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Jin-Lei Wang, Director
Xiu-Xia Song, Vice Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-85381891
Fax: +86-10-85381893

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EDITORIAL

Sedation-related complications in gastrointestinal endoscopy

Somchai Amornyotin

Somchai Amornyotin, Department of Anesthesiology and Siriraj Gastrointestinal Endoscopy Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand
Author contributions: Amornyotin S solely contributed to the manuscript.
Correspondence to: Somchai Amornyotin, Associate Professor, Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand. somchai.amo@mahidol.ac.th
Telephone: +66-2-4197990 Fax: +66-2-4113256
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Abstract

Sedation practices for gastrointestinal endoscopic (GIE) procedures vary widely in different countries depending on health system regulations and local circumstances. The goal of procedural sedation is the safe and effective control of pain and anxiety, as well as to provide an appropriate degree of memory loss or decreased awareness. Sedation-related complications in gastrointestinal endoscopy, once occurred, can lead to significant morbidity and occasional mortality in patients. The risk factors of these complications include the type, dose and mode of administration of sedative agents, as well as the patient's age and underlying medical diseases. Complications attributed to moderate and deep sedation levels are more often associated with cardiovascular and respiratory systems. However, sedation-related complications during GIE procedures are commonly transient and of a mild degree. The risk for these complications while providing any level of sedation is greatest when caring for patients already medically compromised. Significant unwanted complications can generally be prevented by careful pre-procedure assessment and preparation, appropriate monitoring and support, as well as post-procedure management. Additionally, physicians must be prepared to manage these complications. This article will review sedation-related complications during moderate and deep sedation for GIE procedures and also address their appropriate management.

Key words: Sedation; Complication; Gastrointestinal; Endoscopy

Core tip: Gastrointestinal endoscopic (GIE) procedures are relatively safe. However, these procedures have been shown to cause various effects on cardiorespiratory systems. Sedation-related complications while providing any level of sedation can occur. Fortunately, these complications during GIE procedures are commonly transient and of a mild degree. In addition, significant unwanted complications can generally be prevented by careful pre-procedure assessment and preparation, appropriate monitoring and support. Periodical assessment of the level of sedation and continuous monitoring of cardiovascular and respiratory systems provides timely information. Standardized discharge criteria should be used to determine the patient's readiness for discharge.

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INTRODUCTION

Gastrointestinal endoscopic (GIE) procedures are relatively safe and now performed routinely because of their minimal invasiveness and diagnostic and therapeutic capabilities. These procedures have been shown to cause various effects on cardiorespiratory systems, which can increase the risks of the procedure in patients with underlying cardiorespiratory diseases[1,2]. Additionally,

complications attributed to moderate and deep sedation levels are more often associated with cardiovascular and respiratory systems. Most predictors of sedation-related complications are patient-centered factors and do not vary significantly from procedure to procedure, although the procedure is complex[3].

Providing sedation has been the most effective strategy employed, with most patients preferring the use of sedation during endoscopy. The use of sedative agents has been found to improve the performance of the endoscopy, enhancing the successful completion of the procedure. The incidence of sedation-related complications associated with a GIE procedure is relatively low. Risk factors for these complications are age > 60 years, high American Society of Anesthesiologists (ASA) physical status, inpatient status and the involvement of a trainee in the procedure[4,5]. Sedation-related complications during GIE procedures are usually transient and of a mild degree. The risk of these complications while providing any level of sedation is greatest when caring for patients already medically compromised. Significant unwanted complications can generally be prevented by careful pre-sedation assessment and preparation, appropriate monitoring and support, as well as post-sedation management.

PRE-SEDATION ASSESSMENT

All patients scheduled to receive sedation should have an up-to-date history and relevant physical examination. Many risk factors to be aware of are a history of sleep apnea, alcohol or substance abuse, adverse reaction to sedative drugs, and prolonged duration of procedure. Patients should be classified using the criteria of the ASA[6]. Cardiorespiratory problems which could occur during the GIE procedure should be carefully evaluated.

Before undertaking any GIE procedure, endoscopists should obtain informed consent from the patient, be familiar with the latest guidelines on sedation, be aware of any medical, surgical and drug history elicited in the pre-admission process, and risk factors should be identified in both out-patients and in-patients[7,8]. Additionally, physicians must be prepared to manage sedation-related complications. Respiratory depression and oxygen desaturation from the sedative agents used to achieve sedation are thought to be important risk factors for these complications. So, safety and monitoring should be part of a quality assurance program for endoscopy units. This article will review sedation-related complications during GIE procedures and also address their appropriate management.

POST-SEDATION PERIOD

Most sedation-related complications occur during the GIE procedure. Standard monitoring, including non-invasive blood pressure, heart rate, pulse oximetry and ECG, is also routinely used in the post-sedation period. Post-procedural nausea/vomiting and pain need to be resolved, especially in ambulatory patients. Fortunately, a lower incidence of procedural nausea/vomiting and pain after the GIE procedure is observed even in a therapeutic endoscopy[9]. Opioid and cyclo-oxygenase-2-inhibitors can be safely and effectively used for procedural pain in GIE patients[10].

Sedated patients are discharged from the recovery area when the discharge criteria are met. My previous study showed that periodic objective evaluation of home-readiness revealed that the majority of patients would achieve a satisfactory score on or before 1 h after the GIE procedure[11]. So, patients that have undergone GIE procedures should be admitted to the recovery room unit for at least 30-60 min before discharge. The time to home-readiness by objective evaluation correlates with the type of procedure. Most delays after satisfactory home-readiness scores were reached were due to non-medical reasons.

Sedation-related cardiorespiratory complications also occur immediately after the GIE procedure. The types of complications in the post-sedation period are similar to the intra-sedation period. Patients who receive benzodiazepine and/or opioid antagonists should be closely observed in the recovery room unit longer than the other patients. If the patient received a reversal agent, the patient must be in a recovery room for at least 2 h after the last administration of that reversal agent.

REVERSAL DRUGS

Naloxone

Naloxone is a pure mu-opioid antagonist with a high affinity for the receptor. It can reverse both the analgesic and respiratory effects of opioids[12]. Naloxone may be administered intravenously, intramuscularly, subcutaneously and *via* an endotracheal tube. The dosage of intravenous naloxone is 1 mcg/kg to 2 mcg/kg every 2-3 min with a maximum dose of 0.1 mg/kg, up to 2 mg. Because of its rapid removal from the brain, naloxone has a short duration of action and one dose typically only lasts for 30-45 min. The patient should be monitored for at least 2 h after administration of naloxone to ensure that resedation does not occur. Potential adverse reactions of naloxone include reversal of opioid withdrawal, nausea/vomiting, hypertension, tachycardia, pulmonary edema and cardiac dysrhythmias.

Flumazenil

Flumazenil is a benzodiazepine antagonist that can safely reverse the sedative and respiratory effects caused by benzodiazepines[1]. It is a highly specific benzodiazepine receptor antagonist. The usual adult dose is 0.01 mg/kg, up to 1 mg. Its clinical duration of action is approximately 1 h[12]. However, its effects are reversible, so it is not recommended for routine use. Similar to naloxone, patients should be monitored for at least 2 h after administration of flumazenil to ensure that resedation does not occur. Potential adverse reactions of flumazenil include sweating, flushing, nausea/vomiting, hiccups, agitation,

abnormal vision, paresthesia and seizures.

CARDIOVASCULAR-RELATED COMPLICATIONS

The autonomic nervous system plays an important role in maintaining normal hemodynamics and an adequate coronary blood flow. The sympathetic nervous system regulates the heart rate and rhythm and increases the excitability of the myocardium. The parasympathetic nervous system regulates the heart rate and rhythm, which when stimulated can lead to sinus bradycardia[13]. Cardiorespiratory complications account for about 50% of potentially serious morbidity and about 50% of all procedure-related deaths associated with the GIE procedure. In many cases, these complications are a direct or indirect consequence of elderly or at risk patients being given unnecessarily high doses of sedative and analgesic drugs[1].

Hypotension

A significant decline in blood pressure from baseline should alert clinicians. Hypotension is defined as systolic blood pressure less than 90 mmHg which is due to a fall in either cardiac output or total peripheral resistance, lowering the patient's mean arterial pressure[14]. Episodes of hypotension in clinical practice are most commonly associated with vasovagal events and are generally transient. However, they may become prolonged in the presence of central nervous system depressants[1]. Blood pressure is a reflection of cardiac output and total peripheral resistance and a fall in either or both will lower the patient's mean arterial pressure. In general, a systolic blood pressure of 90 mmHg should sustain mean arterial blood pressure sufficiently to perfuse tissues in the recumbent patient. Blood pressure lower than this, combined with evidence of inadequate perfusion, requires intervention.

The evaluation of tissue perfusion is the most significant component of cardiovascular assessment. Hypotension encountered during sedation is usually attributed to either vasovagal episodes or the use of sedative and anesthetic agents that depress sympathetic outflow to the cardiovascular system. Benzodiazepines, such as midazolam and diazepam, have a mild vasodilator effect and usually produce a slight fall in arterial blood pressure, even in normal sedative doses. The combination use of a benzodiazepine and an opioid can profoundly drop blood pressure. Propofol has been shown to be safe and effective for sedation during endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography and small bowel enteroscopy because these procedures require more time and patient co-operation[15-19].

Cardiovascular effects of propofol include decreases in cardiac output, systemic vascular resistance and arterial pressure. A fall in heart rate and/or cardiac stroke volume will also lower blood pressure. Additionally, more profound falls in blood pressure occur in a hypovolemic patient. Propofol has also been proven to reduce postprocedural hypoxemic events, which may be of significance in critically ill elderly patients[20,21] and sick pediatric patients[22,23]. Prevention of this complication is to take a relevant medical and drug history before the procedure with particular detail required regarding current antihypertensives, antianginal and antiarrhythmic therapy and the use of systemic corticosteroids. The use of volume supplementation might be beneficial and could therefore be recommended in order to avoid propofol-induced hypotension. Additionally, blood pressure and heart rate should be recorded before, during and after the endoscopic procedure.

Hypertension

Blood pressure continuously fluctuates due to the cyclic nature of the pumping action of the heart. The highest pressure occurs during ventricular contraction. The lowest pressure occurs during ventricular relaxation[24]. Generally, hypertension is defined as the systolic blood pressure greater than 160 mmHg. Sudden elevations of systolic blood pressure $\geqslant$ 180 mmHg or diastolic blood pressure $\geqslant$ 110 mmHg are generally regarded as an acute hypertensive episode[25]. The causes of hypertension are background systemic hypertension, anxiety or pain, and a reflex pressure response from intubation of the esophagus. Generally, asymptomatic patients and patients without acute end-organ symptoms should not receive antihypertensive agents in the endoscopy unit.

Cardiac arrhythmias

Autonomic control of the heart rate will respond to demands placed on the patient and may be initiated *via* several baroreceptor-mediated reflexes[20]. Electrocardiogram (ECG) is also a useful monitor for heart rate and a better assessment of heart rhythm. Continuous ECG monitoring is recommended for a high risk patient with relevant cardiac history. Cardiac arrhythmias are frequently observed during GIE procedures. Fortunately, most of them are not clinically significant.

In healthy patients, a heart rate of up to 120 beats/min will usually allow adequate filling. Sinus tachycardia can be caused by a patient's anxiety or be related to pain, a compensatory mechanism in patients who are hypotensive as a result of either dehydration or blood loss, and following intravenous anticholinergic drugs such as buscopan. Heart rate < 50 beats/min in healthy patients may allow for more time in diastole, but ventricular filling becomes maximized[24]. Sinus bradycardia is most frequently seen in patients who are taking beta blockers. It can also be induced by vagal stimulation, which occurs at the time of intubation of the esophagus or the stretching of the sigmoid mesentery during colonoscopy or flexible sigmoidoscopy.

Myocardial ischemia/infarction

Myocardial infarction occurs either during or in the few days after endoscopic procedures with or without sedation. A proportion of these are undoubtedly causally related to the endoscopic procedure. The causes of angina

or myocardial infarction are two factors: increased myocardial oxygen demand and reduced myocardial perfusion[26].

Increased myocardial oxygen demand is due to an increase in the mean arterial blood pressure and heart rate. This can cause angina in patients with ischemic heart disease or occult symptomless myocardial ischemia. Additionally, marked hypertension and/or tachycardia increase myocardial oxygen consumption. On the other hand, hypotension and/or bradycardia reduce myocardial perfusion. Stress-induced myocardial ischemia can occur even in patients with or without clinically significant coronary disease[27]. This myocardial ischemia is related to the activation of the sympathetic nervous system, resulting in hemodynamic changes causing an increase in cardiac demand.

Prevention or minimization of myocardial ischemia/infarction during GIE procedure: (1) pre-oxygenation in at risk patients and give continuous supplemental oxygen; (2) give patients their normal anti-hypertensive and/or antianginal therapy right up to the time of the endoscopy; (3) angina developing during an endoscopy is usually best managed by giving sublingual nitroglycerine, oxygen supplementation and discontinuing the examination; and (4) if angina or myocardial infarction is suspected during or following an endoscopy, arrange an ECG to exclude an myocardial infarction.

RESPIRATORY-RELATED COMPLICATIONS

Airway management is the most important aspects of patient care and examination of the patient's airway is an essential component of the preoperative assessment. Mallampati score correlates with increased difficulty in airway management. High oxygen concentration is indicated for patients who are spontaneously breathing, regardless of their level of consciousness during medical urgencies and emergencies. The equipment required to provide supplemental oxygen includes a 100% oxygen source, a regulator, tubing and either a nasal cannula or mask. Every office should be equipped with a portable E-cylinder of oxygen.

Respiratory depression

A higher dose of benzodiazepine and/or opioid and the greater the percentage benzodiazepine and/or opioid receptor occupancy in the central nervous system, the greater is the degree of depression of consciousness. Intravenous benzodiazepines such as midazolam and diazepam can cause respiratory depression. Intravenous opioids, such as meperidine and fentanyl, occupy opioid receptor sites within the brain and brainstem and can similarly cause respiratory depression[26]. Drug induced hypoventilation may cause both hypoxemia and carbon dioxide retention.

Pulse oximetry is a very useful indicator of oxygenation but not ventilation. However, when supplemental oxygen is used, the fall in SpO_2 may be significantly delayed for between 30-90 s, so continuous capnography monitoring is recommended in patients being deeply sedated with propofol[1]. As for over-sedation, loss of verbal contact due to a reduced conscious level may be the first sign of impending respiratory depression. Reduction in SpO_2 on pulse oximetry is a good indicator but it can be a late sign of respiratory depression. Increased $PaCO_2$ is the most sensitive early warning of respiratory depression[28]. However, several controlled randomized studies showed a beneficial effect of capnography regarding some surrogate parameters of patients, such as the occurrence of hypoxemia detected by pulse oximetry, but a clear effect on patient outcome has not been demonstrated. Therefore, most national guidelines do not recommend its routine use currently.

Management of over-sedation is to stimulate the patient, both verbally and/or by light shaking, to wake up and take deep breaths. If the patient is not responding, then a benzodiazepine antagonist such as flumazenil and/or opioid antagonist such as naloxone may be required. The airway may need to be protected with chin lift, jaw thrust and, if necessary, airway or laryngeal mask[26].

Airway obstruction

Obstruction may result in hypoventilation and hypoxia. However, airway obstruction must be distinguished from respiratory depression. Hypoxia is common in patients undergoing an upper GIE procedure with or without sedation. Sedation significantly increases the incidence of desaturation and hypoxia. Supplementary nasal oxygen at 3 L/min in sedated patients abolishes desaturation and hypoxia. Upper airway obstruction may be attributed to anatomical structures or a foreign body[29]. Independent predictors of airway modifications include male sex, ASA class of Ⅲ or higher, and increased body mass index[1].

Laryngospasm is a reflex closure or spasm of the glottic muscles, including the false and true vocal cords. It is more likely to occur during deep sedation. Laryngospasm occurs more frequently in adults who are smokers. Bronchospasm is a lower airway obstruction due to contraction or spasm of the bronchial smooth muscle. It may be a result of an anaphylactoid reaction or a consequence of a hyper-reactive airway in asthmatic patients[30]. Management of laryngospasm and bronchospasm depends on the severity and the cause.

Hypoxia

Hypoxia may be a consequence of respiratory depression or airway obstruction. The incidence of hypoxia is 1.5% to 70%, which makes it the most common cardiorespiratory complication during endoscopy[31]. Hypoxemia can lead to several complications, depending on the severity of hypoxemic attack. The use of supplemental oxygen during a GIE procedure is routinely used by many endoscopists. However, oxygen supplementation will delay the detection of apnea and hypoxia[5]. Additionally, in patients given supplemental oxygen, saturation may be maintained

in the progression of hypercapnia.

Multivariable logistic regressions revealed that independent risk factors for hypoxemia include high body mass index, hypertension, diabetes, gastrointestinal diseases, heart diseases and procedures that combined esophagogastroduodenoscopy (EGD) and colonoscopy[32]. Hypoxemia occurs typically within 5 min of medication administration or endoscope intubation and only one third of all apnea and abnormal ventilation events eventually lead to hypoxemia[31].

Pulmonary aspiration

Aspiration of gastric contents into the lungs during a GIE procedure is relatively common. It may cause pneumonia and may result in death. Risk factors for aspiration are the elderly, over-sedated patients, patients with gastrointestinal bleeding, gastric stasis, gastric outlet obstruction, hepatic encephalopathy and a full stomach. Aspiration can also occur when a local anesthetic spray is used in combination with intravenous sedation[26].

Aspiration may be suspected when a patient starts coughing violently either during or soon after an endoscopic procedure and cyanosis may occur. The higher incidence of pulmonary aspiration is because of the better sensitivity of 2-[^{18}F] fluoro-2-deoxy-D-glucose positron tomography. However, the low incidence of clinical events needing intervention may still reflect the safety of sedation used for the GIE procedure[33]. Treatments of pulmonary aspiration includes suction of fluids from oral cavity and throat, increasing the rate of supplemental oxygen, encouraging the patient to cough, chest film, antibiotics and physiotherapy.

ALLERGIC REACTIONS

Pre-sedation assessment includes a comprehensive evaluation of the patient's allergic history. Generally, it is important not to confuse an increased sensitivity or side effect of a drug. Although rare, severe allergic reactions can occur during anesthesia or sedation. The spectrum of allergic reactions can include a minor local reaction to more severe anaphylactic reactions. The diagnosis of anaphylactic reaction is not always easy to establish.

The potential risk of propofol administration in patients with a known allergy against soy beans and egg should be stated[34]. In addition, propofol usually produces a burning sensation at the injection site. Some opioids such as meperidine can cause a transient red wheal which is caused by local release of histamine. However, this reaction is a transient phenomenon with no sequelae. Anaphylactic reactions can present with mild dyspnea in mild cases or lead to hypotension and shock in severe cases. When a life threatening anaphylactic reaction does occur, it simulates an acute cardiac, respiratory and metabolic crisis and requires urgent acute critical care. Treatment for anaphylactic reactions includes the discontinuation of the suspected allergen, airway management, fluid resuscitation, anti-histamine drugs, hydrocortisone and epinephrine.

OTHER COMPLICATIONS

Nausea and vomiting

Nausea and vomiting are common side effects of opioids. Additionally, the over distension of the stomach or colonic loop can produce nausea and vomiting after the endoscopic procedure. The prevention of this complication is to reassure the patient and to minimize the opioid dose. In severe cases, anti-emetic agents such as metoclopramide and ondansetron may be required[35].

Paradoxical reactions

Paradoxical reactions are characterized by combativeness, agitation, talkativeness, disorientation and tachycardia. This reaction frequently occurs with benzodiazepines, in particular midazolam and diazepam, and is more common in children[36]. Inadequate sedation or cerebral hypoxia may mimic paradoxical reactions. Early recognition of paradoxical reactions is imperative for proper management. The administration of a benzodiazepine antagonist such as flumazenil has been shown to be effective in managing paradoxical reactions with minimal side effects.

PREVENTION OF SEDATION-RELATED COMPLICATIONS

Generally, GIE procedures can be performed by using topical anesthesia, intravenous sedation and general anesthesia[17,37,38]. Topical anesthesia and intravenous sedation techniques can be effectively done by non-anesthetic personnel. Most national guidelines and several studies from the literature demonstrate that non-anesthetic personnel can safely perform propofol sedation[39-41]. However, non-anesthetic personnel should sedate patients only to mild and moderate (conscious) sedation levels[42]. Several previous studies demonstrated the feasibility and safety of computer-assisted personalized sedation (CAPS) to facilitate propofol sedation by non-anesthetic personnel in patients who underwent EGD and colonoscopy procedures[43-45]. The SEDASYS System is the first CAPS system designed for physicians to provide minimal to moderate sedation levels with propofol. The system continuously monitors and records patient parameters, including oxygen saturation, blood pressure, heart rate, respiratory rate, end tidal carbon dioxide and patient responsiveness.

The risk of GIE procedures can be associated with sedation. The depth of sedation level is one of the risk factors of sedation-related complications. High sedation depth can significantly create sedation-related complications greater than a low sedation depth. Patients with mild hypotension, with co-morbidities and the elderly should be carefully sedated. The titration technique should be used to sedate these patients. Additionally, physicians should continuously monitor the depth of sedation[46,47].

Prevention of complications in the first place is the best form of management. It is also the professional responsibility of health providers to prevent the avoidable

risks by following national standards for safe sedation. Patients under sedation must have physiological monitoring, including heart rate, blood pressure, oxygen saturation and an expired concentration of carbon dioxide. An anesthesiologist consultation should be done in patients with moderate to severe hypotension (systolic blood pressure < 90 mmHg), patients with severe cardiac and/or respiratory abnormalities, patients with a history of failed sedation, alcoholic or drug addicted patients, phobic or uncooperative patients, such as children, dementia and psychiatric patients, patients being sedated with intravenous propofol, and patients with a high risk of aspiration and requiring endotracheal tube with general anesthesia, including patients with depressed levels of consciousness and patients associated with encephalopathy[48,49].

CONCLUSION

Sedation-related complications are relatively common. However, the majority of these complications are transient and easily treated. Serious complications are rare for GIE procedural sedation. Sedation-related complications may be severe if physicians do not detect and treat patients earlier. Appropriate pre-sedation assessment and proper patient selection, preparation and optimization of patients, as well as the availability of skilled professionals for sedation administration are key components to provision of quality patient care. Periodical assessment of the level of sedation and continuous monitoring of cardiovascular and respiratory systems provides timely information. Pulse oximetry and oxygen supplementation are recommended for the reduction of hypoxemia. Capnography monitoring is considered in patients undergoing prolonged endoscopic procedures who are at risk of deep sedation. Additionally, standardized discharge criteria should be used to determine the patient's readiness for discharge. Lastly, physicians should remember that the risk for an unintended deeper level of sedation may be more common after the stimulation of the endoscopic procedure has been removed.

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FIELD OF VISION

Recent advances in photoacoustic endoscopy

Tae-Jong Yoon, Young-Seok Cho

Tae-Jong Yoon, Department of Applied Bioscience, CHA University, Seoul 135-081, South Korea
Young-Seok Cho, Division of Gastroenterology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea College of Medicine, Uijeongbu 480-717, South Korea
Author contributions: Yoon TJ collected materials and wrote the manuscript; Cho YS collected materials, mainly wrote the manuscript and supervised the publication of this commentary.
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Correspondence to: Young-Seok Cho, MD, PhD, Division of Gastroenterology, Department of Internal Medicine, Uijeongbu St. Mary's Hospital, The Catholic University of Korea College of Medicine, 271 Cheonbo-ro, Uijeongbu 480-717, South Korea. yscho@catholic.ac.kr
Telephone: +82-31-8203658 Fax: +82-31-8472719
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Abstract

Imaging based on photoacoustic effect relies on illuminating with short light pulses absorbed by tissue absorbers, resulting in thermoelastic expansion, giving rise to ultrasonic waves. The ultrasonic waves are then detected by detectors placed around the sample. Photoacoustic endoscopy (PAE) is one of four major implementations of photoacoustic tomography that have been developed recently. The prototype PAE was based on scanning mirror system that deflected both the light and the ultrasound. A recently developed mini-probe was further miniaturized, and enabled simultaneous photoacoustic and ultrasound imaging. This PAE-endoscopic ultrasound (EUS) system can offer high-resolution vasculature information in the gastrointestinal (GI) tract and display differences between optical and mechanical contrast compared with single-mode EUS. However, PAE for endoscopic GI imaging is still at the preclinical stage. In this commentary, we describe the technological improvements in PAE for possible clinical application in endoscopic GI imaging. In addition, we discuss the technical details of the ultrasonic transducer incorporated into the photoacoustic endoscopic probe.

Key words: Photoacoustic techniques; Tomography; Endoscopy; Endosonography; Gastrointestinal neoplasm

Core tip: Photoacoustic imaging is an emerging modality, and provides image information of optical contrast or functional properties by detecting ultrasonic waves. The major advantage of photoacoustic imaging is the greater penetration depth, of millimeters to centimeters, in tissue. The aim of this article is to introduce the technological improvements in photoacoustic endoscopy (PAE) for possible clinical application in endoscopic gastrointestinal imaging. In addition, the technical details of an integrated PAE and endoscopic ultrasound imaging system are discussed.

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COMMENTARY ON HOT TOPICS

Photoacoustics is described as laser induced ultrasound[1]. Imaging based on photoacoustics uses short light pulses (nanosecond range) as the source. As pulsed light is absorbed by tissue absorbers, such as hemoglobin or melanin, a transient temperature increase is generated, resulting in local thermoelastic expansion, giving rise to ultrasonic waves[2]. These ultrasonic waves are then detected by ultrasonic detectors placed around the sample (Figure 1). An important advantage of photoacoustic imaging is that the method can overcome the high degree of scattering of optical photons in biological tissue, resulting in high spatial resolution deep within tis-

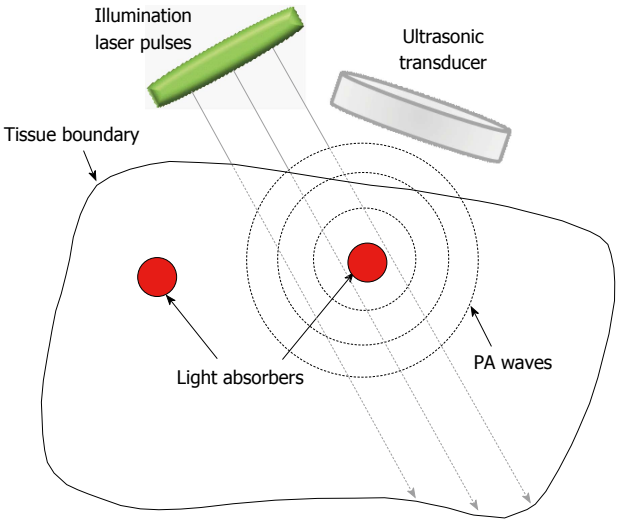

Figure 1 Illustration of the photoacoustic effect and photoacoustic imaging. Reproduced with permission from Yao *et al*[6]. PA: Photoacoustic.

sue[3]. Although photoacoustic spectroscopy and simple imaging was developed in the 1970s, only recently has photoacoustic imaging become important in biomedical research[4]. A major photoacoustic imaging for biomedical applications is photoacoustic tomography (PAT). PAT is similar to conventional ultrasound imaging, because image information is provided by capturing the ultrasonic waves using mechanical scanning or by detection arrays[2]. However, while conventional ultrasound imaging measures only mechanical contrasts, PAT detects optical and thermoelastic contrasts[5]. Currently, PAT has four major implementations: raster-scan based photoacoustic microscopy (PAM), inverse-reconstruction based photoacoustic computed tomography (PACT), rotation-scan based photoacoustic endoscopy (PAE), and hybrid PAT systems with other imaging methods (Figure 2)[6].

Recently, Yang *et al*[7] showed photoacoustic images of the rat gastrointestinal tract *ex vivo* using a novel photoacoustic endoscope with a miniaturized imaging probe, which integrated a light-guiding optical fiber, ultrasonic sensor, and mechanical scanning unit for circumferential sector scanning. More recently, the same group[8] developed an integrated PAE and endoscopic ultrasound (EUS) imaging system for simultaneous photoacoustic and ultrasonic imaging of internal organs *in vivo*. In this commentary, we describe the technological improvements in PAE for possible clinical application in endoscopic gastrointestinal (GI) imaging. We also discuss the technical details of the ultrasonic transducer incorporated into the photoacoustic endoscopic probe.

PAT

PAT is cross-sectional or three-dimensional imaging using photoacoustic effect, an emerging optical imaging modality that can offer volumetric images of biological tissues *in vivo* with high spatial resolution and deep tissue optical contrast[5]. PAT is similar to ultrasound imaging in that both use detected ultrasonic waves to produce images[8]. However, PAT uses optical absorption-based contrast of tissue. PAT can provide high spatial resolution because ultrasonic scattering coefficients in tissue are two to three orders of magnitude less than optical scattering coefficients[5]. Additionally, unlike ultrasonography or optical coherence tomography, PAT produces speckle-free images. As mentioned above, "PAT" includes PAM, PAE, PACT (Table 1). While PAM and PAE can image millimeters deep at microscopic resolution, PACT is available for microscopic and macroscopic imaging. In addition, PAT has been integrated into other imaging modalities, including ultrasound imaging[9], optical coherence tomography (OCT)[10], confocal microscopy[11], two-photon microscopy[6], and magnetic resonance imaging[12].

Single-wavelength photoacoustic measurements of hemoglobin, a prominent light absorber in tissue, can provide images of blood vessels without exogenous contrasts. Deeper-seated vascular structures can be detected using a red or near infrared wavelength shift[2]. In addition, the technique can evaluate oxygen saturation inside blood vessels because oxyhemoglobin and deoxyhemoglobin have significantly different optical absorption spectra[13]. Other endogenous optical absorbers, such as melanin and other tissue chromophores, can contribute to photoacoustic signals. Sound reflectors such as calcification are useful in images of some tumors, including leiomyomas, leiomyosarcomas, or mucinous adenocarcinomas[2].

Multispectral optoacoustic tomography (MSOT) with multiple illumination wavelengths can help differentiate extrinsic contrast agents (such as common fluorochromes, or photoabsorbing nanoparticles) from intrinsic contrasts (such as hemoglobin or melanin) by their unique spectral signatures[14]. This imaging modality can offer differentiation of physiological conditions with the combination of each image of different absorbers[2]. Using this method, Oh *et al*[15] reported three-dimensional images of subcutaneous melanomas and their surrounding vasculature in nude mice by dual-wavelength reflection-mode PAM, in which melanin distribution was imaged with a near-infrared light source and vascular system surrounding the melanoma with visible light. Extrinsically administered contrast agents for MSOT should have a sufficiently high optical absorption to be detected in tissues[3]. Such agents include near-infrared cyanine dyes, such as indocyanine green[16], reporter gene products[17], and light-absorbing nanoparticles, such as gold nanoparticles[18] and carbon nanotubes[19]. Several nanoparticles produce significantly stronger photoacoustic signals than organic dyes[2]. However, they also have limitations, including their larger size and safety concerns. MSOT can also detect activatable contrast agents, such as "smart probes" or molecular beacons, that are dark in their base state but produce fluorescence after target interaction[20]. MSOT can provide functional, genetic, and molecular imaging using these extrinsic contrast agents[5].

In recent years, PAT has been used in a number of preclinical applications, including imaging of angiogenesis, the microcirculation, drug responses, brain func-

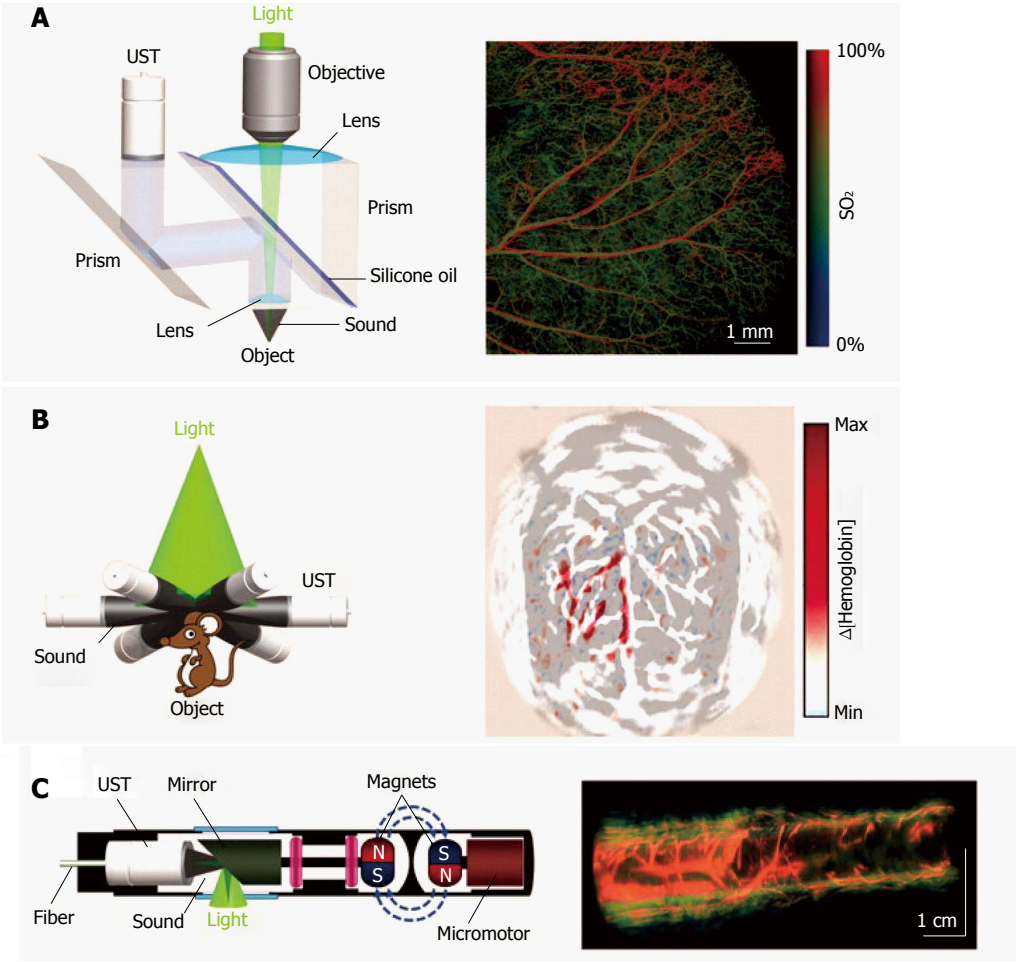

Figure 2 Three major implementations of photoacoustic tomography, with representative *in vivo* images. A: Optical-resolution photoacoustic microscopy and an image of hemoglobin oxygen saturation (SO_2) in a mouse ear; B: Circular-array photoacoustic computed tomography and an image of cerebral hemodynamic changes, Δ[hemoglobin], in response to one-sided whisker stimulation in a rat; C: Photoacoustic endoscopy and an image of a rabbit esophagus and adjacent internal organs, including the trachea and lung. Reproduced with permission from Wang *et al*[5]. SO_2: Oxygen saturation; UST: Ultrasonic transducer.

tion, tumor microenvironments, biomarkers, and gene expression[5]. PAT is also in the early stages of clinical application including breast cancer diagnosis[21], melanoma imaging[22], prostate cancer treatment[23], and non-invasive sentinel lymph node imaging[24]. Further developments in photoacoustic imaging techniques may provide better diagnosis of diseases and patient-management strategies.

PAE

Conventional white light endoscopic imaging of GI tract allows direct visualization of morphological changes and lesions, and subsequent histological analysis of tissue is the gold standard for final diagnosis. However, this method is limited by human vision and the lack of sensitivity to subsurface activity[2]. Recent advances in optics and digital imaging techniques have been introduced in GI endoscopy. Several methods, including narrow-band imaging, autofluorescence imaging, confocal endomicroscopy, OCT, and two-photon microscopy, have been developed and are under investigation. Some of these methods have been used in clinical practice; however, their diagnostic accuracy and efficacy need to be confirmed in large-scale clinical trials. Additionally, these imaging methods cannot achieve greater penetration depth[25]. EUS-based imaging can penetrate for several millimeters to centimeters in tissue. However, its limitations include poor contrast and difficult interpretation of data[2]. In addition, the mechanical contrast in EUS images often does not provide the required sensitivity and specificity[26].

PAE may be useful as a new, minimally invasive diagnostic imaging tool because it provides functional optical contrast with high spatial resolution and maintains the benefits of traditional ultrasound endoscopy[7]. Although the penetration depth of PAT can provide images that are centimeters deep, internal organs, such as the gastrointestinal tract and cardiovascular system, are not reachable[6]. The photoacoustic probe must be positioned close to the area of interest by means of endoscopy in hollow organs[7]. Viator *et al*[1] first developed a photoacoustic endoscopic probe for 1D sensing. Sethuraman *et al*[27] demonstrated photoacoustic images of rabbit blood vessels *ex vivo* using a high-frequency intravascular ultrasound imaging catheter. However, the system was not truly endoscopic because it used external illumination.

PAE has been investigated intensively as a tool of GI tract imaging. A prototype PAE system with a miniatur-

Table 1 Overview of currently available photoacoustic imaging technologies

Technology	Full name	Brief physics	Current applications	Future applications	Additional value to standard endoscopy
PAT	Photoacoustic tomography	Optical excitation of light absorbers in tissues by a pulsed laser and ultrasonic detection using mechanical scanning or detector arrays	Three major implementations include PAM, PACT, PAE	Functional information with the aid of an exogenous contrast	-
MSOT	Multispectral optoacoustic tomography	Utilization of multiple illumination wavelengths, spectral separation of optical reporter of interest from background absorption	Functional imaging of blood vessels, melanoma imaging of primary tumors and metastasis, characterization of atherosclerotic plaques, *etc.*	Tissue anatomy, function, molecular biomarkers, and gene expression	-
PAM	Photoacoustic microscopy	Based on a scanning focused ultrasonic transducer	Anatomical images of cutaneous microvasculature	Noninvasive imaging of individual cell nuclei	-
PACT	Photoacoustic computed tomography	Based on an array of unfocused ultrasonic transducers, use of an inverse algorhithm to reconstruct a tomographic image	Tumor boundaries and connections with surrounding blood and lymphatic vessels	Same as PAT	-
PAE	Photoacoustic endoscopy	Probe that combines light delivery, acoustic sensing, and mechanical scanning in one small unit placed at the distal end of the endoscope	Gastrointestinal tract imaging	Improve the accuracy of cancer staging	Optical absorption-based contrast with high spatial resolution at depths
PAE-EUS	Photoacoustic endoscopy and Endoscopic ultrasound	Integrated system for ultrasonic images produced with conventional pulse-echo imaging and photoacoustic images formed through detection of acoustic waves	Gastrointestinal tract and lymphovascular imaging	Early-stage tumor detection or *in situ* characterization of diseased tissues	Angiographic and spectral imaging function would enhance EUS's role

PAT: Photoacoustic tomography; MSOT: Multispectral optoacoustic tomography; PAM: Photoacoustic microscopy; PACT: Photoacoustic computed tomography; PAE: Photoacoustic endoscopy; EUS: Endoscopic ultrasound.

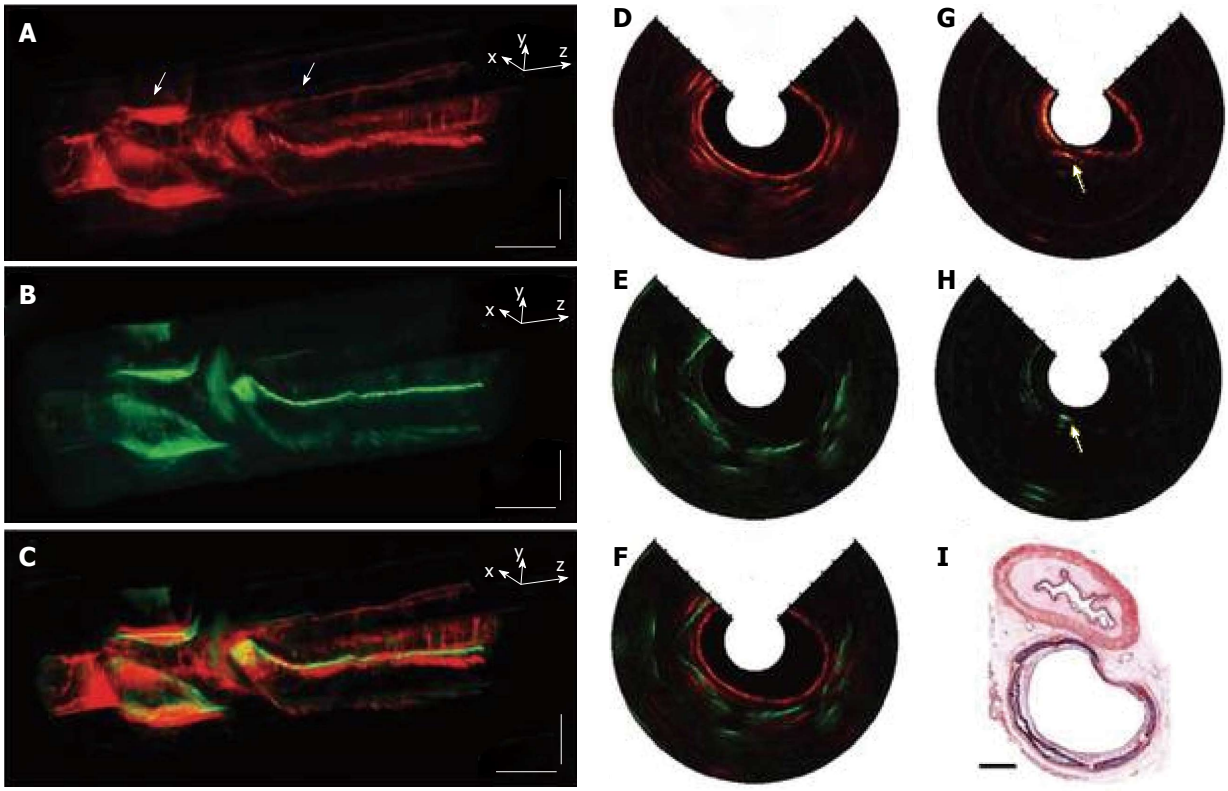

Figure 3 Simultaneous, co-registered, photoacoustic endoscopy and endoscopic ultrasound images of rabbit esophagus. A: Three-dimensionally rendered photoacoustic structural image. The left- and right-hand sides of this image correspond to the lower and upper esohagus, respectively, and the lower portion (-y axis) to the ventral side of the rabbit; B: Co-registered ultrasonic structural image for the same volume of A; C: An overlaid images of A and B. In A-C, horizontal and vertical scale bars represent 2 cm and 5 mm, respectively; D: A representative photoacoustic x-y cross-sectional image (18 mm in diameter) near the lung, as indicated by the left arow in A; E: Corresponding ultrasonic cross-sectional image of D; F: A combine image of D and E; G: A photoacoustic x-y cross-sectional image near the trachea, as indicated by the right arow in A; H: Corresponding ultrasonic cross-sectional image of G. In G and H, the dotted arrows indicate the contact point between the trachea and the esophagus; I: Histology of the esophagus (top) and the trachea (bottom) (HE stain). Scale bar, 1 mm. Reproduced with permission from Yang *et al*[8].

ized imaging probe integrates a light-guiding optical fiber, an ultrasonic sensor, and a mechanical scanning unit into one small unit placed at the distal end of the endoscope[7]. This probe used a scanning mirror system instead of conventional flexible shaft-based mechanical scanning, enabling circumferential sector scanning without moving other illumination optics or the ultrasonic detector. The large intestinal tract of a rat was imaged *ex vivo* with this probe. However, probe diameter was 4.2 mm due to the larger transducer size. One recently developed probe is 3.8 mm in diameter and approximate 38 mm in length, enabling simultaneous photoacoustic and ultrasound imaging using a single device[8]. In this endoscopic system, a focused ultrasonic transducer detects one-dimensional, depth-resolved signals (or the A-line). Additionally, cross-sectional images (or B-scan) can be achieved by constant rotation of a scanning mirror that directs both optical and acoustic waves. This system records and shows a set of dual wavelength photoacoustic to differentiate oxy- and deoxyhemoglobin, two of the dominant absorbers of visible light in soft biological tissues, and ultrasonic B-scan images in real time. It provides anatomical information about a rabbit esophagus and organs surrounding the esophagus, covering an approximately 14-cm long and 18-mm diameter volume (Figure 3). Volume rendering enabled three-dimensional visualization of the morphology and configuration of tissues and proximal organs surrounding the esophagus. Also, simultaneous, co-registered PAE-EUS colonoscopic pseudo-color images of the rat colon *in vivo*, and images of the lymphovascular system near the rat colon, could be achieved using the same scanning parameters as imaging of the esophagus. Thus, PAE-EUS system can provide high-resolution information on the GI tract vasculature and display differences between optical and mechanical contrast compared with single-mode EUS. However, the probe was too large to fit in the working channel (usually approximate 2.8- or 3.7-mm diameter) of a standard endoscope. More recently, a newer generation probe was further miniaturized, with probe diameter of 2.5 mm and a approximate 35 mm rigid length[28]. This mini-probe may be inserted into the working channel of a standard endoscope and be used with endoscopic guidance.

In conclusion, PAE is an emerging modality, and provides image information of optical contrast or functional properties by detecting ultrasonic waves. The major advantage of PAE is the greater pentration depth, of millimeters to centimeters, in tissue. It has great potential for *in vivo* endoscopic applications, such as early-stage tumor detection, accurate diagnosis of submucosal lesions, and *in situ* characterization of diseased tissues. Targeted contrast agents may improve the capabilities of endoscopic imaging, resulting in the earlier and more accurate detection of malignant and premalignant lesions, and further extend PAE to molecular imaging. Several technical challenges regarding the use of PAE in biomedical applications must be overcome. High-repetition lasers with fast wavelength tuning at each scan position are required for high-speed multicontrast PAE. Additionally, further miniaturization of the PAE probe is essential so that it can be inserted into the working channel of a standard endoscope. Although PAE for GI endoscopic imaging is at the preclinical stage, it would become an important imaging modality with further technological improvements.

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MINIREVIEWS

Imaging pancreatobiliary ductal system with optical coherence tomography: A review

Mohammad S Mahmud, Gray R May, Mohammad M Kamal, Ahmed S Khwaja, Carry Sun, Alex Vitkin, Victor XD Yang

Mohammad S Mahmud, Carry Sun, Victor XD Yang, Department of Electrical and Computer Engineering, Biophotonics and Bioengineering Lab, Ryerson University, Toronto, M5B 2K3, Canada
Ahmed S Khwaja, Department of Electrical and Computer Engineering, Ryerson University, Toronto, M5B 2K3, Canada
Gray R May, Division of Gastroenterology, Saint Michael's Hospital, University of Toronto, Toronto, M5B 1W8, Canada
Mohammad M Kamal, Department of Burn and Plastic Surgery, Dhaka Medical College, Dhaka 1200, Bangladesh
Alex Vitkin, Department of Medical Biophysics, University of Toronto, Ontario Cancer Institute/University Health Network, Toronto, M5G 2M9, Canada
Author contributions: Mahmud MS prepared the article; May GR and Kamal MM provided technical supports during the study; Khwaja AS, Sun C and Vitkin A reviewed the manuscript; Yang VXD provided support of finance.
Correspondence to: Mohammad S Mahmud, PhD, Department of Electrical and Computer Engineering, Biophotonics and Bioengineering Lab, Ryerson University, 350 Victoria Street, Toronto, M5B 2K3, Canada. ssujann1@gmail.com
Telephone: +1-647-8854428 Fax: +1-416-9795280
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Abstract

An accurate, noninvasive and cost-effective method of *in situ* tissue evaluation during endoscopy would be highly advantageous for the detection of dysplasia or early cancer and for identifying different disease stages. Optical coherence tomography (OCT) is a noninvasive, high-resolution (1-10 μm) emerging optical imaging method with potential for identifying microscopic subsurface features in the pancreatic and biliary ductal system. Tissue microstructure of pancreaticobiliary ductal system has been successfully imaged by inserting an OCT probe through a standard endoscope operative channel. High-resolution OCT images and the technique's endoscopic compatibility have allowed for the microstructural diagnostic of the pancreatobiliary diseases. In this review, we discussed currently available pancreaticobiliary ductal imaging systems to assess the pancreatobiliary tissue microstructure and to evaluate varieties of pancreaticobiliary disorders and diseases. Results show that OCT can improve the quality of images of pancreatobiliary system during endoscopic retrograde cholangiopancheatography procedure, which may be important in distinguishing between the neoplastic and non-neoplastic lesions.

Key words: Optical coherence tomography; Endoscopy; Common bile duct; Main pancreatic duct; Sphincter of Oddi; Benign and malignant strictures

Core tip: Optical coherence tomography is a high-resolution diagnostic tool for pancreatobiliary system during endoscopic retrograde cholangiopancheatography procedure.

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INTRODUCTION

Outstand from various existing diagnosis methods such as, endoscopic retrograde cholangiopancheatography (ERCP), percutaneous transhepatic cholangiography (PTC), magnetic resonance cholangiopancreatography (MRCP), computed tomographic cholangiography (CTC), endoscopic ultrasound guided fine-needle aspiration (EUS-FNA), available for the assessment of pancreatic

Table 1 Imaging methods for diagnosis of bile duct strictures *n* (%)

Techniques	SEN (%)	SPEC	PPV	NPV	Accuracy
BC/FNA[2,11,23]	30 (30-60)	95 (90-100)	100 (90-100)	28 (28-50)	48 (30-50)
Forceps biopsy[2,11,23]	43 (40-70)	90 (90-100)	95 (90-100)	31 (30-50)	48 (30-70)
BC + FNA + biopsy[2,11,23]	62 (60-75)	90 (90-100)	96 (90-100)	39 (35-60)	55 (45-75)
ERCP/MRCP[9,17,32,50-52]	70 (67-90)	75 (70-80)	80 (68-90)	88 (70-95)	70 (50-80)
ERCP-BC/BX[9,11,33,38]	43 (36-60)	80 (75-100)	95 (94-100)	90 (56-100)	70 (60-75)
EUS[17,32,33,47,53]	80 (70-100)	80 (75-100)	80 (76-100)	80 (54-90)	80 (78-90)
EUS-FNA[9,23]	85 (80-100)	95 (90-100)	95 (95-100)	80 (60-90)	85 (80-90)
IDUS[32,38]	90 (85-100)	85 (80-100)	85 (80-100)	90 (80-100)	90 (83-90)
IDUS + ERCP/biopsy[32,33,38,54]	91 (90-100)	93 (90-100)	94 (84-100)	90 (84-95)	92 (90-100)
OCT[1,2]	79 (75-90)	69 (65-90)	75 (70-90)	73 (70-90)	74 (70-85)
OCT-BC/BX[2]	84 (80-90)	69 (70-90)	76 (70-90)	78 (70-100)	77 (70-90)

True positive (TP) and true negative (TN) represent the accurate diagnosis of biliary and non-biliary strictures respectively; False positive (FP) reflects the incorrect diagnosis of non-malignancy, whereas, false negative (FN) reflects incorrect diagnosis of the benign strictures; Sensitivity, specificity, positive predictive values and negative predictive values were calculated as Ref. [54]. BC: Brush cytology; BX: Forceps biopsy; FNA: Fine-needle aspiration; ERCP: Endoscopic retrograde cholangiopancheatography; MRCP: Magnetic resonance cholangiopancreatography; EUS-FNA: Endoscopic ultrasound-guided FNA biopsy; IDUS: Intraductal ultrasonography; OCT: Optical coherence tomography; SEN: TP (TP + FN); SPEC: TN/(TN + FP); PPV: TP/(TP + FP); NPV: TN/(TN + FN).

and biliary disorders; optical coherence tomography (OCT) shows great potential for identifying dysplastic or early malignant epithelial changes and for differentiating between neoplastic and non-neoplastic lesions[1,2]. This is because ERCP and PTC are not risk free and in some cases, patients must undergo subsequent surgical or percutaneous procedures[3-5]. Additionally, diagnosis accuracy of ERCP-based tissue sampling (brush cytology and/or forceps biopsy) is relatively low (less than 70%) and highly variable[6-11]. Sometimes, tissue specimens collected with forceps biopsy and/or brushes may contain superficial tissue layers that are inherently insensitive to diagnosis and prone to false-negative results. MRCP[12-16] method is noninvasive, and is apparently less operator-dependent and its diagnostic accuracy is comparable (or slightly less) to ERCP. However, MRCP is expensive which requires additional tests for data analysis and diagnose diseases. Computed tomography[15-18] may provide better diagnostic information, but usually should be avoided due to the radiation exposures and contrast materials.

EUS-FNA is used for diagnosing cholangiocarcinoma and/or tumors in the biliary duct, especially in patients with negative brush cytology and forceps biopsy findings[19-27]. The technique shows diagnosis accuracy over 80%, however, the performance is hindered by system resolution; additionally expensive equipments are required during procedure. Intraductal ultrasonography (IDUS) is another safe and effective method performed during ERCP to diagnose localized stenosis and early malignant changes in main pancreatic duct[28,29], common bile duct stone[30,31] and to identify malignant biliary strictures[32-39]. During IDUS, a high-frequency ultrasound probe is placed into the pancreaticobiliary duct under ERCP guidance. IDUS shows diagnosis accuracy over 90% in patients with biliary strictures[31-38]. The major drawbacks of IDUS are the impossibility of tissue sampling and IDUS findings that might have showed limited reproducibility[30]. Therefore, more reliable and adequately sensitive diagnostic procedure is on demand for early detection of pancreatic and biliary diseases.

OCT an optical modality shows great potential for identifying dysplastic or early malignant epithelial changes and for differential diagnosis between neoplastic and non-neoplastic lesions. OCT is a noninvasive, high-resolution, cross-sectional *in vivo* imaging method based on the principle of low-coherence interferometry[40,41]. This technology has been widely used in various clinical and pathological applications, such as, in the field of ophthalmology[40,42], cardiology[43], gastroenterology[44,45], oncology[46], respiratory airways[47,48] and oral cavity disorder[49]. Main limitation OCT is its shallow penetration depth (2-3 mm) of imaging which depends upon the tissue structure, depth of focus of the probe used and absorption and/or scattering properties of the tissue sample.

General criteria (accuracy, sensitivity and specificity, positive and negative predictive values) of various imaging methods used to diagnose biliary duct strictures (malignant and benign) are summarized in Table 1. The advantages and disadvantages of these imaging modalities are listed in Table 2.

In this review, we focused on the feasibility of OCT approach that improves the diagnostic accuracy of the ductal epithelial changes, with a potential to diagnose neoplastic and non-neoplastic lesions as well as pancreatic cysts. We discussed the mechanism of an OCT imaging system and then image pancreatobiliary ductal system with OCT. The images of pancreaticobiliary ductal system are divided into two categories: normal pancreatico-biliary ductal system and pathological (neoplastic) ductal structure. Various pancreatic cysts with OCT are also discussed at the end of this review.

OCT IMAGING OF THE PANCREATOBILIARY DUCTAL SYSTEM

Introduction to OCT imaging system

Figure 1 shows the schematic diagram of an endoscopic

Table 2 Comparison of various imaging modalities

Imaging modality	PTC	ERCP	MRCP	US/HFUS/EUS/IDUS	CT	OCT
Projection/ tomograph	Projection	Projection	Projection or tomographic	Tomographic	Tomographic	Projection or tomographic
Resolution	1-2 mm	1-2 mm	Fairly poor 3-5 mm	US/EUS 100-250 μm HFUS/IDUS 50-100 μm	300-500 μm μCT: 3-125 μm	Fairly high 1-10 μm
Imaging depth	1-5 mm	5-60 mm	Entire biliary tree	US/EUS: 5-10 cm HFUS/IDUS: 1-3 cm	Entire biliary tree	1-3 mm
Tissue sampling	+ +	+ + +	-	US + EUS + + +	+	-
Portability	-	+	-	US + + + EUS + +	-	+ +
Therapy	+ + +	+ + +	-	US - EUS +	-	+
System cost	+ +	+ + + +	+ + +	US - EUS + +	+ +	+ +
Operator dependence	High	High	Low	Very high	Low	Low
Staging of malignancy	-	-	+ +	US + EUS + + +	+ + +	-
Safety	-	+	+ + +	+ +	+ +	+++
Experiment duration	2-4 h	30-120 min	10-30 min	20-40 min	15-30 s	5-10 min
Complications	+ + + Risk (5%-10%) of Infection, bleeding and bile leaks	+ + Risk (< 5%) Bleeding, perforationpancreatitis cholangitis	- Claustrophobia in some patients	+ Risk (1%) of failure rate, bleeding and perforation	- Rare allergic reaction (< 1%) to iodinated agents	- No complication
Comments pros	+ Diagnosis and therapeutic (treatment) procedure	+ Diagnosis and treatment procedure	Non-invasive + No ionizing radiation + Relatively operator -independent	Usually non-invasive (sedation) + Diagnosis tool combined with tissue and/or lesion sampling	Non-invasive + Faster method + High resolution + Operator-independent	Non-invasive + No ionizing radiation + High resolution + Faster method + Operator-independent
Cons	Invasive ionizing radiation Operator- dependent	Invasive Ionizing radiation Operator dependent	Expensive-poor resolution Solely diagnostic method Motion sensitive claustrophobia	Operator dependent Highly motion sensitive Thermal effects and cavitations	Ionizing radiation Solely diagnostic method	Low imaging depth 3 mm Motion sensitive

PTC: Percutaneous transhepatic cholangiography; ERCP: Endoscopic retrograde cholangiopancheatography; MRCP: Magnetic resonance cholangiopancreatography; US: Ultrasound; EUS: Endoscopic ultrasound; HFUS: High frequency ultrasound (> 10 MHz); IDUS: Intraductal ultrasonography; CT: Computed tomography; OCT: Optical coherence tomography.

OCT system. Light generated from a low coherence infrared light source spits into two parts: the sample and reference arms. The back-reflected light from the tissue interferes with the reference signal which then fed to a detector and then sent the signal to a computer for visualization. OCT is analogous to the ultrasound imaging[1], but uses light waves rather than ultrasound waves. Therefore, OCT provides high resolution (1-10 μm) which is at-least ten times better than the currently available high-frequency ultrasound imaging system. For investigating the epithelial layers of the main pancreatic duct (MPD), common bile duct (CBD) and sphincter of Oddi (SOD) an OCT probe (guide wire) is inserted through the working channel of an endoscopic catheter (Figure 1). The outer diameter of this endoscopic catheter can be made as small as 1.2 mm. Repeated frames are taken by the "pull-back" technique while connecting the catheter with a rotator, giving a large number of transitional-rotational images. Diagnoses of the intraductal pathology of the pancreatobiliary system, such as biliary and/or pancreatic stricture, are improved with OCT method where the conventional biopsy is technically difficult and is associated with risk[6,7]. After the targeted tissue is identified with a conventional endoscopy, a narrow-diameter (about 1.2 mm) OCT probe is inserted through the operating channel of the endoscope and positioned on the site of interest. No special patient preparation is required during OCT imaging and images can be acquired within several minutes (5-10 min). Three different types of OCT systems are wildly used in various research and clinical applications (Table 3). Companies currently produce OCT systems are: Novacam, Bioptigen, Heidelberg Engineering, Alcon/LenSx, Canon/Optopol, Volcano Crop, Optovue, Thorlabs, Topcon, Imalux, Nidek, Tomey, Schwind, Wasatchphotonics, OptiMedica, Optos/OTI, Volcano Crop, LightLab Imaging, Shenzhen Moptim Imaging, Techno-

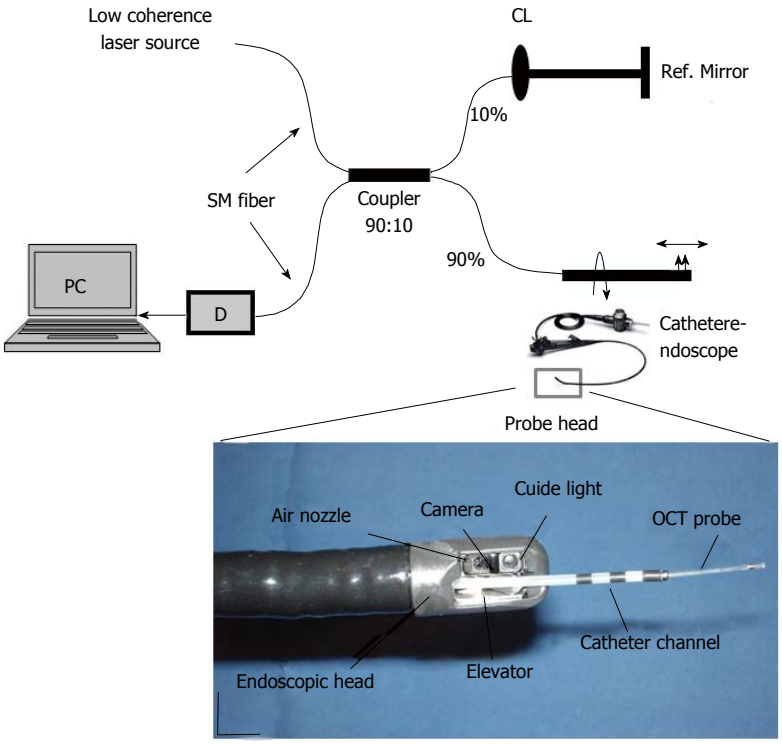

Figure 1 Schematic diagram of an endoscopic optical coherence tomography system. The endoscopic probe is connected to the sample arm (Color online). Light generated from a low coherence laser source spits into two parts, the sample arm and reference arm. Both back-reflected lights from sample and reference arms recombine in a fiber coupler (10:90). If both back-reflected reference and sample light travels the same distance (optical) then interference will occur and the interference signal will fed to a detector (D). Magnified region of interest in the second image is the endoscopic probe head, consisting primarily of an optical fiber (OCT probe), catheter channel, elevator, video camera and aiming light[55]. Scale bar: 10 mm.

Table 3 Comparison of different types of optical coherence tomography systems

Parameters	TD-OCT	SD-OCT	SS-OCT/OFDI
Mechanism	Interference signals are detected as a function of optical time delay between obj. and ref. arm.	Interference signals are detected with a camera as a function of optical frequency	Spectral fringes are mapped to time domain by use of a swept laser and are measured with a detector as a function of time
Major components	Broadband laser, optical delay line and a detector	Broadband laser, spectrometer and camera	Tunable laser, digitizer and a balanced detector
Spectrum	800 nm, 1000 nm, 1300 nm	800 nm, 1000 nm, 1300 nm	800 nm, 1000 nm, 1300 nm
Imaging depth	1-3 mm	1-3 mm	1-3 mm
Resolution	≥ 10 μm	1-10 μm	1-10 μm
Imaging speed (axial scan rate)	Slow (≤ 5 kHz)	Fast (20-150 kHz)	Fairly fast (20-400 kHz)
SNR	Low	High	High
Image quality	Moderate	Fairly high	High
Sensitivity	Low (70-90 dB)	High (85-105 dB)	High (≥ 100 dB)
Phase stability	Low	High	Moderate
Portability	Yes	Yes	Yes
System cost	Low	High	Moderate

SNR: Signal-to-noise ratio; dB: Decibel; TD-OCT: Time domain OCT; SD-OCT: Spectral-domain OCT; ODFI: Optical frequency domain imaging; SS-OCT: Swept source OCT.

las Perfect Vision, and Carl Zeiss Meditec. Cost of an OCT system varies with imaging engines (consisting of an interferometer, light source, and detector) and imaging devices (or OCT probes) and ranges from $20000-$80000. The cost per correct diagnosis (or procedure cost) is approximately $100 (100-200).

Normal pancreatobiliary ductal system

Visualization of epithelium layer structure of main pancreatic duct has been obtained from post-mortem[56] and *ex vivo* in humans[57-60], while *in vivo*, it comes from single study in animals[61] and another in humans[62]. Normal biliary ductal system was investigated in humans, *ex vivo* in a study[58,60], post-mortem[56] and *in vivo* and *ex vivo* in animals[61,63] and *in vivo* in ERCP-based OCT studies[2,64,65]. The SOD structure was investigated in normal and pathological conditions either in *ex vivo* or *in vivo* studies[2,58,65].

Human pancreatobiliary duct studies: Tearney *et al*[56] first performed *ex vivo* OCT imaging from the post-mortem cadaveric pancreatobiliary tissue. OCT images obtained from CBD-wall were able to identify layered structures and could resolve the submucosa-muscularis and muscularis-adventitia boundaries. Mucosa, submucosa, muscularis propria and adventitial layers, serosa in the gallbladder and biliary duct were visualized due to different back-

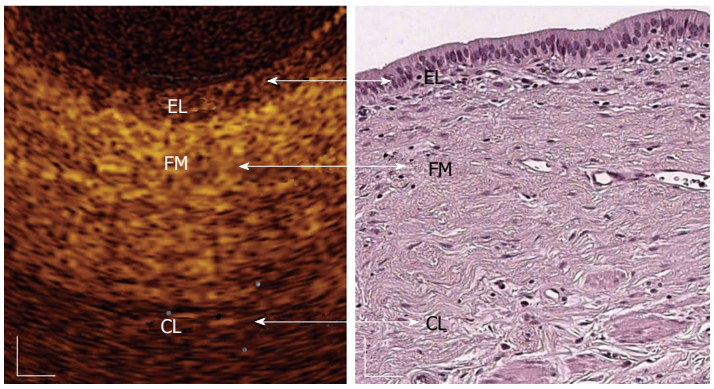

Figure 2 *In vivo* optical coherence tomography image of a normal common bile duct wall. Three recognizable layers were observed from the surface of the duct to a depth of 1 mm (Color online). The inner single layer of epithelial (EL) cells (400-600 μm thick) is visible as a superficial, hypo-reflective layer. The intermediate connective fibro-muscular (FM) layer surrounding the epithelium is visible as a hyper-reflective layer (350-480 μm thick) and the outer connective layer (CL) is visible as a hypo-reflective layer with longitudinal relatively hyper-reflective strips (smooth muscle fibers)[58]. White scale bar: 150 μm.

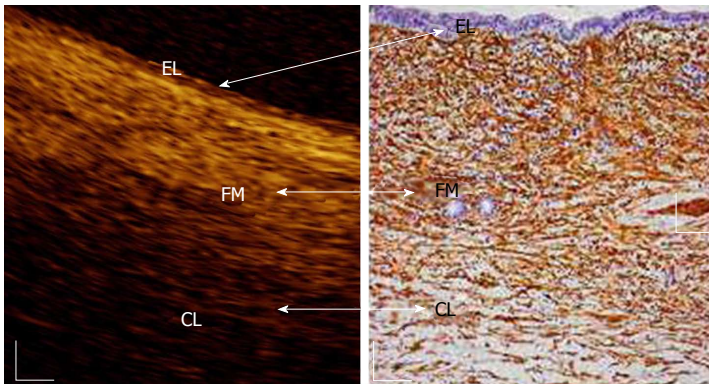

Figure 3 *In vivo* optical coherence tomography image of a normal main pancreatic duct wall compared with histology. Three recognizable layers were observed from the surface of the duct to a depth of 1 mm (Color online). The inner single layer of epithelial (EL) cells (400-800 μm thick) is visible as a superficial, hypo-reflective layer. The intermediate, connective fibro-muscular (FM) layer surrounding the epithelium, is visible as a hyper-reflective layer (350-600 μm thick). The outer connective-acinar (CL) structure close to the ductal wall epithelium is visible as a hypo-reflective layer[58]. White scale bar: 150 μm (right image).

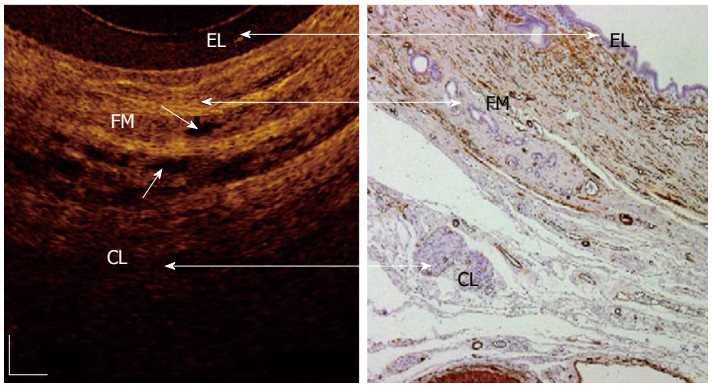

Figure 4 *In vivo* optical coherence tomography image of a normal sphincter of Oddi wall. Three recognizable layers were observed from the surface of the duct to a depth of 1 mm (Color online). The inner single layers of epithelial (EL) cells are visible as a superficial, hypo-reflective layer (400-800 μm thick). The intermediate connective-muscular (FM) layer surrounding the epithelium is visible as a hyper-reflective layer (250-400 μm thick). The outer connective layer (CL) is visible as a hypo-reflective layer with longitudinal relatively hyper-reflective strips (smooth muscle fibers). Within intermediate and outer layer, vessels could be visualized (marked with arrows) as nonreflecting areas. The boundaries between the intermediate and outer layers are not clearly recognizable due to irregular distribution of the connective and muscular structure[59]. White scale bar: 150 μm.

scattering characteristics within each layer. For example, submucosa and/or muscularis layers showed higher intensities and regular scattering pattern than the adventitial layer, most likely due to the presence of adipose tissue into the adventitial layer. The tissue microstructure, such as secretions within individual glands (glandular structure), and cross-sectional imaging of islets Langherans cells were visualized. The pancreatic duct appeared as a highly backscattering band near the lumen of the tissue and the pancreatic stroma was seen beneath the pancreatic duct.

Testoni *et al*[58,59,62,66] further studied *in vivo* MPD, CBD and SOD wall structures with OCT. Three different layers (Figures 2-4) were recognized from the surface of the duct to a depth of about 1 mm. The inner layer defined from the surface to the lumen, consisting of single layers of epithelial cells. The intermediate layer is homogeneous, consisting of connective fibro-muscular layer surrounding the epithelium. The outer layer is less definite and corresponds to the smooth muscular structure within a connective tissue in the CBD and at the level of the SOD, and connective-acinar structure in the MPD.

The inner hypo-reflective layer showed a mean thickness of 500 μm (range: 400-800 μm). Layer thickness, surface roughness and reflectance of inner layer were not substantially differing in CBD, MPD and SOD. Thickness of the intermediate hyper-reflective layer (about 400 μm) is substantially similar to MPD and CBD, whereas it reduces by 25% at the level of SOD[55]. Tiny, multiple, nonreflective areas can be appeared within the intermediate MPD layer and at the level of SOD (Figures 3 and 4). The outer hypo-reflective layer was recognizable up to a depth of about 1 mm (focus distance of the OCT probe) from the lumen. Multiple, smooth-muscle longitudinal strips appeared within hypo-reflective layer at the level of CBD and SOD and were particularly more

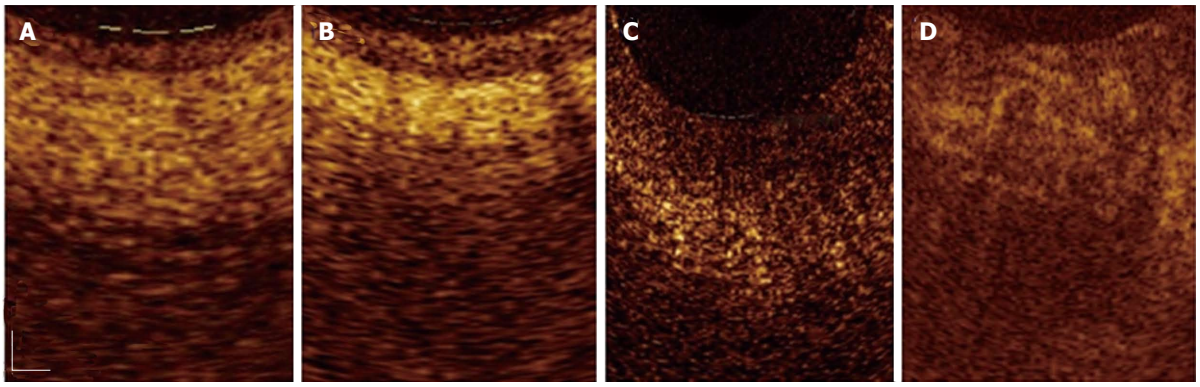

Figure 5 Magnified optical coherence tomography images. A: Sections with normal main pancreatic duct (MPD) wall; B: The presence of chronic pancreatitis; C: Low-grade dysplasia; D: Adenocarcinoma. Three differentiated layer architecture with a linear, regular surface, and a homogeneous back-scattered signal from each of the layer was observed in the normal condition. In the presence of chronic pancreatitis the optical coherence tomography (OCT) image still showed three-layer architecture, however, the inner epithelial layer appeared slightly larger than normal and the intermediate layer appeared more hyper-reflective; probably due to the presence of the dense mononuclear cell infiltrate. In the presence of dysplasia, OCT image showed thickened, strongly hypo-reflective and hetero-geneous inner MPD layer. Irregular surfaces were observed in the whole MPD structure. None of these layers were recognizable in the presence of adenocarcinoma[66]. Scale bar: 200 μm (Color online).

pronounced in SOD than in CBD. Furthermore, OCT images can identify veins, arteries and/or secondary pancreatic ducts which were characterized by hypo- or non-reflective, well delimited areas.

All of these layers showed linear, regular surface and each layer had a homogeneous back-scattered signal in every frame. However, the differentiation between outer and intermediate layer appeared more difficult than that of between inner and intermediate layer. The muscular and connective-acinar structure was visible until the focus distance (about 1 mm) of the OCT probe into the tissue.

Other biliary ductal studies: Singh *et al*[61] reported *in vivo* OCT images of animal (dog) pancreatic biliary ducts. Hwang *et al*[63] observed the normal structures of an *ex vivo* pig pancreas including small pancreatic ducts and pancreatic acini. OCT image identified biliary duct wall structure, features within lamina propria and some of the surrounding fibrous tissue. But OCT could not identify the nuclei or subcellular structures and/or adjacent structures such as blood vessels. A thin, low-scattering superficial layer appeared on the majority of the images, corresponding to the cuboidal epithelium. The lamina propria appeared as highly reflecting layer underneath the mucosal surface. Irregular reflections from layers underlying the lamina propria were from the dense connective tissue. Low reflected peribiliary glands were viewed as large open spaces with a single layer epithelium. The pancreatic duct in dogs has a flat mucosal layer composed of cuboidal epithelium and virtually has no lamina propria. OCT was able to image wall of the pancreatic duct but not the surrounding parenchyma. The pancreatic duct images were homogeneous and moderately reflective.

Pathological (dysplastic/neoplastic) pancreatobiliary ductal system

Imaging pathological pancreatic ductal system with OCT was first investigated by Testoni *et al*[59,60] in humans in two *ex vivo* studies. MPD chronic inflammatory changes showed a conserved, three-layer architecture. However, the inner hypo-reflective layer was slightly larger than the normal tissue layer and the intermediate layer was more hyper-reflective than normal condition. Additionally back-scattered signal from each layer is more heterogeneous than the normal layer condition.

In the presence of dysplasia, OCT showed thickened, strongly hypo-reflective and hetero-geneous inner layer of MPD (Figure 5C). Irregular surfaces were observed between the inner and intermediate layers. The intermediate layer is strongly hyper-reflectance, particularly close to the inner layer. The outer layer was homogeneously hypo-reflective and did not differ from normal condition. The agreement between OCT and histology in chronic pancreatitis and dysplasia were 62% in these cases. Overall, approximately one-third sections of normal wall structure and chronic inflammatory/low-grade dysplastic changes were not distinguishable with OCT.

In the presence of adenocarcinoma, MPD wall structure with OCT is shown in Figure 5D. All three layer structures and their linear, regular surface were not recognizable. No clear identifiable margin was seen between connective fibro-muscular layer and acinar tissue. The back-scattered signal was strongly heterogeneous with multiple nonreflective areas in the disorganized pancreatic microstructure. The OCT and histology were 100% concordant for sections with adenocarcinoma. OCT images from sections of MPD with normal tissue, tumor-associated chronic inflammation, low-grade dysplasia, and adenocarcinoma are shown in Figure 5.

OCT can differentiate three-layer architecture in either normal MPD or chronic pancreatitis; however, in a neoplastic lesion the layer architecture is totally subverted with heterogeneous light back-scattering. In addition, OCT can distinguish non-neoplastic from neoplastic lesions of MPD and can gave 100% accuracy for

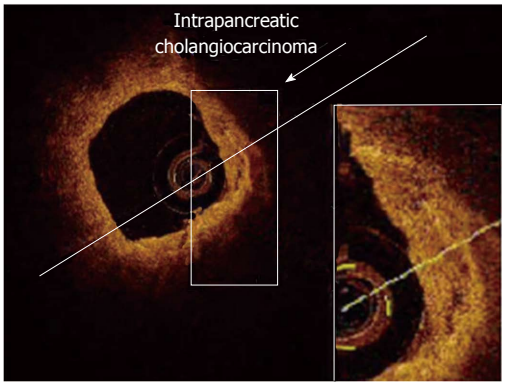

Figure 6 Adenocarcinoma (neoplasia) of the common bile duct at early stage, detected with optical coherence tomography probe maintained inside the endoscopic retrograde cholangiopancheatography catheter. In the presence of Adenocarcinoma (neoplasia), optical coherence tomography (OCT) patterns showed distorted common bile duct (CBD) wall structure (Color online). All three-layer architecture and their linear and regular surface, normally giving a homogeneous back-scattered signal, are not recognizable. OCT image shows heterogeneous back-scattered signal with minute, multiple, nonreflective areas (necrotic areas) in the highly disorganized CBD microstructure. Therefore, epithelial structure and various biliary disorders in early-stage of cancer can be distinguishable with OCT[67].

detection of neoplastic tissue compared with 66.7% for brush cytology[62]. MPD layer architectures derived from different back-scattered signals from each layer were confirmed as a reliable OCT parameter for distinguishing non-neoplastic from neoplastic tissue. However, this technology is unable to discriminate between a normal MPD structure and other MPD benign lesions. Further studies are necessary which might improve the diagnostic accuracy of OCT in this challenging imaging scenario.

OCT imaging during ERCP can identify CBD layer structure and diagnose neoplastic lesions and/or adenocarcinoma at early stages which is usually missed by cytology and X-ray imaging[55-67]. The normal CBD wall shows three recognizable layers, with a linear, regular surface and different homogeneous back-scattering of the light[58]. These inner to outer layers are: epithelium, connective-fibromuscular, and muscular layer in normal CBD wall (Figure 2). However, with the presence of neoplastic tissue, OCT patterns showed distorted CBD wall structure with heterogeneous light back-scattering (Figure 6). Therefore, epithelial structure and various biliary disorders in early-stage of cancer can be distinguishable with OCT.

Arvanitakis *et al*[2] conducted biliary intraductal OCT during ERCP studies in thirty-seven patients with biliary strictures and assess the potential of this method for improving the diagnosis accuracy of the malignant biliary strictures. This study concluded to satisfactory accuracy levels regarding distinction between malignant and benign strictures, especially when combined to biopsies. Based on OCT images, two malignancy criteria were considered: (1) disorganized and subverted layer architecture and (2) presence of large nonreflective areas compatible with tumor vessels. Figure 7A shows the cross-sectional OCT image of a patient with a benign stricture. The probe is surrounded by ERCP catheter (marked with arrow). The three-layered structure of the biliary wall is recognizable. Figure 7B-D show images of the malignant bile duct strictures. Disorganized layer architecture of the stricture wall which is one of the criteria for malignancy is shown in Figure 7B. Large, nonreflective, surface of at least 0.03 mm^2 tumor vessels were observed in Figure 7C. Malignant stricture due to hilar metastases of an esophageal squamous carcinoma was observed in Figure 7D.

Studies of pancreatic cysts with OCT

OCT modality shows great potential to reveal specific morphologic features of pancreatic cysts and thus to differentiate between the interior structures of low risk (*i.e.,* serous cyst adenomas) and high risk (*i.e.,* mucinous cystic neoplasms and intraductal papillary mucinous neoplasms) pancreatic cysts with over 95% sensitivity and specificity[68,69]. Fresh pancreatic specimens (pancreatic cysts) from patients were made available immediately after the surgery and then examined with OCT. An OCT probe was inserted into the cut surface of the pancreatic cysts. The main characteristics of each type of cystic lesion are shown in Figure 8.

Based on OCT images, the cysts were prospectively divided into two groups: mucinous (*i.e.,* Mucinous Cystic Neoplasms and Intraductal Papillary Mucinous Neoplasms) and non-mucinous (*i.e.,* Serous Cysts Adenomas and others). Multiple tiny cysts with well-defined outlines are seen in low-risk (*i.e.,* Serous Cysts Adenomas) of pancreatic cystic lesions. Thin septae between cysts create honeycomb appearance. The cyst content usually appears as dark due to lack of the scattering effect. Focal intra-luminal scattering can be found in some cysts which usually correspond to hemorrhage. In high-risk (*i.e.,* Mucinous Cystic Neoplasms, Intraductal Papillary Mucinous Neoplasms) pancreatic cyst multiple small cysts present (marked with white arrow), which may sometime surround the main cystic cavity (marked with red arrow). The cystic content may show some scattering due to presence of dead epithelial cells.

The above criteria mainly based on the visual appearance of the cystic wall morphology and on the scattering properties of the cystic fluid. Although relatively simple, they provide a very good discrimination between serous and mucinous pancreatic cysts. This *ex vivo* study suggests that OCT could be used by clinicians in future to more reliably differentiate between benign and malignant pancreatic cysts.

CONCLUSION

Limitations of standard endoscopic practices are addressed by the OCT technology described in this review. OCT identified layer structures of common bile duct, main pancreatic duct and sphincter of oddi and could resolve the submucosa-muscularis and muscularis-adven-

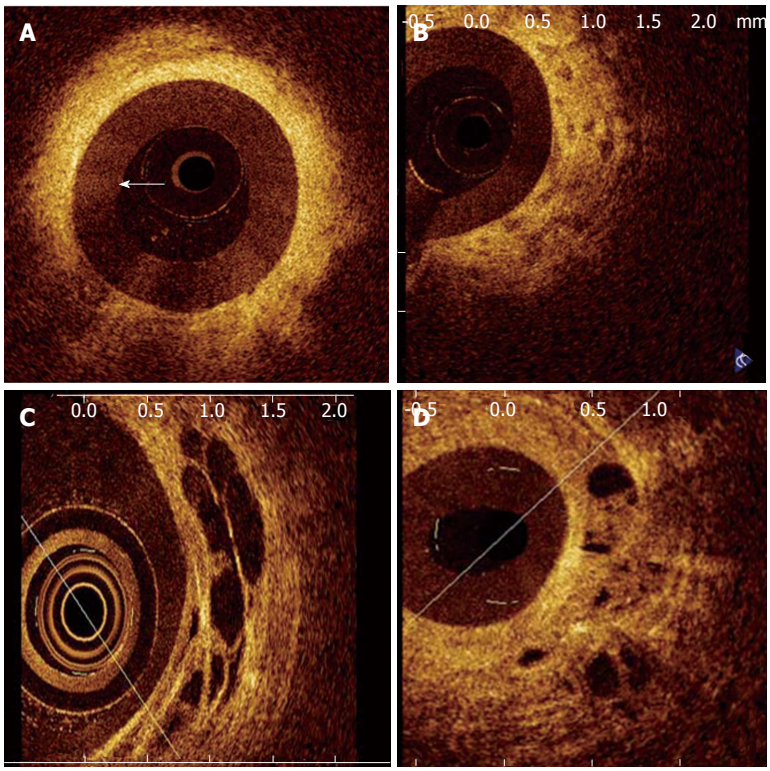

Figure 7 Optical coherence tomography image of a patient with a benign stricture. The three-layered structure of the biliary wall is recognizable (Color online). A-D shows images of malignant bile duct strictures. B: Disorganized layered structure with unidentifiable margins and a strongly heterogeneous backscattering signal; C: Large, nonreflective areas in the intermediate layer suggesting the tumor vessels; D: Malignant stricture due to hilar metastases of an esophageal squamous carcinoma showing nonreflective areas and disorganized layer architecture[2].

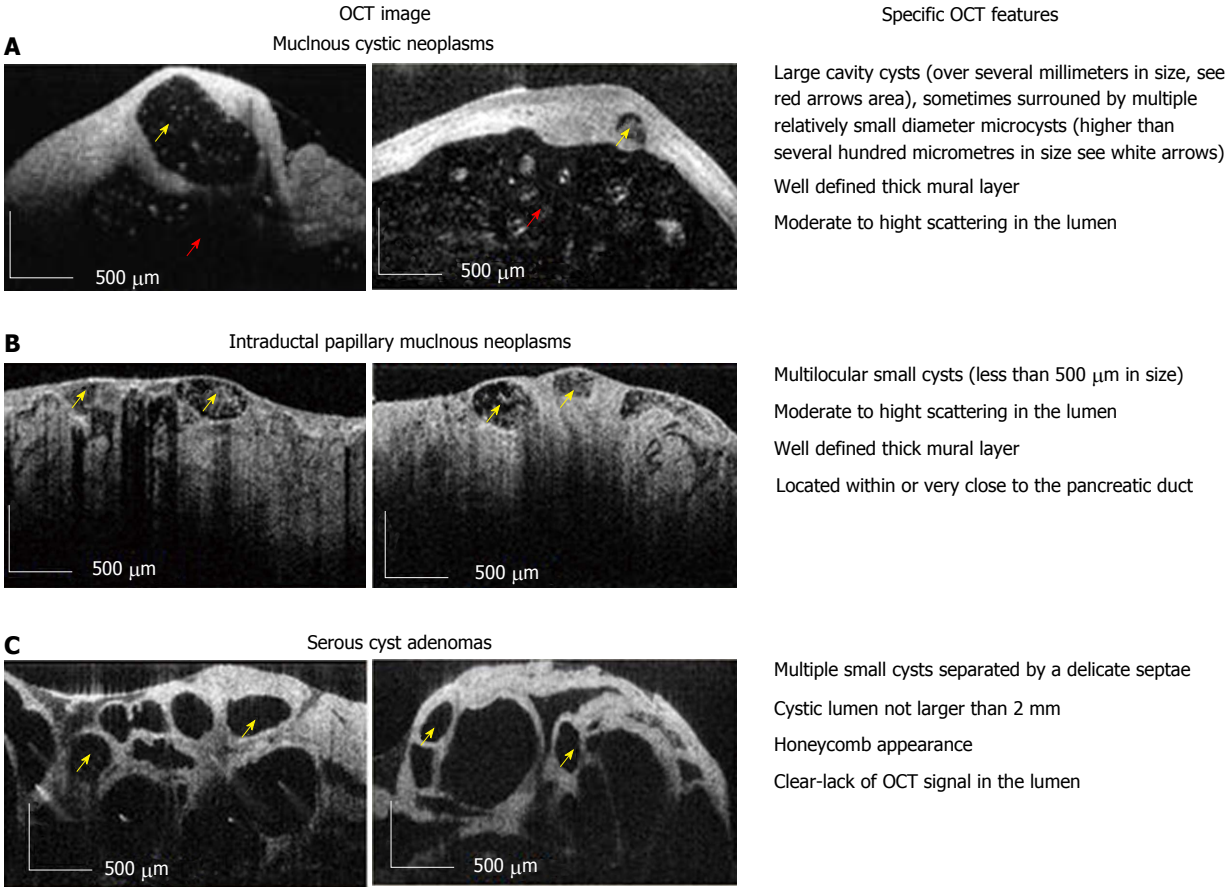

Figure 8 Optical coherence tomography image. A, B: Diagnostic criteria for high-risk (*i.e.*, Mucinous Cystic Neoplasms, Intraductal Papillary Mucinous Neoplasms); C: Low risk (*i.e.*, Serous Cysts Adenomas) pancreatic cysts. Multiple small cysts are marked with yellow arrow, while surrounded main cystic cavity is marked with red arrow. Scale bar = 500 μm[69]. OCT: Optical coherence tomography.

titia boundaries. Layers of these biliary ducts showed linear, homogeneous and regular surface; however, the difference between hypo-reflective intermediate and hypo-reflective outer layer appeared more difficult than that of between the hypo-reflective inner and intermediate layer. Potentially, OCT shows real-time, high-resolution, cross-sectional images, or "optical biopsies" for detecting the early stages of pancreatiobiliary diseases. OCT can improve the quality of images obtained during ERCP, which may be important in distinguishing between the neoplastic and non-neoplastic lesions. Further studies are necessary for the proper clinical applications of this promising method in the pancreaticobiliary duct system and diagnosis of pancreatic cysts.

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BRIEF ARTICLE

Outcome in obscure gastrointestinal bleeding after capsule endoscopy

Alex Cañas-Ventura, Lucia Márquez, Xavier Bessa, Josep Maria Dedeu, Marc Puigvehí, Sílvia Delgado-Aros, Ines Ana Ibáñez, Agustin Seoane, Luis Barranco, Felipe Bory, Montserrat Andreu, Begoña González-Suárez

Alex Cañas-Ventura, Lucia Márquez, Xavier Bessa, Josep Maria Dedeu, Marc Puigvehí, Sílvia Delgado-Aros, Ines Ana Ibáñez, Agustin Seoane, Luis Barranco, Felipe Bory, Montserrat Andreu, Department of Gastroenterology, Hospital del Mar Research Institute, Pompeu Fabra University, 08003 Barcelona, Spain

Begoña González-Suárez, Endoscopic Unit, Gastroenterology Department, ICMDiM. Hospital Clínic, 08036 Barcelona, Spain

Author contributions: Cañas-Ventura A, Marquez L and Gonzalez-Suarez B designed the study; Cañas-Ventura A, Marquez L, Bessa X, Dedeu JM, Puigvehi M, Delgado-Aros S, Ibañez IA, Seoane A, Barranco L, Andreu M, Bory F and Gonzalez-Suarez B performed the research; Cañas-Ventura A, Marquez L and Gonzalez-Suarez B analyzed the data; Cañas-Ventura A, Marquez L, Andreu M and Gonzalez-Suarez B wrote the paper; all authors have approved the final version to be published.

Correspondence to: Alex Cañas-Ventura, MD, Department of Gastroenterology, Hospital del Mar Research Institute, Pompeu Fabra University, Passeig Maritim 25, 08003 Barcelona, Spain. alexcanasventura@yahoo.es
Telephone: +34-93-2483217 Fax: +34-93-2218644

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Abstract

AIM: To investigate the clinical impact of capsule endoscopy (CE) after an obscure gastrointestinal bleeding (OGIB) episode, focusing on diagnostic work-up, follow-up and predictive factors of rebleeding.

METHODS: Patients who were referred to Hospital del Mar (Barcelona, Spain) between 2007 and 2009 for OGIB who underwent a CE were retrospectively analyzed. Demographic data, current treatment with non-steroid anti-inflammtory drugs or anticoagulant drugs, hemoglobin levels, transfusion requirements, previous diagnostic tests for the bleeding episode, as well as CE findings (significant or non-significant), work-up and patient outcomes were analyzed from electronic charts. Variables were compared by χ^2 analysis and Student *t* test. Risk factors of rebleeding were assessed by Log-rank test, Kaplan-Meier curves and Cox regression model.

RESULTS: There were 105 patients [45.7% women, median age of 72 years old (interquartile range 56-79)] and a median follow-up of 326 d (interquartile range 123-641) included in this study. The overall diagnostic yield of CE was 58.1% (55.2% and 63.2%, for patients with occult OGIB and overt OGIB, respectively). In 73 patients (69.5%), OGIB was resolved. Multivariate analysis showed that hemoglobin levels lower than 8 g/dL at diagnosis [hazard ratios (HR) = 2.7, 95%CI: 1.9-6.3], patients aged 70 years and above (HR = 2.1, 95%CI: 1.2-6.1) and significant findings in CE (HR = 2.4, 95%CI: 1.1-5.8) were independent predictors of rebleeding.

CONCLUSION: One third of the patients presented with rebleeding after CE; risk factors were hemoglobin levels < 8 g/dL, age ⩾ 70 years or the presence of significant lesions.

Key words: Capsule endoscopy; Obscure gastrointestinal bleeding; Small bowel; Angiodysplasia; Enteroscopy

Core tip: This paper describes a large cohort of patients with obscure gastrointestinal bleeding who underwent a capsule endoscopy. The diagnostic yield was analyzed with further exploration motivated by the capsule findings, as well as the outcome during follow-up. Risk factors of rebleeding were also analyzed. Interestingly, old age, a lower hemoglobin level at diagnosis and significant lesions in capsule endoscopy were found to be predictors of rebleeding in this cohort.

Cañas-Ventura A, Márquez L, Bessa X, Dedeu JM, Puigvehí M, Delgado-Aros S, Ibáñez IA, Seoane A, Barranco L, Bory F, Andreu M, González-Suárez B. Outcome in obscure gastrointestinal bleeding after capsule endoscopy. *World J Gastrointest Endosc* 2013; 5(11): 551-558 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i11/551.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i11.551

INTRODUCTION

Since 2001, video capsule endoscopy (CE) has become an important tool for the diagnosis of small bowel diseases. Its most important indication is in the study of obscure gastrointestinal bleeding (OGIB), defined as persistent or recurrent bleeding from the gastrointestinal (GI) tract after a non-conclusive conventional endoscopic examination [upper-GI endoscopy (GIE)] and colonoscopy. Two different presentations of OGIB can be distinguished: obscure-occult GI bleeding [persistent or recurrent iron deficiency anemia and/or positive fecal occult blood test (occult-OGIB)] and obscure-overt GI bleeding [recurrent visible blood loss: melena or hematochezia (overt-OGIB)][1]. CE provides a non-invasive examination of the small intestine that is not accessible through conventional endoscopy or push or balloon enteroscopy. Several studies have shown good specificity and sensitivity of CE in the setting of OGIB and better diagnostic yield than other techniques (radiological or endoscopic procedures)[2-5]. CE is well-tolerated and its rate of complications is very low. The disadvantages of CE are the impossibility to treat and the impossibility to obtain tissue biopsies. Although the diagnostic yield of CE is high, the impact on the outcome of the patients with OGIB after a CE is still unclear.

A single center retrospective study of a long follow-up cohort of 105 patients with OGIB who underwent a CE study is presented. The aim of this study was to evaluate the usefulness of CE, focusing on the subsequent treatment and the outcome of the OGIB episode. Secondary objectives were to define predictive factors of rebleeding.

MATERIALS AND METHODS

Patient inclusion

All patients with OGIB referred to the endoscopy unit (Hospital del Mar, Barcelona, Spain) between January 2007 and June 2009 were analyzed retrospectively. On all these patients, at least one upper-GIE and one colonoscopy were run. Those endoscopies were considered normal or the findings were insufficient to explain the patient's symptoms. By using the electronic charts of all patients, we collected data on the complete episode of OGIB; including previous procedures to CE and follow-up data. The collected variables were: demographic data, history of intake of non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulant and antiplatelet therapy (aspirin and clopidogrel), hemoglobin levels (Hb) at diagnosis, transfusion requirements, time from overt bleeding to CE procedure, and results of previous diagnostic tests [upper-GIE, colonoscopy, computed tomography (CT) scan, radiographic series of small bowel, angiography, Tc^{99} red cell scan and Meckel's scan].

CE procedure

The procedure was performed in ambulatory and in-hospital patients, using PillCam SB2© (Given Imaging, Yoqneam, Israel). Bowel preparation consisted of an oral purge (two liters of polyethylene glycol-based solution) ingested the night before the procedure. CE was swallowed in the morning and the data recorder was removed 8-9 h later. Patients were allowed to drink fluids 2 h after the administration of CE and to eat 4 h after the ingestion. Patients were asked to verify the excretion of the capsule in the stool and to alert the endoscopy unit if it was not excreted.

In order to test small bowel patency, a previous exam was performed with Agile capsule© (Given Imaging, Yoqneam, Israel) on patients with a history of sub-occlusive intestinal episodes, chronic NSAID intake, *i.e.,* longer than 6 mo, established or suspected inflammatory bowel disease, previous abdominal surgery of small bowel or bowel strictures demonstrated by radiological techniques. Capsule retention was defined as the presence of the capsule in the GI tract for at least 2 wk after ingestion. Two gastroenterologists with extensive experience in small bowel endoscopy (González-Suárez B and Dedeu JM) evaluated the images recorded by CE.

Diagnostic and therapeutic strategy after CE

The CE findings were classified as significant and non-significant. Significant findings were those that explained the clinical situation (*i.e.,* ulcers, active bleeding, tumors and angiodysplasias). Non-significant findings were those where the mucosa was normal or with minimal changes with an uncertain relationship to the bleeding (*i.e.,* small erosions, small and isolated angiodysplasia).

Therapeutic strategy was classified into two different groups: (1) specific treatment focused on the main cause of bleeding: invasive therapies (*i.e.,* endoscopic treatment or surgery) and medical treatment (*i.e.,* proton-pump inhibitors (PPIs), NSAIDs or anticoagulant drugs withdrawal); and (2) non-specific treatment (*i.e.,* iron supplementation, blood transfusions, watchful waiting and NSAID withdrawal if CE findings were not significant or different to ulcer/erosion). Therapeutic strategy was chosen based on the patient's overall condition and the nature of the disease.

Follow-up

Complete follow-up information was obtained from electronic charts: hemoglobin levels, transfusion requirement after treatment, recurrence of OGIB and CE complications. Follow-up time was defined as the time between the CE and the date of rebleeding or the last

Table 1 Patients' baseline characteristics

Characteristics	Overall	Occult-OGIB	Overt-OGIB	*P* value
Patients	100.00%	63.80%	36.20%	-
Age [yr, median (IQR)]	72 (5-79)	71 (5-78)	73 (49-82)	0.800
Gender (female)	45.70%	55.20%	28.90%	0.014
Bleeding-related drugs	41.90%	37.30%	50%	0.200
NSAIDs	30.50%	26.90%	36.80%	0.300
Hemoglobin level [g/dL, median (IQR)]	7.5 (6.4-9.3)	7.4 (6.0-9.1)	7.6 (6.5-9.4)	0.600
Transfusion requirements	61%	55.20%	71.10%	0.080
Transfusion requirements (blood units, mean ± SD)	2.01	1.7 ± 1.7	2.5 ± 2.3	0.037
Follow-up [d, median (IQR)]	326 (123-641)	330 (154-691)	217 (84-476)	0.500

NSAIDs: Non-steroidal anti-inflammatory drugs; OGIB: Obscure gastrointestinal bleeding; IQR: Interquartile range.

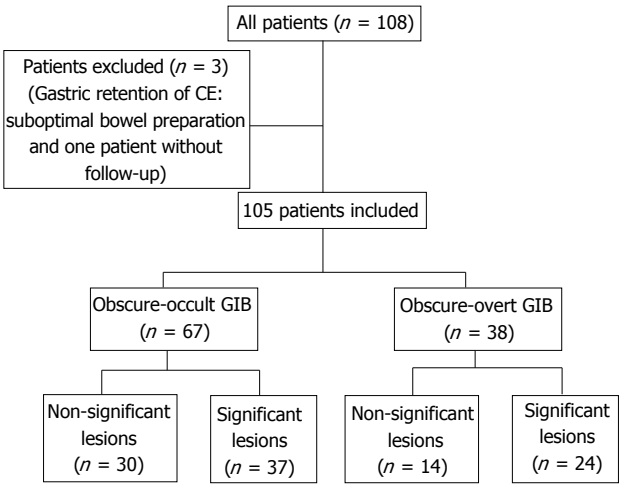

Figure 1 Patients included and group distribution. CE: Capsule endoscopy; GIB: Gastrointestinal bleeding.

follow-up visit. Anemia was defined as Hb level < 13 g/dL in men and < 12 g/dL in women. A patient's outcome was considered favorable or resolved if no overt bleeding was present and the anemia was resolved completely after treatment. Rebleeding was defined as overt bleeding or reappearance of anemia.

Statistical analysis

Continuous data were expressed as median and percentiles [interquartile range (IQR) 25th-75th percentile] and were compared using the Student *t* test or the *U* test. Categorical data were expressed by percentages with a 95%CI and compared by the χ^2 test or the *F* test.

Independent predictors for rebleeding were first analyzed by univariate analysis using the Log-rank test in the Kaplan-Maier model (setting the rebleeding variable as "event"). All variables from the univariate analysis with a $P < 0.05$ were included in a Cox proportional hazards regression using the stepwise selection method. Results were reported as hazard ratios (HR) with 95%CI. All *P* values were two-sided and $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

There were 108 patients included in the study. In two patients, the CE failed to achieve complete small bowel visualization: in one patient CE was retained for eight hours in the stomach and in the other one, bowel preparation was not optimal for image evaluation. In one patient, follow-up was not available because she moved back to her country the day after CE. Hence, 105 patients were available for data analysis (Figure 1).

According to the definition of OGIB, 67 patients (64.2%) with occult-OGIB and 38 patients (35.8%) with an overt-OGIB were identified. The baseline characteristics of patients included in the cohort are summarized in Table 1. Follow-up time and hemoglobin at diagnosis were similar in both groups. Mean of transfusion units was higher in the overt-OGIB group than in the occult-OGIB group (2.5 *vs* 1.7 units, $P = 0.037$).

There were 44 patients (41.9%) that had been taken a bleeding-related drug before the OGIB episode: clopidogrel ($n = 8$); warfarin ($n = 9$) or NSAIDs (including acetylsalicylic acid) ($n = 26$), without statistical significant differences comparing the two groups ($P = 0.2$).

All patients were previously submitted to at least one upper-GIE and colonoscopy that were considered normal or whose findings were insufficient to explain the bleeding episode. Other procedures were performed before CE in 12 patients: four CT-scans focused on small bowel, two mesenteric angiographies, three Tc^{99} red cell scans, three Meckel's scans, and all of them were negative for the diagnosis of cause of bleeding.

CE findings

CE findings were considered significant, according to previous definition, in 37 patients of the occult-OGIB group and in 24 patients of the overt-OGIB group, which represent a diagnostic yield of 55.2% and 63.2%, respectively ($P = 0.5$). The overall diagnostic yield of CE in our cohort was 58.1%. Intestinal angiodysplasia (21%) and small bowel ulcers (27%) were the most frequent lesions (Figure 2). A total of seven lesions (6.6%) were found in the upper GI tract of these patients: five ulcers and two erythematous duodenitis, classified as non-significant lesions.

In two patients, CE was retained in the small bowel. In one patient, retention was due to a pelvic relapse of a previous colorectal cancer that involved the ileum; the patient remained asymptomatic until surgery and the device was removed. Another patient was diagnosed with an intestinal T-cell lymphoma and CE was removed during an oral balloon enteroscopy performed to take biopsies.

All patients with overt-OGIB were submitted to a CE within the first three weeks after the bleeding episode. There were no differences between patients with significant and non-significant lesions regarding the time interval between bleeding and CE [8.5 d (95%CI: 11.4-5.6) *vs*

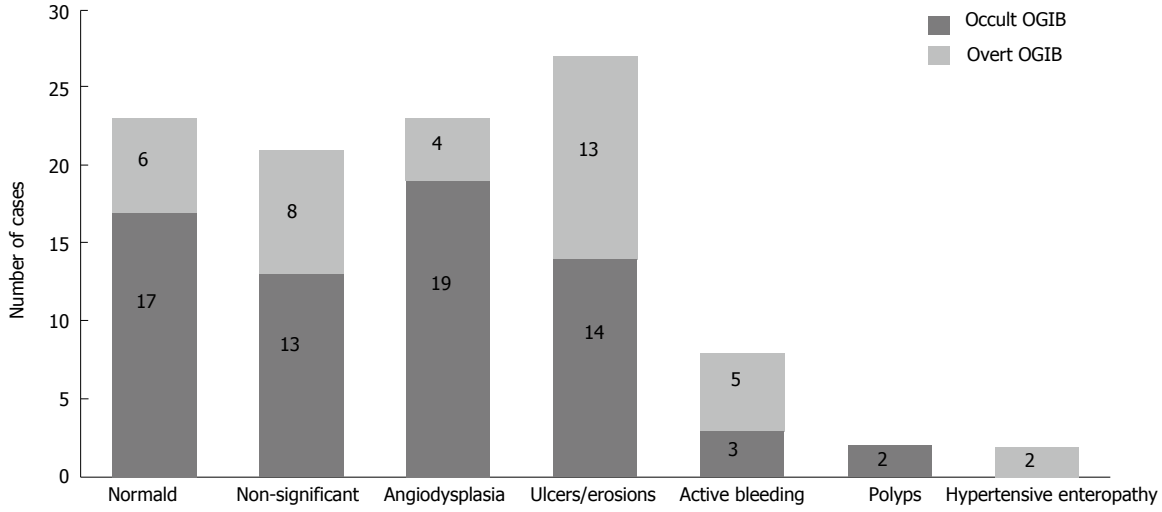

Figure 2 Capsule endoscopy findings according to obscure gastrointestinal bleeding presentation: occult or overt. OGIB: Obscure gastrointestinal bleeding.

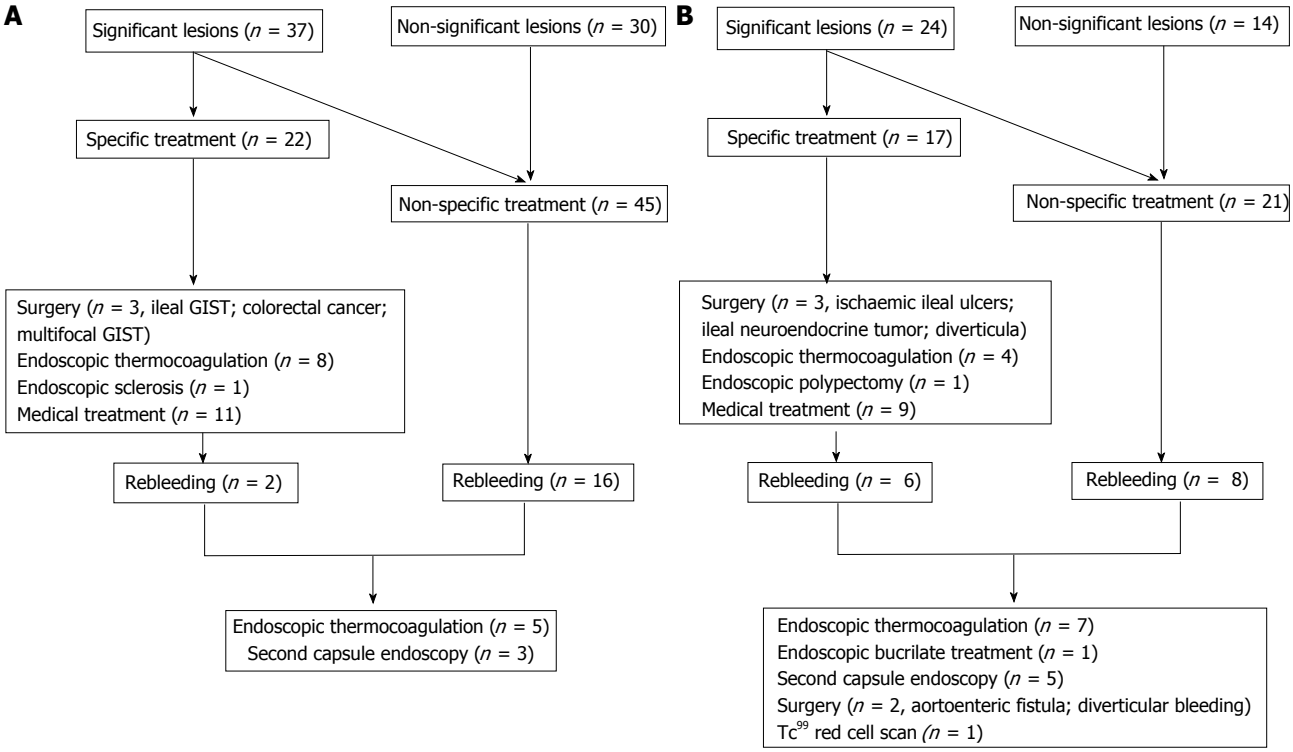

Figure 3 Therapeutic strategy and outcome: occult-obscure gastrointestinal bleeding group (A) and overt-obscure gastrointestinal bleeding group (B).

6.9 d (95%CI: 8.5-5.3), $P = 0.06$, respectively].

Therapeutic strategy

Therapeutic strategy after CE and outcome according to OGIB presentation and CE findings are detailed in Figure 3. Specific treatment was performed in 39 patients (37.5%): surgery ($n = 6$), endoscopic therapy with thermocoagulation or sclerosis ($n = 13$) and specific medical treatment ($n = 21$). Up to 87% of patients with significant lesions in CE received specific treatment. NSAIDs were withdrawn in 22 patients (21%): 9 of them with small bowel ulcers and 13 with normal capsule or non-significant lesions.

Outcome

Overall follow-up time was 321 d (IQR 115-626). In the cohort, 73 patients (69.5%) had a favorable outcome according to the definition and hemoglobin levels improved significantly [ΔHb 4.4 (95%CI: 5.0-3.9) g/dL, $P < 0.001$]. Surgery was curative in 100% of patients ($n = 6$). Endoscopic therapies ($n = 13$) such as thermocoagulation, sclerosis or polypectomy had a resolution rate of 61.5%.

There were 32 patients (30.8%) who had a recurrence of OGIB, in a median time of 157 d (IQR 81-326) af-

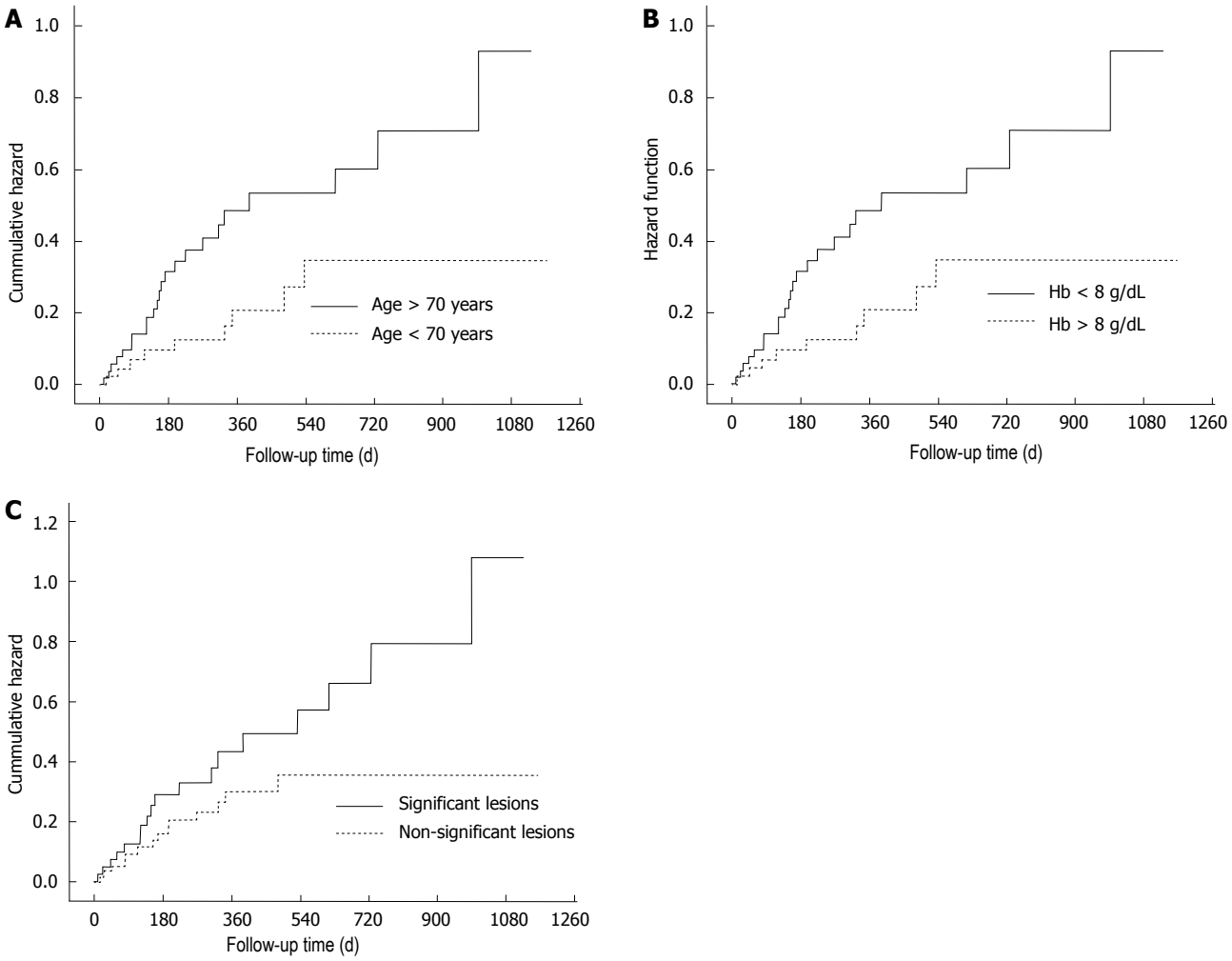

Figure 4 Hazard plots: Age (A), hemoglobin levels level (B) and significant lesions in capsule endoscopy (C). Hb: Hemoglobin.

ter the index episode. Rebleeding rates were 20.5% and 36.4%, depending on specific and non-specific treatment ($P = 0.8$).

In 8 of the 32 patients, a second-look capsule endoscopy was performed, which enabled the diagnosis of angiodysplasias in two patients with a previously normal CE. After rebleeding, specific treatment was performed on 15 of the 32 patients (46.8%): 12 endoscopic thermocoagulation, one bucrylate injection and two surgeries.

In order to elucidate factors associated with a higher risk of rebleeding, univariate and multivariate analysis were performed. Association analysis is detailed in Table 2 and hazard plots are represented in Figure 4. In this study, Hb levels lower than 8 g/dL at diagnosis (HR = 2.7, 95%CI: 1.9-6.3), patients older than 70 years of age (HR = 2.1, 95%CI: 1.2-6.1) and significant findings in CE (HR = 2.4, 95%CI: 1.1-5.8) were independent predictors of rebleeding. The analysis depending on the type of lesion did not show differences. However, angiodysplasia was the lesion that rebled more frequently (8/32 patients, 25%). Moreover, angiodysplasia was diagnosed after rebleeding in another eight of the 32 patients (25%), whose cause of OGIB was different or unknown after the CE in the index episode.

DISCUSSION

Diagnostic work-up and treatment of OGIB is an important challenge for gastroenterologists. Obscure gastrointestinal bleeding is the first accepted indication for capsule endoscopy and there are several diagnostic algorithms proposed by different medical societies[1,6,7]. In the present study of 105 patients with OGIB, a high diagnostic yield of CE in patients with occult-OGIB and overt-OGIB is described.

Optimal bowel preparation is essential to improve CE diagnostic yield[8] and a two liter, polyethylene glycol-based solution ingested the day before CE permitted adequate bowel visualization in almost all patients. Several studies have already shown the superiority of CE compared to other techniques[5,9]. In this cohort, a diagnostic yield of 58.1% was observed, which is concordant with published data[10-16]. However, differences between obscure-overt bleeding and obscure-occult bleeding[17,18] were not observed. The time between the acute bleeding episodes and CE has been analyzed in previous stud-

Table 2 Risk factors for rebleeding

Risk factors	Univariate Log-rank test	Multivariate		
	P	HR	95%CI	*P*
Age > 70 yr	0.037	2.1	1.2-6.1	0.05
Gender	0.800	-	-	-
Overt OGIB presentation	0.130	-	-	-
Hb < 8.0 g/dL	0.027	2.7	1.9-6.3	0.03
Blood units transfused	0.180	-	-	-
Transfusions requirement	0.020	-	-	-
T ⩾ 2 blood units	0.023	-	-	-
NSAID intake	0.900	-	-	-
Significant lesions in CE	0.036	2.4	1.1-5.8	0.01
Specific treatment carried out	0.500	-	-	-

OGIB: Obscure gastrointestinal bleeding; CE: Capsule endoscopy; NSAID: Non steroidal anti-inflammatory drugs; Hb: Hemoglobin; HR: Hazard ratios.

ies, showing that the diagnostic yield would be higher in ongoing bleeding cases if CE were performed within the first 48 h[12,19,20], although this factor does not seem to influence the diagnostic yield in this study.

As has been previously described, the most frequent findings in capsule studies were angiodysplasia and intestinal ulcers[12,21,22]. In seven patients (6.6%), CE diagnosed lesions in the upper-GI tract that were not seen in previous upper-GIE. These results suggest that the repetition of upper- or lower-GIE prior to a CE could be useful in diagnosing accessible lesions by conventional endoscopy[20].

A favorable outcome after CE, reaching bleeding resolution, was observed in two-thirds of patients in this study. Capsule retention occurred in 1.9% of patients, which is consistent with previously published data[23].

The diagnostic and therapeutic work-up were based on CE results in our series: patients with significant lesions received specific treatment more frequently compared with those who had no lesions or non-significant lesions. Nevertheless, this treatment was not associated with a higher resolution rate (20.5% *vs* 36.4% of rebleeding after specific or non specific treatment, $P = 0.8$, respectively). These results may have several explanations. Firstly, despite not finding differences according to the kind of lesions and risk of rebleeding, the lesion that most frequently rebled was angiodysplasia. Secondly, angiodysplasia often has a multifocal nature and it has a high rate of rebleeding, even when patients are treated by an endoscopy[14,24].

Moreover, special attention is required in patients treated with NSAIDs and antiplatelet drugs. It is well established that a high percentage of NSAID consumers may present small bowel erosions or ulcers in CE[25]. In this study's cohort, the use of NSAIDs was stopped in 22 patients after CE findings and 14 of them (14/22, 63.6%) achieved a resolution of the bleeding. However, in eight of these patients, CE findings were non-significant. It is important to remark that an accurate anamnesis regarding NSAID intake is important and its withdrawal should be individually evaluated.

In this study's cohort, one-third of patients presented with rebleeding episodes during follow-up. Hemoglobin levels lower than 8 g/dL at diagnosis, patients older than 70 years of age, and significant findings in CE were independent predictors of rebleeding, as has been described in previous papers[20,26]. So far, the role of CE findings as a rebleeding risk factor remains controversial. Macdonald *et al*[27] described a higher rebleeding rate in patients with significant lesions, although no regression analysis was performed in that study[27]. On the contrary, Park *et al*[28] did not find significant differences in the cumulative rebleeding rate between significant and non-significant findings in the CE. Type of lesion was not a predictor of rebleeding, probably due to stratification and the low number of relapses. However, nearly 50% of patients that presented with rebleeding had a final diagnosis of angiodysplasia in CE. Interestingly, second-look CE or conventional endoscopy after rebleeding revealed angiodysplasia not found in previous procedures, underlining the usefulness of a second-look CE in selected patients, as has been published before[29,30].

The main limitation of this study is that it is a retrospective design. However, data were collected from electronic charts that permitted accuracy in terms of in-hospital and outpatient data, reducing data collection bias. Strengths of the study were the long follow-up that allowed the outcome to be evaluated and the regression analysis of rebleeding risk factors.

In conclusion, this study offers a long follow-up of a large, clinical based, cohort from a single tertiary hospital. Diagnostic yield of CE was high in both OGIB presentations. One-third of the patients presented with rebleeding after CE; risk factors of rebleeding were Hb < 8 g/dL, age ⩾ 70 years or the presence of significant lesions in CE.

COMMENTS

Background

Capsule endoscopy (CE) is a device that allows visualization of the entire small bowel mucosa. It has become essential in the diagnosis work-up of gut pathologies, especially evaluation of obscure gastrointestinal bleeding (OGIB). Although published studies are focused on diagnostic yield of CE, outcome of patients that undergo a CE has not been analyzed extensively.

Research frontiers

CE is widely used in OGIB diagnosis. However, reports about patient outcomes presenting OGIB that received a CE are rare in the medical literature.

Innovations and breakthroughs

This study analyzed a large group of OGIB patients during a long follow-up time. The authors concluded that CE is useful in different types of OGIB and further treatments permitted the resolution of OGIB in a high proportion of patients. Ulcers and angiodysplasias were the most frequently diagnosed lesions by CE. The authors identified several risk factors of rebleeding: old age, a low hemoglobin level at diagnosis and the presence of significant lesions in the CE.

Applications

CE is safe, well tolerated and useful in the diagnosis of several gastrointestinal disorders. The risk factors described in this study should help physicians in OGIB management.

Terminology

CE is a device a little bit bigger than a pill that can be easily swallowed by patients. It is able to take photos as it passes through the gut that are saved in an external memory disk *via* wireless technology. Photos are studied later by a

gastroenterologist at a workstation.

Peer review

In this retrospective study, the authors investigated the outcome of obscure gastrointestinal bleeding after capsule endoscopy. They concluded that hemoglobin levels < 8 g/dL at diagnosis, patients > 70 years and significant findings in CE were independent factors of a high rebleeding rate.

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BRIEF ARTICLE

PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy

Lucian Negreanu, Ruxandra Babiuc, Andreea Bengus, Roxana Sadagurschi

Lucian Negreanu, Ruxandra Babiuc, Andreea Bengus, Roxana Sadagurschi, Internal Medicine 2 Gastroenterology Department, University Hospital, Carol Davila University of Medicine Bucharest, 011465 Bucharest, Romania
Author contributions: All authors participated in the study; Negreanu L designed, wrote the article and made corrections; Sadagurschi R helped with article redaction and corrections.
Supported by ESGE–GIVEN Research Grant 2010
Correspondence to: Lucian Negreanu, MD, PhD, Internal Medicine 2 Gastroenterology Department, University Hospital, Carol Davila University of Medicine Bucharest, 169 splaiul Independentei Street, sector 5, 011465 Bucharest, Romania. negreanu_99@yahoo.com
Telephone: +40-72-2546405 Fax: +40-21-3180505
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Abstract

AIM: To assess the feasibility, accuracy and acceptability of PillCam Colon 2 in detection of significant lesions in colorectal cancer risk patients, unable or unwilling to perform colonoscopy.

METHODS: This is a prospective, single center study using the second generation of PillCam Colon capsule. In all patients the readers were instructed to review the entire colon capsule endoscopy (CCE) examination using Rapid 7 software and additionally to note significant extra-colonic findings. Colonic significant findings were described according to European Society of Gastrointestinal Endoscopy guidelines. CCE procedure completion rate, level of bowel preparation and rate of adverse events were assessed.

RESULTS: A total of 70 patients at risk of colorectal cancer were enrolled in the study. In three patients the procedure failed because the capsule was not functioning when entered the colon. PillCam Colon 2 showed positive findings in 23 (34%, 95%CI: 21.6%-44.1%) of the remaining 67 patients. Six patients were diagnosed with tumors: 4 with colon cancers, 1 with gastric cancer and 1 with a small bowel cancer. The capsule findings were confirmed after surgery in all these patients. The capsule excretion rate in twelve hours was 77% with 54 patients having a complete examination. The rectum was not explored during CCE procedure, in 16 patients (23%, 95%CI: 13.7%-34.1%). Every patient accepted CCE as an alternative exploration tool and 65/70 (93%) agreed to have another future control by CCE. No complications were reported during or after CCE examination.

CONCLUSION: PillCam Colon 2 capsule was effective in detecting significant lesions and might be considered an adequate alternative diagnostic tool in patients unable or unwilling to undergo colonoscopy.

Key words: Colon cancer; Colonoscopy failure; Colonoscopy refuse; Colon capsule; Pillcam Colon 2

Core tip: This is an important article on the second generation colon capsule endoscopy. It shows that it has a high diagnostic yield in an enriched population that have had incomplete colonoscopy or refused colonoscopy. We also diagnosed significant extracolonic lesions. The method had a high acceptability among patients and we did not encounter any complications.

Negreanu L, Babiuc R, Bengus A, Sadagurschi R. PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy. *World J Gastrointest Endosc* 2013; 5(11): 559-567 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i11/559.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i11.559

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer and second most common cause of cancer-related

deaths in Europe. CRC screening has been proven to reduce disease-specific mortality[1]. The choice of a screening test takes into consideration parameters such as patient age and the presence of different risk factors for the development of CRC. Several European countries employ national screening programs. They rely almost exclusively on stool tests, with colonoscopy used as an adjunct in some countries. Colonoscopy has been shown to reduce colorectal cancer risk. Its increased use in the population aged 50 years and older in the United States since the 1980s is the reason for decreasing CRC incidence rates, particularly in the sigmoid, colon although some environmental factors may also have contributed to the decreasing risk[2].

A prediction for 2012 expects a decline in mortality from colorectal cancer of 7% in men and 11% in women in the European Union compared with 2007 mainly due to the screening programs[3].

Nevertheless the uptake of patients in the screening programs is disappointingly low. The degree of acceptance of colonoscopy is low because it is perceived by some patients/physicians as invasive and painful and with a degree of complications/risks. Another drawback is the rate of failed colonoscopic examinations. The caecal intubation failure rate is up to 20% of colonoscopies in clinical practice[4]. No guideline exists for these patients but several options are being used with different success rates. Computed tomographic colonography (CTC) is a useful option and seems supported by recent studies[5].

Colon capsule endoscopy (CCE) PillCam Colon was developed by Given Imaging especially for increasing the acceptability and safety of a colorectal examination. Although a bowel preparation similar to colonoscopy is necessary, this technique requires no intubation, insufflation or sedation and has minimal complication rates/risks[6,7].

A second-generation, improved, CCE system (PillCam Colon 2) was developed to increase sensitivity for colorectal polyp detection compared with the first-generation system. A recent study using a second-generation colon capsule showed a higher sensitivity than the first generation, of almost 90% for detection of patients with significant colonic lesions[8]. Recently the European Society of Gastrointestinal Endoscopy published an updated and extensive guideline regarding the current status of capsule endoscopy. It gives a clear perspective about the indications, bowel preparation, reporting and level of evidence[9].

According to these guidelines, CCE is feasible and safe and appears to be an accurate screening tool when used in average-risk individuals. A CCE based screening may be cost-effective if it increases uptake compared with colonoscopy. In high risk patients (alarm symptoms or signs, family or personal history of CRC), which are at increased risk of advanced colorectal neoplasia or cancer, colonoscopy should be the first choice. However, in patients for whom colonoscopy is inappropriate or not possible, the use of CCE could be discussed with the patient[9].

Study aim

We conducted a pilot trial to asses the feasibility, accuracy and acceptability of PillCam Colon 2 in detection of significant lesions in patients at risk of CRC which were unable or unwilling to perform colonoscopy. Following recent European Society of Gastrointestinal Endoscopy (ESGE) capsule endoscopy guideline, a significant colorectal lesion that requires colonoscopy follow-up was considered to be a colorectal polyp > 6 mm or presence of at least 3 colonic polyps[9].

End points

Since we could not compare colon capsule endoscopy CCE to the gold standard (colonoscopy) we introduced a new end point of "positive" examination: the diagnostic utility index (findings directly explaining symptoms or requiring specific treatment in asymptomatic patients). Although using this end point even a normal examination can be considered successful for a certain patient if it is important for the clinical decision and follow up, we decided to consider significant the capsule findings that required medical or surgical treatment. Also a patient follow up of one year was mandatory. CCE procedure completion rate level of bowel preparation and rate of adverse events were also assessed.

MATERIALS AND METHODS

Patients

A total of 70 patients of mean age 58.3 years (range 29 to 87) were enrolled in this prospective, single center study.

Indications

Inclusion criteria were as follows: (1) patients at risk for CRC unable to undergo the colonoscopic examination because of the anesthetic risk and co-morbidities; (2) patients at risk for CRC who refused colonoscopy.

We considered as patients at risk for CRC, patients with personal or family history of adenomas or colorectal cancer, but also with digestive symptoms such as bleeding, recent bowel habits change, weight loss, anemia, abdominal pain, positive fecal occult blood test and suspect imaging-abdominal ultrasound, computed tomography (CT)/positron emission CT scan were included in the study.

Majority of patients unwilling to undergo the colonoscopic examination have had a negative experience with a prior colonoscopy (either an incomplete or failed colonoscopy because of the abdominal discomfort). The PillCam Colon 2 examination was proposed as an alternative tool to explore the colon to these patients. Exclusion criteria comprised: (1) patients with pacemakers; (2) patients with suspected digestive stenosis or intestinal occlusion; and (3) patients with dysphagia or swallowing disorders.

Ethical considerations

The study was approved by the Ethics Committee of the University Hospital of Bucharest and patients signed

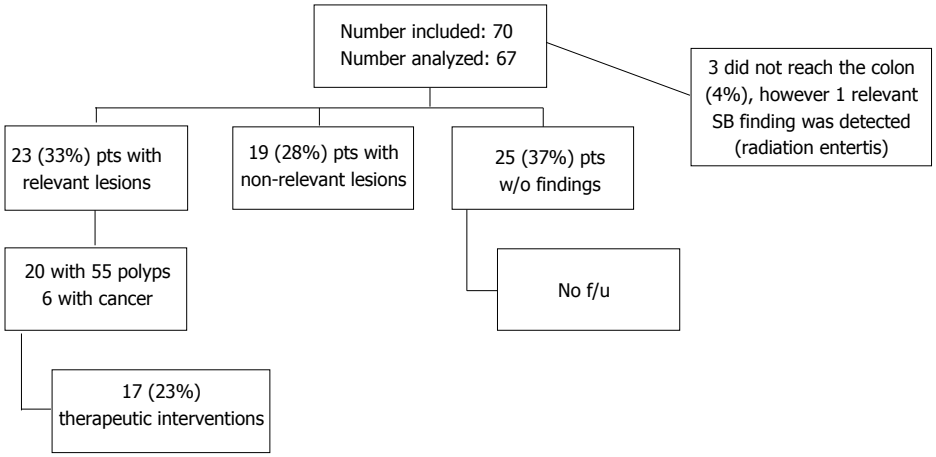

Figure 1 In all patients the readers were instructed to review the entire colon capsule endoscopy examination and additionally significant extra-colonic findings. All patiets had at least one year follow up. The case no f/u will disapear.

an informed consent for the investigation. Enrollment started in February 2011.

PillCam Colon 2 procedure

The second generation PillCam Colon 2 capsule and Rapid reader 7 software were used in this study. The Pillcam Colon 2 capsule is slightly longer than the previous generation with 11.6 mm × 31.5 mm in size. It has been designed to work for at least 10 h and it has a variable frame rate (from 4 to 35 frames/second in order to correctly visualize the mucosa when accelerated peristalsis). The angle of view was increased to 172 degrees in both capsule lenses, thus covering almost 360 degrees of the colonic surface. A new smaller and more ergonomic data recorder with a liquid crystal display allowing real time viewing was developed. It permits a bidirectional communication with the capsule and also is friendlier and easier to use by the patient providing automatic visual and audio signals for procedure activities (boost administration).

All the investigators reading the capsule videos had extensive experience in digestive endoscopy and they had previous experience using the small-bowel capsule. Before the study start a training session was organized by Given Imaging. This 2-d training session included several hours of sessions addressing different issues as preparation, procedure and software utilization. It was followed by a self-assessment test consisting of reading ten colon capsule videos. The first three examinations in the study were performed under supervision from Given Imaging.

Colon preparation and cleanliness estimation

Participating patients received written and oral explanations of colonic preparation details. The preparation consisted in a low-residue diet starting 48 h before investigation and a clear liquid diet 24 h before ingestion. A 4 L of split-dose polyethylene glycol (PEG) Fortrans® (Macrogol 4000, Ibsen, France) prep was administered in the evening and 2 h prior to capsule ingestion. Since in Romania oral sodium phosphate is not available, PEG was used as booster. Upon capsule exit from the stomach a first liter of PEG was administered and a second boost of one liter of PEG was administered if the capsule was not excreted 3 h after the first one.

Colon cleanliness was graded using a two point scale. This scale was a development of the original 4-point scale used in previous studies and grades preparation as inadequate (poor or fair on the 4-point scale) or adequate (good or excellent on the 4-point scale)[10]. The cleanliness was assessed in each of the five colon segments (cecum, right colon, transverse, left colon and rectum) and then a general estimate of the entire colon was made.

RESULTS

In all patients the readers were instructed to review the entire CCE examination and additionally significant extra-colonic findings (Figure 1).

Indications

The main indication for initial colonoscopy or for the otherwise contraindicated/refused colonoscopy had been: 35 symptomatic patients (abnormal transit 8, abdominal pain 4, anemia or overt bleeding 22, weight loss 1), 29 average and high risk colorectal cancer screening patients (familial 21 or personal history of polyps or cancer 5, acromegaly 1, long standing inflammatory bowel disease 1, screening 1) and 6 patients with abnormal imaging or tumor markers. The indications for referral of the patients are detailed in the Table 1.

The indication of capsule examination was: refusal of a colonoscopy in 37 patients, previous incomplete colonoscopy (mostly technical failures of initial colonoscopy) in 30 patients or unable to perform colonoscopy (the examination risks-cardiovascular or anesthetic were considered excessive by their own physicians) in 3 patients.

Findings

In three patients the procedure failed because the capsule was not functioning when it entered the colon. In the remaining 67 patients a significant diagnosis was made

Table 1 The main indication for initial colonoscopy or for the otherwise contraindicated/refused colonoscopy, the indications for referral of the patients

Patient	Sex	Age	Reason	Indication for CCE	Findings	Completion	Preparation
1	Female	85	Suspect CT	Refuse	3 pedunculated polyps in the descending colon 7-9 mm, voluminous diverticula in the sigmoid	c	a
2	Female	45	Transit troubles (diarrhea), family history	Failure	Diverticula	c	a
3	Male	76	Anemia	Failure	3 polyps 3-8 mm left colon	c	a
4	Male	39	Family history	Refuse	4 polyps 3-8 mm left colon	c	a
5	Male	52	Personal history of colorectal polyps	Refuse	4 polyps 4-8 mm left colon	c	a
6	Male	60	Abdominal pain weight loss	Failure	6 mm polyp cecum	c	a
7	Female	69	Transit troubles	Refuse	6 mm polyp right colon, diverticula	c	a
8	Female	57	Personal history of polyps	Failure	6 polyps 3-5 mm 2 transverse 4 left colon, diverticula	c	a
9	Male	80	Anemia severe, weight loss	Failure	Angiomas	c	a
10	Male	53	Transit troubles	Refuse	Diverticula	c	a
11	Female	61	Family history	Failure	Diverticula	c	a
12	Female	58	Transit troubles (diarrhea)	Refuse	Diverticula	c	a
13	Male	54	Family history (mother, aunt and uncle with CRC)	Refuse	Diverticula	c	a
14	Female	65	Abdominal pain history of resected transverse cancer history of urinary bladder cancer	Failure	Diverticula	c	a
15	Male	39	Family history	Refuse	Diverticula	c	a
16	Female	56	Family history (father with CC at 82) polyps	Refuse	Diverticula	c	a
17	Male	58	Personal history of cancer,colectomy	Refuse	Diverticula	c	a
18	Male	31	Family history(father CRC at 46)	Refuse	Diverticula	c	na
19	Male	62	Screening	Failure	Diverticula peridiverticular inflammation small erosion on the IC valve 3 mm polyp in the cecum	c	a
20	Male	69	Anemia weight loss	Refuse	Diverticula polyp 5 mm in the descedent colon internal hemorrhoids	c	a
21	Female	49	Transit troubles	Refuse	Diverticula small polyp 3 mm left colon some petechiae on the descendent colon	c	na
22	Male	75	Transit troubles	Failure	Diverticula,16 mm ulcerated submucosal mass in the sigmoid	c	a
23	Male	59	Family history	Refuse	Diverticula, 4 mm polyp sessile left colon	c	na
24	Male	64	Family history CRC resection of polyps	Failure	Normal	c	a
25	Female	60	Family history (mother with rectal cancer)	Refuse	Normal	c	a
26	Female	55	Suspect mass on CT	Refuse	Normal	c	a
27	Female	77	Anemia	Failure	Normal	c	a
28	Male	64	Anemia weight loss	Failure	Normal	c	a
29	Female	60	Family history	Refuse	Normal	c	a
30	Female	56	Transit troubles	Refuse	Normal	c	a
31	male	36	Family history, transit troubles	Refuse	Normal	c	a
32	Female	39	Family history	Failure	Normal	c	a
33	Female	29	Anemia, grandmother with colon cancer constipation	Refuse	Normal	c	a
34	Female	44	Anemia	Refuse	Normal	c	a
35	Male	59	Family history (colorectal cancer in the mother at early age) abdominal pain	Failure	Normal	c	a
36	Female	39	Acromegaly	Refuse	Normal	c	a
37	Female	42	Tumoral markers	Failure	Normal	c	a
38	Female	59	Anemia weight loss diarrhea suspect CT	Cardiologist choice	Normal	c	a
39	Female	49	Abdominal pain	Refuse	Normal	c	a
40	Male	59	Transit troubles (diarrhea), family history	Refuse	Normal	c	na
41	Male	42	Family history	Refuse	Normal	c	na
42	Male	51	Family history	Failure	Normal	c	na
43	Female	43	suspect pet scan, ovarian cancer	Failure	Normal	c	na
44	Male	34	Family history (mother and father operated with ccr)	Refuse	Normal	c	na
45	Female	66	Tumoral markers	Failure	Normal	c	na
46	Female	65	Family history	Failure	Normal	c	na

47	Male	68	Bleeding, personal history of polyps	Refuse	Normal	c	na
48	Female	65	Personal history (colon resection)	Refuse	Normal resected colon	c	a
49	Female	41	Anemia, fh	Refuse	Polip cecum < 5 mm	c	a
50	Male	65	Long standing uc, renal transplantation	Failure	Ulcerative colitis, pseudopolyps	c	a
51	Female	75	Anemia, suspect ultrasound exam	Refuse	Small bowel tumor 22 × 22 mm, 6 mm polyp descending	c	a
52	Female	56	Anemia weight loss	Failure	Ulcerated tumor in the cecum	c	a
53	Female	65	Anemia	Failure	Ulcerated tumor in the cecum	c	a
54	Male	45	Abdominal pain	Refuse	Ulceration on the ileon and ileal valve, Crohn's? diverticula	c	a
55	Female	78	Anemia	Failure	10 right transverse polyps 4-9 mm, angiomas, left side not seen, diverticula	i	na
56	Female	45	Family history	Failure	13 mm pedunculated polyp transverse colon, diverticula	i	na
57	Male	77	Anemia weight loss	cardiologist Choice	3 polyps 10 mm and 5 and 4 mm left colon	i	na
58	Female	68	Family history	Failure	3 polyps 3-4 mm left colon,diverticula	i	na
59	Female	84	Personal history (hemicolectomy for right sided cancer)	Failure	4 polyps 5-7 mm left colon	i	a
60	Female	76	Family history of CRC (mother and brother)	Refuse	7 mm polyp on the ileo-caecal valve; caecal angiodysplasia; multiple diverticula in the right and left colon	i	a
61	Female	87	Suspect CT and barium enema	Failure	Angiomatosis	i	a
62	Male	52	Bleeding, hematochezia	Refuse	Diverticula	i	na
63	Male	58	Anemia, suspect ct, personal and family history	Failure	gastric cancer, 5 polyps 3-4 mm left side, diverticula	i	a
64	Male	75	Weight loss	Refuse	Normal but cancer discovered after 3 mo	i	na
65	Male	73	Anemia weight loss	Refuse	Diverticula battery depleted	I battery	na
66	Female	61	Anemia	Refuse	Cancer	Impaction on cancer	a
67	Male	38	Anemia	Failure	Cancer two tumors	Impaction on cancer	na
68	Female	61	Anemia, weight loss, diarrhea	Failure	Impaction on radiation enteritis stenosis	Impaction on radiation enteritis	
69	Male	60	Family history	Refuse	Impaction	Retention gastric	
70	Male	65	Anemia melena, Normal endoscopy	Cardiologist choice	Impaction	Retention small bowel	

a: Adequate; na: Non-adequate; c: Complete; i: Incomplete; CRC: Colorectal cancer; CCE: Colon capsule endoscopy; CT: Computed tomography.

in 23 (34%, 95%CI: 21.6%-44.1%). The significant lesions reported were: polyps > 6 mm in five patients, ⩾ 3 polyps in 10 patients, multiple colonic angiomas in 2 patients, colon cancer in 4 patients, other digestive cancers in 2 patients, a newly discovered Crohn's disease in 1 patient and radiation enteritis in another. A total of 19 patients had insignificant lesions (17 with diverticulosis, 1 with ulcerative colitis and inflammatory pseudopolyps and 1 with a < 6 mm polyp).

Twenty five patients had no findings with normal colonic examinations. Fifty-five colonic polyps were identified by CCE in twenty patients. In the 15 patients with polyps over 6 mm or more than 3 polyps we identified 50 polyps with a median size of 5.8 mm (range 3 to 13 mm) and a median number of 3.5 polyp/patient (range 1 to 10), with locations in the right colon (3), transverse colon (13), left colon and rectum (34). We found 5 polyps < 6 mm in five patients (2 polyps located in the right colon and 3 in the left colon).

Four patients had colon tumors detected by CCE: (1) patient with two synchronous lesions in the cecum and ascending colon, (2) patients with ulcerated cecal tumors (Figure 2A and B) and 1 patient with a left angle stenotic tumor (Figure 2C). Two other digestive tumors were discovered by the CCE examination. In one patient with iron deficiency anemia, suspect CT scan (abdominal mass) and failure of colonoscopy an ulcerated lesion was discovered by capsule in the stomach. An upper endoscopy with biopsies established the diagnosis of undifferentiated gastric cancer (Figure 2D). In another patient with anemia and suspect imaging (mass seen on ultrasound) and refusing a colonoscopy an ulcerated tumor in the small bowel was visualized at capsule (Figure 2E).

In one of the patients with capsule impaction in the small bowel, we made the diagnosis of radiation enteritis which was considered significant. For the other two patients where capsule did not reach the colon while functioning, no significant lesions were described in the examined segments.

Preparation

Bowel cleanliness was reported as adequate (good or excellent) in 48 of cases (72%, 95%CI: 60.8%-82.4%) and inadequate (fair or poor) in 19 cases (28%, 95%CI: 17.6%-39.1%). In the three cases where capsule did not reach the colon we could not analyze the preparation.

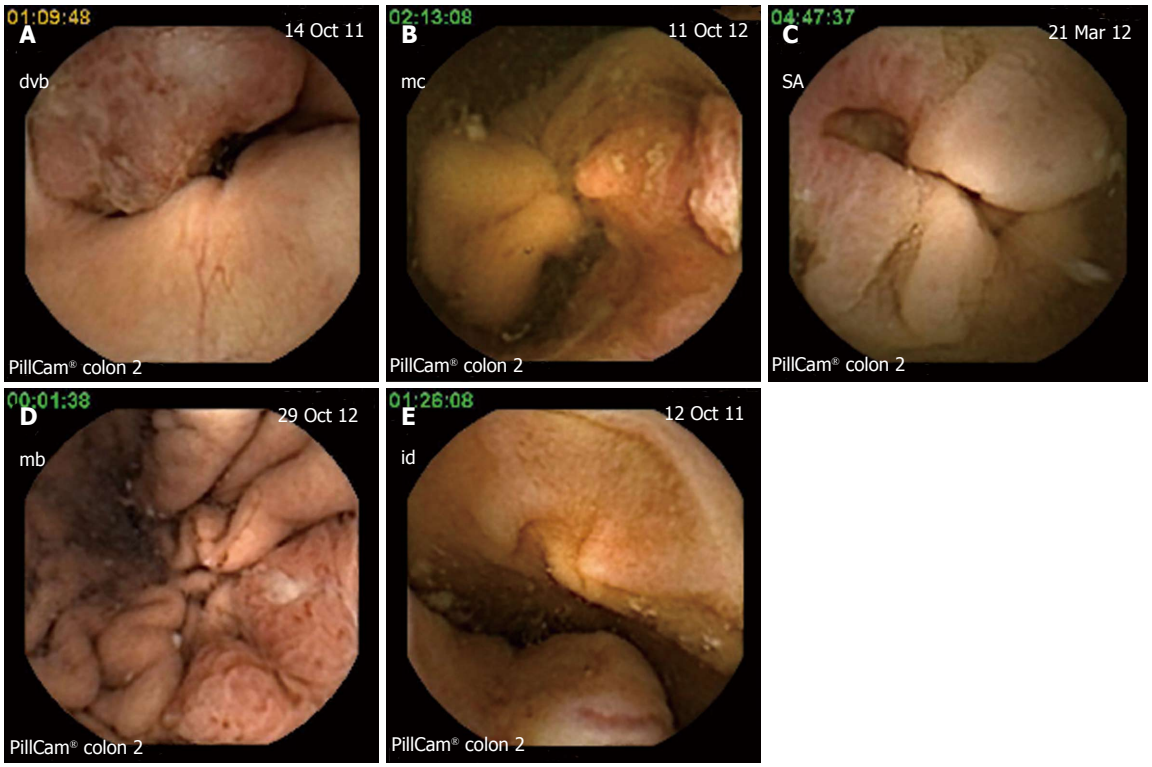

Figure 2 The results of colon capsule endoscopy examination. A: Cecum tumor-transvalvular vue; B: Ulcerated tumor in the cecum; C: Ulcerated stenosis of the left colon angle; D: Gastric cancer; E: Small bowel tumor.

Transit time and capsule egestion

The capsule excretion rate in 12 h was 77% with 54 patients having a complete examination. The median colonic transit time CTT was 189 min (range 3 to 665 min) with important differences between patients. The rectum was not explored during CCE procedure, in 16 patients (23%, 95%CI: 13.7%-34.1%). Of these 16 patients who did not have a complete capsule procedure, in 3 patients (4%) the capsule did not reach the colon at all. In 11 cases recording ceased in the left colon and in 2 it impacted above tumors of the right and left colon angle, respectively. In 9 of these 11 patients the capsule indication was a failure of a previous colonoscopy so we considered having a complete colonic examination.

All patients but two eliminated the capsule in the following 48 h. A true capsule retention (capsules remaining in the digestive tract more than 14 d and extracted during surgical treatment of the lesions) was seen only in 2 patients due to digestive stenosis. First impaction occurred in an ileal stenosis related to radiation enteritis. This patient was referred from another hospital for suspicion of colon cancer in the descending colon after a failed colonoscopy with impossibility to pass the sigmoid. She had no symptoms suggestive of a digestive stenosis or occlusion but a history of irradiation 24 years ago for uterine cancer. The other case was an impaction in a stenotic tumor of the left colonic angle in a patient referred for anemia and transit troubles and refusing colonoscopy. In both patients surgery was decided based on capsule findings and was successful and without complications and realized in the following month.

We encountered another capsule transient impaction above a tumoral colonic stenosis in a young patient referred for iron deficiency anemia where two lesions of the cecum and right colonic angle were visualized during the examination. The patient eliminated the capsule in the following day. He had surgery after a complete pre operative check up including colonoscopy and CT scan which confirmed the two synchronous lesions. Besides the patient with radic ileal stenosis, the other two where the capsules did not reach the colon while working, excreted the after 48 h without complications. In one patient with a history of colon cancer in both parents and refusing colonoscopy the capsule remained in the stomach during the entire battery lifetime. He refused an upper endoscopy to push the capsule. He remained asymptomatic during and after capsule passage. The other patient was morbidly obese and confined to bed and the capsule remained in the small bowel until battery depletion.

Follow up, clinical decision and treatment

Seventeen patients (74%) out of the 23 with relevant lesions diagnosed by CCE agreed to have a therapeutic intervention. The 4 patients detected with colon tumors had successful surgery. Only 2 of them had colonoscopies before surgery, for the other 2 patients the surgical indication being decided based single on CCE results. The capsule findings were confirmed after surgery. Diagnosis of adenocarcinoma was established in all cases and the tumor location was similar to the capsule findings.

One patient detected with small bowel tumor had surgery after the CCE and an ulcerated gist was removed. For the gastric ulcerated lesion visualized by capsule, an upper endoscopy with biopsies was realized. After histological confirmation of undifferentiated gastric cancer, the patient had a subtotal gastric resection.

In the two patients with severe iron deficiency anemia and multiple hospitalizations for transfusions and where previous colonoscopies failed, the CCE made the diagnosis of multiple angiomas. Before CCE both patients had extensive check ups including upper endoscopies, failed colonoscopies, CT scans and barium contrast enemas and they have at least three hospitalizations only in our institution. After CCE repeated séances of argon plasma coagulation were realized with a great deal of improvement of their anemia. In order to reach the cecum a single balloon enteroscope was used for one patient and a variable stiffness colonoscope was used for the other. Six patients with relevant lesions which previously denied colonoscopy accepted the examination after a discussion of the CCE results. Colonoscopy confirmed the findings of the CCE and polypectomy was performed in all cases.

In a patient with a suspicion of locally invading cecal tumor on CT scan, the CCE ruled out this diagnosis and showed only three colonic polyps one in the cecum and two in the descending colon. In this case the CCE had an important role in the clinical decision since it ruled out a colonic cancer. After careful examination of the imaging; exploratory laparotomy established a diagnosis of abdominal wall sarcoma was established. She had surgery soon afterwards. No colonoscopy for the three left side polyps was realized. The newly diagnosed Crohn's disease patient had a complete check up and he is currently under immune modulator therapy.

We had one clinical failure revealed by the follow up, 4 mo after CCE. A 76-year-old patient with family history and abnormal transit who refused colonoscopy had an incomplete colon examination by CCE caused by poor visualization due to low compliance to the preparation and the booster regimen. He refused a rectoscopy after CCE. Since he remained symptomatic he agreed to have a rectoscopy which revealed a small ulcerated rectal tumor. This patient had successful surgery after pre operatory radiotherapy. Six patients either refused colonoscopy and polypectomy or decided to postpone the procedure. At the moment they are followed up in our center.

Acceptability

The patients included in the study had the indication of a colonoscopy that either failed or was refused. When offered the alternative of having a CCE examination all the 70 patients accepted it, although they were aware that the preparation regimen was more difficult than for a classic colonoscopy. Moreover the examination was subjectively appreciated by all patients as being non invasive and harmless and 65 of them where willing to have the next surveillance exam by CCE.

Adverse events

Capsule ingestion went smoothly in all patients. Although most patients had to ingest a total of six liters of PEG (preparation and boosters) no electrolyte disturbances or adverse effects related to bowel preparation were recorded. No other side effects related to capsule were encountered.

Technical failures

We had one CCE technical failure due to a recorder dysfunction which required another examination.

DISCUSSION

The existing national CRC screening programs are far from perfect due to different issues: lack of a universal screening policy despite recommendations, lack of uniform measures in all countries, cost issues. One major problem is the disappointingly low number of patients accepting the current screening tools. Furthermore is not negligible that a variable proportion (4%-20%) of patients will have an incomplete colonoscopy although the rate of completeness is as high as 97% in expert centers[4].

After an incomplete examination with a standard adult colonoscope different approaches are available: variable stiffness colonoscope, use of gastroscope, single or double balloon enteroscopy (available in some centers). Changing the centre or the endoscopist is an alternative. However a first failed colonoscopy is significantly associated with a lower cecal intubation rate at further attempts, particularly when stopped in the sigmoid colon[4].

Radiological procedures have been tested and they are proposed as a potential screening test in the average risk population[11], for high risk patients' colonoscopy remaining the first option. For patients with colonoscopy failure or contraindication, radiological imaging is an option recommended by current guidelines[11].

The use of double contrast barium enema (DCBE) was disappointing considering the low sensitivity for polypoid lesions and adenomas, when compared to colonoscopy or CTC[12]. In a recent Italian meta-analysis, DCBE showed statistically lower sensitivity and specificity than CTC for detecting colorectal polyps $\geqslant$ 6 mm, and its use as an alternative imaging test is appropriate only when CTC is not available[12].

Two studies reported varying results using computed CTC after a failed or an incomplete colonoscopy[13,14], with an estimated sensitivity of 88% for advanced neoplasia $\geqslant$ 10 mm. Radiation exposure remains a concern despite the evolution of technique and improvement of examination protocols. The cost effectiveness of a CTC based screening program is debatable as the medical and economic impact of extra colonic findings remains unknown[15]. We could not make a direct comparison in our population of patients, since CTC is not reimbursed by the Romanian health system and its availability is very

limited. The current ESGE capsule endoscopy guidelines take into consideration the utilization of CCE after failure or refuse of colonoscopy. According to these guidelines, CCE is feasible and safe and appears to be accurate when used in average-risk individuals and in high risk patients for whom colonoscopy is inappropriate or not possible. For these patients the use of CCE could be an alternative[9].

We report the Pillcam Colon 2 use in high risk patients unwilling or unable to perform colonoscopy. Therefore we lack the comparison with colonoscopy which is the gold standard. The introduction of diagnostic utility index and the careful follow-up of the patients partially solved this issue. Clinical significant lesions were seen by Pillcam Colon 2 in 23 patients out of 67 analyzed (34%) CCE had a high clinical impact as endoscopic or surgical treatment was proposed in all these cases based on capsule results and seventeen patients (74%) of the 23 with relevant lesions agreed to and had a therapeutic intervention (Figure 1).

Complete colorectal examination was realized by CCE in 54 patients (77%, 95%CI: 67.3%-86.94%). The rate of complete examinations observed in our group is lower than in the study of Spada *et al*[8] of 88% but much like the findings of Eliakim *et al*[6] who reported a capsule egestion rate of 74% in their first generation capsule study. Several factors may have influenced the progression rate: in the absence of classic sodium phosphate boosters unavailable on the local market, the use of Macrogol as a booster has been a factor affecting the transit times. Also our study population included patients with previous difficult colonoscopies or with various co-morbidities and bed confined patients. The presence of fixed sigmoid loops in patients with previous colonoscopy failure might have contributed to slow transit times. Also in three patients with incomplete CCE examination, this was due to impaction over significant lesions (one postradic stenosis and two cancers) during the procedure. Compared with CTC, CCE has the intrinsic advantage of directly visualizing the colonic mucosa. This may be very important as clinically relevant lesions like angiectasias or flat adenomas are missed by CTC and are easily visible in capsule endoscopy. This is confirmed in our study where capsule endoscopy established the definitive diagnosis of multiple angiomas in two patients who had previous CT scans and barium enemas in several occasions.

In a recently published multicenter (17 hospitals and private practices) study using first generation Pillcam Colon 1 in patients with failure or contraindications to colonoscopy, the CCE showed positive findings in 36 patients out of 107 analyzed (diagnostic yield 33.6%). The Pillcam Colon 1 was considered as having a high clinical impact as in 21% of patients a medical or surgical treatment was proposed. In this study the colon examination by CCE was complete in 83.2% of cases[16]. Our results are comparable. However it is a single center study with a different study design. Also the classical boosts with sodium phosphate where not available for our population leading to the lower excretion rates.

In our study the acceptability of the examination by CCE was extremely high. All patients with a previous failed colonoscopy proposed to take part in the study accepted the CCE examination. The method was perceived as non invasive and harmless by all patients. Moreover the vast majority of patients with significant findings, either failure or refusal of a colonoscopy, agreed to perform a therapeutic gesture (implying colonoscopy) after the discussion of the CCE findings.

The PillCam Colon 2 appears to be effective for the detection of clinically relevant lesions with great acceptability rate, and it might be considered as a useful tool for colorectal imaging in patients unable or unwilling to undergo colonoscopy. Further studies are necessary to validate the best approach to these patients.

The Given Imaging Research Grant supports innovative, original research in Gastroenterology with substantial involvement of capsule endoscopy and is awarded yearly by the European Society of Gastrointestinal Endoscopy. The project "Role of PillCam Colon 2 capsule in patients at risk of CRC unable or unwilling to perform colonoscopy" was awarded with the 2010 grant. The study design, data analysis, results and conclusions of the article are exclusively the investigators work. Given Imaging supported the study, by donating the capsules and loan of equipment.

COMMENTS

Background

There is growing evidence that colon capsule endoscopy is a reliable and well tolerated diagnostic method. A lot of technical improvements were made to the capsule endoscopy, including a second generation, more performant, colon capsule.

Research frontiers

Since the introduction of the second generation Pillcam Colon 2 very few studies addressed its use after colonoscopy failure or refusal.

Innovations and breakthroughs

This is a 70 patients' pilot study using the second generation of PillCam Colon capsule endoscopy to detect colon cancers as well as other tumors in the gastrointestinal (GI) tract. They included a heterogeneous population at risk of colorectal cancer that either failed or refused colonoscopy. This study indicated that PillCam Colon 2 capsule endoscopy is feasible and of high acceptance by patients.

Applications

This study suggests that PillCam colon 2 capsule endoscopy may eventually used for population-wide colon cancer screening, although more cost effectiveness studies are needed.

Terminology

Pillcam Colon 2 capsule has 11.6 mm × 31.5 mm in size and has been designed to work for at least 10 h with a variable frame rate (from 4 to 35 frames/second in order to correctly visualize the mucosa when accelerated peristalsis). The angle of view was increased to 172 degrees in both capsule lenses, thus covering almost 360 degrees of the colonic surface.

Peer review

This is an interesting manuscript describing a pilot lot study using the second generation of PillCam capsule endoscopy to detect colon cancers as well as other tumors in the GI tract. Although case controlled studies are ultimately needed to demonstrate the sensitivity and specificity of PillCam capsule endoscopy, this pilot study indicated that PillCam capsule endoscopy is feasible and of high acceptance by patients. This study suggests that PillCam capsule endoscopy may eventually used for population-wide colon cancer screening. This

is a descriptive paper on a new generation colon capsule. Since no comparison with the gold standard technique (colonoscopy) is made specificity and sensitivity of the method could not be assessed. One important point is that lesions outside the colon were found and this point should be underlined.

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BRIEF ARTICLE

A modified Rendezvous ERCP technique in duodenal diverticulum

Mehmet Odabasi, Mehmet Kamil Yildiz, Haci Hasan Abuoglu, Cengiz Eris, Erkan Ozkan, Emre Gunay, Ali Aktekin, MA Tolga Muftuoglu

Mehmet Odabasi, Mehmet Kamil Yildiz, Haci Hasan Abuoglu, Cengiz Eris, Erkan Ozkan, Emre Gunay, Ali Aktekin, MA Tolga Muftuoglu, Department of Surgery, Haydarpasa Education and Research Hospital, Istanbul, 34688, Turkey

Author contributions: Odabasi M performed the endoscopic procedures; Yildiz MK, Ozkan E, Eris C, Gunay E, Aktekin A, Muftuoglu MAT and Abuoglu HH contributed to writing the article and reviewing the literature in a comprehensive literature search; Odabasi M designed and prepared the manuscript.

Correspondence to: Mehmet Odabasi, MD, Department of Surgery, Haydarpasa Numune Education and Research Hospital, Tibbiye cad No. 1, Uskudar 34688, Istanbul, Turkey. hmodabasi@gmail.com

Telephone: +90-532-4310630 Fax: +90-216-3360565
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Abstract

AIM: To postoperative endoscopic retrograde cholangiopancreatography (ERCP) failure, we describe a modified Rendezvous technique for an ERCP in patients operated on for common bile duct stone (CBDS) having a T-tube with retained CBDSs.

METHODS: Five cases operated on for CBDSs and having retained stones with a T-tube were referred from other hospitals located in or around Istanbul city to the ERCP unit at the Haydarpasa Numune Education and Research Hospital. Under sedation anesthesia, a sterile guide-wire was inserted *via* the T-tube into the common bile duct (CBD) then to the papilla. A guide-wire was held by a loop snare and removed through the mouth. The guide-wire was inserted into the sphincterotome *via* the duodenoscope from the tip to the handle. The duodenoscope was inserted down to the duodenum with a sphincterotome and a guide-wire in the working channel. With the guidance of a guide-wire, the ERCP and sphincterotomy were successfully performed, the guide-wire was removed from the T-tube, the stones were removed and the CBD was reexamined for retained stones by contrast.

RESULTS: An ERCP can be used either preoperatively or postoperatively. Although the success rate in an isolated ERCP treatment ranges from up to 87%-97%, 5%-10% of the patients require two or more ERCP treatments. If a secondary ERCP fails, the clinicians must be ready for a laparoscopic or open exploration. A duodenal diverticulum is one of the most common failures in an ERCP, especially in patients with an intradiverticular papilla. For this small group of patients, an antegrade cannulation *via* a T-tube can improve the success rate up to nearly 100%.

CONCLUSION: The modified Rendezvous technique is a very easy method and increases the success of postoperative ERCP, especially in patients with large duodenal diverticula and with intradiverticular papilla.

Key words: Endoscopic retrograde cholangiopancreatography; Retained stones; Antegrade cannulation; Intradiverticular papilla; T-tube

Core tip: A postoperative endoscopic retrograde cholangiopancreatography (ERCP) is used as a treatment modality for common bile duct stone (CBDS) clearance when a laparoscopic common bile duct exploration has failed or retained stones are discovered after an operation. If a secondary ERCP fails, the clinicians must be ready for a laparoscopic or open exploration. Because of this, different techniques are required to exclude surgical intervention. We describe a modified Rendezvous technique for an ERCP in patients operated on for CBDSs having a T-tube with retained CBDSs and with intradiverticular papilla. The modified Rendezvous tech-

nique is a very easy method and increases the success of postoperative ERCP, especially in patients with large duodenal diverticula and with intradiverticular papilla.

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INTRODUCTION

Common bile duct stones (CBDSs) can precipitate a variety of clinical events such as biliary colic, jaundice, and sepsis. In the treatment of this condition, stone removal is the primary intervention for dealing with clinical symptoms. The treatment options are an endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) and a laparoscopic or open surgical intervention[1].

Postoperative ERCP is used as a treatment modality for CBDS clearance when a laparoscopic common bile duct exploration (LCBDE) has failed or retained stones are discovered after an operation (2.5%)[2]. If a secondary ERCP fails, the clinicians must be ready for a laparoscopic or open exploration. A duodenal diverticulum is one of the most common failures of an ERCP, especially in patients with an intradiverticular papilla[3]. Because of this condition, we need different techniques to exclude surgical intervention. Percutaneous techniques are used for this purpose. The Rendezvous technique combines an endoscopy with a percutaneous transhepatic cholangiography to facilitate cannulation of the bile duct when previous attempts have failed[1,4]. We describe a modified Rendezvous technique for an ERCP in patients operated on for CBDSs having a T-tube with retained CBDSs.

MATERIALS AND METHODS

Five cases operated on for CBDSs and having retained stones with a T-tube were referred to the ERCP unit at the Haydarpasa Numune Education and Research Hospital from other hospitals located in or around Istanbul city.

The preoperative findings were unclear because we could not obtain reliable information about the patients' preoperative status. All of the patients had a history of failed ERCP attempts at other ERCP units before surgery; five of these cases had papilla in their duodenal diverticulum. To prevent possible complications associated with a premature extraction of the T-tube, we waited three weeks before it was removed.

Technique

A contrast material was injected *via* the T-tube, and the stone was observed in the common bile duct (CBD). Under sedation anesthesia with midazolam 3-5 mg and meperidine 30-50 mg by the intravenous route, a sterile guide-wire was inserted *via* the T-tube to the CBD then to the papilla (Figure 1). All of the patients with a diverticulum had a large diverticulum with an intradiverticular papilla. In our cases, the guide-wire was held by a loop snare and removed through the mouth (Figure 2). The sphincterotome was inserted into the working channel. The guide-wire was inserted into the sphincterotome *via* the duodenoscope from the tip to the handle (Figure 3). Subsequently, the duodenoscope was inserted down to the duodenum. Using the guidance of the guide-wire, the ERCP and sphincterotomy were successfully performed, the guide-wire was removed through the mouth, the stones were removed and the CBD was reexamined for retained stones by contrast (Figure 4). The T-tube was removed after 1-2 d because of the possibility of edema at the papilla.

RESULTS

In the time period between August 2009 and March 2012, 5 patients who underwent CBD exploration and who had retained stones with a T-tube were referred to the ERCP unit at our institution.

There were 1 man and 4 women ranging in age from 51 to 78 years with a mean age of 65 years. The patients all had a successful stone removal by a modified rendezvous technique.

The length of the hospital stay was 3.4 d. The T-tubes were removed. The patients were followed up for possible complications of the ERCP and T-tube removal. No morbidity or mortality occurred.

All the patients were followed up regularly through the first postoperative year. There has been no incidence of residual disease, and all the patients who were regularly followed-up have been asymptomatic.

DISCUSSION

An ERCP should be used as a therapy rather than a diagnosis; it should be therapeutic in more than 90% of cases[5]. An ERCP can be used either preoperatively or postoperatively. Although the success rate in isolated ERCP treatments ranges from 87% to 97%, 5%-10% of patients require two or more ERCP treatments[6]. This method is associated with morbidity and mortality rates of 15% and 1%, respectively[7,8]. ERCP is not possible in 3%-10% of all patients[9]. These patients need laparoscopic or open surgical intervention.

An LCBDE is the treatment of choice in many centers with successful stone clearance rates ranging from 85% to 95%, a morbidity rate of 4%-16% and a mortality rate of approximately 0%-2%[10,11]. If this fails, alternate approaches such as an intraoperative or postoperative ERCP/EST, laparoscopic choledochotomy,

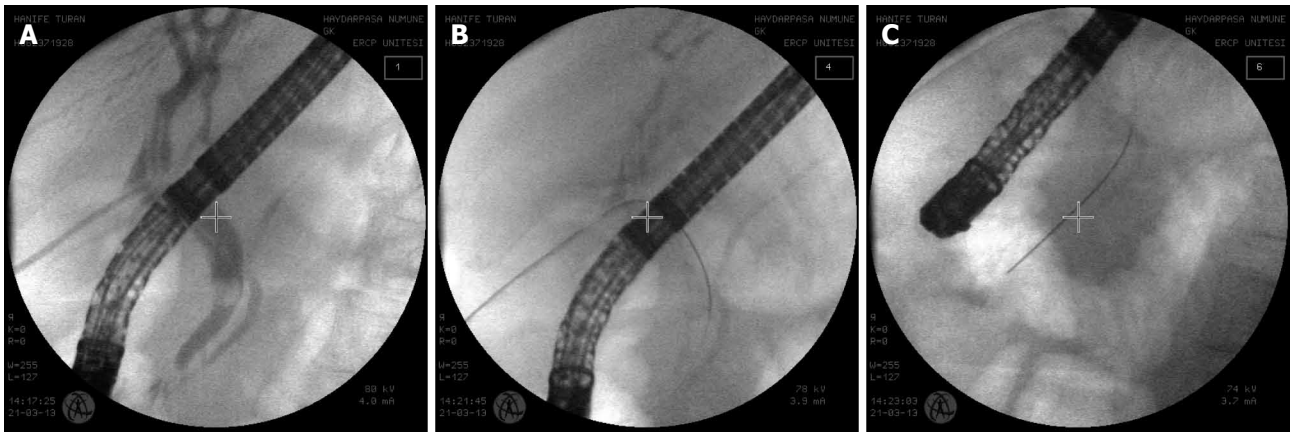

Figure 1 A sterile guide-wire was inserted *via* the T-tube to the common bile duct stone then to the papilla. A: Retained stone with a T-tube in the common bile duct; B: The antegrade insertion of a guide-wire through the T-tube; C: The extension of the guide-wire through the papilla into the duodenum.

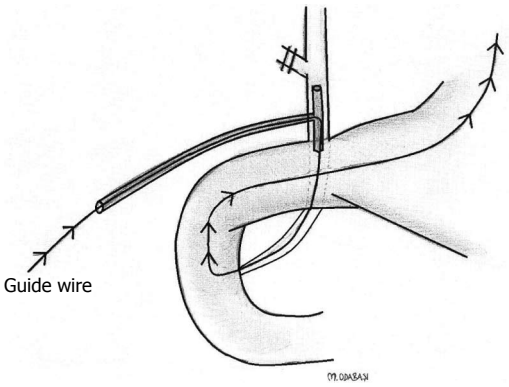

Figure 2 Schematic diagram of a guide-wire.

or open CBDE may be used[12]. A transcystic approach is generally used for small stones in a small bile duct whereas a transductal approach is preferred for large occluding stones in a large duct, for intrahepatic stones, or a tortuous cystic duct[9]. If the transcystic approach fails, a laparoscopic choledocholithotomy is recommended. After the stones are removed under endoscopic visualization, the ductotomy is usually closed either primarily or over an appropriately sized T-tube. The indication for a T-tube insertion is a decompression of the duct in patients with a residual distal obstruction, ductal imaging in the postoperative period to provide an access route for the removal of residual CBDSs[13-16]. When an LCBDS and a postoperative ERCP have failed, the surgeon must use the open approach to surgery. In the era of open cholecystectomy, open bile duct surgery was superior to ERCP in achieving CBD stone clearance. In the laparoscopic era, the data are close to excluding a significant difference between the laparoscopic and ERCP clearance of CBD stones. The use of an ERCP necessitates an increased number of procedures per patient[14].

The routine use of intraoperative cholangiography (IOC) is still controversial. However, it can be a useful tool for identifying choledochal stones[17]. Supporters of the IOC routine claim that this practice ensures fewer retained stones, fewer postoperative ERCPs, and a reduction in the number of CBD injuries[18]. One drawback is the consequent lengthening of the operation time by approximately 15 min[19].

Although an LCBDE or open surgical explorations are performed, 2.5% of the patients still have retained stones[2]. Percutaneous transhepatic therapies can be considered for CBDS under US guidance in selected patients[17]. The extraction of stones, a sphincterotomy, or percutaneous drainage can be performed using this method[20]. A percutaneous extraction is successful in more than 95% of the patients with retained stones; otherwise a postoperative ERCP can be required[21].

A T-tube cholangiography should be performed before the removal of the tube (6-18 d postoperatively). The removal of the T-tube has been suggested as early as 5-6 d postoperatively and as late as 4-5 wk after surgery. Retained stones identified by a T-tube cholangiography may be effectively removed percutaneously after allowing for the maturation of the T-tube tract. Although all these techniques have high success rates, there is still a group of patients who need a second surgical intervention because of CBDSs. A duodenal diverticulum is one of the most common failures of an ERCP, especially in patients with an intradiverticular papilla[3]. The prevalence of a duodenal diverticulum is approximately 5% in postmortem studies, but endoscopic evaluations have documented higher rates (5%-23%)[22]. For this small group of patients, antegrade cannulation *via* a T-tube can raise the success rate up to nearly 100%[23].

When a selective CBD cannulation cannot be performed by ERCP despite trying various endoscopic techniques, a percutaneous transhepatic biliary drainage (PTBD) followed by a combined rendezvous technique is often successful. This combined technique increases the success rate of the biliary tract cannulation and facilitates the diagnosis and treatment of biliary tract diseases.

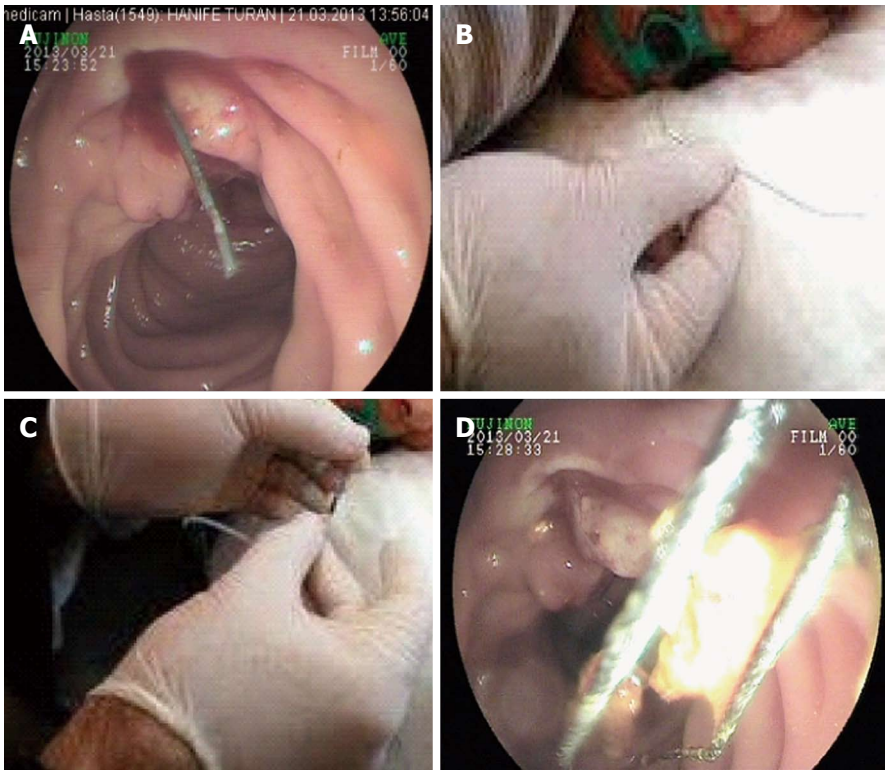

Figure 3 Appearance of the technique. A: A guide-wire through the papilla during an endoscopic sphincterotomy; B: The guide-wire taken out by a snare; C: The guide-wire inserted in the tip of the sphincterotome, which is inserted *via* the endoscope channel of the duodenoscope; D: The stone is extracted by a basket catheter.

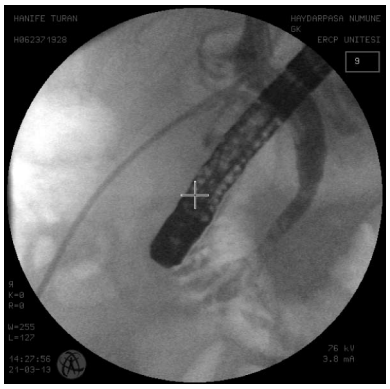

Figure 4 Control images of the common bile duct stone after the extraction of the stone.

Antegrade cannulation *via* a T-tube is a modified rendezvous technique described by our ERCP unit. This technique can be performed using sedation anesthesia; this is a very easy technique that increases the success rate and decreases the complications of an ERCP. In this technique, because there is no false insertion of a catheter and a guide-wire to the pancreatic duct, the accidental occurrence of symptoms of pancreatitis is low and, unlike in a normal ERCP, the success rate appears to be higher[24].

In other Rendezvous techniques, the guide-wire is grasped with a snare or forceps and pulled back through the working channel of the duodenoscope for subsequent over the wire cannulation[25]. However, it is not always easy to grasp the guide-wire, which may be kinked, and its coating can be damaged during the withdrawal through the working channel of the duodenoscope, thus making it difficult, sometimes impossible, to pass a catheter over it[26].

Although this patient group is small, this technique should be kept in mind. Percutaneous techniques are used worldwide but cannot be applied in all centers, and they require experienced personnel. Even beginners can apply our technique. You can examine the CBD with a contrast material *via* a T-tube. We recommend our technique, especially in cases of an intradiverticular papilla.

In conclusion, the antegrade cannulation of a guide-wire passing *via* a T-tube to the papilla is a very easy method and increases the success rate of postoperative ERCP, especially in patients with large duodenal diverticula with an intradiverticular papilla. Because the number of participants is small, this study must be supported by further studies. We recommend this modified technique for the centers that have an ERCP unit because other techniques are not appropriate for all clinical circumstances in all centers.

COMMENTS

Background

A postoperative endoscopic retrograde cholangiopancreatography (ERCP) is used as a treatment modality for common bile duct stone clearance when a

laparoscopic common bile duct exploration has failed or retained stones are discovered after an operation. If a secondary ERCP fails, the clinicians must be ready for a laparoscopic or open exploration. Because of this condition, the authors need different techniques to exclude surgical intervention. The rendezvous technique combines an endoscopy with a percutaneous transhepatic cholangiography to facilitate the cannulation of the bile duct when previous attempts have failed.

Research frontiers

The antegrade cannulation of a guide-wire passing *via* a T-tube to the papilla is a very easy method and increases the success of postoperative ERCP, especially in patients with large duodenal diverticula with an intradiverticular papilla.

Innovations and breakthroughs

Antegrade cannulation *via* a T-tube is a modified rendezvous technique described by our ERCP unit. This technique can be performed under sedation anesthesia, and it is a very easy technique that increases the success rate and decreases the complications of an ERCP. In this technique, because there is no false insertion of a catheter and a guide-wire to the pancreatic duct, the accidental occurrence of the symptoms of pancreatitis is low and, unlike a normal ERCP, the success rate appears to be higher.

Applications

The study recommends the modified technique for centers that have an ERCP unit because other techniques are not appropriate for all clinical circumstances at all centers.

Terminology

Rendezvous technique: The rendezvous technique combines an endoscopy with a percutaneous transhepatic cholangiography to facilitate the cannulation of the bile duct when previous attempts have failed.

Peer review

The concept of this technique seems logical and promising; the study conclusions are based on preliminary experience with a small number of participants. Therefore, caution should be taken in regard to the widespread use of the technique before further studies are pursued.

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BRIEF ARTICLE

Establishing a quality indicator format for endoscopic ultrasound

Jesse Lachter, Benjamin Bluen, Irving Waxman, Wafaa Bellan

Jesse Lachter, Departments of Gastroenterology, Head of EUS Service, Rambam Healthcare Campus, Haifa 30196, Israel
Jesse Lachter, Technion-Israel Institute of Technology, Bruce and Ruth Rappaport Faculty of Medicine, Rambam Healthcare Campus, Haifa 30196, Israel
Benjamin Bluen, Department of Internal Medicine, Hahnemann University Hospital, Philadelphia, PA 19102, United States
Benjamin Bluen, Wafaa Bellan, Israel Institute of Technology, Bruce and Ruth Rappaport Faculty of Medicine, Rambam Healthcare Campus, Haifa 30196, Israel
Irving Waxman, Department of Gastroenterology, University of Chicago Medical Center, Chicago, IL 60637, United States
Author contributions: Lachter J conceived and designed this study, acquired data, instrumental in article drafting and revision, approved article; Bluen B drafted, revised, and submitted this article, analyzed data; Waxman I designed study, contributed cases for international comparison, and assisted in the article's final approval; Bellan W performed key research, acquired and analyzed data.
Correspondence to: Dr. Jesse Lachter, MD, Departments of Gastroenterology, Head of EUS Service, Rambam Healthcare Campus, 6 Ha'Aliya Ha'Shniya Street, Bat Galim, Haifa 30196, Israel. bbluen@gmail.com
Telephone: +972-4-8542887 Fax: +972-4-8542887
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Abstract

AIM: To perform a quality control (QC) review of endoscopic ultrasound (EUS) with emphasis on current consensus established quality indicators.

METHODS: A national quality control study of EUS was performed with expanded international comparison. Ten different healthcare institutions in Israel participated in coordination with University of Chicago Medical Center. Each Israeli center provided ten patient reports, compared with twenty reports from University of Chicago Medical Center. Quality indicator forms were prepared with sections to be completed before, during, and after EUS. Physician compliance to all listed indicators was evaluated. Quality indicators were evaluated prior to, during, and after performing EUS.

RESULTS: One hundred different EUS procedural reports were analyzed. The mean patient age was 59 years old. Indications for referral were mostly for pancreatic or biliary reasons. QC showed several strongly reported areas, including indications for EUS (97%), anesthesia given (94%), periprocedural pancreatic evaluation (87%), and an overall summary of the EUS examination (82%). Intermediately reported areas included patients' pertinent past medical history (71.7%), evaluation of the biliary tree (63%), and providing medical guidance about potential procedural adverse events, including pancreatitis and bleeding (52%). Half of the reports (50%) did not include a systemic organ evaluation. Other areas, including systematic reporting of screened organs (36%), description of fine needle aspiration (15%), tumor description *via* tumor-node-metastasis (5%), and listing of adverse events (0%) were largely lacking from procedural documentation.

CONCLUSION: Documenting specific EUS quality indicators including listing post-procedural recommendations may improve the quality and efficiency of future EUS examinations and subsequent patient follow-up.

Key words: Endoscopic ultrasound; Quality indicators; Quality control; Fine needle aspiration; Malignancy

Core tip: Certain key points of quality control have been delineated as quality indicators by American and European Gastrointestinal Societies, which serve to establish and maintain high-quality gastrointestinal minimally invasive procedures and reports, minimize potential adverse events, and to optimize costs, resulting in savings for both hospitals and patients while optimizing patient care in the process. This national quality control study of endoscopic ultrasound (EUS) with expanded international comparison emphasized developing a

standardized quality indicator table for EUS and subsequently evaluating physician adherence.

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INTRODUCTION

The advent of computerized documentation and electronic medical records (EMR) allows organized and effective quality control (QC) analysis of gastrointestinal procedures[1]. The burgeoning costs of medicine have led to pushback efforts, including ensuring that value for cost is being delivered by high-quality examinations[2]. Several studies have been undertaken by endoscopists have demonstrated the importance of QC in achieving these goals. One example of this effect was demonstrated for colonoscopy. A retrospective study by Imperiali *et al*[3] in Northern Italy found wide variation in polyp detection rates and in the percent of procedural completion, both of which were significantly increased after offering more colonoscopy training sessions to less experienced endoscopists. As continuous quality control studies have shown to be useful in improving the effectiveness of colonoscopy, one can infer that other endoscopic procedures may be improved in a similar manner. QC analysis for endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) has also demonstrated several methods of improving the yield of tissue sample aspirates. Among these are simplified recommendations to take more passes from suspected lesions and to use newer flexible 25 gauge needles when attempting to biopsy masses that are very hard in consistency due to desmoplasia. Recent QC of EUS-FNA cytology has determined procedural FNAs to have 94% accuracy in diagnosing malignancy of the upper gastrointestinal tract and surrounding areas, further promoting its worth in medicine's evolving minimally invasive procedures[4,5]. QC may identify remediable areas of practice for which low-cost solutions might be implementable to increase procedural efficiency.

One way to bolster QC of endoscopic procedures is by establishing quality indicators. Quality indicators are established by expert physicians possessing years of experience operating gastrointestinal endoscopy on a more or less daily basis while taking into account new emerging technology being integrated into gastroenterology. These quality indicators are a compilation of guidelines and/or instructions designed for optimal procedural performance and safety. One procedure in particular studied was colonoscopy, where the investigators emphasized the importance of performing a complete examination including a thorough evaluation of any discovered polyps and adenomas[6]. In 2000, the American Society for Gastrointestinal Endoscopy (ASGE) published the first listing of quality indicators for common gastrointestinal procedures, including upper endoscopy and colonoscopy[7,8], which have also been set forth by the American College of Gastroenterology (ACG). These indicators also served to demonstrate to physicians areas of potential improvement and encourage periodic self-assessment. Therefore, this may lead to improved overall gastrointestinal (GI) procedural quality and efficiency.

Similar to quality improvement in EGD and colonoscopy, QIs also play a valuable role in endoscopic ultrasound. Perhaps as important as measuring the quality of EUS will be the measures found to be useful in raising the quality of less than optimal endoscopy. Although quality measures have been set by multiple well-known organizations including ACG, European Society of Gastrointestinal Endoscopy (ESGE)[9], and ASGE quality indicator guidelines[10], few healthcare centers have rigorously applied these guidelines and reported their results. Such an attempt was undertaken by Coe *et al*[11], who studied adherence of physicians to EUS quality indicators over an eight year period and subsequent improvements in areas of poorer quality. The study's outcome resulted in statiscally significant improvement in those areas of EUS found to be weakest by QC. This study aimed to investigate adherence to the aforementioned EUS QI guidelines across various medical centers in Israel along with a cross-sectional international comparison with the University of Chicago. The assessed quality indicators were studied based upon the aforementioned EUS quality indicator table, which allows identification of quantitatively weaker areas that may be remedied in a cost-effective manner to improve EUS performance and documentation. In doing so, this may increase the overall effectiveness of EUS, optimize treatment, and encourage patient follow-up.

MATERIALS AND METHODS

Data evaluation

A quality indicator table was assembled that emphasized important factors compiled after thorough literature review. The table was modeled after quality indicators presented by the various relevant societies including ASGE, ACG, ESGE quality indicators for EUS.

Population

Fifteen different healthcare centers in Israel that perform routine EUS examinations were asked to participate in this study. Each center was requested to send ten randomized consecutive EUS reports which would be evaluated for purposes of this research. Ten of these healthcare centers agreed to participate in this study which accumulated one hundred total reports. Twenty additional reports were sent in cooperation of the University of Chicago gastrointestinal department. Thus, this study represents a national cross-sectional assessment of EUS QIs with expanded international comparison.

Table 1 Endoscopic ultrasound quality indicators

Pre-EUS indicators
Indications for procedure
Detailed description of the patient by the referring physician
Patient completed procedural preparation of minimum 6 h NPO
Antibiotics per protocol were given in the need to perform FNA of pancreatic cysts
Listing of sedatives administered prior to and during EUS
Patient signed agreement of informed consent for EUS and/or if consented for research study
Intra-procedural indicators
A detailed description of the methods used to visualize routinely evaluated EUS organs. If there is any suspicion of organ pathology, the respective organ parenchyma should be described:
Suspected pancreatic lesions should include a parenchymal description including the body, head, tail, and duct
Common bile ducts and gallbladder contents should be detailed and a description of the biliary tree for sludge, stones, or other findings
If found, prominent lymph nodes should be described in detail as well as the kidneys and left liver lobe for the presence or absence of lesions
The celiac axis should be described for general arterial structure along with the aorta and superior mesenteric artery as well as the presence or absence of identifiable lymph nodes
Description of abnormal/pathological results:
Description of any tumor by the tumor, node, and metastasis system
Accurate detailing of the lesions and its surroundings in accordance with layers visualized by EUS
Degree of tumor penetration into organ mucosa and surrounding structures
Detailing the presence of lymph nodes when suspicious for malignancy and when performing FNA
Intra-procedural issues
Presence or absence of any mechanical problems or difficulties including past abdominal surgeries or ascites
Patient awakened/uncooperative during the procedure
Details of the number of FNAs performed with respective number of passes into each suspected lesion including:
Number of passes
Needle size
Number of needles
Impressions of aspirate (bloody, mucinous, color, *etc.*)
Cytology and/or histological examination
In-room tentative diagnosis
Post-procedural indicators
Summary of medical diagnoses
Examination findings, even if not relevant to the reason for EUS referral, should be listed
Physician recommendations shall be listed with respect to examination findings including instructions for the patient
Instructions for how patients will receive the results and for referring physician
After EUS, the incidence of adverse events should be listed, including pancreatitis, bleeding, and/or infections and the need for hospitalization

The above table is the standardized table of endoscopic ultrasound (EUS) quality indicators. This includes an itemized list for documentation prior to, during, and after performing EUS. FNA: Fine needle aspiration.

Research methods

Each EUS report was evaluated by the quality indicator table. QIs were evaluated prior to, during, and after performing EUS. Subsequent statistical analyses were then performed for the frequency of each indicator if listed or not listed in the various EUS reports. Reporting frequencies of each QI were calculated as percentages from which conclusions could be drawn. Each of the ten participating healthcare centers were provided with the results of this study so that they may be able to practically implement changes on their own respective terms that may improve the overall effectiveness of EUS as a whole. From the QI table, a sample EUS reporting document was proposed to be used by physicians performing EUS. Institutional Review Board approval was obtained prior to initiation of this study ensuring the privacy of all physicians, patients, and personal records. No direct patient contact took place nor were any patients harmed as a result of this research.

RESULTS

One hundred different EUS procedural reports were collected from ten different healthcare centers of which each center contributed ten reports. These reports were evaluated for adherence to the quality indicator table developed, based upon the indicators presented by ACG[9] (Table 1). The mean patient age was 59 years old, 52.8% of patients were female. The primary reasons for referral to EUS included suspected choledocholithiasis, suspicion of pancreatic tumor, suspicious lesions seen on imaging including ultrasound and computed tomography (Table 2).

Of the pre-procedural QIs, 71.7% of reports indicated patients' pertinent past medical history including cardiovascular disease, diabetes mellitus, gallstones, IBD, rheumatologic conditions, past surgeries, and malignancy among others. This is also to state that 29.3% of reports failed to mention the presence or absence of such conditions. Nearly of all the reports (97%) included indications for performing EUS, 82% included a detailed patient description, 61% of reports included that patients had signed a document evidencing informed consent, and 8% of reports mentioned the pre-procedural preparation. Ninety-four percent of patients received anesthesia with fentanyl combined with one or more sedatives includ-

Table 2 Indications for endoscopic ultrasound referral

Reason for EUS referral	Percent of cases
Suspected choledocholithiasis	31%
Pancreatic tumor suspicion	17%
Pathologic finding of imaging	16%
Suspicion of esophageal of stomach Tumor	12%
Pancreatic cyst	8%
Pancreatitis	3%
Obstructive Jaundice	3%
Other	19%

The above table displays the various main reasons for endoscopic ultrasound (EUS) referral. Although most commonly due to gallstone of pancreatic pathology, one can observe that EUS may be used to diagnose and to stage other areas in the gastrointestinal tract and surrounding areas.

ing propofol and midazolam. Three patients received ketamine and three patients received flumazenil (anexate) during the procedure. These agents were generally administered in the minimum accepted therapeutic intervals. For 6% of patients it was unknown which type of anesthesia, if any, which was administered (Table 3).

The most frequently documented intra-procedural QIs were pancreatic and bile duct pathology as these were the main reasons for referral. Thirty-six percentage of reports described the systematic evaluation of organs during EUS while half of the reports (50%) did not follow this systematic method. Therefore, 87% of reports included a thorough description of the pancreas including parenchyma and its different segments while 63% of reports included a description of the biliary tree. Thirty-four percent of reports outlined the evaluation of the celiac axis, and none of the reports mentioned the adrenal glands. Six percent of procedures documented intra-procedural problems which included insufficient anesthesia (2%), anesthesia-related complications (2%), ascites, and past abdominal surgeries. In cases where FNA was performed, 15% of reports documented the number of passes, needle size, and results of immediate cytological examination. Most reports simply stated that FNA was performed. Because of the high suspicion for tumors in nearly half of the reports, great care was placed on assessing the tumor-associated quality indicators (Table 3).

Post-Procedural QIs also primarily focused on the reason for referral. Although 81.9% of reports contained a clear summary of EUS findings, 37.2% of examinations contained findings unassociated with the original reason for referral, such as liver, stomach, or pancreatic pathology that were subsequently not documented. 79.8% of reports listed treatment recommendations, and 52.1% listed medical guidance about potential procedural adverse events, including pancreatitis and bleeding, of which none of the reports indicated if such adverse events occurred (Table 3). The post-procedural quality indicators are most vital as they allow physicians to summarize diagnostic findings, detail any EUS adverse effects, and outline treatment with proper follow-up and patient education. Upon expansion of this research to include twenty additional EUS reports in collaboration with two expert US endosonographers, it was found that significantly greater adherence to quality indicators was observed.

Table 3 Endoscopic ultrasound pre-procedural, tumor-associated, post-endoscopic ultrasound quality indicators

Quality indicators	Percent documented
EUS pre-procedural[1]	
Listed indications for procedure	97%
Detailed patient description from the referring phycisian	82%
Received minimum six hour fast	8%
Given antibiotics per protocol prior to FNA of pancreatic cyst	40%
Listing of anesthesia administered prior to starting EUS	94%
Patient signed agreement of informed consent	61%
EUS findings consistent with or highly suspicious for tumor[2]	
Description by the TNM system	5%
Tumor description (or suspected)	78%
Description of degree of tissue invasion	65%
Presence or absence of lymph nodes	46%
Reports malignant or suspicious lesions	48.50%
Post-EUS[3]	
Summary of medical diagnoses	81.90%
Examination findings, even if not relevant to the reason for EUS referral, should be listed	37.20%
Treatment recommendations with respect to examination findings	79.80%
Advice given to patients after performing EUS	52.10%
Incidence of adverse events, including pancreatitis, bleeding, and/or infections and the need for hospitalization	0%

[1]The above chart lists the percent of endoscopic ultrasound (EUS) reports in which pre-procedural quality indicators were documented. Indications and anesthesia were most frequently listed, while pre-procedural preparation, administration of antibiotics prior to fine needle aspiration of pancreatic cysts, and signing informed consent were less often listed in reports; [2]This chart demonstrates the adherence to EUS quality indicators for lesions consistent with or suspected to be of malignant etiologies. Although tumors and depth of invasion were commonly described, the tumor, node, and metastasis system was seldom used; [3]This table lists the physician adherence to post-procedural EUS quality indicators. Diagnoses, procedural findings relevant to reason for referral and treatment recommendations were most often documented whereas findings inconsistent with the reason for referral, post-procedural patient advice, and listing adverse events were far less often emphasized. FNA: Fine needle aspiration; TNM: Tumor, node, and metastasis.

DISCUSSION

Statistical analysis allowed the formation a quality indicator table composed of indicators prior to, during, and after EUS as proposed earlier in accordance with ACG guidelines[9]. QI emphasized many factors including past medical conditions, current medications, comprehensive intra-procedural documentation, and implications of the procedure including treatment and potential adverse events that were not always documented. High-quality EUS examinations in particular include documenting a thorough exam, medical equipment used, nursing data, patient status, and discharge notes, among others. Physician adherence to QIs may produce a clear concise report that not only ensures a comprehensive examination, but

also that future medical providers can quickly reference a patient's past EUS[12]. Analysis of EUS reports sent from the University of Chicago showed significantly greater adherence to the documentation of quality indicators, thus producing a higher quality report.

In regards to pre-procedural indicators, most reports were thorough in listing the indications for EUS. Frequently detailed also were the anesthesia and respective dosage of each sedative administered, although a small but significant percentage of reports failed to document this (Table 3). It is very important to describe the type and dose of sedative administered as well as any medication-related adverse effects. There was no mention of which patients were evaluated by the operating endoscopist prior to EUS. Open access is frequently used for EUS patients, and reports that lack such a description make it difficult for the echo-endoscopist to perform a thorough yet focused examination thus resulting in increasing amounts of EUS procedures in which smaller pathologic conditions may be missed that would have otherwise been detected had the patient had prior appropriate documentation. The risk of missing important findings may be even greater if the operating echo-endoscopist is unfamiliar with the patient undergoing EUS. Furthermore, 61% of reports mentioned that patients had signed forms of informed consent, which is a glaring number when one considers the ethical and legal concerns. Although it is likely that every patient had given informed consent, documentation should nevertheless report this. Forty percent of reports listed antibiotic prophylaxis when FNA was performed on pancreatic cysts. Although it is not evidence-based, expert opinion suggests benefits of prophylactic antibiotics on decreasing the infection rate after FNA of pancreatic cysts[13]. Lastly, pre-EUS preparation consisting of a minimum of 6 h fasting was very seldom documented (8%). This indicator bears great importance because poorly prepared procedures will be of diminished quality due to impaired operator visibility and greater risk of aspiration that may increase the likelihood of missed findings and adverse events occurring during EUS.

As EUS is capable of diagnosing a wide range of pathologies in multiple organ systems, intra-procedural indicators were developed to optimize procedural effectiveness. After review of the various reports, it was discovered that they often lacked a comprehensive system for assessing and documenting organ systems, especially those not directly related to the reason for admission. For example, the adrenal glands were not listed in any of the EUS reports, although any discovered lesions may significantly impact patients' health. For this reason and others, it is important that a standardized table of quality indicators be used for documentation. The advantage of a standardized QI table is that it includes a list of all organs examined during EUS as well as a description of their structure to describe potential lesions, those that have suspicious characteristics, and also as a method to exclude regions as a cause for a patient's chief complaint (Table 1).

Approximately half of the total reasons for EUS referral were for suspicion of malignancy. This is due to EUS being a highly sensitive and specific procedure for tumors in the GI tract and surrounding areas and thus may optimize subsequent treatment[14]. Therefore, all suspected tumors should be staged according to the tumor, node, and metastasis system, based characteristics including tumor size, depth of invasion, and surrounding vascular involvement (Table 3). The diagnostic ability of EUS is further augmented by taking fine needle aspirations of such lesions. Although one third of the EUS reports involved FNAs, few reports documented the number of passes, the size of the needle, or if immediate cytological examination of the aspirated contents was performed. These details are necessary in evaluating the EUS procedural standards, which may be remedied by quality control to optimize FNA effectiveness[3]. Therefore, proper diagnoses and thorough documentation based upon each of the described lesion characteristics described during EUS may further guide the decision for optimal treatment for the diverse benign and malignant conditions affecting the GI tract.

A number of interventions may lead to improved EUS quality. Granting quality recognition awards for those who have been consistently able to produce high-quality EUS reports is one such widely-implemented method[2]. Especially in the era of quality driven markets, delivering high-quality endoscopic reports may lead to increased healthcare recognition and funding. Weak areas may be remedied *via* continuous quality control monitoring of reports listed on EMR. However, despite these efforts, the brunt of quality improvement relies on the individual physician to perform his or her duty of delivering the best medical care possible while ensuring minimal harm coming to patients. High-quality reports, as seen by evaluation of the twenty reports from the United States, also help protect and reduce the costs of litigation as proper documentation may lead to fewer malpractice lawsuits.

It must be acknowledged that EUS gives rise to infrequent but important adverse events. It was noted that while analyzing the 100 EUS reports from Israeli centers, there was no mention of adverse events that arose during EUS. Although there are always those present in healthcare systems who fail to comply with procedures and documentation policies, procedural complications should always be recorded. Such adverse events may include bleeding, infection, pancreatitis, intestinal perforation, and others should be listed[15] as it is important for quality control purposes to identify and promptly remedy possible causes of such adverse events. Follow-up protocols should be included and clearly detailed according to EUS findings and diagnoses. The key advantage of post-procedural quality indicators is to have an area for summary of findings, diagnoses, and for medical recommendations with follow-up instructions (Table 3). It is important to note that by alone ensuring thorough EUS performance

and subsequent documentation does not cover all aspects of EUS quality control. There are many aspects of quality control that can and should be investigated in order to further augment the quality of EUS.

Summarizing important procedural findings for tailoring optimized treatment and to encourage patient follow-up is key to the long-term success of EUS and for patient care in general. Patient diagnoses must be summarized based on findings or lack thereof during EUS. As evidenced by this study, there is very little standardization was found among Israeli gastroenterologists; EUS findings need to be properly detailed with appropriate clinical correlation (Table 3). It is important as well to include incidentally discovered findings that are not connected to patients' primary complaints as these discovered lesions may significantly impact patients' future well-being and may be treated at an early stage. In adhering to a standardized QI table specific for EUS, doctors and patients alike may benefit from higher quality and more fruitful procedures while identifying cost-effective ways to remedy weak areas in its performance.

This study involved a multitude of diverse healthcare centers in Israel, each with its individual unique staff that causes variability in performing and documenting of EUS, which may or may not reflect the healthcare setting in other countries. Reports were evaluated multitude of diverse healthcare centers in Israel, causing variability in EUS performance and documentation of EUS, which may or may not reflect the healthcare setting in other countries.

In conclusion, having a standardized table including relevant quality indicators for EUS may increase the overall effectiveness and quality of EUS by ensuring comprehensive procedural documentation while simultaneously limiting error and strengthening patient education of potential findings during EUS.

COMMENTS

Background

Quality control in gastroenterology has focused on the implementation of quality indicators (QIs). Such QIs are established pre, peri, and post procedural features that various gastrointestinal societies have deemed necessary for documentation to achieve and maintain high quality in procedures and subsequent reports. Maintaining high-quality gastrointestinal procedures and reports *via* physician adherence to QIs may also minimize potential adverse events, and to optimize costs, thus saving hospitals and patients alike while improving patient care in the process.

Research frontiers

While quality indicators have been established for procedures such as colonoscopy, their effectiveness has not been well studied in regards to endoscopic ultrasound (EUS). This study assesses physician adherence to American Society for Gastrointestinal Endoscopy (ASGE) and European Society of Gastrointestinal Endoscopy (ESGE)-established quality indicators for EUS and offers a sample table intended for ease of implementing such QIs.

Innovations and breakthroughs

This study demonstrates that EUS reports compiled from Israeli centers most often adhered to indicators closely linked with the presenting pathology and infrequently documented a fully-detailed comprehensive report. In contrast to EUS reports evaluated from the University of Chicago, such reports were consistently found to adhere to EUS QIs. Therefore, the authors have prepared a table based on established QIs for ease of documenting a high-quality EUS report.

Applications

In using the proposed standardized table, physicians may find it easier to document high quality reports which may optimize costs, limit error, and ensure proper patient follow-up.

Terminology

Endoscopic ultrasound is a method of upper endoscopy that allows the operator to utilize ultrasound to accurately visualize deeper areas of the GI tract and to identify and biopsy suspicious lesions. Although it has been proven to be a highly accurate diagnostic method for malignancies in multiple regions of the GI tract, its effectiveness is operator dependent. Therefore, physician adherence to quality indicators *via* the proposed QI table is a low cost option that may augment the effectiveness of EUS that may benefit patients and healthcare providers alike.

Peer review

This study assesses physician adherence to ASGE and ESGE-established quality indicators for EUS and presents a table based on established QIs for ease of documenting a high-quality EUS report. The novelty and innovation of the research is high. The presentation and readability of the manuscript is good.

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CASE REPORT

Esophageal tuberculosis presenting with hematemesis

Samit S Jain, Piyush O Somani, Rajeshkumar C Mahey, Dharmesh K Shah, Qais Q Contractor, Pravin M Rathi

Samit S Jain, Piyush O Somani, Dharmesh K Shah, Qais Q Contractor, Pravin M Rathi, Department of Gastroenterology, Bai Yamunabai Laxman Nair Hospital, Topiwala National Medical College, Mumbai 400008, India
Rajeshkumar C Mahey, Department of General Surgery, Bai Yamunabai LaxmanNair Hospital, Topiwala National Medical College, Mumbai 400008, India
Author contributions: Jain SS, Somani PO, Mahey RC and Shah DK designed the research; Jain SS, Somani PO and Shah DK performed the research; Contractor QQ and Rathi PM analyzed the data; Jain SS and Somani PO wrote the paper.
Correspondence to: Pravin M Rathi, Professor, Head, Department of Gastroenterology, Bai Yamunabai Laxman Nair Hospital, Topiwala National Medical College, Dr A L Nair Road, Mumbai Central, Mumbai 400008, India. rathipmpp@gmail.com
Telephone: +91-22-23016139 Fax: +91-22-23021168
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Abstract

Esophageal tuberculosis is rare, constituting about 0.3% of gastrointestinal tuberculosis. It presents commonly with dysphagia, cough, chest pain in addition to fever and weight loss. Complications may include hemorrhage from the lesion, development of arterioesophageal fistula, esophagocutaneous fistula or tracheoesophageal fistula. There are very few reports of esophageal tuberculosis presenting with hematemesis due to ulceration. We report a patient with hematemesis that was due to the erosion of tuberculous subcarinal lymph nodes into the esophagus. A 15-year-old boy presented with hemetemesis as his only complaint. Esophagogastroduodenoscopy (EGD) revealed an eccentric ulcerative lesion involving 50% of circumference of the esophagus. Biopsy showed caseating epitheloid granulomas with lymphocytic infiltrates suggestive of tuberculosis. Computerised tomography of the thorax revealed thickening of the mid-esophagus with enlarged mediastinal lymph nodes in the subcarinal region compressing the esophagus along with moderate right sided pleural effusion. Patient was treated with anti-tuberculosis therapy (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol) for 6 mo. Repeat EGD showed scarring and mucosal tags with complete resolution of the esophageal ulcer.

Key words: Esophageal tuberculosis; Esophagogastroduodenoscopy; Hematemesis

Core tip: Esophageal tuberculosis is very rare, constituting about 0.3% of gastrointestinal tuberculosis cases. Esophageal tuberculosis presents commonly with dysphagia, cough, chest pain in addition to fever and weight loss. Complications may include hemorrhage from the lesion, development of arterioesophageal fistula, esophagocutaneous fistula or tracheoesophageal fistula. There are very few case reports of esophageal tuberculosis presenting with hematemesis due to esophageal ulceration. We report a patient with hematemesis that was later attributed to the erosion of tuberculous subcarinal lymph nodes into the esophagus.

Jain SS, Somani PO, Mahey RC, Shah DK, Contractor QQ, Rathi PM. Esophageal tuberculosis presenting with hematemesis. *World J Gastrointest Endosc* 2013; 5(11): 581-583 Available from: URL: http://www.wjgnet.com/1948-5190/full/v5/i11/581.htm DOI: http://dx.doi.org/10.4253/wjge.v5.i11.581

INTRODUCTION

Esophageal tuberculosis is rare, constituting about 0.3% of gastrointestinal tuberculosis cases[1]. Usual presentation is due to dysphagia, retrosternal pain, fever, cough and weight loss. Complications may include hemorrhage from the lesion, development of arterioesophageal fistula, esophagocutaneous fistula or tracheoesophageal fistula[2] and intramural pseudo-diverticulum[3]. There are very few case reports of esophageal tuberculosis presenting with hematemesis due to esophageal ulceration[2,4,5]. We report a patient with hematemesis that was due to the

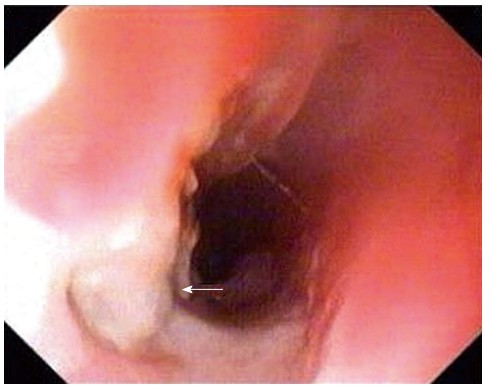

Figure 1 Esophagogastroduodenoscopy showing eccentric ulcerative lesion involving 50% of circumference of the esophagus (white arrow).

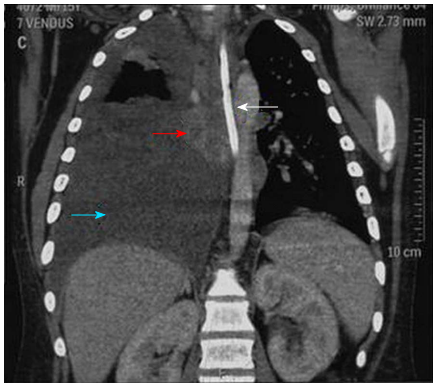

Figure 2 Computerised tomography of the thorax showing thickening of the mid-esophagus (red arrow) along with Ryle's tube *in situ* (white arrow). Right sided pleural effusion seen (blue arrow).

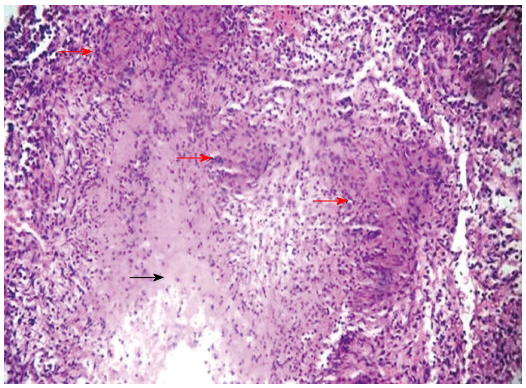

Figure 3 Histopathological examination of esophageal ulcer biopsy showing epitheloid cell granulomas (red arrows) with caseation (black arrow) in the exudate suggestive of esophageal tuberculosis (HE stain x 10).

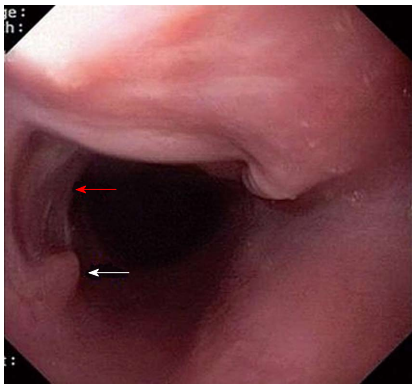

Figure 4 Esophagogastroduodenoscopy after 6 mo of anti-tuberculosis therapy showing resolution of esophageal ulcer along with scarring (red arrow) and mucosal tags (white arrow).

erosion of tuberculous subcarinal lymph nodes into the esophagus.

CASE REPORT

A 15-year-old male presented to the emergency room with five bouts of hematemesis and melena since past 2 d. There was no history of dysphagia, dyspnea, cough, abdominal pain or syncope. On examination his pulse was 110 beats per minute and blood pressure 90/60 mmHg. He appeared pale. Rest of the examination was unremarkable. Laboratory investigations revealed a hemoglobin level of 7 g/dL with normal blood chemistry. Human immunodeficiency virus screening antibody was negative. Erythrocyte sedimentation rate was 72 mm in the first hour. Patient was resuscitated and esophagogastroduodenoscopy (EGD) was performed which revealed an eccentric ulcerative lesion involving 50% of circumference of the esophagus at 26 cm from the incisors (Figure 1). Biopsy of the ulcer margin was sent for histopathological examination. It revealed caseating epitheloid granulomas with lymphocytic infiltrate suggestive of tuberculosis (Figure 2). Computed tomography (CT) of the thorax showed thickening of the mid-esophagus with enlarged mediastinal lymph nodes in the subcarinal region compressing the esophagus along with moderate right sided pleural effusion (Figure 3). Polymerase chain reaction of the tissue was highly specific for mycobacterium tuberculosis. Diagnostic thoracocentesis revealed a turbid pleural exudates with pH = 7.38, glucose = 72 mg/dL, total protein = 4.3 mg/dL, total cells = 2200/mm^3, consisting of 80% lymphocytes and 20% polymorphonuclear cells and lactate dehydrogenase = 724 U/L. Pleural fluid adenosine deaminase was 69 U/L, while smears, cultures and cytology, were negative. Patient was initiated on a four-drug antitubercular therapy (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol) with marked improvement in his symptoms. Repeat EGD after 6 mo showed only scarring and mucosal tags with complete resolution of the ulcer (Figure 4) and chest X-ray showed complete resolution of pleural effusion.

DISCUSSION

Esophageal tuberculosis is very rare and primary esophageal tuberculosis is seemingly even more exceptional. Esophageal tuberculosis is considered primary when there is no other detectable tubercular site and secondary when the esophagus is involved by spread from adjacent structures. Primary tuberculosis of the esophagus is extremely rare, perhaps owing to intrinsic protective

mechanisms, such as stratified epithelial lining, presence of saliva. Besides, mucous coated tubular structure, peristalsis discourages stasis and mucosal invasion by organisms, which needs a physiologically stable environment. Several mechanisms have been proposed to explain the spread of infection to the esophagus, resulting in secondary esophageal tuberculosis: (1) infection of the esophageal mucosa from swallowed tuberculous sputum; (2) contiguous extension from laryngeal and pharyngeal lesions; (3) contiguous extension from other adjacent infected structures, such as the mediastinum, hilar lymph nodes or vertebrae; (4) retrograde lymphatic spread; and (5) hematogenous infection in the course of generalized disseminated miliary tuberculosis[2].

Common site of tubercular involvement is mid-esophagus, near carina due to proximity to mediastinal lymph nodes[6]. Damtew *et al*[7] in an analysis of 19 cases of esophageal tuberculosis, found that the majority of patients had direct extension from an adjacent caseous mediastinal or hilar lymph node. Most of these cases were diagnosed late and showed predominant involvement of the upper or middle third of the esophagus.

Three histomorphologically distinct types exist: (1) Ulcerous type (most common): mycobacteria initially involve submucosa of esophagus followed by formation of tubercle. As the disease progresses, caseous necrosis occurs within the nodule, followed by ulceration. Usually it is a superficial ulcer with pale grey purulent base, rough, irregular edge, only involving the mucosa and submucosa. The more serious ulcers occur rarely, often can penetrate the muscle layer, break through the esophageal adventitia resulting in esophageal perforation, esophagomediastinal fistula or esophagopleural fistula. Invasion of the trachea results in tracheoesophageal fistula. Death due to massive hemorrhage can occur due to aortoesophageal fistula. Esophageal tuberculous ulcer often has a self-healing tendency due to proliferation of fibrous tissue and scar formation, leading to local esophageal stenosis; (2) Hyperplastic type: is due to excessive amount of tuberculous granulation tissue and fibrous tissue hyperplasia. Sometimes due to massive hyperplasia, there can be false tumor-like mass (pseudotumor) formation into the esophageal lumen, resulting in luminal narrowing; and (3) Granular esophageal tuberculosis (least common): occurs in the severe systemic disease where the mucosa and submucosa show many gray-white nodules[8].

Esophageal tuberculosis presents commonly with dysphagia, cough, chest pain in addition to fever and weight loss, which might simulate esophageal malignancy. Presentation with complications is rare[2]. Hematemesis most often is due to arterioesophageal fistula with grave prognosis. In this patient upper gastrointestinal bleeding was due to ulceration in the mid-esophagus due to erosion of tuberculous subcarinal lymph nodes.

Diagnosis of esophageal tuberculosis is difficult and a high index of suspicion is required. Plain radiography of the chest and CT scan could reveal pulmonary or mediastinal lymph node involvement. CT scan may also reveal thickening of the mid-esophagus as in our case. Endoscopy is valuable to diagnose the lesion and for achieving biopsy for histopathology and isolating the organism[6]. Histology shows epithelioid granuloma with Langhans cells and central caseous necrosis. Classical granulomas are seen only in 50% of cases, whereas acid fast bacilli are demonstrated in less than 25%[9]. Endoscopic mucosal biopsy has sensitivity of 22% as reported by Mokoena *et al*[2]. Recently, cytology and polymerase chain reaction have also proven useful in cases where the initial biopsies showed non-specific changes[10].

Anti-tubercular chemotherapy (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol) for 6 to 9 mo is the main stay in the treatment. Surgical intervention is warranted if bleeding persists or gets complicated with perforation or fistula formation occur.

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Both personal authors and an organization as author

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Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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