ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2015 November 10; 7(16): 1197-1232

Published by Baishideng Publishing Group Inc

WJGE World Journal of Gastrointestinal Endoscopy

A peer-reviewed, online, open-access journal of gastrointestinal endoscopy

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2014-2017

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WJGE World Journal of Gastrointestinal Endoscopy

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Biweekly Volume 7 Number 16 November 10, 2015

World Journal of Gastrointestinal Endoscopy
Volume 7 Number 16 November 10, 2015

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NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Biweekly

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PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
November 10, 2015

World Journal of Gastrointestinal Endoscopy

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v7.i16.1197

World J Gastrointest Endosc 2015 November 10; 7(16): 1197-1207
ISSN 1948-5190 (online)

TOPIC HIGHLIGHT

2015 Advances in Laparoscopic Surgery

Pancreatic insulinomas: Laparoscopic management

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Conflict-of-interest statement: No conflict of interest to declare.

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Received: April 28, 2015
Peer-review started: May 6, 2015
First decision: June 2, 2015
Revised: June 22, 2015
Accepted: August 25, 2015
Article in press: November 7, 2015
Published online: November 10, 2015

Abstract

Insulinomas are rare pancreatic neuroendocrine tumors that are most commonly benign, solitary, and intra-pancreatic. Uncontrolled insulin overproduction from the tumor produces neurological and adrenergic symptoms of hypoglycemia. Biochemical diagnosis is confirmed by the presence of Whipple's triad, along with corroborating measurements of blood glucose, insulin, proinsulin, C-peptide, β-hydroxybutyrate, and negative tests for hypoglycemic agents during a supervised fasting period. This is accompanied by accurate preoperative localization using both invasive and non-invasive imaging modalities. Following this, careful preoperative planning is required, with the ensuing procedure being preferably carried out laparoscopically. An integral part of the laparoscopic approach is the application of laparoscopic intraoperative ultrasound, which is indispensable for accurate intraoperative localization of the lesion in the pancreatic region. The extent of laparoscopic resection is dependent on preoperative and intraoperative findings, but most commonly involves tumor enucleation or distal pancreatectomy. When performed in an experienced surgical unit, laparoscopic resection is associated with minimal mortality and excellent long-term cure rates. Furthermore, this approach confers equivalent safety and efficacy rates to open resection, while improving cosmesis and reducing hospital stay. As such, laparoscopic resection should be considered in all cases of benign insulinoma where adequate surgical expertise is available.

Key words: Pancreatic insulinoma; Laparoscopic surgery; Technique; Outcomes; Minimally invasive surgery

Core tip: Insulinomas have always fascinated physicians and surgeons alike, due to the difficulties in: (1) diagnosing them; (2) obtaining accurate preoperative and intraoperative localization; and (3) actually performing

the operation safely and effectively. Laparoscopy stands out in the current literature as the approach of choice, and is employed for virtually all benign insulinomas. Enucleations for insulinomas in the head and body, as well as distal pancreatectomies for lesions in the body and tail of the pancreas, have been shown to be safe and effective in the current series. Laparoscopic intraoperative ultrasound localization has emerged as a standard adjunct to these procedures.

Antonakis PT, Ashrafian H, Martinez-Isla A. Pancreatic insulinomas: Laparoscopic management. *World J Gastrointest Endosc* 2015; 7(16): 1197-1207 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i16/1197.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i16.1197

INTRODUCTION

Insulinomas are insulin-secreting neuroendocrine tumors deriving from neoplastic pancreatic islet cells, and occurring almost exclusively in the pancreas[1,2]. They are gastroenteropancreatic neuroendocrine tumors (GEP-NETs) belonging to the subgroup of neuroendocrine tumors (NETs) known as pancreatic endocrine tumors (PETs)[3]. In contrast to other PETs, approximately 90% of insulinomas are sporadic, solitary, and benign, measuring less than 2 cm in diameter[1,2,4-6]. These characteristics, along with their highly symptomatic presentation, make complete surgical removal the treatment of choice for affected patients[2,7,8]. Surgical treatment options include tumor enucleation and regional pancreatic resection[8]. However, until recently, the only available approach was open surgery.

Laparoscopic enucleation and distal pancreatectomy were first reported in the 1990s by Gagner *et al*[9]. In fact, the small, benign, and solitary nature of insulinomas makes them ideal candidates for a laparoscopic approach, particularly in overweight or obese patients. In the last 20 years, several case reports[10,11] and case series[9,12-31], including our own[32-34], have explored the technical aspects of laparoscopic insulinoma resection. The results presented in these studies demonstrate the feasibility, safety, and reproducibility of laparoscopic insulinoma resection in experienced hands. Consequently, recently published guidelines now consider laparoscopic enucleation an appropriate treatment modality for the majority of insulinomas[8,35-37]. This article reviews the current status of laparoscopic insulinoma management and discusses both the strategic and technical aspects of surgical care in these patients.

BACKGROUND

Insulinomas are rare and exhibit a number of unique characteristics when compared to other PETs. These differences in the epidemiology, clinical features, and biological behavior of insulinomas impact significantly on their management and define the role and limitations of laparoscopic surgical intervention.

EPIDEMIOLOGY: SURGICAL MANAGEMENT OF RARE PATHOLOGY

The estimated annual incidence of insulinomas is 0.7-4 diagnosed cases per million persons[38]. Their rarity, combined with the unique challenges presented throughout the course from diagnosis to therapy, requires expert referral and management. Centralization of care is therefore of utmost importance for these patients, and tertiary referral to centers of excellence that follow a multidisciplinary approach is strongly advocated in current treatment guidelines[8,35-37]. The low incidence of insulinomas makes it difficult for any surgeon outside of pancreatic centers of excellence to gain sufficient experience in insulinoma resection[8,35-37]. Furthermore, although a laparoscopic approach is encouraged, the choice between open and laparoscopic surgery should be left to the discretion of the surgical team. It is therefore paramount that surgeons making such decisions are experienced in both open and minimally invasive procedures, in order to offer their patients the optimal treatment.

INSULINOMAS IN THE CONTEXT OF MULTIPLE ENDOCRINE SYNDROME TYPE 1

The vast majority of insulinomas are sporadic, but in 5%-10% of cases they present in the context of multiple endocrine syndrome type 1 (MEN1)[6,7]. MEN1-related insulinomas are frequently multifocal and coincide with several other pancreatic lesions (most commonly non-functioning pancreatic endocrine tumors)[6,39]. It therefore becomes very difficult preoperatively to determine with certainty the lesions for resection that are responsible for the clinical syndrome. This is further confounded by the fact that not all pancreatic lesions with immunohistochemically proven insulin production capacity produce clinical symptoms[39,40].

As such, it is both difficult to determine preoperatively the lesions responsible for the clinical syndrome and to definitively state whether surgical resection has been curative, even when insulin-producing lesions are documented in the pathology report. Consequently, significantly higher failure and recurrence rates are documented after surgery for MEN1-related insulinomas when compared to sporadic lesions[39,41].

In view of the difficulty in achieving complete clearance, a more radical surgical approach is preferred in MEN1-associated insulinomas[39,41,42]. Current surgical practice depends on the site of the tumor. For distal lesions, distal pancreatectomy with or without splenic preservation is required. Proximal tumors located in the pancreatic head may be enucleated, but total pancreatectomy may be required in selected

cases[35,36,39,41-44]. Local resections are not routinely indicated, despite some recently promising results in selected solitary or dominant lesions[45]. Moreover, the procedure of choice should be decided after careful preoperative localization, and take into account the need for symptom alleviation (*i.e.*, complete resection of all insulinomas), the malignant potential of all existing pancreatic lesions (including, but not limited to, insulinomas), and the expected complications, together with the existence of any previous surgical attempts. It is notable that laparoscopic resection in the context of MEN1 requires advanced minimally-invasive surgical skills due to the inherent difficulties of laparoscopic distal pancreatectomy, particularly where combined enucleations in the head of the pancreas are required. Finally, it should be mentioned that, in our recent experience, enucleation of single lesions in the head of the pancreas in the context of MEN has been successful in rendering the patient asymptomatic 12 mo after surgery.

BIOLOGICAL BEHAVIOR

Although the majority of insulinomas are benign and curable by surgical resection, approximately 5%-10% show malignant behavior[38]. However, with an annual incidence of approximately 0.1 per million persons per year[46], malignant insulinomas are extremely rare. Similar to all other neuroendocrine pancreatic tumors, the malignant potential of insulinomas is assessed by tumor differentiation (extent of resemblance to normal cells), grade (degree of biologic aggressiveness), and stage (extent of tumor spread)[47]. Of note, although a number of different pathological grading and clinicopathologic staging classifications have been suggested, no single system has been universally adopted[47].

Local invasion and/or evidence of liver metastases clearly demonstrate malignancy[7]. However, in the absence of these findings, malignant behavior must be determined from the pathologic characteristics of preoperative tissue biopsies when they were taken, because in most cases, EUS-guided Fine Needle Aspiration is performed at most. Although the course of malignant insulinomas is more indolent than other malignant neuroendocrine pancreatic tumors, the median survival is only 2 years, while the 10-year survival rate is only 29%[5,6,48]. Although, in some cases, malignant insulinomas have been reported with higher survival rates[49], this prognosis remains significantly poorer than for benign insulinomas, which present a 95%-100% surgical cure rate[5-7,48].

These key facts define the role and the limitations of both laparoscopic and open surgery in patients with malignant insulinoma. However, it is possible that extensive surgical resection of the primary tumor, affected lymph nodes, and distant metastases may provide alleviation for hypoglycemia and long-term survival when combined with adjunctive therapy such as medical treatment, radiofrequency ablation, transarterial chemoembolization, somatostatin analogues, chemotherapy, or biological agents. In resectable malignant disease, surgical options may provide a cure, and include distal pancreatectomy, pancreaticoduodenectomy with or without metastasectomy, segmentectomy, formal hepatectomy, or even liver transplantation[6,30,36,37,49,50]. Where the disease is unresectable in its entirety, debulking surgery may provide symptomatic relief when combined with medical and ablative therapy. Whenever malignancy is determined preoperatively, these operations are performed exclusively *via* laparotomy. Laparoscopic resection is not routinely practiced and no guidelines currently exist as to the role of laparoscopic intervention in these cases. Conversely however, in some cases the malignant potential of an insulinoma may only be acknowledged after laparoscopic resection as a result of specimen histology, symptom recurrence, and/or metastasis development during follow-up. In these cases, a multidisciplinary assessment is mandatory, and is most commonly followed by secondary radical open resection in combination with adjunctive therapy.

CLINICAL SYMPTOMS AND BIOCHEMICAL DIAGNOSIS

Insulinomas most commonly present with hypoglycemia caused by inappropriate excessive endogenous insulin production. Physical exercise and fasting usually provoke the symptoms, which fall in two major categories: Neurologic and adrenergic[4,6,7,43,51]. Neurologic symptoms are attributed to the effects of low blood glucose on the nervous system (neuroglycopenia) and include visual disturbances (diplopia and blurred vision), altered mental status, abnormal behavior, seizures, amnesia, and even coma[4,6,7,43,51]. Adrenergic symptoms are attributed to reactive catecholamine overproduction and include nausea, excessive sweating, anxiety, palpitations, weakness, tremors, increased appetite, and heat intolerance[4,6,7,43,51]. Each patient usually reports a specific collection of symptoms[52,53], which are relieved almost immediately after carbohydrate consumption, a feature that is included in Whipple's diagnostic triad[54]. Furthermore, the combination of weakness and increased appetite, alongside the ability of carbohydrate consumption to act as a relieving factor, frequently leads to excessive calorie consumption, weight gain, and eventual obesity[4,43,51].

When there is clinical suspicion of insulinoma, the autonomous overproduction of endogenous insulin must be confirmed biochemically. The basis of this diagnosis is the Whipple's triad[54] of biochemically-proven hypoglycemia, hypoglycemic symptom development, and swift reversal after carbohydrate consumption that occurs during a supervised fasting period. When symptoms occur concurrently with hypoglycemia (glucose levels around or below 2.2 mmol/L), increased insulin ($\geqslant$ 6 μIU/mL with standard non-specific insulin radioimmunoassay or $\geqslant$ 3 μIU/mL

with immunoradiometric or immunochemiluminescent insulin specific assays which are devoid of cross-reactivity for proinsulin and proinsulin-like components), proinsulin (≥ 5 pmol/L), and C-peptide (≥ 200 mmol/L) levels, this suggests the presence of an autonomous source of insulin production which is insensitive to hypoglycemia[1,8,43]. In order to rule out the presence of exogenous insulin (factitious hypoglycemia), a negative sulfonylurea/meglitinide screen test is also required that corroborates with the increased levels of C-peptide[1]. Surrogate markers of insulin presence, including low β-hydroxybutyrate levels (no more than 2.7 mmol/L) and a generous rise of glucose levels (more than 1.4 mmol/L) after the administration of 1 mg glucagon at the end of the fasting period[55], have been used by some authors for decades[56], especially for patients in which their blood glucose does not fall below 2.5 mmol/L during fasting. Indeed, β-hydroxybutyrate levels have now been included in recent guidelines[8,57], despite recent contradicting reports[58].

The actual cut-off points for insulin during fasting vary throughout the literature[52,59-61]. The reasons for this variation are complex and reflect both the altered biochemistry of insulin produced by insulinomas (increased proinsulin and proinsulin-like components, as well as insensitivity *vs* partial sensitivity of insulinomas to hypoglycemia) and the inherent limitations of detection assays (minimum detection levels and non-specificity to insulin in older radioimmunoassays). As such, despite a general agreement in the published cut-off values for insulinoma diagnosis, it is likely that this will remain a matter of contention. In fact, results from a recent comparative study have demonstrated proinsulin levels exceeding 5 pmol/L to be a more reliable diagnostic test for endogenous hyperinsulinism than absolute insulin levels at the time of hypoglycemia (< 2.5 mmol/L)[62]. Subsequent to this study, proinsulin measurement has since been recognized in recent consensus guidelines[8].

Practically, it is important to also consider the duration of these fasting tests when providing a biochemical diagnosis of endogenous hyperinsulinism. Traditionally, the gold standard has been a 72-h supervised inpatient assessment[52,53]. More recently however, modern insulin and pro-insulin specific assays have shown that a fasting period of 48 h is sufficient[60]. The lower cost and reduced invasiveness of this 48-h test have led to its rapid uptake across many institutions, thereby providing a new standard of care[1,43] that is reflected in updated diagnostic guidelines[8,57].

Surgeons currently have a limited role in the diagnosis of insulinoma, as this is usually confirmed prior to surgical referral. However, this by no means obviates the need for careful clinical assessment and thorough review of the patient's records and biochemistry prior to intervention. In a recent study, out of 17 patients referred to the United States National Institute of Health after a failed blind distal pancreatectomy, 5 were eventually diagnosed as having factitious hypoglycemia[63]. These patients underwent completely unnecessary major surgery. It is therefore the surgeon's professional and ethical responsibility to comprehend and fully agree with the diagnosis of insulinoma prior to undertaking any surgical intervention.

PREOPERATIVE AND INTRAOPERATIVE LOCALIZATION

Once biochemical diagnosis of insulinoma has been confirmed, the next important and demanding task is to accurately determine the location of the lesion within the pancreas[1,2,4-6,48]. In the past, surgeons were reliant on blind distal pancreatectomies for occult impalpable insulinomas due to limited imaging and diagnostic tools[64-66]. However, blind distal pancreatectomy was associated with a high failure rate (> 20%) that was exaggerated by the fact that non-palpable insulinomas often reside in the thicker pancreatic head[63]. Over the past 25 years, novel diagnostic modalities have rendered this blind approach obsolete[67] in favor of targeted resection.

Although in the past open surgeons had often bypassed preoperative localization in favor of intra-operative palpation and ultrasound (IOUS)[64-66], this approach was never widely adopted[1,53,67,68] and is certainly unacceptable for laparoscopy. Reliance on laparoscopic intraoperative ultrasound (LIOUS) alone led to open conversion in one of every three cases[16]. As a result, more recent series[17-19,31], including our own, reflect the current guidelines advocating accurate localization prior to laparoscopic surgical intervention[8]. We strongly advise against laparoscopic intervention without accurate preoperative localization[32] for a number of reasons: Firstly, the lack of intraoperative tactile feedback removes the ability to assess the tumor by palpation; secondly, patient positioning and trocar placement is determined by the location of the tumor; and finally, whilst LIOUS is a mandatory intraoperative adjunct for accurate localization and delineating regional anatomy, it is certainly not a diagnostic tool. Furthermore, the prolonged time required and inability to apply the probe to the whole pancreas without additional port placement limits its diagnostic role. Appropriate use of LIOUS requires knowledge of the regional location of the tumor (head, uncinate process, body, or tail) from preoperative investigations. In this way, the surgeon may utilize this tool to exactly locate and delineate the anatomic relationships of non-palpable lesions. It is the failure of accurate preoperative imaging that makes some authors use LIOUS to detect undiagnosed lesions or those found not to be located in the area indicated by preoperative assessment[9,16,69]. However, it is our opinion that this use limits the diagnostic yield of LIOUS, making it much lower than when used in conjunction with accurate preoperative localization. As such, we believe that accurate preoperative localization is a requirement of the laparoscopic approach. Failure to adequately assess tumor location should initially lead to repeat imaging and reassessment in an attempt

to improve localization accuracy. However, where this fails, surgeons should reconsider the appropriateness of laparoscopic intervention.

STRATEGY FOR PREOPERATIVE LOCALIZATION

There is no consensus on either the optimal type of preoperative localization modalities or on the exact order in which they should be performed. Recent guidelines suggest that non-invasive imaging should be performed first[8,35-37,57], and should include one or two from the following: transabdominal ultrasound (US), computerized tomography (CT), and magnetic resonance imaging (MRI). These modalities are usually readily available and, with the recent addition of contrast enhancement (CE), have been reported to have a high sensitivity in insulinoma detection (about 90% for CE US[70] and about 100% for CE CT and MRI[71]). However, due to variation in technology and radiological expertise, not all institutions may be able to achieve such excellent detection rates. In our experience, transabdominal unenhanced ultrasound has been associated with a sub-optimal diagnostic yield and, as such, we do not routinely employ this modality in our preoperative assessments. Although this approach is in line with recent guidelines[35-37,57], it is contrary to the reports of some authors who have had excellent results from the use of US[7].

Failure to obtain diagnosis through CT or MRI should lead to further assessment using endoscopic ultrasound (EUS)[8,35-37,57]. Although this modality is invasive, operator dependent, and of limited availability, it may yield an accuracy exceeding 90%[72,73], and is thus now advocated in all established guidelines[8,35-37,57]. As EUS performs better in the head, but less well in the body and worse in the tail of the pancreas[74,75], it may be considered a complementary modality to CT[73], which may miss lesions in the pancreatic head[76]. Notably, in our experience, lesions of greater tumor density are best detected on the arterial phase of the CT.

Following these investigations, the next test we routinely employ is selective pancreatic angiography with venous sampling after intra-arterial calcium stimulation (ASVS)[67,77]. Although highly invasive, ASVS is associated with a sensitivity of approximately 95% and is indispensable when previous tests are equivocal. ASVS allows hypervascular insulinomas to be detected by arteriography, with added regional localization in difficult cases through stimulated venous sampling. Using this technique, localization can be determined according to the arterial branch injected. The presence of insulinoma in a particular territory is indicated by a greater than two-fold elevation in insulin levels (sampled at 30 and/or 60 s from the hepatic vein) on calcium gluconate stimulation[78]. The use of ASVS is now widespread[7,79] and is included in most[8,36,37,57], but not all[35], recent guidelines.

Whilst other authors advocate the use of PET/CT[80] and SPECT/CT[81], this is not routine practice in our experience, as both techniques remain investigational[8]. However, promising results have recently been reported with glucagon-like peptide-1 (GLP-1) analogue SPECT/CT[82] imaging. Insulinomas are known to overexpress GLP-1 receptors in high density[83], thus overcoming the limitations of somatostatin-like tracers. The high selectivity of GLP-1 receptor agonists and their high affinity for insulinoma cells provides a promising future for preoperative insulinoma localization, and is likely to have increasing clinical importance with the development of novel tracers and improved imaging diagnostics[84].

SURGICAL DECISION-MAKING

Multidisciplinary assessment should form the cornerstone of insulinoma management. However, prior to intervention, the surgeon must be certain of both the biochemical diagnosis and localization of the insulinomas. Where results remain equivocal, we strongly advocate further testing or repeat imaging until adequate information is provided.

A summary of our surgical decision-making is shown in Figure 1. Of note, although we do not recommend enucleation of lesions less than 2 mm (preferably 3 mm) from the main pancreatic duct (MPD) or portal vein (due the risk of pancreatic fistula), solitary lesions in the head close to the MPD should be considered an exception, as the only alternative is a duodenopancreatectomy.

Malignant insulinomas are generally not amendable to laparoscopic surgery[7,8,35,49,50]. In these cases, resection of liver metastases ideally precedes excision of the pancreatic lesion[35], and the resultant extensive adhesions preclude a laparoscopic approach. When suspicion of malignancy is raised during planned laparoscopic surgery (Table 1), we prefer to convert to open resection[85-87], however we do acknowledge the work of other surgeons who advocate laparoscopic resection of malignant lesions[26].

In the context of MEN1, we follow a conservative but widely-accepted approach[8,37], due to the increased failure and reoperation rate inherent in the resection of MEN1-related insulinomas[43]. However, laparoscopic management of insulinomas in the context of MEN1[20,88,89] is possible in appropriate cases, particularly where only a single lesion is identified preoperatively. Where multiple lesions are present, distal pancreatectomy combined with multiple enucleations of pancreatic head lesions may also be considered. However, the laparoscopic approach to MEN1-related insulinomas is not currently widely accepted, and it should also be noted that MEN1 is considered a contraindication to laparoscopy in several large comparative series[30,31]. As mentioned previously, in our recent experience, enucleation of a single lesion in the pancreatic head has been successful in a single case.

Table 1 Features suggestive of malignant insulinoma[43]

Features suggestive of malignant insulinoma
Hard lesions
Infiltration of the surrounding pancreatic parenchyma
Evidence of tissue scarring
Major pancreatic duct dilatation

Contrary to several other published studies[16-18,21,29], we routinely perform laparoscopic enucleation of solitary pancreatic head insulinomas, not only for protruding lesions, but also for those embedded in the parenchyma, provided there is sufficient distance from the main pancreatic duct and the portal vein (Figure 1). We appreciate that some authors have expressed concern over the high complication rates in these cases[90], however we do believe that enucleation has a valuable role to play in the treatment of solitary lesions of the pancreatic head and uncinate process. Exposure is of paramount importance when dealing with pancreatic head and uncinate process insulinomas, however there are a number of techniques that can be employed to provide direct access to the posterior aspect of both[33,91]. Such approaches minimize unnecessary damage to the pancreatic parenchyma and the subsequent risk of complications.

Non-visible lesions embedded in the pancreatic head present a particular challenge, and classically have been treated with multiple extensive pancreatotomies. However, we have recently described a technique similar to wire-guided breast biopsy, which may enable the surgeon to accurately localize and laparoscopically resect these difficult insulinomas[34], thus minimizing the number and size of pancreatotomies. Assisted by LIOUS, an 18 G fine-needle may be inserted directly into the lesion to act as a probe, accurately defining the position of the insulinoma. The parenchyma of the pancreas can subsequently be divided following the needle, until the dome of the insulinoma is identified and a localized resection is performed[34].

The decision to plan a distal pancreatectomy over enucleation based on preoperative data is a rather difficult one. For lesions > 3 mm away from the pancreatic duct, enucleation is always the procedure of choice; however, we have a low threshold for distal pancreatectomy, and the more distal the position of the insulinoma, the greater the likelihood that this will be required. This is evident in several series[19,29-31] and is a natural consequence of the fact that the metabolic effects of added resection become less as the pancreatic parenchyma becomes thinner towards the tail.

TECHNICAL CONSIDERATIONS

Patient positioning can either greatly assist or hinder laparoscopic resection, and is thus crucially important to surgical set-up. For lesions in the anterior aspect of the head, isthmus, and body/proximal tail of the pancreas, the patient may be placed in a supine position with an anti-Trendelenburg tilt. A right tilt (left side up) is applied for lesions in the body/proximal tail of the pancreas. For lesions of the posterior aspect of the pancreatic head, both supine[12] and left semi-lateral positions have been reported in the literature[88]. In our experience, a full left lateral position is preferable, especially when combined with a retroduodenal and retropancreatic approach to the lesion following full kocherization[33]. We prefer this to the gastrocolic ligament approach proposed by other authors[88]. For lesions in the distal pancreatic tail, positioning may be either supine with a right tilt, right semi-lateral, or right full lateral. The choice of position for these lesions is therefore a matter of personal preference, similar to that with laparoscopic splenectomy[91]. Our practice is the right full lateral position because: (1) the chances of a distal pancreatectomy for lesions located in this area are higher and a right table tilt always facilitates this procedure; and (2) this position can easily be changed to semi-lateral with a generous left table tilt, giving the surgeon the liberty to choose between an anterior approach of the tail without spleen mobilization and a posterior one with full medial mobilization of the spleen.

Similarly, the number and position of trocar placements is at the discretion of the operating surgeon and varies throughout published reports[12,17,24,26,91]. Generally, we use a standard array of five ports: the first for the laparoscope at the center of the operating field, then two working ports for the surgeon on each side of the first, one laterally to the surgeon's right hand for the assistant, and one 5 mm in the epigastric area for a Nathanson liver retractor. For lesions in the posterior aspect of the pancreatic head where retraction of the kidney is sometimes required, a sixth trocar may be introduced to accommodate a second liver retractor for this purpose[33].

Gaining wide access to the pancreatic region of interest is of utmost importance in order to provide adequate space for surgical maneuvers and instruments such as the LIOUS probe and endoscopic stapler. For insulinomas of the posterior aspect of the pancreatic head, full mobilization of the hepatic flexure and the placement of two Nathanson liver retractors (one for the liver and possibly one for the right kidney) greatly facilitates surgical access[33]. On the other hand, for insulinomas of the anterior aspect of the pancreatic head, body, and tail, mobilization of the splenic flexure and retraction of the stomach to access the lesser cavity serves the same purpose.

After adequate mobilization of the pancreatic region of interest, the next step is LIOUS performed by a dedicated radiologist. This forms an integral part of laparoscopic insulinoma resection, as it not only allows for accurate localization of the lesion, but also outlines the surrounding anatomy in terms of tumor size, local invasion, and distance from the pancreatic duct and/or portal vein. If the combination of careful inspection and thorough LIOUS evaluation fails to adequately localize or characterize the insulinoma, we advocate that further

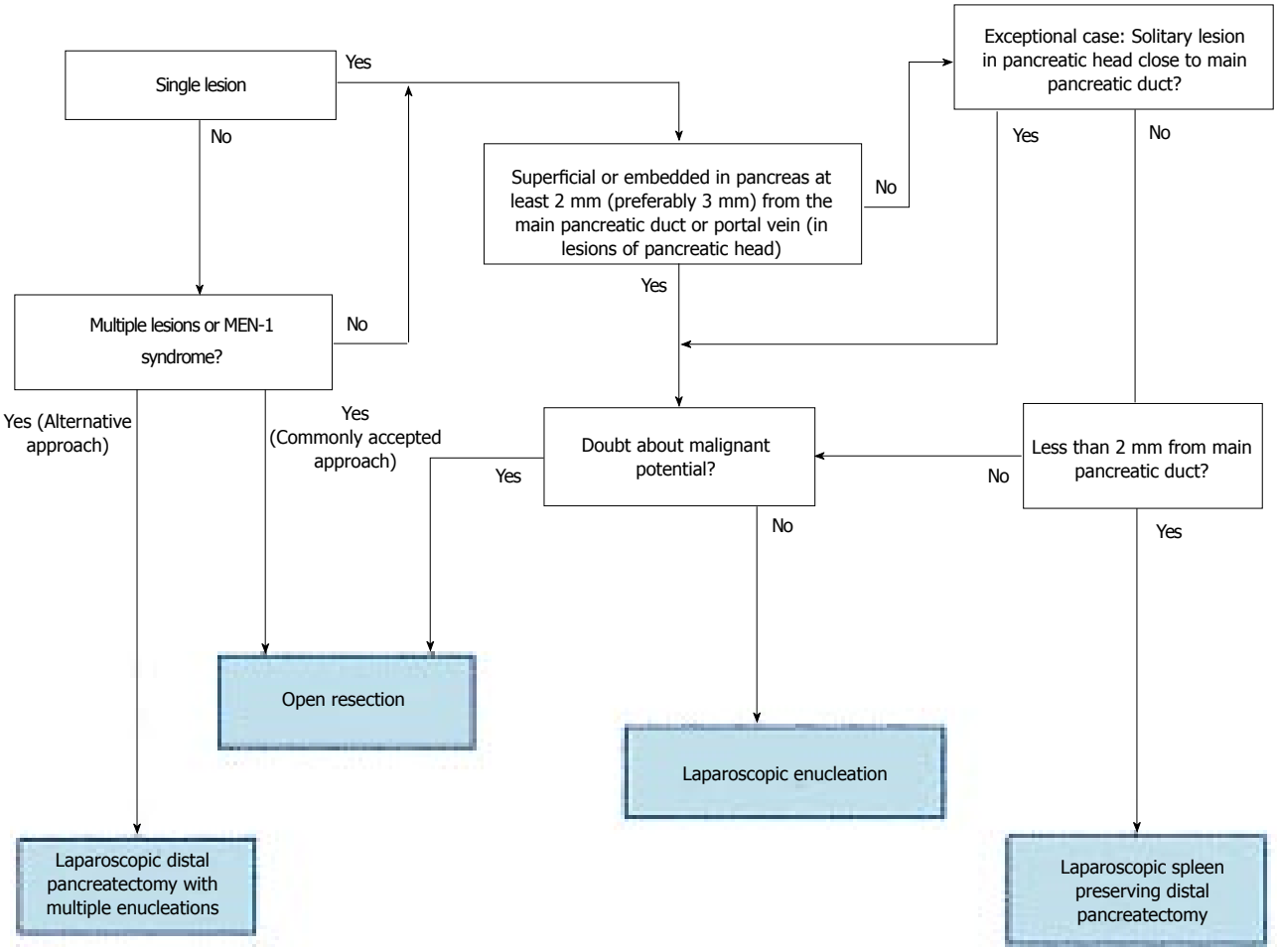

Figure 1 Flow chart demonstrating our surgical decision-making in pancreatic insulinomas. MEN-1: Multiple endocrine syndrome type 1.

surgical intervention be postponed in favor of repeat imaging and biochemical testing[92].

Once accurate intraoperative localization has been determined, surgical dissection is straightforward and performed with hook electrocautery and/or ultrasonic dissection. Generally, this is greatly helped by the placement of a traction suture through the insulinoma, which then can be exteriorized using an Endo Close. For lesions embedded in the pancreatic parenchyma but amenable to enucleation (Figure 1), the shortest route is chosen for dissection in order to minimize surgical trauma to the normal pancreatic parenchyma. As previously described, the LIOUS-guided placement of a fine needle in the center of the insulinoma greatly facilitates this dissection, which may be further aided by the placement of additional traction sutures to progressively open the pancreatotomy. Again, when the dome of the insulinoma becomes apparent, a further traction suture may be placed to improve the ease of enucleation.

For lesions in the body/tail of the pancreas that are not amendable to enucleation, the procedure of choice is spleen-preserving distal pancreatectomy. Careful dissection is necessary to avoid bleeding, particularly in the groove of the pancreas in which the pancreatic vein lies. In the event of inadvertent injury to the splenic vessels, if the left gastroepiploic and short gastric vessels remain intact, splenectomy can be avoided in favor of spleen-preserving distal pancreatectomy without splenic vessel preservation. However, where the left gastroepiploic and the short gastric vessels are not preserved, splenectomy is mandated. Division of the pancreas is usually carried out with an endoscopic linear stapler, combined with either oversewing the entire staple line or selectively oversewing the main pancreatic duct.

LAPAROSCOPIC SURGICAL OUTCOMES IN INSULINOMA MANAGEMENT

Due to the rarity of insulinomas and the retrospective nature of published series, it is difficult to extract robust data on the outcomes of laparoscopic insulinoma resection. Furthermore, these results have often been grouped with other pancreatic NETs and/or pancreatic tumors (*e.g.*, cystadenoma) making it impossible to separate insulinoma specific outcome data[9,17,85,89,93]. This is likely to be as a result of the small number of cases reported in early series and from the collective approach to tumor categorization later employed by major governing bodies and reflected in

published guidelines[8,35-37]. Whilst this classification is taxonomically accurate, it produces difficulties when studying insulinoma-specific outcomes, as insulinomas exhibit very distinct characteristics to other PETs and non-endocrine pancreatic tumors. Fortunately, however, the intriguing nature of these tumors has resulted in a number of laparoscopic case series specific to insulinomas[7,12-16,19-23,28,32], as well as those in the context of other PETs[26] and those comparing open and laparoscopic cases[18,24,25,27,29-31]. Furthermore, a recent meta-analysis comparing safety outcomes between laparoscopic and open approaches has been published[94].

The majority of published series[14,15,18-22,24-32] report established preoperative localization in > 90% of patients, with very few exceptions[12,16]. This highlights that preoperative localization has now become common practice, rather than the sole reliance on intraoperative LIOUS. Furthermore, this practice has increased the intraoperative accuracy of LIOUS to almost 100%, as well as almost eliminating inadequate localization as a cause for open conversion in the majority of cases[14,15,20-22,26,28,32]. Conversely, it is also notable that series reporting low preoperative localization rates[12,16] or limited use of LIOUS[19] also often describe inadequate localization as a common reason for conversion.

Median operative time is between 2 and 3.5 h, and varies significantly in published series[12,14-16,19-22,26,28,32]. However, these figures may be somewhat misleading due to small patient numbers and significant outliers. For example, in our own experience, operating time demonstrates a broad range from 25 to 420 min, with a median of 120 min[32]. Furthermore, although comparative studies demonstrate, as expected, that laparoscopic procedures take longer than their open counterparts[18,24,31] and that enucleation may be performed in a shorter time than distal pancreatectomy[16,19,20,28], this was not evident when pooled operative time was examined in the aforementioned meta-analysis[95].

Estimated median blood loss during laparoscopic insulinoma resection is limited and varies between 50 and 300 mL. Notably, however, there was no reported requirement for blood transfusion[12,15,28,32], and laparoscopic procedures resulted in significantly reduced blood loss when compared to open procedures[18,25,29,30,95]. Again, however, it is important to consider these results in the context of small sample numbers.

Laparoscopic treatment of insulinomas is safe and accompanied by minimal mortality in almost all published series[12,14-16,19-22,26,28,32]. Morbidity, on the other hand, may be high, and is reported to vary between 15% and 77%[12,14-16,18-22,24-32]. The most common complication is pancreatic fistula[95], however these are usually simple to manage and commonly resolve spontaneously within 2-3 wk. Nonetheless, in rare cases, specific treatment, drainage, or reoperation may be required. Importantly, the aforementioned recent meta-analysis has highlighted that laparoscopic insulinoma resection is not associated with a higher rate of fistula formation compared to open surgery[94]. Surgical precautions to avoid fistula formation first and foremost require respect for the minimum distance between the insulinoma and main pancreatic duct. Secondly, it is paramount to limit tissue damage by avoiding unnecessary dissection and keeping electrocautery heat production to a minimum. Oversewing the transection line after distal pancreatectomy and suture closure, or fibrin glue application to the site of enucleation, may also reduce fistulation, however in no cases do these measures counterbalance lacerations in the pancreatic duct, extensive destruction of the parenchyma, or inappropriately applied staples.

The length of in-hospital stay after laparoscopic insulinoma resection is difficult to determine, due to the inherent differences in institutional protocols and because patients from far away can be referred to a tertiary center. Indeed, uncomplicated laparoscopic resection required a hospital stay of one to two days in some studies[16,22,32], while patients remained hospitalized for 5-7 d in others[18,21]. However, it is notable that laparoscopic procedures are associated with a significantly shorter overall hospital stay than open procedures (without significant heterogeneity) when pooled data from directly comparative studies are meta-analyzed[94].

Importantly, laparoscopic insulinoma resection is associated with good long-term outcomes. In fact, whilst some series report long-term normoglycemia to be maintained in at least 95% of cases[24,25,30,31], others demonstrate a long-term cure rate of 100%[12,14,19-22,26,28,32].

CONCLUSION

Insulinomas are rare pancreatic neuroendocrine tumors that may be definitively cured with surgical resection. A dedicated multidisciplinary assessment is paramount prior to surgical intervention and should include thorough clinical and biochemical diagnosis. Localization of the tumor should be achieved through an array of non-invasive (US, CT, and MRI) and inevitably some invasive (EUS and AVSV) investigations, and the subsequent decision to undertake laparoscopic resection should only be made by an experienced laparoscopic pancreatic surgeon. For solitary benign insulinomas, laparoscopic enucleation suffices irrespective of location, provided the lesion lies a safe distance from the pancreatic duct and associated large vessels. Where these conditions are not met, laparoscopic distal pancreatectomy is advisable for lesions of the body/tail of the pancreas. This decision should be aided by LIOUS, which forms an indispensable part of any laparoscopic resection. In this way, localization of the lesion can be confirmed intraoperatively, and the tumor can be clearly delineated from adjacent structures. From a technical perspective, it is paramount to ensure ample access to the operating field in order to minimize damage to the

normal parenchyma, pancreatic duct, and associated vessels. Although no prospective randomized trials exist comparing laparoscopic and open approaches to insulinoma resection, case series, comparative series, and a recent meta-analysis supports the notion that laparoscopic resection is equally as safe and effective as an open approach. Moreover, laparoscopic intervention may not only improve cosmesis, but also reduce post-operative stay. Further large series and comparative studies are required in order to establish the true potential for laparoscopic resection and to continue to advance both diagnostic and technical aspects of surgical insulinoma management.

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P- Reviewer: Kleeff J **S- Editor**: Ma YJ **L- Editor**: Rutherford A **E- Editor**: Wu HL

World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v7.i16.1208

World J Gastrointest Endosc 2015 November 10; 7(16): 1208-1215
ISSN 1948-5190 (online)

Cutting edge of endoscopic full-thickness resection for gastric tumor

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Conflict-of-interest statement: There is no conflict of interest regarding this article.

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Received: May 2, 2015
Peer-review started: May 9, 2015
First decision: July 17, 2015
Revised: August 18, 2015
Accepted: September 29, 2015
Article in press: September 30, 2015
Published online: November 10, 2015

Abstract

Recently, several studies have reported local full-thickness resection techniques using flexible endoscopy for gastric tumors, such as gastrointestinal stromal tumors, gastric carcinoid tumors, and early gastric cancer (EGC). These techniques have the advantage of allowing precise resection lines to be determined using intraluminal endoscopy. Thus, it is possible to minimize the resection area and subsequent deformity. Some of these methods include: (1) classical laparoscopic and endoscopic cooperative surgery (LECS); (2) inverted LECS; (3) combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique; and (4) non-exposed endoscopic wall-inversion surgery. Furthermore, a recent prospective multicenter trial of the sentinel node navigation surgery (SNNS) for EGC has shown acceptable results in terms of sentinel node detection rate and the accuracy of nodal metastasis. Endoscopic full-thickness resection with SNNS is expected to become a treatment option that bridges the gap between endoscopic submucosal dissection and standard surgery for EGC. In the future, the indications for these procedures for gastric tumors could be expanded.

Key words: Gastrointestinal stromal tumor; Early gastric cancer; Full-thickness resection; Laparoscopic and endoscopic cooperative surgery; Sentinel node navigation surgery

Core tip: Several studies have investigated local full-thickness resection techniques using flexible endoscopy for gastric tumors. These techniques are advantageous because a resection line can be determined more precisely using intraluminal endoscopy. Thus, it is possible to minimize the resection area and subsequent deformity, and better secure the surgical margins. In the near future, endoscopic full-thickness resection is expected to become a treatment option that bridges the gap between endoscopic submucosal dissection and standard surgery for gastric tumors.

Maehata T, Goto O, Takeuchi H, Kitagawa Y, Yahagi N. Cutting edge of endoscopic full-thickness resection for gastric tumor. *World J Gastrointest Endosc* 2015; 7(16): 1208-1215 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i16/1208.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i16.1208

INTRODUCTION

Laparoscopic wedge resection (LWR) has been accepted as a minimally invasive surgical technique for gastric tumors such as gastrointestinal stromal tumor (GIST)[1], early gastric cancer (EGC) without the risk of lymph node metastasis[2,3]. However, patients frequently experience severe deformity and gastric stasis as a result of excessive gastric resection. This occurs because identification of the proper incision line is complicated. From this point of view, several studies have reported that endoscopic submucosal dissection (ESD) and endoscopic submucosal enucleation are feasible for the resection of gastric tumors in the muscularis propria[4,5]. Furthermore, ESD has performed for the diagnosis of suspected submucosal EGC. However, some tumors are resected incompletely because they have positive surgical margins; thus, the risk of recurrence exists[6]. Therefore, a full-thickness resection would be more appropriate to secure the surgical margins. This suggests the need for function-preserving or reductive surgeries that bridge the gap between ESD and standard surgery. Recently, some publications have described local resection techniques using peroral flexible endoscopy. Endoscopic full-thickness resection (EFTR) of the gastric wall using a snaring technique has been applied for gastric subepithelial tumors[7-9]. In addition, Hiki *et al*[10] reported that classical laparoscopic and endoscopic cooperative surgery (classical LECS) provides an alternative gastric wedge resection. However, these procedures (EFTR and classical LECS) have inherent risks of peritoneal infection and cancer cell seeding because intentional perforation of the gastric lumen is required during the procedures. As a result, some procedures [*e.g.,* inverted LECS[11], a combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET)[12] and non-exposed endoscopic wall-inversion surgery (NEWS)[13]] have been developed to mitigate these risks. These techniques are advantageous because a more precise resection area can be determined using intraluminal endoscopy, thus minimizing the resection area. This will result in less deformity and better surgical margins.

In the current review, recent developments related to full-thickness resection using flexible endoscopy for gastric tumors are presented and discussed.

EFTR WITHOUT LAPAROSCOPIC ASSISTANCE

Endoscopic full-thickness resection of the gastric wall using a snaring technique has been applied for gastric subepithelial tumors[7]. Nevertheless, this technique has limitations from the perspective of the localization and size of the lesion. Ikeda *et al*[14]. reported EFTR using an ESD technique with a sewing method and have shown that it is possible to resect larger specimens. In addition, Zhou *et al*[8] and Feng *et al*[15] reported successful resection of gastric subepithelial tumors originating from the muscularis propria layer[8,15] (Table 1).

Table 1 Representative publications reporting endoscopic full-thickness resection for upper gastrointestinal tumors

Ref.	*n*	Mean operation time (min)	Mean tumor diameter (mm)	Complete resection rate (%)	Complication rate (%)
Zhou *et al*[8]	26	105	28	100	0
Feng *et al*[15]	48	60	16	100	0
Huang *et al*[16]	35	90	28	100	0
Schmidt *et al*[17]	31	60	20.5	90.3	9.7 (perforation)
Guo *et al*[9]	23	40.5	12.1	100	0

After the periphery of the lesion is marked endoscopically, a solution is injected into the submucosal layer circumferentially. A circumferential incision is then made to the depth of the muscularis propria around the lesion using ESD devices and techniques. Next, the serosal layer around the lesion is incised using ESD devices to create an intentional perforation. The tumor, including the surrounding muscularis propria and serosa, is subsequently removed using the snare. Finally, the gastric wall defect is closed with several metallic clips (Figure 1).

There are difficulties associated with these techniques. For example, it is unknown whether a large iatrogenic perforation can be successfully closed using the endoscopic technique. Guo *et al*[9] have reported the safety and feasibility of the over-the-scope clip system for the closure of gastric defects following EFTR. After all, EFTR is expected to prevent the severe complications can occur due to iatrogenic perforation. Although EFTR seems to be an effective and minimally invasive treatment for patients with gastric subepithelial tumors, it is necessary to demonstrate the efficacy and safety of EFTR in a large number of cases.

CLASSICAL LECS

Hiki *et al*[10] reported that the LECS technique provides an alternative gastric wedge resection for the removal of GISTs, and combines gastrointestinal endoscopy and laparoscopy. The advantage of this technique is that it avoids excessive resection of the gastric wall because a resection line can be determined more precisely using intraluminal endoscopy.

The periphery of the lesion is first marked endoscopically, and after a submucosal injection around the lesion, a circumferential incision is made using ESD devices and techniques. Then, an artificial perforation

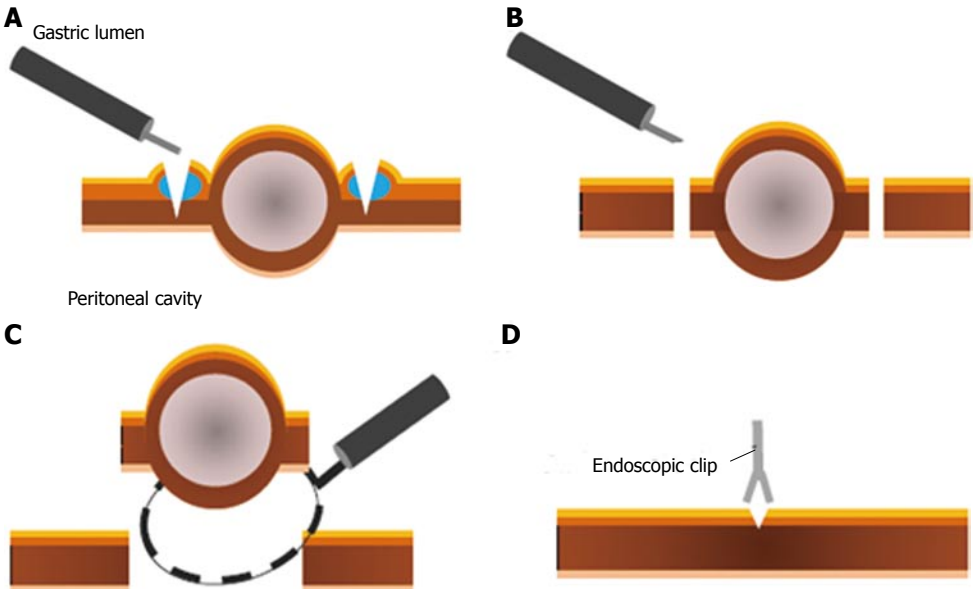

Figure 1 Illustration of the procedure for endoscopic full-thickness resection without laparoscopic assistance. A: A circumferential incision is made to the depth of the muscularis propria around the lesion using endoscopic submucosal dissection (ESD) devices and techniques; B: After intentional perforation, the serosal layer around the lesion is incised using ESD devices; C: The tumor, including the surrounding muscularis propria and serosa, is removed using the snare; D: The gastric wall defect is closed with several metallic clips.

is performed from the inside of the stomach and a seromuscular incision is performed, as much as possible, with laparoscopic assistance. Next, a laparoscopic incision of the remaining seromuscular layer is performed. Finally, the defect closure of the gastric wall is performed by laparoscopic linear staplers or a laparoscopic hand sewn suture technique[16,17] (Figure 2).

Some pilot studies have reported the feasibility of LECS for GISTs, and have presented favorable results[18-20]. This procedure is also feasible for lesions that cannot be treated with LWR[1,21] (*e.g.,* the esophagogastric junction)[22]. However, there is a major limitation associated with classical LECS. This technique requires opening the gastric wall, and the gastric lumen is opened to the abdominal cavity. As a result, gastric contents (*e.g.,* bacteria and tumor cells) flow into and contaminate the clean peritoneal cavity, increasing the risk of bacterial contamination and dissemination of peritoneal tumor cells.

INVERTED LECS

As described above, there are several drawbacks associated with classical LECS especially for gastric cancer. Therefore, a modified LECS procedure, referred to as inverted LECS, was developed to prevent the implanting of tumor cells[11].

The procedure, from placing the markings to performing the artificial perforation, is similar to the classical LECS. To prevent contact between the tumor and the visceral tissue, the gastric wall is pulled up circumferentially to the incision line as a crown using some stitches. Then, the seromuscular layer is dissected using ESD or laparoscopic devices around the incision line of the submucosal layer. The tumor is then resected into the abdominal cavity and the specimen is retrieved perorally. Finally, the gastric wall defect is closed by laparoscopic linear staplers.

This procedure was developed to prevent stomach contents from spilling into the clean abdominal cavity. However, since the gastric lumen is opened to the peritoneal cavity, there is still a risk of gastric content contamination. Furthermore, there is a risk of cancer recurrence caused by instrument contact.

CLEAN-NET

CLEAN-NET is another promising non-exposure method[12]. After mucosal markings are made endoscopically around the tumor, the mucosal layer is fixed to the seromuscular layer with four full-layer stay sutures, and a sub-mucosal cushion is created circumferentially using an endoscopic injection. The seromuscular layer is then dissected laparoscopically around the four stay sutures. Consequently, the full-layer specimen and the mucosal layer that surrounds it are lifted by the stay sutures. Finally, the specimen is resected using a linear stapler (Figure 3). The CLEAN-NET is useful as a non-exposure technique for full-thickness resection.

NEWS

NEWS was developed as a novel, full-thickness resection technique, without intentional perforation[13,23,24]. With this procedure, markings are made around the tumor on the mucosa while serosal markings are made laparoscopically. The serosal markings are made by pressing on the gastric wall, on the side opposite the mucosal markings. A sodium hyaluronate solution, that includes a small amount of indigo carmine dye, is

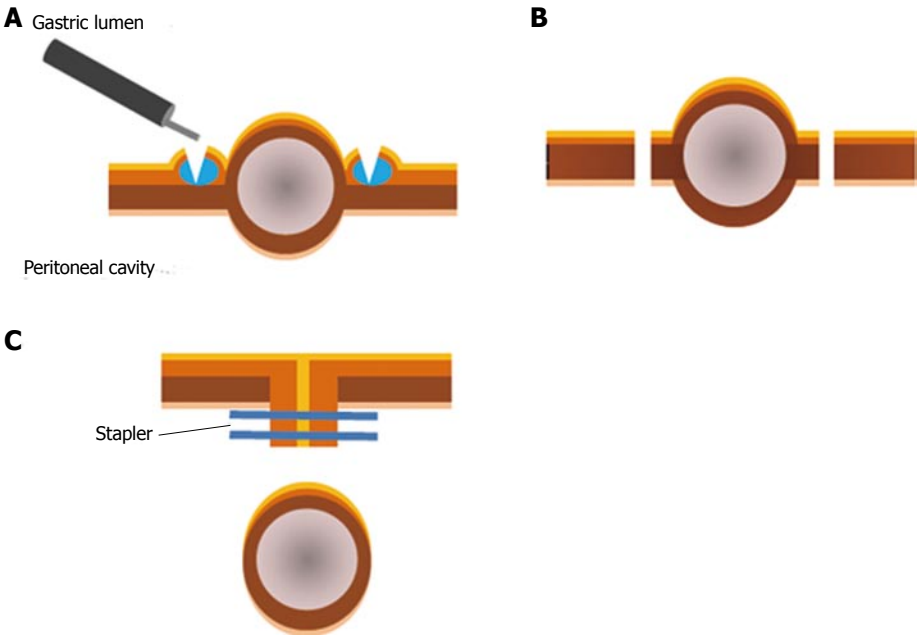

Figure 2 Illustration of the procedure for classical laparoscopic and endoscopic cooperative surgery. A: A circumferential incision is made using endoscopic submucosal dissection (ESD) devices and techniques; B: An artificial perforation is performed from the inside of the stomach and a seromuscular incision is performed along the incision line with laparoscopic assistance. A laparoscopic incision of the remaining seromuscular layer is performed; C: The defect closure of the gastric wall is performed by laparoscopic linear staplers.

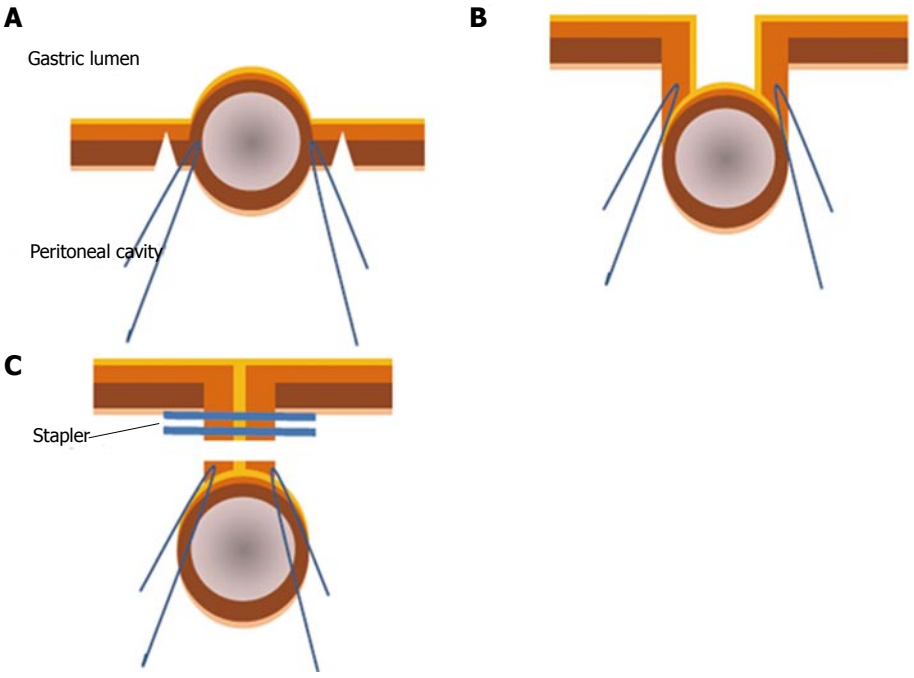

Figure 3 Illustration of the procedure for a combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique. A: Seromuscular layer is dissected using a laparoscopic electrocautery knife; B: Full-layer specimen is lifted by the stay sutures; C: Full-layer specimen is resected using a linear stapler.

endoscopically injected into the submucosal layer circumferentially. A circumferential seromuscular incision is performed laparoscopically around the serosal markings. After a flap is created by cutting the submucosa deeper toward the outside, the seromuscular layers are linearly sutured with the lesion inverted toward the inside of the stomach. Prior to the suturing, a laparoscopic surgical sponge is inserted as a spacer between the serosal layer of the inverted lesion and the suture layer. This is done to provide counter-traction to the mucosa and prevent cutting of the suture. Finally, the circumferential mucosal incision and the subsequent incision of the remnant submucosal tissue are made a few millimeters outside of the mucosal markings around the inverted

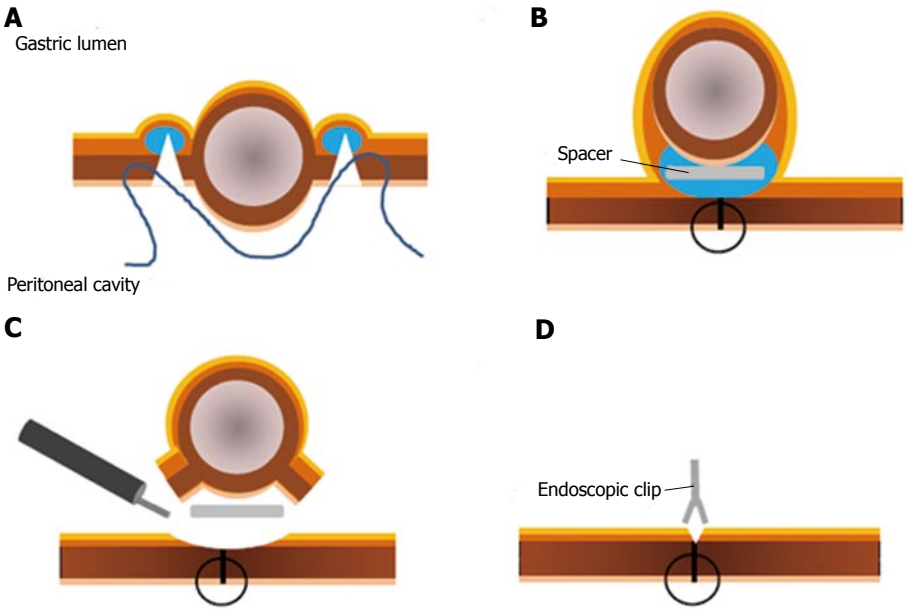

Figure 4 Illustration of the procedure for non-exposed endoscopic wall-inversion surgery. A: circumferential seromuscular incision is performed laparoscopically outside the serosal markings after endoscopic submucosal injection; B: seromuscular layers are linearly sutured with the lesion inverted toward the inside of the stomach. A surgical sponge as a spacer is inserted between the serosal layer of the inverted lesion and the suture layer; C: Circumferential mucosal incision and the remnant submucosal incisions are made using ESD devices and techniques; D: Defect is closed with several metallic clips. ESD: Endoscopic submucosal dissection.

Table 2 Comparison of each procedure

	Instruments	Indication for EGC	Retrieval route	Intentional gastric perforation	Advantage	Limitation
EFTR	Endoscopy only	No	Transroral	Required	Simple methods using intraluminal endoscopy only	Risk of contamination, endoscopic skills required
Classical LECS	Endoscopy = laparoscopy	No	Transabdominal	Required	Accurate to determine the resection line, laparoscopic assistance	Risk of contamination Risk of contact to tumor surface
Inverted LECS	Endoscopy = laparoscopy	Indefinite	Transoral	Required	Accurate to determine the resection line, laparoscopic assistance	Risk of contact to cancer surface, tumor size
CLEAN-NET	Endoscopy < laparoscopy	Yes	Transabdominal	Not required	No transluminal communication	Excessive resection of the mucosa, difficult to determine the resection line
NEWS	Endoscopy = laparoscopy	Yes	Transoral	Not required	Accurate to determine the resection line, laparoscopic assistance, no transluminal communication	Tumor size, experience required, time-consuming

EFTR: Endoscopic full-thickness resection; LECS: Laparoscopic and endoscopic cooperative surgery; CLEAN-NET: Combination of laparoscopic and endoscopic approaches to neoplasia with a nonexposure technique; NEWS: Nonexposed endoscopic wall-inversion surgery; EGC: Early gastric cancer.

lesion using ESD techniques. The resected specimen and the spacer are retrieved perorally and the mucosal edges are closed with several endoscopic clips (Figures 4 and 5).

The NEWS technique has been developed as a full-thickness resection method without transluminal communication and is similar to the CLEAN-NET. It is a non-exposure technique. However, there are several differences between the two procedures. First, the seromuscular hand suturing and circumferential mucosal incision can be skipped in CLEAN-NET, which results in a shorter procedural time than that for NEWS. Secondly, the incision line is determined from the serosal side; as a result, proper mucosal incision could be complicated to determine resulting in a relatively large resection area. However, due to the lower risk of peritoneal cavity infection and the seeding of tumor cells, NEWS has already been clinically introduced for gastric subepithelial tumors as well as gastric cancers at selected hospitals[24]. This procedure is technically feasible and, theoretically, safe.

APPLICATION TO GASTRIC CANCER

ESD is widely accepted as a minimally invasive curative treatment for early stage gastrointestinal cancer[25-27]

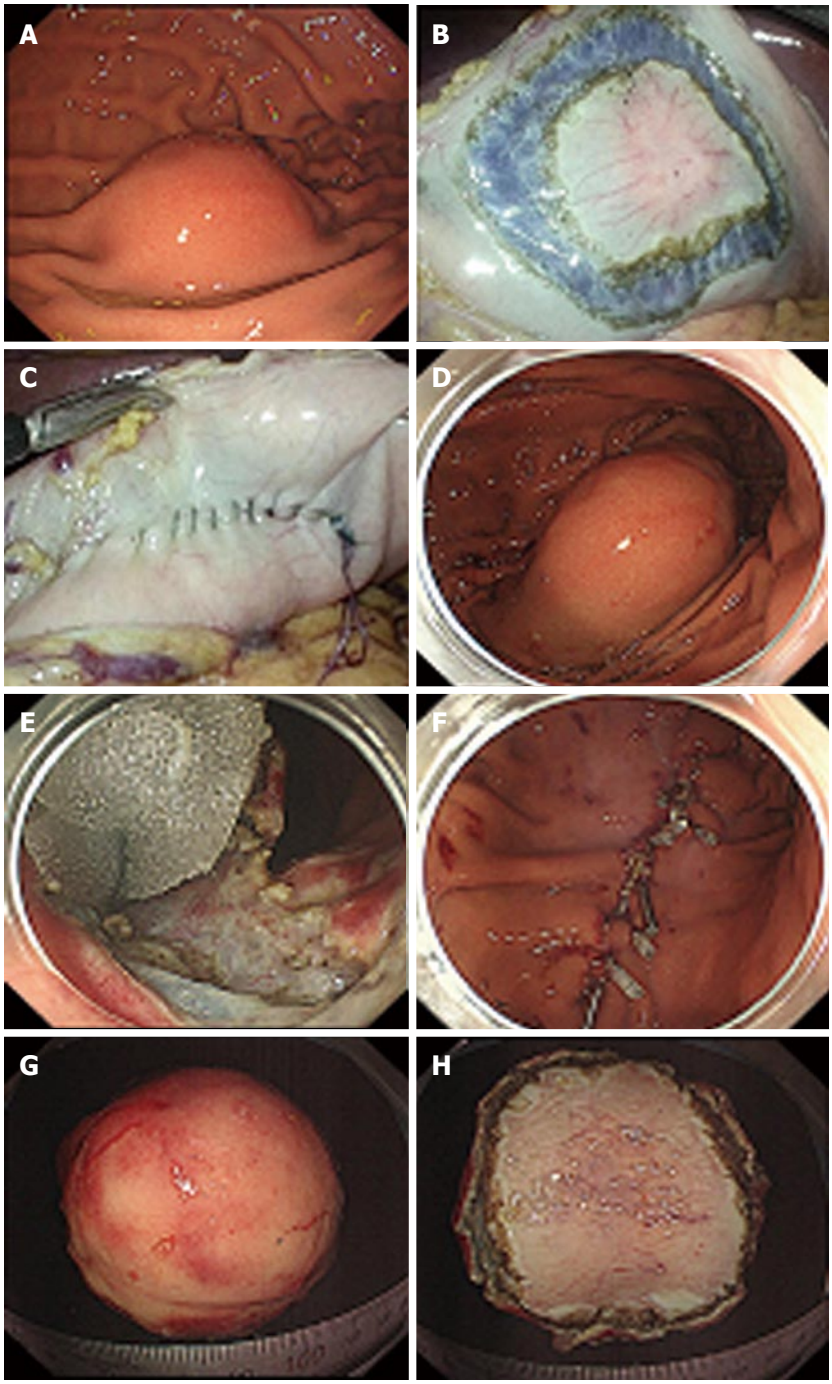

Figure 5 Procedures of non-exposed endoscopic wall-inversion surgery. A: Protruding submucosal lesion is seen at the greater curvature of the middle gastric body; B: Circumferential seromuscular incision is made outside the serosal markings after endoscopic submucosal injection; C: Lesion is inverted with a surgical sponge used as a spacer; D: Massive protrusion of the inverted tissue; E: Surgical sponge as a spacer and a suturing line during endoscopic mucosal incision; F: Mucosal clipping after the resection; G: Resected specimen: Mucosal side; H: Resected specimen: Serosal side.

that enables the preservation of function and maintains the patients' quality of life. However, ESD still requires a skilled and experienced surgeon for large lesions located at the greater curvature of the upper gastric body and fornix, and for lesions with severe ulcerative changes. In these situations, ESD has a higher incidence rate of complications such as perforation and bleeding. Furthermore, ESD may be associated with longer operation times[28]; therefore, LECS may be an alternative treatment option especially for lesions difficult to resect by ESD[11].

In contrast, EGC with possible lymph node metastasis should be treated with gastrectomy with wide resection of the regional lymph nodes because the presence and site of lymph node metastasis are unclear. Approximately 10%-20% of patients with EGC, especially those with deep submucosal invasion, have lymph node metastasis[29]. In other words, the incidence of node-negative gastric cancer accounts for at least 80% of all EGCs and therefore, most of the patients

with EGC have undergone an unnecessarily wide gastrectomy with lymphadenectomy. If node-negative gastric cancer is confirmed, local resection (*e.g.,* full-thickness resection) might be the best option.

Sentinel node navigation surgery (SNNS) is expected to be able to diagnose lymph node metastasis intraoperatively, and this could result in minimally invasive and function-preserving gastrectomy with selective lymphadenectomy[30]. Theoretically, the sentinel node (SN) is the first lymph node or group of nodes capable of draining cancer cells and is considered the first site of metastasis along the route of lymphatic drainage. However, it remains controversial whether the SN concept is feasible in EGC. In response, the Japan Society of Sentinel Node Navigation Surgery conducted a prospective multicenter trial to confirm the SN concept. It reported that patients with clinical T1N0 ($\leqslant$ 4 cm) gastric cancer can undergo sentinel node mapping and biopsy without limitation of tumor location[31]. Currently, surgical treatment of cT1N0 gastric cancer, of $\leqslant$ 4 cm, can be individualized on the basis of the SN concept. Furthermore, some studies have reported that in the absence of metastasis to the SNs, a surgery that combines ESD and SNNS[32] may be adequate. However, ESD cannot guarantee secure vertical margins or accurate preoperative diagnosis of tumor invasion. Hence, for submucosal EGC, a full-thickness resection would be more appropriate to secure the vertical margins and identify intramural cancer cells. Abe *et al*[33] first reported EFTR for EGC under laparoscopic guidance, combined with lymphadenectomy. Similarly, Hur *et al*[34] reported laparoscopy-assisted endoscopic full-thickness resection with sentinel node navigation surgery. However, as previously mentioned, these procedures require opening of the gastric wall, thus opening the gastric lumen to the peritoneal cavity. As a result, cancer cells may spill into the peritoneal cavity. Consequently, peritoneal dissemination of cancer cells as well as bacterial contamination during the procedure might occur. Therefore, it is desirable to use a non-exposure technique to prevent bacterial contamination and peritoneal dissemination of tumor cells. Hence, full-thickness resection such as NEWS and CLEAN-NET, in combination with sentinel node basin dissection, may be an ideal treatment that bridges the gap between ESD and standard surgery with respect to the invasiveness of the treatment[35,36] (Table 2).

CONCLUSION

The endoscopic full-thickness resection for upper gastrointestinal subepithelial tumors and EGC has been developed as a novel and minimally invasive surgery. In particular, NEWS with sentinel node basin dissection may be an ideal, minimally invasive, and function-preserving gastrectomy with selective lymphadenectomy for EGC. However, reports of these procedures are limited to case reports. Pilot studies need to be performed, and the long-term efficacy of these procedures need to be clarified. Therefore, further studies such as prospective clinical trials with a large number of patients are required to show the feasibility of these treatment methods, especially with regard to safe and complete resection. In the near future, the concept of endoscopic full-thickness resection is expected to become a treatment option that bridges the gap between ESD and standard surgery for subepithelial tumors and EGC.

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P- Reviewer: Habic A, Tan KY **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Wu HL

World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v7.i16.1216

World J Gastrointest Endosc 2015 November 10; 7(16): 1216-1221
ISSN 1948-5190 (online)

MINIREVIEWS

Emerging role of narrow band imaging in duodenum

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Author contributions: Dutta AK was involved in the concept of this study, search and review of literature and preparation of manuscript; Chacko A was involved in the concept of this study, search and review of literature, preparation of manuscript and critical appraisal.

Conflict-of-interest statement: None.

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Received: April 26, 2015
Peer-review started: April 27, 2015
First decision: July 29, 2015
Revised: August 20, 2015
Accepted: September 29, 2015
Article in press: September 30, 2015
Published online: November 10, 2015

Abstract

Endoscopy using magnification narrow band imaging (mNBI) allows detailed assessment of mucosal surface and vascular pattern. This may help in better identification and prediction of the nature of the lesion. The role of this technology in duodenum is still evolving. Studies have shown that mNBI has high accuracy in predicting villous atrophy in the duodenum. Limited data suggests that this technique can provide additional information on duodenal polyps, nodules and ampullary tumour which can help guide their management. In this paper we describe the technique for duodenal assessment using NBI and review the existing literature evaluating its role in diagnosis of various duodenal pathologies.

Key words: Narrow band imaging; Duodenum; Villous atrophy; Correlation; Polyp

Core tip: Narrow band imaging endoscopy with magnification (mNBI) enables detailed assessment of duodenal villous morphology. This advantage over white light endoscopy has potential clinical benefits. There is good evidence to show that villous morphology on mNBI correlates well with histopathology. Hence villous atrophy can be diagnosed with good accuracy during mNBI and targeted biopsy can be obtained from abnormal appearing areas. Preliminary data suggest that this technology may also aid in assessment of neoplastic lesions in duodenum.

Dutta AK, Chacko A. Emerging role of narrow band imaging in duodenum. *World J Gastrointest Endosc* 2015; 7(16): 1216-1221 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i16/1216.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i16.1216

INTRODUCTION

Endoscopic examination of mucosal surface of the gut

is an integral part of evaluation of patients presenting with gastrointestinal symptoms. The quest for obtaining additional information from direct visualisation of mucosa has led to several advances in imaging techniques. These include narrow band imaging (NBI, Olympus), optical coherence tomography, Fujinon intelligent chromo endoscopy (FICE, Fujinon) system, I-Scan (Pentax) and confocal laser endomicroscopy[1,2]. NBI, as the name suggests, uses a narrow wavelength of light in the blue and green region instead of the entire visible spectrum which gives a dark appearance to blood vessels[3]. This in combination with magnification endoscopy enables characterisation of microsurface and microvascularity of mucosa and identifies abnormalities in different part of digestive tract[4]. Magnification NBI (mNBI) has been shown to play a useful role in evaluation of duodenal villus abnormalities seen in diseases associated with malabsorption as well as in assessment of polyps and tumours of the duodenum[5-9]. A search of published literature reveals that among the more than one thousand publications relating to NBI, less than thirty have focussed on duodenum. However, the number of publications on the role of NBI in duodenum has risen in recent years as its value in assessment of duodenal disorders is recognised. In this paper we have reviewed the available literature on use of NBI in evaluating the duodenum.

ASSESSMENT OF DUODENUM USING MAGNIFICATION NBI

In our experience we have found the following scheme of examination adequate for comprehensive assessment of duodenum[5]. The examination should begin with an initial assessment of duodenal mucosa with conventional white light endoscopy. Any debris on the mucosal surface should be cleared. In most situations examination is performed upto second part of duodenum. The characteristics of duodenal mucosal folds including atrophy, scalloping and nodularity should be assessed and presence of any surface lesion like polyp, nodule or tumour determined. Duodenal ampulla should also be examined although a forward viewing endoscope makes this slightly difficult.

Next the endoscope should be switched to magnification NBI mode. mNBI examination is undertaken in two steps. In the first step, the morphology of duodenal villi in second part of duodenum is evaluated. The magnification and contrast offered by mNBI enables clear visualisation of duodenal villi. Bile appears pink and blood appears black on NBI. Due to use of narrow band of light, the images on NBI are not very bright but as the duodenal lumen is narrower than stomach, this is less of a problem. This limitation is also being overcome by newer endoscope processors. Some centers have reported the use of water instillation in lumen to improve the visualisation of villi and we have also found it useful in our experience[10]. This technique can be used in selected situations where the assessment is otherwise difficult. Several studies have reported excellent performance of mNBI in assessing villous morphology[5,7,11,12]. In normal subjects the villi have greater length than breadth which gives them a leaf or finger like appearance (Figure 1)[5,7]. Atrophy of villi alters this ratio and makes them appear shortened or convoluted or stubbed or even absent in patients with total villous atrophy (Figure 1)[5,7]. The next step involves assessment of any protruding mucosal lesion like polyp, nodule and tumour. The microsurface and microvascular pattern with special attention to irregularity should be determined. There are only few reports on mNBI characteristics of various duodenal mucosal lesions which makes confident correlation of surface/vessel pattern with histology of lesion difficult but presence of irregularity of pattern generally signifies a high grade lesion[6,13].

NBI IN ASSESSMENT OF DUODENAL VILLOUS MORPHOLOGY

Emerging data from several studies have shown that mNBI has a very good correlation with histology in assessment of duodenal villous atrophy[5,7,10,11]. This has few potential benefits: (1) in situations where duodenal biopsy is taken only to evaluate for villous atrophy, normal villi on mNBI may preclude biopsy and save procedure cost and time. The same is not the case with white light endoscopy where mucosal fold abnormalities like atrophy, scalloping and nodularity have a poor sensitivity when compared to histology[14]. Therefore all patients undergoing white light endoscopy for suspected celiac disease will require duodenal mucosal biopsy irrespective of endoscopic appearance; (2) in subjects with patchy villous atrophy, mNBI may help target the biopsy to regions with atrophy and improve the diagnostic yield[15]; (3) ease of the procedure which does not require spray of dye to improve contrast; and (4) ease of identification of villous morphology as evidenced by most studies reporting very good interobserver agreement[5,10,11].

While celiac disease is the dominant cause of villous atrophy in developed nations, other diseases like tropical sprue associated with villous atrophy and malabsorption are seen in tropical countries. It is therefore not surprising that about half of the studies on the role of NBI in duodenal villous assessment are from India[5,11,16]. We have recently published a prospective study from our center in India on a hundred patients with suspected malabsorption and evaluated the ability of mNBI to assess duodenal villi[5]. Celiac disease was present in seven patients with villous atrophy while conditions like tropical sprue, infections and Crohn's disease were present in eight patients and the cause of atrophy was unknown in one. Overall, villous atrophy was present in 16 patients and mNBI had a sensitivity of 87.5% and specificity of 95.2% in detecting this

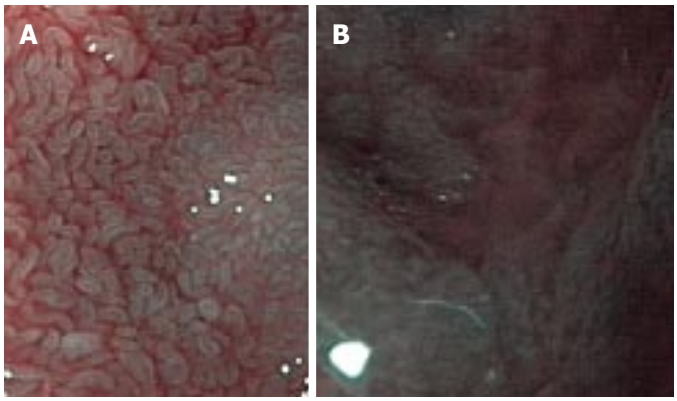

Figure 1 Appearance of normal duodenal villi on magnification narrow band imaging (A) and severe villous atrophy on magnification narrow band imaging (B).

by one of the two examiners. The sensitivity and specificity were 81.3% and 92.9% respectively for the second assessor with high interobserver agreement (kappa 0.87). We therefore found mNBI examination of duodenum to be a promising modality in predicting villous atrophy. Subsequently another study from India on 105 subjects with suspected malabsorption (villous atrophy in 58 on histology) showed that mNBI had a sensitivity of 95% and specificity of 90.2% (interobserver kappa 0.89)[11] in predicting villous atrophy. A third study from north India, published only in abstract form also assessed correlation of mNBI with histology for detection of duodenal villous atrophy in 80 patients and reported a sensitivity of 87.03% and specificity of 84.61%[16].

A couple of studies have been published from Italy comparing standard white light endoscopy and mNBI in patients with celiac disease. De Luca *et al*[12] prospectively studied 44 patients and found that mNBI was able to identify villous atrophy in all 17 patients with confirmed celiac disease (100% sensitivity) while standard white light endoscopy showed abnormalities in only 7 of them (41% sensitivity). All cases of partial villous atrophy were identified on mNBI while standard endoscopy was normal in all of them. The mean additional time required for NBI examination was four and half minutes. Another study from Italy on pediatric patients with suspected celiac disease investigated the use of NBI with water immersion technique and obtained single NBI guided biopsy instead of conventional multiple biopsies[10]. NBI guided single biopsy had a sensitivity of 87.5% in diagnosing celiac disease, suggesting that this technique has the potential to reduce the need for multiple biopsies. An earlier study from Australia assessing villous atrophy using mNBI showed mNBI to have a sensitivity of 93.3% and specificity of 97.8% in patients with suspected celiac disease[7].

We performed a meta-analysis on diagnostic accuracy of mNBI to detect duodenal villous atrophy with histology as a reference standard. The above six studies were screened for inclusion[5,7,10-12,16]. The study by Sinha *et al*[16] was excluded as only abstract was published and more data was required for meta-analysis[16]. The study by Singh *et al*[7], included 10 videos from 3 patients with celiac disease which implied multiple assessments for same patient. This significantly differed from other study designs and hence was not appropriate for pooling of data with other studies. Valitutti and colleagues studied pediatric patients only and for this reason their data was also not included. Finally we included three studies in the meta analysis[5,11,12]. The analysis was performed using the software Meta-DiSc[17]. The pooled sensitivity (Figure 2) was 0.96 (95%CI: 0.89-0.99) and the pooled specificity (Figure 3) was 0.94 (95%CI: 0.89-0.97). These impressive data further strengthen the evidence in favour of mNBI in assessing duodenal villous atrophy.

Atrophy of villi may be patchy in some patients with celiac disease and this may be missed on random mucosal biopsy. By identifying atrophic villi based on morphology, mNBI can overcome this limitation and help obtain targeted biopsies. Few case series and reports have demonstrated the capability of mNBI to detect patchy villous atrophy[15,18,19]. This perhaps is one area where mNBI can play an important role in avoiding false negative biopsies but more data is required. It is clear from the above studies that mNBI can play a useful role in aiding the diagnostic evaluation of celiac disease and other malabsorption syndromes.

NBI IN ASSESSING PROTRUDING DUODENAL MUCOSAL LESIONS

Unlike gastric, colonic and esophageal lesions, mNBI characteristics of duodenal mucosal lesions like polyps and tumours have been less well studied. Most of the available studies are from Japan and except for a few, these are in the form of case reports[6,13,20,21]. In contrast to assessment of villous morphology where surface characteristic is the focus of attention, both surface and vascular characteristics are important in assessing neoplastic lesions. Abnormal angiogenesis is a feature of neoplasia and alteration in vascular pattern is a reflection of this.

Kikuchi *et al*[6] retrospectively analysed the surface/vascular pattern of duodenal non-ampullary tumours on mNBI and identified characteristics suggestive of high grade dysplasia and invasive tumour. The surface patterns were classified as monotype or mixed type

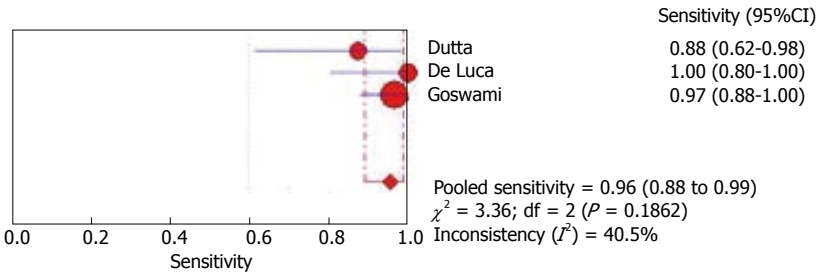

Figure 2 Pooled sensitivity of narrow band imaging in detecting duodenal villous atrophy.

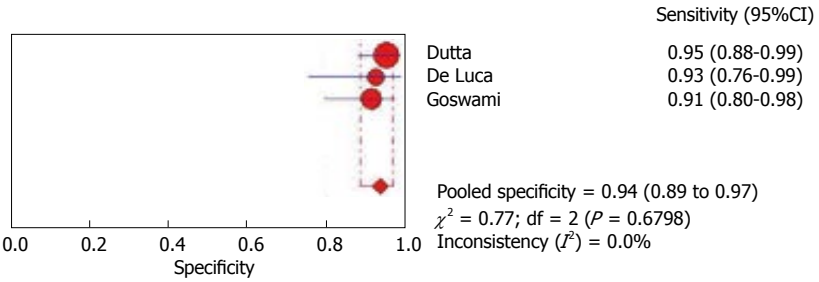

Figure 3 Pooled specificity of narrow narrow band imaging in detecting duodenal villous atrophy.

when they had single or multiple surface patterns respectively. Vascular patterns were classified as network, intrastructural vessel, unclassified or absent. They found that presence of mixed type surface pattern was suggestive of high grade dysplasia or invasive lesion in all 23 cases. In the remaining 23 lesions which had monotype surface, presence of unclassified vascular pattern and intrastructural vessels were associated with advanced lesions. Other vascular patterns were also seen with advanced lesions. The study therefore suggested that a mixed surface pattern was strongly suggestive of advanced lesion but confident diagnosis of low grade dysplastic or non-neoplastic lesion based on surface/vessel characteristics was not accurate. Another study assessed 65 duodenal sites in 36 subjects which were normal or had polyps[22]. Duodenal polyp with dysplasia was seen at 24 sites and mNBI had sensitivity of 83% and specificity of 78% in detecting dysplasia. They also examined the mucosa using probe based confocal endomicroscopy which was found to be better than mNBI. These data suggest that mNBI may help the endoscopist avoid biopsy (which makes subsequent resection difficult) and proceed directly to EMR in suspected dysplastic lesions.

A couple of case reports have described the appearance of follicular lymphoma in duodenum on mNBI. Chowdhury *et al*[20] from Morioka, Japan reported coiled, elongated microvascular pattern in two patients with follicular lymphoma and similar findings was observed by Iwamuro *et al*[23] in a 57-year-old patient from Niihama, Japan[20,23]. Inoue *et al*[24] reported whitish areas in enlarged villi in a patient with primary follicular lymphoma of duodenum. Elongated microvessels with white spots on surface was observed in a case of duodenal lymphangioma[21]. Another case report described saucer shaped lesions and multiple swollen villi like "moth eggs" on mNBI in a case of interdigitating dendritic cell sarcoma in duodenum[25]. While mNBI showed interesting abnormalities in the above reported lesions, its impact on management of patient is uncertain as biopsy may still be required.

NBI TO SCREEN FOR DUODENAL POLYPS IN POLYPOSIS SYNDROMES

Duodenum is an important site of polyps in familial adenomatous polyposis[26]. Surveillance endoscopy is recommended as duodenal tumours are the second most common cause of mortality in FAP after colonic tumours[27]. A study from Netherlands on 37 patients with FAP who underwent surveillance endoscopy using mNBI found NBI detected more adenomas than high resolution endoscopy and increased the Spigelman stage in 2 patients[28]. Another group used NBI for surveillance of polyps in patients with carriers of PTEN mutation seen in Cowden's syndrome[29]. Nine out of ten patients were found to have duodenal polyps but the role mNBI in this high diagnostic yield was not very clear.

NBI FOR DUODENAL AMPULLARY LESIONS

Ampullary adenomas may harbour malignant foci which may be missed on random biopsy due to sampling error. A study on 14 patients with bulky ampulla investigated the correlation between findings on mNBI and histology[13]. The surface pattern was divided into three types (type Ⅰ - oval villi; type Ⅱ - pinecone/leaf

Table 1 Overview of current status of magnification narrow band imaging technology in duodenum

Merits	Real time assessment of duodenal villous morphology with excellent accuracy
	Enables targeted biopsy of abnormal appearing area
Demerits	Added procedure time and cost
Potential applications	Assessment of duodenal villous atrophy in malabsorption syndromes
	Data on role in assessing duodenal neoplastic lesion is still preliminary

shaped villi; type Ⅲ - irregular or nonstructured villi). Presence of tortuous, dilated and network vessels were considered abnormal. Inflammatory and hyperplastic lesions had type Ⅰ surface pattern while adenomas and adenocarcinomas had type Ⅱ and/or Ⅲ surface pattern. Adenomas did not have abnormal vessels. A case report also showed the absence of vascular abnormality to be associated with no foci of malignancy on histology[30]. This is another potential area where NBI may play a role in obtaining targeted biopsies and help decide management strategy. Apart from assessing lesion characteristics, mNBI may also help in determining the lesion margin in patients undergoing duodenal papillectomy. Itoi *et al*[31] found mNBI to be better than indigo carmine chromoendoscopy for this indication. These preliminary observations suggest that mNBI may be useful in assessment and management of ampullary lesions. Larger studies are however required before recommending this technique for routine use.

CONCLUSION

Magnification endoscopy with NBI (mNBI) seems to have a potential role in evaluating duodenal mucosal morphology. Table 1 summarises the merits, demerits and potential application of this technology in clinical practice. While there is robust evidence for its role in assessing villous morphology, more data is required before recommending it for routine use in assessment of duodenal neoplastic lesions. There is also a need for uniform terminology and classification in describing villous morphology and protruding lesions which can enable comparison of published literature and facilitate training. The recent increase in interest on NBI in duodenum is encouraging because it can lead to new diagnostic possibilities which may impact therapy.

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P- Reviewer: Kumagai Y, Tischendorf JJW **S- Editor**: Tian YL
L- Editor: A **E- Editor**: Wu HL

World Journal of Gastrointestinal Endoscopy

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v7.i16.1222

World J Gastrointest Endosc 2015 November 10; 7(16): 1222-1229
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Basic Study

Optimization of the generator settings for endobiliary radiofrequency ablation

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Author contributions: Barret M analysed the data and drafted the manuscript; Leblanc S, Vienne A and Prat F conceived and performed the animal experiments; Rouquette A and Beuvon F preformed the histologic study; Chaussade S provided critical revision related to the intellectual content of the manuscript; all authors approved the final version of the article to be published.

Institutional review board statement: Ethical permission from our institutional review board was obtained for participation in the study.

Institutional animal care and use committee statement: The study received approval from our animal care and use committee.

Conflict-of-interest statement: To the best of our knowledge, no conflict of interest exists.

Data sharing statement: Technical appendix, statistical code, and dataset are available from the corresponding author at frederic.prat@aphp.fr.

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Received: February 27, 2015
Peer-review started: March 2, 2015
First decision: June 18, 2015
Revised: July 21, 2015
Accepted: September 7, 2015
Article in press: September 8, 2015
Published online: November 10, 2015

Abstract

AIM: To determine the optimal generator settings for endobiliary radiofrequency ablation.

METHODS: Endobiliary radiofrequency ablation was performed in live swine on the ampulla of Vater, the common bile duct and in the hepatic parenchyma. Radiofrequency ablation time, "effect", and power were allowed to vary. The animals were sacrificed two hours after the procedure. Histopathological assessment of the depth of the thermal lesions was performed.

RESULTS: Twenty-five radiofrequency bursts were applied in three swine. In the ampulla of Vater (n = 3), necrosis of the duodenal wall was observed starting with an effect set at 8, power output set at 10 W, and a 30 s shot duration, whereas superficial mucosal damage of up to 350 μm in depth was recorded for an effect set at 8, power output set at 6 W and a 30 s shot duration. In the common bile duct (n = 4), a 1070 μm, safe and efficient ablation was obtained for an effect set at 8, a power output of 8 W, and an ablation time of 30 s. Within the hepatic parenchyma (n = 18), the depth of tissue damage varied from 1620 μm (effect = 8, power = 10 W, ablation time = 15 s) to 4480 μm (effect = 8,

power = 8 W, ablation time = 90 s).

CONCLUSION: The duration of the catheter application appeared to be the most important parameter influencing the depth of the thermal injury during endobiliary radiofrequency ablation. In healthy swine, the currently recommended settings of the generator may induce severe, supratherapeutic tissue damage in the biliary tree, especially in the high-risk area of the ampulla of Vater.

Key words: Endobiliary radiofrequency ablation; Biliary stricture; Ampullary tumor; Endoscopic retrograde cholangio-pancreatography

Core tip: The use of endoscopic retrograde cholangio-pancreatography-guided endobiliary radiofrequency ablation is expanding quickly, from the clearing of obstructed biliary stents in malignant biliary stenoses, to the treatment of benign biliary strictures. However, the morbidity associated with this procedure remains high, of course because of the severity of the disease treated, but also possibly due to suboptimal generator settings. Therefore, we conducted an animal study in live pigs. We report novel data, highlighting the importance of the effect setting on the generator, and suggesting specific settings for radiofrequency ablation in the ampulla of Vater.

Barret M, Leblanc S, Vienne A, Rouquette A, Beuvon F, Chaussade S, Prat F. Optimization of the generator settings for endobiliary radiofrequency ablation. *World J Gastrointest Endosc* 2015; 7(16): 1222-1229 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i16/1222.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i16.1222

INTRODUCTION

Radiofrequency (RF) ablation is currently used for the destruction of a wide range of liver neoplasms, including hepatocarcinoma, intrahepatic cholangiocarcinoma, and colorectal metastases[1]. RF waves can be applied either intraoperatively or percutaneously. The recent development of endobiliary RF ablation devices has been justified by two situations in which pre-existing methods were non or partially satisfactory: (1) unresectable extrahepatic cholangiocarcinoma[2], in which chemotherapy is poorly efficient and tumor response is difficult to assess[1]; and (2) obstruction of biliary stents by tumor ingrowth in unresectable pancreatic head cancers, which requires endoscopic desobstruction. Endobiliary RF ablation is currently performed using a device which can be used percutaneously[3,4] or through retrograde endoscopic cannulation of the main bile duct[5]. After preclinical studies in *ex vivo*[6] and *in vivo* pig livers[7], early endobiliary RF experience has been reported in patients. Because of the lack of control group in these retrospective or pilot prospective studies, the clinical efficacy of the method cannot be assessed with a high degree of confidence. However, endobiliary RF ablation in the setting of malignant biliary strictures of the common bile duct was technically feasible in a small series of patients presenting one of the above-mentioned indications. The method seems capable of clearing occluded metal stents[4] and may have the potential to improve medium to long-term biliary stent patency[5,8]. Other indications of choice could be foreseen, such as the destruction of benign biliary lesions or the ablation of shallow intraductal or intra-ampullary neoplasia. However, in view of the limited preclinical data and the need for an accurate assessment of tolerable electrosurgical settings before using endobiliary RF in such indications, additional animal data is needed. We therefore conducted a preclinical study on live pig liver to assess the tissular effect of endobiliary RF ablation in the intrahepatic, common, and periampullary bile ducts with various generator settings.

MATERIALS AND METHODS

Landrace pigs weighing 30-35 kg and stemming from the same farm were used for the study. The pigs were accommodated at our facility for 48 h prior to the procedure. Procedures were performed under general anesthesia. The animal protocol was designed to minimize pain or discomfort to the animals. All animals were prepared for anesthesia with a 12-h diet, and administered an intramuscular injection of 10 mg/kg ketamine and 2 mg/kg azaperone 30 min before induction. After induction with 8 mg/kg intravenous 1% propofol and endotracheal intubation, anesthesia was maintained through inhalation of 1% to 2% isoflurane. All animals received an intravenous infusion of 10 mg/kg per hour crystalloid solution. Median laparotomy was performed, and anterior duodenotomy at the level of the first portion of the duodenum was made in order to expose the duodenal papilla, which is located 15 mm distal to the pylorus. The common bile duct was cannulated using a 0.035 Inch guidewire (Jagwire, Boston Scientific, Natick, MA, United States) and its actual position was ascertained by direct visualization of the hepatic pedicle. A Habib EndoHPB™ (EMcision UK, London, United Kingdom) probe was used for RF ablation. It is a bipolar device, 8 F (2.6 mm) in diameter, 1.8 m long, that passes over 0.035-inch guidewires, has 2 ring electrodes disposed on the catheter 8 mm from one another, with the distal electrode 5 mm from the leading edge; bipolar current activation allows for tissue ablation by creating coagulation necrosis over a 2.5 cm length[9]. The endoHPB™ probe was connected to a VIO300D electrosurgical generator (Erbe, Tübingen, Germany) in bipolar mode, delivering a high-frequency (450 kHz) electrical effect. The catheter was

Table 1 Outcomes of endobiliary radiofrequency ablation in the liver parenchyma

Effect	Power (W)	Time (s)	Maximal extent of tissue necrosis mean ± SD (depth in μm)
4	20	90	3950 ± 71[a]
4	40	90	3385 ± 21[a]
6	10	90	2850 ± 212[a]
6	20	90	3850 ± 71[a]
8	4	90	2850
8	6	90	3200
8	8	90	4480
8	10	15	1620
8	10	30	1720
8	10	60	2500
8	10	90	3578 ± 698[b]

[a]Mean ± SD (n = 2); [b]Mean ± SD (n = 4).

introduced manually inside the common bile duct and RF ablation was performed: (1) in the ampulla of Vater by positioning the space between both electrodes, which is the zone of highest energy deposition, exactly within the ampullary area, meaning that the most distal electrode was inside the bile duct and the most proximal one mostly within the duodenum; and (2) in the common bile duct. One or two separate thermal lesions could be performed along the bile duct, and only one in the ampullary region. The RF procedures on the ampulla of Vater are shown on Figure 1. Because of the limited space in the biliary tract and the ampullary region, separate tests were performed on the hepatic parenchyma prior to those biliary lesions, in order to predetermine a range of parameters most likely to provide the best safety-to-effectiveness balance for biliary lesions. Liver thermal injuries were performed by inserting the RF probe into the liver after a small incision in the Glisson's capsule. Different ablation parameters, such as effect and power, but also duration of RF shots, were allowed to vary. Two hours after the procedure, with the animals still under general anesthesia, the pigs were euthanized with 100 mg/kg intravenous injection pentobarbital. The liver, the common bile duct, and the duodenum were collected en-bloc with the pancreatic head and fixed for 24 h in 10% buffered formalin. After macroscopic examination, ablated segments were embedded in paraffin, processed into 3 μm-thick sections, and stained with hematoxylin, eosin and saffron. Histological assessment was performed by a pathologist experienced in digestive pathology (AR), using an ocular micrometer to measure the maximal extent of tissue necrosis in depth from the epithelial surface. Tissue presenting disorganization of the layers, absence of normally shaped native cells, edema and/or inflammatory cell infiltrate was considered necrotic. Statistical analysis was performed using Graphpad Software (GraphPad Software Inc., San Diego, CA). Results are expressed as mean values ± SD.

The experimental protocol was approved by the scientific committee of the Surgery School of Paris (Ecole de Chirurgie de l'Assistance Publique-Hopitaux de Paris, France) and the experiments were performed according to the standard animal research guidelines established by the French Ministry of Agriculture.

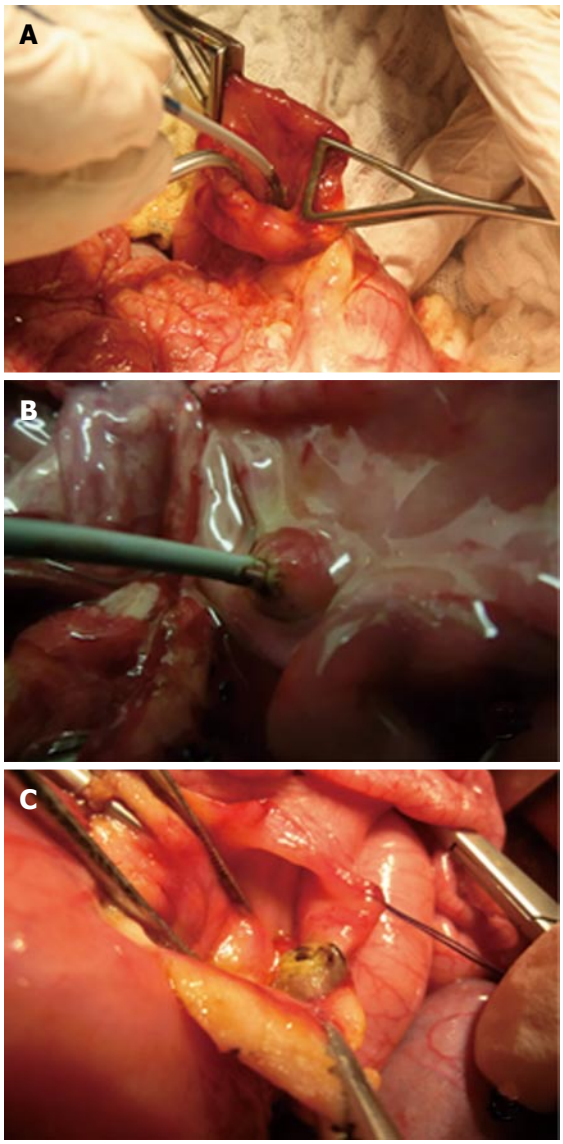

Figure 1 Radiofrequency ablation on the ampulla of Vater. A: The introduction of the probe (pig #3); B: The early mucosal changes visible during radiofrequency procedure (pig #2); C: Features of early and excessive tissue damage after probe withdrawal (pig #1).

RESULTS

Three pigs, on which 25 RF ablations were conducted, were included in the study. Eighteen RF ablations were conducted in the hepatic parenchyma allowing the testing 11 ablation conditions. The depth of tissue necrosis ranged from 1620 μm for an effect of 8, a power of 10 W, and a 15 s ablation time, up to 4480 μm for an effect of 8, a power of 8 W, and a 90 s ablation. The full set of corresponding figures is displayed in Table 1. Based on those results, RF shots conducted in the common bile duct allowed the testing of three ablation settings. With an effect varying from 4 to 8, a

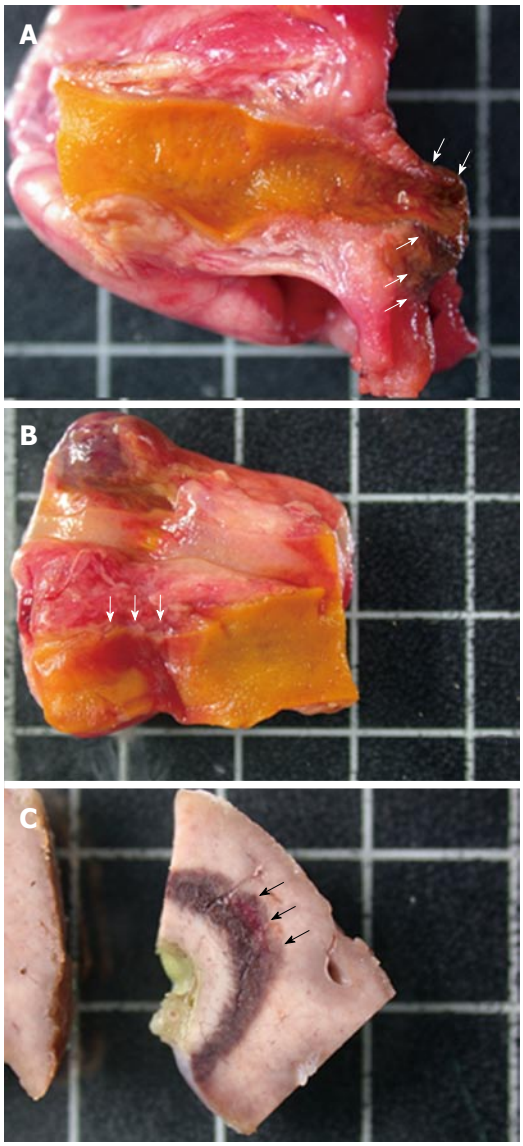

Figure 2 Macroscopic findings on the bile tract after radiofrequency ablation in pig #2. A: The papillary region and distal common bile duct, with tissue damage reaching the duodenal wall (arrows); B: An ablated zone limited to the wall of the common bile duct (arrows); C: An example of intrahepatic parenchymal damage up to 4 mm away from the bile ducts (arrows).

power output from 6 to 20 W, and shot duration from 30 to 90 s, a depth of tissue injury allowing for deep, yet non transmural tissue necrosis up to 1075 μm was obtained with an effect set at 8, a power of 8 W, and a short ablation time of 30 s; longer or more powerful or intensive shots led to transmural tissue necrosis up to 2700 μm away from the epithelium, with destruction of the peribiliary adipose tissue. Finally, three RF ablations were conducted in the ampullary region under three different ablating conditions. Effect was set at 8, power varied from 6 to 10 W, and the duration of ablation shots from 30 to 90 s. The depth of the tissue injury ranged from 350 μm, with ablation limited to the mucosa, for a power output of 6 W and an ablation time of 30 s, up to 2810 μm, with extensive tissue necrosis involving the adipose tissue and the pancreas, for a power of 10 W and a 90 s long shot. The results of RF in the bile duct and the ampulla of Vater are presented in Table 2. Macroscopic assessment of the ablated tissues is presented in Figure 2, and histological views of ablated ampullae are shown in Figure 3. Figure 4 presents the respective impact of power and ablation time variation on tissue damage after RF. Whereas power and ablation time appeared to be linearly correlated to the depth of tissue damage, variations in effect settings only had a modest influence on tissue damage, although our results showed an inverse relationship between effect and power output (Figure 5).

Table 2 Outcomes of endobiliary radiofrequency ablation in the main bile duct and ampulla of Vater

Effect setting	Power output (W)	Shot duration (s)	Shot location	Depth of tissue injury (μm)	Observations
4	20	90	Bile duct	2700	Transmural necrosis
6	10	90	Bile duct	2600	Transmural necrosis
8	10	90	Ampulla	2810	Extensive necrosis of the papilla, involving pancreas and adipose tissue
8	10	30	Ampulla	1530	Deep coagulation, necrosis of the duodenal wall. No significant pancreatic injury
8	6	60	Bile duct	1420	Deep transmural coagulation, involving peribiliary adipose tissue
8	8	30	Bile duct	1075 ± 417[1]	Coagulation involving almost the entire duct wall
8	6	30	Ampulla	350	Superficial coagulation, moderate duodenal lesion

[1]Mean ± SD, 2 measurements have been performed.

DISCUSSION

Clinical studies of RF endobiliary ablation with the EndoHPB™ probe have not been undertaken without previous animal studies designed to assess the depth of tissue damage[6,7,10]. It is noteworthy that EndoHPB probes are designed to be used only with VIO200-300, which is one of the most popular HF units in endoscopy wards. This should make comparisons between studies relatively easy and reliable, since the parameters used are strictly comparable. Itoi *et al*[6] assessed thermal injury in the hepatic parenchyma in three *ex vivo* pig livers, and tested 12 ablation settings, with power varying from 5 to 20 W and ablation times ranging from 60 to 120 s. Their observations were mainly macroscopical, and the authors reported tissue necrosis extending from 4.3 ± 0.6 mm to 11.3 ± 1.2

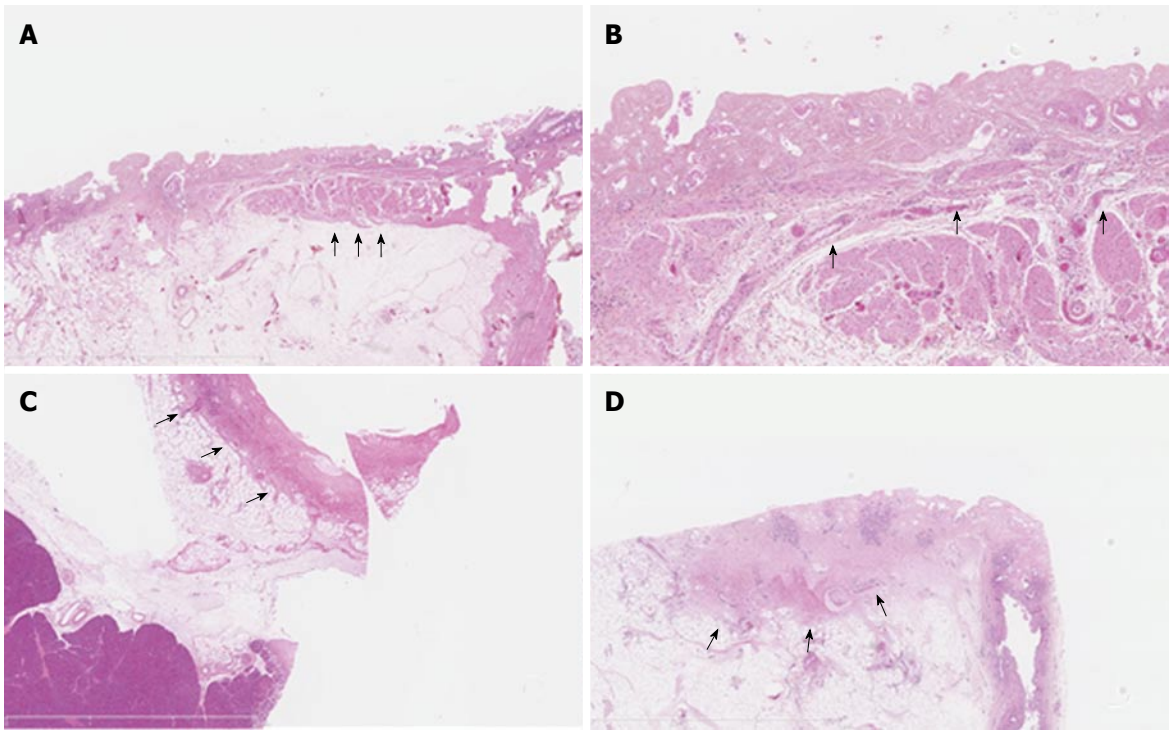

Figure 3 Histological findings in the three ampullae Vaterii treated by radiofrequency ablation. A: Taken from pig #3, shows satisfying ablation of the ampulla of Vater sparing the submucosa; arrows indicate the intact submucosa; hematoxylin eosin and saffron, original magnification × 25; B: The vertical extension of tissue damage in pig #1, reaching the muscularis mucosae; arrows indicate the muscularis mucosae; hematoxylin eosin saffron, original magnification × 100; C and D: The ampullae of pigs #1 and 2 (respectively), with deep tissue necrosis extending far beyond the muscularis propria up to the adipose tissue; arrows indicate the extent of coagulation necrosis; hematoxylin eosin and saffron, original magnification × 25.

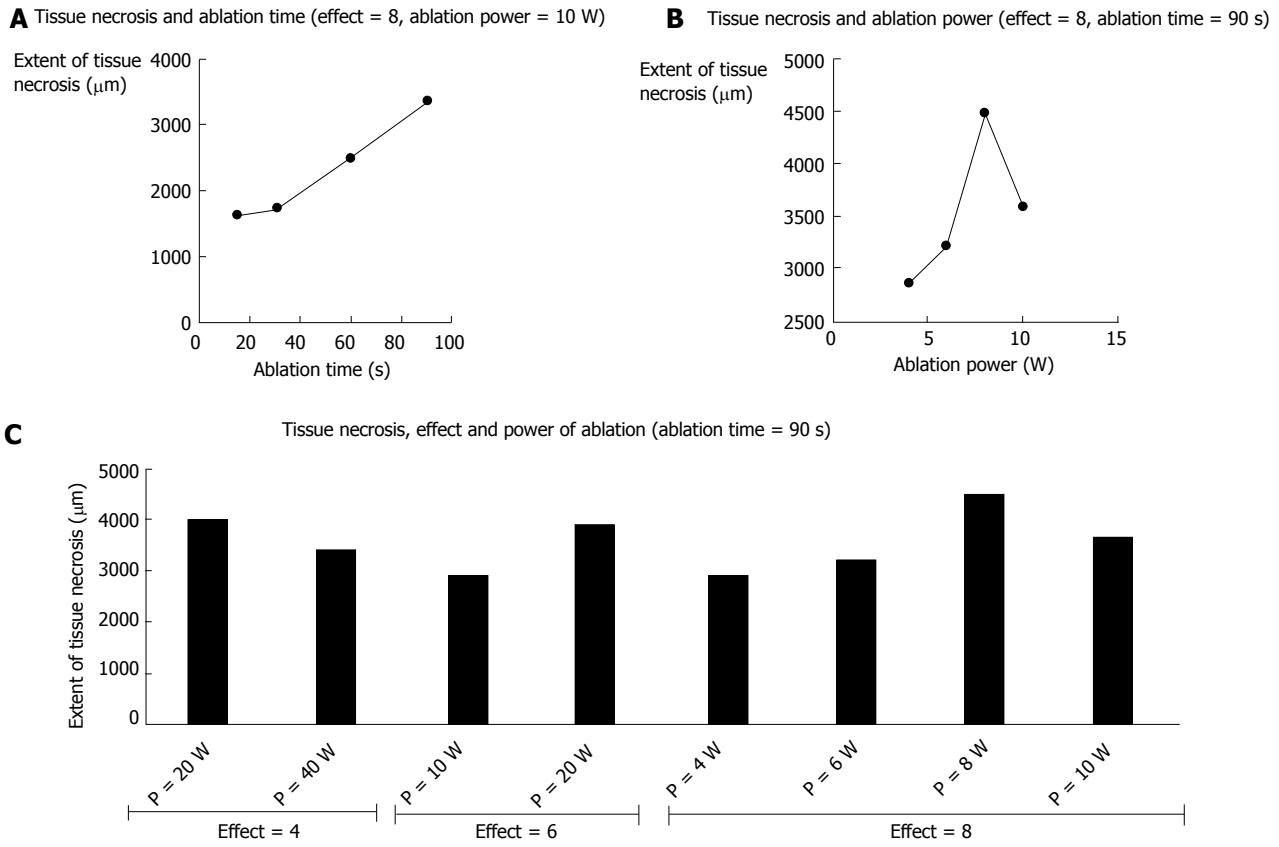

Figure 4 Variation of the extent in depth of thermal tissue damage after radiofrequency ablation in the liver according to electrical settings (VIO 300D). A: Variation of depth with shot duration; B: Variation of depth with power output setting; C: Variation of depth with effect.

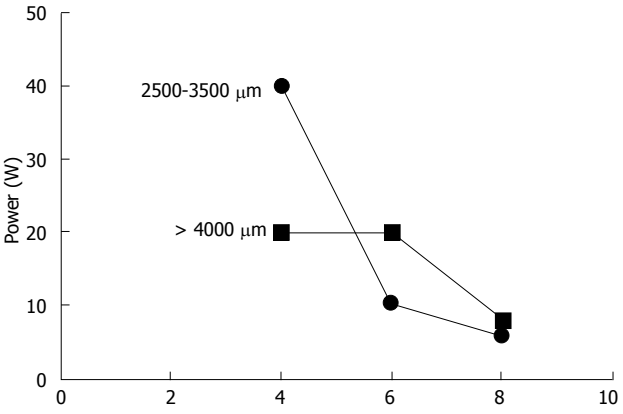

Figure 5 Relative variation of power output and effect setting for a given depth of tissue ablation and a 90 s ablation time in the liver.

mm in depth. However, these numbers are hardly comparable with ours, as the authors measured the entire thickness of the damaged tissue, including the proper width of the catheter. They concluded that: (1) for the 5 W power value, 60 and 90 s ablation times were insufficient to achieve tissue necrosis; (2) the 5-10 W power output range was a zone of continuously increasing tissue damage, as opposed to power values of 15 W and over, for which tissue necrosis seemed to be stable. However, this study was performed *ex vivo*, lacked thorough histological analysis, was limited to the liver parenchyma, and did not take into account the effect parameter, which was set a priori at 8. In a study closer to clinical conditions, Zacharoulis *et al*[7] assessed the effects of endobiliary RF ablation on the bile ducts of 20 live pigs. The authors tested 10 different conditions of power output ranging from 1 to 10 W, left a plastic stent in the common bile duct, and performed histological assessment of the common bile duct 24 h after the procedure. They concluded that power as well as ablation time had an impact on the depth of tissue damage, and found the optimal settings to be a power of 6-7 W and an ablation time of 60 s[7]. In this study however, the variation of the effect was also not taken into account, histological assessment was semi-quantitative, and only the common bile duct was studied.

Based on the results of those preclinical studies, it has been suggested that the Habib EndoHPB™ probe be set at a power of 10 W, an effect of 8, and a shot duration of 90-120 s[9]. In published clinical reports, endobiliary RF has been associated with a 10%-20% morbidity rate[5,8,11,12], including cases of cholangiosepsis, liver infarction, hepatic coma, cholecystitis, and pancreatitis, all of which can be explained at least in part by excessive tissue damage to the distal bile duct or to the hepatic parenchyma. Moreover, generator settings reported in clinical studies have been heterogeneous, ranging from 5 W and 120 s[13] to 10 W and 120 s[4], and frequent use of intermediate power values or ablation times[5,8,11,12]. Only one publication reported the use of endobiliary RF ablation on a periampullary tumor, but RF was actually used to treat a malignant stricture at the proximal end of a biliary stent, thus at a distance from the ampulla[14]. For these reasons, we chose to re-assess the effects of RF on living pig liver before undertaking evaluations on the healthy bile duct and the ampullary region.

In its step-by-step guide to endobiliary RF procedures, the manufacturer suggests that for periampullary procedures, the power should be lowered to 7 W, and the procedure should be stopped as soon as the duodenal mucosa started blanching[9]. We first confirmed that the standard settings of the RF generator (effect 8, power 10 W) resulted in excessive damage to the ampulla of Vater, even with very short RF ablation times such as 30 s. An effect of 8, a low power of 6 W, and a short ablation time of 30 s seemed to provide optimal tissue ablation of the epithelium and the lamina propria in the ampulla. In the common bile duct, we observed a deep tissue necrosis reaching the entire bile duct wall and the peribiliary adipose tissue with settings as low as effect 8, power 6 W, and a 60 s ablation. This is consistent with the observations of Zacharoulis *et al*[7] who observed damage to adjacent organs or full thickness tissue necrosis (leading to bile duct perforation in three cases out of four at 24 h) in all animals treated with a power > 6 W. We can also conclude from these data that the effect setting has a major importance in the RF energy delivered: indeed, for a 90 s RF shot, a four point variation (from 4 to 8) of the effect causes the same tissue damage as a 30 W variation of the power (from 10 to 40 W). In the hepatic parenchyma, a 3 mm tissue damage around the probe could be achieved equally with either high power values or a 2 point increase of the effect setting. Power values, as reported by others, seemed to clearly influence the depth of tissue damage up to 10 W[6,7]: The impact of raising the power beyond 10 W did not appear to be significant. By contrast, the time of RF ablation was linearly correlated to the extent of tissue necrosis.

To our knowledge, this is the first study that considers the impact of effect variation in endobiliary RF. Furthermore, based on consistent data obtained in the hepatic parenchyma, we tested RF ablation in the whole biliary tree, including the ampulla of Vater.

However, our study presents some limitations; first, given the small number of animals, we only tested a limited number of generator settings, and did not duplicate the measurements for most values obtained in the common bile duct, although the figures found are in keeping with those reported by other authors[6,7]. Second, the short time span between RF and the sacrifice of animals could have led us to overlook the actual extent of the lesions. However, we waited for two hours before the animals were euthanized in order for the tissue damage to appear, which was sufficient to make coagulation necrosis clearly visible with standard staining. Third, although the *in vivo* pig liver is currently the cheapest and most easily available, it may not be a perfect model for thermal ablation, since it lacks

tumoral or inflammatory thickening of the biliary wall. This could account for the supratherapeutic effects of the recommended RF generator settings in swine. Other explanations have been suggested, such as different blood supplies between the swine and human common bile duct, or major heat sink phenomenon in humans compared with swine due to higher blood flow in the hepatic pedicle[7]. Furthermore, the dramatic RF impact in other swine epithelia, such as esophageal has also been reported to be more severe than in humans[15].

In conclusion, our work demonstrates that the currently recommended settings for endobiliary radiofrequency ablation may result in supratherapeutic effects in the pig liver, bile duct and periampullary region. Our data also underlined the critical importance of the effect setting on the VIO™ RF generator for this application. These points should be kept in mind when designing RF ablation clinical trials, especially since clinical indications of endobiliary RF ablation tend to spread outside the field of malignant stricture management, such as benign biliary stricture[16] or possibly residual neoplastic tissue after endoscopic papillectomy.

ACKNOWLEDGMENTS

The authors wish to thank Mrs Alice Bertucat for her help in the animal experiments, as well as the animal attendants from the Ecole de Chirurgie de l'Assistance Publique-Hopitaux de Paris.

COMMENTS

Background

Endoscopic endobiliary radiofrequency (RF) ablation has been developped for the treatment of malignant biliary obstructions. It currently allows to clear occluded metal stents and may have the potential to improve medium to long-term biliary stent patency.

Research frontiers

Endobiliary RF ablation has mainly been studied for lesions of the common bile duct. The optimal generator settings for the treatment of ampullary or intrahepatic lesions is uncertain. Moreover, the consequences of the variations of « effect » parameter of the generator have not been studied.

Innovations and breakthroughs

This is the first study that considers the impact of effect variation in endobiliary RF. Furthermore, based on consistent data obtained in the hepatic parenchyma, the authors tested RF ablation in the whole biliary tree, including the ampulla of Vater.

Applications

Results of this study should be kept in mind when performing endobiliary radiofrequency ablation for intrahepatic or ampullary lesions, or for non-neoplastic, shallow lesions of the common bile duct.

Terminology

Endobiliary radiofrequency ablation consists in the application of radiofrequency energy using a bipolar probe inserted into the biliary tree, either percutaneously, or by retrograde cannulation *via* endoscopic retrograde cholangiopancreatography.

Peer-review

This study gave a good result for using endobliary radiofrequency ablation or not in clinic, and did have clinical value to guide the treatment procedure.

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P- Reviewer: Misra SP, Xu Z **S- Editor**: Song XX
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DOI: 10.4253/wjge.v7.i16.1230

World J Gastrointest Endosc 2015 November 10; 7(16): 1230-1232
ISSN 1948-5190 (online)

PillCam COLON 2© as a pan-enteroscopic test in Crohn's disease

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Author contributions: Hall B and McNamara D wrote this letter; all authors contributed equally to the gathering of data and statistical analysis.

Conflict-of-interest statement: The authors declare no conflict of interest.

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Received: July 28, 2015
Peer-review started: July 30, 2015
First decision: August 31, 2015
Revised: September 8, 2015
Accepted: September 29, 2015
Article in press: September 30, 2015
Published online: November 10, 2015

Abstract

A recent paper by Boal Carvalho *et al* demonstrates the potential of PillCam COLON 2© (PCC2) as a pan-enteric investigation in Crohn's disease (CD). Our own prospective data in patients with known CD also shows good correlation between PCC2 and small/large bowel investigations (R = 0.896, $P < 0.0004$/R = 0.6667, $P < 0.035$). Larger studies are warranted to prospectively validate the use of PCC2 in the investigation and monitoring of both small and large bowel CD.

Key words: Capsule endoscopy; Panenteroscopy; Small bowel Crohn's disease; Mucosal healing; Colon capsule

Core tip: Mucosal healing has been shown to reduce the need for surgery and hospitalisation in patients with Crohn's disease. Currently, assessing small bowel and colonic mucosal healing requires separate imaging/endoscopic modalities. Recent data suggests that the PillCam Colon 2© (PCC2) is capable of assessing mucosal healing of the small intestine and colon in a single, non-invasive test. Our own prospective data corroborates these findings demonstrating good correlation between investigations. Larger studies assessing the viability of PCC2 as a pan-enteric investigation are warranted.

Hall B, Holleran G, McNamara D. PillCam COLON 2© as a pan-enteroscopic test in Crohn's disease. *World J Gastrointest Endosc* 2015; 7(16): 1230-1232 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i16/1230.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i16.1230

TO THE EDITOR

We read with interest the recent article by Boal Carvalho *et al*[1] entitled "PillCam COLON 2© in Crohn's disease: A new concept of pan-enteric mucosal healing assessment". Mucosal healing in Crohn's disease (CD) remains a current hot topic. Numerous colonic studies suggest that mucosal healing leads to increased steroid-free remission and decreases surgical and hospitalisation rates[2-5]. More recent studies have established that small bowel capsule endoscopy (SBCE) is capable

Table 1 Bowel preparation regime for study participants undergoing same day colon capsule and colonoscopy

Schedule	Intake
Day 1	
All day	10 glasses of water throughout the day
Evening	Four senna tablets
Day 2	
All day	Clear liquid diet
Evening	2l Klean prep
Day 3 (exam day)	
Morning	2l Klean prep
10-11 am	Colonoscopy + capsule ingestion
1st boost	1 sachet sodium picosulfate
(upon small bowel entry)	
2nd boost (4 h later)	1 sachet sodium picosulfate

Table 2 Baseline characteristics of study patients (n = 10)

Median age in years (range)	31 (19-47)
Female	7 (70%)
Smoker	5 (50%)
Disease extent	
Ileo-colonic	10 (100%)
Disease subtype	
Inflammatory	4 (40%)
Stricturing	6 (60%)
Previous resection	
Ileo-caecal surgery	4 (40%)
Ilealsurgery	1 (10%)
Medications	
Thiopurine	3 (30%)
Biologic	9 (90%)

of safely monitoring small bowel mucosal healing[6,7] although long-term follow up studies are required to demonstrate the efficacy of small bowel mucosal healing. The use of PillCam COLON 2 (PCC2) as a pan-enteric device has been previously investigated by Negreanu *et al*[8].

This current study by Boal Carvalho *et al*[1] again demonstrates the potential of PCC2 as a "one-stop", non-invasive mucosal healing assessment of both the large and small bowel. In total, 12 patients were enrolled in the study. Each patient underwent an ileocolonoscopy and SBCE at diagnosis. All patients had a PCC2 performed following one year from diagnosis. The aim was to evaluate the ability of PCC2 to assess mucosal response to therapy in both the large and small bowel. At one year, mucosal healing of the small bowel and large bowel was 33% and 50%, respectively. The combined mucosal healing rate was only 25%. However, perhaps most importantly, PCC2 was shown to be capable of adequately assessing both small and large bowel CD.

Our own data would appear to support these findings in terms of the viability of PCC2 as a pan-enteric device. We performed a prospective comparative study of PCC2 *vs* both ileo-colonoscopy and SBCE in patients with known CD. Following ethical approval, patients were recruited from our clinic at Tallaght hospital over a 6-mo period. Major exclusion criteria included known small bowel stricture, recent gastrointestinal surgery (within 3 mo of study recruitment) and chronic NSAID use or NSAIDS within 6 wk of study recruitment (apart from 5-ASA therapy). SBCE and PCC2 investigations were performed using PillCam technology (Given Imaging, Yoqneam, Israel). SBCE followed our standard protocol without bowel preparation. PCC2 and colonoscopy were performed no longer than 14 d following SBCE. Bowel preparation regimen was performed over a 3 d period (Table 1). One experienced endoscopist performed all study colonoscopies. PCC2 was performed on the same day as ileo-colonoscopy. All SBCE and PCC2 images were reviewed by two clinicians experienced in reading and interpreting capsule examinations. The capsule endoscopy CD activity index (CECDAI) was utilised to assess the severity of disease activity. The CECDAI divides the small bowel into proximal and distal segments and uses three major criteria to grade severity: Inflammation, extent of disease and the presence of stenosis with the addition of proximal and distal scores leading to an overall CECDAI score. The authors utilised the CECDAI score for this study due to the fact that it is the only capsule scoring system which has been prospectively validated to date[9]. Activity was graded as follows; inactive disease (CECDAI = 0), mild disease activity (3.5 < CECDAI < 5.8), moderate to severe disease activity (CECDAI $\geqslant$ 5.8). Colonic disease activity was based on the Simple Endoscopic Score for Crohn's Disease (SES-CD); inactive disease (SES-CD = 0-3), mild disease activity (SES-CD = 4-10), moderate disease activity (SES-CD = 11-19) and severe disease activity (SES-CD $\geqslant$ 20).

In total, 10 participants were enrolled; median age of 31 years (range 19-47), 7 (70%) female. Every participant had previously documented ileo-colonic disease. Baseline demographics are summarised in Table 2. All capsules reached the caecum ensuring complete small bowel views for both SBCE and PCC2. Overall image quality was adequate for both modalities. Upon review of SBCE images, 2 (20%) had no small bowel disease activity, 5 (50%) had mild/moderate severity with the remaining 3 (30%) having severe small bowel CD. In terms of disease distribution, the majority 7 (88%) had distal ileal disease only with only one (12%) participant having evidence of more proximal small bowel disease. In comparison, PCC2 detected the following disease activity; 2 (20%) normal, 6 (60%) mild/moderate with the remaining 2 (20%) having severe disease. There appeared to be good correlation between SBCE and PCC2 images in terms of the recognition and grading of disease activity (R = 0.896, P < 0.0004). The caecal intubation rate for colonoscopic procedures was 100%. Overall, the terminal ileum was intubated in 9 (90%) participants. All CCE procedures successfully reached the rectum. Of note, there were no complications with any of the capsule or colonoscopic procedures. On colonoscopy, 8 (80%) had no disease activity with 2 (20%) having mild disease. The majority of participants (9, 90%) had

no disease activity on PCC2 with only one participant meeting the criteria for mild disease activity. There was good correlation between the two modalities (R = 0.6667, $P < 0.035$).

Despite limited numbers between all of the studies performed to date, PCC2 does appear capable of successfully examining the small and large bowel and also accurately detecting small bowel and colonic CD. With regard to our own data, PCC2 did appear to miss disease in the proximal small bowel that was detected by SBCE. This may be due to the PCC2 technology itself which "shuts down" in the proximal small bowel to conserve battery life. Alternatively, reader error may be at fault. The development of a "pan-enteric" capsule designed specifically for both small and large bowel imaging may ultimately be required. In terms of colonic disease, the correlation between modalities was not quite as strong as that witnessed for small bowel images. However, this may be due to the scoring system utilised. There was discrepancy between PCC2 and colonoscopic disease activity scores in only two participants. The actual numerical difference in the SES-CD scores for both participants was a solitary point. In both cases, this increased the disease severity into a higher bracket of disease activity which likely skews the correlation between the two modalities. The development of a combined scoring system encapsulating both small and large bowel disease activity may be a viable option in the progression of this technology. Certainly based on the evidence to date, larger studies are warranted to prospectively validate the use of PCC2 in the investigation and monitoring of both small and large bowel CD.

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P- Reviewer: Figueiredo PN, Mentes O, Naito Y
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