malignant		
Malignant	20	2
Nonmalignant	17	18
If any dysplasia regarded as benign		
Malignant	14	0
Nonmalignant	23	20
Total	37	20

ERCP, endoscopic retrograde cholangiopancreatography.

Diagnostic accuracy of endoscopic retrograde cholangiopancreatography-guided biopsy in our study

ERCP-guided biopsy was done in 57 cases and Table 4 shows the results of its histopathological examination opposed to the final diagnosis, with comparison between the results when dysplasia was regarded as malignant lesion, when moderate dysplasia was regarded malignant, when high-grade dysplasia was regarded malignant, and when dysplasia was regarded as benign lesion. The diagnostic accuracy of ERCP-guided grasp biopsy was calculated as illustrated in Table 5.

We started our analysis by regarding any dysplasia as a malignant lesion. In this condition, the sensitivity of grasp biopsy was 67.5% but the specificity was only 70%, although when moderate-grade dysplasia was regarded as a malignant lesion, the sensitivity and specificity were 59.5 and 80%, respectively. Moreover, when only high-grade dysplasia was considered malignant the sensitivity reached 54% when the contrast specificity increased to 90%. Finally, when any dysplasia was considered benign the sensitivity was 37.8% while specificity reached 100%. The area under the receiver operating characteristics curve was (0.753) (Fig. 3).

Diagnostic accuracy of brush cytology in the current study

The results of cytological examination of ERCP-guided biliary brushing opposed to the corresponding final diagnosis are as illustrated in Table 6 and the diagnostic accuracy was calculated as illustrated in Table 7.

Discussion

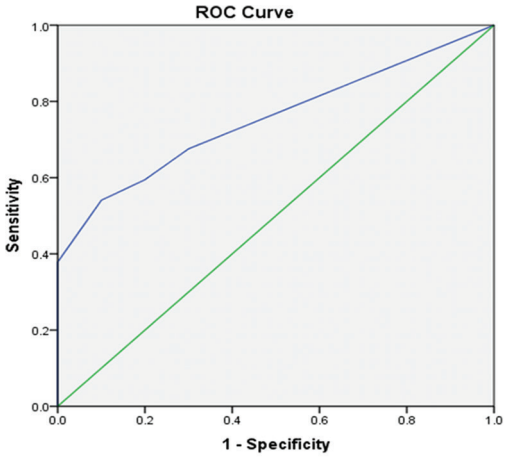
Periampullary lesions represented about 18.8% of all cases who underwent ERCP for obstructive jaundice

Table 5 Diagnostic accuracy of endoscopic biopsy in the current study

Indices	Values (%) when			
	Any dysplasia regarded as malignant	Mod dysplasia regarded as malignant	High-grade dysplasia regarded as malignant	Any dysplasia regarded as benign
Sensitivity	67.5	59.5	54	37.8
Specificity	70	80	90	100
Positive predictive value	80.6	84.6	90.9	100
Negative predictive value	38.8	51.6	51.4	35
Accuracy	68.4	66.6	66.6	59.6
P	<0.025	<0.005	<0.005	<0.001
Area under the ROC curve	0.753			

ROC, receiver operating characteristic curve. *P* value is significant if<0.05.

Figure 3



Receiver operating characteristics curve for diagnostic accuracy of endoscopic retrograde cholangiopancreatography biopsy (area under the receiver operating characteristics curve = 0.753).

Table 6 Cross-tabulation between results of brush cytology and final diagnosis

Endoscopic diagnosis	Final diagnosis	
	Malignant	Nonmalignant
Malignant	17	0
Nonmalignant	35	23
Total	52	23

Table 7 Diagnostic accuracy of brush cytology in the current study

Indices	**%**
Sensitivity	32.7
Specificity	100
Accuracy	53.3
P	<0.001

P value is significant if <0.05.

during the study period and this reflects the importance to study these lesions thoroughly. About two-thirds of these lesions were neoplastic (48.1% malignant and 16.2% benign) and about one-third were non-neoplastic lesions including distal CBD stones and inflammatory conditions. This was consistent with the known fact that this area has a high potentiality for neoplastic changes and from about one-third up to 50% of its lesions are malignant or premalignant in nature [4]. As reported previously, age and gender were not significantly different between malignant and nonmalignant periampullary lesions [9].

The main presentation of patients was jaundice (85%) and regarding laboratory investigations, the total bilirubin level was much higher in the malignant group (about fourfolds) than that in the benign or nonneoplastic group. This is consistent with that the development of jaundice is more commonly associated with a periampullary carcinoma (70%) than with benign lesions (20–30%) [3].

Successful cannulation rate was 89.6% in general and 97.5% in nonmalignant cases. Stone extraction was done in 92% of cases of distal CBD stones within the period of study. It is reported that in the hands of experts, the success rate of common bile duct cannulation, cholangiography, and stone extraction should reach more than 90% [10–12].

Despite its limited sensitivity, brush cytology is considered the first-line easy and safe method of sampling by ERCP [13]. In our study, it had 32.7% sensitivity with 100% specificity and 53.3% accuracy. Numerous studies of biliary brush cytology have reported a wide range of sensitivity in the detection of malignant lesions, from 30 to 69% [8,14] and to enhance the diagnostic yield, obtaining two separate brush cytology specimens is usually recommended.

Regarding grasp biopsy the sensitivity was 67.5% when we regarded any dysplasia as a malignant lesion but the specificity was only 70% and the diagnostic accuracy was 68.4%, but when only moderate-grade dysplasia was regarded as a malignant lesion, the sensitivity and specificity were 59.5 and 80%, respectively. Moreover, when only high-grade dysplasia was considered malignant the sensitivity reached 54%, while specificity increased to 90% with a diagnostic accuracy of 66.6%. The area under the receiver operating characteristic curve was 0.753, denoting a good diagnostic test and it is recommended to regard high-grade dysplasia as a malignant lesion.

Many studies have reported that grasp biopsy has a high diagnostic accuracy (75.9%) with no increased rate of post-procedure complications when compared with ERCP alone [15,16]. False negative results may be due to sampling error. The accuracy rate was reported in another study to be ranging from 62 to 79% [17].

William and colleagues [14] in 2008, after their retrospective study, stated that despite the lower sensitivity of brushings and biopsies guided by ERCP compared with an EUS-guided fine needle aspiration that may reach 83%, they successfully detected cancers missed by an EUS-FNA, in addition to its availability, less operator dependence, and the importance of the therapeutic role of ERCP.

Conclusion

(1) Periampullary area has high potentiality for neoplastic changes
(2) ERCP has a prominent role and is often considered the method of choice for the diagnosis of periampullary lesions
(3) ERCP-guided biopsy has reasonable diagnostic yield
(4) Using several techniques at the same time for tissue diagnosis of malignancy during ERCP is recommended to increase diagnostic accuracy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Lerch M, Domschke W. Abraham Vater of the ampulla (papilla) of Vater. Gastroenterology 2000; 118:379.
2 Sadler TW, Langman J. *Langman's Medical Embryology*. 10th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2006. 371.
3 Farnell MB, Sakorafas GH, Sarr MG, Rowland CM, Tsiotos GG, Farley DR, *et al.* Villous tumors of the duodenum: reappraisal of local vs. extended resection. J Gastrointest Surg 2000; 4:13–21. discussion 22–23.
4 Fischer HP, Zhou H. Pathogenesis of carcinoma of the papilla of Vat.er. J Hepatobiliarypancreat Surg 2004; 11:301–309.
5 Mohamed S, Syed AI. Management of obstructive jaundice: experience in a tertiary care surgical unit. Pak J Surg 2007; 23:2325.
6 Weber SM, Cubukcu-Dimopulo O, Palesty JA, Suriawinata A, Klimstra D, Brennan MF, *et al.* Lymphoplasmacytic sclerosing pancreatitis: inflammatory mimic of pancreatic carcinoma. J Gastrointest Surg 2003; 7:129–139.
7 Himal HS. The SAGES manual, fundamentals of laparoscopy and GI. Endoscopy 1999; 46:485.
8 Jailwala J, Fogel EL, Sherman S, Gottlieb K, Flueckiger J, Bucksot LG, *et al.* Triple-tissue sampling at ERCP in malignant biliary obstruction. Gastrointest Endosc 2000; 51:383–390.
9 Kennedy T, Preczewski L, Stocker SJ, Rao SM, Parsons WG, Wayne JD. Incidence of benign inflammatory disease in patients undergoing Whipple procedure for clinically suspected carcinoma: a single-institution experience. Am J Surg 2006; 191:437–441.
10 Baron TH, Fleischer DE. Past, present, and future of endoscopic retrograde cholangiopancreatography: perspectives on the National Institutes of Health Consensus Conference. Mayo Clin Proc 2002; 77:407–412.
11 Mangiavillano B, Pagano N, Baron TH, Luigiano C. Outcome of stenting in biliary and pancreatic benign and malignant diseases: a comprehensive review. World J Gastroenterol 2015; 21:9038–9054.
12 Navaneethan U, Hasan MK, Lourdusamy V, Njei B, Varadarajulu S, Hawes RH. Single-operator cholangioscopy and targeted biopsies in the diagnosis of indeterminate biliary strictures: a systematic review. Gastrointest Endosc 2015; 82:608–614.
13 Korc P, Sherman S. ERCP tissue sampling. Gastrointest Endosc 2016; 84:557–571.
14 Ross WA, Wasan SM, Evans DB, Wolff RA, Trapani LV, Staerkel GA, *et al.* Combined EUS with FNA and ERCP for the evaluation of patientswith obstructive jaundice from presumed pancreatic malignancy. Gastrointest Endosc 2008; 68:461–464.
15 Dacha S, Chawla S, Lee JE, Keilin SA, Cai Q, Willingham FF. Endoscopic retrograde cholangiopancreatography with ampullary biopsy vs ERCP alone: a matched-pairs controlled evaluation of outcomes and complications. Gastroenterol Rep (Oxf) 2017; 5:277–281.
16 Shieh FK, Luong-Player A, Khara HS, Liu H, Lin F, Shellenberger MJ, *et al.* Improved endoscopic retrograde cholangiopancreatography brush increases diagnostic yield of malignant biliary strictures. World J Gastrointest Endosc 2014; 6:312–317.
17 Grobmyer SR, Stasik CN, Draganov P, Hemming AW, Dixon LR, Vogel SB, *et al.* Contemporary results with ampullectomy for 29 'benign' neoplasms of the ampulla. J Am Coll Surg 2008; 206:466–471.