ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2022 September 16; 14(9): 512-580

Published by Baishideng Publishing Group Inc

World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 14 Number 9 September 16, 2022

World Journal of Gastrointestinal Endoscopy

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Contents

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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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INDEXING/ABSTRACTING

The *WJGE* is now abstracted and indexed in Emerging Sources Citation Index (Web of Science), PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJGE* as 0.33.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Gastrointestinal Endoscopy

ISSN

ISSN 1948-5190 (online)

LAUNCH DATE

October 15, 2009

FREQUENCY

Monthly

PUBLICATION DATE

September 16, 2022

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 September 16; 14(9): 512-523

DOI: 10.4253/wjge.v14.i9.512

ISSN 1948-5190 (online)

MINIREVIEWS

Simulation-based mastery learning in gastrointestinal endoscopy training

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Al-Ani RM, Iraq; Toyoshima O, Japan; Isac S, Romania

Received: June 4, 2022
Peer-review started: June 4, 2022
First decision: June 18, 2022
Revised: July 3, 2022
Accepted: August 16, 2022
Article in press: August 16, 2022
Published online: September 16, 2022

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Abstract

Simulation-based mastery learning (SBML) is an emerging form of competency-based training that has been proposed as the next standard method for procedural task training, including that in gastr-ointestinal endoscopy. Current basic gastrointestinal endoscopy training relies on the number of procedures performed, and it has been criticized for its lack of objective standards that result in variable skills among trainees and its association with patient safety risk. Thus, incorporating simulators into a competency-based curriculum seems ideal for gastrointestinal endoscopy training. The curriculum for SBML in gastrointestinal endoscopy is currently being developed and has promising potential to translate into the clinical performance. Unlike the present apprenticeship model of "see one, do one, teach one," SBML integrates a competency-based curriculum with specific learning objectives alongside simulation-based training. This allows trainees to practice essential skills repeatedly, receive feedback from experts, and gradually develop their abilities to achieve mastery. Moreover, trainees and trainers need to understand the learning targets of the program so that trainees can focus their learning on the necessary skills and trainers can provide structured feedback based on the expected outcomes. In addition to learning targets, an assessment plan is essential to provide trainees with future directions for their improvement and ensure patient safety by issuing a passing standard. Finally, the SBML program should be planned and managed by a specific team and conducted within a developed and tested curriculum. This review discusses the current state of gastr-ointestinal endoscopy training and the role of SBML in that field.

Key Words: Simulation training; Education; Endoscopy; Mastery learning; Competency-

based education; Curriculum

Core Tip: The traditional apprenticeship model for gastrointestinal training has been widely criticized for its lack of standards and patient safety risks. Thus, the basic gastrointestinal endoscopy training method needs to be revised from the apprenticeship model to a simulation-based mastery learning (SBML) model, which relies on specific learning objectives with the integration of simulators. SBML is a competency-based training method aimed at creating highly competent trainees and reducing differences in skills among them. The present review discusses the current state of gastrointestinal endoscopy training, the role of SBML in that field, and recent experiences and future prospects of SBML.

Citation: Maulahela H, Annisa NG, Konstantin T, Syam AF, Soetikno R. Simulation-based mastery learning in gastrointestinal endoscopy training. *World J Gastrointest Endosc* 2022; 14(9): 512-523
URL: https://www.wjgnet.com/1948-5190/full/v14/i9/512.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i9.512

INTRODUCTION

Endoscopy is the gold standard technique for the diagnosis of various gastrointestinal (GI) tract diseases and also allows examiners to directly provide therapeutic interventions if needed. This procedure is performed by a trained gastroenterologist or endoscopic surgeon. The need for endoscopic procedures is projected to increase every year due to the growing prevalence of GI diseases and technical improvements in GI endoscopy[1]. Most GI endoscopy training still follows the traditional apprenticeship model of "see one, do one, teach one." This model relies on the number of exposures to procedural caseloads, which causes varying results among trainees[2]. This lack of a standardized curriculum has recently come under intense scrutiny because it is associated with patient safety risks, as trainees cannot safely perform a medical procedure after having observed it only once[3].

A mastery learning model is an approach to competency-based training, in which participants must acquire specific skills before moving on to the next stage of training. The basic principle of mastery learning is that all participants can achieve the highest standard of learning objectives with the minimum possible variation in results. Meta-analyses show that mastery learning significantly leads to skill improvement, has a moderate effect on patient outcomes compared to the traditional apprenticeship method, but might demand more time than other methods. Mastery learning-based training provides consistent positive results and has a beneficial effect on both patient care and the budget spent during the training process[4].

A simulation-based training (SBT) method has been also proposed as an alternative to replace the old teaching method. The use of simulators to acquire psychomotor abilities has been widely studied and recommended by leading educational institutions. With a SBT method, trainees can achieve procedural competence without compromising patient safety, particularly in those procedures that require practical experience and visual-spatial skills[5]. Additionally, skills of the operator can be improved and the length of the procedure reduced by using a simulator. Finally, simulators can also be used to evaluate trainee progress[6].

SBT and mastery learning methods have several benefits over the traditional apprenticeship model. This article reviews the role of simulation-based mastery learning (SBML) in GI endoscopy and describes the planning and management for the implementation of this model, including experiences regarding its application.

DEVELOPMENT OF GI ENDOSCOPY TRAINING

Since 1962, the American Society for Gastrointestinal Endoscopy has held symposiums about teaching methods in GI endoscopy and later formed a formal endoscopy training program. Along with the development of science and advancement in the complexity of endoscopic procedures, gastroenterological education began to be developed independently as part of a subspecialty of internal medicine[4]. The development of specific training in endoscopy and gastroenterology also impacted the education period for this field, which initially consisted of 1 year to 2 years and then was extended to 3 years[4]. Currently, there is no global standardization of the gastroenterology education length. Some countries, such as the Netherlands, are now expanding their gastroenterology curriculum to 3 years to 4 years,

starting with 2 years of general internal medicine training[7,8]. In Korea, endoscopy training is conducted for 1 year to 2 years during a gastroenterology fellowship program[9]. Meanwhile, in Japan, a physician must complete 3 years of internal medicine residency and 5 years of gastroenterology fellowship to become a board-certified endoscopist[10]. The World Gastroenterology Organization states that a student must complete 3 years of internal medicine residency before pursuing gastroenterological-specific education and training for the next 3 years[11].

The current state of endoscopy training is defined by the conventional apprenticeship model, with a strong emphasis on case/procedure volume and without a formal curriculum. Trainees are usually assigned the minimum number of cases or procedures they need to achieve competency or practical eligibility. The duration of the training program is commonly fixed, and an assessment is conducted near the end of the program. This training method has potential variability in terms of skill outcomes. As trainees might be overwhelmed at the start of the program, the initial cases they encounter can be ineffective for learning. A European survey showed significant differences in various gastroenterology training among 16 European countries, ranging from the minimum number of procedures required, training period, form of supervision to whether some interventional procedures were performed[12]. Recently, curriculum-based medical education (CBME) has recently been proposed to improve endoscopy training. The CBME model includes The American Society of Gastrointestinal Endoscopy Skills, Training, Assessment, and Reinforcement program with a curriculum that combines hands-on training, formative feedback, and postcourse skills and knowledge assessments[13].

One of the learning methods that has been developed for endoscopy training is a simulated-based approach. Endoscopy simulator models have continued to be developed and advanced in the last decades, ranging from mechanical simulators, animal model simulations, and computer simulators[14]. The evolution of endoscopy simulators is described in Table 1. These developments provide opportunities for trainees to learn various diagnostic and therapeutic techniques. Generally, these simulators use an endoscope that is inserted into a mannequin. Consequently, trainees can be more familiar with endoscopic procedures and be able to practice them on an actual patient. Some advanced computer simulators also provide a realistic picture on the monitor and can simulate a patient's response. The computer simulator also combines training to learn hand-eye coordination, recognition of pathological features, and immediate feedback output[15]. A systematic review showed that skills acquired from SBT were transferable to the clinical setting, as participants of SBT scored higher global assessment scores and fewer errors[16]. Moreover, forms of simulation that can be considered in endoscopy training include the following[17-24].

Patient simulation: A simulated mannequin that resembles a human with respiration, pulse, and other vital signs is used. This type of simulation can be used for simple physical examination scenarios.

Clinical environment simulation: In this simulation, a room that resembles an actual clinical practice room, for example, an operating room, is prepared. Thus, trainees become more familiar with the actual situation.

Virtual procedure simulation: These simulations have equipment relevant to the procedure, such as esophagogastroduodenoscopy or colonoscopy, and can also present various disease scenarios according to the needs of trainees.

Electronic medical record simulation: This simulation uses artificial data about cases, including disease history and laboratory results, which can be integrated with other systems.

MASTERY LEARNING IN GI ENDOSCOPY

Mastery learning is a form of competency-based training in which trainees have to achieve specific skills or be deemed good enough to perform a procedure before moving on to the next stage of training. Competence is the minimum level of skill, knowledge, or expertise acquired through training necessary to perform a task or procedure and to ensure that safe and technically successful procedures are carried out and that observations and results are accurate[25,26]. Mastery learning focuses on the trainees instead of the patient. The old teaching has resulted in inconsistent teaching, testing, and retention of skills, while mastery learning demands trainees to acquire and maintain specific skills and knowledge through deliberate practice without time limit. Deliberate practice consists of nine elements: highly motivated learners with good concentration, clear learning objectives, an appropriate difficulty level, repetitive practice, rigorous measurements, informative feedback, monitoring and error correction, performance evaluation, and advancement to the next task[27]. Mastery learning effectively develops both therapeutic skill and high self efficacy to utilize the skill[28].

Mastery of basic endoscopic techniques is essential for every endoscopist, because if the procedure is performed incorrectly, it can cause severe complications that might threaten the condition of patients. The essential steps of endoscopy are endoscope insertion, precise observation, and appropriate imaging [29]. Skills developed by each endoscopist may vary and are influenced by differences among supervisors during the procedure. Hence, standardized training is necessary to maintain the competence of trainees[30].

Table 1 Development of endoscopy simulators

Ref.	Developer	Yr	Characteristics
Telleman *et al*[19], 2009	Erlangen-Nuremberg University Clinic	1974	An anatomical model of the esophagus, stomach, and duodenum used to train for endoscopic maneuvers
Williams *et al*[20], 2000	Imperial College/St Mark's Hospital	1980	An anatomical model of the colon to train for angling maneuver in the organ
			Constant supervision is needed because trainees could damage the endoscope by excessive maneuvering
			The appearance of the colon surface is not realistic in the model
Classen and Ruppin [21], 1974	Imperial College/St Mark's Hospital	1980	More realistic control compared to previous models as the endoscope can be rotated, and endoscope insertion and withdrawal can be detected
			Integrated with a monitor showing live simulation
			The length of the endoscope that can be inserted is limited
Williams *et al*[22], 1990	Imperial College/St Mark's Hospital	1985	The endoscope can be fully inserted
			A sensation of resistance and an audio simulation that mimics patient's complaints are included
			Still unrealistic
Long and Kalloo[15], 2006	Immersion Medical	2001	Provides an opportunity to practice various procedures, including biopsy
			Provides immediate feedback
			Realistic simulation as a sensation of resistance and contraction is included
Koch *et al*[23], 2008	Simbionix	2008	Provides realistic simulation
			Can be used to practice endoscopic maneuvers
			Can distinguish between the ability level of endoscopy experts and intermediate level
Triantafyllou[24], 2014	CAE Healthcare	2013	Can be accompanied by the patient's history and various clinical parameters that can change during the endoscopy by the participant
			Combines endoscopic procedures with virtual backgrounds

Traditionally, competence in endoscopy is acquired after completing a specific number of recommended procedures based on expert opinions published by medical gastroenterology societies or associations, as described in Table 2. However, according to the aforementioned mastery learning principles, competence cannot be determined only by the number of procedures performed. A defined and detailed assessment tool should be incorporated to objectively assess trainees to deliver high-quality care[31].

To ensure competence in mastery learning, two aspects are needed: training and subsequent assessment by endoscopy experts or trainers. Through this training, trainees acquire the necessary technical and cognitive skills[25]. Examples of technical and psychomotor skills associated with endoscopy include scope handling and strategies for scope advancement, loop reduction, recall, and mucosal inspection. Cognitive competence reflects knowledge acquired about endoscopy and its application in clinical practice. Cognitive skills include choosing the most appropriate endoscopy test to assess and treat clinical problems, recognizing the lesion, and managing sedation. Crucial integrative competencies to endoscopy include decision-making, teamwork, communication, leadership, awareness of the situation, professionalism, and patient safety awareness[26].

Based on the psychological aspect, three factors underlie mastery learning: Behavioral development, constructive learning, and social cognition. Behavioral development pursues the acquisition and maintenance of technical and communication skills. Clinical thinking, community approach, ethics, advocacy, and regular self-reflection aim to shape social and cognitive constructs. Social cognition is a prerequisite for professionalism. These three aspects support the formation of SBML, which includes a curriculum design to set learning objectives[32-37].

SIMULATION-BASED TRAINING IN GI ENDOSCOPY

The SBML method uses an instructional approach, meaning that trainees must have a certain level of competence in a simulated environment before performing procedures on actual patients[24]. With this method, trainees progress through different simulations with increasing difficulty. SBML provides opportunities for students to practice as often as possible to improve their performance before operating

Table 2 Minimum number of trainings needed to achieve competence in different procedures according to gastroenterology associations

Source	EGD	Colonoscopy	ERCP
European Diploma of Gastroenterology[32]	300	100	150
ASGE[33]	130	140	200
SAGES[34]	35	50	-
Korean Society of Gastrointestinal Endoscopy[35]	1000	150	30
British Society of Gastroenterology[36]	300	100	150

ASGE: American Society for Gastrointestinal Endoscopy; EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography; SAGES: Society of American Gastrointestinal and Endoscopic Surgeons.

on patients. This method can optimize clinical outcomes and reduce the risk of complications or other hazards for patients that may occur during the operation period of a novice endoscopist[17,38]. In addition, SBML can minimize variations between trainees upon completion of the program[24,39].

Several studies in other fields of medical procedural training have shown the benefits of SBT and mastery learning over the traditional apprenticeship model. A meta-analysis by Harrison *et al*[40] included 14 studies involving 633 trainees in cardiology procedures and found that SBT followed by structured training provided superior results than traditional methods. The quality of patient care and patient feedback obtained by this method were better than those obtained by a conventional training approach. A meta-analysis by Cook *et al*[41] included 82 studies evaluating SBML in procedural settings such as surgeries and airway management. They found that SBML was significantly better at improving procedural skills than traditional methods but might takes more time. A systematic review on patient outcomes in simulation based medical education also reported small to moderate patient benefits in comparison with no intervention[38]. A study published in 2014 revealed the effectiveness of colonoscopy training with virtual simulation in the early learning curve of novices. Performance improvements were also found later during patient-based colonoscopy[42]. Another multicenter study found higher objective competency rates during the early phase of colonoscopy training[43].

A prospective randomized study that evaluated the diagnostic abilities of trainees using upper GI endoscopy concluded that structured SBT was superior to SBT or clinical training alone. This study also found that the use of the simulator was valuable as the first step in developing diagnostic skills to perform upper GI endoscopy, but it was not sufficient to ensure the overall competencies[30]. Several reports on SBT for GI endoscopy are described in Table 3.

Generally, studies on SBT in GI endoscopy training have shown favorable results, especially in the early phase of training, as it reduces the time required to reach technical competence and the number of endoscopic procedures needed to perform it independently. With SBT, trainees can perform the procedures and exercises repeatedly using a simulator. This repetition improves the cognitive and practical skills of students and allows them to become more acquainted with endoscopic features and settings. A meta-analysis showed that simulation can increase patient safety and decrease the risk of adverse events, as trainees are more skilled and familiarized with the clinical settings at the moment of performing the endoscopy[44-49]. It also provides an opportunity for trainees to learn at their own pace [50-54].

However, some systematic reviews have reported inconclusive evidence supporting SBT as a replacement for conventional training. SBT might be more beneficial as a supplement to conventional training, especially in the early phase. Nevertheless, reducing patient-based training in favor of SBT is not recommended as it cannot replace conventional patient-based training[48,51,52]. Hence, simulation must be accompanied by direct clinical experience with patients in order to understand the actual clinical setting[39]. A study conducted in 2004 found that simulation without feedback from experts did not improve the skills of trainees. Providing trainees access to a simulator cannot guarantee appropriate learning by itself. Therefore, SBT should be delivered purposefully within a developed curriculum to allow trainees to practice essential skills, receive feedback from experts, and develop skills gradually and appropriately to achieve mastery[55]. Feedback and debriefing are essential in SBT to allow trainees identify their weakness and improve their performance accordingly[56]. Simulation with a proper environment or scenario is also beneficial to the improvement of endoscopic non-technical skills such as communication and teamwork, situation awareness, leadership, judgment, and decision making[57]. A previous study showed that integrating endoscopic non-technical skills training improved novice trainees' performance and competency, which might benefit patients[58].

Table 3 Studies on simulation-based endoscopy training

Ref.	Study design	Methods	Conclusion
Ferlitsch *et al* [39], 2002	Prospective randomized trial	13 endoscopy trainees were divided into two groups: simulator training and no simulator training	Simulator-trained group had better skills, shorter scope insertion time, and fewer adverse events
Giulio *et al*[44], 2004	Prospective randomized trial	22 fellows with no experience in endoscopy were divided into two groups: preclinical training with computer-based simulator and no preclinical training	The first group performed a more complete procedure, required less assistance, and was assessed as better by the instructor
Cohen *et al*[43], 2006	Prospective randomized trial	45 1st-yr GI fellows were divided into two groups: unsupervised simulator training using GI mentor and no simulator	Fellows in the simulator group had significantly higher objective competency rates during the first 100 cases. Fellows who underwent GI mentor training performed significantly better during the early phase of real colonoscopy training
Shirai *et al*[45], 2008	Prospective randomized trial	10 trainees were divided into two groups: simulator and non-simulator	5 h of simulator training improved EGD performance
Ferlitsch *et al* [46], 2010	Prospective randomized trial	28 internal medicine residents were divided into two groups: simulator-trained before conventional training and conventional training only	Virtual simulator training improved technical accuracy during the early and mid-term phase of training, thus reducing the time needed to reach technical competency. However, the clinical effect is limited
Haycock *et al* [47], 2010	Prospective randomized trial	36 novice colonoscopists were divided into two groups: simulator training and patient-based training	Simulator-trained group performance matched the patient-based group performance, and showed superior technical skills on simulated cases
Ende *et al*[30], 2012	Prospective randomized trial	Residents with no previous experience in endoscopy were divided into three groups: clinical and simulator training, clinical training only, and simulator training only	First group showed better results than the other groups. Third group showed a shorter procedure duration
Qiao *et al*[48], 2014	Systematic review	Fifteen studies comparing virtual colonoscopy or gastroscopy training with other intervention were analyzed	Virtual endoscopy simulator training might be effective for gastroscopy, but no data are available for colonoscopy
Singh *et al*[49], 2014	Systematic review and meta-analysis	Thirty-nine articles, including twenty-one randomized trials on simulation-based training in gastrointestinal endoscopy were analyzed	Simulation-based training significantly enhanced the skills of trainees, reduced the time needed to finish a procedure, and improved patient outcomes
Ekkelenkamp *et al*[50], 2016	Systematic review	Twenty-three studies on simulator training and learning curves, including seventeen randomized controlled trials, were analyzed	Validated VR simulator training in the early phase accelerated the learning of practical skills. Assessment of performance level on GI endoscopy procedures should be done continuously with validated assessment tool, rather than threshold number
Mahmood *et al* [5], 2018	Systematic review	Twenty-one randomized controlled trials on VR simulation in endoscopy training were analyzed	VR simulation showed improved skills in all areas at the beginning of learning; nonetheless it was not effective as a replacement for conventional training
Khan *et al*[51], 2018	Systematic review	Eighteen trials on endoscopic procedures were analyzed	VR-based training in combination with conventional training showed superior result over VR training alone. Evidence was inconclusive regarding whether VR-based training can replace conventional training
Smith *et al*[52], 2021	Systematic review and meta-analysis	Twenty-four studies on simulation of EGD, colonoscopy, ERCP, flexible sigmoidoscopy, or hemostasis procedures were analyzed	Likely positive impact of simulation training on patient comfort, cecal and biliary intubation. However, studies on the effect of simulation training are small and have a short follow-up time
Zhang *et al*[53], 2021	Systematic review	Twenty-two studies on endoscopy VR simulation training were analyzed	VR simulation training resulted in comparable or significantly better performance than clinical training, no training, other types of simulation, and another form of VR

GI: Gastrointestinal; ERCP: Endoscopic retrograde cholangiopancreatography; EGD, Esophagogastroduodenoscopy; VR: Virtual reality.

EXPERIENCES IN SIMULATION-BASED MASTERY LEARNING FOR ENDOSCOPY TRAINING

Several studies have shown endoscopy mastery learning experiences. Nguyen-Vu *et al*[59] reported a 2-wk course for gastroenterology fellows at the University of California with no prior experience in endoscopy. They divided the learning period into two phases: the 1st week for learning the basics of endoscopy and the 2nd week for learning various therapies in endoscopy. These phases were further divided into specific endoscopic skills such as endoscopic tip control, image documentation, biopsy, and clip administration. Trainees were assigned readings and underwent online assessments before attending hands-on training with a simulator. They had to pass the competency assessment for a specific skill before moving to the next topic. This study showed that the SBML program could rapidly

help trainees acquire endoscopic skills through a comprehensive curriculum. Online reading and assessments enabled trainees to learn at their own pace, and using a simulator provided them with a chance to engage in repetitive practice. Dividing endoscopic skills also allowed trainees to focus on the specific skills they needed to refine.

Ritter *et al*[60] reported an endoscopy training system (ETS) using an SBML curriculum implemented with general surgery residents to pass the Fundamentals of Endoscopic Surgery (FES) skills examination. They divided ETS into five tasks which were organized in two tabletop units. The first unit included scope manipulation, tool targeting, and retroflexion tasks using a simple endoscopic tool. The second unit consisted of loop management and mucosal inspection tasks using a stylized body form. Most participants completed this simulation-based curriculum in less than 1 wk with more than 90 min of practice per day. This study suggested that the application of the SBML curriculum to flexible endoscopes provides significantly improved results on posttraining assessments compared with pretraining assessments. This study also found that after five sessions of SBT, participants could produce posttest scores equivalent to those of doctors who had performed 150-300 endoscopy procedures. This result implies that vast clinical experience is not needed to participate in the SBML program. The ETS was further developed by setting the training standards for the SBML curriculum, resulting in attainable standards that improved FES scores in the skills exam[61]. Another subsequent study published in 2021 evaluated the effect of SBML curriculum implementation early in residency. It revealed that early implementation of SBML curriculum for flexible endoscopy training resulted in comparable performance to those with high level of clinical endoscopic experience[62].

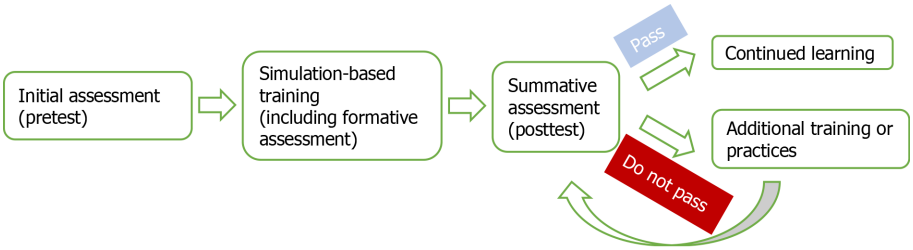
Soetikno *et al*[61] developed a 6-wk SBML program for 1st-year gastroenterology fellows of the Philippine Society of Digestive Endoscopy. SBML involved learning fine-tip control, structured upper endoscopy examination, and endoscopic therapies. Basic knowledge and interpretation of endoscopy findings were learned simultaneously. Interestingly, the first 5 wk of the program were conducted remotely using virtual coaching. Trainees used simulators and recorded their own performance, number of attempts, and completion time for each attempt, and then supervisors provided feedback based on these attempts. During the last week, trainees underwent in-person endoscopic therapy training after having passed the standard for fine-tip control and structured upper endoscopy examination. This study found that the adoption rates for basic endoscopic techniques such as image documentation and biopsy were 93% and 100%, respectively, after 2 mo of training. Meanwhile, the adoption rates of endoscopic therapies such as clipping, band ligation, and injection were more variable (7%-79%)[63]. Soetikno *et al*[64] also conducted an SBML course in GI bleeding endoscopic therapy and found that SBML quickly disseminated technical knowledge and skills. They proposed SBML as an additional method for teaching before trainees performed the procedure on patients.

PLANNING AND MANAGEMENT OF SIMULATION-BASED MASTERY LEARNING IN GI ENDOSCOPY

As stated above, the SBML program requires a developed and tested curriculum to ensure that all trainees can achieve competence in endoscopy. Kern *et al*[65] constructed a six-step approach to build an SBML curriculum. The steps are problem identification and general need assessment, specific need assessment, targets and objectives, educational strategies, implementation, and evaluation and feedback. Hospitals and medical institutions should delegate a specific team to plan the SBML curriculum. After planning, a pilot study should be conducted to evaluate satisfaction of trainees with the program and patient outcomes. Once SBML has been implemented, continuous monitoring and evaluation should be performed to maintain the quality of the program[37].

SBML begins with an initial assessment of the knowledge and abilities of trainees. After training, students will be tested again, and training will continue until they meet the minimum passing standards. Once trainees meet the minimum passing standards, they can advance to the next stage of training (Figure 1). Periodic examinations will be conducted along with planned practices to ensure that expected competencies are maintained[37]. Some training centers might provide materials for self learning before the simulation starts to improve the initial knowledge of trainees. A study by Cheung *et al*[66] showed that preparation before SBML is substantial to improve the effectiveness of SBML. They found that web-based observational practice is superior to reading materials alone, as it increases learner engagement with instructional materials.

Learning targets should be determined from the beginning of the SBML program and arranged according to the SMART acronym: specific, measurable, attainable, relevant, and time-bound[59,60]. Trainees, trainers, and supervisors have to understand learning targets before starting the program. This understanding is beneficial because trainees can focus their learning on the important and necessary skills, and trainers and supervisors can provide structured feedback. Feedback is important in SBML and should be delivered in a specific manner: with only one or two important points at a time and preferably immediately after the procedure or simulation to be properly understood by trainees[67,68]. Feedback should also be constructive and not vague, allowing trainees to self-reflect and come up with potential solutions[31].



DOI: 10.4253/wjge.v14.i9.512

Figure 1 Stages in simulation-based mastery learning. Simulation-based mastery learning begins with a pretest to assess trainees' initial knowledge and abilities. Subsequently, trainees will undergo simulation based-training with formative assessment to direct their training. Lastly, trainees will be evaluated for competency through summative assessment (posttest) according to the minimum passing standards. Trainees who pass the test can advance to the next stage of training, while those who do not pass must receive additional training and practice until they meet the minimum passing standards.

In addition to training or lesson planning, an assessment plan is needed to create a training environment with maximum results. Assessment is vital to provide trainees with future directions for improvement and to ensure patient safety by issuing a passing standard[69]. At the beginning of mastery learning, a pretest has to be conducted to evaluate the initial knowledge of trainees[67]. Within the program, assessments are classified as formative or summative assessments. Formative assessment aims to direct training and support the self reflection and intrinsic motivation of trainees[70]. Meanwhile, summative assessment seeks to evaluate competency and practice eligibility[71]. There are five criteria to indicate the quality of an assessment: reliability, which shows the accuracy and reproducibility of a test: validity, which shows whether the test can be performed to evaluate the intended focused parameter; future impact of the assessment; acceptability by trainees and supervisors; and reasonable cost. Assessments can be conducted through written examinations, direct evaluations by clinical supervisors, direct observations, clinical simulations, or portfolios[69].

THE FUTURE OF SIMULATION-BASED MASTERY LEARNING IN GI ENDOSCOPY

It is reasonable and expected that novice endoscopists do not perform endoscopic procedures on human patients unless they have shown satisfactory skills on a simulator. Endoscopy training should move from the traditional apprenticeship model to objective competency-based mastery learning, integrating simulators, deliberate practice, and prompt feedback from supervisors. The SBML curriculum is acknowledged as a method to boost the efficiency and efficacy of endoscopy training through repetitive practice and expert feedback, which allow trainees to learn the basic structure of endoscopic techniques. One of the limitations of the traditional apprenticeship model is the reduced time for questions, feedback, and adequate skill assessment during a procedure on an actual patient, which results in self learning; thus, not all trainees might develop a proper form and technique. Incorporating simulators can reduce this limitation of the conventional apprenticeship model by allowing trainees to practice basic endoscopic maneuvers repeatedly, as each trainee has a different absorption rate. In fact, acquiring proper techniques is essential for trainees, as they can progress to the next stage of training which is more complex. Simulators also limit the possibility of patient discomfort and injury, thereby allowing trainees to improve their skills. Additionally, the standardization of simulator-based instruction methods is essential to maximize the positive impact of the training method[8]. The integration of simulator in endoscopy training should be within a structured curriculum that combines constructive feedback and complementary knowledge[72]. A previous randomized trial compared the outcome of structured comprehensive curriculum to progressive learning-based curriculum, and revealed that those who received SBT that progressed in complexity and difficulty had superior technical and communication skills and global performance in the simulated setting[73].

A proper SBML curriculum for GI endoscopy should subsequently consist of cognitive, technical, and integrative skill training. The coronavirus disease 2019 pandemic has accelerated the acceptance of online video/web-based learning, video mentoring, and video proctoring. Web-based learning in the form of online modules is now expected for cognitive skill training, which allows trainees to review learning modules at their own pace and to avoid cognitive overload due to a stressful environment[59]. The main drawbacks of simulation-based learning are model realism and less real-world experience for new endoscopists. Hence, hybrid learning that combines simulator-based and one-on-one training is ideal for building the learning curves of trainees and identifying their deficiencies[74]. Improved performance in simulator training has been shown to translate into the clinical area[60].

CONCLUSION

The traditional apprenticeship model in GI endoscopy training must be revised to ensure competency and practical eligibility of novice endoscopists. By moving the focus from a case volume-based to a competency-based training, mastery learning can help lower the variability between skills of trainees and provide optimal results. Previous experiences with the SBML program in endoscopy training showed promising results and positioned that method as an additional course to be incorporated before the apprenticeship is started and also as a complementary course to one-on-one training. The use of a simulator in SBML can help trainees become acquainted with the endoscopic equipment, settings, and situations that might arise during their direct practice on patients. The SBML program should be planned and managed by a specific team and conducted within a developed and tested curriculum.

FOOTNOTES

Author contributions: Maulahela H conceived the study, and wrote and edited the manuscript; Annisa NG performed the data analysis and drafted the manuscript; Konstantin T edited and finalized the manuscript for submission; Syam AF and Soetikno R reviewed and approved the submitted manuscript.

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

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S-Editor: Wang LL
L-Editor: A
P-Editor: Wang LL

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World J Gastrointest Endosc 2022 September 16; 14(9): 524-535

DOI: 10.4253/wjge.v14.i9.524

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Case Control Study

Endoscopic ultrasound elastography for malignant pancreatic masses and associated lymph nodes: Critical evaluation of strain ratio cutoff value

Miguel Puga-Tejada, Raquel Del Valle, Roberto Oleas, Maria Egas-Izquierdo, Martha Arevalo-Mora, Jorge Baquerizo-Burgos, Jesenia Ospina, Miguel Soria-Alcivar, Hannah Pitanga-Lukashok, Carlos Robles-Medranda

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Chen SY, China; Chen C, China; Mahmoud MZ, Saudi Arabia

Received: May 24, 2022
Peer-review started: May 24, 2022
First decision: June 27, 2022
Revised: July 15, 2022
Accepted: August 25, 2022
Article in press: August 25, 2022
Published online: September 16, 2022

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Abstract

BACKGROUND

Endoscopic ultrasound (EUS) can detect small lesions throughout the digestive tract; however, it remains challenging to accurately identify malignancies with this approach. EUS elastography measures tissue hardness, by which malignant and nonmalignant pancreatic masses (PMs) and lymph nodes (LNs) can be differentiated. However, there is currently little information regarding the strain ratio (SR) cutoff in Hispanic populations.

AIM

To determine the diagnostic accuracy of EUS elastography for PMs and LNs with an SR cutoff value in Hispanics.

METHODS

A retrospective study of patients who underwent EUS elastography for PMs between December 2013 and December 2014. A qualitative (analysis of color maps) and quantitative (SR) analysis of PMs and their associated LNs was performed. The accuracy of EUS elastography in identifying malignant PMs and LNs and cutoff value for SR were analyzed. A PM and/or its associated LNs were considered malignant based on histopathological findings from fine-needle aspiration biopsy samples.

RESULTS

A sample of 121 patients was included, 45.4% of whom were female. 69 (57.0%) PMs were histologically malignant, with a median SR of 50.4 *vs* 33.0 for malignant *vs* nonmalignant masses (P < 0.001). EUS evaluation identified associated LNs in 43/121 patients (35.5%), in whom 22/43 (51.2%) patients had histologically confirmed malignant diagnosis, with a median SR of 30 *vs* 40 for malignant *vs* nonmalignant LNs (P = 0.7182). In detecting malignancy in PMs, an SR cutoff value of > 21.5 yielded a sensitivity of 94.2%, while a cutoff value of > 121 yielded a specificity of 96.2.2%. There were significant differences in the Giovannini scores, a previously established elastic score system, between the patients grouped by their final histology results (P < 0.001). For LNs, SR cutoff values of > 14.0 and > 155 yielded a sensitivity of 90.9% and a specificity of 95.2%, respectively, in detecting malignancy.

CONCLUSION

EUS elastography is a helpful technique for the diagnosis of solid PMs and their associated LNs. The proposed SR cutoff values have a high sensitivity and specificity for the detection of malignancy.

Key Words: Ultrasound; Elastography; Pancreas; Lymph nodes; Neoplasm

Core Tip: This single-center retrospective study aimed to determine the diagnostic accuracy of endoscopic ultrasound (EUS) elastography in the diagnosis of pancreatic masses (PMs) and associated lymph nodes (LNs) with a defined strain ratio (SR) cutoff value in a Hispanic population. In determining if PMs were malignant, an SR cutoff value > 21.5 had a sensitivity of 94.2%, while a cutoff value > 121 had a specificity of 96.2.2%. For diagnosing LNs, an SR cutoff value > 14.0 had a sensitivity of 90.9%, while a cutoff value > 155 had a specificity of 95.2% for malignancy. The proposed SR cutoff values have high sensitivity and specificity for malignancy detection during EUS elastography.

Citation: Puga-Tejada M, Del Valle R, Oleas R, Egas-Izquierdo M, Arevalo-Mora M, Baquerizo-Burgos J, Ospina J, Soria-Alcivar M, Pitanga-Lukashok H, Robles-Medranda C. Endoscopic ultrasound elastography for malignant pancreatic masses and associated lymph nodes: Critical evaluation of strain ratio cutoff value. *World J Gastrointest Endosc* 2022; 14(9): 524-535
URL: https://www.wjgnet.com/1948-5190/full/v14/i9/524.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i9.524

INTRODUCTION

Pancreatic masses (PMs) include neoplastic and nonneoplastic lesions (*i.e.*, anatomical variants, inflammatory lesions). One of the essential tasks during the assessment of PMs is identifying their benign or malignant nature. Along with the identification of malignant lesions, the presence of involved lymph nodes (LNs) is a prognostic factor of the disease. To date, one of the most sensitive methods for detecting PMs is endoscopic ultrasound (EUS), which allows for the visualization of small lesions throughout the digestive tract; however, EUS has a limited capacity in accurately determining the malignant or nonmalignant nature of a lesion. In addition, EUS-guided fine-needle aspiration (EUS-FNA) provides a histological diagnosis for lesions suspicious of malignancy; nevertheless, this invasive technique has a false-negative rate of 25%[1].

These shortcomings have been addressed with EUS elastography, an additional imaging technique used to determine tissue hardness. Malignant tissue is often more rigid than the normal surrounding tissue; thus, EUS elastography can differentiate between malignant and nonmalignant lesions. As a result, this technique has been applied in the diagnostic workup of PMs and their associated LNs[2-4]. EUS elastography is considered an accurate imaging technique for characterizing and detecting pancreatic lesions[2].

EUS elastography can be used to evaluate PMs and their associated LNs through qualitative and quantitative analyses; the former involves the analysis of color maps, while the latter is achieved by assessing the strain ratio (SR). However, previous studies, such as the one published by Altonbary *et al* [4], have reported differences in the SR cutoff value and the optimal internal sensitivity and specificity, suggesting a potential limitation of this technique[3,4]. The accuracy of this technique in differentiating malignant from nonmalignant lesions has only been assessed for masses consisting of solid tissue. The suitability of EUS elastography for solid-cystic lesions, which comprise an important percentage of

pancreatic tumoral lesions, has not been reported.

Based on the above, through this retrospective study, we aim to determine the diagnostic accuracy of EUS elastography for diagnosing malignant PMs and LNs in a Hispanic cohort and define the SR cutoff values in this population, comparing the results with those obtained through FNA biopsy.

MATERIALS AND METHODS

Study design

This was an observational, analytic, retrospective, case-control study performed at the Instituto Ecuatoriano de Enfermedades Digestivas (IECED, Guayaquil, Ecuador) from December 2013 to December 2014. Consecutive Hispanic patients (≥ 18 years old) were referred for the evaluation of suspected PMs using EUS following computed tomography (CT) or magnetic resonance imaging (MRI). Patients with incomplete clinical records were excluded. The patients were allocated into two groups (malignant or nonmalignant) according to the histological findings of biopsy samples and results from a 6-mo clinical follow-up (*i.e.*, laboratory tests, imaging, and surgical findings). All participants or their legal guardians gave written informed consent before the procedure. The Institutional Review Board approved the use and management of the corresponding data, and the study was conducted in accordance with the Declaration of Helsinki.

EUS elastography

All procedures were performed by two expert endoscopists (CRM and RV), who perform ≥ 300 EUS procedures *per* year. The patients were examined under general anesthesia using a 3.8 mm working-channel linear-array echoendoscope (EG3870UTK, Pentax Medical, Pentax, Hamburg, Germany) attached to a Hitachi AVIUS Ultrasound Console (Avius Hitachi, Tokyo, Japan).

First, PMs or any associated LNs were examined under conventional B-mode scanning. Then, EUS elastography of the region of interest was performed using the ultrasound console. Tissue hardness was measured qualitatively and quantitatively in all regions of interest *via* EUS color maps and the SR, respectively. Subsequently, EUS-guided FNA was performed using a 22-gauge needle (Expect®, Boston Scientific, Marlborough, MA). A pathologist blinded to the EUS elastography results performed the histological analysis.

Scoring system

Two expert endoscopists (CRM and RV) performed the qualitative assessed by classifying the elastography images using the elastic score, as reported by Giovannini[3]. Giovannini elastic scores of 1 and 2 correspond to large green areas of soft and nonmalignant tissue; a score of 3 corresponds to a mainly blue area, considered a small adenocarcinoma; scores of 4 and 5 correspond to blue areas of hard and malignant tissue. For practical purposes, scores of 1 and 2 were considered nonmalignant lesions, whereas scores of 3, 4, and 5 were considered malignant lesions. Conventional EUS B-mode characteristics, such as size, shape, density, and ability to determine the border of suspicious lesions, were also recorded as part of the qualitative analysis. According to these factors, lesions with a size greater than 1 cm, irregular shape, anechoic density, or undefined borders were considered malignant[3-6].

The quantitative diagnosis was performed by calculating the *semiquantitative proportion* of tissue elasticity by measuring the SR of the region of interest. According to the method described by Iglesias-Garcia *et al*[6], at least three elasticity measurements for the mass lesion (A) and one for the surrounding area (B) were obtained. The corresponding SRs were then calculated by dividing B by each of the A values, and their mean was calculated[7]

Data collection

Baseline data were extracted from medical records. The location, size, diameter, and color pattern of PMs and their associated LNs on EUS elastography, SR, and histological diagnosis were thoroughly described. Malignancy in solid and solid-cystic PMs was defined following the Fukuoka Consensus Guidelines, as detailed in Table 1[5].

Statistical analysis

Technical considerations: All statistical analyses were performed by an institutional GI attending and biostatistician (MPT) with 8 years of experience, sing R v4.0 (R Foundation for Statistical Computing; Vienna, Austria). A P value < 0.05 was considered statistically significant.

Sample size: The sample size was estimated considering a 100% specificity for an SR > 6.04 on EUS elastography in predicting malignancy in solid PMs, with a corresponding disease prevalence of 67.4% [5], δ = 10%, and α- and β-errors of 5% and 20%, respectively. Using these parameters, a sample size of twenty-four cases and eleven controls was estimated, with 80% statistical power. To respect the central limit theorem (in which thirty observations are necessary to reach a Gaussian distribution), we aimed to analyze no fewer than thirty patients with malignant PMs during the study period.

Table 1 Classification of pancreatic lesions

	Malignant	Nonmalignant
Solid	Adenocarcinoma	Acute pancreatitis
	Lymphoma	Chronic pancreatitis
	PNETs	Adenoma
	Pancreatoblastoma	Insulinoma
	Metastatic cancer	
Solid-Cystic	Mucinous cystadenoma[1]	Serous cystadenoma
	Serous cystadenocarcinoma	
	Mucinous cystadenocarcinoma	
	IPMN[1]	

[1]Considered malignant if the Fukuoka criteria are met.

PNET: Pancreatic neuroendocrine tumor; IPMN: Intraductal papillary mucinous neoplasm.

Comparisons of baseline data, EUS, and EUS elastography diagnostic outcomes: Quantitative variables are described as the mean (standard deviation) or median (minimum-maximum range) according to their statistical distribution (Kolmogorov-Smirnov test). Qualitative variables are described as frequency (%). The potential differences in baseline data (*i.e.*, age, sex, PM location) and EUS elastography diagnostic outcomes between malignant and nonmalignant PMs and LNs were confirmed with statistical hypothesis testing and illustrated with a boxplot, when necessary. Associations of PM and LN SR with diameter were demonstrated through Spearman's rank correlation (rho).

EUS and EUS elastography qualitative analysis: The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of a Giovannini elastic score of 3 to 5 (cyan and dark blue) in predicting malignancy in PMs and their associated LNs were estimated. In the case of PMs, the subgroup analysis considered only solid PMs (excluding solid-cystic PMs). In the case of associated LNs, the sensitivity, specificity, PPV, NPV, and accuracy of conventional B-mode EUS criteria in predicting malignancy were also determined.

EUS elastography quantitative analysis: The sensitivity, specificity, PPV, NPV, and accuracy of SR measurements in predicting malignancy in PMs and their associated LNs were estimated. Subgroup analysis was also performed for only solid PMs (excluding solid-cystic PMs). In each situation, two internally derived SR cutoff values, one yielding the optimal sensitivity (and accuracy) and the other the optimal specificity, were calculated from the study data. We also calculated the corresponding areas under the receiver operating characteristic curve (AUROCs), in which AUROCs of 0.5 suggested a prediction of malignancy equivalent to chance, with values of 0.7 to 0.8 considered acceptable, 0.8 to 0.9 considered excellent, and more than 0.9 considered outstanding discriminability[6]. The corresponding ROC curves were also generated and compared using the *roc.test* function of the *pROC* (v1.16.2; Robin X, 2020) package when necessary.

RESULTS

A sample of 121 patients with previous CT or MRI scans for PMs underwent EUS evaluation and were enrolled in the study. In this cohort, 55/121 (45.5%) were female, and the median age was 67 years (13–99). There was a histologically confirmed diagnosis of malignancy in 69/121 (57%) patients who were allocated to the malignant group; the remaining patients were placed in the nonmalignant group. Additionally, 43/121 (35.5%) patients had associated LNs surrounding the gastrointestinal tract. The baseline data and EUS elastography diagnostic outcomes of the cohort are summarized in Table 2.

We compared both PM groups in terms of the variables obtained from the EUS elasticity qualitative and quantitative analyses. Regarding the qualitative outcomes, there were significant differences in the Giovannini scores between the patients grouped by their final histology results ($P < 0.001$). For the quantitative outcomes, there was a significant difference in the median SR between patients with malignant (50.4, range 7.8–22.5) and nonmalignant PMs (33.0, range 2.6–321.0) ($P < 0.001$). In the solid PM subgroup, the median SR values were 51.0 (7.8–225.0) and 21.9 (2.6–321.0), respectively (Figure 1). A proportionally significant association was demonstrated between a higher PM SR and a larger PM diameter (rho = 0.251, 95%CI: 0–0.481; $P = 0.05$).

Table 2 Baseline data and endoscopic ultrasound elastography diagnostic outcomes of pancreatic masses

	Malignancy (*n* = 69)	Nonmalignancy (*n* = 52)	*P* value
Age (yr), median (range)	67 (13–93)	68 (20–99)	0.8907[a]
Sex (female), *n* (%)	36 (52.2)	19 (36.5)	0.1271[b]
PM location, *n* (%)			0.6891[b]
Head	50 (72.5)	35 (67.3)	
Neck	3 (4.3)	4 (7.7)	
Body	13 (18.8)	12 (23.1)	
Tail	3 (4.3)	1 (1.9)	
PM diameter (mm), median (range)	37.0 (7.4–70.0)	30 (10.0–60.0)	0.0616[a]
Giovannini elastic score, *n* (%)			< 0.001[b]
Green (score 1 to 2)	-	11 (21.2)	
Cyan (score 3)	5 (7.2)	11 (21.2)	
Dark blue (score 4 to 5)	64 (92.8)	30 (57.7)	
Strain ratio, median (range)	50.4 (7.8–225.0)	33.0 (2.6–321.0)	< 0.001[a]
Firmness/histopathology, *n* (%)			< 0.001[b]
Solid-cystic masses (*n* = 36)	26/69	10/52	< 0.001[b]
Serous cystadenoma	-	10 (19.2)	
Mucinous cystadenoma	5 (7.2)	-	
Mucinous cystadenocarcinoma	3 (4.3)	-	
IPMN	18 (26.1)	-	
Solid masses (*n* = 85)	43/69	42/52	< 0.001[b]
Normal	-	4 (7.7)	
Acute pancreatitis	-	10 (19.2)	
Chronic pancreatitis	-	26 (50.0)	
Adenoma	-	1 (1.9)	
Insulinoma	-	1 (1.9)	
Adenocarcinoma	33 (47.8)	-	
Lymphoma	3 (4.3)	-	
PNETs	6 (8.7)	-	
Pancreatoblastoma	1 (1.4)	-	

[a]Mann-Whitney U test.
[b]Pearson Chi-Quadrat Test.
IPMN: Intraductal papillary mucinous neoplasm; PNET: Pancreatic neuroendocrine tumor; PM: Pancreatic masses.

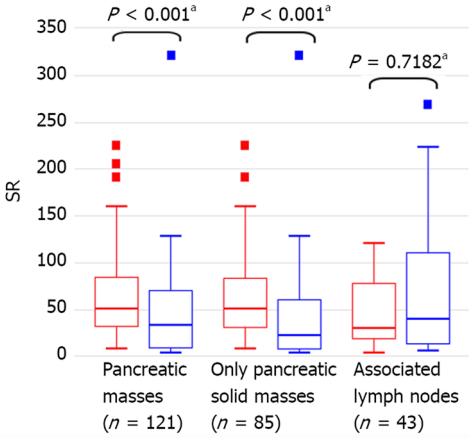
In detecting malignancies among all PMs, a Giovannini elastic score of 3 to 5 had a sensitivity, specificity, PPV, NPV, and accuracy of 100.0%, 21.2%, 62.7%, 100.0%, and 66.1%, respectively. For the subgroup of solid PMs, the corresponding sensitivity, specificity, PPV, NPV, and accuracy were 100%, 23.8%, 57.3%, 100%, and 62.4%, respectively (Table 3).

In the quantitative analysis, we found that optimal sensitivity and specificity values were obtained for SR cutoff values of 21.5 and 121.0, respectively, for both all PMs and solid PMs. The diagnostic accuracy parameters for both groups of PMs are shown in Table 3. Notably, in the overall PM analysis, the lower SR cutoff value (≥ 21.5) was associated with a higher sensitivity (94.2%) and NPV (84.0%), and the higher SR cutoff value (≥ 121.0) was associated with higher specificity (96.2%) and PPV (83.3%). A similar observation was made in the solid PM subgroup analysis; however, the SR cutoff value of ≥ 121.0 yielded higher accuracy in the subgroup analysis than in the overall PM analysis (54.1% *vs* 49.6%), while the SR cutoff of ≥ 21.5 yielded a lower accuracy (69.4% *vs* 71.1%). Additionally, the AUROC was slightly higher in the solid PM subgroup analysis (AUROC = 0.713) than in the overall PM analysis

Table 3 Qualitative and quantitative diagnostic accuracy of endoscopic ultrasound elastography for detecting malignant pancreatic masses: All lesions (*n* = 121) and only solid pancreatic masses (*n* = 85)

	EUS-elastography qualitative analysis		EUS-elastography quantitative analysis			
	All masses	Only solid pancreatic masses	All PMs		Only solid PMs	
			SR ≥ 21.5[1]	SR ≥ 121.0[2]	SR ≥ 21.5[1]	SR ≥ 121.0[2]
Sensitivity (%)	100.0	100.0	94.2	14.5	90.7	14.0
Specificity (%)	21.2	23.8	40.4	96.2	47.6	95.4
PPV (%)	62.7	57.3	67.7	83.3	63.9	70.0
NPV (%)	100.0	100.0	84.0	45.9	83.3	52.0
Accuracy (%)	66.1	62.4	71.1	49.6	69.4	54.1

[1]Internally derived optimal strain ratio (SR) cutoff for sensitivity (and accuracy).
[2]Internally derived optimal SR cutoff for specificity.
EUS: Endoscopic ultrasound; SR: Strain ratio; PPV: Positive predictive value; NPV: Negative predictive value; PM: Pancreatic masses.



DOI: 10.4253/wjge.v14.i9.524

Figure 1 Distribution of strain ratio values among malignant (red) and nonmalignant (blue) pancreatic masses and their associated lymph nodes. [a]Mann-Whitney U test. SR: Strain ratio.

(AUROC = 0.685) (*P* = 0.7073) (Figure 2A and B).

Among the 43 patients with associated LNs, the median age was 67.5 (39–95) years, and 14/43 (32.6%) were female. Histology confirmed malignancy in 22/43 (51.2%) patients, who were subsequently placed in the malignant group. There were no significant differences between the malignant and nonmalignant LN groups in LN location, diameter, EUS characteristics, Giovannini elastic score, or SR (Table 4). Specifically, the average SR was 30.0 (3.0–120.0) for malignant LNs and 40.0 (5.0–269.0) for nonmalignant LNs (*P* = 0.7182) (Figure 1). There was no association between LN SR and diameter (rho = -0.017, 95%CI: -0.503–0.421; *P* = 0.937).

Qualitative EUS elastography analysis yielded a sensitivity, specificity, PPV, NPV, and accuracy of 68.1%, 38.1%, 53.6%, 53.3%, and 53.5%, respectively; these values were lower than those obtained using the structural characteristics detected *via* conventional B-mode scanning (Table 5). For the PMs, we obtained two SR cutoff values by identifying the values that yielded optimal sensitivity and specificity. Specifically, an SR cutoff value of 14.0 yielded a sensitivity, specificity, PPV, NPV and accuracy of 90.0%, 28.6%, 51.4%, 75.0% and 60.4, respectively; the corresponding values for an SR cutoff value of 155.0 were 4.5%, 95.2%, 50.0%, 48.8% and 48.8% (Table 5). The use of SR for diagnosing malignancy yielded an AUROC of 0.417 (Figure 2C).

DISCUSSION

In the present study, we found that qualitative EUS elastography analysis was highly sensitive for solid PMs. Moreover, in the quantitative assessment, an SR cutoff value of ≥ 21.5 had a 90% sensitivity for

Table 4 Baseline data, endoscopic ultrasound, and endoscopic ultrasound elastography diagnostic outcomes of the associated lymph nodes

	Malignancy (*n* = 22)	Nonmalignancy (*n* = 21)	*P* value
Age (yr), median (range)	76 (57–95)	65 (39–85)	0.2037[a]
Sex (female), *n* (%)	8 (36.4)	6 (28.6)	0.5860[b]
LN location, *n* (%)			0.4250[b]
Esophagus	13 (59.1)	15 (71.4)	
Stomach	2 (9.1)	1 (4.8)	
Liver	1 (4.5)	-	
Pancreas	5 (22.7)	5 (23.8)	
Kidney	1 (4.5)	-	
LN diameter, median (range)	20.0 (4.0–50.0)	15.5 (7.0–21.6)	0.2662[a]
EUS-LN characteristics, *n* (%)			
Irregular shape	11 (50.0)	10 (47.6)	0.8760[b]
Undefined border	13 (59.1)	8 (38.1)	0.2730[b]
Anechoic density	7 (31.8)	3 (14.3)	0.1740[b]
Giovannini elastic score, *n* (%)			0.7970[b]
Green (score 1 to 2)	1 (4.5)	2 (9.5)	
Cyan (score 3)	6 (27.3)	6 (28.6)	
Dark blue (score 4 to 5)	15 (68.2)	13 (61.9)	
Strain ratio, median (range)	30.0 (3.0–120.0)	40.0 (5.0–269.0)	0.7182[a]
Histopathology, *n* (%)			< 0.001[b]
Acute lymphadenitis	-	10 (47.6)	
Chronic lymphadenitis	-	11 (52.4)	
Lymphoma	2 (9.1)	-	
Metastasis	20 (90.9)	-	

[a]Mann-Whitney U test.
[b]Pearson Chi-Quadrat Test.
EUS: Endoscopic ultrasound; LN: Lymph node.

defining malignancy in solid PMs (Figure 3). In contrast, a cutoff value of ≥ 121.0 had a 95% specificity for malignant PMs. For the evaluation of associated LNs, an SR of ≥ 14.0 had a 91% sensitivity, whereas an SR of ≥ 155.0 had a 95% specificity.

Various studies have shown the ability of EUS to distinguish between malignant and nonmalignant lesions. Itokawa *et al*[8] proposed that a Giovannini elastic score of 5 during EUS elastography evaluation is a characteristic of pancreatic malignancy[8,9], with 98.6% of patients having a score of five and a confirmed pancreatic malignancy. However, our study found that 91.4% of patients with malignant PMs had a score of 4 to 5.

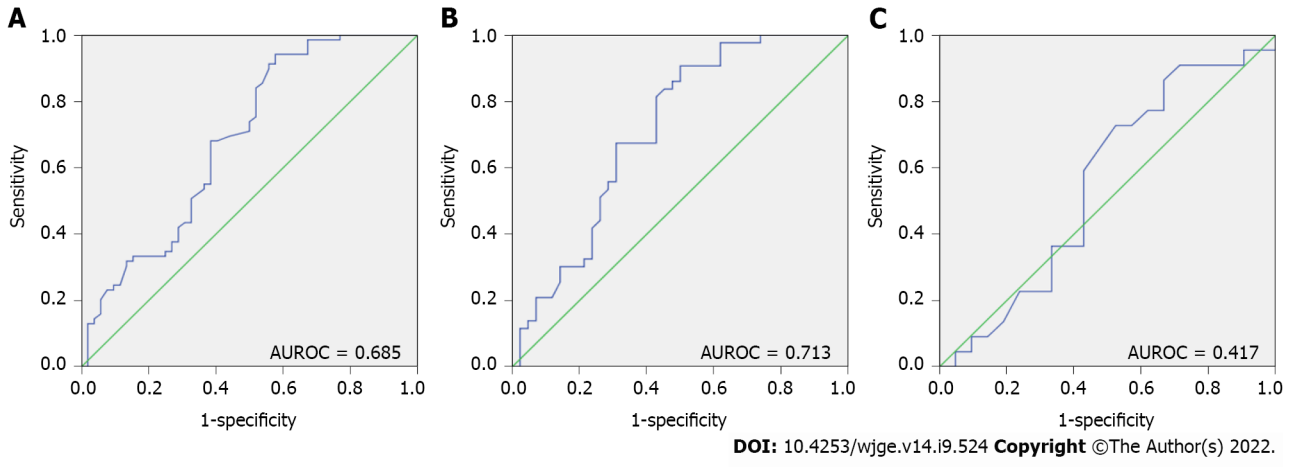
The qualitative elastic score had a high sensitivity of 100.0% in our study for solid and solid-cystic PMs. On the other hand, Itokawa *et al*[8] found that a considerable number of nonmalignant cases scored 5, decreasing the specificity of the elastic score to 64.3%[2]. Our study found a specificity of 21.15% for solid and solid-cystic PMs and 23.81% for solid masses alone. No malignant pancreatic lesions had an elastic score of 1 or 2 following Giovannini's classification. According to the qualitative analysis, our cases reported high sensitivity and NPV.

Iglesias-Garcia *et al*[6], in a prospective study of 86 patients, described one of the highest diagnostic accuracy values based on qualitative and quantitative EUS elastography analysis. For the qualitative measurements, the sensitivity, specificity, PPV, NPV, and overall accuracy were 100%, 71%, 87%, 100%, and 90%, respectively. For the quantitative values, a lower SR cutoff value of > 6.0 had a sensitivity, specificity, PPV, NPV, and overall accuracy of 100%, 92%, 96%, 100%, and 97%, respectively[6].

Table 5 Diagnostic accuracy of conventional B-mode endoscopic ultrasound and qualitative and quantitative endoscopic ultrasound elastography analysis for malignancy in the associated lymph nodes (*n* = 43)

	Conventional B-mode EUS				EUS-elastography qualitative analysis	EUS-elastography quantitative analysis	
	Size	Shape	Border	Density		SR ≥ 14.0[1]	SR ≥ 155.0[2]
Sensitivity (%)	59.1	50.0	59.1	31.8	68.1	90.9	4.5
Specificity (%)	42.9	52.4	61.9	85.7	38.1	28.6	95.2
PPV (%)	52.0	52.4	61.9	70.0	53.6	51.4	50.0
NPV (%)	50.0	50.0	59.1	54.6	53.3	75.0	48.8
Accuracy (%)	51.2	51.2	60.5	58.1	53.5	60.4	48.8

[1]Internally derived optimal strain ratio cutoff for sensitivity (and accuracy).
[2]Internally derived optimal cutoff for specificity.
EUS: Endoscopic ultrasound; SR: Strain ratio; PPV: Positive predictive value; NPV: Negative predictive value.



DOI: 10.4253/wjge.v14.i9.524

Figure 2 Areas under the receiver operating characteristic curve. A: Areas under the receiver operating characteristic curve (AUROC) of the strain ratio in the detection of malignancy in pancreatic masses [AUROC = 0.685 (0.586–0.783)], B: AUROC of the strain ratio in the detection of malignancy in only solid pancreatic masses [AUROC = 0.713 (0.602–0.825)]; C: AUROC of the strain ratio in the detection of malignancy in associated lymph nodes [AUROC = 0.417 (0.076–0.757)]. There was no significant difference between AUROC–A and AUROC–B (*P* = 0.7073). AUROC: Areas under the receiver operating characteristic curve.

Dawwas *et al*[10] obtained a higher diagnostic accuracy for EUS elastography using an SR cutoff value of 4.65 to achieve a 100% sensitivity and a cutoff value of 59.25 to achieve a 100% specificity. Okasha *et al*[11] concluded that the best SR cutoff level was 7.8, which gave a sensitivity of 92%, a specificity of 77%, a PPV of 91%, an NPV of 80%, and an accuracy of 88%[11]. Our study achieved a higher sensitivity using a lower cutoff value. Actors such as tissue inflammation, fibrosis, necrosis, advanced age, or ethnicity may affect the hardness of tissue, explaining the difference in the cutoff values proposed in the literature[12-14]. Moreover, the size of the region of interest and tissue compression level could affect the quantitative evaluation of EUS elastography.

Additionally, a study published by Kongkam *et al*[15] showed that a cutoff SR level of 3.17 along with EUS-FNA provided a sensitivity, specificity, PPV, NPV and accuracy of 95.2%, 71.4%, 90.9%, 83.3%, and 89.3%, respectively, compared to the 90%, 100%, 100% 80% and 92.8% of EUS elastography alone. Based on these results, the authors raised the possibility of a future combination of both techniques for evaluating PMs[15].

Paterson *et al*[12] focused their research on the utility of quantitative EUS elastography analysis for defining malignancy in the LNs related to esophageal and gastric cancer and compared this approach to an analysis using conventional EUS LN features. Compared to our results, they found a lower diagnostic accuracy for conventional EUS but a higher diagnostic accuracy for EUS elastography[12].

The present study has several limitations, including its retrospective design and single-center nature, leading to a limited number of operators. A few patients from the malignant case group underwent surgery, limiting the histological description of this research. The nonmalignant control group was defined as patients with nonmalignant masses instead of a healthy population. However, this study has

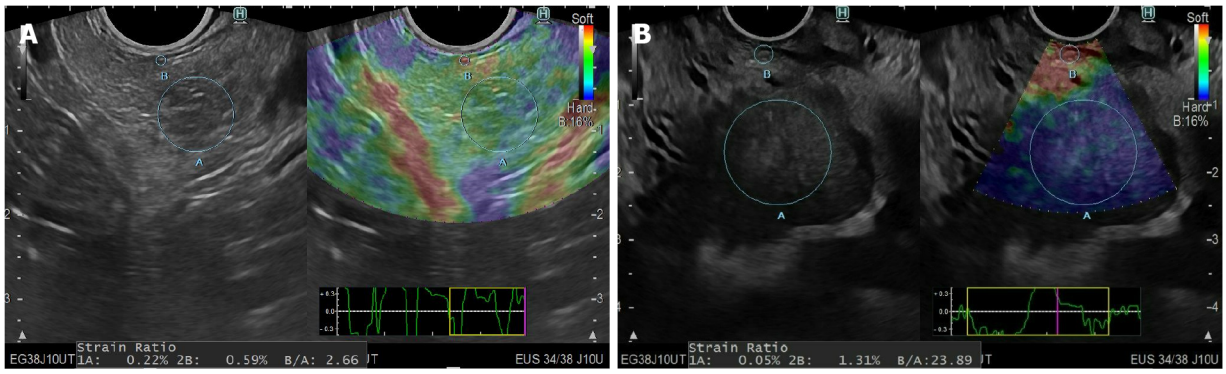


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Figure 3 Quantitative and qualitative endoscopic ultrasound elastography assessment. A: Case No. 84: A 26-year-old women with a pancreatic mass. A plain B-mode image (left) and a color-code strain image (right) are shown, strain ratio (SR) = 2.66, Giovannini elastic score of 2 (green). Biopsy confirmed chronic pancreatitis; B: Case No. 73: A 46-year-old man with a pancreatic mass. A plain B-mode image (left) and a color-coded strain image (right) are shown, SR = 23.8, Giovannini elastic score of 4 (dark blue). Biopsy confirmed pancreatic adenocarcinoma.

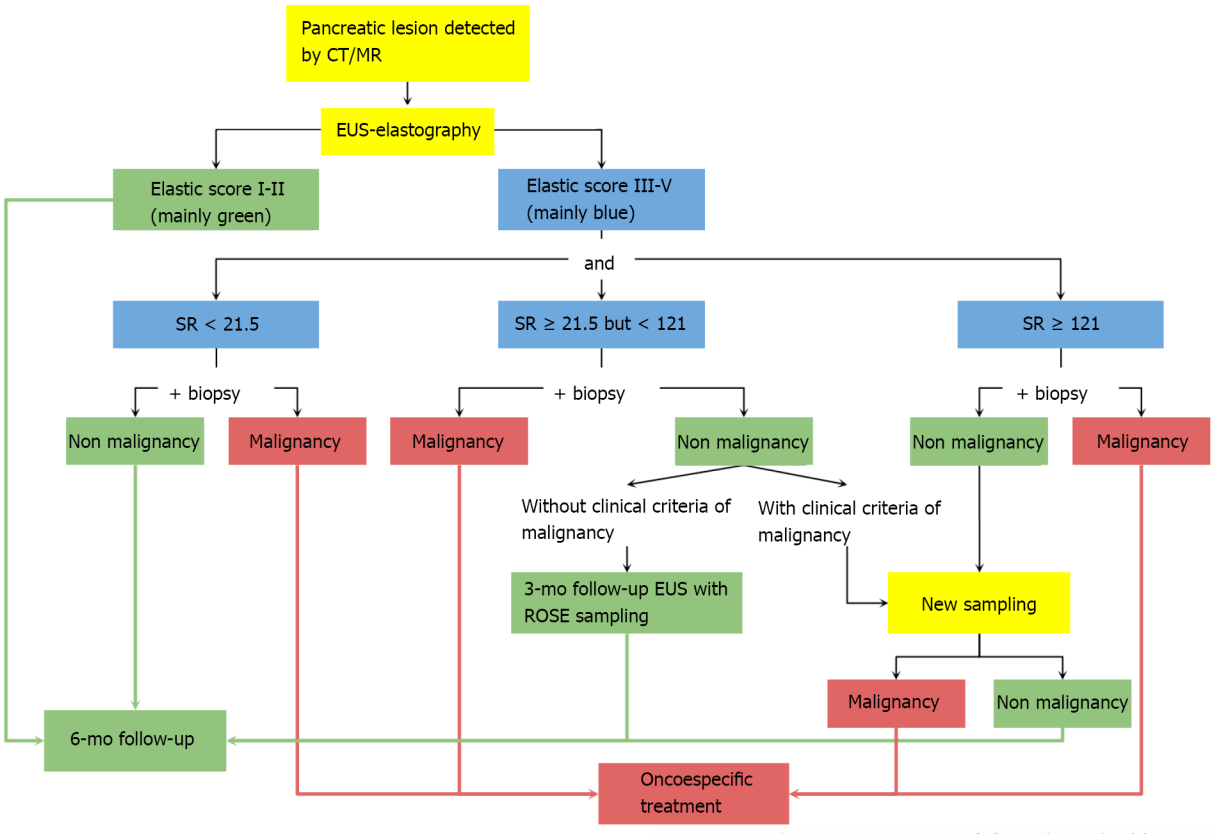

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Figure 4 Proposed algorithm for the workup of pancreatic masses. SR: Strain ratio; EUS: Endoscopic ultrasound; CT: Computed tomography; MR: Magnetic resonance.

the advantage of using the qualitative elastic score proposed by Giovannini[3]. For the interpretation of PMs and their associated LNs, instead of the 4-score by Furukawa *et al*[16], and may be one of the first studies to evaluate the utility of EUS elastography in Hispanic patients. Future research on this topic will be designed as diagnostic trials, considering the Giovannini score for PMs and associated LN descriptions.

Finally, hard PMs are not necessarily malignant all the time, whereas soft lesions are not necessarily nonmalignant[2,17]. Therefore, a validated cutoff value for defining malignancy in PMs and their associated LNs is imperative for obtaining an appropriate diagnosis and providing management guidance. Based on our findings, we recommend an SR cutoff values of > 121.0 and > 155.0 as criteria for supporting the need for FNA sampling of pancreatic lesions or their associated LNs, respectively. In

patients with SR values ranging from 21.5-121.0 and 14.0-155.0, sampling should be indicated if there is a high clinical suspicion of malignancy. Figure 4 shows a proposed clinical algorithm using EUS elastography evaluations. We recommend starting with a qualitative measurement. For those with a low risk of malignancy (elastic score I-II), a 6-mo follow-up is necessary. However, for those with an elastic score between 3 and 5, a quantitative evaluation is required to define the SR measurement and determine the necessity of FNA and whether a malignancy is suspected.

CONCLUSION

We found that EUS combined with qualitative and quantitative elastography analysis *via* SR is a helpful resource when assessing PMs and their associated LNs. This approach is more effective and convenient than limiting the evaluation to only conventional EUS-fine needle aspiration for the detection of malignancy. Although histological analysis is mandatory for a final diagnosis, elastography should be included in the diagnostic workup of PMs and their associated LNs. However, validating this recommendation through a prospective, multi-center, controlled trial is preferable.

ARTICLE HIGHLIGHTS

Research background

Endoscopic ultrasound (EUS) elastography can be a useful technique for the evaluation of pancreatic masses (PMs) and their associated lymph nodes (LNs) through qualitative (analysis of color maps) and quantitative (assessing the strain ratio).

Research motivation

The accuracy of this technique in differentiating malignant from nonmalignant lesions has only been assessed for masses consisting of solid tissue. For the evaluation of solid-cystic lesions, the suitability of EUS-elastography has not been reported.

Research objectives

To determine the diagnostic accuracy of EUS elastography and the strain ratio (SR) cutoff value for malignant PMs and LNs in a Hispanic cohort.

Research methods

A retrospective study of patients who underwent EUS elastography for PMs between December 2013 and December 2014. A qualitative and quantitative (SR) analysis of PMs and their associated LNs was performed. The accuracy of EUS elastography in identifying malignant PMs and LNs and cutoff value for SR were analyzed. A PM and/or its associated LNs were considered malignant based on histopathological findings from fine-needle aspiration biopsy samples.

Research results

Malignant PMs have a superior median SR compared to nonmalignant lesions (50.4 *vs* 33.0, respectively) ($P < 0.001$). When analyzing LNs, there was no statistical significance (SR 30.0 for PMs *vs* 40.0 for LNs) ($P = 0.7182$). An SR cutoff value > 21.5 in PMs yielded a 94.2% sensitivity. Meanwhile, an SR cutoff value > 14.0 yielded a 90.9% sensitivity.

Research conclusions

The proposed EUS elastography SR cutoff values have a high sensitivity and specificity for the detection of malignancy.

Research perspectives

Future research evaluating the utility of EUS elastography in Hispanic patients through a prospective, multi-center, controlled trial is necessary to validate our data.

FOOTNOTES

Author contributions: Puga-Tejada M and Oleas R performed design of the work, acquisition, analysis, and interpretation of data, drafting and critical revision of the manuscript for important intellectual content, and final approval of the version to be published; Del Valle R, Egas-Izquierdo M, Ospina J and Soria-Alcivar M contributed to the acquisition of data for the work, critical revision of the manuscript for important intellectual content, and final approval of the version to be published; Egas-Izquierdo M performed the final database consolidation and

encryption; Arevalo-Mora M and Baquerizo-Burgos J contributed to the acquisition and analysis of data, drafting the manuscript, and final approval of the version to be published; Pitanga-Lukashok H contributed to the conception and design of the work, critical revision of the manuscript for important intellectual content, and final approval of the version to be published; Robles-Medranda C contributed to the conception and design of the work, drafting and critical revision of the manuscript for important intellectual content, and final approval of the version to be published.

Institutional review board statement: The Institutional Review Board approved the use and management of the corresponding data, No. 11-01-02103.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

Conflict-of-interest statement: Carlos Robles-Medranda is a key opinion leader and consultant for Pentax Medical, Boston Scientific, Steris, Medtronic, Motus, Microtech, G-Tech Medical Supply, CREO Medical, EndoSound, and Mdconsgroup. The other authors declare no conflicts of interest.

Data sharing statement: The Institutional Review Board approved the use and management of the corresponding data, and the study was conducted in accordance with the Declaration of Helsinki.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

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World Journal of Gastrointestinal Endoscopy

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World J Gastrointest Endosc 2022 September 16; 14(9): 536-546

DOI: 10.4253/wjge.v14.i9.536

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Screening for hilar biliary invasion in ampullary cancer patients

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Costache RS, Romania; Dhaliwal A, United States; Li HL, China

Received: January 5, 2022
Peer-review started: January 5, 2022
First decision: June 16, 2022
Revised: June 28, 2022
Accepted: August 7, 2022
Article in press: August 7, 2022
Published online: September 16, 2022

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Abstract

BACKGROUND

The treatment for ampullary cancer is pancreatoduodenectomy or local ampullectomy. However, effective methods for the preoperative investigation of hilar biliary invasion in ampullary cancer patients have not yet been identified.

AIM

To determine the necessity of and an appropriate method for investigating hilar biliary invasion of ampullary cancer.

METHODS

Among 43 ampullary cancer patients, 34 underwent endoscopic treatment (n = 9) or surgery (n = 25). The use of imaging findings (thickening and enhancement of the bile duct wall on contrast-enhanced computed tomography, irregularity on endoscopic retrograde cholangiography, thickening of the entire bile duct wall on intraductal ultrasonography (IDUS), and partial thickening of the bile duct wall on IDUS) and biliary biopsy results for diagnosing hilar biliary invasion of ampullary cancer was compared.

RESULTS

Hilar invasion was not observed in every patient. Among the patients who did not undergo biliary stent insertion, the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results showed the highest accuracy (100%) for diagnosing hilar biliary invasion. However, each imaging method and biliary biopsy yielded some false-positive results.

CONCLUSION
Although some false-positive results were obtained with each method, the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results was useful for diagnosing hilar biliary invasion of ampullary cancer. However, hilar invasion of ampullary cancer is rare; therefore, the investigation of hilar biliary invasion of ampullary cancer might be unnecessary.

Key Words: Ampullary cancer; Biliary biopsy; Contrast-enhanced CT; Hilar biliary invasion; Intraductal ultrasonography

Core Tip: The standard treatment for ampullary cancer is surgical resection. However, the necessity of and appropriate diagnostic method for assessing hilar invasion is unknown. In this study, the use of contrast-enhanced computed tomography, endoscopic retrograde cholangiography, intraductal ultrasonography (IDUS), and biliary biopsy for diagnosing hilar invasion of ampullary cancer was compared. Although false positives were observed for each method, the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results was efficient for accurately diagnosing hilar invasion of ampullary cancer. On the other hand, hilar invasion of ampullary cancer is rare; thus, hilar biliary investigation might be unnecessary.

Citation: Takagi T, Sugimoto M, Suzuki R, Konno N, Asama H, Sato Y, Irie H, Nakamura J, Takasumi M, Hashimoto M, Kato T, Kobashi R, Yanagita T, Hashimoto Y, Marubashi S, Hikichi T, Ohira H. Screening for hilar biliary invasion in ampullary cancer patients. *World J Gastrointest Endosc* 2022; 14(9): 536-546
URL: https://www.wjgnet.com/1948-5190/full/v14/i9/536.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i9.536

INTRODUCTION

The standard treatment for ampullary cancer is pancreatoduodenectomy. In addition, local surgical resection of the ampulla or endoscopic ampullectomy has been recently performed for ampullary cancer that does not invade the sphincter of Oddi[1-6]. To perform these treatments, an accurate assessment of the extent of biliary invasion is important. Although ampullary lesions show ductal invasion[7-9], hilar biliary invasion by ampullary lesions has not been reported. When a tumor advances to the hilar biliary duct, the extent of resection is modified accordingly.

The efficacy of contrast-enhanced computed tomography (CECT), endoscopic retrograde cholangiography (ERC), and intraductal ultrasonography (IDUS) for diagnosing the horizontal progression of bile duct cancer has been reported[10-15]. The diagnostic accuracy of CECT for lateral extension of hilar biliary cancer has been reported to be 71%-96%[13,14,16-23]. In addition, ERC following IDUS has been reported to be useful for diagnosing lateral extension of biliary ductal cancer[24-27]. The diagnostic accuracy of mapping biopsy for lateral extension of biliary ductal cancer has been reported to be 73.0%-89.0%[28-31]. However, whether these methods are effective for investigating hilar invasion in ampullary cancer patients is unknown. In this study, we aimed to reveal the best method for diagnosing hilar invasion in ampullary cancer patients.

MATERIALS AND METHODS

Study design and ethics

This retrospective study aimed to identify an appropriate screening method for hilar biliary invasion of ampullary cancer. This study was approved by the Institutional Review Board of Fukushima Medical University (approval number: 2453).

Patients

This study enrolled 43 ampullary cancer patients who were treated at Fukushima Medical University between September 2009 and December 2020. Among them, 34 patients underwent resection by endoscopic treatment (n = 9) or surgery (n = 25) (Table 1). Endoscopic ampullectomy was performed when invasion into the muscular layer or bile and pancreatic ducts was not observed by ERC or IDUS. It was not necessary to obtain informed consent from the patients because this study was retrospective in design and used previously anonymized clinical data. All the patients agreed to the clinical examination and treatment by providing written consent; in the case of participants under 18 years of age, consent was obtained from a parent and/or legal guardian. The details of the study can be found on the homepage of Fukushima Medical University. All methods were carried out in accordance with relevant guidelines and regulations.

Examination items

The final diagnosis of hilar biliary invasion was determined according to histological diagnosis and the nonexistence of local recurrence during follow-up for more than six months. When the horizontal margin of the resected specimen was negative, hilar invasion was considered negative.

Useful methods for diagnosing hilar invasion were investigated in 34 ampullary cancer patients who underwent endoscopic therapy or surgery. The assessed imaging findings of hilar biliary invasion were thickening and enhancement of the bile duct wall on CECT (Figure 1A), irregularity on ERC (Figure 1B), thickening of the entire bile duct wall on IDUS (Figure 1C), and partial thickening of the bile duct wall on IDUS (Figure 1D). The usefulness of hilar biliary biopsy was also considered. Thickening of the bile duct wall on IDUS was defined as a diameter of the bile duct wall greater than 2 mm.

All imaging findings were evaluated by more than two pancreaticobiliary disease specialists. Endoscopic retrograde cholangiopancreatography (ERCP) was performed as follows. With the patient in a prone position, a duodenoscope was inserted after sufficient sedation was achieved with midazolam. When the duodenoscope reached the Vater papilla, biliary cannulation was initiated. Tumor progression was evaluated by using ERC, IDUS, and hilar biliary biopsy. It is difficult to observe the whole circumference of the bile duct wall by EUS. Therefore, the evaluation of hilar invasion by EUS was not considered in this study.

JF260 V, JF240, and TJF240 duodenoscopes (Olympus, Tokyo, Japan) were used. An MTW ERCP tapered catheter (MTW Endoskopie, Wesel, Germany) and Tandem XL cannula (Boston Scientific Japan, Tokyo, Japan) were used as the ERC catheters. Endo Jaw FB231K (Olympus) or Radial Jaw™ 4 Biopsy Forceps (Boston Scientific Japan) were used for biliary biopsy.

Post-ERC pancreatitis (PEP) and adverse events were diagnosed according to Cotton's criteria[32]. PEP was defined as an elevated serum amylase level more than three times the normal upper limit with abdominal pain for more than 24 h after ERC. In addition, all PEP patients were confirmed to have peripancreatic inflammation by CECT. The severity of PEP was categorized as follows: mild: extended hospitalization for 2-3 d; moderate: extended hospitalization for 4-10 d; and severe: Extended hospitalization for more than 10 d, hemorrhagic pancreatitis, and pseudocysts that required intervention. The severity of bleeding was categorized as follows: Mild: Clinical evidence of bleeding, hemoglobin decrease < 3 g/dL, and no need for transfusion; moderate: Transfusion (4 units or less) and no angiographic intervention or surgery; and severe: Transfusion (5 units or more) or intervention (angiographic or surgical).

Statistical analyses

The imaging findings and biliary biopsy results were compared with respect to their ability to diagnose hilar invasion of ampullary cancer by Fisher's exact test. The Bonferroni method and Holm method were used to adjust for multiple comparisons. EZR (Saitama Medical Centre, Jichi Medical University, Saitama, Japan) was used for statistical analysis. A P value < 0.05 was considered indicative of a significant difference.

RESULTS

Patient characteristics and treatment

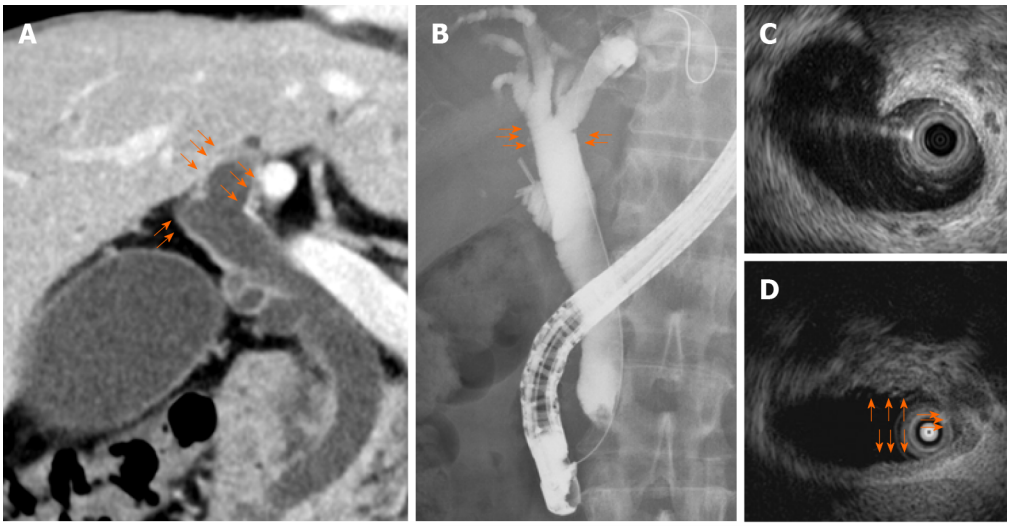
The patient characteristics and treatment results are shown in Table 1. The mean age of the patients was 68.0 ± 11.1 years. There were 20 male patients and 14 female patients. The numbers of the different lesion stages were as follows: I: 16; II: 8; and III: 10. Disease stage was classified according to the Union for International Cancer Control classification 8th edition[33]. Four patients had already undergone biliary stent insertion in other hospitals. No histological hilar biliary invasion or local recurrence was observed in any patient.

Imaging findings and biopsy results of all patients

Among the methods explored for diagnosing hilar biliary invasion of ampullary cancer, hilar biliary

Table 1 Patient characteristics and treatment

Parameter	
Total patients, *n*	43
Unresectable or treated in other hospitals, *n*	9
Underwent resection, *n*	34
Age, yr (mean ± standard deviation)	68.0 ± 11.1
Sex, *n* (male/female)	20/14
UICC stage 8th edition, *n*	
I	16
II	8
III	10
Patients already having biliary stents, *n*	4
Treatment, *n*	
Endoscopic ampullectomy	9
Surgery	25
Hilar biliary invasion, *n*	0
Local recurrence, *n*	0



DOI: 10.4253/wjge.v14.i9.536

Figure 1 Imaging findings of the hilar biliary duct. A: Thickening and enhancement of the bile duct wall on contrast-enhanced computed tomography; B: Irregularity on endoscopic retrograde cholangiography; C: Thickening of the entire bile duct wall on intraductal ultrasonography (IDUS); D: Partial thickening of the bile duct wall on IDUS.

irregularity on ERC showed the highest diagnostic accuracy (thickening and enhancement of the bile duct wall on CECT: 53.1% (17/32); irregularity on ERC: 89.7% (26/29); thickening of the entire bile duct wall on IDUS: 87.5% (21/24); partial thickening of the bile duct wall on IDUS 87.5% (21/24), biliary biopsy results 72.7% (8/11), *P* value < 0.01) (Figure 2A). The diagnostic accuracy of irregularity on ERC for hilar invasion of ampullary cancer was significantly higher than that of thickening and enhancement of the bile duct wall on CECT (*P* value = 0.02).

Comparisons of the various combinations [imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion revealed that the diagnostic accuracies of irregularity on ERC + biliary biopsy results (96.7% (29/30)], thickening of the entire bile duct wall on IDUS + biliary biopsy results [95.8% (23/24)], and partial thickening of the bile duct wall on IDUS + biliary biopsy results [95.8% (23/24)] were significantly higher than that of thickening and enhancement of the bile duct wall on CECT + biliary biopsy results [62.5% (20/32), *P* value < 0.01, = 0.02, and = 0.02, respectively] (Figure 2B).

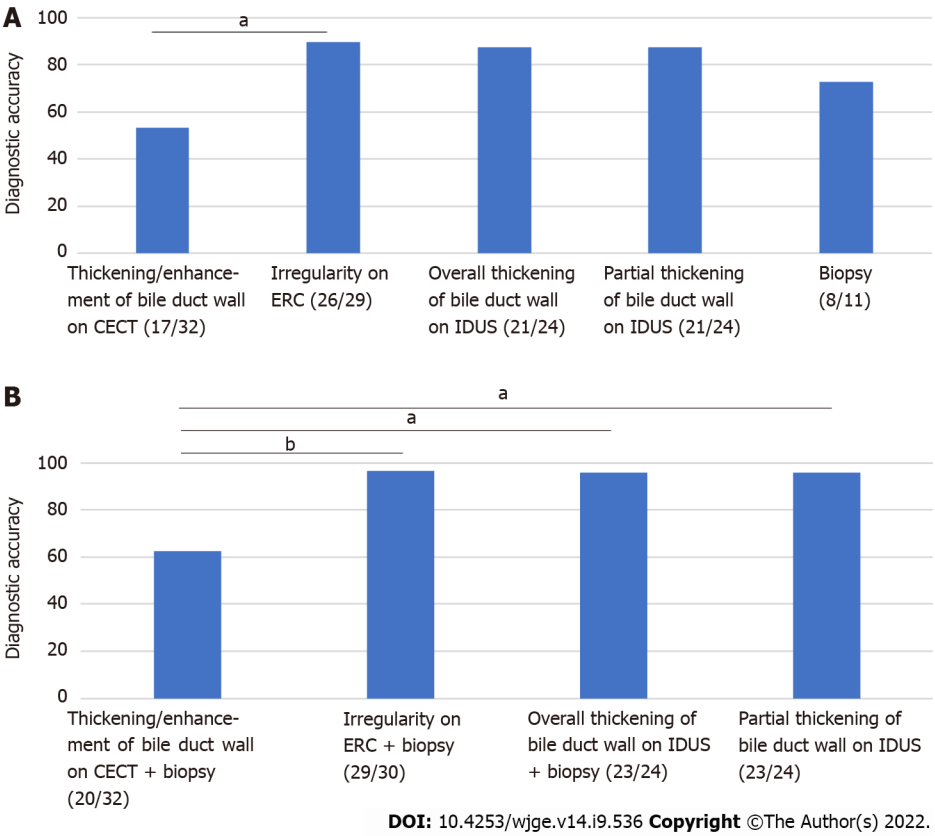


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Figure 2 Comparison of methods for diagnosing hilar biliary invasion of ampullary cancer in all patients. A: Irregularity on endoscopic retrograde endoscopic retrograde cholangiography (ERC) showed the highest diagnostic accuracy; B: Among the various combinations (imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion, irregularity on ERC + biliary biopsy results showed the highest diagnostic accuracy. [a]*P* < 0.05, [b]*P* < 0.01. CECT: Contrast-enhanced computed tomography; ERC: Endoscopic retrograde cholangiography; IDUS: Intraductal ultrasonography.

Imaging findings and biopsy of patients who had not received biliary duct stents

Partial thickening of the bile duct wall on IDUS showed the highest diagnostic accuracy among the explored methods (thickening and enhancement of the bile duct wall on CECT: 57.1% (16/28); irregularity on ERC: 88.0% (22/25); thickening of the entire bile duct wall on IDUS: 84.2% (16/19); partial thickening of the bile duct wall on IDUS 89.5% (17/19); biliary biopsy: 66.7% (6/9); *P* value < 0.035 but no significant differences in pairwise comparisons) (Figure 3A).

Among the investigated combinations (imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion of ampullary cancer, the combination of partial thickening of the bile duct on IDUS and biliary biopsy results showed the highest diagnostic accuracy (thickening and enhancement of the bile duct wall on CECT + hilar biliary biopsy results: 64.3% (18/28); irregularity on ERC + biliary biopsy results: 96.2% (25/26); thickening of the entire bile duct wall on IDUS + biliary biopsy results: 95.0% (19/20); partial thickening of the bile duct wall on IDUS + biliary biopsy results: 100% (20/20); *P* value < 0.01) (Figure 3B). The combination of irregularity on ERC and biliary biopsy results and the combination of partial thickening of the bile duct wall on IDUS and biliary biopsy results each had a significantly higher diagnostic accuracy for hilar biliary invasion of ampullary cancer than the combination of thickening and enhancement of the bile duct wall on CECT and biliary biopsy results (*P* value = 0.027, 0.017).

Adverse events

The adverse events are listed in Table 2. Postendoscopic ampullectomy bleeding occurred in two patients. Both patients improved with endoscopic hemostasis and transfusion. PEP occurred in three patients, all of whom improved with conservative treatment.

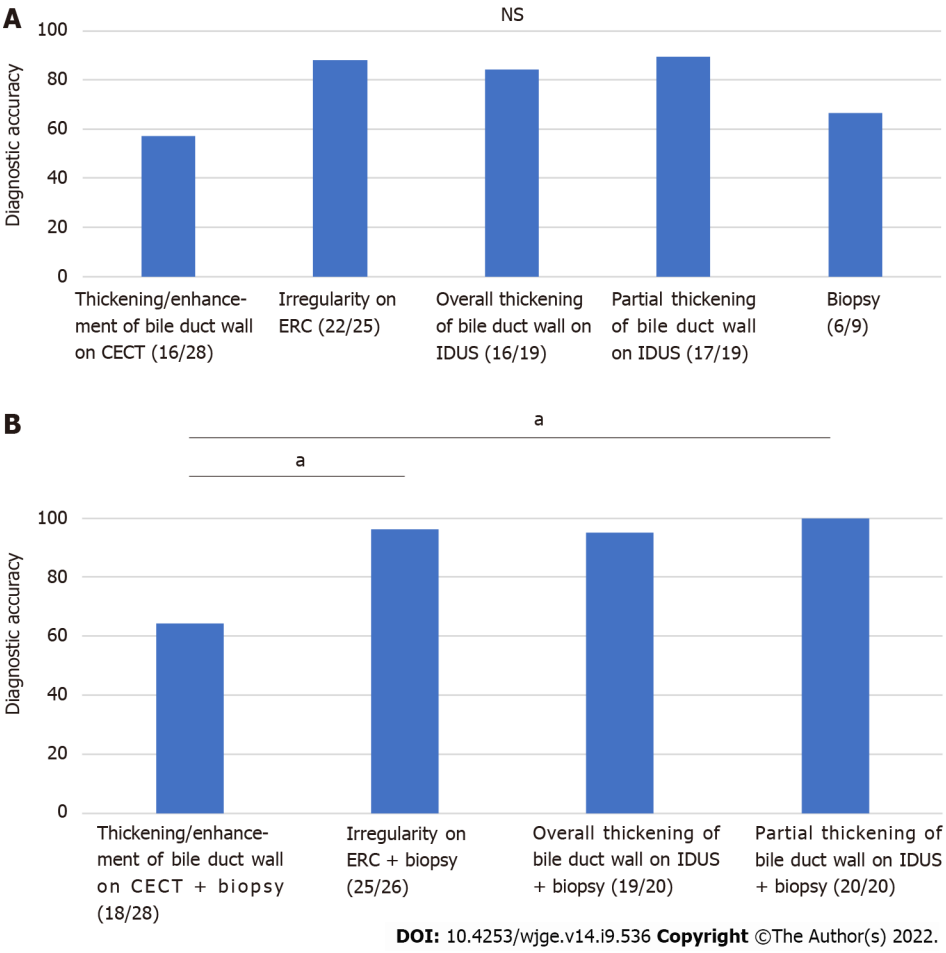
DISCUSSION

In this study, we investigated appropriate methods for diagnosing hilar biliary invasion of ampullary cancer. Hilar biliary invasion was not observed in all ampullary cancer patients. Although some false-positive results were obtained with each method, the diagnostic accuracy of the combination of partial

Table 2 Adverse events of treatment

Adverse event	*n*
Post-endoscopic ampullectomy bleeding	
Mild	0
Moderate	2
Severe	0
Post-ERC pancreatitis	
Mild	0
Moderate	3
Severe	0

ERC: Endoscopic retrograde cholangiography.



DOI: 10.4253/wjge.v14.i9.536

Figure 3 Comparison of methods for diagnosing hilar biliary invasion of ampullary cancer in patients without biliary stents. A: Partial thickening of the bile duct wall on IDUS showed the highest diagnostic accuracy; B: Among the various combinations (imaging findings and biliary biopsy results) for diagnosing hilar biliary invasion, partial thickening of the bile duct wall on IDUS + biliary biopsy results showed the highest diagnostic accuracy. [a]*P* < 0.05. CECT: Contrast-enhanced computed tomography; ERC: Endoscopic retrograde cholangiography; IDUS: Intraductal ultrasonography; NS: Not significant.

thickening of the bile duct wall on IDUS and hilar biliary biopsy results for hilar biliary invasion was 100% for patients without biliary stents. On the other hand, thickening and enhancement of the hilar bile duct wall on CECT was not effective for diagnosing this condition.

Ampullary cancer occasionally develops concurrently with upstream biliary ductal cancer[34,35]. However, as described in the introduction, hilar biliary invasion of resectable ampullary cancer has rarely been reported. In fact, hilar invasion of ampullary cancer was not observed in this study. In past reports that have described the results of treatment or surgery for ampullary cancer, pancreaticobiliary

type, lymph node metastasis, advanced T stage, and large tumors were identified as risk factors for poor prognosis[36-41]. Hilar biliary invasion was not listed as a risk factor in these reports. Taking the risk of PEP into consideration, it is possible that investigation of hilar biliary invasion in ampullary cancer is not necessary.

Thickening of the bile duct wall on CECT has been reported in cholestasis caused by several diseases (for example, cholangitis, common bile duct stones, pancreatitis and malignant biliary stricture)[42]. In a past systematic review and meta-analysis, the diagnostic accuracy of computed tomography (CT) for assessing the extent of bile duct invasion was 64%-96%[13]. In this study, the diagnostic accuracy of CECT for assessing hilar biliary invasion of ampullary cancer was lower than that reported in a previous meta-analysis. Regarding the CECT findings of ampullary cancer, papillary bulging and organ invasion have been identified as predictive factors of tumor recurrence or poor survival[43]. However, hilar bile duct wall thickness was not mentioned in the associated study. Thickening and enhancement of the hilar bile duct wall on CECT was not useful. It is thought that ampullary cancer exists at the exit of the bile duct and that the tumors more often close the biliary duct than other biliary diseases. This closure leads to thickening of the hilar bile duct wall; however, in this study, ampullary cancer did not invade the hilar bile duct.

The diagnostic accuracy of IDUS was higher among those patients without biliary stents. Biliary drainage can cause thickening of the bile duct wall, and IDUS should be performed before biliary drainage. Thickening on the cancerous portion of the bile duct wall has been reported to be heterogeneous and partially protruded[24-27,44]. In this study, partial thickening of the bile duct wall on IDUS showed the best accuracy among the investigated methods for diagnosing hilar invasion of ampullary cancer in patients without a biliary stent. Naitoh *et al*[45] reported that bile duct wall thickening in the nonstricture region was unremarkable in bile duct cancer patients. However, false-positive cases (diameter of the hilar bile duct wall from 2-3.3 mm) were observed in this study. Therefore, the evaluation of the nonstricture portion on IDUS in patients with ampullary cancer is not believed to be equivalent to that in patients with common bile duct cancer. Therefore, the detection of partial thickening of the bile duct wall should be combined with other methods.

False-positive hilar biliary biopsy results were found in three cases. Although this number is low, such results might influence the operative method. Therefore, false positives in hilar biliary biopsy should be avoided. Regarding the reason for these false positives, it is highly likely that biopsy forceps contact the ampullary cancer. The efficacy of cholangioscopy in diagnosing biliary lesions has been reported[46-56]. However, passing the ampullary cancer is difficult with cholangioscopy. To avoid contact of the biopsy forceps with the tumor and to improve the diagnostic accuracy of hilar biliary biopsy for ampullary cancer patients, biliary biopsy with a catheter that introduces biopsy forceps could be useful[30,31]. When biliary biopsy with a catheter is unavailable, the combination of biliary biopsy and IDUS should be considered.

This study has some limitations. First, this was a retrospective study performed at a single institution. A multicenter prospective study is needed to verify the results of this study. Second, a few patients underwent all examinations (CECT, ERC, IDUS, and biliary biopsy). In future studies, a higher number of cases would be desirable. Third, as described above, ampullary cancer patients with hilar biliary invasion were not included in this study. To improve the false-negative rate, a study involving cases of hilar biliary invasion is needed.

CONCLUSION

Although false-positive results were obtained with each method, the combination of partial thickening of the bile duct on IDUS and biliary biopsy results was useful for diagnosing hilar biliary invasion of ampullary cancer. In addition, it is recommended that hilar biliary biopsy be performed through a catheter to avoid contamination from the cancer. However, hilar invasion of ampullary cancer is rare, and the risk of PEP from hilar investigation exists. Therefore, hilar investigation might be unnecessary for ampullary cancer patients.

ARTICLE HIGHLIGHTS

Research background

The standard treatment for ampullary cancer is pancreaticoduodenectomy or focal ampullectomy. Before resection, it is important to accurately diagnose the biliary invasion of ampullary cancer. However, the method that accurately evaluates hilar invasion of ampullary cancer is unknown.

Research motivation

Several methods [contrast-enhanced computed tomography (CECT), endoscopic retrograde cholangiography (ERC), intraductal ultrasonography (IDUS), biliary biopsy] can be used to diagnose the range

of ampullary cancer invasion. However, detailed data of these methods for diagnosing the biliary invasion range of ampullary cancer have not been previously reported. Therefore, presurgical examination is not established in ampullary cancer patients.

Research objectives

To reveal the necessity of hilar investigation in ampullary cancer and a useful method for diagnosing whether ampullary cancer invades the hilar biliary duct.

Research methods

Diagnosability was compared between CECT, ERC, IDUS, and biliary biopsy in ampullary cancer patients who underwent pancreaticoduodenectomy or focal ampullectomy.

Research results

The combination of biliary biopsy results and partial thickening of the bile duct wall on IDUS was efficient for diagnosing hilar invasion of ampullary cancer.

Research conclusions

Although false positives were observed for each method, hilar invasion was appropriately diagnosed based on the combination of biliary biopsy results and partial thickening of the bile duct wall on IDUS. However, hilar biliary invasion is rare in ampullary cancer. Therefore, hilar investigation might be unnecessary for ampullary cancer patients.

Research perspectives

The results of this study contribute to the establishment of a systematic method for diagnosing hilar invasion and selecting treatments for ampullary cancer patients.

ACKNOWLEDGEMENTS

We thank all the staff at the Department of Gastroenterology of Fukushima Medical University, the Department of Endoscopy of Fukushima Medical University Hospital, and the gastroenterology ward of Fukushima Medical University Hospital. We also thank American Journal Experts for providing English language editing.

FOOTNOTES

Author contributions: Takagi T and Sugimoto M wrote the paper and designed and performed the study; Ohira H designed and oversaw the study; Suzuki R, Konno N, Asama H, Hikichi T, Nakamura J, Takasumi M, Sato Y, Irie H, Hashimoto M, Kato T, Kobashi R, and Yanagita T provided clinical advice; Hashimoto Y performed pathological diagnoses, and all authors read and approved the final version of the manuscript.

Institutional review board statement: This study was approved by the Institutional Review Board of Fukushima Medical University (approval number: 2453).

Informed consent statement: The patients were not required to give informed consent because this study "Screening for Hilar Biliary Invasion in Ampullary Cancer Patients" used anonymous clinical data obtained after each patient had agreed to medical activities by written consent. For full disclosure, the details of this study are published on the home page of Fukushima Medical University.

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

Data sharing statement: The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

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World J Gastrointest Endosc 2022 September 16; 14(9): 547-554

DOI: 10.4253/wjge.v14.i9.547

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Endoscopic therapy using a self-expandable metallic stent with an anti-migration system for postorthotopic liver transplantation anastomotic biliary stricture

Larissa Wermelinger Pinheiro, Fernanda Prata Martins, Gustavo Andrade De Paulo, Mônica Lúcia Campos Contini, Angelo Paulo Ferrari, Ermelindo Della Libera

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Ferrarese A, Italy; Lynch EN, Italy

Received: February 3, 2022
Peer-review started: February 3, 2022
First decision: April 12, 2022
Revised: April 19, 2022
Accepted: August 6, 2022
Article in press: August 6, 2022
Published online: September 16, 2022

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Abstract

BACKGROUND

Endoscopic therapy using multiple plastic stents (MPSs) is the standard therapy for postorthotopic liver transplantation (p-OLT) anastomotic biliary stricture (ABS). However, this approach demands repeated procedures. Recent studies us-ing fully covered self-expandable metallic stents (FCSEMS) have shown en-couraging results, but migration occurs in 10% to 40% of cases. The objective of this retrospective study was to evaluate the efficacy of endoscopic treatment using FCSEMS with an anti-migration system (Am-FCSEMS) in patients with p-OLT ABS.

AIM

To evaluate the efficacy of endoscopic treatment using an Am-FCSEMS in patients with p-OLT ABS.

METHODS

This study was conducted in a private tertiary care centre in São Paulo, Brazil and was approved by our institution's Human Research Committee. From April 2018 to October 2020, regardless of previous endoscopic treatment (MPS or FCSEMS), 17 patients with p-OLT ABS and indications for endoscopic therapy were in-cluded in this study. The exclusion criteria were pregnancy, nonanastomotic

biliary or hilar stricture, hepatic artery stenosis/thrombosis, isolated biliary fistulae, a distance shorter than 2 cm from the stricture to the hepatic hilum, and patient refusal. The primary endpoint was the efficacy of p-OLT ABS endoscopic treatment using an Am-FCSEMS that re-mained in place for a 12-mo period. Biliary sphincterotomy was performed in patients with native papilla, and an Am-FCSEMS (10 mm in final diameter and 60 or 80 mm in length) was placed (Hanarostent™ MI Tech, Co). Balloon stricture dilation was performed only if necessary to introduce the stent.

RESULTS

Three patients were excluded due to loss to follow-up before stent removal. Among the 14 patients included and followed, 7 were women, and the average age was 56 years (range: 28-76). The average period of Am-FCSEMS placement was 362 ± 109 d. Technical success occurred in all 14 patients (100%). There were no cases of distal stent migration. Complete resolution of the stricture occurred in 13/14 patients (92.85%). Adverse events occurred in 3/14 patients (21.42%): 2 patients with mild acute pancreatitis (14.28%) and 1 patient (7.14%) with stent dysfunction (occlusion by biliary sludge and stones, which was treated endoscopically without the need for stent removal). No deaths occurred related to therapy. All stents were removed using foreign body forceps or snares without difficulty. After Am-FCSEMS removal, all 13 patients who had ABS resolution were followed-up for an average of 411 ± 172 d, and there was no stricture recurrence or need for further endoscopic therapy.

CONCLUSION

In this retrospective study, endoscopy therapy using an Am-FCSEMS for p-OLT ABS was safe and effective, with a high stricture re-solution rate that was probably due to the absence of stent migration.

Key Words: Liver transplantation; Endoscopy; Endoscopic retrograde cholangiopancreatography; Biliary strictures; Self-expandable metallic biliary stents

Core Tip: This retrospective study evaluated the efficacy of endoscopic treatment using an anti-migration fully covered self-expandable metallic stents (Am-FCSEMS) in patients with postorthotopic liver transplantation (p-OLT) anastomotic biliary stricture (ABS). Technical success occurred in all patients (100%). Stricture resolution occurred in 13/14 patients (92.85%). Adverse events occurred in 3/14 patients (21.42%). There were no cases of distal stent migration. After Am-FCSEMS removal, all 13 patients who had ABS resolution were followed-up for an average of 411 d, and there was no stricture recurrence or need for further endoscopic therapy. Endoscopic therapy using an Am-FCSEMS for p-OLT ABS is safe and effective, with a high stricture resolution rate, probably due to the absence of stent migration.

Citation: Pinheiro LW, Martins FP, De Paulo GA, Contini MLC, Ferrari AP, Della Libera E. Endoscopic therapy using a self-expandable metallic stent with an anti-migration system for postorthotopic liver transplantation anastomotic biliary stricture. *World J Gastrointest Endosc* 2022; 14(9): 547-554

URL: https://www.wjgnet.com/1948-5190/full/v14/i9/547.htm

DOI: https://dx.doi.org/10.4253/wjge.v14.i9.547

INTRODUCTION

Biliary tract lesions are common postoperative adverse events (AEs) after orthotopic liver transplantation (OLT). Anastomotic biliary strictures (ABSs) occur most frequently and are responsible for approximately 40% of all complications after OLT[1-4].

Endoscopic balloon dilation followed by placement of side-by-side multiple plastic stents (MPSs) in repeated procedures every 3-4 mo, up to 12 mo, is the standard treatment for ABS. This treatment strategy has a high success rate, ranging from 70% to 100%[1,5].

Despite such a high success rate, this strategy demands repeated procedures[1,6-9]. Recent studies using fully covered self-expandable metallic stents (FCSEMS) have shown encouraging results, with resolution rates similar to those observed with the MPS strategy[5,7,10]. However, a high FCSEMS migration rate of between 10% and 40% has been reported, which is a possible limitation for its use[5-7, 10].

We hypothesized that a FCSEMS with an anti-migration system (Am-FCSEMS) could be an alternative for postorthotopic-OLT (p-OLT) ABS treatment. Recently, a study with promising results compared the use of an Am-FCSEMS with other types of conventional metallic stents in regards to the p-OLT ABS resolution rate and their respective migration rates[11].

The objective of this study was to evaluate the efficacy of endoscopic treatment using an Am-FCSEMS in patients with p-OLT ABS.

MATERIALS AND METHODS

This study was conducted at Hospital Israelita Albert Einstein (HIAE), São Paulo, Brazil. HIAE is a private tertiary care referral centre where approximately 150 OLTs are performed yearly.

Patients

From April 2018 to October 2020, 17 patients between 18 and 76 years of age diagnosed with p-OLT ABS who were referred to the endoscopy unit were considered for inclusion in this retrospective study, regardless of previous endoscopic treatment (MPS or FCSEMS). The exclusion criteria were pregnancy, nonanastomotic biliary or hilar stricture, hepatic artery stenosis/thrombosis, isolated biliary fistulae, and patient refusal. To avoid the risk of biliary intrahepatic duct occlusion secondary to stent placement, a distance shorter than 2 cm from the stricture to the hepatic hilum was also considered an exclusion criterion.

This study was conducted in accordance with the World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects and was approved by our institution's Human Research Committee. The patients provided written informed consent prior to inclusion in the study.

Procedures

Endoscopic retrograde cholangiopancreatography (ERCP) was performed using a therapeutic video duodenoscope (TJF-180 Olympus Optical Co., Ltd., Tokyo, Japan) with patients under monitored anaesthesia. After selective biliary cannulation, cholangiography was performed for the evaluation and characterization of biliary stricture, followed by the passage of a guidewire. After positioning the guidewire, biliary sphincterotomy was performed in patients with native papilla, and an Am-FCSEMS (10 mm in final diameter and 60 or 80 mm in length, BCT Hanarostent™ M.I. Tech, Co.) was placed (Figure 1A and B). Balloon dilation of the stricture was performed only if necessary to introduce the stent. According to the physician's choice, the length of the stent was determined during cholangiography to place the proximal end between the stricture and the hepatic hilum and the distal end in the duodenum. Patients were followed up for clinical signs of biliary obstruction and scheduled to have the stent removed after 12 mo if no complications occurred.

Endpoints

The primary study endpoint was the efficacy of the endoscopic treatment of p-OLT ABS using an Am-FCSEMS for a 12-mo period. Efficacy was evaluated based on ABS resolution. After stent removal, the biliary stricture was considered resolved if there was no stricture observed on cholangiography or a minimum stricture that allowed the passage of a 12-mm inflated extractor balloon without difficulty. Secondary endpoints were technical success (defined as stent placement), adverse effects related to ERCP (bleeding or pancreatitis), and stent dysfunction (migration or obstruction).

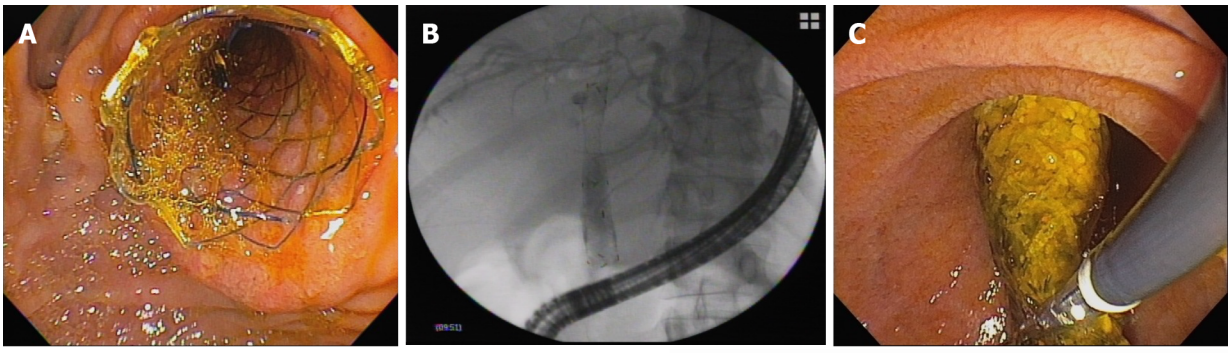
RESULTS

A total of 17 patients were included. Three patients were excluded due to loss to follow-up before stent removal (12 mo) (Figure 2). The average age of the 14 patients included and followed was 56 years (range: 28-76); 7 women had an average age of 42 ± 11.2 years, and 7 men had an average age of 69 ± 5.8 years. Patient characteristics are shown in Table 1. Among the 14 patients, 8 (57.14%) had already undergone treatment with FCSEMS and/or MPSs, but endoscopic management was considered unsuccessful, with an average number of procedures before inclusion in this study of 2.25 ± 1.04 (range: 1-4). The other 6 patients (42.85%) received an Am-FCSEMS as the first treatment. Regardless of previous treatment, the average interval from p-OLT to the first ERCP was 116 wk (range: 4-570). The average duration of placement of an Am-FCSEMS in this study was 362 ± 109 d (range: 226-609). The length of stent placement was 6 cm in 8 patients and 8 cm in 6 patients. Technical success (stent placement) occurred in all 14 patients (100%). The clinical follow-up after stent removal was 411 ± 172 d (range: 55-692). All stents were removed using foreign body forceps or snares without any technical difficulty (Figure 1C).

Table 1 Demographics of patients and baseline characteristics

Overall patient characteristics	Results
No. of patients, *n*	14
Gender, female sex, *n* (%)	7 (50)
Age (yr), mean (range)	56 (28-76)
Cause of liver transplant: *n*	
HBV	2
HBV + HCV	1
Alcohol	3
Cryptogenic	2
NASH	1
Autoimmune hepatitis	2
Primary biliary cirrhosis	1
Familial amyloidosis	1
Primary hyperoxaluria	1
Presence of HCC: *n*	4
Time from OLT to ERCP (wk)	
mean ± SD	116 ± 156
Median	45
Range	4-570
Patients with previous endoscopic treatment before Am-FCSEMS, *n* (%)	8 (57.14)
Procedures before Am-FCSEMS (mean)	2.25
Patients with no previous endoscopic treatment, *n* (%)	6 (42.86)

HBV: Hepatitis B virus; HCV: Hepatitis C virus; NASH: Nonalcoholic steatohepatitis; HCC: Hepatocellular carcinoma; ERCP: Endoscopic retrograde cholangiopancreatography; Am-FCSEMS: Fully covered self-expandable metal stents with anti-migration flaps.



DOI: 10.4253/wjge.v14.i9.547

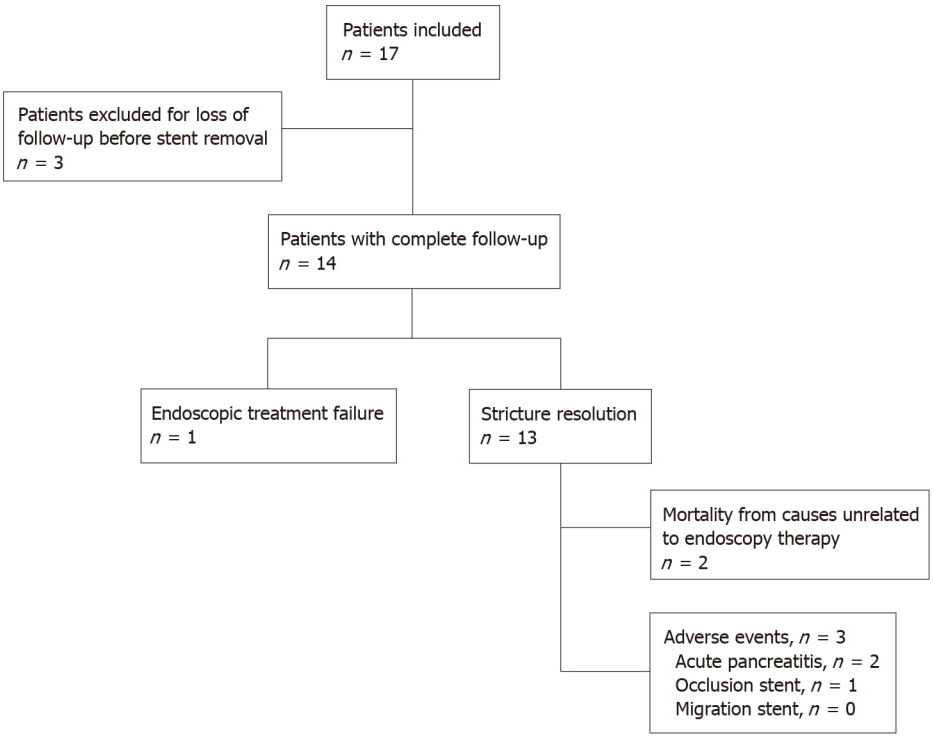
Figure 1 Images of the fully covered self-expandable metallic stent with an anti-migration system or flaps. A: Endoscopic view of the stent; B: Radiographic view of the stent in the biliary tract; C: Removal of the stent.

Complete resolution of the stricture occurred in 13/14 patients (92.85%). Only 1 patient (7.14%) experienced endoscopic treatment failure after 338 d with the stent in place, which was determined by cholangiography as persistence of stricture. This patient was referred for endoscopic treatment using MPSs for a longer period. AEs occurred in 3 out of 14 patients (21.42%). There were 2 patients (14.28%) with mild acute pancreatitis and 1 patient (7.14%) with stent dysfunction (occlusion by biliary sludge and stones with cholangitis), which was treated endoscopically without the need for stent removal. There was no distal migration of the stent in any patient (Table 2). There was no mortality related to ERCP and/or endoscopic therapy with the stent. After removal of the Am-FCSEMS, all 13 patients who

Table 2 Overall results

Overall results	
No. of patients, *n*	14
Technical success, *n* (%)	14 (100)
Stricture resolution, *n* (%)	13 (92.85)
Treatment failure, *n* (%)	1 (7.14)
Mean ALT before stent (U/L)	144
Mean ALT at the end of follow-up (U/L)	16
Mean total bilirubin before stent (mg/dL)	1. 88
Mean total bilirubin at the end of follow-up (mg/dL)	0. 49
Stricture recurrence, *n*	0
Stent migration	0
Other complications, *n* (%)	3 (21.42)
Acute pancreatitis	2 (14.28)
Stent occlusion	1 (7.14)
Mean follow-up after stent removal (d)	411 ± 172

ALT: Alanine aminotransferase.



DOI: 10.4253/wjge.v14.i9.547

Figure 2 Flowchart of the selection of patients in the study.

had ABS resolution were followed-up (411 ± 172 d), and there was no need for further endoscopic therapy or stricture recurrence. Two patients died from causes unrelated to endoscopy therapy.

DISCUSSION

Our present study shows that p-OLT ABS treatment with an Am-FCSEMS is effective and safe, with a stricture resolution rate of 92.85%, which is comparable to the results of other studies involving MPSs[5,9,12] and FCSEMSs[5,7,13]. In our study, the average time between liver transplantation and endoscopy therapy for ABS was lengthy (116 wk), which may have impacted the results and thus, is a possible limitation of this study[3,6,8]. Nevertheless, our results were comparable with those of other studies that used this anti-migration stent model[11].

The longer stent maintenance period (12 mo) in our study in relation to other studies with metallic stents[2,7] and the absence of migration possibly related to the antimigration mechanism may have contributed to the favourable result observed in our patients.

The technical success rate of 100% in this series, which is comparable to that in other studies[6,12,14], demonstrates the applicability of this technique. No patients experienced distal migration of the stent. As described in previous studies, the main disadvantage of using FCSEMS is the high migration rate of up to 37.5%[10,12,14,15]. It is possible that treatment with an Am-FCSEMS may present better results due to the lower risk of migration and longer stent patency. Although in our study assessment of costs was not an included objective, it is possible that since this stent has a lower migration rate its use could result in a lower number of procedures and thus lower costs, but this hypothesis should be verified in future controlled studies.

The AEs observed with ERCP-related therapy and/or stenting were mild pancreatitis and delayed stent obstruction. All patients in whom the stent was placed underwent biliary sphincterotomy, and mild acute pancreatitis was related to the ERCP procedure in 2 out of the 14 patients (14.2%). Despite this higher rate of complications compared to that in the literature[5-7,13], these patients underwent successful clinical treatment. Stent dysfunction (obstruction) occurred late and was caused by biliary sludge or stones, with jaundice and cholangitis occurring in only one patient (7.1%). This complication and its endoscopic treatment with or without stent replacement is described in the literature[5,6]. This patient was treated with antibiotics and endoscopy without the need for stent replacement.

No complications occurred during stent removal. In this study, no serious complications or deaths related to endoscopic treatment were reported. The average follow-up of patients who had stricture resolution after removal of the metallic stent was 411 d. There was no ABS recurrence during follow-up. This positive result may be related to the prolonged maintenance of the metallic stent, which was longer than 6 mo[2,5].

Considering the treatment of patients with p-OLT ABS, the use of FCSEMSs may be an interesting alternative in relation to MPS therapy, considering FCSEMS placement presents comparable results with fewer ERCP procedures[4,5,7,10]. However, spontaneous stent migration may be a limitation of FCSEMS placement[10,12,14].

This retrospective study has some limitations, such as a small sample size from a single centre. Another limiting point for this study is the lack of a control group. However, our results showed that treatment with Am-FCSEMS can be an alternative for patients with p-OLT ABS. Therefore, prospective and comparative studies should be encouraged to evaluate the efficacy of endoscopic treatment using Am-FCSEMS versus MPSs. Nevertheless, we present similar results for the resolution of ABS compared to those in other studies using MPSs and FCSEMSs as well as a recent study using an Am-FCSEMS. In this series, the advantage of treatment using an Am-FCSEMS in relation to treatment with MPSs was the need for only two ERCP procedures over 12 mo, while the advantage in relation to FCSEMS therapy was the absence of migration.

CONCLUSION

In conclusion, in this retrospective study, endoscopy therapy using an Am-FCSEMS or flaps for p-OLT ABS is safe and effective, with the stricture´s high-resolution rate probably being due to the absence of stent migration.

ARTICLE HIGHLIGHTS

Research background

Endoscopic therapy using multiple plastic stents is the standard therapy for postorthotopic liver transplantation (p-OLT) anastomotic biliary stricture (ABS). However, this approach demands repeated procedures. Recent studies using fully covered self-expandable metallic stents (FCSEMS) have shown encouraging results, but migration occurs in 10% to 40% of cases. We hypothesized that a FCSEMS with an anti-migration system (Am-FCSEMS) could be an alternative for treatment in patients with p-OLT ABS.

Research motivation
The efficacy of treatment using an Am-FCSEMS for p-OLT ABS is not yet well established. The outcomes of endoscopic treatment using this type of stent have become clinically relevant.

Research objectives
This study aimed to evaluate the efficacy of endoscopic treatment using an Am-FCSEMS in patients with p-OLT ABS.

Research methods
This study was conducted in a private tertiary care centre in São Paulo, Brazil. From April 2018 to October 2020, patients with p-OLT ABS and indications for endoscopic therapy were included in this study, and an Am-FCSEMS (10 mm in final diameter and 60 or 80 mm in length) was placed (Hanarostent MI Tech, Co).

Research results
Technical success occurred in all 14 patients (100%). There were no cases of distal stent migration. Complete resolution of the stricture occurred in 13/14 patients (92.85%). Adverse events occurred in 3/14 patients (21.42%): 2 patients with mild acute pancreatitis and 1 patient with stent dysfunction (occlusion). No deaths occurred related to therapy. After Am-FCSEMS removal, all 13 patients who had ABS resolution were followed-up for an average of 411 ± 172 d, and there was no stricture recurrence or need for further endoscopic therapy.

Research conclusions
Endoscopy therapy using an Am-FCSEMS for p-OLT ABS is safe and effective, with the stricture´s high-resolution rate probably being due to the absence of stent migration.

Research perspectives
This study shows that treatment using Am-FCSEMS has a high rate of stenosis resolution, probably due to the absence of stent migration, and may result in a lower number of procedures.

FOOTNOTES

Author contributions: Pinheiro LW, Martins FP, Contini MLC, and De Paulo GA contributed to the data acquisition; Pinheiro LW, De Paulo GA, Ferrari AP, and Della Libera E contributed to the data analysis and interpretation; Pinheiro LW contributed to the elaboration of article draft; Martins FP and Contini MLC contributed to the elaboration and review of article draft, critical review for important intellectual content; De Paulo GA contributed to the critical review of final paper for important intellectual content; Ferrari AP and Della Libera E contributed to the critical review and approval of the final submitted version.

Institutional review board statement: This retrospective study was approved by the Institution's Human Research Committee of Hospital Israelita Albert Einstein (No. 37755020.3.0000.0071).

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

Data sharing statement: No additional data are available.

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S-Editor: Yan JP
L-Editor: A
P-Editor: Yan JP

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 September 16; 14(9): 555-563

DOI: 10.4253/wjge.v14.i9.555

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Observational Study

Clinical profile, diagnostic yield, and procedural outcomes of single balloon enteroscopy: A tertiary care hospital experience

Maha Inam, Masood M Karim, Umar Tariq, Faisal Wasim Ismail

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Beyene B, Ethiopia; Innocenti T, Italy

Received: April 16, 2022
Peer-review started: April 16, 2022
First decision: May 12, 2022
Revised: May 21, 2022
Accepted: August 10, 2022
Article in press: August 10, 2022
Published online: September 16, 2022

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Abstract

BACKGROUND

Single balloon enteroscopy (SBE) allows ease of access for small bowel visualization and has multiple diagnostic and therapeutic indications. It provides the advantage of performing various therapeutic interventions alongside the diagnostic procedure. SBE has also been considered a relatively safe procedure with no major complications.

AIM

To investigate the indications, safety, and clinical yield of SBE, and determine its effect on disease outcome.

METHODS

A retrospective, descriptive study was conducted at a tertiary care hospital in Karachi, Pakistan. Medical records of 56 adult patients (≥ 18 years) who underwent SBE between July 2013 and December 2021 were reviewed and data were collected using a structured proforma. A descriptive analysis of the variables was performed using Statistical Package of Social Sciences Version 19. Results are reported as the mean ± SD for quantitative variables and numbers and percentages for qualitative variables. Missing data are reported as unknown.

RESULTS

A total of 56 patients who underwent 61 SBE procedures were included. The mean age was 50.93 ± 16.16 years, with 53.6% of them being males. Hypertension (39.3%) and diabetes mellitus (25.0%) were the most common pre-existing comorbidities. Obscure gastrointestinal bleed (39.3%) was the most common indication for enteroscopy, followed by chronic diarrhea (19.7%) and unexplained anemia (16.4%). The majority of procedures were performed in the endoscopy

suite (90.2%) under monitored anaesthesia care (93.4%). Most procedures were diagnostic (91.8%) and completed without complications (95.1%). The depth of examination ranged from 95 cm to 500 cm with a mean of 282.05 ± 90.04 cm. The most common findings were inflammation and ulcerations (29.5%), followed by masses (19.7%) and vascular malformations (14.8%). As a result of the findings, a new diagnosis was made in 47.5% of the cases and a previous one was ruled out in 24.6% of them; 65.6% of the cases had a change in management.

CONCLUSION

SBE is a suitable modality for investigating diseases in the small bowel. It is shown to be technically efficient and reasonably safe and is associated with high diagnostic and therapeutic yield.

Key Words: Single balloon enteroscopy; Small bowel diseases; Gastrointestinal bleed; Small bowel endoscopy; Small bowel; Balloon-assisted enteroscopy

Core Tip: Single balloon enteroscopy (SBE) is a safe and effective modality which allows ease of access for small bowel visualization. The procedure has multiple diagnostic and therapeutic indications. However, there is insufficient data published reporting its efficacy and impact. In this study, we analysed our single centre data of adults who underwent SBE between 2013 and 2021. We report patient demographics, procedure indications, and procedure findings. Based on our results, we can assess the indications, safety, and clinical yield of SBE, and determine its effect on disease outcome.

Citation: Inam M, Karim MM, Tariq U, Ismail FW. Clinical profile, diagnostic yield, and procedural outcomes of single balloon enteroscopy: A tertiary care hospital experience. *World J Gastrointest Endosc* 2022; 14(9): 555-563
URL: https://www.wjgnet.com/1948-5190/full/v14/i9/555.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i9.555

INTRODUCTION

For decades, gastroenterologists have been challenged by the lack of proper visualization provided by standard endoscopies to the small intestine, with many of its areas being difficult to access without an intra-operative endoscopy procedure[1]. Enteroscopy has been a significant breakthrough in this field, allowing access to most of the small bowel using endoscopic techniques without the need for surgery [2]. Initially, Push enteroscopy was established in the 1980s. However, it was associated with a limited depth of penetration into the small bowel, up till the level of the proximal jejunum, due to difficulty in manoeuvring it further. This was followed by the advent of the push-and-pull enteroscopy in 2001, also known as double balloon enteroscopy (DBE). DBE, as its name suggests, consists of two balloons: One on the tip of the enteroscope and the other on an overtube at the scope's distal end. The controlled inflation and deflation of the balloons allow the enteroscope to properly proceed without causing over-looping of the intestine. The volumes and pressures in the balloons are also measurable and are monitored throughout the procedure. As a result, DBE furthered the reach of the enteroscope and was seen to improve diagnostic yield, thereby overcoming the limitations of its preceding modality[1-4].

The single balloon enteroscopy (SBE) system was launched in 2007 as an alternative to DBE. SBE consists of only one balloon attached to the overtube at the scope's distal end and is relatively easier to use. The tip of the enteroscope is angled during withdrawal of the scope in the small bowel to achieve stable positioning and insufflation of the overtube is performed using a pressure-controlled pump[5]. Both methods have been shown to yield significant and similar therapeutic and diagnostic yield[6-9].

Small bowel capsule endoscopy is currently the first-line recommended technique for investigation of the small bowel in patients with obscure gastrointestinal bleed. This is often used as a preliminary examination prior to device assisted enteroscopy (DAE) if further investigation is clinically indicated[10, 11]. According to the most recent European Society of Gastrointestinal Endoscopy guidelines, DAE is also particularly recommended in patients with co-morbidities and/or those undergoing a therapeutic procedure since all endoscopic therapeutic procedures can be undertaken at the time of DAE[12].

The most common indication for small bowel enteroscopy is obscure gastrointestinal bleeding, defined as bleeding from the gastrointestinal (GI) tract that persists or recurs without an obvious cause after esophagogastroduodenoscopy, colonoscopy, and radiographic evaluation of the small bowel[13]. Other indications include chronic diarrhea, Crohn's disease, refractory celiac disease, small bowel malignancies, suspected nonsteroidal anti-inflammatory drug-induced small bowel injury, suspicion of

small bowel obstruction, and detection of polyps in patients with polyposis syndromes[7]. Enteroscopy can also be performed in patients presenting with several different symptoms, with no specific diagnostic results yielding from regular endoscopy. The advantage of SBE compared to other techniques for visualizing the small bowel, such as capsule endoscopy and radiologic methods, is in the ability to perform a wide variety of therapeutic interventions alongside the diagnostic procedure[14]. SBE has also been considered a relatively safe procedure with no major complications. The safety profile has been shown to match that of DBE overall, and the only major complications seen have been those that have resulted due to perforations[15].

While the existing literature has highlighted great diagnostic and therapeutic benefits of SBE, the data regarding its outcomes are scarce and not widely generalizable. The equipment costs and specialized training requirements could be reasons as to why SBE is not a commonly practiced procedure.

There is currently limited published data from developing countries detailing enteroscopy utility and outcomes. We aimed to explore the role of small bowel push enteroscopy in our population and study its indications, safety, findings, complications, diagnostic yield, and effect on disease outcome, in order to increase the body of knowledge regarding this procedure.

MATERIALS AND METHODS

This was a retrospective observational study conducted in a tertiary care referral centre in Karachi, the largest and most populated metropolitan city of Pakistan. Ethical approval and exemption were granted by the Ethical Review Committee of the institution on December 31, 2020 (2020-5760-15324).

Medical records of all adult patients above the age of 18 years who underwent a SBE procedure at the Aga Khan University Hospital from July 3, 2013 to December 31, 2021 were identified by random sampling, using the hospital's information medical record system. A chart review was conducted for all eligible patients. For each medical record, a proforma was completed regarding patient demographics, comorbidities, clinical presentation, medication history, procedure details, and enteroscopy and biopsy findings. In order to determine the procedure yield, a through chart review of the in- and out-patient hospital course was conducted (see Appendix: Enteroscopy questionnaire).

Our inclusion criteria were all adult patients over the age of 18 years who underwent a SBE procedure at the hospital within our study period. There were no exclusion criteria. All patients signed an informed consent form prior to the procedure (see Appendix: Consent form). Patient outcomes were defined as a change or otherwise in the patient's diagnosis and management as a result of the findings of the procedure.

A descriptive analysis was performed for patient demographics, clinical characteristics, and enteroscopy details. Data were analysed descriptively. Results are reported as the mean ± SD for quantitative variables and numbers and percentages for qualitative variables. Missing data are reported as unknown. Data were analysed using Statistical Package of Social Sciences (SPSS) Version 19. The statistical methods of this study were reviewed by Safia Awan of the Aga Khan University Hospital.

RESULTS

Our final study population comprised of a total of 56 patients (Table 1) who underwent a total of 61 procedures. The mean age of our sample was 50.93 ± 16.16 years, with the majority being males (53.6%, n = 30). Hypertension (39.3%, n = 22) and diabetes mellitus (25.0%, n = 14) were the most common pre-existing comorbidities. Prior medication use included antiplatelet (5.4%, n = 3) and non-steroidal anti-inflammatory drug (3.6%, n = 2) therapy, which is known to be associated with GI injury such as obscure bleeding and inflammation[13-14]. No patient in our study sample was on anticoagulation medications.

The clinical findings and outcomes of the 61 enteroscopy procedures are outlined in Table 2. Obscure gastrointestinal bleed was the most common enteroscopy indication (39.3%, n = 24), followed by chronic diarrhea (19.7%, n = 12). Other indications included unexplained anemia (16.4%, n = 10), enteric thickening and inflammatory changes on imaging (11.5%, n = 7), small intestinal space occupying lesion (11.5%, n = 7), persistent vomiting (9.8%, n = 6), weight loss (6.6%, n = 4), and malabsorption syndrome (6.6%, n = 4). Most of the procedures were performed in the endoscopy suite (90.2%, n = 55) under monitored anaesthesia care (93.4%, n = 57). However, 9.8% (n = 6) of cases were done in the main operating room, with 8.2% (n = 5) due to patient comorbidities and 1.6% (n = 1) in conjunction with an additional surgical procedure.

The majority of the enteroscopy procedures were diagnostic (91.8%, n = 56). Interventions were carried out following 27.8% of the cases. Out of these, 13.1% (n = 8) were enteroscopic interventions like polypectomy, argon plasma coagulation, adrenaline sclerotherapy, hemoclip attachment and stent removal, 9.8% (n = 6) were surgical interventions, and 4.9% (n = 3) were radiological interventions like angioembolization, which followed post procedure.

Table 1 Patient characteristics (*n* = 56)

	mean ± SD	Median	Range
Age	50.93 ± 16.16	47	26-87
		n	%
Gender	Male	30	53.6
	Female	26	46.4
Comorbidities	Hypertension	22	39.3
	Diabetes mellitus	14	25
	Chronic kidney disease	6	10.7
	Chronic liver disease	4	7.1
	Ischemic heart disease	3	5.4
	Inflammatory bowel disease	3	5.4
	Cerebrovascular accident	2	3.6
	Asthma	2	3.6
	Rheumatoid arthritis	1	1.8
Prior medications	Antiplatelets	3	5.4
	Non-steroidal anti-inflammatory drugs	2	3.6
	Anticoagulation	0	0

The depth of the enteroscopy examination ranged from 95 cm to 500 cm with a mean of 282.05 ± 90.04 cm. Enteroscopy examination was normal in 44.3% (*n* = 27) of the cases, while inflammation and ulcerations were seen in 29.5% (*n* = 18), space occupying lesions and masses in 19.7% (*n* = 12), vascular malformations in 14.8% (*n* = 9), and active bleeding in 8.2% (*n* = 5). A biopsy was obtained in 33 (54.1%) cases and the results included non-specific inflammation (63.6%, *n* = 21), malignancies or dysplasia (27.2% *n* = 9), villous atrophy (3.0% *n* = 1), and presence of Giardia (3.0%, *n* = 1). Out of the malignancies/dysplasia, 15.2% (*n* = 5) of the cases were adenocarcinoma, and there was one case each of adenomatous polyp (3.0%), inflammatory polyp (3.0%), hamartomous polyp (3.0%), and lymphoma (3.0%).

There was no mortality recorded in our study. Most procedures were successfully completed without any complications, while complications were seen in three (4.9%) procedures. All complications were either conservatively managed or resolved spontaneously following the procedure.

One patient had premature ventricular contractions during the procedure which were conservatively managed and resolved while another developed hemodynamic instability which resolved spontaneously post procedure. The third patient developed aspiration pneumonia post procedure which resolved with antibiotics.

The clinical yield of the SBE procedures in our study was determined by quantifying the change in diagnosis and management. A classification of a change in diagnosis was made when a diagnosis which was made prior to the enteroscopy procedure was either modified or disproven following the procedure findings. There was a change in diagnosis in 72.1% (*n* = 44) of the cases. Out of these, a new diagnosis was made in 47.5% (*n* = 29) of the cases (termed as positive changes) while a previous diagnosis was disproven in 24.6% (*n* = 15) (termed as negative changes). A classification of a change in management was made when a management plan which was made prior to the enteroscopy procedure was either modified or disproven following the procedure findings. There was a change in management in 65.6% (*n* = 40) of the cases.

DISCUSSION

Our study adds to the limited published literature regarding SBE experience from a tertiary care hospital in a developing country. A few studies analysing the indications, efficacy, outcomes, and safety of enteroscopy procedures have been carried out in various countries. The efficacy of SBE was also compared with that of double balloon enteroscopy in several retrospective studies and meta-analyses [16-20]. Moreels *et al*[21] conducted a case series in 2016 evaluating the therapeutic actions of SBE using a new prototype and highlighting its benefits. Studies have also been carried out to evaluate the efficacy of SBE in non-invasive evaluation of obscure gastrointestinal bleeding and Crohn's disease, but there

Table 2 Clinical variables of single balloon enteroscopy (*n* = 61)

		n	%
Enteroscopy indication	Obscure gastrointestinal bleeding	24	39.3
	Chronic diarrhea	12	19.7
	Unexplained anemia	10	16.4
	Enteric thickening/inflammatory changes on imaging	7	11.5
	Small intestinal space occupying lesion	7	11.5
	Persistent vomiting	6	9.8
	Weight loss	4	6.6
	Malabsorption syndrome	4	6.6
Procedure location	Endoscopy suite	55	90.2
	Operating room	6	9.8
Sedation	Monitored anaesthesia care	57	93.4
	General anaesthesia	4	6.6
Procedure	Diagnostic	56	91.8
	Therapeutic	5	8.2
	mean ± SD	Median	Range
Depth of procedure (cm)	282.05 ± 90.04	300	95-500
Enteroscopy findings	Normal	27	44.3
	Inflammation and ulcerations	18	29.5
	Space occupying lesions and masses	12	19.7
	Vascular malformations	9	14.8
	Bleeding	5	8.2
	Ascaris worm	1	1.6
Biopsy findings (*n* = 33)	Non-specific inflammation	21	63.6
	Malignancy/dysplasia		
	Adenocarcinoma	5	15.2
	Adenomatous polyp	1	3
	Inflammatory polyp	1	3
	Hamartomous polyp	1	3
	Lymphoma	1	3
	Villous atrophy	1	3
	Presence of Giardia	1	3
	Normal	1	3
Complications	Yes	3	4.9
	No	58	95.1
Change in diagnosis	Yes		
	Positive change	29	47.5
	Negative change	15	24.6
	No	17	27.9
Change in management	Yes	40	65.6
	No	21	34.4
Interventions	Enteroscopic		

Angioembolization	4	6.6
Argon plasma coagulation	3	4.9
Polypectomy	3	4.9
Adrenaline sclerotherapy	3	4.9
Red blood cell scintography	1	1.6
Surgical	6	9.8
Radiological	3	4.9

was a dearth of data describing experiences over many years for all cause indications, which additionally limits data providing information regarding the safety and efficacy of the procedure[22-24].

The demographics of our patient population are comparable to those of other studies from Korea and India, which reported a mean age of 50-55 years and the majority of males (52.9%-69.1%). However, a study conducted in the United States had a higher mean age at 62 ± 17 years[25]. In agreement with our results, published studies report obscure GI bleeding as the most common indication, ranging from 48% to 97%, in patients undergoing SBE. Other common indications included anemia, chronic diarrhea, lesions, polyposis, and Crohn's disease, amongst others, in various proportions[18,22,25].

Ulcers (19.6%), tumors (16.7%), and vascular malformations (14.7%) were the most common findings in a single-centre retrospective study conducted in China to test the diagnostic yield and safety of SBE [23]. Overall, the findings reported in the literature are similar and proportional to those seen in our study population.

We determined a high safety profile of SBE in our patients, with non-severe complications arising in only three (4.9%) of the cases, which were subsequently conservatively managed. There were no cases of severe complications reported in our patients. This is in accordance with the previous literature which shows a very low incidence of any adverse effects following SBE. A meta-analysis including four studies showed no evidence of any severe adverse effects such as bowel perforation, bleeding, or pancreatitis [26]. It has also been previously reported that the adverse effects seen in SBE procedures were comparable to those seen in DBE procedures, with both being marked as safe according to a single-centre retrospective analysis. However, the study accounted for a performance bias as all the procedures were carried out by a single endoscopist, who was trained in the procedure[20]. One study on the usage of emergency SBE concluded that the incidence of adverse effects was lower when general anaesthesia was used as compared to when it was performed under conscious sedation[23]. Our SBE procedures were always performed by the same team of endoscopists with significant expertise as well, resulting in no major adverse effects.

A similar study reported a mean depth as 23 ± 87 cm beyond the ligament of Treitz with a range of 20-400 cm, in accordance with our findings[22]. In a randomized controlled trial, the mean depth of insertion of anterograde SBE procedures was found to be 203.8 cm[24]. A previous study has also been shown to explain a method used by endoscopists to assess the depth of insertion which is based on advancement with each push-and-pull manoeuvre in cases of DBE[25].

In our study, 65.6% (n = 40) of the procedures resulted in a change in management and 72.1% (n = 44) had a change in diagnosis following enteroscopy findings. The literature reports diagnostic yields of SBE ranging from 47% to 65%, and therapeutic yields from 25% to 42%[18,20,22,25].

A single centre retrospective study published in 2020 studied the safety and diagnostic yield of capsule endoscopy in the investigation of obscure gastrointestinal bleeds[10]. The study population included 58.6% of males with a mean age of 67.7 ± 14.4 years. The results showed a diagnostic yield of 73.8%, revealing clinically significant bleeds which were missed at gastroscopy or colonoscopy in 30.3% of patients.

The limitations of our study include a retrospective, single-centre analysis. While our sample size is relatively small compared to that of other similar studies, it included all patients who underwent a SBE procedure at our institution over an 8-year period. However, our study findings are solely representative of a South Asian population in a low-middle income country (LMIC). Our study also notes a lack of a standardized reporting template for SBE depth of examination that may be used internationally.

Our observed findings can be used to guide further research, as the current literature on the clinical indications, safety profile, diagnostic yield, and patient outcomes of enteroscopy is not sufficient to provide the basis for the development of guidelines, especially in LMICs. Additional prospective studies with larger sample sizes are recommended to grasp a thorough understanding of the indications and efficacy of SBE. Long-term follow-up studies will also be beneficial in demonstrating the clinical impact of SBE.

CONCLUSION

Our study reports an encouraging single centre tertiary care experience of SBE over an 8-year period. We conclude that SBE is a safe and effective method with a high clinical impact on precise diagnosis and management of small bowel diseases.

ARTICLE HIGHLIGHTS

Research background

Single balloon enteroscopy (SBE) is a procedure that has greatly improved the access to small bowel visualization, particularly of the mid and distal parts of the small bowel. In addition to being used as a diagnostic tool, SBE can also be used to perform a number of therapeutic interventions. SBE is a relatively safe procedure with a low incidence of complications and a good diagnostic and therapeutic yield. One of the most common indications generally seen is intestinal bleeding.

Research motivation

Since SBE is a relatively new procedure, there is still an absence of viable literature about it from the developing world countries like Pakistan. Due to the good yields from this procedure, proper adaptation of this technique in these places can greatly be used to improve healthcare outcomes particularly pertaining to small bowel problems by improving timely diagnosis and management.

Research objectives

To investigate the indications, procedures, findings, and safety of SBE procedures and to correlate their effects on the disease outcomes.

Research methods

We performed a retrospective descriptive study at a tertiary care hospital in Pakistan and investigated all the SBE procedures carried out between July 2013 and December 2021. A total of 56 patients underwent 61 SBE procedures during this time period. We collected data using patient files and electronic health records using a structured proforma. It was interpreted and then categorized and analyzed using the SPSS software.

Research results

Our study population consisted of 56 patients who underwent 61 SBE procedures at a tertiary care hospital over the study period. The mean age of the sample was 50.93 ± 16.16 years and 53.6% of the sample was male. The most common comorbidities in the patient population were hypertension (39.3%) and diabetes mellitus (25.0%). The most common indications for conducting the SBE procedure were obscure gastrointestinal bleed (39.3%), chronic diarrhea (19.7%), and unexplained anemia (16.4%). Other indications included enteric thickening or inflammatory changes on imaging, space occupying lesions, persistent vomiting, weight loss, and malabsorption syndromes. Most of the procedures were conducted in the endoscopy suite while 9.8% (n = 6) required the operation room due to patient comorbidities or being in conjunction with a surgical procedure. The majority of the procedures were carried under monitored anesthesia care (93.4%) while the rest were done under general anesthesia. Most procedures were diagnostic (91.8%) and completed without complications (95.1%). The depth of examination ranged from 95 cm to 500 cm with a mean of 282.05 ± 90.04 cm. The most common enteroscopy findings were inflammation and ulcerations (29.5%), followed by masses (19.7%) and vascular malformations (14.8%). Biopsy samples were taken in 33 of the cases and the most common biopsy finding was non-specific inflammation (63.6%). As a result of the findings, a new diagnosis was made in 47.5% of the cases and a previous one was ruled out in 24.6% of them; 65.6% of the cases had a change in management.

Research conclusions

Through our study findings, we concluded that SBE is a useful method in diagnosing small bowel problems with a good yield. It is also relatively safe and has a low risk of complications.

Research perspectives

More research needs to be conducted on the usage and yields from SBE procedures in low-middle income countries with larger samples. There also needs to be a standardized method to record the details of enteroscopy procedures.

FOOTNOTES

Author contributions: Inam M participated in the acquisition, analysis, and interpretation of the data, and assisted in manuscript writing and review; Karim MM participated in the acquisition and interpretation of the data, and assisted in manuscript writing and review; Tariq U participated in the acquisition of the data and assisted in manuscript writing and review; Ismail FW conceptualized, designed, and supervised the study, participated in the acquisition and interpretation of the data, and assisted in manuscript writing and review; all authors have read and approved the final manuscript.

Institutional review board statement: Approval was obtained for this study from the Ethical Review Committee of the Aga Khan University Hospital, Karachi, Pakistan.

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

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: Pakistan

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S-Editor: Wang LL
L-Editor: Wang TQ
P-Editor: Wang LL

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World J Gastrointest Endosc 2022 September 16; 14(9): 564-574

DOI: 10.4253/wjge.v14.i9.564

ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Prospective Study

Role of endoscopic ultrasound in evaluation of patients with missed common bile duct stones

Mohamed Eissa, Hussein Hassan Okasha, Mohamed Abbasy, Ahmed Kamal Khamis, Abeer Abdellatef, Mohamed Akl Rady

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Er LM, China; Pelaez-Luna M, Mexico

Received: June 2, 2022
Peer-review started: June 2, 2022
First decision: July 12, 2022
Revised: July 26, 2022
Accepted: September 6, 2022
Article in press: September 6, 2022
Published online: September 16, 2022

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Abstract

BACKGROUND

Choledocholithiasis develops in up to 20% of patients with gall bladder stones. The challenge in diagnosis usually occurs with small stones that may be missed by magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS) is accurate in detecting common bile duct (CBD) stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

AIM

To evaluate the accuracy of EUS in detecting CBD stones missed by MRCP.

METHODS

Patients with an intermediate likelihood of choledocholithiasis according to ESGE guidelines and those with acute pancreatitis of undetermined cause were included. The presence of choledocholithiasis was evaluated by MRCP and EUS, and then results were confirmed by endoscopic retrograde cholangiopancreatography (ERCP). The sensitivity and specificity of EUS and MRCP were compared regarding the presence of stones, the size, and the number of detected stones.

RESULTS

Ninety out of 100 involved patients had choledocholithiasis, while ten patients were excluded as they had pancreatic or gall bladder masses during EUS examination. In choledocholithiasis patients, the mean age was 52.37 ± 14.64 years, and 52.2% were males. Most patients had biliary obstruction (74.4%), while only 23

(25.6%) patients had unexplained pancreatitis. The overall prevalence of choledocholithiasis was 83.3% by EUS, 41.1% by MRCP, and 74.4% by ERCP. Also, the number and size of CBD stones could be detected accurately in 78.2% and 75.6% by EUS and 41.1% and 70.3% by MRCP, respectively. The sensitivity of EUS was higher than that of MRCP (98.51% *vs* 55.22%), and their predictive value was statistically different ($P < 0.001$). Combination of both tools raised the sensitivity to 97.22% and specificity to 100%.

CONCLUSION

EUS could be a useful tool in assessing patients with suspected choledocholithiasis especially if combined with MRCP. However, its usefulness depends on its availability and the experience of the local centers.

Key Words: Magnetic resonance cholangiopancreatography; Endoscopic ultrasonography; Choledocholithiasis; Missed common bile duct stones

Core Tip: Still, there is a great challenge in diagnosing suspected cases of choledocholithiasis that could develop in up to 20% of patients with gall bladder stones. Endoscopic ultrasound (EUS) can easily detect small stones that magnetic resonance cholangiopancreatography (MRCP) could miss. EUS still has many diagnostic purposes with high accuracy in detecting common bile duct (CBD) stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

Citation: Eissa M, Okasha HH, Abbasy M, Khamis AK, Abdellatef A, Rady MA. Role of endoscopic ultrasound in evaluation of patients with missed common bile duct stones. *World J Gastrointest Endosc* 2022; 14(9): 564-574
URL: https://www.wjgnet.com/1948-5190/full/v14/i9/564.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i9.564

INTRODUCTION

Choledocholithiasis is considered one of the most important causes of abdominal pain in patients with gall bladder stones. It can occur in 3%-16% of patients with gall stones and can reach up to 21% in patients with gall stone pancreatitis[1,2]. Diagnosis of choledocholithiasis is not always straightforward [3]. Clinical evaluation and biochemical tests are insufficient to establish a firm diagnosis without reliable confirmatory testing, so magnetic resonance cholangiopancreatography (MRCP) is routinely used to clarify the diagnosis after ultrasound results[4]. Endoscopic retrograde cholangiopancreatography (ERCP) is now considered the gold standard for diagnosis; however, its invasive nature and complications such as pancreatitis defer its use in diagnosis as a first option[5].

Since the recommendations by the ASGE and ESGE guidelines for diagnosing patients with an intermediate likelihood of choledocholithiasis by MRCP, endoscopic ultrasound (EUS) is now widely used to assess the presence of choledocholithiasis[6,7]. Despite its overall high accuracy, the role of EUS in the diagnosis of choledocholithiasis has not been firmly established since EUS is relatively invasive compared with MRCP and computed tomography[8].

The cause of biliary obstruction is not always detected by the available non-invasive imaging modalities like MRCP and may be detected later during biliary drainage as small stones, so in our study, we evaluated the usefulness and accuracy of EUS in detecting missed stones by MRCP as a cause of biliary obstruction.

MATERIALS AND METHODS

Methodology

This observational cohort study aimed primarily to evaluate the usefulness and accuracy of EUS in detecting missed stones by MRCP as a cause of biliary obstruction.

Patients and assessments

This prospective study was conducted on 100 patients recruited from National Liver Institute and Internal Medicine Department, Kasr Al-Ainy Hospital from 2019 to 2021. We included patients with dilated CBD (diameter ranging from 6 to 10 mm), those with unexplained elevated liver enzymes, and

those with unexplained causes of acute pancreatitis. All patients with cholangitis were excluded from the study and referred for urgent ERCP drainage. Also, we excluded patients with malignant masses found by EUS and confirmed by histopathology. All included patients were above 18 years of age.

Assessment of our patients was performed by liver function tests, serum amylase, lipase, abdominal ultrasound, MRCP, and EUS. ERCP was conducted on all patients for confirmation of the findings of MRCP and EUS. MRCP was done few days before EUS, then ERCP was done later on. The EUS operator was blind to MRCP examination. We followed up with the patients for 3 mo after the procedures clinically and biochemically.

Results from MRCP and EUS were compared with those from ERCP to calculate the sensitivity and specificity of EUS and MRCP in detecting choledocholithiasis in our patients. Also, the accuracy of both MRCP and EUS in detecting the size and number of stones in CBD was evaluated.

Our institution's Research Ethical Committee approved the study, and all patients gave their informed written consent before inclusion in the study, according to the ethical guidelines of the 1975 Declaration of Helsinki.

Examination procedure

All the patients, after thorough full history taking and clinical examination, were subjected to: (1) EUS examination using a linear Echoendoscope Pentax EG3870UTK (HOYA Corporation, PENTAX Life Care Division, Showanomori Technology Center, Tokyo, Japan) connected to a Hitachi AVIUS machine (Hitachi Medical Systems, Tokyo, Japan). All examinations were performed under deep sedation with IV propofol. For EUS-FNA, we used the Cook 19G and 22G needles (Echotip; Wilson-Cook, Winston Salem, NC). Prophylactic ceftriaxone (1 g) was administrated before the procedure; and (2) ERCP examination that was performed using a side view scope Pentax ED-3490TK (HOYA Corporation, Tokyo, Japan). All examinations were performed under deep sedation with IV propofol. Prophylactic ceftriaxone (1 g) was administrated before the procedure.

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software version 20.0 (Armonk, NY: IBM Corp). Qualitative data are described using numbers and percentages. The Kolmogorov-Smirnov test was used to verify the normality of distribution. Quantitative data are described using range (minimum and maximum), mean, standard deviation, median, and interquartile range. The significance of the obtained results was judged at the 5% level. The chi-square test was applied to compare categorical variables between different groups. The Fisher's exact test was used for correction for chi-square when more than 20% of the cells had an expected count of less than 5.

RESULTS

After excluding the ten patients with malignancy, the total number of male patients was 47 (52%), and that of female patients was 43 (48%), who were included till the end of the study with a mean age of 52.37 ± 14.64 years (Figure 1). The number of patients who fulfilled the criteria of an intermediate probability of biliary obstruction were 67 (74.4%), while that of patients with unexplained acute pancreatitis was 23 (25.6%). Only seven patients proved to have CBD stones, of whom all were detected by EUS, but only four were detected by MRCP. No other causes of acute pancreatitis as cystic pancreatic lesions, pancreatic divisum, or pancreatic duct stones could be detected by MRCP or EUS. Most patients had elevated liver enzymes (60%) and direct hyperbilirubinemia (81%), as shown in Table 1. Abdominal ultrasound showed that 72.2% of patients had gall bladder stones; meanwhile, only nine had a history of cholecystectomy with a mean CBD diameter of 9.13 ± 2.35 mm (Figure 2).

Choledocholithiasis was detected in 83.3% of patients by EUS, 74.4% by ERCP but only 41.1% by MRCP. EUS detected the number of stones more accurately than MRCP (95% *vs* 41%, respectively), as shown in Table 2.

Regarding the size of stones, EUS had a higher accuracy in detecting stones less than 5 mm (25 out of 53 negatives for stones by MRCP), as shown in Table 2.

EUS was statistically more accurate than MRCP in detecting stones ($P < 0.001$), especially in stones less than 5 mm (88.8% *vs* 66.6%, respectively). The sensitivity of EUS was 98.51%, while that of MRCP was only 55.5%, but the specificity of MRCP was higher than that of EUS (100% *vs* 60.87%, respectively), as shown in Table 3. The combination of EUS with MRCP showed a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and overall accuracy of 97.22%, 100%, 100%, 91.67%, and 97.87%, respectively (Table 4).

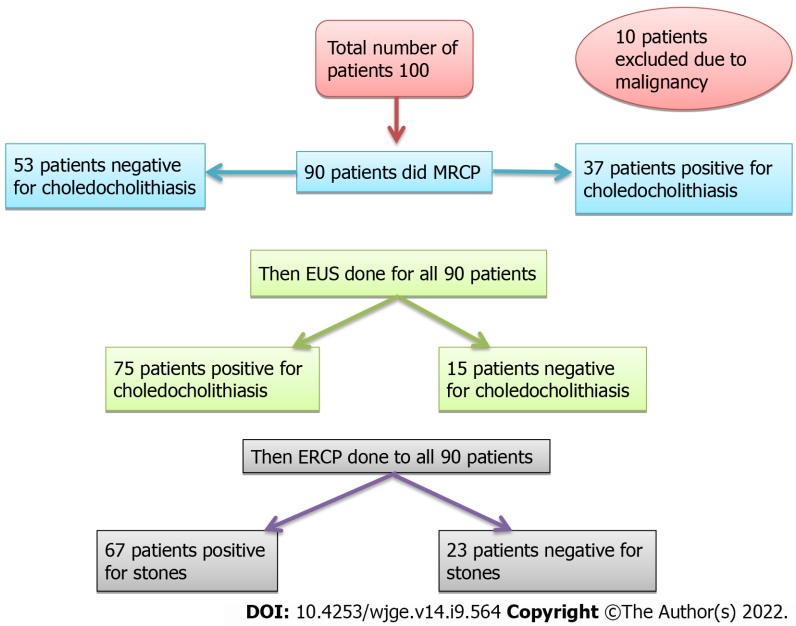
Indeed, there are differences in endoscopic skill between endoscopists, so we analyzed the data for expert and non-expert endoscopists (Table 5).

We found ten cases considered false negative by EUS, where six cases had gravels on EUS, three had small non-floating stones less than 5 mm, and one had a stone over the old plastic stent. Figures 3-5 show different forms of detected CBD stones from our patients.

Table 1 Biochemical data of the included patients

	n	%
Alanine transaminase, aspartate aminotransferase	Up to 33 U/L	
Normal	36	40.0
< 3 fold	44	48.9
≥ 3 fold	10	11.1
Bilirubin	Up to 1.1 mg/dL	
Normal	17	18.9
Yes	73	81.1
< 5 mg/100 mL	54	74.0
≥ 5 mg/100 mL	19	26.0
Min-Max	1.40-20.0	
mean ± SD	3.99 ± 3.30	
Median (IQR)	3.0 (2.0-5.0)	
Alkaline phosphatase	35-104 U/L	
GGT	Up to 40 U/L	
Normal	7	7.8
< 3 fold	24	26.7
≥ 3 fold	59	65.6

IQR: Interquartile range; GGT: Gamma glutamyl transpeptidase.



DOI: 10.4253/wjge.v14.i9.564

Figure 1 Flow chart of the studied patients. MRCP: Magnetic resonance cholangiopancreatography: EUS: Endoscopic ultrasound; ERCP: Endoscopic Retrograde Cholangiopancreatography.

The ten cases with the malignant cause of biliary obstruction were detected by EUS as seven cases with pancreatic head mass, two with gall bladder carcinoma, and one with CBD mass (diagnosed as cholangiocarcinoma by further evaluation with spyglass).

Table 2 Cases of choledocholithiasis detected by endoscopic ultrasound

Common bile duct stones detected by endoscopic ultrasound	Patients (*n*)	%
Common bile duct stones detected by endoscopic ultrasound		
No	15	16.7
Yes	75	83.3
Stones (*n*)		
No stones	20	22.2
1	42	46.7
2	12	13.3
3	5	5.6
4	1	1.1
5	1	1.1
6	1	1.1
Multiple	8	8.9
Size of stones (mm)		
No stones	20	22.2
Gravels (1-2 mm)	2	2.2
3-5	25	27.8
> 5	43	47.8

Table 3 Accuracy, sensitivity, and specificity of endoscopic ultrasound and magnetic resonance cholangiopancreatography in detecting choledocholithiasis

	Endoscopic retrograde cholangiopancreatography findings				Sensitivity	Specificity	PPV	NPV	Accuracy
	No (*n* = 23)		Yes (*n* = 67)						
CBD stones detected by EUS	*n*	%	*n*	%					
No	14	60.9	1	1.5	98.51	60.87	88.0	93.33	88.89
Yes	9	39.1	66	98.5					
^{FE}P value	43.464 (< 0.001)								
MRCP stones	*n*	%	*n*	%					
No	23	100.0	30	44.8					
Yes	0	0.0	37	55.2	55.22	100.0	100.0	43.40	66.67
P value	21.569 (< 0.001)								

PPV: Positive predictive value; NPV: Negative predictive value; CBD: Common bile duct; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

DISCUSSION

MRCP has been used to detect biliary obstruction in the last decade, but the cause cannot be detected in many patients[5]. The latest ASGE and ESGE guidelines recommend performing MRCP or EUS for evaluating patients with an intermediate probability of choledocholithiasis. However, it does not recommend one modality over the other[6,7]. Since the wide use of EUS, many studies have evaluated its role in detecting the cause of biliary obstruction[8]. EUS has a high accuracy in diagnosing pancreatic diseases and sampling tissues, but its role in diagnosing choledocholithiasis has not been confirmed like in pancreatic diseases[9].

Table 4 Agreement (sensitivity, specificity, and accuracy) for combined endoscopic ultrasound and magnetic resonance cholangiopancreatography

Combined EUSMRCP	ERCP findings				Sensitivity	Specificity	PPV	NPV	Accuracy
	No (n = 11)		Yes (n = 36)						
	n	%	n	%					
No	11	100.0	1	2.8	97.22	100.0	100.0	91.67	97.87
Yes	0	0.0	35	97.2					
^{FE}P value	41.887 (< 0.001)								

PPV: Positive predictive value; NPV: Negative predictive value; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

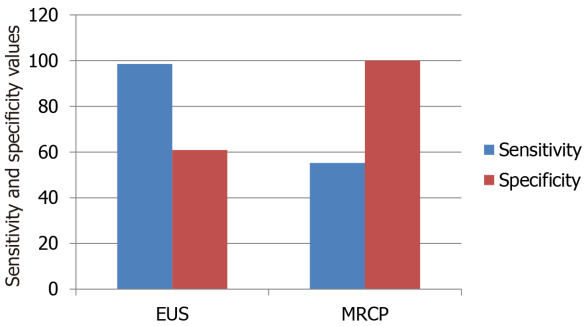


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Figure 2 Comparison of sensitivity and specificity of endoscopic ultrasound and magnetic resonance cholangiopancreatography in detecting choledocholithiasis. EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography.

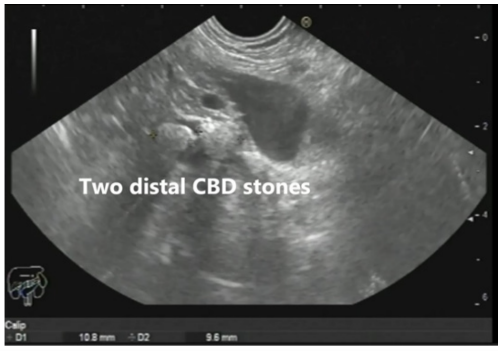

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Figure 3 Two distal common bile duct stones as seen from the gastric body. CBD: Common bile duct.

This study evaluated the accuracy of EUS in detecting CBD stones, especially those missed by MRCP in patients with an intermediated probability of CBD stones and recurrent unexplained pancreatitis. Our study included 100 patients, which is considered a large number compared to other studies like Rana *et al*[10] (40 patients) and Patel *et al*[11] (78 patients), but a small number compared to Wee *et al*[12] who included 593 patients but only 35.3% of those patients had MRCP (all our patients had MRCP).

Similar to the previously mentioned studies[10,11], we found no statistically significant variables regarding clinical and laboratory data that could predict the presence of CBD stones on EUS, MRCP, or ERCP.

In the current study, we found that EUS had a higher accuracy in detecting choledocholithiasis than MRCP (88.8% *vs* 66.6%, respectively) with a higher sensitivity (98% *vs* 55%, respectively) but lower specificity (60.8% *vs* 100%, respectively). This lower specificity of EUS might be attributed to the time gap between EUS and ERCP (passed stones), missed gravels during balloon sweeping, and false perception of air as stones in some cases. Many other studies that evaluated the diagnosis of

Table 5 Differences in endoscopic skill between expert and non-expert endoscopists

CBD stones detected by EUS	Total (*n* = 90)					Non-expert (*n* = 27)		Expert (*n* = 63)	
	n				%	*n*	%	*n*	%
No	15				16.7	11	40.7	4	6.3
Yes	75				83.3	16	59.3	59	93.7
Number									
No.	20				22.2	14	51.9	6	9.5
1	42				46.7	8	29.6	34	54.0
2	12				13.3	2	7.4	10	15.9
3	5				5.6	0	0.0	5	7.9
4	1				1.1	0	0.0	1	1.6
5	1				1.1	0	0.0	1	1.6
6	1				1.1	0	0.0	1	1.6
Multiple	8				8.9	3	11.1	5	7.9
Size (mm)									
No.	22				24.4	14	51.9	8	12.7
≤ 5	25				27.8	4	14.8	21	33.3
> 5	43				47.8	9	33.3	34	54.0
Other findings of EUS									
No	65				72.2	14	51.9	51	81.0
Yes	25				27.8	13	48.1	12	19.0
	ERCP findings				Sensitivity	Specificity	PPV	NPV	Accuracy
	No		Yes						
	n	%	*n*	%					
Total sample (*n* = 90)	*n* = 23		*n* = 67						
No	14	60.9	1	1.5					
Yes	9	39.1	66	98.5	98.51	60.87	88.0	93.33	88.89
^{FE}P value	43.464 (< 0.001)								
Non-expert (*n* = 27)	*n* = 13		*n* = 14						
No	10	76.9	1	7.1					
Yes	3	23.1	13	92.9	92.86	76.92	81.25	90.91	85.19
^{FE}P value	13.595 (< 0.001)								
Expert (*n* = 63)	*n* = 10		*n* = 53						
No	4	40.0	0	0.0					
Yes	6	60.0	53	100.0	100.0	40.0	89.83	100.0	90.48
^{FE}P value	22.637 (< 0.001)								

PPV: Positive predictive value; NPV: Negative predictive value; EUS: Endoscopic ultrasound; MRCP: Magnetic resonance cholangiopancreatography; ERCP: Endoscopic retrograde cholangiopancreatography.

choledocholithiasis by EUS showed variable results regarding sensitivities and specificities. For example, Jagtap *et al*[13] showed that the sensitivities of both EUS and MRCP were similarly high (92%-98%). Also, Patel *et al*[11] showed that the sensitivity and specificity of EUS were 93% and 97.3%, respectively, but most included patients had a high probability of choledocholithiasis. Wee *et al*[12] reported sensitivities from 85% to 100% for EUS and 73% to 99% for MRCP. In a meta-analysis of five head-to-head studies comparing EUS to MRCP for choledocholithiasis, the pooled sensitivity and

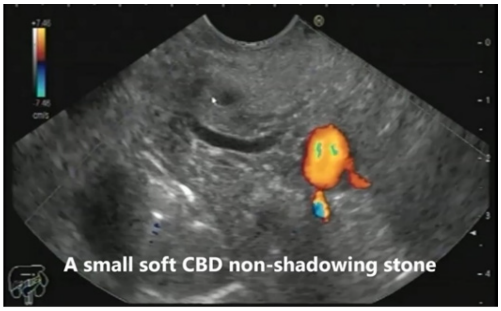

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Figure 4 A small soft non-shadowing common bile duct stone as seen from the bulb of the duodenum. CBD: Common bile duct.

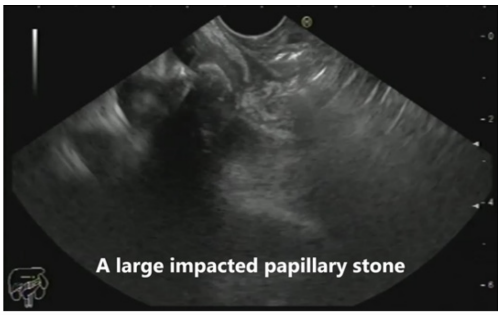

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Figure 5 An impacted stone in the region of the major papilla as seen in the mid-second part of the duodenum.

specificity of EUS were 97% and 90%, respectively, *vs* 87% and 92% for MRCP, respectively[14].

Also, de Lédinghen *et al*[15] reported a good sensitivity (100%) but low specificity (62%) for MRCP in diagnosing choledocholithiasis. Meanwhile, Materne *et al*[16] showed a 91% sensitivity and 94% specificity for MRCP, close to the values for EUS. The study conducted by Scheiman *et al*[17] reported significantly better results with EUS (sensitivity, 95%; specificity, 80%) than with MRCP (sensitivity, 40%; specificity, 96%) in diagnosing choledocholithiasis.

Another study compared the accuracy of EUS with ERCP in detecting choledocholithiasis and showed that EUS had a sensitivity of 100% and specificity of 94.7%.

One of the reasons for missed stones by MRCP that were detected by EUS was non-floating stones at the papillary region or distal CBD, as this is considered one of the pitfalls in MRCP interpretation, as mentioned by Irie *et al*[18]. Another reason was the stones with a diameter less than 5 mm (25 cases detected by EUS *vs* only 10 by MRCP), which suggests the accuracy of EUS in detecting small stones [19]. Also, EUS was superior to MRCP in detecting the number of stones inside the CBD (70 cases by EUS *vs* only 26 by MRCP), which is contradictory to the study of Aubé *et al*[20] that found no significant difference between the two modalities (MRCP detected four of six cases while EUS detected five of six cases).

Many studies comparing EUS and MRCP in idiopathic acute pancreatitis have shown that EUS has higher diagnostic yields than MRCP[21]. In this context, EUS should be considered the first choice in diagnosing idiopathic acute pancreatitis[22]. Biliary diseases such as cholelithiasis, choledocholithiasis, microlithiasis, and biliary sludge are the leading cause of idiopathic acute pancreatitis[23].

In our study, cases with unexplained pancreatitis were evaluated by EUS and MRCP, which showed that EUS was more sensitive in detecting stones than MRCP (90% *vs* 78%, respectively), as only seven patients proved to have CBD stones, of whom all were detected by EUS but only four were detected by MRCP[23]. Meanwhile, no other causes of acute pancreatitis as cystic pancreatic lesions, pancreatic divisum, or pancreatic duct stones could be detected by MRCP or EUS. And this finding is in agreement with Akkuzu *et al*[24], who reported a sensitivity of EUS and MRCP in evaluating acute pancreatitis of 89.65% and 72.4%, respectively.

Combining EUS with MRCP is very valuable in diagnosis of missed CBD stones than each one alone. In our study, the combination of the two tools raised the sensitivity, specificity, PPV, NPV, and overall accuracy into 97.22, 100, 100, 91.67, and 97.87, respectively.

The main limitation in our study was the financial cost of doing EUS, ERCP, and MRCP for all of the included patients. The second limitation was that we considered ERCP as the gold standard in detecting CBD stones. Although it is an accurate modality for detecting CBD stones, some false-negative cases may occur. Small stones may be missed if the CBD is under- or over-filling with contrast. Minute stones

or gravels may be missed during balloon sweeping. Also, in some cases, there was a time gap between ERCP and EUS that might give a chance of passage of small stones out of the CBD that could give false-positive results on EUS.

CONCLUSION

Our study showed that EUS and MRCP are not equal tools in diagnosing choledocholithiasis in patients with an intermediate probability of choledocholithiasis. EUS is more accurate than MRCP in detecting non-floating stones in the papillary region and small stones, especially those less than 5 mm, and defining the size and number of stones. Furthermore, combining EUS with MRCP proved to be very valuable in accurate diagnosis of patients with an intermediate probability of choledocholithiasis.

EUS could be a good first option for evaluating patients with an intermediate probability of choledocholithiasis when it is available with good experience.

Combining EUS with MRCP is recommended for accurate evaluation of patients with an intermediate probability of choledocholithiasis if both are available.

ARTICLE HIGHLIGHTS

Research background

Choledocholithiasis develops in up to 20% of patients with gall bladder stones. The challenge in diagnosis usually occurs with small stones that may be missed by magnetic resonance cholangiopancreatography (MRCP). Endoscopic ultrasound (EUS) is accurate in detecting common bile duct (CBD) stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

Research motivation

Still, there is a great challenge in diagnosing cases with an intermediate probability of choledocholithiasis that develop in up to 20% of patients with gall bladder stones. EUS can easily detect small stones that MRCP could miss. EUS still has many diagnostic purposes with a high accuracy in detecting CBD stones missed by MRCP, especially the small ones or those impacted at the distal CBD or the papillary region.

Research objectives

To evaluate the accuracy of EUS in detecting CBD stones missed by MRCP.

Research methods

Patients with an intermediate likelihood of choledocholithiasis according to ESGE guidelines and those with acute pancreatitis of undetermined cause were included. The presence of choledocholithiasis was evaluated by MRCP and EUS, and then results were confirmed by endoscopic retrograde cholangiopancreatography (ERCP). The sensitivity and specificity of EUS and MRCP were compared regarding the presence of stones, the size, and the number of detected stones.

Research results

Ninety out of 100 involved patients had choledocholithiasis, while ten patients were excluded as they had pancreatic or gall bladder masses during EUS examination. In choledocholithiasis patients, the mean age was 52.37 ± 14.64 years, and 52.2% were males. Most patients had biliary obstruction (74.4%), while only 23 (25.6%) patients had unexplained pancreatitis. The overall prevalence of choledocholithiasis was 83.3% by EUS, 41.1% by MRCP, and 74.4% by ERCP. Also, the number and size of CBD stones could be detected accurately in 78.2% and 75.6% by EUS and 41.1% and 70.3% by MRCP, respectively. The sensitivity of EUS was higher than that of MRCP (98.51% *vs* 55.22%), and their predictive value was statistically different ($P < 0.001$). Combination of both tools raised the sensitivity to 97.22% and specificity to 100%.

Research conclusions

EUS could be a useful tool in assessing patients with suspected choledocholithiasis especially if combined with MRCP. However, its usefulness depends on its availability and the experience of the local centers.

Research perspectives

EUS could be a good first option for evaluating patients with an intermediate probability of choledocholithiasis when it is available with good experience. Combining EUS with MRCP is recommended for

accurate evaluation of patients with an intermediate probability of choledocholithiasis if both are available.

ACKNOWLEDGEMENTS

We would like to acknowledge our great hospital, and its workers, nurses, and staff members, for all the support and help in this study and throughout our careers.

FOOTNOTES

Author contributions: Eissa M and Rady MA contributed equally in collecting the data and writing the manuscript; Abdellatef A read and revised the manuscript; Abbasy M and Kamal A read and approved the manuscript; Okasha HH revised and approved the final manuscript; all authors have read and approved the final manuscript.

Institutional review board statement: Our institution's Research Ethical Committee approved the study, and all patients gave their informed written consent before inclusion in the study, according to the ethical guidelines of the 1975 Declaration of Helsinki. The National Liver Institute IRB protocol number is 00305/2022.

Clinical trial registration statement: The clinical trial is registered with Brazilian Clinical Trials Registry (ReBec).

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

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

Data sharing statement: No additional data are available.

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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S-Editor: Wang LL
L-Editor: Wang TQ
P-Editor: Wang LL

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World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: https://www.f6publishing.com

World J Gastrointest Endosc 2022 September 16; 14(9): 575-580

DOI: 10.4253/wjge.v14.i9.575

ISSN 1948-5190 (online)

CASE REPORT

Isolated esophageal tuberculosis: A case report

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Specialty type: Gastroenterology and hepatology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): E

P-Reviewer: Anandan H, India; Meng FZ, China; Novita BD, Indonesia

Received: May 3, 2022
Peer-review started: May 5, 2022
First decision: June 16, 2022
Revised: July 11, 2022
Accepted: August 6, 2022
Article in press: August 6, 2022
Published online: September 16, 2022

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Abstract

BACKGROUND

Tuberculosis is endemic in Senegal. While its extra-pulmonary localization is rare, esophageal tuberculosis, particularly the isolated form, is exceptional. We report here a case of isolated esophageal tuberculosis in an immunocompetent patient.

CASE SUMMARY

A 58-year-old man underwent consultation for mechanical dysphagia that had developed over 3 mo with non-quantified weight loss, anorexia, and fever. Upper digestive endoscopy showed extensive ulcerated lesions, suggesting neoplasia. The diagnosis was confirmed by histopathology, which showed gigantocellular epithelioid granuloma surrounding a caseous necrosis. Thoracoabdominal computed tomography scan did not show another localization of the tuberculosis. The outcome was favorable with treatment.

CONCLUSION

Esophageal tuberculosis should be considered when dysphagia is associated with atypical ulcerated lesions of the esophageal mucosa, in an endemic area.

Key Words: Tuberculosis; Esophagus; Endoscopy; Case report

Core Tip: Isolated esophageal tuberculosis is rare. Often discovered during the exploration of dysphagia, the endoscopic aspects are not specific, and can simulate several pathologies. Biopsies can help with diagnosis by showing the granuloma to histology or by allowing molecular biology examinations. In this manuscript, we report a case of isolated esophageal tuberculosis with vast ulcers of the esophagus, which evolved without sequelae after treatment.

Citation: Diallo I, Touré O, Sarr ES, Sow A, Ndiaye B, Diawara PS, Dial CM, Mbengue A, Fall F. Isolated esophageal tuberculosis: A case report. *World J Gastrointest Endosc* 2022; 14(9): 575-580
URL: https://www.wjgnet.com/1948-5190/full/v14/i9/575.htm
DOI: https://dx.doi.org/10.4253/wjge.v14.i9.575

INTRODUCTION

Tuberculosis is endemic in Senegal, where it constitutes a major public health problem. In 2020, 12808 new cases of tuberculosis were reported in Senegal, the majority of which were pulmonary (National Controlling Tuberculosis Program, data not published). Extrapulmonary forms of tuberculosis are frequent, whether or not they are associated with pulmonary involvement. In the digestive tract, the terminal ileum and the cecum are most often affected. Esophageal localization is rare, especially in its isolated form. We report herein a case of isolated esophageal tuberculosis in an immunocompetent patient who responded well to antibacillary treatment.

CASE PRESENTATION

Chief complaints

A 58-year-old patient was seen in our department for dysphagia that had developed over 3 mo.

History of present illness

The patient had dysphagia that had been evolving for 3 mo with non-quantified weight loss, nonselective anorexia, and nocturnal fever.

History of past illness

The patient had undergone appendectomy at 23-years-old.

Personal and family history

The patient's other personal and family histories were unremarkable.

Physical examination

The patient was in good general condition (World Health Organization performance status of 0), with a body mass index of 21.55 kg/m^2. Clinical examination was normal.

Laboratory examinations

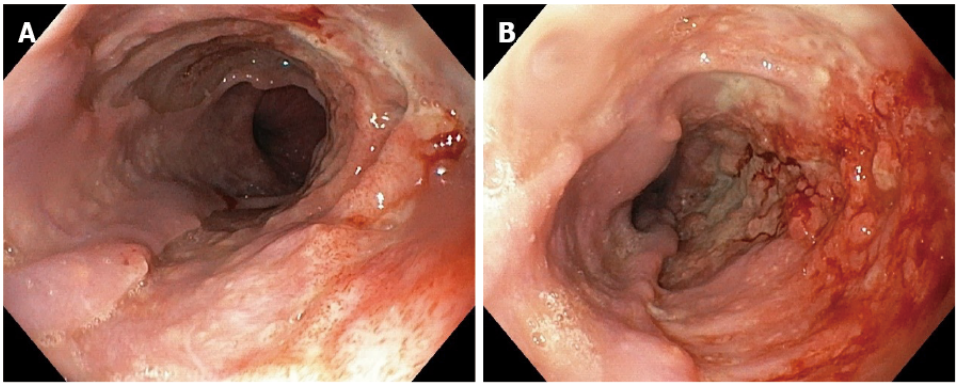
Biological investigations (blood count, liver function tests, glycemia, renal function, and C-reactive protein) were normal. The viral serologies for hepatitis B, hepatitis C, and human immunodeficiency virus were negative.

Imaging examinations

The thoracoabdominal computed tomography (CT) scan did not show any mediastinal lymph nodes in contact with the esophagus or other foci of tuberculosis.

ENDOSCOPIC EXAMINATION

Upper gastrointestinal (GI) endoscopy showed a jagged appearance of the thoracic esophageal mucosa for about 12 cm, stopping 3 cm above the cardia, with large irregular ulcers and raised contours. Nodules were present both at the level of the ulcers and in the normal-appearing mucosa (Figure 1A). Chromoendoscopy with narrow-band imaging did not detect areas that might suggest dysplasia or carcinoma (Figure 1B).



DOI: 10.4253/wjge.v14.i9.575

Figure 1 Upper gastrointestinal endoscopy. A: Esophageal ulcer; B: Esophageal ulcer with nodules.

ANATOMICAL PATHOLOGY

Esophageal biopsies revealed a deep loss of wall tissue, reaching the muscularis mucosa. The normal tissue was replaced by granulation tissue containing a tuberculoid granuloma with several follicles consisting of epithelioid and multinucleated Langerhans histiocytes, surrounding a caseous necrosis (Figure 2). Neither culture of tissue samples nor PCR test for *Mycobacterium tuberculosis* were performed. Sputum and gastric acid liquid after aspiration were negative for acid-fast bacilli (AFB).

FINAL DIAGNOSIS

Isolated esophageal tuberculosis.

TREATMENT

An antituberculosis treatment was initiated [rifampicin, isoniazid, ethambutol, and pyrazinamide (RHEZ) and administered for 2 mo, and with rifampicin and isoniazid (RH) for 4 mo]. The patient showed good tolerance.

OUTCOME AND FOLLOW-UP

The patient's outcome was favorable, with a clear improvement of dysphagia after 15 d of treatment, which disappeared after 5 wk. Upper digestive endoscopy after 4 mo of treatment showed a normal esophageal mucosa. Six months after stopping the treatment, the patient was well, had regained weight, and did not complain of dysphagia.

DISCUSSION

Described for the first time in 1837 by Denonvilliers during an autopsy, infectious esophagitis due to tuberculosis is rare, even in countries with high tuberculosis endemicity. The esophageal localization represents 0.2%-1% of tuberculosis cases of the GI tract[1,2]. This low incidence can be explained by several mechanisms that allow the esophagus to fight infection, in particular, peristaltic movements leading to emptying of the contents into the stomach, and the presence of mucus and saliva lining the mucosa and its squamous epithelium[1]. These mechanisms provide a barrier against primary contamination caused by the ingestion of food or saliva containing germs such as *M. tuberculosis*. However, secondary contamination by contact with neighboring organs, especially in cases of tuberculosis in paraesophageal lymph nodes, is possible[3]. Blood-borne contamination is rare.

The most common symptom during esophageal tuberculosis is dysphagia (90% of cases), which was the main sign in our patient. Odynophagia, pyrosis, and chest pain may also be present[4]. The occurrence of coughing at mealtime should raise suspicion of an esotracheal or esophageal-mediastinal fistula, which is present in 13%-50% of cases[5]. The presence of hematemesis can also provide further evidence of a fistula[6].

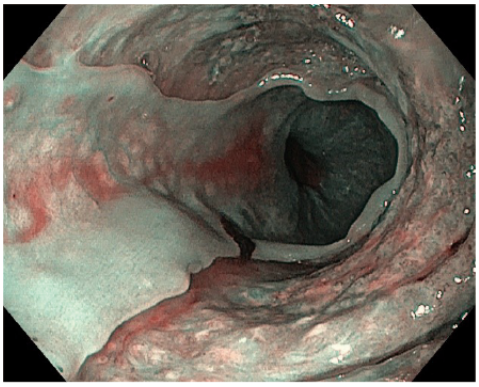


Figure 2 Esophageal biopsies. Esophageal ulcer detected in narrow band imaging.

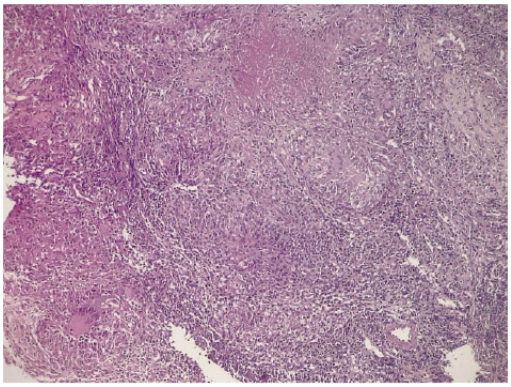


Figure 3 Granuloma with caseous necrosis (hematoxylin-eosin: 10 ×).

The endoscopic appearance of esophageal tuberculosis is variable and nonspecific. In our patient, the lesion was located in the lower two-thirds of the esophagus and consisted of a large ulcer with raised contours, associated with micronodules. The esophagus can be affected throughout its length, although the lesion is most often located in the middle third[3,7,8], because of the extensive lymphoid tissue in this region. Endoscopy may show an ulcer of variable size, superficial with regular contours or irregular and infiltrative simulating neoplasia, or show a more or less ulcerated budding aspect of the mucosa[3, 9]. An extrinsic compression aspect with a mucosa of normal appearance can also be found[8]. Endoscopic ultrasound can be helpful for diagnosis, allow analysis of the thick esophageal wall, and guide biopsies[7]. It also allows for exploration of the mediastinum and performance of fine-needle biopsy of potentially involved lymph nodes[7]. Thoracic CT scan often shows a thickening of the eso-phageal wall and allows for searching of adjacent lymph nodes, pulmonary location, or esotracheal or esophago-mediastinal fistulas.

Histology can help in the diagnosis of esophageal tuberculosis. Mucosal biopsies during upper GI endoscopy can show the presence of a tuberculous granuloma or AFB in about 50% of cases[10,11], but sometimes neither of these lesions is found[12]. In our patient, an epithelioid gigantocellular granuloma with caseous necrosis was present on histology (Figure 3), confirming the diagnosis of esophageal tuberculosis. To improve diagnostic success, deep biopsy samples should be taken from ulcerated areas, as granulomas are most often found in the submucosa[1,8,11]. If endoscopic biopsies are not contributive, deep esophageal biopsy or fine-needle aspiration of a satellite lymph node, guided by endoscopic ultrasound, make it possible to find an epithelioid granuloma on histology (reportedly in 94.7% to 100% of cases, with caseous necrosis and/or AFB present in 55% to 75% of those cases)[7,11]. Histological samples are also used for PCR or culturing methods to identify *M. tuberculosis*. If an epithelioid granuloma without caseous necrosis is present, a differential diagnosis with sarcoidosis, Crohn's disease, or a carcinoma must be considered.

The treatment of esophageal tuberculosis is essentially medical, according to the standard protocol (rifampicin, isoniazid, ethambutol, and pyrazinamide daily for 2 mo, followed by rifampicin and isoniazid daily for 4 mo) for at least 6 mo. However, the optimal duration is not clinically established. In the case of fistula, clips are the reference treatment for lesion closure[11,13]. The outcome during treatment for esophageal tuberculosis is favorable and without sequelae in almost all cases[3,7,8,11]. In

our patient, no sequelae were noted during the follow-up. Upper digestive endoscopy, 4 mo after the beginning of treatment, was normal. The patient had no complaints at 6 mo after the end of treatment.

CONCLUSION

Esophageal tuberculosis is a rare cause of infectious esophagitis, even in a country where tuberculosis is endemic. Nevertheless, esophageal tuberculosis should be considered when dysphagia is associated with atypical ulcerated lesions of the esophageal mucosa. The presence of gigantocellular epithelioid granulomas on esophageal biopsies confirms the diagnosis. The patient's outcome is generally favorable after antibacillary treatment, as illustrated by our observation.

FOOTNOTES

Author contributions: Diallo I performed the upper digestive endoscopy, followed up with the patient, and wrote the manuscript; Touré O, Sow A, and Ndiaye B contributed to collecting the patient's clinical data, and participated in the follow-up; Sarr ES and Dial CM conducted the anatomopathological examinations; Diawara PS conducted the biological tests; Mbengue A performed the radiological examinations; Fall F supervised the manuscript; all authors have read and approved the final manuscript.

Informed consent statement: Consent was obtained from the patient.

Conflict-of-interest statement: All authors report no relevant conflict of interest for this article.

CARE Checklist (2016) statement: The authors have read the CARE Checklist (2016), and the manuscript was prepared and revised according to the CARE Checklist (2016).

Country/Territory of origin: Senegal

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S-Editor: Wu YXJ
L-Editor: A
P-Editor: Wu YXJ

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