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ORIGINAL ARTICLE

Retrospective Study

Safety of endoscopy in patients undergoing treatments with antiangiogenic agents: A 5-year retrospective review

Mohammad Azam, Amit Hudgi, Pearl Princess Uy, Jinal Makhija, John Erikson L Yap

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Mohammad Azam, Amit Hudgi, Department of Internal Medicine, Medical College of Georgia/Augusta University, Augusta, GA 30912, United States

Pearl Princess Uy, John Erikson L Yap, Division of Gastroenterology, Medical College of Georgia/Augusta University, Augusta, GA 30912, United States

Jinal Makhija, Department of Internal Medicine, Rush University Medical Center, Chicago, IL 60612, United States

Corresponding author: John Erikson L Yap, MD, Assistant Professor, Division of Gastroenterology, Medical College of Georgia/Augusta University, 1120 15th Street, Augusta, GA 30912, United States. jyap@augusta.edu

Abstract

BACKGROUND

Antiangiogenic agents (AAs) are increasingly used to treat malignant tumors and have been associated with gastrointestinal (GI) bleeding and perforation. Elective surgeries and endoscopy are recommended to be delayed for 31 d until after AAs treatment. Data regarding the safety of endoscopy while on antiangiogenic agents is extremely limited. No guidelines are in place to address the concern about withholding these anti-angiogenic drugs.

AIM

To evaluate the risks of endoscopy in patients on antiangiogenic agents from 2015 to 2020 at our institution.

METHODS

This is a single centered retrospective study approved by the institutional review board statement of the institution. Patients that underwent endoscopy within 28 d of antiangiogenic agents' treatment were included in the study. Primary outcome of interest was death, and secondary outcomes included perforation and GI bleeding. Data were analyzed utilizing descriptive statistics. Fifty-nine patients were included in the final analysis and a total of eighty-five procedures were performed that were characterized as low risk and high risk.

RESULTS

Among the 59 patients a total of 85 endoscopic procedures were performed with 24 (28.2%) categorized as high-risk and 61 (71.8%) procedures as low-risk. Of the

total number of patients, (50%) were on bevacizumab and the rest were on imatinib (11.7%), lenvatinib (6.7%) and, ramucirumab (5%). The average duration between administration of AAs and the performance of endoscopic procedures was 9.9 d. No procedure-related adverse events were noted among our study population. We did observe two deaths with one patient, on lenvatinib for metastatic hepatocellular carcinoma, who had persistent bleeding despite esophageal variceal banding and died 4 d later from hemorrhagic shock. Another patient was diagnosed with acute myeloid leukemia died 24 d after an esophagogastroduodenoscopy with biopsy after transition to comfort care.

CONCLUSION

As per this single center retrospective study, the rate of endoscopic procedure-related adverse events and death within 28 d of AA administration appears to be low.

Key Words: Antiangiogenics; Endoscopy; Bevacizumab; Lmatinib; Lenvatinib; Adverse events

Core Tip: This single centered study highlights low adverse events of anti-angiogenics after endoscopic procedures. Currently, the consensus recommends holding anti-angiogenics 28 d prior to the procedure. This small sample study sheds light on the need to hold anti-angiogenics prior to endoscopic procedure and affirms to not delay emergent endoscopic procedures.

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INTRODUCTION

Angiogenesis is a complex process of forming vascular network by endothelial cells proliferation mediated by growth factors like vascular endothelial growth factors (VEGF), insulin like growth factors, fibroblast growth factors and hypoxia inducible factors. It is first initiated during embryogenesis from mesodermal precursor cells, later repeated during process of healing. Similarly, when tumor cells are subjected to hypoxia, they produce growth factor leading to angiogenesis. This not only provide a source of nutrition but also a means for metastasis.

Folkman postulated the idea of antiangiogenic agents (AAs) as an effective cancer therapy in early 1970[1]. Currently, AAs are widely used in the treatment of malignant tumors owing to their effectiveness in increasing survival. Monoclonal antibodies, VEGF decoy receptor, and small molecule tyrosine kinase inhibitors are three major classes of anti-angiogenics currently in clinical practice[2]. However, VEGF also play a crucial role in wound healing and the use of AAs may potentially lead to complications such as bleeding and impaired wound healing[1,3].

Post-procedure adverse events were higher among patients receiving AAs[4]. The potential for increased occurrence of complications such as bleeding among cancer patients on AAs after procedures have led to the postponement of elective surgical procedures and endoscopies for at least 28 d after AA treatment. The mechanism of gastrointestinal (GI) perforation is attributed to splanchnic or mesenteric thrombi, impaired healing and proliferation, decreased blood supply to intestinal wall, and decreased stability secondary to tumor destruction have been postulated[5]. There is limited and inconsistent data in the literature regarding the rate of adverse events during endoscopy among patients on AAs. Imbulgoda *et al*[6] reported two complications of perforation (2/80 patients) in patient receiving bevacizumab while undergoing placement of self-expanding metal stent. More recently Kachaamy *et al*[7] revealed a low adverse event of 1.6% (7/455) in patients receiving AA. The cautious approach of delaying even low risk endoscopic procedures among patients receiving AAs may have resulted from the extrapolation of findings from studies of surgical procedures where increased adverse events like bleeding and impaired wound healing were observed[4]. It is important to note that endoscopic procedures are not as invasive as other surgical procedures and recommendations should not be solely based on data from surgical procedures.

In this single centered study, we reviewed medical records of the patients who underwent GI endoscopy after receiving anti-angiogenics therapy within the past 28 d. Here we aim to investigate 30 d adverse events in patients receiving AA undergoing an endoscopic procedure.

MATERIALS AND METHODS

Study design and patient population

This is a single center retrospective study conducted at a non-National Cancer Institute (NCI) designated hospital specializing in treatment of cancers in the state of Georgia, United States. Inclusion criteria for the study were: (1) Patients receiving treatment with AAs including vascular endothelial growth factor (VEGF), VEGF receptor inhibitors, epidermal growth factor receptor inhibitors, multi-targeted tyrosine kinase inhibitors, and mammalian target of rapamycin inhibitor; and (2) Patients undergoing endoscopic procedures within 28 d of AA administration between from January 1, 2015 - March 31, 2020. Exclusion criteria included: Age less than 18 years old. All patients undergoing endoscopic procedures within 28 d after administration of AAs were included in the study analysis. The Augusta University Investigation Review Boards approved this study.

Patients who met the inclusion and exclusion criteria were identified using I2B2 software, and details regarding the endoscopic procedures and the timing of AA administration were obtained from the electronic medical records. Endoscopic procedures were categorized as either high risk or low risk based on existing literature regarding endoscopic procedural risks associated with antithrombotic agents[8]. Low risk procedures included diagnostic endoscopies or with biopsy. In contrast, high risk procedures consisted of stent placements, gastrostomy tube placements, snare polypectomy, endoscopic retrograde cholangiopancreatography, and endoscopic ultrasound with fine needle aspiration.

Statistical analysis

Statistical analyses were performed utilizing simple descriptive statistics including percentages and frequencies. The demographic data, the mortality rate and the endoscopic adverse events were analyzed using descriptive statistics. The primary outcome measure was mortality rate within 30 d of endoscopy whereas the secondary outcome measures were procedure-related adverse events such as bleeding and perforation within 30 d of endoscopy. The adverse events were labeled according to the common terminology criteria for adverse events version (have version 5.0 now) which defines adverse events (AEs) as an unintended and unfavorable outcome associated with a medical treatment or procedure that may or may not be associated to the medical treatment or procedure. Classification of the severity of AEs were based on a grading system from 1 to 5 wherein 1 is mild, 2 is moderate, 3 is severe, 4 is life-threatening and 5 is death. The mortality rate and incident rate of AEs were determined using the total number of study participants as the denominator.

RESULTS

Patient characteristics

Fifty-nine patients (M/F = 25/34) were included in this study who underwent a total of 85 endoscopic procedures. The mean age of the study population was 64.9 years at the time of endoscopy. Majority of the patients were Caucasians (54.2%) or African Americans (40.7%). The most common malignancy types were colorectal cancer (20.7%), liver (11.9%), ovarian (10.2%) and lung (10.2%); and the majority (59.3%) had stage IV metastatic disease at the time of endoscopy (refer to Table 1). Thirty patients (50%) were on bevacizumab whereas other patients were on imatinib (11.7%), lenvatinib (6.7%), ramucirumab (5%) as detailed on Table 2. One of the patients with the diagnosis of acute myeloid leukemia (AML) who was being treated with two anti-angiogenic agents bevacizumab and sorafenib.

Procedures

A total of 85 endoscopic procedures were performed with 24 (28.2%) categorized as high-risk and 61 (71.8%) procedures as low-risk. High risk procedures included variceal bleeding control, percutaneous gastrostomy tube placement, pneumatic balloon dilation, and stent placement while low-risk included diagnostic procedures along with mucosal biopsies. The average duration between administration of AAs and the performance of endoscopic procedures was 9.9 d (Table 3).

Adverse events and mortality

Among the eighty-five endoscopic procedures that were performed, there were no procedure related adverse events that were documented. One patient on lenvatinib therapy for metastatic hepatocellular carcinoma had persistent bleeding despite esophageal variceal banding and died 4 d later from hemorrhagic shock. Another patient on sorafenib therapy for AML died 24 d after an esophago-gastroduodenoscopy with biopsy while on hospice care (Table 4).

Table 1 Baseline characteristics of patient population on anti-angiogenic agents

Characteristics	Anti-angiogenic agents (*n* = 59)
Age	64.9
Female	34 (57.62%)
Race	
Caucasian	32 (54.2%)
African American	24 (40.7%)
Hispanic	3 (5.1%)
Malignancy sites	
Colorectal cancer	12 (20.3%)
Hepatocellular cancer	7 (11.9%)
Ovarian cancer	6 (10.2%)
Lung	6 (10.2%)
CML/AML	5 8.5%)
Renal cell cancer	4 (6.8%)
Oropharyngeal cancer	3 (5.1%)
Uterine	2 (3.4%)
Pancreas	2 (3.4%)
Gastric cancer	2 (3.4%)
Fibrosarcoma	2 (3.4%)
Peritoneal carcinomatosis	2 (3.4%)
Cervical cancer	2 (3.4%)
Fallopian tube	1 (1.7%)
Breast cancer	1 (1.7%)
Other	2 (3.4%)
HHT/Hereditary eosinophilia	
Stage of malignancy	
Unstageable	9 (13.6%)
Stage I	1 (1.7%)
Stage II	3 (5.1%)
Stage III	11 (18.6%)
Stage IV	35 (59.3)

AML: Acute myeloid leukemia.

DISCUSSION

There is limited data on the safety of endoscopy in patients undergoing treatment with AA for oncological malignancies. Most recently, in a retrospective multi-center study by Kachaamy *et al*[7], the safety of endoscopy was investigated to identify adverse events and mortality in cancer patients being treated with AAs and undergoing endoscopy within 31 d of administration of AAs. It was concluded that endoscopy is well tolerated in patients on AAs and the incidence of adverse events was 0.7%, while the 30 d mortality was estimated at 6.5[7]. In our study, no procedural adverse events were observed, and the mortality rate was 2.35%. One of the two patient succumbed to persistent variceal bleeding, and the other patient died after transition to comfort care.

The first AA to be approved for use was bevacizumab for treatment of breast cancer and since then, AAs have played an integral role in the treatment of many oncological conditions[9]. Various AAs have shown a survival benefit for patients undergoing treatment of colorectal, liver, renal-cell, ovarian,

Table 2 Indication for endoscopic procedures

Indication for endoscopy (*n* = 86)	
GI bleed	29 (33.7%)
Symptomatic (weight loss, abdominal pain, diarrhea, nausea, vomiting, obstruction)	22 (25.6%)
Anemia	5 (5.8%)
Elective diagnostic + follow-up	16 (18.6%)
Dysphagia	9 (10.5%)
Enteral access	5 (5.8%)

GI: Gastrointestinal.

Table 3 Total endoscopic procedures performed and complications

Endoscopic procedures (*n* = 85)	
1 Esophagogastroduodenoscopy	56
(A) With biopsy	17
(B) With variceal banding	10
(C) With stent	2
(D) With pneumatic dilation	1
(E) With percutaneous gastrostomy tube placement	8
(F) Enteroscopy	1
2 Flexible sigmoidoscopy	6
(A) With biopsy	2
3 Colonoscopy	23
(A) With biopsy	7
(B) With snare	3
(C) With control of bleeding	2
(D) With stent placement	1
Complications	
1 Perforation	0
2 Bleeding	2 (2.35%)
Mortality	2 (2.35%)

endometrial, cervical, breast, and gliomas[10-14]. Bevacizumab and other AAs have been associated with poor wound-healing and increases the risk of complications if undergoing surgical and endoscopic procedures. Current literature suggest that the use of bevacizumab and other VEGF inhibitors can impair wound healing and potentially lead to severe wound healing complications[3]. It is therefore recommended to delay elective surgeries for at least 28 d from the time of AA administration[15,16]. At present, there is no recommendation regarding the timing of endoscopic procedures among patients on AAs. Our study indicates that there were no procedure related AEs when AAs were administered within 28 d of an endoscopic procedure including high-risk ones.

Use of AAs have also been associated with an increased bleeding risk. This was demonstrated in a meta-analysis of 38 randomized controlled trials evaluating safety and efficacy of bevacizumab, which revealed a dose-dependent increased risk of bleeding (RR: 1.36 *vs* 2.87)[17]. Another meta-analysis evaluating 22 studies identified an incidence of high-risk bleeding of 2.8% (95%CI 2.1%-3.8%) among patients receiving bevacizumab[18]. In comparison to the findings of the previously mentioned meta-analysis, our study did not identify any patients with post-procedure bleeding. However, one patient had persistent variceal hemorrhage despite attempts for endoscopic control with variceal ligation.

Table 4 List of antiangiogenic agents

Anti-angiogenic agents (*n* = 60)	
Vascular-endothelial growth factor inhibitors	
1 Bevacizumab	30
2 Ramucirumab	3
3 Lenvatinib	4
4 Sorafenib	2
Epidermal-growth factor receptor inhibitors	
1 Cetuximab	3
2 Osimertinib	1
Tyrosine-kinase inhibitors	
1 Lapatinib	1
2 Pazopanib	2
3 Imatinib	7
4 Dasatinib	1
5 Sunitinib	2
Mammalian target of rapamycin inhibitor	
1 Everolimus	2
2 Temsirolimus	2

AAs have also been linked with increased gastrointestinal perforation especially if endoscopic interventions like colonic self-expanding stents (SEMS) are attempted. The rate of perforation ranges between 2%-12% among patients undergoing SEMS placement[19,20]. A meta-analyses evaluating effectiveness and safety of monoclonal antibodies including bevacizumab, cetuximab and panitumumab concluded that the use of these agents have serious adverse events including gastrointestinal perforation[20]. This risk of gastrointestinal perforation, even with the performance of high-risk endoscopic procedures, was not seen in our study which supports the findings of the multicenter outcome study by Kachaamy *et al*[7] regarding the safety of endoscopy among patients on AAs.

Strengths of our study include the removal of any potential selection bias with the inclusion of all patients who underwent endoscopic procedures while on AAs. Given that our facility is not an NCI-designated cancer center, the findings of our study are generalizable and applicable to the general practice. Nonetheless, this study is limited by its retrospective nature and small sample size.

CONCLUSION

In this single center retrospective study, the rate of endoscopic procedure-related adverse events and death within 28 d of AA administration are low. Our study results further support the findings of Kachaamy *et al*[7] on the safety of endoscopy among patients on AAs. While it is recommended to hold AAs 28 d prior to the performance of an elective endoscopic procedure, this should not delay the performance of an emergent or urgent endoscopic procedure given its good safety profile. Our study reiterates the safety data of low-risk endoscopic procedures in this sub-group of patients. This also raises further questions about whether there is a need to hold anti-angiogenics in patients on anti-angiogenics prior to high-risk endoscopic procedures. Awareness of newer medication and its implication on our current practice of gastroenterology are crucial for delivering optimal patient care. Future prospective studies should be evaluated in a multicentric larger population groups while keeping in mind that the GI cancers have an inherent increased risk of bleeding and perforation.

ARTICLE HIGHLIGHTS

Research background

High-grade bleeding and perforation are some of the side effects of antiangiogenic agents. The safety of

endoscopy in patients receiving this therapy is unknown. Here we attempt to explore the incidence of bleeding, perforation, and mortality in our single centered study.

Research motivation

With the increased survival rate of cancer patients with newer chemotherapy, more patients would require endoscopic procedures for further surveillance and screening. It is important to assess the safety of endoscopic procedures among patients receiving therapy such as antiangiogenic agents who are at higher risk for bleeding and perforation.

Research objectives

To understand the risk of endoscopy in patients on antiangiogenic agents.

Research methods

We performed a retrospective analysis of patients, on antiangiogenic agents, who were admitted to the hospital at our institute. We used simple descriptive statistics to primarily assess mortality within 30 d of the procedure along with the incidence of bleeding and perforation.

Research results

We found no procedure-related adverse events in our small population study among the patients receiving antiangiogenic agents. These results need to be further confirmed in a multicentric larger population group.

Research conclusions

Our study reveals that endoscopic procedures are safe in patients receiving antiangiogenic agents. It affirms to not delay emergent or urgent endoscopic procedures among this population.

Research perspectives

Future research should be carried out in a multicentric and larger group of the population than the one in this study to further assess the safety of the endoscopic procedure among this population group.

FOOTNOTES

Author contributions: Azam MU and Hudgi AR performed the research, collected the data, wrote the paper, contributed to analysis and reviewed the article; Uy P collected the data and reviewed the article; Makhija J performed the formal analysis; Yap JE conceptualized, supervised the report and approved the final draft submitted.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Augusta University Medical Centre.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: All authors declare that they have no conflict of interest.

Data sharing statement: The technical appendix, statistical code, and dataset are available from the corresponding author at jyap@augusta.edu. Consent was not obtained as this was a retrospective study. No additional data are available.

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ORCID number: Mohammad Azam 0000-0002-3847-5285; Amit Hudgi 0000-0002-3062-7694; Pearl Princess Uy 0000-0002-0884-3104; Jinal Makhija 0000-0002-6931-5188; John Erikson L Yap 0000-0002-0441-3211.

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Randomized Clinical Trial

Feasibility of endoscopic papillary large balloon dilation to remove difficult stones in patients with nondilated distal bile ducts

Julio Carlos Pereira Lima, Giusepe Saifert Moresco, Ivan David Arciniegas Sanmartin, Isabela Contin, Guilherme Pereira-Lima, Guilherme Watte, Stephan Altmayer, Carlos Eduardo Oliveira dos Santos

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Julio Carlos Pereira Lima, Giusepe Saifert Moresco, Ivan David Arciniegas Sanmartin, Isabela Contin, Guilherme Pereira-Lima, Department of Gastroenterology, Endoscopy Division, Federal University of Health Sciences of Porto Alegre/Santa Casa Hospital, Porto Alegre 90020-090, RS, Brazil

Guilherme Watte, Stephan Altmayer, Department of Biostatistics and Epidemiology, Pontifical Catholic University of Rio Grande do Sul, Porto Alegre 90619-900, RS, Brazil

Carlos Eduardo Oliveira dos Santos, Department of Gastroenterology and Endoscopy, Santa Casa Hospital, Bagé 96400-130, RS, Brazil

Corresponding author: Julio Carlos Pereira Lima, FASGE, MD, MSc, PhD, Professor, Department of Gastroenterology, Endoscopy Division, Federal University of Health Sciences of Porto Alegre/Santa Casa Hospital, Rua Professor Annes Dias, 295, Porto Alegre 90020-090, RS, Brazil. pereiralimajulio@gmail.com

Abstract

BACKGROUND

Current guidelines recommend not performing papillary large balloon dilation in patients with nondilated distal bile ducts.

AIM

To assess the feasibility of balloon dilation to remove difficult stones in patients with nondilated distal bile ducts.

METHODS

Data from 1289 endoscopic retrograde cholangiopancreatography (ERCP) procedures were obtained from two prospective studies. While 258 cases had difficult stones (> 1 cm, multiple > 8, impacted, or having a thin distal duct), 191 underwent biliary dilation up to 15 mm after endoscopic sphincterotomy. Cholangiographies of these cases were retrospectively reviewed in order to classify the distal bile duct and both the stone size and number. Primary outcomes were clearance rate at first ERCP and complications.

RESULTS

Of the 191 patients (122 women and 69 men; mean age: 60 years) who underwent biliary dilation for difficult stones, 113 (59%) had a nondilated or tapered distal

duct. Patients with a dilated distal duct were older than those with nondilated distal ducts (mean 68 and 52 years of age, respectively; $P < 0.05$), had more stones (median 4 and 2 stones per patient, respectively; $P < 0.05$), and had less need for additional mechanical lithotripsy (6.4% *vs* 25%, respectively; $P < 0.05$). Clearance rate at first ERCP was comparable between patients with a dilated (73/78; 94%) and nondilated distal ducts (103/113; 91%). Procedures were faster in patients with a dilated distal duct (mean 17 *vs* 24 min, respectively; $P < 0.005$). Complications were similar in both groups (6.4% *vs* 7.1%, respectively).

CONCLUSION

Large balloon dilation for difficult stones is feasible in patients with a nondilated or even tapered distal duct.

Key Words: Difficult bile duct stones; Endoscopic retrograde cholangiopancreatography; Balloon dilation; Complications; Biliary dilation; Cholangiography

Core Tip: Endoscopic papillary large balloon dilation is increasingly being used in treating difficult bile duct stones, since it is faster and less laborious than mechanical lithotripsy, with comparable results in terms of safety and effectiveness. However, this method is not recommended in patients with nondilated distal ducts, due to a higher complication rate, especially perforation. This study evaluated a large cohort of difficult duct stones patients submitted to large balloon dilation and found that patients with dilated and nondilated distal ducts had similar complication rates. This study suggests that large balloon dilation may be feasible in the latter group of patients.

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INTRODUCTION

Endoscopic sphincterotomy with stone extraction by balloon and/or basket is the method of choice for treating bile duct stones[1]. However, in patients with difficult bile duct stones (impacted, multiple or > 1 cm, or having a tapered distal duct), additional methods such as mechanical lithotripsy, intracorporeal lithotripsy, or papillary large balloon dilation are needed. Lithotripsy techniques, especially intracorporeal lithotripsy, which need to be guided by cholangioscopy, increase procedure time, cost, and the number of endoscopic retrograde cholangiopancreatography (ERCP) sessions required to clear the biliary tree[2]. Ersoz *et al*[3] pioneered the use of large balloon dilation of the distal bile duct in order to widen the pre-papillary portion of the common duct and facilitate stone retrieval.

The American Society for Gastrointestinal Endoscopy (ASGE) does not recommend papillary large balloon dilation for nondilated distal ducts because of the "increased risk of perforation"[4]. However, two Japanese studies[5,6] and another by the original technique description by Ersoz *et al*[3] successfully and safely employed endoscopic papillary or biliary large balloon dilation in patients with a nondilated or tapered distal bile duct. The current study analyzes the feasibility of using large balloon dilation of the distal biliary tree to remove difficult stones from patients with a nondilated distal bile duct.

MATERIALS AND METHODS

Data collection

Data were retrieved and analyzed from 1289 ERCPs conducted in two prospective trials during 2014-2019 that assessed post-ERCP pancreatitis (PEP) prevention[7,8]. Eligible subjects were all adults scheduled to undergo ERCP at our institution, and whose cannulation target was the biliary tree. Patients were excluded if they had non-naïve papilla, a previous ERCP at other institutions, failed bile duct cannulation, patients who primarily underwent an infundibulotomy due to an impacted stone at the papilla or papillary neoplasia, Billroth II gastrectomy, or were lost to follow up or refused to enter the studies. All patients gave signed informed consent to the procedure and inclusion in the study. Both

study protocols were approved by the Research Ethics Commission of our Institution and registered in the Brazilian Protocol Registry under UTN codes U1111-1207-7823 (http://www.ensaiosclinicos-.gov.br/rg/RBR-979wh3) and U1111-1176-4646 (http://www.ensaiosclinicos.gov.br/rg/RBR-6zkm5k/. The study was approved by the Institutional Review Board of our hospital and conformed to the provisions of the Declaration of Helsinki (as revised in Fortaleza, CE, Brazil, 2013). Both trials followed CONSORT guidelines.

In the two randomized trials assessing post-ERCP pancreatitis prevention, 258 cases had difficult bile duct stones (≥ 8 stones, > 1 cm or impacted)[7,8]. Of these, 67 patients had the duct cleared by endoscopic sphincterotomy with or without mechanical lithotripsy and without the need for an endoscopic biliary large balloon dilation (EBLBD) since their distal ducts were wide enough to allow stone passage without balloon dilation. The remaining 191 patients underwent an EBLBD up to 15 mm after a full-length endoscopic sphincterotomy. The operator filled out a procedure evaluation form immediately after the ERCP. The research team, which was blinded to patient randomization, contacted the patients personally or by phone 48-72 h after ERCP and 15-30 d after the procedure to complete the follow-up forms. Patients who experienced post-ERCP pain or bleeding received laboratory and abdominal imaging, or endoscopic evaluation.

Definitions

A nondilated or tapered distal bile duct was defined when the lower part of the biliary tract was < 8 mm in diameter and > 15 mm in length measured by cholangiography. The number of stones and the maximum diameter of each patient's largest stone were independently verified by three of the authors of the present study. Radiographs of the 191 cases who received an EBLBD are stored in our hospital's computer system and were retrospectively evaluated.

Procedure methods

ERCP was performed by one of the authors who performs more than 700 ERCPs annually or by a fellow under supervision. All procedures were performed under sedation with propofol, midazolam, and fentanyl which was supervised by an anesthesiologist. Hyoscine was administered to abolish duodenal peristalsis. After the cholangiographic diagnosis of a difficult stone, a complete sphincterotomy was performed *via* the papillary ostium or the access obtained after pre-cut papillotomy (Jag Wire straight tip, Ultratome XL short nose 20 mm, Microknife XL, Boston Scientific Marlborough, Massachusetts, United States or Tritome triple lumen sphincterotome 25 mm, Tracer Metro Direct wire guide, Huibregtse Triple lumen needle knife 4 mm, Cook Endoscopy, Winston-Salem, NC, United States). A large dilation esophageal/pyloric balloon (CRE PRO Wireguided – esophageal, pyloric, colonic, biliary Balloon Dilatation Catheter 12-15 mm, Boston Scientific, Marlborough, Massachusetts, United States)was inserted into the bile duct and gradually inflated across the papilla at 12-15 mm (3.5-8 ATM according to the manufacturer's recommendations), in order to try and obliterate its waist regardless of the presence of a distal situated stone, a peri-papillary diverticulum, or a nondilated distal duct. Additional upstream dilations in the duct were performed at the endoscopists' discretion if the bile duct distal to the stone was considered not dilated enough to facilitate stone retrieval. For each dilation, the balloon was left inflated in place for 10-30 s. After the EBLBD, a retrieval balloon and/or a basket were used to remove the stones. If stone removal was incomplete, a plastic stent was left in place. Procedure time was measured in minutes from the insertion of the duodenoscope into the patient's oral cavity to its retrieval.

Outcome measurements

The primary outcome was ERCP complications, notably perforation and pancreatitis (PEP). Secondary outcomes were clearance rate at first ERCP, procedure time, and need for mechanical lithotripsy. Procedure-related complications and severity were determined using definitions from a previously published guideline[9].

Statistics

Data were presented as the frequency (percentage) or mean ± SD. The Shapiro-Wilk test was used to assess the normality of the data distribution. The Mann–Whitney test was used to compare continuous variables and a chi-square was used to compare associations between variables. Statistical significance was accepted at a two-sided significance level of 0.05. Statistical analyses were performed using STATA v.15 (STATA Corporation, College Station, Texas, United States).

RESULTS

Of the 191 cases with difficult bile duct stones who received an EBLBD, 122 were women (63.8%) and 69 were men, the mean age was 60 years (range, 26-93 years), and 185 were Caucasians (European-derived) and 6 were black. While 113 of the 191 cases had a nondilated or tapered distal bile duct, 78 had a large distal duct. Cases with a nondilated distal duct had fewer duct stones (mean and median = 2, range, 1-5)

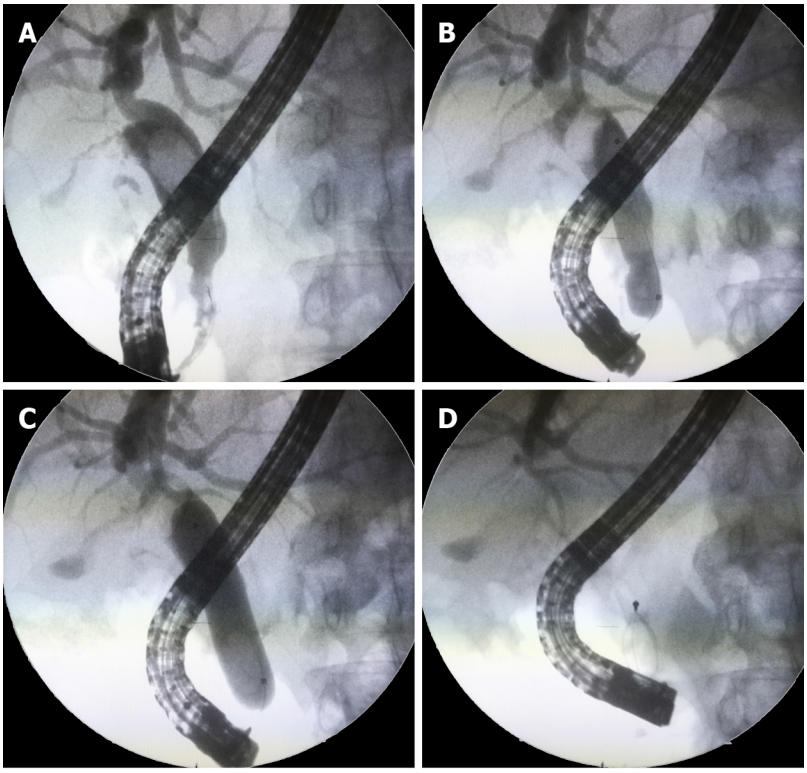

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Figure 1 Large balloon dilation in a patient with tapered distal duct. A: A 60-year-old female patient with a nondilated distal common duct; B: Large balloon dilation of the distal duct; C: Full dilation to 15 mm was performed; D: Stone retrieval without intracorporeal or mechanical lithotripsy was allowed by this technique.

than patients with dilated distal ducts (mean = 4.1, median = 4, range, 1-15; $P < 0.01$). The main bile duct stone size was smaller in patients with nondilated than dilated distal ducts (mean 1.1 cm (range, 0.7-1.5 cm) *vs* 1.7 cm (range, 1.3-2.5 cm), respectively; $P < 0.01$). Patients with a nondilated distal duct were also significantly younger and more likely to have received mechanical lithotripsy (Table 1).

The ERCP technique is described in Figures 1-3. Figure 1 shows a patient with a long intrapancreatic choledochal segment, which was balloon dilated to widen the distal biliary tree and allow easier stone removal after lithotripsy. Figures 2 and 3 show the results from patients with long-segment nondilated distal ducts and impacted stones in the middle common duct. These individuals had large balloon dilation until waist disappearance, resulting in a faster and easier stone extraction in the same sitting.

The clearance rate at first ERCP was comparable between the two groups. Patients with a dilated distal duct had a 94% stone clearance rate (73/78 patients) and those with a nondilated distal duct had a 91% clearance rate (103/113 patients). Procedures were also faster in patients with a dilated than nondilated distal duct (mean = 17 *vs* 24 min, respectively; $P < 0.05$).

The complication rate was similar in both groups. Eight of 113 (7.1%) patients with a nondilated distal duct had complications (two had perforations, three had overt bleedings, and three had PEP), while five of the 78 (6.4%) patients with a large distal duct who received an EBLBD had complications (two had bleeding, one experienced cholangitis, and two had PEP) (Table 2). All complications were treated conservatively and no patients died from the procedure. Of five cases with a dilated distal duct and no bile duct clearance at first ERCP (with a plastic stent left in place), two underwent surgery, and three had their ducts cleared during a second ERCP using lithotripsy techniques. One of these three cases developed fever (mild cholangitis) after the second procedure. In all ten cases with a narrow distal duct for whom the first ERCP attempt failed to complete stone extraction, a second ERCP successfully achieved bile duct clearance. Ductal clearance was accomplished using another EBLBD after stent removal and lithotripsy techniques. Two patients experienced overt bleeding without the need for transfusion and two had mild cholangitis at the second ERCP.

DISCUSSION

In this study, EBLBD up to 15 mm was shown to be feasible and safe for patients with nondilated distal ducts though there were two cases of perforation in this group. Patients with nondilated ducts had the same complication rate of those with dilated distal ducts. An *ex vivo* porcine model showed that biliary

Table 1 The primary features and endoscopic biliary large balloon dilation outcomes of dilated and nondilated distal bile duct patients

	Non-dilated DD (*n* = 113)	Dilated DD (*n* = 78)	*P* value
Mean age (SD)	52 ± 8	68 ± 11	< 0.001
Female/Male	75/38	47/31	0.387
Number of MBD stones (SD)	2 ± 0.7	4.1 ± 2.9	< 0.001
Biggest MBD stone size (SD)	1.1 ± 0.1	1.7 ± 0.2	< 0.001
Additional ML	28 (25%)	5 (6.4%)	0.001

ML: Mechanical lithotripsy; DD: Distal bile duct; MBD: Main bile duct.

Table 2 The complications of dilated and nondilated distal bile duct patients who received endoscopic biliary large balloon dilation

	Non-dilated DD (*n* = 113)	Dilated DD (*n* = 78)
Complication rate, *n* (%)	8 (7.1)	5 (6.4)
Post-ERCP pancreatitis	3	2
Overt bleeding	3	2
Perforations	2	-
Cholangitis	-	1
Death	-	-

ERCP: Endoscopic retrograde cholangiopancreatography; DD: Distal bile duct.

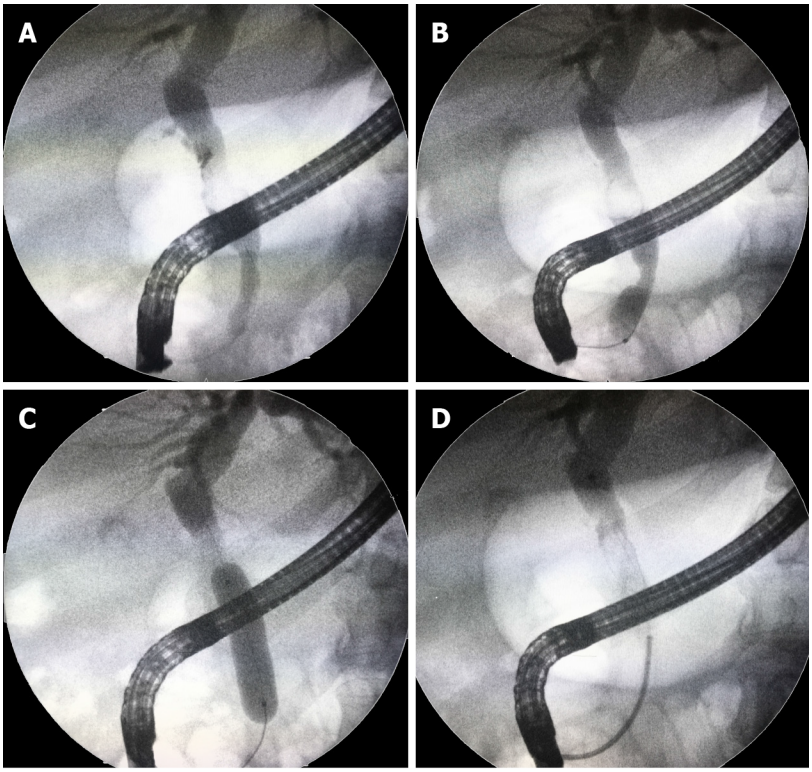

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Figure 2 Large balloon dilation in a patient with a long nondilated distal duct segment. A: A patient with a long non-dilated distal duct and impacted stone; B: Beginning of balloon dilation with choledochal waist; C: Full dilation to 15mm was obtained; D: Stone removal without the need of lithotripsy.

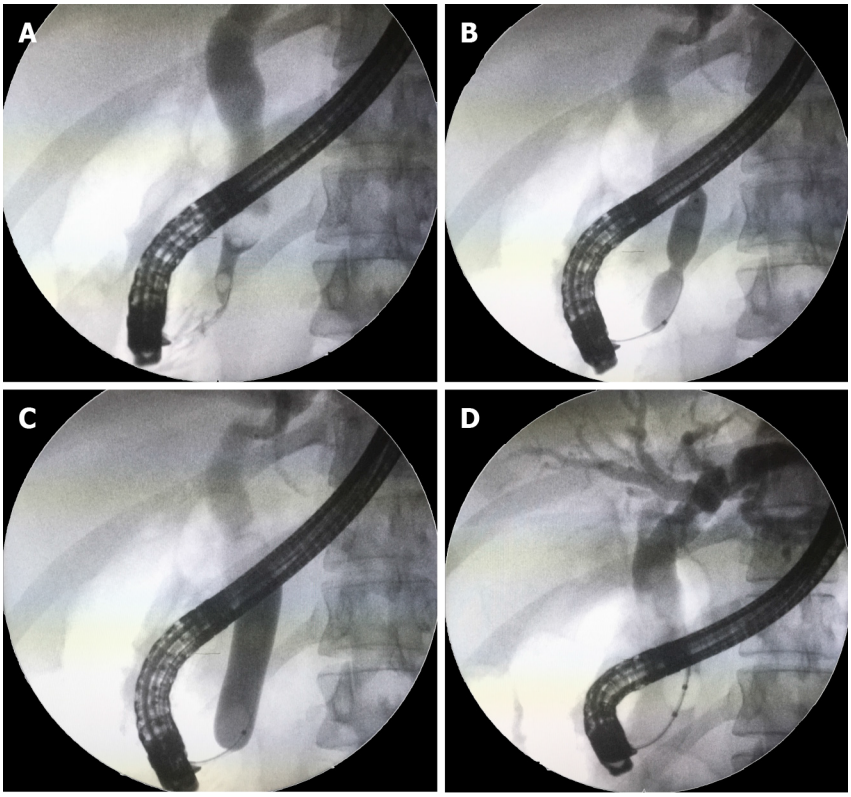

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Figure 3 Large balloon dilation technique. A: Cholangiography demonstrates an impacted stone above a nondilated distal duct in a young patient; B: Balloon dilation at the tapered distal common duct segment with a balloon waist still observed; C: Full dilation up to 15 mm pushing the stone upstream; D: Balloon stone extraction is achieved.

duct tears are caused by overdistention of narrow ducts after large balloon dilation[10]. However, studies indicate that a tear in a nondilated distal bile duct in humans does not necessarily result in a retroperitoneum or peritoneal cavity rupture because this thinner portion is located within the pancreas [10]. This is one explanation for why only two of 113 (< 2%) patients with nondilated distal bile ducts who received EBLBD experienced overt perforations. Despite physical compression resulting from balloon dilation inside the pancreatic head, PEP rates were relatively low and similar in both groups (2.7% *vs* 2.6% for patients with non-dilated and dilated distal bile ducts, respectively). Another possible explanation for our findings was the fact that we always dilate the bile duct and the ampullary region with balloons up to 15 mm. In a Korean study analyzing 672 EBLBD for difficult stones, perforations and fatal complications only occurred in patients dilated > 15-20 mm. No perforation was observed in patients dilated 12-15 mm[11].

ASGE guideline C level recommendation that EBLBD should not be performed in patients with a nondilated distal duct is based on one study in which three deaths occurred as a result of perforation following EBLBD and, in two of the three cases, a full incision sphincterotomy was also performed[4,12]. The guideline used the same study to recommend at evidence level of III that the maximum diameter of the balloon should not exceed that of the distal common bile duct[4,12]. Fujita *et al*[5] analyzed 209 cases submitted to EBLBD and found no differences in the incidence of PEP, bleeding, or perforation when comparing EBLBD in patients with and without a nondilated distal bile duct. Ersoz *et al*[3], the first endoscopists who employed large balloon dilation for difficult stones, evaluated 18 cases with a nondilated distal duct and 40 with a dilated distal duct in their original report. There were no cases of perforations in either group, but bleeding occurred more often in patients with a nondilated distal duct.

In patients with large stones and no distal duct dilation, a common finding in our experience, it can be more difficult and labor-intensive to clear the common duct. As a result of stone impaction in the pre-papillary portion of the bile duct, this process usually requires multiple mechanical lithotripsies and stone retrieval with baskets until extraction balloons can be used. EBLBD has been avoided and contraindicated in these cases[4]. Based on the original report by Ersoz *et al*[3] and two additional series [5,6], we hypothesized that EBLBD could be extended to patients with a nondilated distal bile duct. In our technique, we perform additional dilations in the proximal part of the duct and found that the full balloon length could frequently be inserted into the bile duct. As a result, we named this technique "endoscopic biliary large balloon dilation" and not papillary dilation as usually described. The goal of EBLBD is to create a wide opening in the distal biliary tree and papillary orifice to facilitate stone

removal using extraction balloons or baskets. Importantly, this patient population is more difficult to manage even with the help of EBLBD in those with a nondilated distal duct. In the current study, patients with a nondilated distal duct were more likely to require mechanical lithotripsy (25% *vs* 6.4% for those with a nondilated and dilated distal duct, respectively) despite having significantly smaller stones and a lower number of stones than those with a dilated distal duct. This may be because even dilating the distal duct to 8 ATM (according to the manufacturer's instructions, this pressure should theoretically dilate the duct to 15 mm), the promised duct width of more than 1 cm is not actually reached, as we observed in our practice. An explanation for this phenomenon is that the distal portion of the bile duct is located within the pancreas.

The use of sphincterotomy plus EBLBD significantly reduces the use of mechanical lithotripsy and procedural time in comparison to sphincterotomy alone, as demonstrated by a French multicenter study only evaluating patients with wide distal ducts, since these authors excluded patients with "stenotic" distal ducts[13]. In 150 difficult stone cases, the use of sphincterotomy plus EBLBD had the same complication rate as sphincterotomy alone and presented a higher clearance rate at the initial ERCP[13]. A meta-analysis of six other studies reached similar conclusions[14]. Of note, patients with nondilated distal ducts are more difficult to manage and were not included in these studies[13,14]. The use of EBLBD in patients with nondilated distal bile ducts would reduce the use of lithotripsy, shorten procedure time, and—in a cost containment reality such as ours—would significantly reduce costs by avoiding the employment of cholangioscopy-guided lithotripsy. In a general population of difficult stone patients, EBLBD is demonstrated to be as safe and as effective as single operator cholangioscopy-guided lithotripsy[15].

There are limitations to the current study. Data were extracted from two prospective randomized controlled trials evaluating PEP prevention and not difficult stone management. Data were retrospectively collected by reviewing the cholangiographies of the 191 patients who underwent EBLBD. The indications for EBLBD may not have been standardized in the sample, despite its single-center nature, since treatment for difficult choledocholithiasis was not the aim of the study. On the other hand, this study analyzed a significant sample of large biliary balloon dilated patients with nondilated distal ducts and we ensured that they were prospectively evaluated for complications given their involvement in two prospective trials.

CONCLUSION

EBLBD for stone removal may be feasible and effective option for patients with a nondilated or tapered distal bile duct and may be a significantly less costly and time-saving alternative to cholangioscopy-guided intracorporeal lithotripsy. Our technique, in which proximal parts of the duct and not just the pre-papillary region are dilated, may explain the success of EBLBD. This method requires prospective validation by future studies.

ARTICLE HIGHLIGHTS

Research background

Endoscopic papillary large balloon dilation is increasingly being used in treating difficult bile duct stones, since it is faster and less laborious than performing multiple mechanical lithotripsies, with comparable results in terms of safety and effectiveness. However, this method is not recommended in patients with nondilated distal bile ducts, due to a theoretically higher complication rate, especially perforation.

Research motivation

Papillary large balloon dilation is an important tool to extract difficult duct stones and very few studies examined this technique in patients with nondilated distal ducts, although in its original report, this method was used in this setting.

Research objectives

To analyze the feasibility of papillary large balloon dilation in patients with difficult bile duct stones and nondilated distal bile ducts, as well as the complication rate and effectiveness of this method in this subset of stone patients. To investigate the demographic characteristics of this patient group. Data on these issues may stimulate future research and assist endoscopists in choosing the best endoscopic modality to treat difficult bile duct stones.

Research methods

We retrieved data from 1289endoscopic retrograde cholangiopancreatography (ERCP) procedures from

2 prospective randomized controlled trials dealing with post-ERCP pancreatitis (PEP). Of these, 258 cases had difficult stones (> 1 cm, multiple > 8, impacted, or having a thin distal duct) and 191 underwent papillary large balloon dilation up to 15 mm after endoscopic sphincterotomy for stone retrieval. Cholangiographies of these cases were retrospectively reviewed by the authors in order to classify the distal bile duct as dilated or nondilated, as well as stone size and number. Primary outcomes were clearance rate at first ERCP and complications.

Research results

Of the 191 patients, 113 (59%) had a nondilated or tapered distal duct (75 F/38 M, mean age: 52 years) and 78 (47 F/31 M mean age: 68 years) a dilated distal duct. Cases with a nondilated distal duct had fewer (mean = 2 *vs* 4.1, $P < 0.05$) and smaller (mean 1.1 cm *vs* 1.7 cm, $P < 0.05$) stones than those with a dilated distal duct and were significantly younger than patients with dilated distal). Patients with a nondilated distal duct were also significantly younger and more likely to receive mechanical lithotripsy (25% *vs* 6.4%, $P < 0.05$). Clearance rate at first ERCP was comparable between patients with a dilated (73/78; 94%) and nondilated distal ducts (103/113; 91%). Procedures were faster in patients with a dilated distal duct (mean 17 *vs* 24 min, $P < 0.005$). Complications were similar in both groups: 8/113 (7.1%) *vs* 5/78 (6.4%), however the 2 perforations occurred in patients with nondilated ducts. There was no mortality.

Research conclusions

Large balloon dilation for difficult stones is feasible in patients with a nondilated or even tapered distal duct. Although the latter patients had smaller stones, they are more difficult to remove, since ERCP procedures in these patients require mechanical lithotripsy more often and last longer.

Research perspectives

Future prospective multicenter studies should evaluate the feasibility of large balloon dilation in patients with nondilated distal bile ducts and difficult stones, since current guidelines do not recommend the procedure in this group of patients.

FOOTNOTES

Author contributions: Pereira Lima JC, Saifert Moresco G, Sanmartin IDA, Contin I, Pereira-Lima G, Watte G, Altmayer S, Oliveira dos Santos CE, have been involved equally and have read and approved the final manuscript; Pereira Lima JC, Saifert Moresco G, Sanmartin IDA, Contin I, Pereira-Lima G, Watte G, Altmayer S, Oliveira dos Santos CE meet the criteria for authorship established by the International Committee of Medical Journal Editors and verify the validity of the results reported.

Institutional review board statement: This study and protocols were approved by the Research Ethics Commission of our Institution and registered in the Brazilian Protocol Registry under number RBR-979wh3 (http://www.ensaiosclinicos.gov.br/rg/RBR-979wh3) and UTN Number: U111-1207-7823 (URL: http://www.ensaiosclinicos.gov.br/rg/RBR-6zkm5k/). Written informed consent was obtained from all patients. The study adheres to the declaration of Helsinki.

Clinical trial registration statement: Brazilian Protocol Registry under number RBR-979wh3 (http://www.ensaiosclinicos.gov.br/rg/RBR-979wh3) and UTN Number: U111-1207-7823 (URL: http://www.ensaiosclinicos.gov.br/rg/RBR-6zkm5k/).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Prof. Dr. Julio Pereira Lima (jpereiralima@terra.com.br) is on the speakers' board of Takeda Pharmaceutical Latin America and receives honoraria as consultant of Boston Scientific, Latin America and Cook Endoscopy, Brazil. Dr. Carlos Eduardo Oliveira dos Santos (ddendo@uol.com.br) receives speaker fees and is a consultant of the speakers' board of Fujinon Co., Latin America. Drs. Giusepe Saifert Moresco (giusepemoresco@outlook.com), Ivan David Arciniegas Sanmartín (davidarciniegas23@gmail.com), Isabela Contin (isabeladbcontin@gmail.com), Guilherme Pereira Lima (guilhermepl14@gmail.com), Guilherme Watte (g.watte@gmail.com), and Stephan Altmayerstephanaltmayer@gmail.com) have no conflicts of interest or financial ties to disclose.

Data sharing statement: Dataset available from the corresponding author at pereiralimajulio@gmail.com. Participants gave informed consent for data sharing.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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ORCID number: Julio Carlos Pereira Lima 0000-0002-6070-6916; Giusepe Saifert Moresco 0000-0003-4667-3772; Ivan David Arciniegas Sanmartin 0000-0003-2074-5221; Isabela Contin 0000-0001-7341-2581; Guilherme Pereira-Lima 0000-0002-8152-5161; Guilherme Watte 0000-0002-6948-3982; Stephan Altmayer 0000-0001-9214-1916; Carlos Eduardo Oliveira dos Santos 0000-0003-4333-3182.

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SYSTEMATIC REVIEWS

Role of balloon enteroscopy for obscure gastrointestinal bleeding in those with surgically altered anatomy: A systematic review

Mahmoud Aryan, Tyler Colvin, Ali M Ahmed, Kondal Rao Kyanam Kabir Baig, Shajan Peter

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Mahmoud Aryan, Tyler Colvin, Department of Internal Medicine, University of Alabama at Birmingham, Birmingham, AL 35294, United States

Ali M Ahmed, Kondal Rao Kyanam Kabir Baig, Shajan Peter, Department of Gastroenterology and Hepatology, University of Alabama at Birmingham, Birmingham, AL 35294, United States

Corresponding author: Shajan Peter, MD, Associate Professor, Department of Gastroenterology and Hepatology, University of Alabama at Birmingham, 1808 7th Avenue South, BDB 391, Birmingham, AL 35294, United States. ssugandha@uabmc.edu

Abstract

BACKGROUND

Obscure gastrointestinal (GI) bleeding is defined as persistent bleeding despite negative evaluation with both esophagogastroduodenoscopy and colonoscopy and can be secondary to small intestinal pathology. Standard endoscopy as well as push endoscopy can be a challenge in those with altered anatomy given inaccessible areas as well as perforation risk. Single and double balloon enteroscopy can be warranted in this patient population in instances of obscure GI bleed.

AIM

To assess the safety and diagnostic efficacy of balloon enteroscopy for obscure GI bleeding in patients with surgically altered anatomy.

METHODS

A search was conducted through PubMed, MEDLINE, Google Scholar, Scopus, and Embase with the key words "enteroscopy," "obscure bleeding," and "altered anatomy," to identify relevant articles in English with no restricted time frame. A search within the Reference Citation Analysis database was conducted to ensure inclusion of the latest high impact articles. Study types included in the review were prospective and retrospective reviews, case series, and case reports. The reference lists of these papers were also reviewed to find further papers that were applicable. The authors extracted the data from the studies that fit inclusion criteria. Data of interest included type of study, type of procedure, and type of altered anatomy, as well as the number of patients with any diagnostic or therapeutic intervention. Data was also recorded on procedure tolerance and complications. The data was analyzed with descriptive statistics.

RESULTS

Our literature search yielded 14 studies that were included. There were 68 procedures performed with 61 unique patients subjected to these procedures. Forty-four (65%) of the procedures were double balloon, 21 (31%) were single balloon, and 3 (4%) were classified as through the scope balloon assisted. The most common altered anatomy types included Gastric Bypass Roux-en-Y, Pylorus Sparing Whipple, Orthotopic Liver Transplantation with Roux-en-Y, and Gastrojejunostomy Roux-en-Y. The procedures were successfully performed in each patient. There were 5 (7%) procedures that were complicated by perforation. Amongst the available data, the diagnostic yield was 48/59 (81%) and a therapeutic yield of 39/59 (66%). One patient was recommended surgical revision of their altered anatomy following enteroscopy.

CONCLUSION

Balloon enteroscopy is a useful diagnostic modality in investigating obscure GI bleeding within those with surgically altered anatomy; however, precautions must be taken as this population may have increased perforation risk.

Key Words: Altered anatomy; Single balloon enteroscopy; Double balloon enteroscopy; Obscure; Bleed; Gastrointestinal

Core Tip: Balloon enteroscopy is often warranted in patients with surgically altered anatomy who suffer from obscure gastrointestinal (GI) bleeding. Data remain limited on the clinical utility of single or double balloon enteroscopy in those with altered anatomy. The primary aim of this systematic review was to assess the diagnostic and therapeutic efficacy of balloon enteroscopy for obscure GI bleeding in patients with surgically altered anatomy. The secondary aim was to investigate the safety of balloon enteroscopy in this patient population.

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INTRODUCTION

Obscure gastrointestinal (GI) bleeding is defined as persistent bleeding despite negative evaluation with both esophagogastroduodenoscopy and colonoscopy. Most obscure GI bleeding can be secondary to small intestinal pathology and has now become manageable with the introduction of single balloon enteroscopy (SBE) or double balloon enteroscopy (DBE) in 2001[1]. The overall diagnostic utility of DBE has ranged from 59%-90%[2-5]. In patients with surgically altered anatomy, endoscopic procedures may be challenging. Given distortion of native anatomy, areas that may have been accessible with standard endoscopy may be inaccessible or difficult to reach. In such instances, anastomotic areas remain at risk for perforation especially when larger diameter endoscopes are inserted at longer lengths. Deep enteroscopy can also be implemented to access sites unreachable by standard endoscopy[6]. Those with distorted anatomy may require thorough investigation of the upper GI tract in instances such as refractory abdominal pain or obscure GI bleeding. Balloon enteroscopy can be warranted in such cases where standard and push endoscopy are unrevealing.

SBE and DBE have been shown to be effective in patients with surgically altered anatomy in regards to endoscopic retrograde pancreatography (ERCP) and biliary complications. However, there remains limited information regarding management of obscure GI bleeding in patients with surgically altered anatomy. This systematic review aims to assess the overall safety and diagnostic efficacy of balloon enteroscopy for obscure GI bleeding in patients with surgically altered anatomy.

MATERIALS AND METHODS

Literature search

Data for this review was identified and performed by two independent reviewers (MA, TC) with

consensus to avoid bias. Discrepancies and the decision over whether to include or exclude a study were resolved by means of discussion with consensus to avoid bias. Searches were done on PubMed, Google Scholar, Scopus, and Embase. All relevant articles were carefully reviewed with a review of each article's references as well. Terms used for the search included "enteroscopy," "obscure bleeding," "gastrointestinal bleeding," and "altered anatomy." The literature search was performed in December 2021. Study types included in the review were prospective and retrospective reviews, case series, and case reports. Reference lists from these articles were also reviewed to find pertinent articles. Inclusion criteria for our systematic review included studies that were subjected to peer review and had available text in English. Only studies accessible through the search engines listed above were included in our review. Solitary abstract reports were excluded from our study in addition to any studies performed on animals. Studies that were not subject to peer review or were of pediatric focus (< 18 years) were also excluded from the study. A specific PRISMA flow diagram is included in Figure 1 to summarize our search methods. A further literature search was conducted with the reference citation analysis (RCA) engine, an artificial intelligence technology-based open multidisciplinary citation analysis database (https://www.referencecitationanalysis.com). This database was implemented to ensure the latest high impact articles were included in our study. Following a search of "balloon enteroscopy" within the RCA database no further studies were identified that fit our inclusion criteria.

Data from each study were extracted into an excel file in a systematic fashion. Extracted data included type of study, type of procedure, and type of altered anatomy, as well as the number of patients with any diagnostic findings or therapeutic intervention. Data were also recorded on procedure tolerance and complications. Due to the lack of controlled trials, retrospective and prospective observational studies were also included, as were case reports. We considered all clinical studies or reports that had been published until December 2019. As the current work only involved previously performed studies, approval by the Institutional Review Board or individual patient consent was deemed unnecessary.

Statistical analysis

Statistical analysis in the form of descriptive statistics was reported from each study. This data was organized and included in a structured table (Table 1).

RESULTS

Following the search of these databases, 14 studies in total were included in our review. Of these studies, 6 were retrospective studies[7-12], 2 were prospective studies[13,14], 1 was a case series[15], and the remaining 5 were case reports[16-20]. In total, there were 68 procedures performed with 61 unique patients that had undergone these procedures. All patients were above the age 17 years old at the time of procedure. Forty-four (65%) of the procedures were double balloon, 21 (31%) were single balloon, and 3 (4%) were classified as through the scope balloon assisted. There were a variety of altered anatomy types with the most common being Gastric bypass Roux-en-Y (GBR), Pylorus sparing Whipple (PSW), Orthotopic Liver Transplantation with Roux-en-Y (OLTR), and Gastrojejunostomy Roux-en-Y (GJR).

The procedures (SBE *vs* DBE) were performed in all patients; however, five (7%) procedures were complicated by perforation. There were no reported complications in the remaining 63 (93%) patients. Amongst the 5 reported procedure related perforations, 2 (40%) patients had a Roux-en-Y. The remaining 3 patients consisted of an ileal-sigmoid anastomosis, a right hemicolectomy with ileostomy, and an unspecified altered anatomy type. From the available data in each study, there was an overall diagnostic yield of 48/59 (81%) and a therapeutic yield of 39/59 (66%). Common diagnostic findings included ulcers (Figure 2A), arteriovenous malformations, angioectasia, anastomotic site bleeding (Figure 2B), and other post-surgical bleeding (Figure 2C). Therapeutic interventions consisted of argon plasma coagulation (APC), endoscopic clip placement, epinephrine injection, and N-butyl-2-cyanoacrylate (Histoacryl) injection. There was 1 patient who was recommended surgical revision of their altered anatomy following enteroscopy.

DISCUSSION

Obscure GI bleeding accounts for 5% of all GI bleeds with the culprit most often being small bowel origin[21]. Balloon enteroscopy has been implemented to assess for obscure GI bleeding and can be performed through different approaches. SBE utilizes an enteroscope (200 cm in length) with an overtube (140 cm in length) and balloon inflation device. DBE on the other hand has the same enteroscope and overtube but consists of two balloons: one at the tip of the enteroscope and the other acting as an anchoring leverage on the distal part of the overtube. These procedures can be performed anterograde (through the mouth) or retrograde (through the anus)[21].

Despite the differences in the devices, the techniques for these procedures are similar. The overtube is backloaded on the enteroscope after which the enteroscope is advanced deeply into the small intestine.

Table 1 Overview of literature on balloon enteroscopy for obscure gastrointestinal bleeding in those with altered anatomy

Cases (*n*-patients)	Anatomy	Device	Study type	Yield	Complications	Ref.
17 (12)	8 GBR, 6 PSW, 2 OLTR, 1 GJR	DBE	Retrospective	15/17 diagnostic; 14/17 therapeutic	1/17 perforation	[7]
3 (3)	Not specified	TTS-BAE	Retrospective	1/3 diagnostic; 1/3 therapeutic	None	[8]
3 (3)	1 OLTR, 1 Ileal-sigmoid anastomosis, 1 right hemicolectomy with ileostomy	DBE	Retrospective	3/3 diagnostic; 0/3 therapeutic	3/3 perforation	[9]
15 (15)	Not specified	SBE	Retrospective	8/15 diagnostic; 5/15 therapeutic	None	[10]
3 (1)	Most OLTR	DBE	Retrospective	3/3 diagnostic; 1/3 therapeutic	None	[11]
5 (5)	Not specified	DBE	Retrospective	5/5 diagnostic; 5/5 therapeutic	None	[12]
9 (9)	Not specified	DBE	Prospective	Does not specify	1/9 perforation	[13]
3 (3)	3 GBR	DBE	Prospective	3/3 diagnostic; 3/3 therapeutic	None	[14]
5 (5)	2 HJ, 1 PSW, 1 GBR, 1 right hemihepatectomy w/RYHJ	3 DBE 2 SBE	Case Series	5/5 diagnostic; 5/5 therapeutic	None	[15]
1 (1)	OLTR	SBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[16]
1 (1)	HJ	SBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[17]
1 (1)	Whipple	DBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[18]
1 (1)	GBR	SBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[19]
1 (1)	OLT	SBE	Case Report	1/1 diagnostic; 1/1 therapeutic	None	[20]

TTS-BAE: Through the scope balloon assisted enteroscopy; GBR:Gastric bypass Roux-en-Y; PSW: Pylorus sparing Whipple; OLTR: Orthotopic Liver Transplantation with Roux-en-Y; OLT: Orthotopic Liver Transplantation; GJR: Gastrojejunostomy Roux-en-Y; HJ: Hepaticojejunostomy; RYHJ: Roux-en-Y hepaticojejunostomy.

Anchoring of the endoscope is secured by the balloon tip on the enteroscope in DBE *vs* the flexible tip with no balloon assisted anchoring in SBE. The overtube with its deflated balloon is advanced all the way to the distal tip of the enteroscope. Once the overtube has reached the distal end of the enteroscope, a stepwise pattern of inflation and deflation of the single *vs* double balloon apparatus is used to assist enteroscope transit in visualizing the area of small bowel[21,22].

The SBE model frequently utilized is the Olympus SIF-Q180 with an outer diameter of 13.2 mm, inner diameter of 11 mm, and balloon diameter of 40mm. DBE models are developed by Fujinon and consist of the EN-450T5, EN-450PS/20, and the EC-450BI5 with outer diameter ranging from 12.2-13.2 mm, inner diameter ranging from 10-10.8 mm, and balloon diameter being 40 mm[23].

Obscure GI bleeding has been estimated to account for 5%-10% of all GI bleeding, with increasing number of patients requiring balloon enteroscopy for small bowel evaluation[24]. The diagnostic yield of balloon enteroscopy amongst those without altered anatomy has been reported around 45%-55%[21,25]. Adverse rates are overall low at 3.2% with most common complications including intestinal bleeding, perforation, or post-procedure pancreatitis[26,27]. With the emerging surgical techniques for various GI pathologies, surgically altered GI anatomy remains prevalent. The obesity epidemic in the United States has led to increased referrals to bariatric surgeries. Additionally, the advancements in liver transplant (LT) have led to increasing number of patients receiving LT over the past several years [28]. Given their surgically altered GI anatomy, these patients remain at risk for GI bleeding. Furthermore, the management of these patients may be complicated by surgical anastomotic sites often serving as culprits of obscure GI bleeding[7,17,18]. These patients may require work up leading to SBE or DBE for underlying diagnosis.

Besides a substantial diagnostic yield, therapeutic interventions can be effectively achieved using the enteroscope channel. Balloon enteroscopy allows the endoscopist to safely deploy and advance ablation catheters, injection needles, and mechanical or hemostatic clips. These devices can even be modified to

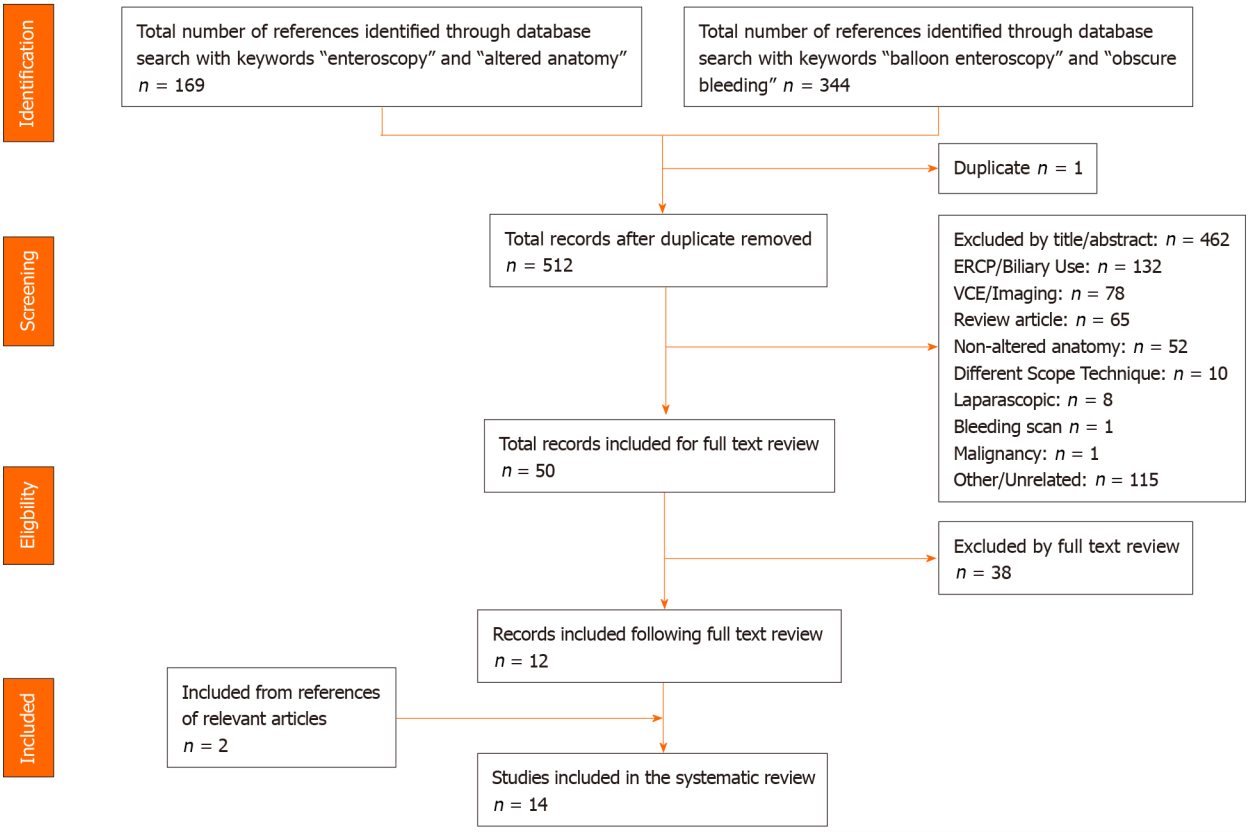

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Figure 1 Prisma diagram of literature review.

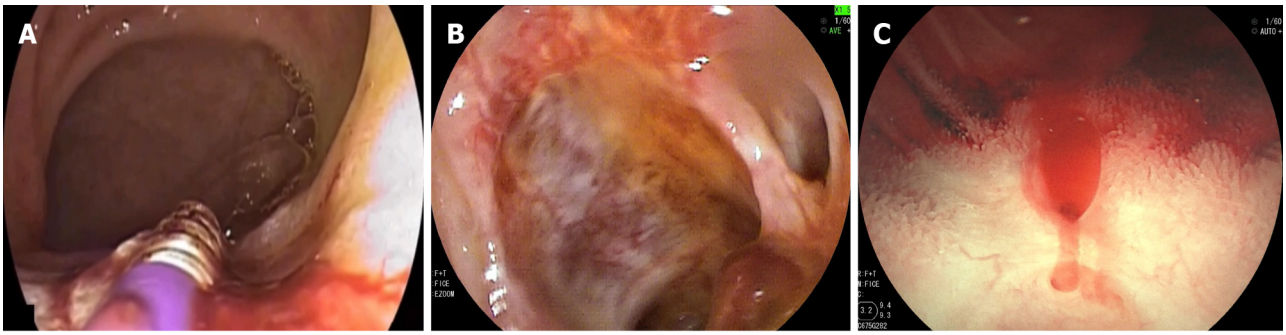

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Figure 2 Balloon enteroscopy. A: Endoscopic depiction of a bleeding duodenal ulcer undergoing thermal therapy in a post RYGB patient; B: Visualization of anastomotic neovascularization and bleeding in a patient with hepaticojejunostomy; C: Illustration of intraluminal bleeding in a patient following pancreatojejunostomy at the surgically altered site.

deliver Hemospray®. According to our literature, perforation remains the most frequently reported complication following balloon enteroscopy in those with altered anatomy. Post-surgical small bowel adhesions are prone to tearing during enteroscopy which can lead to perforation. Overall perforation rates in enteroscopy amongst those with both unaltered and altered anatomy from meta-analysis data have been reported to be as low as 0.24%[10,29,30]. Colonoscopy and upper endoscopy on the other hand have perforation rates as low as 0.1%[31]. From the available literature in this review, perforation rates were as high as 7% in those with surgically altered anatomy requiring single or double balloon enteroscopy. Such risk should be considered by clinicians during procedure planning in this patient population. Notably, the presence of post-surgical adhesions and overtube maneuvering through tight bends can be potential factors leading to added complications. The use of fluoroscopy can aid in navigating the enteroscope in challenging situations.

GBR, PSW, OLTR, and GJR were the most reported altered anatomy types observed in our review. The various types of altered anatomy structures may have an impact on the underlying procedure regarding luminal passage and scope maneuvers. No trend was identified regarding an association

between diagnostic or therapeutic yield with altered anatomy types. We observed that 20% of the perforations were seen in patients with a Roux-en-Y. Those with altered small bowel anatomy may be more prone to suffer procedure related complications; however, further work is needed to verify these findings.

When compared to previous systematic reviews of balloon assisted ERCP in those with surgically altered anatomy, our study has notable differences. Diagnostic yields have varied between 70%-90% with procedure success rates approaching 62%-93% amongst single or double balloon assisted ERCP[32-34]. These studies depicted overall adverse event rates between 4%-7% with perforations making up a minority of these complications[32-34]. Such variance from our study may stem from the purpose of procedure with balloon enteroscopy for obscure GI bleeding requiring a thorough investigation of the small bowel, whereas balloon assisted ERCP typically focuses on assessment and interventions within the biliary tree. Although both procedures can be technically challenging, underlying maneuvers and interventions can vary. The higher incidence of perforation rate in our study when compared to balloon assisted ERCP may be attributed to aspects related to altered anatomy including procedure time, more extended exploration of the small bowel, presence of underlying adhesions and different targeted therapeutic techniques. Further studies are needed to further characterize these differences.

We recognize that our study has limitations. Foremost, given the small number of relevant published literature on this topic, our review is limited by a small sample size within these 14 reports. The lack of extensive literature that fits our inclusion criteria highlights the need for further studies to continue to assess the role of balloon enteroscopy in surgically altered anatomy patients. Additionally, most of our accessed studies being retrospective in nature as well as inclusion of case reports without controlled studies limit the conclusions taken from our review. Given the limited availability of studies to fit our inclusion criteria, we included case reports which may have skewed our overall results given many having 100% diagnosis rates and 0% complication rates. Furthermore, we were unable to perform analysis based on the procedure approach (retrograde *vs* anterograde) given reporting variability amongst the studies. The variety of altered anatomy types and the variability in data reporting in each of these studies also places further limits on the generalizability of our findings.

CONCLUSION

Our systematic review indicates that the data on the clinical utility of balloon enteroscopy in the evaluation of small bowel bleeding remains limited in those with surgically altered anatomy. The compiled data from the available literature demonstrates that balloon enteroscopy represents a clinically useful diagnostic modality in identifying culprit lesions for this subset of patients with diagnostic and therapeutic yields as high as 83% and 64% respectively. However, precautions and appropriate selection of cases must be taken within this patient population with an incidence of perforation as high as 7%.

ARTICLE HIGHLIGHTS

Research background

Obscure gastrointestinal (GI) bleeding is defined as persistent bleeding despite negative evaluation with both esophagogastroduodenoscopy and colonoscopy and is often secondary to small intestinal pathology. This form of GI bleeding has now become manageable with the introduction of single balloon enteroscopy or double balloon enteroscopy. Those with distorted anatomy may require thorough investigation of the upper GI tract during obscure GI bleeding, and balloon enteroscopy may be warranted.

Research motivation

Balloon enteroscopy can be warranted in instances of obscure GI bleeding in those with altered anatomy; however, literature remains limited on the overall diagnostic and therapeutic yields as well as the overall safety of these procedures in this patient population.

Research objectives

The primary aim of this systematic review was to assess the diagnostic and therapeutic efficacy of balloon enteroscopy for obscure GI bleeding in patients with surgically altered anatomy. The secondary aim was to investigate the safety of balloon enteroscopy in this patient population.

Research methods

We performed an extensive literature search on PubMed, Google Scholar, Scopus, and Embase where relevant articles were carefully reviewed. Terms used for the search included "enteroscopy," "obscure bleeding," "gastrointestinal bleeding," and "altered anatomy." Further search with the Reference

Citation Analysis database was conducted to ensure inclusion of the latest high impact articles. Prospective and retrospective reviews, case series, and case reports were all included. Data from each study that fit our inclusion criteria were extracted into an excel file in a systematic fashion. Statistical analysis in the form of descriptive statistics was reported from each study.

Research results

Following our literature search, 14 studies were included in our review. In total, there were 68 procedures performed with 61 unique patients that had undergone these procedures. From the available data in each study, there was an overall diagnostic yield of 48/59 (81%) and a therapeutic yield of 39/59 (66%). Five (7%) procedures were complicated by perforation.

Research conclusions

Our systematic review shows that balloon enteroscopy can be implemented in obscure GI bleeding in those with altered anatomy. Diagnostic and therapeutic yields were as high as 83% and 64% respectively. Given the overall perforation of 7%, caution is warranted in such cases. Further literature is needed to expand upon our findings.

Research perspectives

Balloon enteroscopy remains a viable option to investigate obscure GI bleeding in those with altered anatomy. Caution is warranted given the reported perforation rates; however, further studies are needed to add to the limited available literature.

FOOTNOTES

Author contributions: Aryan M, Colvin T, and Shajan P designed the research; Aryan M and Colvin T performed the systematic review; Aryan M analyzed the data; Aryan M, Colvin T, and Shajan P wrote the paper; Shajan P, Kyanam Kabir Baig KR, and Ahmed A supervised the paper; all authors read and approved the final manuscript.

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Country/Territory of origin: United States

ORCID number: Mahmoud Aryan 0000-0003-3028-8618; Tyler Colvin 0000-0001-7976-5679; Ali M Ahmed 0000-0002-8940-6757; Kondal Rao Kyanam Kabir Baig 0000-0003-1550-4853; Shajan Peter 0000-0003-3214-2989.

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SYSTEMATIC REVIEWS

Quality of life after surgical and endoscopic management of severe acute pancreatitis: A systematic review

Emmanouil Psaltis, Chris Varghese, Sanjay Pandanaboyana, Manu Nayar

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Emmanouil Psaltis, Sanjay Pandanaboyana, Department of HPB and Transplant Surgery, Newcastle upon Tyne NE7 7DN, United Kingdom

Emmanouil Psaltis, Sanjay Pandanaboyana, Department of Surgery, Freeman Hospital, Newcastle upon Tyne NE7 7DN, United Kingdom

Chris Varghese, Department of Surgery, Faculty of Medical and Health Sciences, University of Auckland, Auckland 1010, New Zealand

Sanjay Pandanaboyana, Manu Nayar, Population Health Sciences Institute, Newcastle University, Newcastle upon Tyne NE1 7RU, United Kingdom

Manu Nayar, Department of Gastroenterology, Freeman Hospital, Newcastle upon Tyne NE7 7DN, United Kingdom

Corresponding author: Manu Nayar, MBBS, MD, MRCP, Consultant Physician-Scientist, Doctor, Department of Gastroenterology, Freeman Hospital, Freeman Road, High Heaton, Newcastle Upon Tyne NE7 7DN, United Kingdom. manu.nayar@nhs.net

Abstract

BACKGROUND

Treatment for severe acute severe pancreatitis (SAP) can significantly affect Health-related quality of life (HR-QoL). The effects of different treatment strategies such as endoscopic and surgical necrosectomy on HR-QoL in patients with SAP remain poorly investigated.

AIM

To critically appraise the available evidence on HR-QoL following surgical or endoscopic necrosectomy in patient with SAP.

METHODS

A literature search was performed on PubMed, Google™ Scholar, the Cochrane Library, MEDLINE and Reference Citation Analysis databases for studies that investigated HR-QoL following surgical or endoscopic necrosectomy in patients with SAP. Data collected included patient characteristics, outcomes of interventions and HR-QoL-related details.

RESULTS

Eleven studies were found to have evaluated HR-QoL following treatment for severe acute pancreatitis including 756 patients. Three studies were randomized

trials, four were prospective cohort studies and four were retrospective cohort studies with prospective follow-up. Four studies compared HR-QoL following surgical and endoscopic necrosectomy. Several metrics of HR-QoL were used including Short Form (SF)-36 and EuroQol. One randomized trial and one cohort study demonstrated significantly improved physical scores at three months in patients who underwent endoscopic necrosectomy compared to surgical necrosectomy. One prospective study that examined HR-QoL following surgical necrosectomy reported some deterioration in the functional status of the patients. On the other hand, a cohort study that assessed the long-term HR-QoL following sequential surgical necrosectomy stated that all patients had SF-36 > 60%. In the only study that examined patients following endoscopic necrosectomy, the HR-QoL was also very good. Three studies investigated the quality adjusted life years suggesting that endoscopic and surgical approaches to management of pancreatic necrosis were comparable in cost effectiveness. Finally, regarding HR-QoL between open necrosectomy and minimally invasive approaches, patients who underwent the later had a significantly better overall quality of life, vitality and mental health.

CONCLUSION

This review would suggest that the endoscopic approach might offer better HR-QoL compared to surgical necrosectomy. However, the available comparative literature was very limited. More randomized trials powered to detect differences in HR-QoL are required.

Key Words: Acute pancreatitis; Pancreatic necrosis; Surgical necrosectomy; Endoscopic necrosectomy; Minimally invasive drainage; Quality of life

Core Tip: Acute pancreatitis is a common disease with potentially life-threatening complications. Treatment for severe acute pancreatitis can significantly affect health-related quality of life (HR-QoL). The effects of different treatment strategies such as endoscopic and surgical necrosectomy on HR-QoL remain poorly investigated. In this review, we critically analyze the available evidence on HR-QoL following treatment for severe acute pancreatitis. It could be suggested that endoscopic necrosectomy could offer better HR-QoL compared to surgical necrosectomy.

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INTRODUCTION

Acute pancreatitis is a common disease with potentially serious complications. Most patients present with a mild and self-limiting disease which is associated with low morbidity and mortality[1]. However, some patients present with moderate to severe or severe acute pancreatitis which can be complicated by organ failure and local complications such as pancreatic or peripancreatic necrosis[2-4]. Approximately, one third of these patients will develop infection of the necrosis which carries significant morbidity and mortality and will necessitate intervention[5,6].

Historically, open necrosectomy with debridement and post-operative lavage has been the treatment of choice[7]. In the last decade, the surgical step up-approach using a percutaneously inserted drain combined with minimally invasive necrosectomy has become increasingly popular and replaced open surgery as the standard approach[8,9]. As an alternative to surgery, endoscopic procedures for debridement of pancreatic necrosis have become increasingly popular as they offer significantly lower morbidity and mortality rates[10-14]. The endoscopic procedure can also be performed in a step-up approach only to be followed by surgical necrosectomy if endoscopic does not result in clinical improvement. However, there is no evidence to favor any of the surgical, minimally invasive, or endoscopic procedures as the better treatment of severe acute pancreatitis in terms of quality of life.

Traditionally, the outcome of different treatment strategies was determined only in terms of cure, morbidity and mortality[15]. However, in the era of patient-centered medicine, the health-related quality of life (HR-QoL) also needs to be considered[15]. HR-QoL is defined as the perceived physical and mental health of an individual over time. Several studies have investigated the effect of severe acute pancreatitis on HR-QoL and provided some contradictory results[16-22]. Hochman *et al*[19] as well as

Symersky *et al*[20] reported the HR-QoL of patients with SAP was significantly impaired. On the other hand, Soran *et al*[18] and Halonen *et al*[23] stated that patients treated for SAP returned to normal activities. The number of studies that examined HR-QoL of patients with SAP who underwent necrosectomy either surgically or endoscopically is very limited. The aim of this systematic review was to identify and critically appraise the available studies evaluating HR-QoL in patients who underwent either surgical or endoscopic necrosectomy for SAP with necrosis.

MATERIALS AND METHODS

Search strategy

A search for all relevant literature was performed on PubMed, Google™ Scholar, the Cochrane Library and MEDLINE databases in September 2021. The complete search strategy can be found in the Supplementary material. The search was performed without restrictions for date but was limited for full-text articles only. Due to the limited resources available, the search was also restricted to articles available in the English language. Studies investigating HR-QoL in patients with chronic pancreatitis as well as review articles, case reports, guidelines, protocols and abstracts were excluded.

Studies identified through the search strategy were initially assessed for inclusion by the title and abstract and subsequently by full text review (EP). Studies were included when the outcome measure of HR-QoL was either a primary or secondary endpoint. Only studies reporting on adult patients who underwent necrosectomy for severe acute pancreatitis were included. Duplicate studies and populations were cross-referenced and removed. The bibliography of the included studies was also reviewed. Figure 1 demonstrates the preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram[24].

Data extraction

Data were extracted by two independent reviewers (CV and EP) from the included studies with discrepancies resolved by a third (SP) reviewer. Data were collected on the details of each study (authors, year, level of evidence, study type, number of centres involved and country), patient characteristics within each study (sample size, diagnosis, mean age and gender), and HR-QoL details (QoL instruments used, scoring methodology, type of intervention, response and follow-up).

Risk of bias

To assess bias (EP and CV) in the included randomized trials The Cochrane risk of bias tool for randomized control trials (RoB 2.0)[25] was used which focuses upon random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias) and selective reporting (reporting bias). The risk of bias for the included observational studies was performed using the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) assessment tool[26]. This tool focuses upon confounding factors (confounding bias), selection bias, classification of interventions (classification bias), deviation from the intended interventions (performance bias), incomplete outcome data (attrition bias), blinding of outcome assessment (detection bias) and selective reporting (reporting bias). Each study was ranked as low, moderate or high risk of bias based on these criteria (Tables 1 and 2).

RESULTS

Overall, eleven studies were included of which most were from European centres (n = 7)[17,27-32]. Three studies were conducted in American centres[11,16,33] and one in Asia[34]. The studies were undertaken between 1993 and 2020 including an overall number of 756 patients. Three studies were randomized trials[11,28,30], four were prospective cohort studies[17,29,31,32], and four were retrospective cohort studies with prospective follow-up[16,27,33,34]. Only four studies compared surgical intervention to endoscopic intervention[11,27,28,34], while five studies investigated surgical approaches[16,17,29,30,32], and one study investigated endoscopic intervention alone[33]. Most studies were of cohorts with confirmed or suspected infected pancreatic or peripancreatic necrosis requiring intervention. Various metrics of HR-QoL were employed including Short Form (SF)-36[11,16,17,30,33-35], and EuroQol (EQ-5D)[28,30]. Time of administration of HR-QoL tools were variable ranging from 3 to 139 months. Other studies tended to use less known or custom, unvalidated measures of quality of life, limiting between study comparability[27,29,31]. Characteristics of the included studies are summarized in Table 3. A meta-analysis of the included studies was not possible because the populations, interventions, study designs, and outcomes reported varied significantly between studies.

Table 1 Risk of Bias assessment [risk of bias assessment using the Revised Cochrane risk-of-bias for randomised trials (RoB 2.0)]

Ref.	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Bang *et al*[11]	+	+	-	?	+	+	-
van Brunschot *et al*[28]	+	+	-	+	+	+	-
Hollemans *et al*[30]	+	-	-	-	+	+	-

Risk of bias assessment: +: Low; ?: Unclear; -: High.

Table 2 Risk of Bias assessment [risk of bias assessment using the Revised Cochrane risk-of-bias for randomised trials (RoB 2.0)]

Ref.	Confounding	Selection bias	Bias in classification of interventions	Bias due to deviation from intended interventions	Incomplete outcome data	Blinding of outcome assessment	Selective reporting	Other bias
Seifert *et al*[27]	-	-	+	+	+	-	+	-
Smith *et al*[33]	+	+	?	?	-	-	+	-
Cinquepalmi *et al*[17]	?	+	+	+	-	-	+	-
Fenton-Lee *et al*[29]	+	-	?	+	+	-	-	-
Kriwanek *et al* [32]	?	?	-	?	+	-	+	-
Reszetow *et al* [31]	+	?	+	+	+	-	+	-
Broome *et al* [16]	-	?	+	-	-	-	+	-
Tu *et al*[34]	?	+	?	+	+	-	+	-

Risk of bias assessment: +: Low; ?: Unclear; -: High.

Quality of life

Four studies compared HR-QoL between patients who underwent endoscopic and surgical interventions of which two were randomized trials[11,28] and two were retrospective cohorts[27,34]. In Bang *et al*[11]'s randomized trial 34 patients underwent endoscopic necrosectomy and 32 patients underwent minimally invasive surgical necrosectomy for necrotizing pancreatitis. It was reported that the physical component scores for the endoscopic treatment group were significantly improved at 3 months compared to the surgical treatment group (P = 0.39)[11]. In terms of quality adjusted life-years (QALYs) per patient, Bang *et al* reported that QALY gained for endoscopy was 0.452 (BCa 95%CI, 0.434-0.472) compared with 0.450 (BCa 95%CI, 0.427-0.468) for surgery, which translates to a mean difference (MD) of -0.002 (95%CI, 0.029-0.025)[11]. Similarly in van Brunschot *et al*[28]'s randomized trial, the QALY gained for endoscopy was 0.452 (BCa 95%CI, 0.434-0.472) compared with 0.450 (BCa 95%CI, 0.427-0.468) for surgery; with a MD of -0.002 (95%CI, 0.029-0.025).

In the GEPARD Study, 75 patients with pancreatic or peripancreatic necrosis were successfully treated endoscopically[27]. Forty-eight of these patients also showed radiological success as there was no evidence of residual necrosis or cyst on the day of discharge[27]. Eleven of those 75 patients had recurrent pancreatic necrosis, 1 patient had a pancreatitis-related death and 6 non-pancreatitis related deaths at long-term follow-up[27]. This was compared to 18 patients who failed endoscopic therapy, of whom 7 patients died secondary to pancreatitis and 11 progressed to surgery[27]. Of those that progressed to surgery, 8 were successful and 3 had recurrences of pancreatic necrosis[27]. At a mean follow-up of 50 months (range 50-96 months) among 68 patients who underwent successful endoscopic therapy and at a mean follow-up of 53 months (range (15-93 months) among 11 patients that successful surgical treatment; 32 (47%) *vs* 4 (46%) were still working, 31 (46%) *vs* 6 (55%) were retired, and only 5 (7%) *vs* 1 (9%) retired due to disease[27]. A higher proportion of patients reported difficulties with

Table 3 Study characteristics

Ref.	Country	Hospital	Study design	Study interval	Treatment	Patient cohort	Relevant patients	Patients in study	Questionnaire	Assessment times
Broome *et al* [16], 1996	USA	Duke University of Medical Centre	Retrospective with prospective follow-up	1988 to 1994	Surgery (operative debridement of necrosis)	Pancreatic necrosis	40 surgically managed patients with pancreatic necrosis	40	SF-36	Average follow-up 51 mo
Fenton-Lee *et al*[29], 1993	UK	Greater Glasgow Health Board	Prospective	April 1991 to March 1992	Surgery (required operative intervention); 9/10 also received endoscopic procedures	Pancreatic necrosis	10; 10 operative intervention, 9/10 also endoscopic intervention	10	Rosser disability and distress index	Admission and follow-up
Kriwanek *et al* [32], 1998	Austria	Rudolfstiftung-Hospital	Prospective	January 1 1988 to June 30 1996	Surgery (open necrosectomy)	Pancreatic necrosis	75; 57 survivors	75 with pancreatic necrosis (72 other sources of intra-abdominal infection)	SF-36	Not stated
Cinquepalmi *et al*[17], 2006	Italy	Not reported	Prospective	1990 to 2005	Surgery (sequential surgical debridement)	Infected pancreatic necrosis	35; all received sequential surgical debridement	35	SF-36	Not reported
Reszetow *et al* [31], 2007	Poland	Medical University of Gdańsk	Prospective	January 1993 to December 1999	Surgery (Bradley procedure)	Infected pancreatic necrosis	28; 44 (16.1%) of 274 patients with acute pancreatitis; 35/44 (63.4%) survivors for follow-up; 5 excluded	44	Functional Assessment of Chronic Illness Therapy scale	24-96 mo
Seifert *et al* [27], 2009	Germany	6 centres	Retrospective with prospective follow-up	1999 to 2005, follow-up 2004 to 2008	Endoscopy *vs* surgery	Infected pancreatic necrosis	93; 75 endoscopic; 18 failed, 11 surgery	93	Study-specific tool	Up to 24 mo
van Brunschot *et al*[28], 2017	Netherlands	19 centres	Randomized trial	September 20 2011 to January 29 2015	Endoscopy *vs* surgery	Confirmed or suspected infected pancreatic or peripancreatic necrosis.	98; 51 endoscopic and 47 surgical	98	EQ-5D-3L	3 and 6 mo
Hollemans *et al*[30], 2019	Netherlands		Randomized trial	November 2005 to October 2008	Surgery (step-up approach (primary percutaneous catheter drainage, followed by, if necessary, minimally invasive retroperitneal necrosectomy) *vs* open necrosectomy	Confirmed or suspected infected pancreatic necrosis.	60; 28/43 step-up approach (8 died), 32/45 open necrosectomy (7 died)	88	SF-36 and EuroQol	3, 6, and 12 mo after discharge
Smith *et al* [33], 2019	USA	Barnes-Jewish Hospital/Washington	Retrospective with	January 2006 to May 2016	Endoscopy	Walled off necrosis	41 (returned QoL questionnaires)	98	SF-36	Mean 37.4 (range 1-139)

		University School of Medicine	prospective follow-up							mo
Bang *et al*[11], 2020	USA	Florida Hospital	Randomized trial	May 12 2014 to March 24 2017	Endoscopy *vs* surgery	Confirmed or suspected infected pancreatic or peripancreatic necrosis.	66; 34 endoscopic and 32 surgery	66	SF-36	3 and 6 mo
Tu *et al*[34], 2020	China	Jinling Hospital, Medical School of Nanjing University	Retrospective with prospective follow-up	January 2000 to February 2015	Surgery (open necrosectomy) *vs* minimally invasive drainage	Infected pancreatic necrosis	109; 101 included in analysis (61 minimally invasive drainage, 40 open necrosectomy)	109	SF-36	Not stated

carrying heavier loads (36% *vs* 28%), walking around the block (27% *vs* 10%), leaving the house (9% *vs* 7%) who underwent surgical compared to endoscopic therapy[27]. After successful endoscopic necrosectomy more patients had to change their diet (62% *vs* 36%) compared to surgical intervention [27]. On self-assessment those that underwent initial successful endoscopic therapy had improved physical scores (2.47 range 0-10) and quality of life (2.35 range 0-10) compared to those that had surgery after failed endoscopic therapy (physical condition 3.82 range 0-10; quality of life 3.54 range 0-10)[27].

Tu *et al*[34] reports a similar cohort of 101 patients with infected pancreatic necrosis of which 61 underwent minimally invasive drainage (which included percutaneous catheter drainage, negative pressure irrigation or endoscopic necrosectomy) and 40 patients that underwent open necrosectomy. The overall quality of life score was significantly higher in the cohort of infected necrosis patients who underwent minimally invasive drainage compared to open necrosectomy (mean 125 ± 13 *vs* 116 ± 17, P = 0.005)[34]. The quality-of-life domains measured by the SF-36 were comparable between these groups with respect to physical functioning, physical role, but mental health scores were significantly better in minimally invasive drainage group[34].

In a study that assessed HR-QoL in a cohort of 35 patients who underwent sequential surgical necrosectomy for infected pancreatic necrosis, all patients had an SF-36 > 60%, and 78% had scores > 70%-80% suggesting overall good quality of life[17]. Quality of life was notably poorer amongst those with alcoholic pancreatitis. Similarly, 12/32 were able to return to employment within 6 months[17]. Comparably, in another study, 50/57 (88%) patients who underwent open surgical intervention for pancreatic necrosis also had good quality of life[32]. However, in this same cohort 9 patients (16%) experienced worsened employment status[32]. In Smith *et al*[33]'s cohort of 41 patients who underwent endoscopic management of walled-off necrosis, the mean SF-36 general health score was 56.93 (SD 25.82).

Physical functioning and physical role

In a cohort of 80 patients that underwent endoscopic management of walled-off pancreatic necrosis, of whom 41 responded to an SF-36 questionnaire; the mean SF-36 score for physical functioning was 82.32 (standard deviation (SD) 18.24), and 58.54 (SD 40.93) for physical role[33]. This was comparable to Broome *et al*[16]'s cohort of 40 patients with pancreatic necrosis managed *via* surgical debridement with slightly lower physical functioning and physical role SF-36 scores than age-matched controls. In Kriwanek *et al*[32]'s surgically managed cohort, only 2/57 (4%) of patients experienced deteriorated

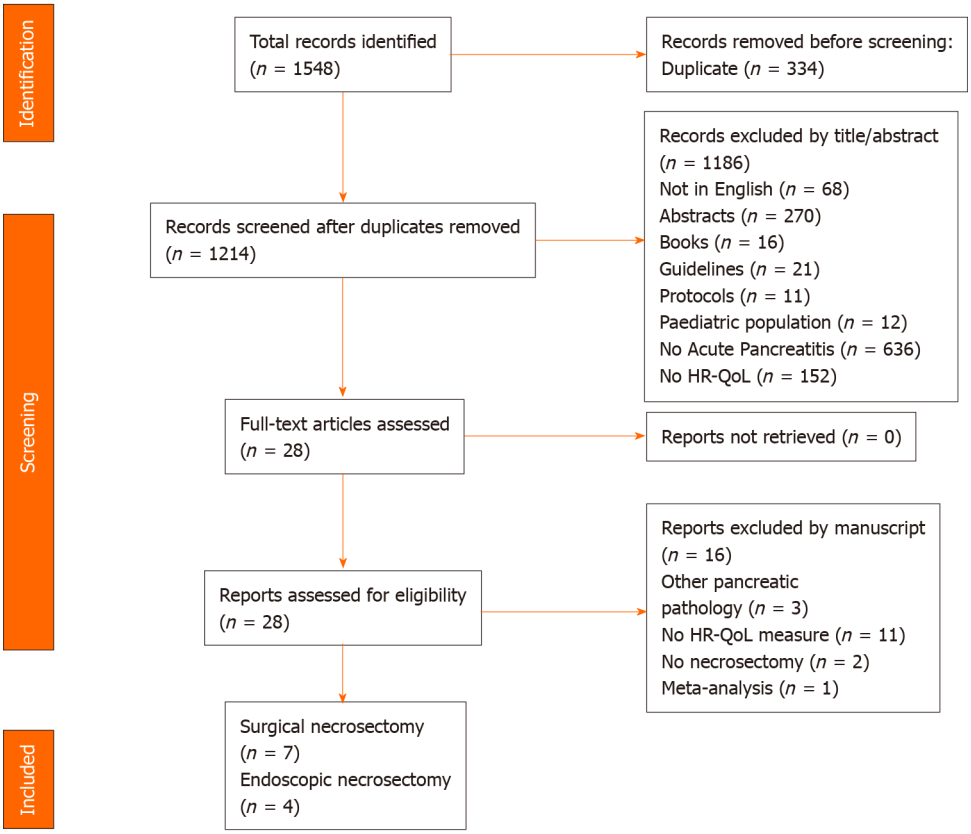

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Figure 1 Preferred reporting items for systematic reviews and meta-analysis PRISMA[24] flow diagram.

functional status as per SF-36. Several studies compared physical component scores of the SF-36 at 3-months and 6-months[11,30,33]. Compared to surgical approach, patients who had endoscopic management of necrotizing pancreatitis had improved physical component scores at discharge, at 3 months, and at 6 months[11,28]. In Holleman *et al*[30]'s randomized trial of step-up approach *vs* straight to open necrosectomy in patients with necrotizing pancreatitis there were no significant differences in the Dutch nor US standard versions of the SF-36 physical health scores between approaches, with scores in both groups being between 42 and 44. These similarities persisted at longer follow-ups[30].

Mental health

Smith *et al*[33] reports in a cohort of 41 patients that underwent endoscopic management of walled of necrosis an SF-36 mental health score of 79.61 (SD 18.52). Only Kriwanek *et al*[32]'s cohort of 57 patients that underwent open surgical intervention for severe intra-abdominal infection and pancreatic necrosis reported on psychosocial functioning and 6 patients (10%) showed depressive mood and 17 (30%) had impaired activity. In contrast to physical function, Bang *et al*[11] found endoscopic intervention compared to surgical intervention was not significantly associated with the mental component score of the SF-36. Broome *et al*[16] found SF-36 mental health scores were comparable between surgically managed patients with necrosis and age-matched controls. Tu *et al*[34]'s cohort also demonstrated improved mental health scores among those who underwent minimally invasive drainage. Similar to the physical functioning, the mental component of the SF-36 questionnaire was similar at baseline and throughout follow-up between step-up approaches and open necrosectomy approaches to necrotizing pancreatitis[30].

Pain

Smith *et al*[33] demonstrated an SF-36 mean bodily pain score of 75.54 (SD 22.78) after endoscopic management of walled-off pancreatic necrosis. This was very comparable to a similar cohort of 40 patients managed with surgical debridement, which in turn was found to be similar to age-matched controls[16]. These findings of equivalence regarding pain between endoscopic and surgical management was further corroborated by Tu *et al*[34]. In another study, 43/57 (75%) patients who underwent open surgical intervention for pancreatic necrosis showed no pain[32].

Other domains of quality of life

Smith *et al*[33]'s cohort of 41 patients with follow-up SF-36 questionnaires after endoscopic management of walled off necrosis reported on the separate domains of the SF-36 HR-QoL measure. Patients' mean vitality scores were 56.83 (SD 23.89), social function scores were 83.84 (SD 20.96), and emotional role scores were 82.30 (SD 34.20). Vitality, social functioning, and emotional role SF-36 scores measured by Smith *et al*[33], were comparable to the scores reported in Broome *et al*[16]' cohort of surgically managed patients with pancreatic necrosis. Tu *et al*[34] was the only remaining cohort which compared these SF-36 domains between surgically managed and endoscopically (minimally invasive drainage) managed patients. It was reported that both social and emotional role functioning were significantly better in the minimally invasive group of patients[34].

Smith *et al*[33] reports that pancreatic exocrine insufficiency (PEI) was the only factor predictive of lower SF-36 scores; and this was true for both the mental and physical components scores. This translated to lower physical role, vitality, emotional role, and mental health scores if patients had PEI [33]. In a randomized trial comparing step-up approach *vs* open necrosectomy for management of necrotizing pancreatitis, they found both approaches were comparable in terms of quality of life[30]. However, quality of life was lower if patients reported abdominal pain, and they did not find PEI (nor pancreatic endocrine function) to affect this[30]. In Cinquepalmi *et al*[17]'s cohort of patients with infected pancreatic necrosis managed with sequential surgical debridement, alcoholic etiology was the only factor associated with poorer SF-36 scores. In contrast, in Reszetow *et al*[31]'s cohort of 24 patients treated with the Bradley procedure for infected pancreatic necrosis, there was no difference in quality of life between those with biliary and alcoholic etiologies.

DISCUSSION

The debridement of pancreatic necrosis remains very challenging for both patients and clinicians as it can have a significant impact on HR-QOL[36,37]. To the best of our knowledge this is the first systematic review to assess HR-QoL following surgical or endoscopic necrosectomy in patients with SAP. Despite the advancements in treatment strategies and the various as well as fundamentally different techniques of necrosectomy, the published data on HR-QoL following each procedure is very limited.

The present review included 11 studies of which 3 were randomized trials[11,28,30] and only four studies compared surgical intervention to endoscopic intervention[11,27,28]. In the overall quality of life following endoscopic intervention *vs* surgical intervention, Bang *et al*[11] reported significantly improved physical component scores for the endoscopic treatment group at the 3-mo follow-up. The authors attributed this to factors such as the shorter duration of the endoscopic procedure, faster resolution of SIRS, fewer disease-related adverse events and shorter length of stay to intensive care unit [11,14,38,39]. In a similar way, patients who were managed endoscopically had improved physical component scores at discharge, at 3 mo, and at 6 mo, whereas Kriwanek *et al*[32] reported that a small number of patients experienced deteriorated functional status following surgical necrosectomy[11,32]. In contrary to Bang *et al*[11], Seifert *et al*[27] stated that less patients reported difficulties in carrying heavy loads, walking around the block or needed to modify their diet following surgical necrosectomy. However, employment status was slightly better in the group of patients who were treated endoscopically[27]. In terms of HR-QoL between patients who underwent open necrosectomy and minimally invasive necrosectomy of the necrotic parenchyma, Tu *et al*[34] reported a significantly better total quality of life as well as vitality and mental health scores following minimally invasive necrosectomy. On the other hand, there was no difference in the physical functioning and bodily pain scores between the two groups of patients. The authors stated that minimally invasive necrosectomy involved a series of procedures that included endoscopic necrosectomy *via* a tract between the stomach and the cavity containing the necrotic parenchyma[34]. The reported results were attributed to pancreatic complications that the open necrosectomy group of patients suffered from[34].

In both randomized trials by Bang *et al*[11] and van Brunschot *et al*[28], the QALY gained following endoscopic necrosectomy was very similar to that following surgical necrosectomy. In terms of mental health, Bang *et al*[11] did not demonstrate any difference in the mental health component of the SF-36 between patients who underwent surgical or endoscopic intervention. However, Kriwanek *et al*[32] reported that 10% of the patients had depressive mood following surgical necrosectomy. With regards to other elements of quality of life, the vitality, social and emotional scores were very good following endoscopic necrosectomy indicating that most patients recovered fully without lasting effects[33]. Patients following open necrosectomy were found to have no pain[32].

Based on this review it is difficult to assess which type of intervention offers the best HR-QoL in patients with severe acute pancreatitis. At present, the strongest evidence has been published by Bang *et al*[11] and favors endoscopic necrosectomy as the treatment of choice. However, all three randomized trials included in this review as well the rest of the included studies were underpowered. Moreover, the lumen apposing metal stents were introduced to clinical practice while the studies by Bang *et al*[11] and Smith *et al*[33] were in progress. Even though this technique was used in some of the patients, it

contributed to the heterogenicity of different endoprostheses that were used. Therefore, more comparative and adequately powered studies are still needed to accurately assess the quality of life following each technique.

None of the included studies assessed the quality of life of the patients while they were hospitalized and therefore the immediate effects of each approach for pancreatic debridement remain unknown. Also, five of the included studies assessed the short-term effect (< 12 mo) and only two studies the long-term effect (> 24 months) while three studies have not stated the intervals or the duration of follow-up. Therefore, even though the SF-36 was designed to primarily assess the long- term effects of a chronic condition[40], the long-term effects of each method of debridement remain grossly unknown.

The SF-36 questionnaire may be a good tool to evaluate HR-QoL and demonstrate the presence of significant changes, but subtle changes might require a different assessment tool to be appreciated. However, other available HR-QoL assessment tools have been compared with the SF-36 and they do not seem to be more accurate[41]. In the era of patient-centered medicine, HR-QoL is regarded as one of cornerstones of the "goal-oriented patient care outcomes" concept[15]. Interestingly, there was significant inconsistency in the use of HR-QoL assessment tools in the included studies. Six out of 10 studies used the SF-36 tool whereas the rest four used either a different or a study-specific tool. This inconsistency made it impossible to safely compare the reported results from different studies and accurately extract outcomes on which treatment approach offers the best outcome. To the best of our knowledge there is no published guidance in the field of pancreatic surgery that recommends a specific tool for HR-QoL assessment. Therefore, the creation of a new tool to evaluate patient reported HR-QoL outcome in patients with pancreatic pathology or even more specifically for acute pancreatitis will deliver a more reliable assessment of different treatment modalities and how they affect the HR-QoL in the sort-, medium- and long-term follow-up period.

The present systematic review has several limitations. The majority of the included studies were observational in nature which might have introduced bias due to confounding. It would be useful if future randomized trials were designed in such a way that HR-QoL was one of the study outcomes. Moreover, the quantitative analysis was challenging to perform due to the various HR-QoL metrics as well as the different timing of administration of the different tools that were employed in the included studies. As mentioned earlier, the SF-36 was originally conceived to evaluate HR-QoL in chronic conditions over a long-term follow-up while three studies in this review have used it to assess short-term follow-up in an acute condition. Another significant limitation of this review was the heterogeneity of the patients among the included studies both in terms of age and severity of the condition as well as the cause of pancreatitis.

CONCLUSION

This systematic review would indicate that the endoscopic approach should be the preferred method for pancreatic necrosectomy. However, more randomized trials in patients with severe acute pancreatitis are needed with HR-QoL as primary endpoint. The goal is to achieve a person-centered coordinated care; through patient reported experience and outcome measures. These instruments are being reported with increasing frequency in the recent years for their ability to bridge the gap between the perceptions of the clinician and patients. This information is then used to adjust treatment and care and to achieve better results, enhance adherence, increase patient satisfaction & quality of life. Finally, it would be useful to create a disease specific HR-QoL assessment tool for acute pancreatitis that will allow comparison of different management options and how they impact the HR-QoL.

ARTICLE HIGHLIGHTS

Research background

Treatment for severe acute pancreatitis (SAP) can significantly affect health related quality of life (HR-QoL). However, the effects of different treatment strategies such as surgical, minimally invasive or endoscopic necrosectomy, on HR-QoL remain poorly investigated. Therefore, there is no evidence to favor any of the existing approaches as the better treatment of SAP in terms of quality of life. To the best of our knowledge this is the first systematic review to assess HR-QoL following pancreatic necrosectomy in patients with SAP.

Research motivation

Traditionally, open necrosectomy has been the standard approach for patients with SAP and necrosis of pancreatic parenchyma. This was followed by the introduction of surgical step up-approach combined with minimally invasive necrosectomy as the treatment of choice. More recently, endoscopic necrosectomy has gained popularity as it offers significantly lower morbidity and mortality rates. However, in the era of patient-centered medicine, HR-QoL also needs to be considered. Unfortunately,

there is no clear evidence to favor any of these procedures as the better treatment of SAP in terms of quality of life.

Research objectives

The objective of this study was to critically appraise the published evidence on HR-QoL in patients with SAP who underwent surgical or endoscopic necrosectomy.

Research methods

A literature search was performed on several databases for studies that examined the HR-QOL following necrosectomy in adult patients with SAP. Studies published in English were excluded due to limited resources. Data were collected on the details of each study, patient characteristics as well as HR-QoL. The Cochrane risk of bias tool for randomized control trials (RoB 2.0) was used to assess bias in the included randomized studies whereas the Risk of Bias In Non-randomized Studies – of Interventions (ROBINS-I) was used to asses bias in the included observational studies.

Research results

Eleven studies evaluated HR-QoL following necrosectomy including 756 patients. Three studies were randomized trials and eight were cohort studies. One randomized trial and one cohort study demonstrated significantly improved physical scores at three months in patients who underwent endoscopic necrosectomy compared to surgical necrosectomy. In the only study that examined patients following endoscopic necrosectomy, the HR-QoL was also very good. Two randomized trials and one cohort study investigated the quality adjusted life years suggesting that endoscopic and surgical necrosectomy were comparable in cost effectiveness. When open necrosectomy was compared with minimally invasive approaches, patients who underwent the later reported better overall quality of life, vitality and mental health.

Research conclusions

This study would suggest that the endoscopic approach should be the preferred method for pancreatic necrosectomy as it might offer better HR-QoL. However, more randomized trials powered to detect differences in HR-QoL are still required.

Research perspectives

Future research should aim to provide the tools for a person-centered coordinated care through a patient reported experience and outcome measures. This will improve results, adherence, patient satisfaction and quality of life. It is also important to create a disease specific HR-QoL questionnaire for acute pancreatitis to allow evaluation of different management strategies and the impact they have on HR-QoL.

FOOTNOTES

Author contributions: Psaltis E, Varghese C, Pandanaboyana S and Nayar M designed the research study; Psaltis E and Varghese C performed the research; Psaltis E and Varghese C analyzed the data and wrote the manuscript; Pandanaboyana S and Nayar M had the overall supervision of the study; all authors have read and approved the final manuscript.

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Country/Territory of origin: United Kingdom

ORCID number: Emmanouil Psaltis 0000-0002-9072-2837; Chris Varghese 0000-0001-7369-8639; Sanjay Pandanaboyana 0000-0003-30992197; Manu Nayar 0000-0002-1196-3406.

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CASE REPORT

Solitary pancreatic metastasis from squamous cell lung carcinoma: A case report and review of literature

Kaouthar Rais, Oumayma El Eulj, Najoua El Moutaoukil, Imane Kamaoui, Amal Bennani, Ghizlane Kharrasse, Abdelkrim Zazour, Wafaa Khannoussi, Zahi Ismaili

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Kaouthar Rais, Oumayma El Eulj, Najoua El Moutaoukil, Ghizlane Kharrasse, Abdelkrim Zazour, Wafaa Khannoussi, Zahi Ismaili, Department of Hepatogastroenterology, Mohammed VI University Hospital Center, Digestive Disease Research Laboratory, Medical School, Mohammed I University, Oujda 60000, Morocco

Imane Kamaoui, Department of Radiology, Mohammed VI University Hospital Center, Digestive Disease Research Laboratory, Medical School, Mohammed I University, Oujda 60000, Morocco

Amal Bennani, Department of Anatomo-Pathology, Mohammed VI University Hospital Center, Digestive Disease Research Laboratory, Medical School, Mohammed I University, Oujda 60000, Morocco

Corresponding author: Kaouthar Rais, MD, Doctor, Department of Hepatogastroenterology, Mohammed VI University Hospital Center, Digestive Disease Research Laboratory, Medical School, Mohammed I University, BP 4806 Oujda University 60049, Oujda 60000, Morocco. kaoutar.rais@gmail.com

Abstract

BACKGROUND

Pancreatic metastases from squamous cell lung carcinoma (SCLC) are unusual. These lesions are often asymptomatic and detected incidentally or during follow-up investigations, occasionally several years after removal of the primary tumor.

CASE SUMMARY

A 56-year-old male with SCLC developed jaundice 1 mo after the cancer diagnosis. An abdominal computed tomography (CT) scan showed a mass in the pancreatic head with distention of both intra- and extrahepatic biliary ducts. Endoscopic retrograde cholangiopancreatography and sphincterotomy were performed first, culminating with plastic biliary stent placement. Cytological examination of the pancreatic mass sample collected by fine-needle aspiration (FNA) under endoscopic ultrasound (EUS) guidance revealed the presence of malignant cells compatible with well-differentiated squamous cell carcinoma. After liver function normalized, chemotherapy was initiated with carboplatin and paclitaxel; however, 4 d later, the patient presented dysphagia. Cervico-thoraco-abdominal CT showed tracheoesophageal fistula and stent migration. After replacement with a 10 cm/10 mm uncovered metallic biliary stent and treatment

of the tracheoesophageal fistula with a fully covered esophageal stent, the patient was able to start oral feeding progressively. He died 9 mo after the initial diagnosis.

CONCLUSION
The diagnosis of pancreatic metastasis from SCLC is challenging for clinicians. EUS-FNA is the primary exam for confirmatory diagnosis.

Key Words: Squamous cell lung carcinoma; Pancreatic metastasis; Jaundice; Esotracheal fistula; Ultrasound endoscopy; Case report

Core Tip: The pancreatic metastasis of squamous lung carcinoma is a rare disease. There are a few cases in the literature that discuss the modality of diagnosis and the treatment of pancreatic metastasis. In this manuscript, we report our experience in the management of this case and the malignant tracheoesophageal fistula as a rare complication of squamous lung carcinoma.

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INTRODUCTION

Pancreatic tumors generally have a poor prognosis, and pancreatic cancer ranks as the fourth deadliest type of cancer among men and women[1]. Pancreatic metastases are rare[2]. Their prevalence is estimated at approximately 1%-5%[3]. Renal, lung, colorectal and breast tumors are the main primary tumor sites responsible for pancreatic metastases[2]. We report a case of squamous cell lung carcinoma with pancreatic metastasis in a 56-year-old male patient.

CASE PRESENTATION

Chief complaints

A 56-year-old male presented to the emergency room with complaints of cholestatic jaundice associated with pancreatic epigastralgia and deterioration of his general condition.

History of present illness

The patient reported that his symptoms had started 1 mo prior.

History of past illness

Three months before admission to our department, he had been diagnosed with and followed up for a left hilar lung squamous cell carcinoma, which had been discovered by bronchoscopy with transbronchial biopsy of the lung mass.

Personal and family history

The patient self-reported being a 52 pack-year smoker, he had no family history.

Physical examination

The patient had obvious jaundice. The patient was afebrile but had epigastric tenderness.

Laboratory examinations

Blood tests showed a disturbance of liver function based on the following findings: total bilirubin, 5.2 mg/dL (normal range: 0.3-1.9 mg/dL); direct bilirubin, 4.1 mg/dL (normal range: 0-0.3 mg/dL); gamma glutamyl transferase, 1088 UI/L (normal range: 12-64 UI/L); alkaline phosphatase, 450 UI/L (normal range: 40-150 UI/L); aspartate aminotransferase, 102 UI/L (normal range: 5-34 UI/L); alanine aminotransferase, 220 UI/L (normal range: 0-55 UI/L); and carbohydrate antigen (CA) 19-9, 40 U/mL

(normal range: 0-33 U/mL).

Imaging examinations

Computed tomographic scanning revealed a tumoral hilar left process, dilation of the intrahepatic bile duct, 11 mm main bile duct and 4 mm Wirsung duct along with a 33 mm × 45 mm pseudotumoral mass of the pancreatic head (Figure 1A and B).

Endoscopic examinations

Endoscopic retrograde cholangiopancreatography was performed and showed dilation of the main bile duct (16 mm) among a stricture (extending to 25 mm) located under the cystic duct. Minimal sphincterotomy was performed, and a plastic stent (10 Fr/7 cm) was placed (Figure 1C). Good drainage was ensured. Histological examination of cytological brushing showed atypical cells, namely, category II of Papanicolaou. The patient's jaundice regressed following these procedures, and his hepatic function blood parameters improved.

First multidisciplinary expert consultation

A multidisciplinary consultation meeting was held. The clinicians decided to begin chemotherapy for lung squamous cell carcinoma.

Treatment

The patient received carboplatin and 80 mg/m^2 paclitaxel every week; however, the treatment was stopped at the 4th week due to poor therapeutic tolerance.

Outcome

Over the 4-d period after treatment cessation, the patient developed total aphagia associated with dysphonia. He also developed stage 4 New York Heart Association dyspnea and was deemed to be undernourished (nutritional risk index of 64). His performance status was 3. A computed tomography arterial portography scan showed a locally advanced left hilar mass invading the left main bronchus and fistulating into a paraseptal formation with intimate contact within the esophageal wall (Figure 2A). The imaging examination also showed left lobar broncho-alveolitis and a cephalic pancreatic tumor invading the second duodenum and the antropyloric portion with dilation of upstream biliary ducts and no pneumobilia. Esophagogastroduodenoscopy showed a tracheoesophageal fistula located 30 cm from the dental arches that easily crossed (Figure 2B). A biliary stent was observed to partially migrate into the duodenum. EUS showed a 4-cm cephalic pancreatic mass invading the second portion of the duodenum (Figure 3A). Fine-needle (22-G) aspiration of the pancreatic mass was performed and confirmed the presence of a carcinomatous proliferation containing nests and large tumoral polygonal cells with atypical voluminous irregular nuclei surrounded by eosinophils. Focal tumoral necrosis was also present, leading us to conclude that the mass was a well-differentiated keratinizing squamous cell carcinoma. Immunohistochemical examination of the mass showed expression of cytokeratin 5/6 (Figure 3B). On the other hand, the cells did not express TTF1. The final histological report confirmed a poorly differentiated squamous cell lung carcinoma located in the pancreas. To address the migrated biliary stent and to ensure definitive and permanent biliary drainage before treating the tracheoesophageal fistula, endoscopic retrograde cholangiopancreatography was performed first with placement of an uncovered metallic stent measuring 10 cm/10 mm (Figure 4A).

MULTIDISCIPLINARY EXPERT CONSULTATION

Moulay Zahi Ismaili, Professor and Chief, Department of Hepato-Gastroenterology, Mohammed VI University Hospital Center.

Mohamed Bouziane, Professor and Chief, Department of General Surgery, Mohammed VI University Hospital Center.

Tijani Harroudi, Professor and Chief, Department of Surgical Oncology, Mohammed VI University Hospital Center.

Ghizlane Kharrasse, Professor of Hepato-Gastroenterology, Department of Hepato-Gastroenterology, Mohammed VI University Hospital Center.

Wafaa Khannoussi, Professor of Hepato-Gastroenterology, Department of Hepato-Gastroenterology, Mohammed VI University Hospital Center.

Abdelkrim Zazour, Assistant Professor of Hepato-Gastroenterology, Department of Hepato-Gastroenterology, Mohammed VI University Hospital Center.

The patient's case was rediscussed in multidisciplinary consultation meetings. The decision was made to retain the diagnosis, and a treatment plan was formulated accordingly (detailed below).

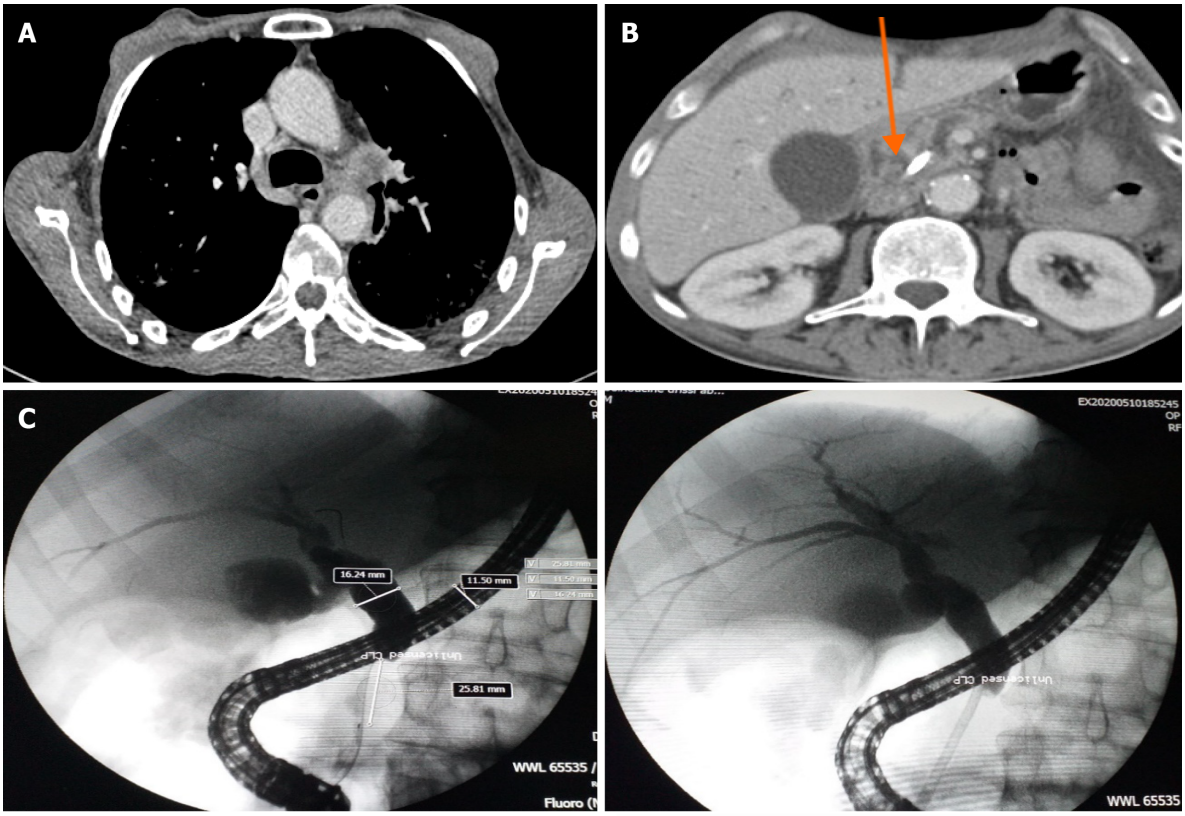

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Figure 1 Imaging and endoscopic images of lung cancer and pancreatic mass. A: Computed tomography scan of the left hilar mass (arrow); B: Computed tomography scan of the mass on the head of the pancreas measuring 4.0 cm × 3.8 cm (arrow); C: Microscopic images showed dilatation of the main bile duct upstream of a very tight stenosis of the cystic duct at 25 mm with insertion of a plastic biliary stent.

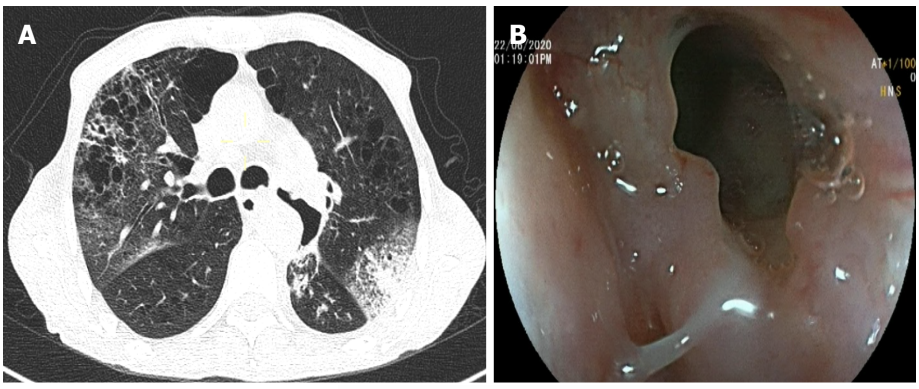

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Figure 2 Tracheoesophageal fistula. A: Computed tomography scan showed left lobar broncho-alveolitis; B: Upper gastrointestinal endoscopy showed a tracheoesophageal fistulae.

FINAL DIAGNOSIS

Pancreatic metastasis of squamous cell lung carcinoma, stage IV.

TREATMENT

A fully covered metallic esophageal stent was placed as a palliative treatment for the tracheoesophageal fistula. Then, a 12-cm stent was placed, the proximal end of which was 24 cm from the dental arches (Figure 4B).

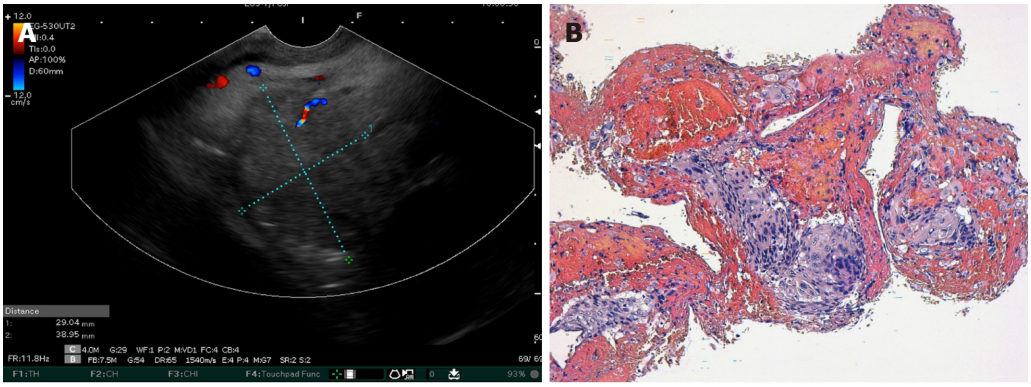

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Figure 3 Images of endoscopic ultrasound and histological analysis of the pancreatic mass. A: Linear endoscopic ultrasound showed a pancreatic head tumor; B: Microphotography showing a proliferation with an easily recognizable squamous differentiation, including apparent intercellular bridges and minimal pleomorphism. Hematoxylin-eosin stain (× 200).

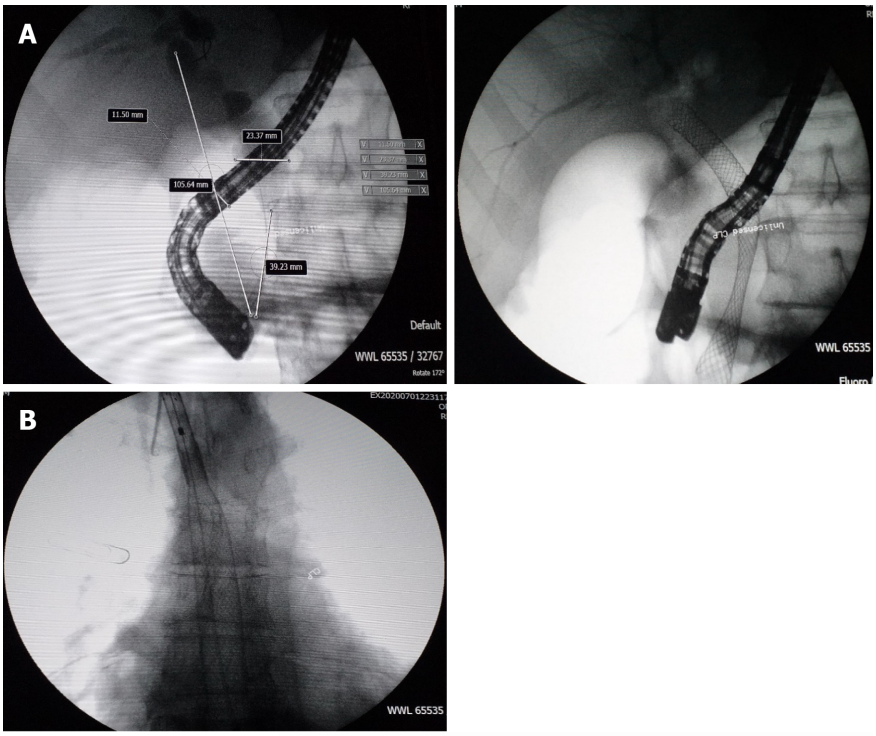

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Figure 4 Placement of metallic biliary stent and esophageal stent. A: An uncovered metallic biliary stent; B: Microscopic image of the fully-covered esophageal stent.

OUTCOME AND FOLLOW-UP

During the following 3 mo, the patient was able to gradually start oral alimentation of a mixed-food diet. However, he lost 5 kg of body weight, and his general state was significantly altered. Thus, palliative chemotherapy was not initiated. Two months later, imaging monitoring using thoracic and abdominal X-rays showed a good position of the esophageal and biliary stents (Figure 5A and 5B), which was confirmed by upper digestive endoscopy (Figure 5C). The patient died 9 mo after the diagnosis.

DISCUSSION

References for this review were identified through searches of the PubMed, Cochrane and Scopus databases using the following Medical Subject Heading terms: (squamous cell lung carcinoma) AND

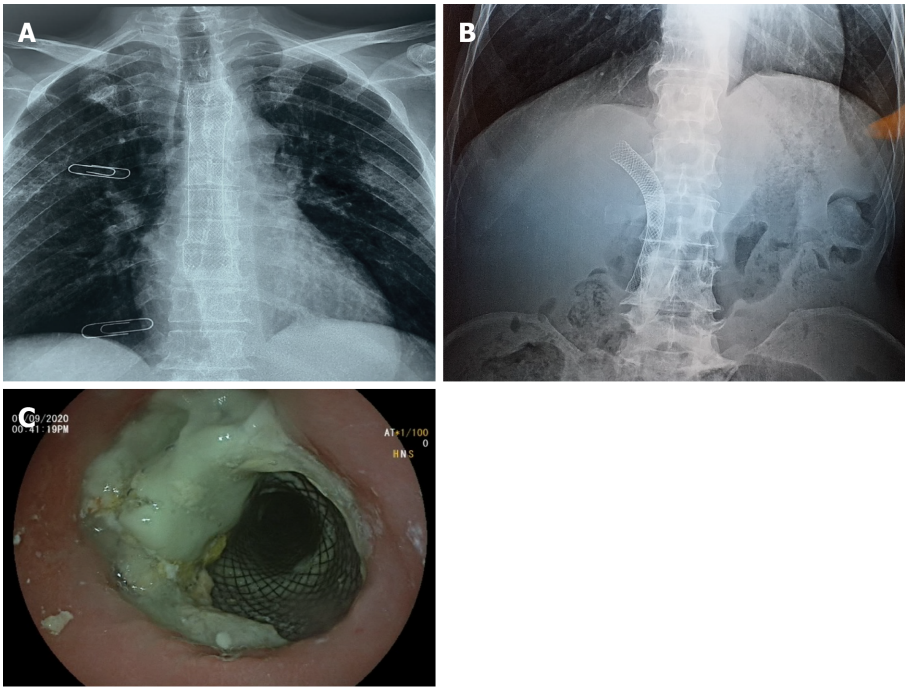

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Figure 5 Chest X-ray and endoscopic images of stents position. A: Position of the esophageal prosthesis; B: Abdomen without preparation showed the position of the biliary metallic stent; C: Covered esophageal stent with food stasis.

(pancreatic metastasis). Only English-language journals were considered, and only full papers were included. A total of 201 studies were initially identified. After reviewing the abstracts, 14 articles were identified with topical relevance (*i.e.*, pancreatic metastasis of a squamous cell lung carcinoma). Reference lists of the selected studies were checked (cross-referenced), but no additional studies were identified (Figure 6). We followed the Preferred Reporting Items for Systematic reviews and Meta-analysis guidelines for this literature review. Only 23 cases of squamous cell lung carcinoma with pancreatic metastasis were reported in the literature at the time of this review. The mean age of the reported patients was 61.5 years, and 92.3% of the patients were male. The most common symptom was jaundice (55.6%) followed by epigastric pain (44.6%). One patient (11.2%) was asymptomatic. Pancreatic metastasis was located in the head of the pancreas in 60% of the patients and was located equally in the body, tail and uncinated process in the remaining patients. EUS benefitted 50% of the patients. Among these patients, 3 patients underwent EUS with fine-needle aspiration (FNA), and 2 patients underwent EUS with fine-needle biopsy (Table 1). The diagnosis of pancreatic metastasis due to squamous cell lung carcinoma was established by EUS in 4 patients, by surgery in 3 patients, by percutaneous FNA of the pancreatic tumor in 1 patient, and upon autopsy in 4 patients. Three patients were treated with biliary drainage. Seven patients received chemotherapy. Two patients received surgical treatment for pancreatic metastasis. The follow-up period for reported patients varied between a few days and 1 year, with the latter noted for 1 patient who was treated with surgery and adjuvant chemotherapy[4] (Table 1).

Lung cancer has a very high rate of morbidity and mortality. In 2018, the World Health Organization reported that lung cancer was responsible for 11.6% of new cancer cases and 18.4% of cancer-related deaths[5]. In total, 20% of non-small-cell lung cancers are classified as squamous cell carcinoma[6]. It has been reported that 40% of cases are already metastatic at diagnosis[7], and the 5-year survival rate is estimated to be only 3.6%[6]. The most common metastatic sites include the bones, lungs, brain, liver and adrenal glands[8]. Pancreatic metastasis is rare, representing only 2% of pancreatic tumors[9]. Primary tumors known to metastasize to the pancreas include renal (25%-48%), lung (15%), breast (8%), colorectal (7%), and bone and melanoma (5%)[9,10]. Through the autopsy of 103 cases of patients with pancreatic metastasis, Nakamura *et al*[11] determined that metastatic dissemination to the pancreas occurred either *via* lymphatic (28%), vascular (27%), lymphatic and vascular (19%) or direct invasion (18%) routes. The authors also assumed that the majority of patients with primary lung cancer (66%) had pancreatic metastasis through vascular dissemination. In another report, the most frequent lung cancer histological type with pancreatic metastasis was cited as small cell carcinoma (10%) followed by large cell carcinoma, squamous cell carcinoma (1.1%), and anaplastic bronchial carcinoma[12]. Frequently, pancreatic metastasis is asymptomatic (> 50%) and discovered accidentally through extension and control assessment[13]. It may be expressed by diverse and nonspecific clinical situations, such as asthenia, weight loss, abdominal pain, jaundice, nausea, or vomiting. Pancreatic metastasis can

Table 1 Summary of the literature review of squamous cell lung carcinoma with pancreatic metastasis

Ref.	Yr	Setting	Number	Age in yr	Sex	Symptoms	Imaging	Endoscopy +/- FNA	Diagnostic means	Treatment	Follow-up	Overall survival	Status at time of publication
Zhou *et al*[29]	2020	China	1	63	M	Epigastric pain with jaundice	Hyperintense mass measuring 4.5 cm in the pancreatic head	No	Surgery of the pancreatic mass	Whipple procedure	UNK	UNK	UNK
Stoupis *et al* [30]	2020	Greece	1	60	F	Fatigue, cough and hemoptysis, loss of appetite and 10-kg weight loss	Increased 2-deoxy-2-[F-18] fluoro-D-glucose uptake in the right lung and pancreatic tail	Yes	EUS-FNB of the pancreatic mass using a 22-gauge needle	7 cycles of anti-PD-L1 antibody pembrolizumab	UNK	UNK	Alive
Wang *et al*[4]	2020	China	1	57	M	Asymptomatic	PET-CT scan showed pancreatic metastasis (1 yr after diagnosis of squamous cell lung carcinoma)	No	Laparoscopic radical pancreatic body tail and splenectomy	4 cycles of gemcitabine (1000 mg/m2) plus cisplatin (65 mg/m2) due to progression of the lung mass and the appearance of a tumor in the head of the pancreas. He received 3 cycles of pembrolizumab (2 mg/kg)	1 yr	21.1 mo	Dead
Ishikawa *et al* [31]	2017	Canada	1	70	M	Abdominal pain and weight loss	3.8 cm hypodense mass in the pancreatic body with lymphadenopathy in the left supraclavicular region and a 3-cm lung mass posterior to the left main stem bronchus	Yes	EUS-FNB of these two lesions with a 25-G needle	Palliative chemotherapy	UNK	UNK	UNK
Fujji *et al*[32]	2015	Japan	1	70	M	High fever and jaundice 6 mo after left lung inferior lobe resection	Low contrast-enhanced mass with relatively clear border and a size of 40 mm × 33 mm in the head of the pancreas	Yes	FNA *via* a transgastric approach with linear EUS	5 cycles of carboplatin plus weekly paclitaxel	226 d	UNK	Dead
Dewanwala *et al*[33]	2012	United States	1	65	M	Dyspnea and recurrent cough	Left hilar mass with an incidental well-defined mass involving the uncinate process of the pancreas measuring 3.7 cm × 2.2 cm	Yes	Pylorus-preserving pancreaticoduodenectomy	Carboplatin plus gemcitabine and completed 5 cycles	17 mo	UNK	Dead
Layfield *et al* [34]	2010	United States	1	UNK	M	UNK	UNK	Yes	EUS + FNA of the pancreatic mass	UNK	UNK	UNK	UNK
Liratzopoulos *et al*[23]	2006	Greece	1	53	M	Jaundice, loss of appetite, nausea and mild abdominal pain	CT scan: carcinoma of the lower lobe of the right lung, a tumor in the pancreatic head measuring 4.0 cm × 4.1 cm × 3.5 cm, dilatation of the biliary tract and multiple enlarged lymph nodes in the cervical area, the mediastinum and the abdomen	No	A percutaneous FNA of the pancreatic tumor under CT guidance	Cholecystojejunostomy + dissection of lymph node near the pancreas	19 d	UNK	Dead

Mesa *et al*[35]	2004	United States	2	UNK	UNK	UNK	Mass in the head of the pancreas measuring 3.6 cm and a lung tumor	Yes	EUS-FNA of the pancreatic mass	UNK	UNK	UNK	UNK
Volkan *et al* [36]	2004	United States	5 of 109 autopsy cases	UNK	UNK	UNK	UNK	UNK	Autopsy	UNK	UNK	UNK	Dead
Tetsuya *et al* [37]	2003	Japan	1	69	M	Jaundice	Lung tumor with hilar and mediastinal lymph node swelling and solitary pancreatic head tumor measuring 3 cm	No	Autopsy	Endoscopic nasobiliary drainage and stent drainage therapy prior to chemotherapy using gemcitabine	4 mo	UNK	Dead
Moazzam *et al* [38]	2002	United States	1	54	M	Anorexia, abdominal pain and jaundice	Mass in right upper lung lobe and mass in the head of pancreas	No	Biopsy of the right upper lobe lung mass	Biliary drainage + carboplatin and paclitaxel	UNK	UNK	Alive: good clinical and radiographic response
Nakamura *et al*[11]	2001	Japan	3 of 103 autopsy cases	UNK	UNK	UNK	UNK	UNK	Autopsy	UNK	UNK	UNK	Dead
Matsukuma *et al*[39]	1997	Japan	3	55	M	UNK	UNK	No	Autopsy	UNK	UNK	UNK	Dead
				64	M								
				58	M								

CT: Computed tomography; EUS: Endoscopic ultrasound; F: Female; FNA: Fine-needle aspiration; FNB: Fine-needle biopsy; M: Male; PD-L1: Programmed death ligand 1; PET: Positron emission tomography; UNK: Unknown.

manifest as upper gastrointestinal bleeding or acute pancreatitis, which were reported in 3 cases[14] and 13 cases[12], respectively. According to Deluzio *et al*[15], 59% of patients with pancreatic metastasis had gastrointestinal symptoms, mostly represented by jaundice and abdominal pain. Jaundice is explained by the obstruction of extrahepatic biliary ducts by pancreatic metastasis, which is essentially observed in small cell lung cancer[16]. The diagnosis of pancreatic metastasis and the differentiation of primary and metastatic tumors represent significant challenges. Pancreatic metastasis shows varied enhancement when imaged. Klein *et al*[17] reported that 76% of pancreatic metastases showed greater vascular enhancement than normal pancreatic parenchyma or primary pancreatic tumors, which is explained by the richness of metastatic vascularization. EUS is the main exam for pancreatic lesions and their locoregional extension. The sensitivity of EUS is estimated at 100% for tumors < 2 cm, whereas the sensitivity values of ultrasound and abdominal scan are 60% and 50%, respectively[16]. A retrospective study by El Hajj *et al*[10] included 49 patients with pancreatic metastasis and found that the lesions were hypoechoic in 80% of patients, hyperechoic in 4% of patients, mixed in 4% of patients, and anechoic in 2% of patients. Regular boundaries were observed in 55% of cases. To confirm the diagnosis, cytological analysis was used in 63% of cases, whereas immunohistochemical analysis was added to the former technique in 33% of these cases. Dewitt *et al*[18] demonstrated that EUS-FNA confirmed the diagnosis of pancreatic metastasis in all patients with a secondary pancreatic tumor. They also deduced that the only ultrasound data that could differentiate between primary and secondary pancreatic tumors involved the

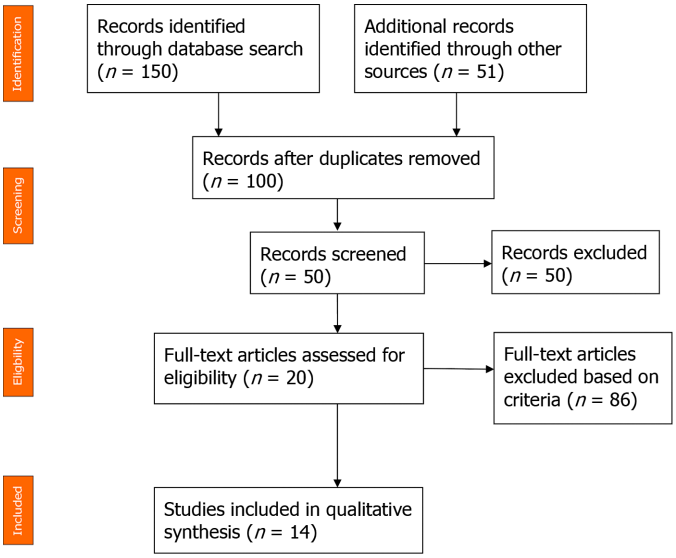

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Figure 6 Flow diagram of the literature review of squamous cell lung carcinoma with pancreatic metastasis.

lesion margins. Margins were well defined when the tumor was secondary (46% *vs* 4%) and irregular in 94% of primary pancreatic tumors (94% *vs* 54%) ($P < 0.0001$). However, no significant differences were noted between primary and metastatic pancreatic tumors regarding tumor number, size, location, or echogenicity parameters. For metastatic lung cancer, therapeutic care consists of palliative chemotherapy and biliary drainage when the tumor compresses the biliary ducts. According to the National Comprehensive Cancer Network guidelines, metastatic squamous cell carcinoma treatment depends on the patient's performance status[19]. These options should be discussed during the multidisciplinary expert consultation. Regimens of pembrolizumab, carboplatin and paclitaxel or pembrolizumab, carboplatin, paclitaxel and albumin are used as the first-line treatment for patients whose performance status is 0 to 1. When the performance status is 2, carboplatin, paclitaxel and albumin or carboplatin and gemcitabine or carboplatin and paclitaxel are the recommended therapeutic options. Our patient had a performance status of 2, indicating that he should be treated with carboplatin and paclitaxel. However, this treatment was stopped due to intolerance. Recently, many scientific publications have discussed the surgical treatment of oligometastatic lung cancer in the pancreas. Kageyama *et al*[3] reported a unique case of a 67-year-old patient who had lung cancer with a pancreatic metastasis that was randomly discovered during follow-up tests 6 years after the primary tumor diagnosis. The patient underwent a distal pancreatectomy and ganglion dissection, which led to survival at 5 years without any recurrence. Ida *et al*[20] showed a longer survival of 8 years in a 70-year-old male patient with metastatic squamous cell lung carcinoma who underwent a total pancreatectomy and a resection of the portal vein. According to a Japanese retrospective study that evaluated global survival in patients receiving a surgical operation for pancreatic metastasis, 6 of the 9 patients survived for more than 23.5 mo. However, patients with longer survival times had pancreatic tumors secondary to renal cancer[21]. Generally, pancreatic metastasis of squamous cell lung carcinoma is discovered at an advanced stage[22], and only 2% of the tumors are resectable[23], revealing why surgical treatment is rarely utilized. Moreover, this case is unusual given the presence of a malignant tracheoesophageal fistula as a rare complication of squamous cell lung carcinoma. Malignant tracheoesophageal or bronchoesophageal fistula develops in 5%-15% of patients with esophageal cancer, and only 0.2% of lung malignancies have been reported to cause esophageal pulmonary fistulae[24]. In patients with prior lung or esophageal cancer, the presence of symptoms, such as dysphagia, recurrent pneumonia or treatment-resistant pneumonia, should raise concern as to whether an underlying fistula is present. If not detected early or left untreated, the fistulae may lead to pneumonitis and lung abscesses that cause sepsis, acute respiratory distress syndrome, and death. In addition, without treatment, the median survival may be 1-6 wk[25]. There is no cure for malignant tracheoesophageal fistulae, and palliative procedures, such as esophageal stenting, esophageal exclusion, esophageal bypass or surgical repair with fistula resection, may prolong survival and provide immediate symptom relief. Based on a comparative study of the survival time and quality of life of patients who received different treatments for tracheoesophageal fistulae, self-expandable stenting did not significantly prolong the survival time of patients but did remarkably improve health-related quality of life[26]. The European Society of Gastrointestinal Endoscopy recommends esophageal self-expandable metallic stent placement as the preferred treatment for sealing malignant tracheoesophageal fistulae[27]. However, the reported success rates of esophageal stent placement vary from 70% to 100%. In addition, some complications may occur,

such as stent migration, bleeding, granulation formation, foreign body sensation, and secondary fistulae, all of which have been reported as late complications of stenting[24]. In our case, the malignant tracheoesophageal fistula was successfully treated by an fully covered esophageal metallic stent. Unfortunately, our patient died 6 mo after the diagnosis of pancreatic metastasis. This was not surprising because stage IV squamous cell lung carcinoma with pancreatic metastasis has a poor prognosis in general with an average reported survival of 8.7 mo after diagnosis[28].

CONCLUSION

Squamous cell lung carcinoma with pancreatic metastasis is rare, and its diagnosis represents a challenge for clinicians. Radiological, endoscopic and anatomopathological methods are needed for an accurate diagnosis. EUS-FNA is the ideal procedure to diagnose pancreatic metastasis. This disease has a poor prognosis because it is generally detected at an advanced stage. Thus, the treatment is typically palliative.

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FOOTNOTES

Author contributions: Rais K and El Eulj O reviewed the literature and contributed to writing of the manuscript; El Moutaoukil N collected the patient's clinical data; Zazour A, Khannoussi W and Ismaili MZ contributed in performing endoscopic retrograde cholangiopancreatography and endoscopic ultrasound + fine-needle aspiration and correcting the manuscript for important intellectual content; Kharrasse G participated in the multidisciplinary consultation meetings and in confirmation of the patient's diagnosis; Kamaoui I interpreted the imaging findings; Bennani A analyzed the biopsies of the pancreatic mass; all authors read and approved the manuscript.

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ORCID number: Kaouthar Rais 0000-0002-9896-3336; Oumayma El Eulj 0000-0002-8545-8832.

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LETTER TO THE EDITOR

Multimodal treatments of "gallstone cholangiopancreatitis"

Serafino Vanella, Mario Baiamonte, Francesco Crafa

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Serafino Vanella, Division of General and Surgical Oncology, St. Giuseppe Moscati Hospital, Center of National Excellence and High Specialty, Avellino 83100, Italy

Mario Baiamonte, General and Emergency Surgery Unit, Civico Benfratelli Di Cristina Hospital, Palermo 90121, Italy

Francesco Crafa, Oncological and General Surgery Unit, St. Giuseppe Moscati Hospital, Center of National Excellence and High Specialty, Avellino 83100, Italy

Corresponding author: Serafino Vanella, PhD, Doctor, Surgeon, Surgical Oncologist, Division of General and Surgical Oncology, St. Giuseppe Moscati Hospital, Center of National Excellence and High Specialty, C/da Amoretta, Avellino 83100, Italy. nekroma@yahoo.it

Abstract

Gallstone cholangiopancreatitis is a potentially life-threatening pathology which requires quick intervention involving endoscopists, interventional radiologists, anesthesiologists and surgeons in relation to clinical conditions. Treatment possibilities are varied, especially with current progress in advanced endoscopy, interventional radiology, and minimally invasive surgery. The following treatments are available: endoscopic sphincterotomy (ES) with stone extraction followed by laparoscopic cholecystectomy; simultaneous endoscopic stone extraction with laparoscopic cholecystectomy (rendezvous technique); combined laparoscopic cholecystectomy and common bile duct (CBD) exploration; open CBD exploration; ES post-cholecystectomy; percutaneous placement of biliary drains for unstable patients, followed by percutaneous cholangioscopy; and lithotripsy with different approaches, including a laser and balloon dilation of the sphincter of Oddi. Each technique has its strengths and weaknesses, and there is great discussion in the literature on choosing the ideal approach based on the patient's clinical conditions.

Key Words: Cholangiopancreatitis; Common bile duct stones; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Laparoscopic common bile duct exploration; Percutaneous

Core Tip: Urgent biliary decompression represents the treatment of gallstone pancreatitis associated with cholangitis. There are different techniques for common bile duct (CBD) clearance. Endoscopic retrograde cholangiopancreatography is not always feasible, as in the case of poor clinical conditions, large stones, or biliodigestive derivations. We analyzed the different approaches for decompression of the CBD in the case of "cholangiopancreatitis".

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TO THE EDITOR

We read with interest the article by Isogai[1] about the definition of "gallstone cholangiopancreatitis," and the assessments regarding the aetiology and prognosis. Although the study is very well worded, we would like to add a few comments.

We think that it is complex to distinguish, with the only dosage of alanine aminotransferase, between a liver disease or the onset of multi-organ failure and cholangitis associated with pancreatitis[2]. However, the reflections expressed in the document stimulate the research activity to realize diagnostic methods that allow distinguishing "cholangiopancreatitis" from other adverse events that can worsen the clinical course of acute pancreatitis.

Moreover, we would like to integrate the different CBD obstruction management techniques even if this was not the main focus of the article.

Acute pancreatitis complicated by cholangitis due to CBD obstruction must be approached with an urgent decompression of the biliary tract to improve the pathology course. There are different approaches to decompress CBD, such as endoscopic retrograde cholangiopancreatography (ERCP), concerning the clinical conditions, the diameter of the stones, and any previous biliodigestive derivation. Urgent ERCP is recommended in patients with gallstone pancreatitis and concomitant cholangitis. The guidelines suggest that ERCP can improve the course in patients with CBD obstruction even in the absence of cholangitis[3-5].

In the study by Schepers *et al*[6], it appears that urgent ERCP associated with sphincterotomy may help in cholangitis complicating acute pancreatitis or in persistent obstruction of CBD. ERCP results in excellent clearance of CBD; nevertheless, in a certain proportion of patients, it may be necessary to resort to multiple procedures. ERCP associated with sphincterotomy is an aggressive approach which can lead to complications in up to 10% of patients[7,8], including bleeding, cholangitis, pancreatitis, duodenal perforation, and CBD lesions. A previous study showed that ERCP could lead to an increase in respiratory complications[9-13]. Sedation and possible aspiration can lead to respiratory complications in clinically critically ill patients. In the study of Schepers *et al*[6], in the urgent ERCP group there were more intensive care unit admissions.

Our clinical approach to patients with severe clinical conditions, unable to withstand general anesthesia or deep sedation is to subject these patients to percutaneous decompression of the CBD with a drain placed under local anesthesia and possible subsequent clearance of the CBD with the use of percutaneous cholangioscopy and laser.

Percutaneous biliary drainage can also have complications such as infections, and it can become blocked or displaced. However, it allows performing cholangiographies that can evaluate the possible presence of residual stones or the complete clearance of the biliary tract throughout their entire course. Once the patient's clinical condition has been improved, surgery and rendezvous ERCP can be carried out; if endoscopic treatment is not feasible, a laparoscopic exploration of CBD (LCBDE) could be performed.

In the study of Aawsaj *et al*[14] the LCBDE has been used in both elective and emergency contexts. A transcystic approach is preferable whenever possible. It is preferable to perform cholecystectomy during the same hospitalization to avoid recurrent gallstone pancreatitis.

A previous review by Dasari *et al*[15] showed no difference in clearance, morbidity, and mortality between open surgery and ERCP. In the ERCP group there were significantly more retained stones than in the open surgery group (16% *vs* 6%; $P = 0.0002$).

Laparoscopic cholecystectomy (LC) + LCBDE had fewer retained stones (8%) than two-staged pre-operative ERCP plus LC or LC plus post-operative ERCP (14%) (P = not significant). In the study by Ding *et al*[16], there were more recurrent CBD stones in the two-stage group at longer-term follow-up (9.5% *vs* 2.1%; $P = 0.037$). In the endoscopic group, there were more procedures per patient ($P < 0.001$) and most costly espenses ($P = 0.002$).

The study of Bansal *et al*[17] showed a shorter hospital stay in the single-stage group but no differences in major complications between the two groups.

Percutaneous or endoscopic balloon dilation represents a valid alternative to ES. It is simpler, has fewer complications in terms of bleeding and sphincter of Oddi lesions but has a lower performance in CBD clearance than ES[18,19]. In the current era, endoscopic approaches guarantee excellent results in the management of the biliary tract. Surgical management of CBD can be a viable option for patients in good condition with large diameter stones, previous biliodigestive derivations, and in case of failure of the endoscopic approach[20-22]. In addition, laparoscopic treatment can be performed with single anesthesia. Exploration of CBD by intraoperative choledochoscopy and simultaneous biliary clearance in a single time is not very aggressive and safe, with excellent results for treating "gallstone cholangiopancreatitis" and should only be performed in high volume centres with surgeons with proven experience. The laparoscopic management of CBD stones also reduces the average hospital stay, the anesthetic risks associated with two different procedures, and the cost of multiple hospitalizations.

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FOOTNOTES

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Country/Territory of origin: Italy

ORCID number: Serafino Vanella 0000-0002-6599-8225; Mario Baiamonte 0000-0001-8323-8118; Francesco Crafa 0000-0002-2038-625X.

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LETTER TO THE EDITOR

Texture and color enhancement imaging for detecting colorectal adenomas: Good, but not good enough

Ying Wang, Chen-Yu Sun, Lowe Scott, Dan-Dan Wu, Xia Chen

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Ying Wang, Dan-Dan Wu, South District of Endoscopic Center, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, Anhui Province, China

Chen-Yu Sun, AMITA Health Saint Joseph Hospital Chicago, Chicago, IL 60657, United States

Lowe Scott, College of Osteopathic Medicine, Kansas City University, Kansas City, KS 64106, United States

Xia Chen, Department of Nursing, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei 230001, Anhui Province, China

Corresponding author: Xia Chen, MSN, RN, Associate Chief Nurse, Department of Nursing, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, No. 17 Lujiang Road, Hefei 230001, Anhui Province, China. 1569265542@qq.com

Abstract

Texture and color enhancement imaging (TXI) has been developed as a novel image-enhancing endoscopy. However, the effectiveness of TXI detecting adenomas is inferior to narrow band imaging. Thus, future studies will need to focus on investigating the feasibility of such combination in clinical settings in order to provide patients with more accurate diagnoses.

Key Words: White light imaging; Texture and color enhancement imaging; Narrow band imaging; Colorectal adenomas

Core Tip: Texture and color enhancement imaging (TXI) is designed to enhance three image factors in white light imaging (texture, brightness, and color) in order to clearly define subtle tissue differences. Latest articles reported that TXI may likely contribute to the detection of early gastric cancer. Notably, the synergistic added value of TXI and near-focus mode was discovered during saline-immersion endoscopic submucosal dissection by improving submucosal space visibility. As the authors put it, the effectiveness of TXI detecting adenomas is inferior to narrow band imaging.

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TO THE EDITOR

With great curiosities, we examined the article "Texture and color enhancement imaging in magnifying endoscopic evaluation of colorectal adenomas" recently published by Toyoshima *et al*[1]. In this study, a total of sixty-one consecutive adenomas with completed white light imaging (WLI), texture and color enhancement imaging (TXI), narrow band imaging (NBI), and chromoendoscopy (CE) were investigated. In the present study, the visibility score for tumor margin of TXI was significantly higher than that of WLI, but lower than that of NBI. Additionally, TXI had a higher visibility score for the vessel as well as surface pattern of the JNET classification than WLI and CE, but a lower visibility score than NBI.

To detect colorectal polyp and gastric cancer, endoscopy with WLI is currently the gold standard. However, the accuracy of WLI for detecting early lesions in both the colorectal and gastric regions is yet to be established[2]. Meanwhile, TXI was proposed as a new image enhancement technology to resolve these drawbacks by Sato[3]. To avoid losing subtle tissue differences, TXI is designed to enhance the three imaging factors in WLI (texture, brightness, and color). According to recent publications, it has been suggested that TXI may likely contribute to the increased detection rate of early gastric cancer[4]. Moreover, a significant synergistic value of TXI and near-focus mode was discovered during endoscopic submucosal dissection performed in saline-immersion by improving the visibility of submucosal spaces [5]. In a study by Nishizawa *et al*[6], WLI, TXI, NBI, and chromoendoscopy were performed on twenty-nine patients with serrated polyps. Similarly, the authors indicated that TXI provided higher degree of clarity in visualization for the detection of serrated, colorectal polyps, as well as sessile serrated lesions.

It is noteworthy that Toyoshima *et al*[1] concluded that the effectiveness of TXI detecting adenomas is inferior to NBI under certain circumstances. Furthermore, TXI could also be combined with other optical image enhancement technology such as NBI, since TXI is implemented entirely in the chain of endoscopic image processing. Finally, it is suggested that future researches should focus on investigating the feasibility of such combination in clinical settings in order to provide patients with more accurate diagnoses.

FOOTNOTES

Author contributions: Wang Y and Chen X conceived and designed the study; Wang Y, Sun CY, Lowe S, Wu DD, and Chen X participated in drafting and critical revision of the manuscript; all authors approved the final version of the manuscript.

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Country/Territory of origin: China

ORCID number: Ying Wang 0000-0002-8983-1307; Chen-Yu Sun 0000-0003-3812-3164; Lowe Scott 0000-0002-3325-6438; Dan-Dan Wu 0000-0003-4171-9751; Xia Chen 0000-0003-1479-9802.

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