ISSN 1948-5190 (online)

World Journal of *Gastrointestinal Endoscopy*

World J Gastrointest Endosc 2017 January 16; 9(1): 1-40

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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World Journal of Gastrointestinal Endoscopy

Contents

Monthly Volume 9 Number 1 January 16, 2017

World Journal of Gastrointestinal Endoscopy
Volume 9 Number 1 January 16, 2017

Contents

NAME OF JOURNAL
World Journal of Gastrointestinal Endoscopy

ISSN
ISSN 1948-5190 (online)

LAUNCH DATE
October 15, 2009

FREQUENCY
Monthly

EDITORIAL OFFICE
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World Journal of Gastrointestinal Endoscopy
Baishideng Publishing Group Inc
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
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E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
8226 Regency Drive,
Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com

PUBLICATION DATE
January 16, 2017

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Gastrointestinal Endoscopy

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Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.4253/wjge.v9.i1.1

World J Gastrointest Endosc 2017 January 16; 9(1): 1-11
ISSN 1948-5190 (online)

REVIEW

Robot-assisted laparoscopic gastrectomy for gastric cancer

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Author contributions: Caruso S wrote and conceived the study; Franceschini F and Annecchiarico M contributed to the literature search and acquisition of data; Patriti A, Roviello F, Ceccarelli G and Coratti A contributed to the critical appraisal of the work, revising the article critically for important intellectual content.

Conflict-of-interest statement: All authors disclose any potential or actual personal, political or financial conflict of interest in the material, information or techniques described in the paper.

Manuscript source: Invited manuscript

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Received: June 22, 2016
Peer-review started: June 27, 2016
First decision: August 11, 2016
Revised: September 15, 2016
Accepted: October 25, 2016
Article in press: October 27, 2016
Published online: January 16, 2017

Abstract

Phase Ⅲ evidence in the shape of a series of randomized controlled trials and meta-analyses has shown that laparoscopic gastrectomy is safe and gives better short-term results with respect to the traditional open technique for early-stage gastric cancer. In fact, in the East laparoscopic gastrectomy has become routine for early-stage gastric cancer. In contrast, the treatment of advanced gastric cancer through a minimally invasive way is still a debated issue, mostly due to worries about its oncological efficacy and the difficulty of carrying out an extended lymphadenectomy and intestinal reconstruction after total gastrectomy laparoscopically. Over the last ten years the introduction of robotic surgery has implied overcoming some intrinsic drawbacks found to be present in the conventional laparoscopic procedure. Robot-assisted gastrectomy with D2 lymphadenectomy has been shown to be safe and feasible for the treatment of gastric cancer patients. But unfortunately, most available studies investigating the robotic gastrectomy for gastric cancer compared to laparoscopic and open technique are so far retrospective and there have not been phase III trials. In the present review we looked at scientific evidence available today regarding the new high-tech surgical robotic approach, and we attempted to bring to light the real advantages of robot-assisted gastrectomy compared to the traditional laparoscopic and open technique for the treatment of gastric cancer.

Key words: Gastric cancer; Gastric resection; Minimally invasive surgery; Robot-assisted gastrectomy

Core tip: Laparoscopic gastrectomy has been shown to be a viable option for early gastric cancer, showing survival rates comparable to those of open procedure. However, there has been criticism concerning the routine use of laparoscopy in patients with advanced gastric cancer, principally because it adapts poorly to complex maneuvers like D2 lymphadenectomy. Robotic surgery has been shown to make certain laparoscopic procedures easier and safer. Reports have recently shown the ever increasing feasibility and safety of robotic assisted laparoscopic gastrectomy for gastric cancer, in some cases even proving superior to traditional laparoscopy.

Caruso S, Franceschini F, Patriti A, Roviello F, Annecchiarico M, Ceccarelli G, Coratti A. Robot-assisted laparoscopic gastrectomy for gastric cancer. *World J Gastrointest Endosc* 2017; 9(1): 1-11 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i1/1.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i1.1

INTRODUCTION

In 1991, Kitano *et al*[1] performed the first laparoscopically assisted gastrectomy for gastric cancer. Subsequently, under the impulse of level Ⅲ studies providing the evidence of the safety of laparoscopic assisted distal gastrectomy (LADG) for distal early-stage gastric cancer, several authors reported comparative studies with better short-term results in favor of this technique with respect to traditional open[2]. As a consequence laparoscopic gastrectomy (LG) has progressively spread worldwide, especially in the East, for the treatment of early gastric cancer[3,4]. On the other hand, the treatment of patients with advanced gastric cancer has always been considered difficult laparoscopically, thus techniques such as laparoscopic assisted total gastrectomy (LATG) and laparoscopic extended lymphadenectomy did not meet the same enthusiasm. As a result, the spread of laparoscopic surgery as a means of performing total gastrectomy and managing advanced gastric cancer was limited. This was mainly due to the technical difficulties and complexity of the D2 lymphadenectomy and the intestinal reconstruction after total gastrectomy[5,6].

Robot-assisted techniques have brought about improvements to certain surgical procedures, particularly those which require precise dissection, making it possible to resolve some of the innate limitations of laparoscopy. So over the years, robot-assisted gastrectomy (RAG) has become increasingly considered as a valid, yet still debatable, alternative to executing gastrectomy for gastric cancer, in particular for total gastric resection and extended lymph node dissection in advanced tumours[7-9]. We analyzed high-quality clinical trials by systematically reviewing the literature published so far in Pubmed comprehending robotic case series, as well as those studies that have compared RAG with LG and/or open gastrectomy for gastric cancer. Our intent is to verify if at present there is actual evidence of an advantage to robotic compared to laparoscopic and traditional open gastrectomy for gastric cancer.

Rational basis of robotic surgery as improvement of laparoscopy

Areas of surgery necessitating precise movements have employed Robotic technology. In 1994 the da Vinci® Surgical System (Intuitive Surgical, Sunnyvale, California, United States) gained the approval of the United States Food and Drug Administration (FDA). The da Vinci® Surgical Robotic has undergone constant improvement over recent years, and now includes additional features including near-infrared technology, and facilitated set-up. The latest generation, which was released in 2014 and is known as the da Vinci Xi™ system, is less bulky and its arms are more ergonomic (Figure 1).

Robotic surgery eliminates some of the disadvantages of conventional laparoscopy. The principal drawbacks of conventional laparoscopy from a technical standpoint are: The instability of the two-dimensional (2D) camera; instruments with limited movement which augment the physiologic tremor of the surgeon's hand, therefore limiting manipulative actions and increasing ergonomic discomfort.

The robotic surgery system has the upper hand over laparoscopy when fine dissection is needed, eliminating the traces of physiologic human tremor, increasing dexterity through its typical internal articulated endoscopic wrist (EndoWrist™ System), and providing stereoscopic vision with 3D high-resolution images[10]. This allows surgeons to perform minimally invasive surgery with greater ease and safety, and more ergonomically. As a consequence it probably makes it possible for more surgeons to complete complex procedure in a minimally invasive fashion.

Moreover, even if laparoscopic surgery may have an effect on the robotic gastrectomy learning process, robotic surgery appears to globally need less time to master compared to a laparoscopic procedure traditionally requiring a steep learning curve[11-14].

Main drawbacks of conventional laparoscopy in gastric cancer surgery

Delicate maneuvers which necessitate excellent visualization and total precision such as intra-corporeal anastomosis and dissection of extra-perigastric lymph nodes along the major arterial structures are the principal pitfalls of conventional laparoscopic gastrectomy for gastric cancer.

The far from perfect and often shallow angulation of the traditional unergonomic laparoscopic technique render the D2 lymphadenectomy especially hard and

Figure 1 New-generation da Vinci Xi™; the system is more versatile and better manoeuvrable, the robotic arms are thinner and arranged in a more ergonomic way, enabling multiquadrant procedures without repositioning the system.

demanding even for minimally-invasive surgeons who have been solidly trained. Areas which are quite hard to reach during laparoscopic lymphadenectomy include lymph node stations 4, 6, 9, 11p and 12a[15]. It may be linked to the risk of important blood loss which can occur particularly during the lymph node dissection around the infra pyloric area and the inferior mesenteric vein, including stations 6 and 14, and the supra pancreatic area including stations 7, 8, and 9[16]. Miura *et al*[15] indicated a far inferior amount of harvested lymph nodes obtained by laparoscopy in comparison to open surgery along the major gastric curvature (Nos. 4 and 6) and second tier nodes along the celiac and splenic arteries (Nos. 9 and 11). Similarly, Bouras *et al*[17] showed a greatly inferior amount of lymph nodes harvested along the common hepatic artery in a series of laparoscopic distal gastrectomy procedures compared to open distal gastrectomy (ODG).

Main technical advantages of robotics over traditional laparoscopy in gastric cancer

The majority of resectable gastric cancer patients are advised to undergo gastrectomy with D2 lymph node dissection surgical procedure[18]. Thus, in gastric cancer treatment, in order to fit oncological criteria, minimally invasive procedures must entail proper lymphadenectomy, as in its traditional open counterpart.

It is widely accepted that D2 lympadenectomy is one of the most difficult steps of the laparoscopic gastrectomy procedure for gastric cancer. The certain advantage produced by the robotic system could be decisive in gastric cancer surgery, mainly ensuring an extremely precise and safe lymphadenectomy with reduced risk of vessel injury[19], thus making this phase a principal indicator for the robot-assisted technique. The advantages of robotic surgery, such as tremor filtration and articulated function of wristed instruments, would be particularly suitable for enabling more complete dissection in demanding areas such as the dorsal part of the pancreas and behind splenic vessels at the hilum, which are not easily identified and are difficult to reach with current laparoscopic instruments and camera system[20]. It is extremely hard to reach the back of the suprapancreatic lymphatic area laparoscopically, and the downward compression of the pancreas which is particular prominent through the laparoscopic instruments may lead to pancreatic damage and pancreatitis. In these sites especially, the EndoWrist® robotic property and a far more stable vision allow the surgeon to complete this surgical step more easily and safely in comparison to the laparoscopic counterpart.

Robotic surgery also has the advantage of making intra-corporeal anastomosis easier, and therefore overcomes one of the greatest limitations of traditional laparoscopy from a technical standpoint in carrying out digestive restoration. This is particularly true after total gastrectomy, otherwise made possible by extracorporeal anastomosis with a small mini-laparotomy. Placing a hand-sewn purse-string suture on the esophagus is made easier by using robotic assistance, and esophageal

anastomosis can subsequently be carried out by using a circular stapler, as in open surgery[7,19]. Another option would be to carry out a full robotic hand-sewn esophagojejunal anastomosis[21], possible because the robotic system gives surgeons the chance to suture more easily and with greater precision compared to laparoscopy, particularly in deep and narrow areas. Thus, increased know-how and confidence with the robotic system will enable the surgeon to perform high-precision and safer intra-corporeal sutures for patients undergoing digestive anastomosis.

LITERATURE EVIDENCE

Studies of feasibility and safety

The earliest reports of robot-assisted gastrectomy (RAG) were published in 2003 by Hashizume *et al*[22] and Giulianotti *et al*[23]. Recent reports have shown the safety and viability of robotic gastrectomy for treating gastric cancer[24,25]. Table 1 summarizes some of the robotic case series published to date[7-9,26-34]. Most of the experience so far derives from non-randomized retrospective studies, while only one available clinical trial to date has been prospectively conducted[34]. The studies mainly hail from the East. In the western countries, reports on RAG are fewer and usually limited to smaller series. In 2007, in the United States Anderson *et al*[7] reported the results of the first western series including 7 gastric cancer patients who were submitted to robot-assisted subtotal gastrectomy, demonstrating that robotic gastrectomy was viable, even if no direct comparison with laparoscopy was made[7].

Several authors worldwide reported their experience on RAG for cancer and the largest single institution series investigating clinical and oncological outcomes so far include (Table 1): Song *et al*[9] in 2009, Jiang *et al*[29] in 2012, Liu *et al*[31] and Park *et al*[32] in 2013, Tokunaga *et al*[34] in 2015, which included respectively 100, 120, 104, 200 and 120 patients. These studies confirmed the safety and feasibility of RAG for cancer, essentially reporting a suitable amount of lymph nodes retrieved, but they did not furnish long-term survival data. Globally, among these various studies RAG appears to be safe in terms of the incidence and severity of postoperative complications. The morbidity rate ranges between 4.9% to 13%, with a mortality rate of 0%-6%, comparable to those of conventional gastric cancer surgery. Among reported potential advantages of the robotic procedure, Tokunaga *et al*[34] noted a very low incidence of intra-abdominal infectious complications (3.3%) in a large cohort of gastric cancer patients (n = 120) submitted to total or subtotal gastrectomy.

Comparative studies

Despite the existence of numerous reports regarding the safety and feasibility of RAG, only few robotic comparative analysis investigated RAG *vs* laparoscopic and/or open gastrectomy (Table 2)[11,12,24,25,35-50]. Most studies comparing robotic gastrectomy with open and laparoscopic surgery are retrospective case-control studies, almost all of these with sample sizes of fewer than 100 cases. Only one multi-centre comparative study was prospectively conducted: Kim *et al*[50], compared a total of 434 gastric cancer patients submitted to robotic and laparoscopic gastrectomy (223 *vs* 211 respectively), and showed similar overall complications rate with no operative mortality in either group, at the expense of significantly higher operative time and higher costs of the robotic group.

However, initial outcome demonstrated comparable or superior short-term results of RAG than the results achieved by open and laparoscopic procedures, at the price of generally longer operation time, as well as higher cost. The prolonged operation time is attributable also to the additional time docking the robotic system, however that time decreases gradually as the expertise of the team increases, and robotic devices are upgraded[9]. Multiple series have reported various ranges in morbidity (5%-17%) after RAG (Table 2). Essentially, outcomes shown in these studies are satisfactory and similar to those of traditional surgical procedures (Table 2). Aforementioned outcomes demonstrate the clinical feasibility in using robotic radical gastrectomy for gastric adenocarcinoma in comparison with the conventional open and traditional minimally invasive laparoscopic approach, in some cases with potential clinical advantages also. For example, Kim *et al*[44] and Suda *et al*[49] showed a statistically significant improvement of the postoperative morbidity rate in gastric cancer patients submitted to RAG compared to LAG. In particular, Suda *et al*[49] noted that local (particularly pancreatic fistula, robotic 0% *vs* conventional laparoscopy 4.3%, P = 0.029) rather than systemic complication rates were attenuated using the surgical robot. Also Seo *et al*[47] reported an advantages of RAG in comparison to LAG in terms of a reduction of the incidence of postoperative pancreatitis or pancreatic fistula, which has been attributed to what is assumed to be a more gentle and steady pancreatic compression through the robotic system compared to laparoscopy during the suprapancreatic lymph nodes dissection.

For the first time Kim *et al*[36] reported the results achieved with robotic surgery with respect to laparoscopic and open gastrectomy for the treatment of early gastric cancer. They compared 16 patients who underwent robotic procedure with 11 and 12 laparoscopic and open gastrectomy respectively, revealing longer operative times of the robotic group, but less bleeding and reduced length of hospital stay. With regards to number of harvested lymph nodes and post-operative outcomes amongst the groups no difference was demonstrated.

The biggest (not meta-analyzed) comparative study so far was carried out by Kim *et al*[41]. They retrospectively looked at data on surgical complications of 5839 gastric cancer patients (4542 open, 861 laparoscopic and 436 robotic gastrectomies), and found no

Table 1 Robot-assisted laparoscopic gastrectomy series for treatment of gastric cancer

Ref.	Country	Patients (*n*)	Stage disease	Resection type		Operative time[1] (min ± SD)	Blood loss[1] (mL ± SD)	Open conversion (%)	Harvested nodes[1] (*n* ± SD)	Morbidity (%)	Mortality (%)	Hospital stay[1] (d ± SD)
				Total	Subtotal							
Anderson *et al*[7]	United States	7	0- Ⅰ -II	-	7	420 ± NR	300 ± NR	0	24 ± NR	11.1	0	4 ± NR
Patriti *et al*[8]	Italy	13	Ⅰ - Ⅱ - Ⅲ	4	9	286 ± 32.6	103 ± 87.5	0	28.1 ± 8.3	7.7	0	11.2 ± 4.3
Song *et al*[9]	South Korea	100	Ⅰ - Ⅱ - Ⅲ	33	67	231.3 ± 43.2	128.2 ± 217.5	0	36.7 ± NR	13	1	7.8 ± 17.1
Pugliese *et al*[26]	Italy	18	All stages	-	18	344 ± 62	90 ± 48	12	25 ± 4.5	6	6	10 ± 3
Lee *et al*[27]	South Korea	12	Ⅰ	-	12	253.7 ± 53.0	135.8 ± 133.9	0	46.0 ± 25.5	8.3	0	6.6 ± 1.6
D'Annibale *et al*[28]	Italy	24	Ⅰ - Ⅱ - Ⅲ	11	13	267.5 ± NR	30 ± NR	0	28 ± NR	8.3	0	6 ± NR
Jiang *et al*[29]	China	120	Ⅰ - Ⅱ - Ⅲ	35	85	245 ± 50	70 ± 45	0.9	22.5 ± 10.7	5	0	6.3 ± 2.6
Isogaki *et al*[30]	Japan	61	Not reported	14	47	520 ± 177 TG 388 ± 85 SDG	150 ± 234 TG 61.8 ± 46.5 SDG	0	43 ± 14 TG 42 ± 18 SDG	4.9	1.6	13.3 ± NR
Liu *et al*[31]	China	104	Ⅰ - Ⅱ - Ⅲ	54	50	272.52 ± 53.91	80.78 ± 32.37	2	23.1 ± 5.3	11.5	0	6.2 ± 2.5
Park *et al*[32]	South Korea	200	All stages	46	154	248.8 ± 55.6	146.1 ± 130.3	7	37.9 ± NR	10	0.5	8.0 ± 3.7
Coratti *et al*[33]	Itlay	98	All stages	38	60	296.1 ± NR	105.4 ± NR	7.1	30.6 ± NR	12.1	4.1	8.7 ± NR
Tokunaga *et al*[34]	Japan	120	Ⅰ	12	108	348.5 ± NR	19 ± NR	2.5	44 ± NR	14.2	0	9 ± NR

[1]Mean value. SD: Standard deviation; NR: Not reported; TG: Total gastrectomy; SDG: Subtotal distal gastrectomy.

significant differences between the three groups with regards to post-operative complication and morbidity.

In another large single institute comparative study[25] the authors made a comparison between 236 patients who had undergone robotic curative resection of gastric cancer and 591 laparoscopic surgery patients (Table 2). The authors revealed a statistical significance difference, the mean duration of surgery was 49 min longer in the robotic group, whereas blood loss was 56.3 mL less. Morbidity, mortality and number of lymph nodes retrieved per level were comparable.

In yet another large comparative study (39 patients with gastric cancer undergoing robotic, 586 open and 64 laparoscopic gastrectomies)[39], RAG was linked to diminished bleeding and reduced hospital stay, but with longer operative time than was necessary for both open and laparoscopic gastrectomy. The amount of harvested lymph nodes was also similar between the open and robotic groups, but less in the laparoscopic group (Table 2). The authors especially underlined that robotic instruments made it a great deal more simple to carry out the lymph node dissection, rather than the conventional laparoscopic approach, more so in the infra-pyloric and supra-pancreatic stations.

Junfeng *et al*[24] retrospectively compared 120 *vs* 394 gastric cancer patients who had undergone RAG and laparoscopic assisted gastrectomy (LAG) respectively, revealing similar results. However, it is interesting to note that the authors showed, in addition to once more less intra operative bleeding and longer RAG operative time compared to the laparoscopic counterpart, that the numbers of harvested lymph nodes were notably superior in the RAG group at tier 2. In the same way, Kim *et al*[44] commented that, with regard to their experience achieved on 87 gastric cancer patients who had undergone robot-assisted distal gastrectomy (RADG) compared to 288 submitted to LADG, RADG seemed to be advantageous over LADG in performing the dissection of the second level lymph nodes, in particular those located in the suprapancreatic space and those around the splenic artery. Also Son's *et al*[45] showed that robotic gastric surgery gave a much larger amount of harvested lymph nodes around splenic vessels in comparison to lymph nodes retrieved during laparoscopic procedure. This current medical research evidence, albeit initial, seems to consolidate the advantage of robotic surgery over LAG in its ability to perform a more complete D2 lymphadenectomy, probably making it possible to overcome one of the greatest surgical drawbacks of the laparoscopy in the treatment of gastric cancer.

An advantage of RAG compared to LAG has been reported in terms of a reduction of the incidence of postoperative pancreatitis or pancreatic fistula. This has been attributed to what is assumed to be a more gentle and constant pancreatic compression obtained using the robotic system compared to laparoscopy during the suprapancreatic lymph nodes dissection, *i.e.*, at station 9 and 11[47].

Review and meta-analysis studies

To date, several review articles[10,19,51-55] have been published which provide a critical appraisal of the effectiveness of RAG for gastric cancer, but they are not systematic research and do not actually supply any statistical

Table 2 Comparative case-control studies of robot-assisted gastrectomy *vs* laparoscopic assisted gastrectomy and/or open gastrectomy

Ref.	Subject	Stage disease	Patients (*n*)			Operation time (min)[1]	Blood loss (mL)[1]	Harvested nodes (*n*)[1]	Morbidity (%)	Mortality (%)	Hospital stay (d)[1]
			RAG	LAG	OG						
Song *et al*[35]	RAG *vs* iLAG2 *vs* rLAG2	I - II	20[2]	20[2] 20[2]	-	230 *vs* 289.5 *vs* 134.1 (RAG < iLAG > rLAG)[3]	94.8 RAG *vs* 39.5 rLAG (NS)	35.3 *vs* 31.5 *vs* 42.7 (NS)	5 *vs* 5 *vs* 10 (NS)	0 *vs* 0 *vs* 0	5.7 *vs* 7.7 *vs* 6.2 (RAG < iLAG)[3] (RAG~rLAG, NS)
Kim *et al*[36]	RAG *vs* LAG *vs* OG	I - II - III	16	11	12	259.2 *vs* 203.9 *vs* 126.7 (RAG > LAG > OG)[3]	30.3 *vs* 44.7 *vs* 78.8 (RAG < LAG < OG)[3]	41.1 *vs* 37.4 *vs* 43.3 (NS)	0 *vs* 10 *vs* 20 (NS)	0 *vs* 0 *vs* 0	5.1 *vs* 6.5 *vs* 6.7 (RAG < LAG < OG)[3]
Eom *et al*[37]	RAG *vs* LAG	I - II - III	30	62	-	229.1 *vs* 189.4 (RAG > LAG)[3]	152.8 *vs* 88.3 (NS)	30.2 *vs* 33.4 (NS)	13.3 *vs* 6.6 (NS)	0 *vs* 0	7.9 *vs* 7.8 (NS)
Woo *et al*[25]	RAG *vs* LAG	I - II - III	236	591	-	219.5 *vs* 170.7 (RAG > LAG)[3]	91.6 *vs* 147.9 (RAG < LAG)[3]	39.0 *vs* 37.4 (NS)	11 *vs* 13.7 (NS)	0.4 *vs* 0.3 (NS)	7.7 *vs* 7.0 (RAG > LAG)[3]
Caruso *et al*[38]	RAG *vs* OG	All stages	29	-	120	290 *vs* 222 (RAG > OG)[3]	197.6 *vs* 386.1 (RAG < OG)[3]	28.0 *vs* 31.7 (RAG~OG)	10.34 *vs* 10.0[4] (NS)	0 *vs* 3.3 (NS)	9.6 *vs* 13.4 (RAG < OG)[3]
Huang *et al*[39]	RAG *vs* LAG *vs* OG	I - II - III	39	64	586	430 *vs* 350 *vs* 320 (RAG > LAG > OG)[3]	50 *vs* 100 *vs* 400 (RAG < LAG < OG)[3]	32 *vs* 26 *vs* 34 (RAG = OG > LAG)[3]	15.4 *vs* 15.6 *vs* 14.7 (NS)	1.4 *vs* 1.6 *vs* 2.6 (NS)	7 *vs* 11 *vs* 12 (RAG < LAG < OG)[3]
Uyama *et al*[40]	RAG *vs* LAG	All stages	25	225	-	361 *vs* 345 (NS)	51.8 *vs* 81.0 (RAG < LAG)[3]	44.3 *vs* 43.2 (NS)	11.2 *vs* 16.9 (NS)	0 *vs* 0	12.1 *vs* 17.3 (RAG < LAG)[3]
Kang *et al*[12]	RAG *vs* LAG	I - II - III	100	282	-	202.05 *vs* 173.45 (RAG > LAG)[3]	93.25 *vs* 173.45 (RAG < LAG)[3]	NR	14.0 *vs* 10.3 (NS)	0 *vs* 0	9.81 *vs* 8.11 (RAG > LAG)[3]
Kim *et al*[41]	RAG *vs* LAG *vs* OG	0- I - II - III	436	861	4542	226 *vs* 176 *vs* 158 (RAG > LAG > OG)[3]	85 *vs* 112 *vs* 192 (RAG = LAG < OG)[3]	40.2 *vs* 37.6 *vs* 40.5 (RAG = OG > LAG)[3]	10.1 *vs* 10.4 *vs* 10.7 (NS)	0.5 *vs* 0.3 *vs* 0.5 (NS)	7.5 *vs* 7.8 *vs* 10.2 (RAG = LAG < OG)[3]
Yoon *et al*[42]	RAG *vs* LAG	I - II - III	36	65	-	305.8 *vs* 210.2 (RAG > LAG)[3]	NR	42.8 *vs* 39.4 (NS)	16.7 *vs* 15.4 (NS)	0 *vs* 0	8.8 *vs* 10.3 (NS)
Hyun *et al*[43]	RAG *vs* LAG	I - II - III	38	83	-	234.4 *vs* 220.0 (NS)	131.3 *vs* 130.48 (NS)	32.8 *vs* 32.8 (NS)	13.1[4] *vs* 16.8[4] (NS)	0 *vs* 0	10.5 *vs* 11.9 (NS)
Kim *et al*[11]	RAG *vs* LAG	I - II - III	172	481	-	206.4 *vs* 167.1 (RAG > LAG)[3]	59.8 *vs* 134.9 (RAG < OG)[3]	37.3 *vs* 36.8 (NS)	5.2 *vs* 4.2 (NS)	0 *vs* 0.6 (NS)	7.1 *vs* 6.7 (NS)
Kim *et al*[44]	RAG *vs* LAG	I - II - III	87	288	-	248.4 *vs* 230.0 (RAG > LAG)[3]	NR	37.1 *vs* 34.1 (RAG > LAG)[3]	5.7 *vs* 9.0 (RAG < LAG)[3]	1.1 *vs* 0.3 (NS)	6.7 *vs* 7.4 (RAG < LAG)[3]
Son *et al*[45]	RAG *vs* LAG	I - II - III	51	58	-	264.1 *vs* 210.3 (RAG > LAG)[3]	163.4 *vs* 210.7 (NS)	47.2 *vs* 42.8 (NS)	16 *vs* 22 (NS)	1.9 *vs* 0 (NS)	8.6 *vs* 7.9 (NS)
Park *et al*[46]	RAG *vs* LAG	I - II - III	30	120	-	218 *vs* 140 (RAG > LAG)[3]	75 *vs* 60 (NS)	34 *vs* 35 (NS)	17 *vs* 7.5 (NS)	0 *vs* 0	7.0 *vs* 7.0 (NS)
Junfeng *et al*[24]	RAG *vs* LAG	I - II - III	120	394	-	234.8 *vs* 221.3 (RAG > LAG)[3]	118.3 *vs* 137.6 (RAG < LAG)[3]	34.6 *vs* 32.7 (RAG > LAG)[3]	5.8 *vs* 4.3 (NS)	NR	7.8 *vs* 7.9 (NS)
Seo *et al*[47]	RAG *vs* LAG	I - II - III	40	40	-	243 *vs* 224 (NS)	76 *vs* 227 (RAG < LAG)[3]	40.4 *vs* 35.4 (NS)	NR	NR	6.75 *vs* 7.37 (RAG < LAG)[3]
Shen *et al*[48]	RAG *vs* LAG	I - II - III	93	330	-	257.1 *vs* 226.2 (RAG > LAG)[3]	176.6 *vs* 212.5 (RAG < LAG)[3]	33.0 *vs* 31.3 (RAG > LAG)[3]	9.8 *vs* 10.0 (NS)	NR	9.4 *vs* 10.6 (NS)
Suda *et al*[49]	RAG *vs* LAG	All stages	88	438	-	381 *vs* 361 (RAG > LAG)[3]	46 *vs* 34 (RAG > LAG)[3]	40 *vs* 38 (NS)	2.3 *vs* 11.4 (RAG < LAG)[3]	1.1 *vs* 0.2 (NS)	14 *vs* 15 (RAG < LAG)[3]
Kim *et al*[50]	RAG *vs* LAG	I - II - III	223	211	-	226 *vs* 180 (RAG > LAG)[3]	50 *vs* 60 (NS)	33 *vs* 32 (NS)	13.5 *vs* 14.2 (NS)	0 *vs* 0	7.8 *vs* 7.9 (NS)

[1]Mean value; [2]The authors compared 20 gastric cancer patients who underwent robotic gastrectomy with 20 initial patients who underwent laparoscopic subtotal gastrectomy (iLAG) and 20 recent laparoscopic subtotal gastrectomy performed during the same period as the 20 robotic gastrectomy (rLAG); [3]Difference statistically significant, $P < 0.05$; [4]Major complications rate base on Clavien-Dindo classification ⩾ 3, such as anastomotic and duodenal leakage. RAG: Robot-assisted laparoscopic gastrectomy; LAG: Laparoscopic assisted gastrectomy; OG: Open gastrectomy; NR: Not reported; NS: Not statistically significant difference.

comparative analysis. Thus, the usefulness of these articles is essentially of scientific expounding and debating, they do not add any new knowledge to that so far evidenced by clinical studies.

On the other hand, 9 meta-analysis[20,56-63] conducted using a systematic method have been published to date in literature trying to focus on RAG utility in treating gastric cancer (Table 3). One meta-analysis included certain reports which compared RAG to OG[57]; 5 meta-analyses utilized high quality studies which compared RAG and LG[56,59-61,63]; and the remaining 3 meta-analyses contained a systematic review and meta-analysis of studies investigating short-term results of RAG *vs* LG and OG[20,58,62]. Exclusively prospective and retrospective

Table 3 Meta-analysis comparing robot-assisted gastrectomy with laparoscopic assisted gastrectomy and/or open gastrectomy in the treatment gastric cancer

Ref.	Subject	Patients (*n*)			Operation time (min)[1]	Blood loss (mL)[1]	Harvested nodes (*n*)[1]	Morbidity (%)	Mortality (%)	Hospital stay (d)[1]
		RAG	LAG	OG						
Hyun *et al*[56]	RAG *vs* LAG	268	650	-	68.77[2] (RAG > LAG)[3]	-41.88[2] (RAG < LAG)[3]	-0.71[2] (NS)	0.74[4] (NS)	1.80[4] (NS)	-0.54[2] (NS)
Liao *et al*[57]	RAG *vs* OG	520	-	5260	65.73[2] (RAG > LAG)[3]	-126.08[2] (RAG < LAG)[3]	-0.78[2] (NS)	0.98[4] (NS)	0.98[4] (NS)	-2.87[2] (RAG < LAG)[3]
Xiong *et al*[58]	RAG *vs* LAG	634	1236	-	61.99[2] (RAG > LAG)[3]	-6.08[2] (NS)	-0.25[2] (NS)	1.12[4] (NS)	NR	-0.60[2] (NS)
	RAG *vs* OG	558	-	5301	65.73[2] (RAG > OG)[3]	-154.18[2] (RAG < OG)[3]	-1.13[2] (NS)	1.37[4] (NS)	NR	-2.18[2] (RAG < OG)[3]
Marano *et al*[20]	RAG *vs* OG	404	-	718	95.83[2] (RAG > OG)[3]	-225.58[2] (NS)	-2.68[2] (NS)	0.93[4] (NS)	NR	-2.92[2] (RAG < OG)[3]
	RAG *vs* LAG	404	845	-	63.70[2] (RAG > LAG)[3]	-35.53[2] (RAG < LAG)[3]	0.50[2] (NS)	0.87[4] (NS)	NR	-0.60[2] (NS)
Xiong *et al*[59]	RAG *vs* LAG	736	1759	-	48.64[2] (RAG > LAG)[3]	-33.56[2] (RAG < LAG)[3]	1.28[2] (NS)	1.13[4] (NS)	1.66[4] (NS)	-1.16[2] (NS)
Liao *et al*[60]	RAG *vs* LAG	762	1473	-	50.0[2] (RAG > LAG)[3]	-46.97[2] (RAG < LAG)[3]	1.61[2] (NS)	0.88[4] (NS)	0.45[4] (NS)	-0.5[2] (NS)
Shen *et al*[61]	RAG *vs* LAG	506	1369	-	48.46[2] (RAG > LAG)[3]	-38.43[2] (RAG < LAG)[3]	1.06[2] (NS)	0.95[4] (NS)	NR	-1.0[2] (NS)
Zong *et al*[62]	RAG *vs* OG	481	-	4674	68.47[2] (RAG > OG)[3]	-106.63[2] (RAG < OG)[3]	-0.78[2] (NS)	0.92[4] (NS)	0.72[4] (NS)	-2.49[2] (RAG < OG)[3]
	RAG *vs* LAG	997	2207	-	57.15[2] (RAG > LAG)[3]	-28.59[2] (NS)	-0.63[2] (NS)	1.06[4] (NS)	1.05[4] (NS)	-0.16[2] (NS)
Chuan *et al*[63]	RAG *vs* LAG	551	1245	-	42.9[2] (RAG > LAG)[3]	-16.07[2] (RAG < LAG)[3]	2.45[2] (NS)	1.05[4] (NS)	NR	-1.98[2] (RAG < LAG)[3]

[1]Mean value; [2]Weighted mean difference; [3]Difference statistically significant, $P < 0.05$; [4]Odds ratio. RAG: Robot-assisted laparoscopic gastrectomy; LAG: Laparoscopic assisted gastrectomy; OG: Open gastrectomy; NR: Not reported; NS: Not statistically significant difference.

studies were included in these meta-analysis, while no randomized controlled trials (RCTs) were found. The aforementioned meta-analysis showed that the RAG short-term clinical results were basically to be compared to LG and OG results. In terms of bleeding in particular, RAG was superior to both LG and OG, in spite of longer operation time. In addition RAG and LG groups did not show differences with regards to the number of harvested lymph nodes and conversion to open rates; RAG comported slightly inferior hospital stay or similar to that for LAG, but much less than OG; complications occurring after the operation were similar for all three operating methods.

Robotic surgery lasts longer mainly because of the additional set-up and docking-time necessary for the robotic system. However, it must be said that operating time noticeably diminished as surgical experience in robotic gastrectomy increased[9,32,46]. Moreover, there are major limits to how these meta-analysis are interpreted. All data came from non-randomized controlled trials, and the included studies are essentially limited in number and with small sample sizes. Moreover, significant heterogeneity exists among the included studies deriving from several factors, such as different surgeon skill levels, different types of gastrectomy, different extent of lymph node dissection, different tumour stage, different rate of adjuvant treatment, and different protocols of post-operative management and discharge of patients. Thus, the overall level of clinical evidence of this pooled data was low and, since there have been no randomized comparative studies, even if a meta-analysis is performed, it seems difficult to reach a clear conclusion.

Long term outcome

At the present time, long-term benefits of RAG for the treatment of gastric cancer are under reported in literature. Pugliese *et al*[26] are among the few who have reported long term results in their minimally invasive surgical experience in gastric cancer patients. Among a cohort-case study of 70 patients who underwent minimally invasive subtotal gastrectomy with D2 lymphadenectomy, the authors included also 18 patients submitted to the robotic procedure. The authors did not provide data specifically referred to the robotic group only, however, always on the basis of analogous short-term results between groups undergoing laparoscopic and robotic procedures, the reported 5-year survival was 81% for the whole cohort. Coratti *et al*[33] were the first to report long-term survival data specifically referring to gastric cancer patients submitted to robot-assisted gastrectomies. They analyzed survival results in a group of 98 patients with either early and advanced gastric cancer submitted to RAG. In a mean follow-up of 46.9 mo, they registered a cumulative 5-year survival rate of 73.3%. Son *et al*[45] carried out the longest follow-up study till now available. They evaluated the survival rates in a cohort-study group of 51 gastric cancer patients submitted to robotic total gastrectomy with D2 lymph nodes dissection and compared it to 58 patients who underwent analogous surgery but through the laparoscopic approach. In a median long-term follow-up of 70 mo, the authors did not find significant differences

in overall survival and disease-free survival between the two groups. Specifically, the authors reported a 5-year overall survival rate of 89.5% for the robotic group, which was not statistically significant different with respect to the rate revealed in the laparoscopic group (91.1%).

The aforementioned results are comforting, but it must be said that the case studies were limited, and selection bias is a real worry as it was a non-randomized study design. Follow-up periods longer than 5 years are needed to show oncological results, and so further RCTs are required in order to validate definitive conclusions.

DISCUSSION

The relative new technological advance in surgery through the introduction of minimally invasive technique can be accepted as an alternative to open surgery, which usually confers better short-term post-operative results, only if the oncologic parameters are as sufficiently respected as for the traditional open approach. Obviously, at the same time the long-term survival rates should not be adversely affected either.

With specific reference to gastric cancer one of the most important oncological criterion is the quality of lymphadenectomy, thus in order for laparoscopic or robot-assisted laparoscopic gastric surgery to be considered adequate, at least the same extent of lymph node dissection as in traditional surgery should be achieved, and moreover favorable postoperative results should also be evident.

Over the last two decades LG with lymph node dissection has developed as minimally invasive surgery for gastric cancer and it has been principally applied to early gastric cancer. Certain RCTs and meta-analysis showed that laparoscopic gastrectomy did not have inferior oncologic results compared to open surgery for early-stage gastric cancer, with instead improved results in the short term[3,64,65]. In fact, laparoscopic extended D1 lymphadenectomy may be seen as sufficient for almost all early gastric cancer in which lymph node metastases rarely occur, and is today the recommended approach in the East. On the other hand, only few high quality reports investigating the oncological adequacy of laparoscopic minimally invasive techniques for advanced gastric cancer are available to date. Recently, some meta-analyses related to this have been published, but there have been contrasting outcomes, particularly regarding complications after total gastrectomy and the actual adequacy of D2 lymphadenectomy in patients affected by advanced-stage of gastric cancer[4,64,66-69]. Even though a complete LG and extended lymph nodes dissection has been demonstrated by several experts to be feasible laparoscopically[5,6,26,70], due to some intrinsic limiting drawbacks of the laparoscopic technique, important oncologic preoccupations have been raised. When in the meta-analysis studies data not restricted to LADG solely for early gastric cancer was considered, but instead included advanced-stage tumour too, it was not possible to guarantee the same amount of lymph node dissection as in conventional surgical procedures[71,72]. Thus, the laparoscopic techniques cannot be considered a standard validated procedure for all gastric cancer sufferers.

Certain inherent drawbacks of conventional laparoscopy may be eliminated by robotics by increasing the use of minimally invasive procedures, especially when more extended lymph nodes dissection and complicated reconstruction are required. In light of this, the introduction of robotic technologies could lead to the improvement of health care and final results. Particularly during typical difficult maneuvers in laparocopy, such as the dissection of the lymphatic tissue around major abdominal vessels (gastric, gastroepiploic, common hepatic, and celiac artery lymph nodes), robotics offers some indisputable advantages, which make it possible to perform the dissection more safely and easily. Consequently, robotic techniques should be viewed more as a technical advancement and auxiliary tool of the traditional minimally invasive laparoscopic approach, rather than an independent device system.

Most surgeons who are experts in robotics reported in their experience amounts of retrieved lymph nodes during RAG similar to those obtainable by the classic open counterpart procedure and sometimes more than those achieved by laparoscopy[8,20,38,56-63]. However, it must be said that the explanation of available comparable data among RAG, LG and OG has notable limitations. The principal issue that could affect the interpretation of these data is essentially the lack of a comprehensive comparative RCT. However, we have also to consider that the number of published high quality observational and retrospective studies is limited, and globally the sample sizes in each singular trial is poor. Ultimately, but not less importantly from the point of view of oncological adequacy, the duration of follow up is almost always limited.

CONCLUSION

RAG appears to be a safe and feasible alternative to conventional open or laparoscopic gastrectomy for the treatment of early stage gastric carcinoma, having demonstrated satisfactory perioperative outcomes and oncological adequacy. The number of collected lymph nodes when comparing RAG to open and laparoscopic gastrectomy are essentially similar when considering early-stage gastric cancer only, while an advantageous lower blood loss estimation was revealed in comparison with the other two approaches.

Basically the robotic system simplifies certain hard conventional laparoscopy techniques and renders them safer, in addition simultaneously possessing a learning curve and reproducibility that appear to be briefer than conventional laparoscopy[11-14]. These results, albeit initial, are promising, but the superiority of robotic gastric surgery over the traditional laparoscopic approach has not yet been solidly proved and its validation is still a long way off for all gastric cancer patients. The main controversial issue regards the possibility of

demonstrating that the supposed superiority of RAG with respect to laparoscopy in carrying out a more adequate extended lymphadenectomy could lead to potential oncological benefit, probably true in gastric cancer of a more advanced stage.

Unfortunately, due to inadequate long-term follow-up results and a limited number of studies to date available, larger and randomized prospective trials are required to draw definitive conclusion.

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P- Reviewer: Aoyagi K, Arigami T, Jonaitis L, Terashima M, Zhu YL
S- Editor: Qiu S **L- Editor**: A **E- Editor**: Lu YJ

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DOI: 10.4253/wjge.v9.i1.12

World J Gastrointest Endosc 2017 January 16; 9(1): 12-18
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Efficacy of multiple biliary stenting for refractory benign biliary strictures due to chronic calcifying pancreatitis

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Institutional review board statement: The study was reviewed and approved by the Chiba University Institutional Review Board.

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

Conflict-of-interest statement: The authors have no conflicts to disclose. All authors disclosed no financial relationships relevant to this publication.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: June 24, 2016
Peer-review started: June 24, 2016
First decision: August 10, 2016
Revised: August 25, 2016
Accepted: November 1, 2016
Article in press: November 3, 2016
Published online: January 16, 2017

Abstract

AIM

To investigate endoscopic therapy efficacy for refractory benign biliary strictures (BBS) with multiple biliary stenting and clarify predictors.

METHODS

Ten consecutive patients with stones in the pancreatic head and BBS due to chronic pancreatitis who underwent endoscopic therapy were evaluated. Endoscopic insertion of a single stent failed in all patients. We used plastic stents (7F, 8.5F, and 10F) and increased stents at intervals of 2 or 3 mo. Stents were removed approximately 1 year after initial stenting. BBS and common bile duct (CBD) diameter were evaluated using cholangiography. Patients were followed for $\geqslant$ 6 mo after therapy, interviewed for cholestasis symptoms, and underwent liver function testing every visit. Patients with complete and incomplete stricture dilations were compared.

RESULTS

Endoscopic therapy was completed in 8 (80%) patients, whereas 2 (20%) patients could not continue therapy because of severe acute cholangitis and abdominal

abscess, respectively. The mean number of stents was 4.1 ± 1.2. In two (20%) patients, BBS did not improve; thus, a biliary stent was inserted. BBS improved in six (60%) patients. CBD diameter improved more significantly in the complete group than in the incomplete group (6.1 ± 1.8 mm *vs* 13.7 ± 2.2 mm, respectively, $P = 0.010$). Stricture length was significantly associated with complete stricture dilation (complete group; 20.5 ± 3.0 mm, incomplete group; 29.0 ± 5.1 mm, $P = 0.011$). Acute cholangitis did not recur during the mean follow-up period of 20.6 ± 7.3 mo.

CONCLUSION

Sequential endoscopic insertion of multiple stents is effective for refractory BBS caused by chronic calcifying pancreatitis. BBS length calculation can improve patient selection procedure for therapy.

Key words: Chronic pancreatitis; Biliary stricture; Biliary stent; Pancreatic stone; Endoscopy

Core tip: Endoscopic biliary stenting for benign biliary strictures (BBS) is useful for symptom relief and less invasive than surgery. Therefore, BBS caused by chronic pancreatitis (CP) is often managed by biliary stenting. However, subsequent treatment for refractory BBS caused by CP is unclear and no predictive factors for therapeutic success have been defined. The results of the present study indicated that endoscopic therapy with multiple biliary stenting was effective against the refractory BBS caused by chronic calcifying pancreatitis. Moreover, our study indicated that stricture length was correlated with therapeutic outcome.

Ohyama H, Mikata R, Ishihara T, Sakai Y, Sugiyama H, Yasui S, Tsuyuguchi T. Efficacy of multiple biliary stenting for refractory benign biliary strictures due to chronic calcifying pancreatitis. *World J Gastrointest Endosc* 2017; 9(1): 12-18 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i1/12.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i1.12

INTRODUCTION

Chronic pancreatitis (CP) is characterized by progressive inflammation of the pancreas, which leads to permanent damage of pancreatic structure, function, or both, resulting in episodic or intractable abdominal pain with progressive exocrine and endocrine insufficiency[1]. Inflammation associated with CP occurs in 2.7% to 45.6% of cases and leads to stricture formation in the common bile duct (CBD)[2]. The stasis of bile caused by strictures increases intraluminal pressure in the CBD and induces cholangitis, choledocholithiasis, and secondary biliary cirrhosis[2,3]. Therefore, to reduce CBD pressure, biliary dilation for benign biliary stricture (BBS) should be attempted, while pressure increase as a result of CP can be managed by surgery or endoscopic therapy.

Nealon *et al*[4] reported that surgical intervention offered a definitive solution for BBS, but was associated with significant morbidity and mortality. Endoscopic biliary dilation by endoscopic retrograde cholangiopancreatography (ERCP) is less invasive than surgery and is the most successful option for patients who are not candidates for surgery[5-7]. Thus, the European Society of Gastrointestinal Endoscopy (ESGE) has recommended endoscopic therapy as a useful therapeutic approach for BBS[8].

A previous study reported the effectiveness of endoscopic therapy with a single stent for BBS due to CP[9]. By comparing single *vs* multiple simultaneous biliary stenting for treatment of strictures, use of multiple stents appeared to be superior to use of a single stent[10]. Other studies suggest that sequential endoscopic insertion of multiple biliary stents leads to medium and long-term success of stricture dilation[11,12]. Patients with calcifications of the pancreatic head were identified as a group nonresponsive to endoscopic single stent insertion[9] and BBS with pancreatic stones was reported as intractable to therapy with multiple biliary stenting[12]. However, the efficacy of multiple biliary stenting for patients with pancreatic stones has not been investigated in detail and predictive factors of therapeutic success remain undefined. The aim of this study was to assess the usefulness of endoscopic therapy for refractory BBS as a result of chronic calcifying pancreatitis with multiple biliary stenting, and to clarify predictors.

MATERIALS AND METHODS

Patients

From November 2012 to April 2014, 50 patients with CP visited at the Chiba University Hospital. Of these 50 patients, ten consecutive patients for whom endoscopic therapy with a single stent was unsuccessful were evaluated. Patients aged < 20 years and with a diagnosis of malignant diseases, existence of coagulopathy, a history of biliary surgery, inability to provide informed consent, or medical contraindications for multiple biliary stenting were excluded from the study. Patients were followed after therapy and interviewed for symptoms of cholestasis. Biochemical testing of liver function was performed at each visit. Written informed consent was obtained from all patients who underwent endoscopic therapy. The study protocol was approved by the institutional review board of Chiba University.

Procedure

Side-viewing duodenoscopes (JF-240/260V, TJF-260V; Olympus Medical Systems, Tokyo, Japan) were used to perform all endoscopic procedures. Endoscopic sphincterotomy was performed for all patients. After insertion of a catheter into the CBD, the existence of a BBS was evaluated and the length of the stricture and CBD diameter,

Table 1 Baseline patient characteristics, imaging findings, and interventions before treatment (n = 10)

Variable	Value
Patient characteristics	
Sex, *n* (%)	
Male	10 (100.0)
Female	0 (0.0)
Age, mean ± SD, yr	56.9 ± 6.9
BMI, mean ± SD, kg/m^2	19.2 ± 2.6
Etiology, *n* (%)	
Alcohol	9 (90.0)
Other	1 (10.0)
Alcohol abuse, *n* (%)	
Presence	8 (80.0)
Absence	2 (20.0)
Duration of CP, mean ± SD, mo	106.4 ± 72.4
Treatment period, mean ± SD, d	350.6 ± 61.0
Follow up period, mean ± SD, mo (complete group)	20.6 ± 7.3
Imaging findings	
CBD diameter, mean ± SD, mm	12.5 ± 2.7
Length of stricture, mean ± SD, mm	23.9 ± 5.7
No. of pancreatic stones, *n* (%)	
Single	5 (50.0)
Multiple	5 (50.0)
Pancreatic stone location, *n* (%)	
Head	10 (100.0)
Body + Tail	0 (0.0)
Pancreatic stone diameter, mean ± SD, mm	10.2 ± 5.5
Interventions	
No. of ERCP sessions, mean ± SD	4.5 ± 1.0
No. of stents, mean ± SD	4.1 ± 1.2
Dilation of CBD stricture, *n* (%)	
Presence	0 (0.0)
Absence	10 (100.0)

BMI: Body mass index; CBD: Common bile duct; CP: Chronic pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography.

which was upstream of the stricture, was measured by cholangiography in all patients. A flexible guide wire was passed through the stricture and a single plastic stent was inserted beyond the stricture. Plastic stents (7F, 8.5F, and 10F) and increased stents at intervals of 2 or 3 mo were used to avoid clogging and development of cholangitis[13]. When symptoms and abnormal liver function test results following cholestasis appeared, stents or exchanged stents were inserted. All stents were removed approximately one year after initial stenting. Then, the stricture and CBD diameter were evaluated by comparisons with values before therapy.

Outcomes and definitions

The main study outcome was the usefulness of multiple biliary stenting for refractory BBSs for symptom relief and maintenance. Diagnosis of CP was based on clinical history and morphological abnormalities of the pancreas, as identified by computed tomography, magnetic resonance cholangiopancreatography, ERCP, and endoscopic ultrasound[14]. Diagnosis of a BBS was based on signs and symptoms of biliary obstruction and evidence of upstream biliary dilatation on imaging[15]. Symptomatic biliary obstruction was defined by clinical and laboratory findings of obstructive jaundice. The stricture was considered sufficiently dilated if there was easy passage of an 8.5 mm balloon and rapid emptying of contrast was evident fluoroscopically[12]. Accordingly, patients with complete stricture dilation were included in the complete group and those with incomplete stricture dilation were included in the incomplete group. Characteristics of the two groups were compared to identify therapeutic predictors. Patient sex, age, body mass index (BMI), etiology, history of alcohol abuse, duration of CP, treatment period, CBD diameter, length of stricture, number of pancreatic stones, pancreatic stone location, pancreatic stone diameter, number of ERCP sessions, and number of biliary stents were evaluated as potential predictors. During the follow-up period, symptom relapse was defined as the appearance of symptomatic biliary obstruction. Complications related to endoscopic therapy were recorded. The severity of these complications was defined and graded according to the consensus criteria proposed by Cotton *et al*[16].

Statistical analysis

The Mann-Whitney *U* test was used to compare continuous variables, while the Fisher's exact test was used for comparison of categorical variables. The Wilcoxon signed-rank test was used to identify differences in the median values of proposed predictors. A probability (P) value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software version 20.0 (IBM-SPSS, Inc., Chicago, IL, United States).

RESULTS

Patients

Baseline patient characteristics, imaging findings, and interventions of all patients enrolled in this study are summarized in Table 1. ERCP procedures were tolerated in all patients. The mean number of biliary stents was 4.1 ± 1.2. Completion of endoscopic therapy was achieved in eight (80.0%) patients. Complete stricture dilation after therapy was achieved in six (60.0%) patients. BBS was not improved in two (20%) patients, thus biliary stents were inserted. CBD diameter was significantly improved after therapy (before therapy; 12.5 ± 2.7 mm, after therapy; 8.7 ± 3.9 mm, $P = 0.022$).

Outcomes

All patients were male and had pancreatic stones in the pancreatic head. Therefore, patient sex and pancreatic stone location were excluded from analysis of therapeutic outcome predictors. Patients' age, BMI, etiology history of alcohol abuse, duration of CP, treatment period, number of pancreatic stones, pancreatic stone diameter, number of ERCP sessions, and number of biliary stents were similar in complete and incomplete groups. CBD diameter improvement was more significant in the complete group than the incomplete group (6.1 ± 1.8 mm *vs* 13.7 ± 2.2 mm, respectively, $P = 0.010$). Furthermore, only the stricture length was significantly associated with

Table 2 Univariate analysis of factors predicting complete stricture improvement

Variable	Complete (n = 6)	Incomplete (n = 4)	P value
Patient characteristics			
Sex, n (%)			
Male	6 (100.0)	4 (100.0)	
Female	0 (0.0)	0 (0.0)	
Age, mean ± SD, yr	58.8 ± 8.2	54.0 ± 3.4	0.61
BMI, mean ± SD, kg/m^2	18.0 ± 1.7	20.6 ± 3.1	0.114
Etiology, n (%)			0.6
Alcohol	5 (83.3)	4 (100.0)	
Other	1 (16.7)	0 (0.0)	
Alcohol abuse, n (%)			0.667
Presence	1 (16.7)	1 (25.0)	
Absence	5 (83.3)	3 (75.0)	
Duration of CP, mean ± SD, mo	83.7 ± 79.4	140.5 ± 51.4	0.257
Treatment period, mean ± SD, d	384.5 ± 16.4	299.8 ± 70.6	0.171
Imaging findings			
CBD diameter before therapy, mean ± SD, mm	12.4 ± 2.3	12.8 ± 3.7	0.762
Length of stricture, mean ± SD, mm	20.5 ± 3.0	29.0 ± 5.1	0.011
No. of pancreatic stones, n (%)			0.738
Single	3 (50.0)	2 (50.0)	
Multiple	3 (50.0)	2 (50.0)	
Pancreatic stone location, n (%)			
Head	6 (100.0)	4 (100.0)	
Body + Tail	0 (0.0)	0 (0.0)	
Pancreatic stone diameter, mean ± SD, mm	7.4 ± 3.7	14.2 ± 6.2	0.067
Interventions			
No. of ERCP sessions, mean ± SD	4.5 ± 0.8	4.5 ± 1.3	> 0.999
No. of biliary stents, mean ± SD	4.0 ± 0.9	4.3 ± 1.7	0.767

BMI: Body mass index; CBD: Common bile duct; CP: Chronic pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography.

complete stricture dilation (complete group; 20.5 ± 3.0 mm, incomplete group; 29.0 ± 5.1 mm, P = 0.011) (Table 2). Successful results were obtained only in patients with a stricture length of less than 24.0 mm (Table 3, Figures 1 and 2).

All six patients who achieved complete stricture dilation at least 6 mo after therapy were followed-up for a mean period of 20.6 ± 7.3 mo. During the follow-up period, there was no incidence of recurrence of symptomatic biliary obstruction.

Complications

Endoscopic therapy could not be completed in two (20%) patients because of acute cholangitis and abdominal abscess, respectively. Therefore, each underwent endoscopic biliary stenting and both recovered following conservative therapy. There were no complications related to ERCP. No instance of severe complication or patient death was noted during the follow-up period.

DISCUSSION

BBS formation is a common complication from either hepato-biliary surgery or diseases, such as CP and primary sclerosing cholangitis, among others[17]. BBS complicates the course of CP in 3% to 23% of patients[18]. BBS causes cholestasis that frequently results in cholangitis. Therefore, endoscopic therapy or surgery for BBS should be attempted. A postoperative BBS is managed with endoscopic therapy, which can improve long-term and very long-term results[12,19,20]. According to the ESGE guidelines, if endoscopic therapy is selected for BBS caused by CP, temporary (one-year) placement of multiple, side-by-side, plastic biliary stents is recommended[8]. Therefore, many patients with BBS caused by CP are managed with multiple biliary stenting. However, Draganov *et al*[12] reported that endoscopic therapy for these patients tended to be more unsuccessful than for patients with postoperative stricture and the results are worse for those with pancreatic stones. This study aimed to evaluate the efficacy of endoscopic therapy for refractory BBS caused by chronic calcifying pancreatitis with multiple biliary stenting and to clarify predictors of therapeutic success.

Alcohol is the most common cause of CP in Japan[21] and is regarded as the leading cause of CP in Western countries[14]. Disease in patients with alcoholic CP often progresses to pancreatic degeneration and pancreatic stone formation occurs more rapidly than in those with idiopathic CP[22]. Moreover, patient compliance tends to be poor[8]. Our study had a relatively larger proportion of patients with alcoholic CP (90.0%) than reported in previous studies (54.1%-69.0%)[6,9]. Since all patients in our study had refractory BBS, those with alcoholic CP were likely the majority. Although alcoholic CP mainly affects men[14], prognosis of all patients in this study might be generally consistent with that of males.

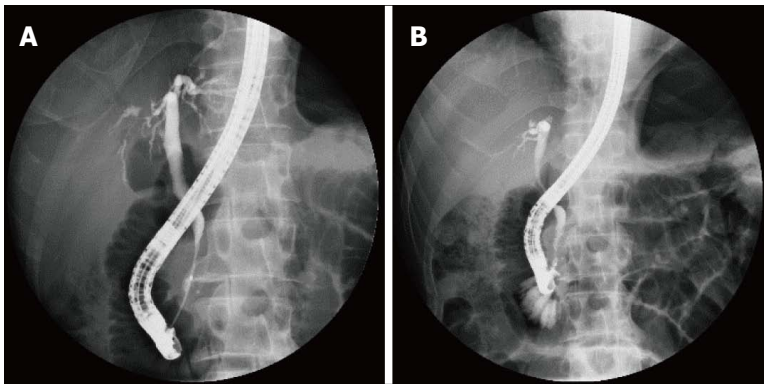

Figure 1 Endoscopic retrograde cholangiopancreatography pictures of successful endoscopic stenting in a male patient with a short stricture (19.3 mm). A: Before stent therapy; B: After 1 year of stent therapy.

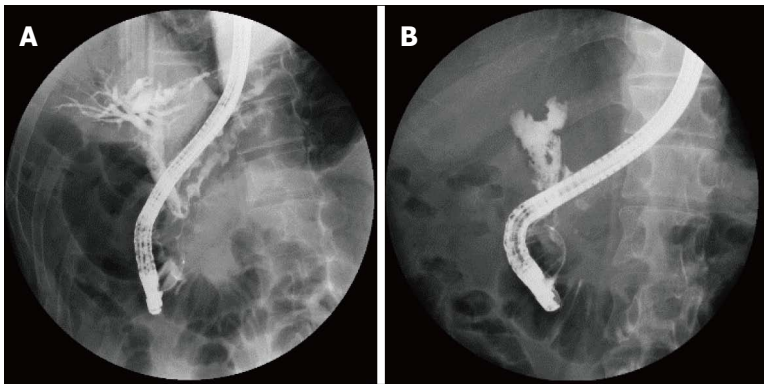

Figure 2 Failure of endoscopic stenting of common bile duct stricture demonstrated by endoscopic retrograde cholangiopancreatography findings in a male patient with a long stricture (36.0 mm). A: Before stent therapy; B: After 1 year of stent therapy.

Table 3 Outcomes of multiple biliary stenting in association with stricture length

Patient No.	Length of stricture (mm)	Outcomes of stricture dilation
1	23.2	Complete
2	20.7	Complete
3	19.3	Complete
4	36	Incomplete
5	20.4	Complete
6	24.9	Incomplete
7	29.4	Incomplete
8	25.5	Incomplete
9	24	Complete
10	15.5	Complete

Biliary stenting was routinely exchanged every 3 mo to avoid clogging and resulting cholangitis based on a study by Dumonceau *et al*[8] and supported by findings of Greiner's group[13,23]. Besides, the ESGE recommends temporary (one-year) placement of multiple, side-by-side, plastic biliary stents. In our study, the mean number of biliary stents was 4.1 ± 1.2 and the mean number of ERCP sessions was 4.5 ± 1.0, similar to those reported in previous studies[5,6,10-12,19,24].

Patients with BBS caused by CP were previously treated by single stent insertion to dilate the stricture, according to the recommendations of Kahl *et al*[9]. Endoscopic therapy was successful for some patients, especially those with a short BBS length. Although the presence of calcification in the pancreatic head and stricture location according to the Bismuth classification was used to predict complete stricture dilation in previous studies[9,12], no report has investigated the relevance of BBS length. Therefore, we evaluated the impact of BBS length on treatment outcome and found that BBS length was indeed a prognostic factor for procedural success. Calculation of BBS length improves the patient selection procedure for therapy. Although it is important to select patients who are likely to achieve favorable outcomes with complete stricture dilation, alternative therapies, including surgery, and avoidance of repetitive therapies could improve the quality of life of others.

In this study, complete stricture dilation was observed in 60% of patients, consistent with previous studies (44%-92%)[6,10-12]. The results suggest that multiple biliary stenting is a useful procedure for treatment of refractory BBS.

Complications were observed in two (20.0%) patients: one developed cholangitis and the other an abdominal abscess. Both recovered by conservative therapy and biliary stent insertion. Moreover, the frequency of these findings was comparable with other reports[6,9,10,12].

In our study, the sample size was small and the patients were all male. In addition, this study was investigated by a single center. Additional multicenter studies with large number of patients involving both male and female patient population are needed to confirm our study.

In conclusion, the results of the present study indicated that endoscopic therapy with multiple biliary stenting was effective against refractory BBS caused by chronic calcifying pancreatitis. Moreover, the stricture length was correlated with therapeutic outcomes. A stricture length of < 24.0 mm is a predictor of good prognosis of complete

stricture dilation. Therefore, the use of this threshold could help in the planning of alternative therapeutic options for patients for whom incomplete stricture dilation is likely.

ACKNOWLEDGMENTS

The authors would like to thank Enago (www.enago.jp) for the English language review.

COMMENTS

Background

To reduce common bile duct (CBD) pressure, biliary dilation for benign biliary stricture (BBS) is often attempted by endoscopic therapy with multiple biliary stenting. However, the efficacy of multiple biliary stenting for patients with pancreatic stones has not been investigated in detail and predictive factors of therapeutic success remain undefined.

Research frontiers

Identifying predictors of good prognosis of complete stricture dilation may help in the planning of alternative therapeutic options for patients for whom incomplete stricture dilation is likely.

Innovations and breakthrough

Endoscopic therapy with multiple biliary stenting was effective against refractory BBS caused by chronic calcifying pancreatitis. Moreover, the stricture length was correlated with therapeutic outcomes.

Applications

This study suggests that calculation of BBS length improves the patient selection procedure for therapy.

Terminology

BBS refers to benign biliary stricture. Inflammation associated with chronic pancreatitis leads to stricture formation in the CBD. The stasis of bile caused by BBS induces cholangitis, choledocholithiasis, and secondary biliary cirrhosis.

Peer-review

This is a meaningful and innovative manuscript based on endoscopic retrograde cholangiopancreatography stenting and BBS therapy. This is an interesting cohort study with small group of patients. However, the data presented is important in identifying a large cohort group involving both male and female patient population in future studies. The studies including the patient selection has been carefully performed. Data analysis was performed carefully and could have been improved with a larger cohort.

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P- Reviewer: Chowdhury P, Yin HK **S- Editor**: Gong ZM
L- Editor: A **E- Editor**: Lu YJ

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DOI: 10.4253/wjge.v9.i1.19

World J Gastrointest Endosc 2017 January 16; 9(1): 19-25
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Gastric antral webs in adults: A case series characterizing their clinical presentation and management in the modern endoscopic era

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Author contributions: Morales SJ and Nigam N are the co-first authors, and contributed equally to this work; Morales SJ, Nigam N, Abdelaziz DI, Lewis JH and Benjamin SB designed research; Morales SJ, Nigam N, Abdelaziz DI, Lewis JH and Benjamin SB performed research; Morales SJ and Nigam N analyzed data; Morales SJ, Nigam N, Abdelaziz DI, Lewis JH and Benjamin SB wrote the paper; all the authors contributied to the article.

Institutional review board statement: The study was reviewed and approved by the Georgetown University Institutional Review Board.

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

Conflict-of-interest statement: No conflicts of interest for any authors.

Data sharing statement: No additional data are available.

Manuscript source: Invited manuscript

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Received: June 14, 2016
Peer-review started: June 16, 2016
First decision: July 20, 2016
Revised: August 18, 2016
Accepted: November 1, 2016
Article in press: November 3, 2016
Published online: January 16, 2017

Abstract

AIM

To investigate the current management of gastric antral webs (GAWs) among adults and identify optimal endoscopic and/or surgical management for these patients.

METHODS

We reviewed our endoscopy database seeking to identify patients in whom a GAW was visualized among 24640 esophagogastroduodenoscopies (EGD) over a seven-year period (2006-2013) at a single tertiary care center. The diagnosis of GAW was suspected during EGD if aperture size of the antrum did not vary with peristalsis or if a "double bulb" sign was present on upper gastrointestinal series. Confirmation of the diagnosis was made by demonstrating a normal pylorus distal to the GAW.

RESULTS

We identified 34 patients who met our inclusion criteria (incidence 0.14%). Of these, five patients presented with gastric outlet obstruction (GOO), four of whom underwent repeated sequential balloon dilations and/or needle-knife incisions with steroid injection for alleviation of GOO. The other 29 patients were incidentally found to have a non-obstructing GAW. Age at diagnosis ranged from 30-87 years. Non-obstructing GAWs are mostly

incidental findings. The most frequently observed symptom prompting endoscopic work-up was refractory gastroesophageal reflux (*n* = 24, 70.6%) followed by abdominal pain (*n* = 11, 33.4%), nausea and vomiting (*n* = 9, 26.5%), dysphagia (n = 6, 17.6%), unexplained weight loss, (*n* = 4, 11.8%), early satiety (*n* = 4, 11.8%), and melena of unclear etiology (*n* = 3, 8.82%). Four of five GOO patients were treated with balloon dilation (*n* = 4), four-quadrant needle-knife incision (*n* = 3), and triamcinolone injection (*n* = 2). Three of these patients required repeat intervention. One patient had a significant complication of perforation after needle-knife incision.

CONCLUSION

Endoscopic intervention for GAW using balloon dilation or needle-knife incision is generally safe and effective in relieving symptoms, however repeat treatment may be needed and a risk of perforation exists with thermal therapies.

Key words: Gastric antral web; Gastric outlet obstruction; Needle knife; Balloon dilation; Triamcinolone injection

Core tip: Gastric antral webs (GAWs) in adults are rare, likely often overlooked, and when seen, considered to be incidental findings on upper endoscopy. They can, however, cause symptoms including gastric outlet obstruction. Herein, we review management of 34 such patients that underwent treatment at our tertiary institution. Our findings indicate that GAWs can be managed safely and effectively *via* endoscopic intervention with balloon dilation and endoscopic incision with needle knife, although repeat procedures were required in some cases, and a small risk of perforation exists. Standards for appropriate surveillance and appropriate indications for surgical intervention are yet to be defined.

Morales SJ, Nigam N, Chalhoub WM, Abdelaziz DI, Lewis JH, Benjamin SB. Gastric antral webs in adults: A case series characterizing their clinical presentation and management in the modern endoscopic era. *World J Gastrointest Endosc* 2017; 9(1): 19-25 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i1/19.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i1.19

INTRODUCTION

Gastric antral web (GAW), or antral diaphragm, is an uncommon endoscopic finding and a rare cause of gastric outlet obstruction (GOO). Evans and Sarani define GAW as a layer of submucosa and that runs perpendicular to the axis of the stomach[1]. The diagnosis of GAW is suspected during esophagogastroduodenoscopy (EGD) if aperture size of the antrum does not vary with peristalsis and is confirmed by demonstrating a normal pylorus distal to the GAW. To date, the majority of cases have been reported in the pediatric population ranging from premature neonates to teenagers[2-4]. The first case in an adult patient was reported by Sames *et al* in 1949, and very few have been described in the last thirty years[5]. Thus, the clinical setting in which GAW is likely to arise, as well as the optimal endoscopic and/or surgical interventions are poorly defined.

The differential diagnosis of a GAW is broad and includes "distal gastrospasm", redundant gastric mucosa, hypertrophic gastric rugae, heterotrophic pancreatic tissue and cholecystogastrocolic bands and perigastric adhesions[6,7]. Historically, upper gastrointestinal (UGI) series were the imaging modality of choice for patients suspected of having GAW or other obstructive pathology. Interestingly, the radiographic incidence of GAW far exceeds that reported in medical and surgical literature with almost half the cases being incidental findings in "asymptomatic" individuals[8]. The characteristic radiographic findings are thin, knife-like linear septae 2-3 mm thick seen as radiolucent lines 1-2 cm proximal to the pylorus projecting from the greater and lesser curvature[6]. The antrum distal to the web may fill giving the appearance of a "double duodenal bulb", and contrast exiting through the central orifice gives a "jet effect"[7]. However, a GAW may easily be confused with the pylorus despite the use of double-contrast radiographs, and it is recommended that right anterior oblique and left posterior oblique views be obtained[7]. A contrast-enhanced computed tomography (CT) scan may demonstrate the cutoff proximal to the pylorus and a normal caliber pylorus and duodenum downstream with greater accuracy. Rarely has a duodenal web been described[9].

In adults, patients with GAW often develop symptoms when the aperture size is less than 1 centimeter in diameter[10]. Symptoms are usually worse post-prandially and include water brash, dysphagia, odynophagia, abdominal distention, nausea, forced or spontaneous vomiting, early satiety, weight loss, epigastric or right upper quadrant abdominal pain, anterior chest pain and non-bloody, watery diarrhea[5,9,11,12]. Historically, most cases are diagnosed during an endoscopic or radiographic work-up to explain various upper gastrointestinal symptoms[1,13].

MATERIALS AND METHODS

Patient characteristics

We evaluated patients with a diagnosis of GAW by EGD performed at Medstar Georgetown University Hospital between 2007 and 2013. In all cases, the diagnosis of GAW was suspected during EGD if aperture size of the antrum does not vary with peristalsis or if a "double bulb" sign is present on upper gastrointestinal (UGI) series. Confirmation of the diagnosis was made by demonstrating a normal pylorus distal to the GAW.

Data collection

For all patients, data were collected retrospectively,

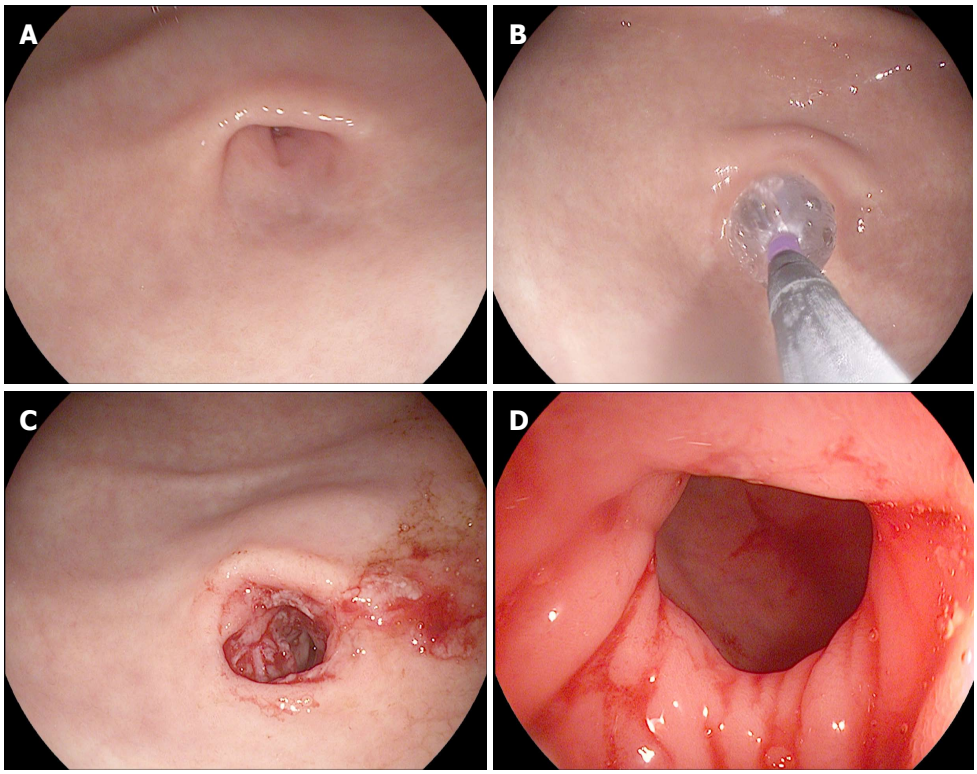

Figure 1 Endoscopic images from Case 1. A: An obstructing gastric antral web (GAW); B: Balloon dilation of the GAW; C: The appearance of the GAW following balloon dilation; D: A normal pylorus seen distally to the GAW.

including demographic data, presenting symptoms, imaging prior to EGD, endoscopic findings, endoscopic interventions, and course following index EGD. These data were gathered *via* a review of procedure reports and other materials found in our electronic medical records systems.

Statistical analysis

Univariate analyses were conducted to describe the distributions of demographic data, presenting symptoms and need for intervention. Significance statements refer to *P* values of two-tailed tests that were < 0.05.

RESULTS

We identified 34 cases of GAW encountered among 24640 EGDs performed at our institution from 2007-2013 for an incidence of 0.14%. These cases included five instances in which GAW was complicated by GOO as described below. There were no significant differences in presenting symptoms between patients with GAW with GOO and non-obstructing GAW.

Case 1

A 60-year-old Caucasian female with hypothyroidism, hyperlipidemia, and functional constipation was evaluated for a three-month history of gastroesophageal reflux. She had been experiencing odynophagia and retrosternal pressure after eating solid foods. Her symptoms were not alleviated with omeprazole, cimetidine, or bismuth subsalicylate. Laboratory testing, including thyroid function tests, were normal. EGD revealed retained food in the stomach and an obstructing antral web (Figure 1A). Balloon dilation to 12 mmHg was performed (Figure 1B and C), allowing visualization of a normal pylorus beyond the narrowing (Figure 1D). Following balloon dilation, needle-knife cuts were made in four quadrants (Figure 2) and 80 mg triamcinolone was injected. The patient remained asymptomatic for five years, at which time symptoms similar to those at initial presentation returned. She underwent a repeat EGD which showed recurrence of the obstructing antral web. The GAW was sequentially balloon dilated to 15 mmHg, followed by repeat four quadrant needle-knife cuts and reinjection of 80 mg triamcinolone. The patient remained asymptomatic for two years at which time EGD showed a third recurrence of the GAW, requiring repeat balloon dilation, four-quadrant needle-knife cuts, and triamcinolone injection. Although her symptoms were alleviated, the patient was advised to seek surgical evaluation for more permanent intervention, should her symptoms recur.

Case 2

A 80-year-old African-American female with hypertension, emphysema and prior breast and lung cancer presented with dysphagia to solids and liquids, persistent nausea and vomiting, and abdominal fullness. CT scan showed a partial GOO without evidence of external compression or intrinsic mass at the pylorus, while UGI series suggested a near complete gastric outlet obstruction. EGD revealed retained food in the body and antrum of the stomach,

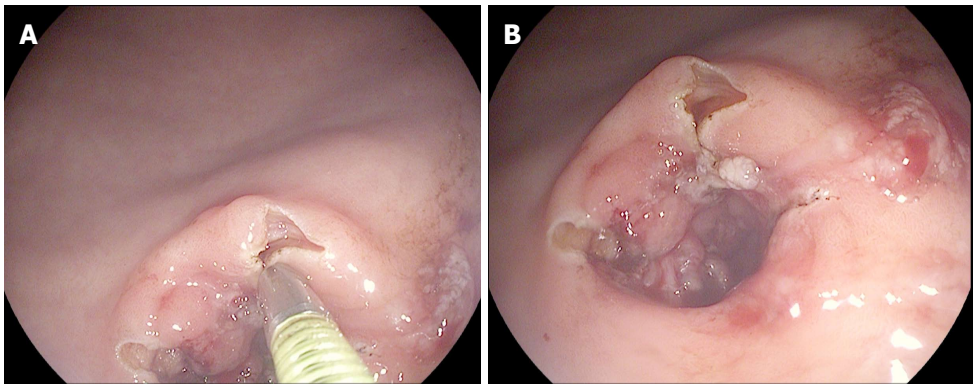

Figure 2 Needle-knife incision of a gastric antral web. A: Four-quadrant needle-knife incision of a gastric antral web (GAW); B: The final appearance of a GAW following balloon dilation, four-quadrant needle-knife incision, and triamcinolone injection.

severe antral erosions, and an obstructing GAW. Sequential balloon dilation to 10 mmHg was performed, allowing the regular 9.8 mm endoscope to be advanced without resistance. Given the partial return of symptoms within two weeks, EGD was repeated, and the GAW was incised using needle-knife cautery. Subsequently, the patient noted alleviation in her symptoms, and during follow-up EGD a week later, the endoscope traversed the antral web with minimal resistance.

Case 3

A 68-year-old Hispanic male with diabetes mellitus, coronary artery disease, and chronic kidney disease was evaluated for a ten-year history of nausea, frequent regurgitation and early satiety with a 90 pound weight. Screening colonoscopy two years prior was unremarkable, as was an UGI series and CT scan of the abdomen. EGD at the time showed antral narrowing, complicated by post biopsy bleeding. After a two year course of esomeprazole, repeat EGD showed retained gastric contents and an obstructing GAW with 6 mm aperture. Balloon dilation to 15 mm was performed, allowing a 9 mm endoscope to be advanced. The patient was seen in our clinic three weeks later and reported a five pound weight gain in the interim with no recurrence of his symptoms.

Case 4

A 74-year-old Caucasian female with hypertension, arthritis and gastroesophageal reflux disease was admitted to the inpatient service for a six-week history of abdominal cramping and diarrhea with intermittent melena. She reported no fever, nausea, vomiting, early satiety, weight loss, recent travel, or recent antibiotic use. Stool studies were unremarkable for enteric pathogens or fecal leukocytes. CT scan of the abdomen and pelvis showed pancolitis and a thickened antrum. The patient was empirically started on budesonide and the frequency of her bowel movements decreased. A colonoscopy performed three weeks later was unremarkable, and biopsies were negative for inflammatory bowel disease or microscopic colitis suggesting a possible transient infectious or ischemic colitis. EGD performed at the same time showed an obstructing GAW, but no intervention was performed given the lack of symptoms suggesting GOO. Of note, an EGD performed five years earlier showed a gastric ulcer, but a GAW was not described. The patient's symptoms continued to improve over the next several weeks.

Case 5

An 81-year-old Caucasian woman with scleroderma and gastric antral vascular ectasia (GAVE) treated previously with argon plasma coagulation presented with persistent nausea and vomiting. A GAW causing GOO had been identified at an outside institution, and she was referred for endoscopic management. Upon our initial EGD, the patient was treated with needle-knife incision and injection of 80 mg of triamcinolone. Following this procedure, her symptoms improved, but did not resolve, and she returned for further endoscopic management 8 wk later. At that time, we again performed needle-knife incision, however a complication of perforation was noted with direct visualization of small bowel through the gastric defect. Three endoscopic clips were placed to close the defect, but CT of the abdomen revealed a large pneumoperitoneum. The patient was then taken emergently to the operating room, where a 1.5 cm perforation in the distal aspect of the lesser curvature of the stomach was identified laparoscopically and closed with full-thickness surgical sutures. On post-operative day five, the patient underwent an UGI series that revealed no evidence of persistent perforation and only mild narrowing in the gastric antrum. She was discharged home the following day, and upon follow-up in clinic reported that she was no longer experiencing her symptoms of GOO.

Summary of all cases

Among the 34 cases of GAW, 19 (55.9%) occurred in women and 15 (44.1%) in men. Ages at the time of diagnosis ranged from 30 to 87 years (mean 65.3, St.dev 12.9). Five patients had an obstructing GAW (14.7%, discussed above) and 29 patients were incidentally found to a have non-obstructing GAW (85.3%). The most frequently reported symptom was chronic gastroesophageal reflux in 24 patients (70.6%), each of whom

Table 1 Age, sex, and symptoms of thirty-three patients found to have gastric antral web on esophagogastroduodenoscopy

Patient No.	Age	Sex	Year of diagnosis	Obstructing GAW	Reflux symptoms	PPI course	Dysphagia	Nausea/ vomiting	Abdominal discomfort	Weight loss
1[1]	60	F	2006	Yes	Yes	Yes	Solid	Yes	No	No
2[1]	80	F	2008	Yes	Yes	Yes	Solid/liquid	Yes	No	No
3[1]	68	M	2013	Yes	Yes	Yes	No	Yes	No	Yes
4	74	F	2011	Yes	No	No	No	No	Diffuse	No
5[1]	81	F	2015	Yes	Yes	Yes	No	Yes	No	No
6	85	F	2003	No	No	No	No	No	Diffuse	No
7	62	F	2003	No	No	No	No	No	Diffuse	No
8	56	M	2003	No	No	No	No	No	No	No
9	38	M	2004	No	Yes	Yes	No	No	No	No
10	49	M	2004	No	Yes	Yes	No	No	No	No
11	68	M	2004	No	Yes	Yes	No	No	No	No
12	53	M	2004	No	Yes	Yes	No	No	No	No
13	61	F	2005	No	Yes	Yes	No	No	No	No
14	67	M	2006	No	No	No	No	No	No	Yes
15	69	M	2006	No	Yes	Yes	No	No	No	No
16	82	M	2007	No	Yes	Yes	No	No	No	No
17	63	F	2007	No	Yes	Yes	No	No	No	No
18	66	F	2007	No	No	No	No	Yes	Diffuse	Yes
19	54	F	2007	No	Yes	Yes	Solid	No	Substernal	No
20	76	F	2007	No	Yes	Yes	No	No	No	No
21	58	F	2007	No	Yes	Yes	No	Yes	No	No
22	70	F	2009	No	Yes	Yes	No	No	Diffuse	No
23	67	F	2009	No	No	No	No	No	Diffuse	No
24	56	F	2010	No	No	No	No	No	Diffuse	No
25	30	F	2010	No	Yes	Yes	No	Yes	No	Yes
26	57	M	2011	No	Yes	Yes	No	No	No	No
27	73	M	2011	No	Yes	Yes	No	Yes	No	No
28	52	F	2011	No	Yes	Yes	No	No	No	No
29	71	M	2011	No	Yes	Yes	No	No	Diffuse	No
30	67	M	2012	No	Yes	Yes	Solid	No	Epigastric	No
31	68	F	2012	No	Yes	Yes	Solid	No	No	No
32	66	M	2013	No	No	No	No	Yes	Diffuse	No
33	87	F	2013	No	Yes	Yes	No	No	No	No
34	86	M	2014	No	No	Yes	Solid	No	No	No

[1]Indicates intervention was performed during esophagogastroduodenoscopy. GAW: Gastric antral web; F: Female; M: Male.

had taken proton-pump inhibitor therapy for various periods without significant improvement. Nine patients complained of diffuse abdominal pain (26.5%), one of epigastric pain (2.94%), and one of substernal discomfort (2.94%). Eight patients reported nausea and vomiting (23.5%). Six patients had dysphagia to solids (17.6%) and one to solids and liquids (2.9%). Four patients complained of early satiety (11.8%), three of whom also experienced weight loss (Table 1).

Among patients undergoing further work-up for their chronic gastroesophageal reflux, eight of 24 were found to have a hiatal hernia on endoscopy (33.3%), four had duodenal ulcers (18.2%), one had an antral ulcer (4.17%), and one had a Schatzki ring in addition to the GAW (4.17%). Of note, eight of the 34 patients in this series had prior endoscopies performed three to 14 years prior without description of a GAW (23.5%).

DISCUSSION

While the cause of GAW in adults is poorly understood, in 1965 Rhind *et al*[12] theorized that GAW was "acquired" in adults, and resulted from scarring as circumferential pyloric and pre-pyloric peptic ulcers heal. This theory fits well with our Case 5 where GAW was likely the result of antral scarring from prior APC treatment of GAVE. Given the higher reported incidence in children, many authors believed the "congenital" theory that rapid proliferation of epithelial cells in the gut lumen was not followed by vacuole formation, fusion and recanalization during early development[11,14]. It was further speculated in the past that a congenital GAW may manifest only in adulthood as a result of a decline in efficacy of mastication from fewer teeth, dentures, or diminished muscle strength, or, alternatively, from hypertrophy and decompensation of the stomach chronically forcing food through a narrowed opening, although to our knowledge, these theories were never validated[5,6,14].

Given the prevalence of chronic gastroesophageal reflux in this cohort, we believe the association between this acidity and GAW may be significant. Two-thirds of our patients had reflux symptoms, five of whom had duodenal or gastric ulcers visualized during endoscopy. This is similar to historical reports of GAWs in three adult patients with gastric ulcer of the lesser curvature, and three others who had a duodenal ulcer[5,7,12]. Eight of our

patients had prior endoscopies in which a GAW was not described, and while this might argue against the notion that GAW is a congenital anomaly, it is equally possible that the web simply may have been missed, as they can easily be overlooked or confused with other entities.

Diagnosis

In our patients, GAW was identified on EGD and fulfilled the criteria set forth by Sokol *et al*[15] in 1965: fixed size aperture or "pseudopylorus"; smooth GAW mucosa devoid of folds; and normal peristalsis to the GAW that stops abruptly but continues beyond in a concordant fashion. Evidence of gastric retention was seen in 14.7% of the patients in our series, further confirming the clinical picture.

Treatment

Conservative management with acid suppression, such as proton-pump inhibitors, has been reported to provide temporary relief, but does not result in a permanent cure. Most of the published literature describing GAW dates back 30-40 years and predates modern endoscopic approaches to treatment. Following preliminary exploratory laparotomy or duodenotomy, an incision of the GAW to the central aperture; enlargement of the aperture *via* lysis with transverse gastroplasty or pyloroplasty; or a finger fracture of the GAW and pyloromyotomy were the most common surgical procedures utilized[11]. Although such surgery successfully restored a functional gastric outlet and alleviated symptoms, an endoscopic "webotomy", first suggested by Swartz and Shepard in 1956, heralded the minimally invasive options currently deemed safe given the lack of a muscularis propia in GAWs, and a low risk of perforation[14]. Endoscopic balloon dilation to 10 mm was first described in 1984, and has proven to be effective and safe to repeat[10,16]. However, frequent recurrence led to the development of more permanent interventions. Endoscopic snaring was used successfully in treating an obstructing GAW in an infant[9], and three radial incisions with a papillotome relieved symptoms from a partially obstructing GAW in a 14-year-old female[17]. In 1988, Al-Kawas reported the use of Nd: YAG laser therapy in a 64-year-old symptomatic woman with an obstructing GAW to create a 14 mm lumen, which alleviated symptoms in 48 h, although she later required surgery[9]. This technique has also proven effective in treating an obstructing duodenal web[9]. In 2013, Salah reported a case of obstructing GAW in an 11 year old boy treated with snare resection, electroincision and balloon dilation[18]. Several cases, including ours, have shown long-term resolution of symptoms after radial incisions using needle-knife electrocautery, but the use of empiric triamcinolone acetate for its anti-inflammatory effects has not been previously reported. However, we believe that a combination of balloon dilation and/or needle knife incisions remain the primary endoscopic management tools with low risk of perforation or significant bleeding. In our series, perforation following needle-knife incision occurred in one patient who was likely predisposed by antral scarring from prio APC treatment. In our practice, interventions were only performed after biopsies had confirmed the absence of malignancy. In addition, interventions were only performed in patients with clinically significant symptoms of GOO that were refractory to medical management. The role of surgical intervention for adults with GAWs refractory to endoscopic treatment remains incompletely defined in the endoscopic era.

In conclusion, GAW is a rare endoscopic finding among adults undergoing endoscopy (0.14% in this series over a 7 year period). It is likely often overlooked and is considered an incidental finding when seen, but may be associated with GOO, refractory GERD or gastric or duodenal ulceration. Through-the-scope balloon dilation with or without a needle-knife incision of the web appears to be effective in many patients, although the need for repeat endoscopic treatment was frequent among those with high-grade GOO. The current role for surgical intervention remains to be defined, as it appears to be less necessary in adults than in the past.

COMMENTS

Background

Gastric antral webs (GAWs) are rare entities in adults which can cause gastric outlet obstruction (GOO). In the endoscopic era, interventional endoscopic techniques have been employed in the management of these patients.

Research frontiers

Optimal technique and devices for intervention on GAWs with GOO have yet to be defined, however several techniques have been described in the literature.

Innovations and breakthrough

Herein, the authors report their experience with GAWs at the tertiary institution. The authors found that endoscopic intervention for GAW using balloon dilation or needle-knife incision is generally safe and effective, however repeat treatment may be required and a risk of perforation exists with thermal therapies.

Applications

These techniques, including needle-knife incision, balloon dilation, and triamcinolone injection are generally safe and effective endoscopic interventions, however repeat treatment may be needed and a risk of perforation exists with thermal therapies. These treatment modalities can be used to treat gastric antral webs associated with gastric outlet obstruction.

Peer-review

It's a quite extensive manuscript especially for a case series.

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P- Reviewer: Garg P, Tomizawa M **S- Editor**: Gong ZM
L- Editor: A **E- Editor**: Lu YJ

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DOI: 10.4253/wjge.v9.i1.26

World J Gastrointest Endosc 2017 January 16; 9(1): 26-33
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Recurrence of choledocholithiasis following endoscopic bile duct clearance: Long term results and factors associated with recurrent bile duct stones

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Author contributions: Konstantakis C and Thomopoulos K contributed equally to this work; Konstantakis C collected and analyzed the data, and drafted the manuscript; Thomopoulos K provided analytical oversight; Thomopoulos K designed and supervised the study; Triantos C, Theopistos V, Theocharis G and Maroulis I revised the manuscript for important intellectual content; Triantos C and Thomopoulos K offered technical or material support; Triantos C and Diamantopoulou G provided administrative support; all authors have read and approved the final version to be published.

Institutional review board statement: The study was reviewed and approved by the Ethics committee of the University Hospital of Patras.

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

Conflict-of-interest statement: The Authors have nothing to declare.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at asraiah@yahoo.com.

Manuscript source: Invited manuscript

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Received: June 29, 2016
Peer-review started: July 1, 2016
First decision: August 22, 2016
Revised: September 17, 2016
Accepted: October 17, 2016
Article in press: October 19, 2016
Published online: January 16, 2017

Abstract

AIM

To evaluate the rate of recurrence of symptomatic choledocholithiasis and identify factors associated with the recurrence of bile duct stones in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) for bile duct stone disease.

METHODS

All patients who underwent ERCP and EST for bile duct stone disease and had their bile duct cleared from 1/1/2005 until 31/12/2008 was enrolled. All symptomatic recurrences during the study period (until 31/12/2015) were recorded. Clinical and laboratory data potentially associated with common bile duct (CBD) stone recurrence

were retrospectively retrieved from patients' files.

RESULTS

A total of 495 patients were included. Sixty seven (67) out of 495 patients (13.5%) presented with recurrent symptomatic choledocholithiasis after 35.28 ± 16.9 mo while twenty two (22) of these patients (32.8%) experienced a second recurrence after 35.19 ± 23.2 mo. Factors associated with recurrence were size (diameter) of the largest CBD stone found at first presentation (10.2 ± 6.9 mm *vs* 7.2 ± 4.1 mm, $P = 0.024$), diameter of the CBD at the first examination (15.5 ± 6.3 mm *vs* 12.0 ± 4.6 mm, $P = 0.005$), use of mechanical lithotripsy (ML) ($P = 0.04$) and presence of difficult lithiasis ($P = 0.04$). Periampullary diverticula showed a trend towards significance ($P = 0.066$). On the contrary, number of stones, angulation of the CBD, number of ERCP sessions required to clear the CBD at first presentation, more than one ERCP session needed to clear the bile duct initially and a gallbladder in situ did not influence recurrence.

CONCLUSION

Bile duct stone recurrence is a possible late complication following endoscopic stone extraction and CBD clearance. It appears to be associated with anatomical parameters (CBD diameter) and stone characteristics (stone size, use of ML, difficult lithiasis) at first presentation.

Key words: Bile duct stone disease; Common bile duct angulation; Choledocholithiasis; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy; Recurrence of choledocholithiasis

Core tip: Recurrence of choledocholithiasis is considered a late complication following endoscopic extraction of bile duct stones. There are various factors associated with the risk of recurrence. In our study the rate of recurrence was 13.5%. Although univariate analysis identified four different risk factors associated with both anatomical parameters (common bile duct diameter) and stone characteristics (stone size, use of mechanical lithotripsy, difficult lithiasis), multivariate analysis confirmed only bile duct diameter as being important. The underlying pathogenetic mechanism of recurrence is likely multi-factorial in nature. Bile stasis, duodenal - biliary reflux and unfavorable stone characteristics probably contribute towards stone reformation.

Konstantakis C, Triantos C, Theopistos V, Theocharis G, Maroulis I, Diamantopoulou G, Thomopoulos K. Recurrence of choledocholithiasis following endoscopic bile duct clearance: Long term results and factors associated with recurrent bile duct stones. *World J Gastrointest Endosc* 2017; 9(1): 26-33 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i1/26.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i1.26

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted as the modality of choice for the endoscopic removal of bile duct stones. Endoscopic sphincterotomy (EST) since its introduction in 1974[1,2], has been extensively used for the endoscopic extraction of bile duct stones. Endoscopic techniques for stone removal are generally considered both safe and effective but, their invasive nature cannot preclude the possibility of complications. In fact complications can occur even in the hands of the most seasoned expert[3]. They can be broadly classified, depending on their timing, as early (up to 3 d post-procedure) or late (> 3 d)[4]. Early complications are mostly related with sedation and endoscopy like bleeding, infection, pancreatitis, perforation, cardiopulmonary events, while late complications concern mainly stent infections due to long-term/permanent stent deployment and post-procedural duct/sphincter of Oddi (SO) inflammatory changes (*i.e.,* ampullary stenosis) because of ductal/SO manipulation[4]. Although not officially listed as a late complication of ERCP in various guidelines[3], recurrence of choledocholithiasis is considered to be one by many authors[5-7]. Rates of recurrence vary across different studies, ranging from 4% to 24% (variable intervals of follow-up of up to 15 years)[8-10]. The goal of this paper is to evaluate the rate of recurrence of symptomatic choledocholithiasis and identify factors associated with the recurrence of bile duct stones in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (EST) for bile duct stone disease.

MATERIALS AND METHODS

Patients

We retrospectively studied a group of patients who underwent ERCP and EST for bile duct stone disease at a tertiary center, Department of Gastroenterology of the University hospital of Patras from 1/1/2005 until 31/12/2008. Only patients in whom complete and successful clearance of the common bile duct (CBD) from stones was achieved were included in the study irrespectively of the number of sessions required to fulfill that requirement. Patients with difficult bile duct stones (large bile duct stones (> 10 mm) and/or multiple stones (≥ 3) or impacted stones)[11] or residual choledocholithiasis were included in the study as long as a patent CBD was achieved in their baseline or any of their subsequent follow-up examinations. Patients with known residual CBD stones (unable to be extracted or referred for surgical treatment), pancreatic/biliary malignant disorders and benign biliary strictures (usually post - surgery) were excluded from the study, finally patients with indwelling biliary stents (permanent or long standing) and patients that were lost to follow - up

were also excluded. Every patient with gallbladder stones was instructed to remove his/her gallbladder surgically after the first (baseline) clearance of the bile duct (if a cholocystectomy was not already performed). All patients were followed up until either termination of the study (31/12/2015) or when they died.

For the purpose of studying recurrence associated risk factors we created two (2) groups. In the first group all patients with a history of symptomatic recurrence were enrolled (after applying exclusion criteria). An equal number (1:1) of age / gender - matched control patients was selected from the pool of recurrent free patients (group two).

Endoscopic treatment

Written informed consent for the ERCP was obtained from all the patients undergoing the procedure. Preparation included local anesthesia of the pharynx using 10% xylocaine, and conscious sedation of the patient with the use of (IV) midazolam - pethidine. Reversal agents (flumazenil) were used when indicated. Antibiotic prophylaxis was used in accordance with published guidelines at the time, the exact regimen depending on the appropriate clinical indication[12]. ERCP was performed using a side-view endoscope (Olympus Optical Corporation, Tokyo, Japan). In patients with native papilla EST was performed, after deep canullation of the CBD with the help of a guidewire, using a standard pull-type papillotome according to the standard technique. Before performing the EST a cholangiogram (using a diluted contrast medium) was attainted to confirm CBD stones. Under fluoroscopic/endoscopic guidance stones were removed from the CBD, mainly with the use of ballon catheters and occasionally with dormia retrieval baskets. Patients with difficult stones were treated with either mechanical lithotripsy at the same session or use of temporary plastic stents. Patency of the CBD/clearance of stones was evaluated by absence of any filling defects at the final cholangiogram. During the enrollment period (2005-2008) large balloon dilation was not a common practice. As such it was not exercised by our unit.

Study of the cholangiograms

Size and number of CBD stones were assessed on the cholangiogram after optimum opacification of the CBD. Stone size was assessed by comparing the diameter of the stone to the (relevant size of the) shaft of the endoscope on the cholangiogram. CBD diameter was measured in a similar manner. Likewise CBD angulation(s) were also calculated from postoperative cholangiograms. All calculations were independently validated by a second observer and any interobserver differences were expressed as mean values.

Data collection and definitions

All data was extracted from the first (baseline) ERCP of all patients.

The following parameters were recorded and investigated for the purpose of studying risk factors. (1) Basic demographics: sex and age; (2) Diameter of the CBD (mm); (3) Stone characteristics: Size (mm) (defined as the diameter of the largest stone), number of stones, difficult CBD lithiasis (defined as presence of large bile duct stone (> 10 mm) and/or multiple stones ($\geqslant$ 3) and/or impacted stones[11]); (4) Angulation of the CBD: Two (2) different angulation scores were assessed (Figure 1)[13,14]; (5) Juxtapapillary duodenal diverticula; (6) Timing of recurrences (early *vs* late); (7) Use of mechanical lithotripsy (ML); (8) Number of ERCP session required to clear the Bile Duct; and (9) Past medical history: Surgical (mainly hepatobiliary/pancreatic): (1) Biliary - enteric anastomosis (BEA); (2) Altered stomach anatomy (gastrectomy or other); and (3) Cholocystectomy/remaining gallbladder (gallbladder that was not surgically removed, termed gallbladder *in situ*)/gallbladder stones (chololithiasis).

Stone recurrence, for the purpose of this study, was defined by the confirmation of the presence of a CBD stone in the appropriate clinical context at least 6 mo after previous (complete) CBD stone removal by ERCP was achieved. Thus we evaluated only clinically significant recurrences (patients exhibiting relevant hepatobiliary symptoms like pain and jaundice).

Multiple recurrences were defined as 2 or more stone recurrences after the first ERCP. In this study early recurrence was defined as a recurrence that occurred up to (and including) 24 mo after the baseline ERCP that CBD patency was achieved (this term applies only to first recurrence episodes). A recurrence after the first 24 month was termed a late one.

Follow-up

Clinical and laboratory data potentially associated with common bile duct (CBD) stone recurrence were retrospectively retrieved from patients' files. Our department belongs in a tertiary hospital. Our hepatobiliary unit acts as regional referral center. The likelihood of patients being referred to another unit would be truly improbable.

Statistical analysis

Clinical and ERCP related factors that might have contributed to the recurrence of common bile duct stones were evaluated. All these parameters were correlated with recurrence, initially by using univariate analysis. Continuous variables were expressed as mean ± SD and were compared by using Student's *t*-test. Categorical variables were expressed as percentages and differences between groups were tested for significance by using the χ^2 test. Variables found to be significant in the univariate analysis (*P*-value less than 0.05) were included in a multivariate stepwise logistic regression model. All analyses were conducted by using statistical software SPSS, version 20 (SPSS, Inc, Chicago, IL,

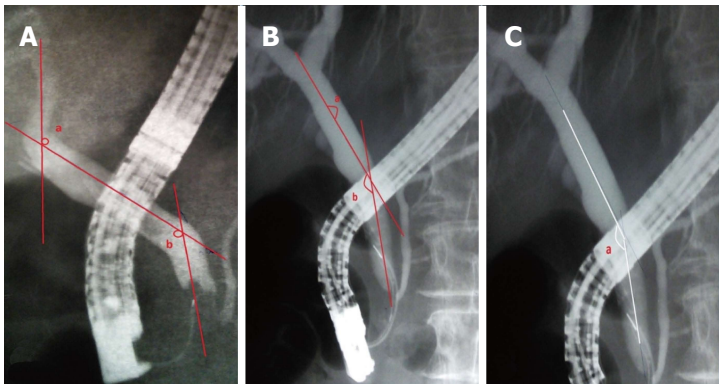

Figure 1 Common bile duct angulation calculation methods. Accumulative score (A and B): The axis (red line) runs through the center of the CBD. Each internal angle was measured at the angulation of the proximal (A) and distal (B) bile duct level respectively. The values of both angles were added (A + B). If either part of the CBD was not angulated a set score of 180 was used[13]. Minimal angle score (C): Angulation (A) was measured as the sharpest angle along the CBD from 1 cm below the bifurcation to 1 cm above the papilla[14]. CBD: Common bile duct.

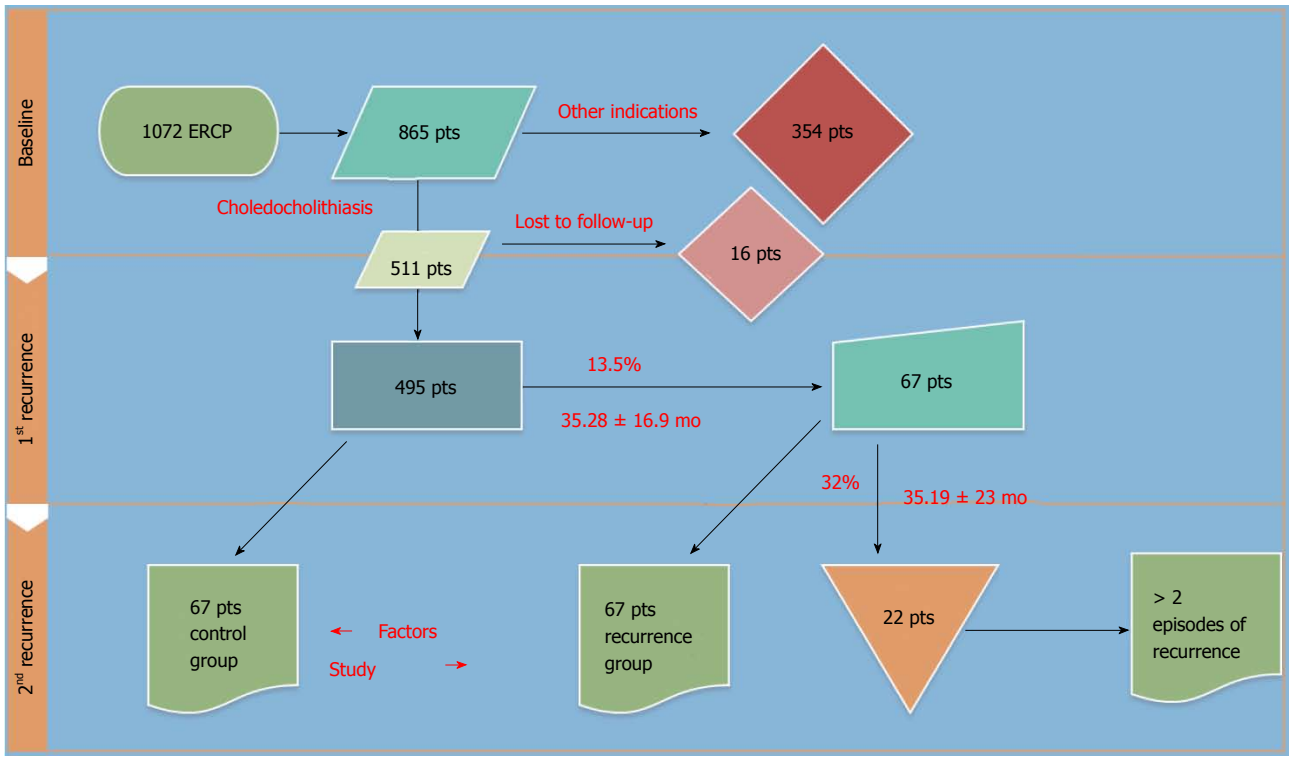

Figure 2 Study flowchart. ERCP: Endoscopic retrograde cholangiopancreatography.

United State).

RESULTS

Between January 2005 and (including) December 2008, 511 unique patients were treated in our center for choledocholithiasis/microcholedocholithiasis (Figure 2). All symptomatic recurrences for the study period (until December 2015) were recorded, after applying exclusion criteria. Sixteen patients that were lost to follow - up were dropped from the study. Sixty-seven (67) out of 495 patients (13.5%) presented with recurrent symptomatic choledocholithiasis after 35.28 ± 16.909 (7-96) mo while twenty-two (22) of these patients (32.83% of the recurrent) experienced a second recurrence after 35.19 ± 23.22 (9-78) mo. A 3rd recurrence occurred to 6 (8.9%) of the recurrent patients at 16.83 ± 15.3 mo (Table 1).

The number of procedures/ERCPs required to treat the recurrent population (baseline ERCP, recurrence examinations including any follow-up procedures that were required to achieve CDB patency) is summarized in Table 2. An impressive total of 199 ERPCs was required to treat the 67 recurrent patients over time. On the other hand for the 67 controls a total of 89 ERCP sessions was needed.

Early recurrences (recurrence during the first 24 mo after the baseline ERCP) occurred in 21/67 patients (46/67 late).

Multiple recurrences occurred in 22 patients (Table 1). We have found that an early recurrence predisposes to multiple recurrences more often than a late one. Thirteen (13) out of the 21 early recurrent patients (13/21) had a second recurrence, while only 14/46 of those with late recurrence suffered from a second episode ($P = 0.0025$).

For the purpose of studying risk factors, the 67 patients with a history of symptomatic recurrence were

Table 1 Number and percentage of patients who experienced one or more (up to five) symptomatic recurrences

No. of recurrences	Patients (n = 67) n (%)
1	45 (67.1)
2	16 (23.8)
3	4 (5.9)
4	1 (1.5)
5	1 (1.5)

Most of the patients experienced only a single episode (67%).

Table 2 Number and percentage of endoscopic retrograde cholangiopancreatography required to treat patients with recurrence

No. of ERCP sessions	Patients (n = 67) n (%)
2	31 (46)
3	16 (23.8)
4	13 (19)
5	5 (7.46)
6	2 (2.98)

ERCP: Endoscopic retrograde cholangiopancreatography.

compared to a group of 67 age/gender - matched control patients that were selected from a pool of 428 patients with a recurrent free history. Baseline characteristics for both groups are presented in Table 3.

No significant differences were found with regard to age, sex, previous surgical history (including cholecystectomy before the baseline (first) ERCP and biliary, gastric surgery) and mean follow -up time between the groups.

Table 4 summarizes the risk factors for recurrence that were evaluated.

Logistic regression analyses were performed to identify the risk factors for stone recurrence, including both baseline characteristics and ERCP-related parameters. Univariate analysis revealed that diameter of the CBD, size (diameter) of the largest CBD stone, use of ML and difficult lithiasis were associated with stone recurrence. Multivariate analysis revealed that CBD diameter was the only independent risk factor associated with CBD stone recurrence (OR = 1.116, 95%CI: 1.005-1.277, P = 002).

DISCUSSION

The recurrence of CBD stones is a possible outcome following endoscopic clearance[5,6]. Rates of recurrence in the literature vary with some authors estimating them being as high as 24%[8-10]. So although it is considered a late complication of stone extraction, it certainly is not a rare one. Many authors report that most recurrences of bile duct stones take place in the first 3 years[15,16], the limit between recurrence and residual stone disease is somewhat arbitrary with many authors advocating for the threshold of 5[16] to 6[15] mo.

Bile duct stones (and as a result also recurrent stones) are classified as primary or secondary stones,

Table 3 Baseline characteristics of the study groups

Variable	Recurrence group (n = 67)	Control group (n = 67)	P value
Age, yr	71.2 ± 12.4	71.9 ± 12.6	0.82
Sex, male	26/67	28/67	0.86
History of cholecystectomy before first ERCP	37	40	0.73
BEA/gastric surgery	4 (2 billroth, 2 BEA)	2 (1 billroth, 1 BEA)	0.68
Mean follow-up time, mo	70,1 ± 31.7 (2-121)	68.5 ± 36.1 (1-129)	0.8

Recurrence group: Patients with a history of recurrent common bile duct stones; Control group: Patients with a history of non recurrent common bile duct stones; BEA: Biliary enteric anastomosis.

both with different pathogenesis and etiologies[17]. A stone is termed primary when located at the site of its formation, while a secondary stone is a stone that has migrated from the site of its origin (in this case usually the gallbladder). Thus, primary CBD stones form de novo in the CBD, these are usually brown pigment (calcium bilirubinate) stones, where they remain either uneventfully or until they are implicated in a clinical sequela (*e.g.,* cholangitis)[18]. Secondary CBD stones are commonly associated with migrating gallbladder (or rarely intrahepatic) stones and thus consist mainly of cholesterol.

There's a plethora of risk factors related with recurrence of choledocholithiasis proposed in the literature; many of these are summarized in Table 5.

The putative mechanism responsible for stone recurrences still eludes us. In some cases, like secondary CBD stones in patients with concurrent chololithiasis, the underlying cause is in most probability also the most obvious one (*i.e.,* stone migration from the stone-ridden gallbladder to the CBD). After reviewing the literature it is obvious that there is no consensus reached in the scientific community on the exact mechanism. We could argue that at the present there are two dominating theories.

Endobiliary bile stasis (endo - Bi.S.)[18,19,22,31]

The term endobiliary bile stasis encloses a variety of risk factors that predispose to biliary stasis, delayed biliary emptying and/or impaired biliary flow. Acute distal CBD angulation, oblique CBD angulation, CBD dilation, periampullary diverticula, billiary strictures, papillary stenosis, cirrhosis, cholocystectomy, possibly genetic factors (like variations of the ABCB4, ABCB11 genes) have been associated with biliary stasis and the formation of primary CBD stones and their recurrence. Mechanical obstruction/blockage as well as variations in the (patho)physiology of bile secretion (bile viscosity, bile secretion rate, loss of bile flushing due to cholocystectomy) could help to explain why a bile duct system exhibiting any number of these anatomic/physiology abnormalities could be predisposed to stone recurrence.

Table 4 Parameters of the first endoscopic retrograde cholangiopancreatography/risk factors for recurrence in patients with or without a history of recurrent common bile duct stones

Variable	Recurrence group (n = 67)	Control group (n = 67)	P value
Stone size, mm	11.0 ± 7.0	7.5 ± 4.5	0.007
Stone number, *n*	4.9 ± 4.4	4.3 ± 4.7	0.53
CBD diameter, mm	16.03 ± 6.1	12.0 ± 4.6	0.001
CBD angulation method 1 (accumulative score)	303.97 ± 34.41	304.84 ± 31.61	0.91
CBD angulation method 2 (minimal angle score)	137.03 ± 17.0	138.41 ± 14.18	0.71
Difficult bile duct stones	24	14	0.04
Use of mechanical lithotripsy	13	5	0.04
No. of ERCP sessions required to clear the bile duct	1.33 ± 0.6	1.34 ± 0.7	0.95
More than one ERCP needed to clear the bile duct initially	14	11	0.43
Gallbladder *in situ*	2	5	1
Periampullary diverticula	25	16	0.066

Gallbladder *in situ* (remaining gallbladder): Patients who did not/could not conform to the instructions to perform cholocystectomy after the first ERCP, or a cholocystectomy was not indicated. ERCP: Endoscopic retrograde cholangiopancreatography; CBD: Common bile duct.

Table 5 Risk factors for recurrence of choledocholithiasis proposed in the literature

Proposed risk factor	Ref.	Comment section
DBR	[19-21]	DBR
Pneumobilia	[19]	Indicative of DBR
Acute distal CBD angulation	[19]	Promotes bile stasis
CBD dilation	[19]	Promotes bile stasis
Periampullary diverticulum	[19]	Promotes bile stasis
Prior EST	[22,23]	Promotes DBR
Intact gallbladder with stones *in situ*	[22]	(Secondary) stone CBD migration
Billiary stricture	[22]	Promotes bile stasis
Papillary stenosis	[22]	Promotes bile stasis
ML	[22]	Small residual microlithiasis acts as nidi for stone formation
Stone size	[24]	Size of the largest stone
Cirrhosis	[22]	Delayed biliary emptying/bile stasis
Delayed biliary emptying	[22]	Promotes bile stasis
Bacterial infection/colonization of the CBD. Bacterial count	[25,26]	Promotes chronic infection, and inflammation, promotes stone formating
Impaired biliary flow	[25]	Scintigraphic study
Cholecystectomy (without stones)	[27]	Impede flushing of nidus/residual stones
Post-procedural sphincter function impaired	[6,27]	EST *vs* EPBD/EPLBD *vs* EPSBD, promote DBR
Number of sessions to clear duct at first presentation	[6]	# of ERCPs required to achieve a patent CBD
Age	[6]	Old age
Previous cholecystectomy (open or lap)	[6]	
Serum lvls of chol	[24]	Lithogenic properties
EST size	[24]	Minimal size is protective
Inflammation CBD	[24]	
Parasites of the CBD	[24]	Parasitic infection
Foreign bodies in the CBD	[24]	
Concurrent cholecystolithiasis and cholelithiasis	[28]	
Post stone removal CBD diameter	[21]	At 72 h after stones removal, cholangiogram *via* nasobiliary tube
EPLBD > 10 mm	[29]	Disruption of SO, DBR
Variations of the *ABCB4*, *ABCB11* genes	[30]	Affect composition of bile. Associated with cholestasis, cholelithiasis and formation of primary intrahepatic stones
Excessive dilation of the CBD	[31]	Recurrence rate was 40% when maximum CBD diameter was more than 20 mm, whereas recurrence rate was 18% when maximum CBD diameter was 20 mm or less

The level of evidence varies. DBR: Duodenal-biliary reflux; CBD: Common bile duct; EST: Endoscopic sphincterotomy; ML: Mechanical lithotripsy; EPBD: Endoscopic papillary balloon dilation; EPLBD: Endoscopic papillary large balloon dilation; EPSBD: Endoscopic papillary small balloon dilation; ERCP: Endoscopic retrograde cholangiopancreatography; Llv: Level; Chol: Cholesterol; SO: Sphincter of Oddi.

Duodenal - biliary reflux[6,19-23,27]

This term encompasses a number of factors that are associated with the reflux of enteric contents (fluid and/or solid chime) inside the biliary tract. Pneumobilia[19], post-procedural impaired sphincter function (EST/EPLBD), bacterial infection/colonization of the CBD, EST size are all factors that have been related to duodenal reflux. Recent studies have drawn our focus towards the role that post - procedural sphincter functional adequacy has in Duodenal - Biliary Reflux (DBR) in particular and in

stone recurrence in general. It has been suggested that sphincter preserving procedures (small size EST, EPSBD) exert a protective role, reducing the risk of recurrence. Permanent sphincter function disruption by EST or EPLBD could result in duodenobiliary reflux.

The underlying pathogenesis of stone recurrence is not yet fully elucidated. To a great extent clinical practice has proceeded basic research[32]. A multifactorial model where chronic inflammation of the bile ducts plays a central role could help to better explain it. Bile stagnation, reflux of duodenal content, bacterial colonization and chronic infection of the CBD as well as mechanical and chemical damaging effects of chronic irritants (from the enteric content) could all contribute to sustain chronic inflammation[25,26].

In our study we found that CBD dilation, stone size at first presentation, difficult lithiasis and use of mechanical lithotripsy were all risk factors for stone recurrence in the univariate analysis. These findings are similar to those of previous reports[6,19,22,24,31]. We could argue that large stone size, presence of difficult lithiasis and need for mechanical lithotripsy is all different aspects of the same factor. In a way they serve to prove that patients with certain "unfavorable stone characteristics" recur more often than others. Multivariate analysis revealed that the diameter of the common bile duct was the only independent risk factor associated with stone recurrence. It has been suggested before that CBD dilation above a certain threshold (13 mm)[21] and especially excessive dilation (> 20 mm)[31] predispose to stone reformation. In our study, the issue of a cut-off value of CBD diameter that predisposes to higher rates of recurrence was addressed but we did not reach a statistically significant result (probably due to the sample size). Periampullary diverticula showed a trend towards significance in our study (P = 0.066), unlike the clear association reported by other authors[19,29]. This is probably so because of the small sample in our study.

It has been proposed that patients with recurring CBD stones are at increased risk for a subsequent recurrence[7]. Data from our study is also in support. Patients who suffered from a recurrence were in a much greater danger. Thirty-two percent of the recurrent population had at least a second episode, while the recurrence rate for a patient who has not experienced a recurrence before was 13.5%. Data from the aforementioned study[7] identified an interval of $\leqslant$ 5 years between initial EST and repeat ERCP as a risk factor for re - recurrence. Likewise, patients from our cohort who suffered from an early ($\leqslant$ 24 mo) recurrence attack, were at increased risk for consequent episodes.

There are several limitations in this study including its retrospective design, single-center site and the relative small sample size. We acknowledge that because of both the retrospective design and the often asymptomatic nature of CBD stones, several methodological issues concerning mainly the follow-up of patients and data collection could arise. A prospective multi center cohort study needs to be conducted to investigate further the association between these risks factors and stone recurrence. This study needs to be powered by both a large sample size and a long follow-up (longer than five years)[29]. Last but not least future studies need to focus more on possible clinical applications. Bedside questions that need to be answered like which patients should we follow-up? Is there any patient group with specific characteristics (*e.g.,* CBD dilation above a certain threshold) that justify more intensive follow-up? What is the importance of asymptomatic stones in multi-recurring patients, can these patients benefit from pre-emptive/prophylactic ERCP, what's the hazard/benefit ratio?

In conclusion, bile duct stone recurrence is a likely late complication following endoscopic stone extraction and CBD clearance. In our study the rate of recurrent symptomatic choledocholithiasis was 13.5%. It appears to be associated with both anatomical parameters (CBD diameter) and stone characteristics (stone size, use of ML, difficult lithiasis) at first presentation.

COMMENTS

Background

Endoscopic retrograde cholangiopancreatography (ERCP) is widely accepted as the modality of choice for the endoscopic removal of bile duct stones. Endoscopic sphincterotomy (EST) since its introduction in 1974, has been extensively used for the endoscopic extraction of bile duct stones. Endoscopic techniques for stone removal are generally considered both safe and effective but, their invasive nature cannot preclude the possibility of complications.

Research frontiers

Many authors report that most recurrences of bile duct stones take place in the first 3 years the limit between recurrence and residual stone disease is somewhat arbitrary with many authors advocating for the threshold of 5 to 6 mo.

Innovations and breakthroughs

In this study, the issue of a cut-off value of common bile duct diameter that predisposes to higher rates of recurrence was addressed but the authors did not reach a statistically significant result (probably due to the sample size). Periampullary diverticula showed a trend towards significance in the study (P = 0.066), unlike the clear association reported by other authors.

Peer-review

This manuscript is very well designed, the authors did a great effort in selecting the articles to be included in the meta-analysis with a proper quality scoring of selected articles. This manuscript is suitable for publication.

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P- Reviewer: Lai KH, Pan H **S- Editor**: Qi Y **L- Editor**: A
E- Editor: Lu YJ

World Journal of Gastrointestinal Endoscopy

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DOI: 10.4253/wjge.v9.i1.34

World J Gastrointest Endosc 2017 January 16; 9(1): 34-40
ISSN 1948-5190 (online)

ORIGINAL ARTICLE

Retrospective Study

Essential role of small bowel capsule endoscopy in reclassification of colonic inflammatory bowel disease type unclassified

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Author contributions: Monteiro S performed the study, statistical analysis, literature search and drafted the manuscript; Dias de Castro F and Boal Carvalho P participated in the design of the study and reviewed the capsule endoscopies; Rosa B, Moreira MJ, Pinho R and Mascarenhas Saraiva M participated in the design of the study, reviewed the capsule endoscopies and revised the manuscript; Cotter J participated in the design of the study and critically revised the manuscript and approved the final version to be submitted.

Institutional review board statement: This retrospective study was performed without direct contact with either patients or providers and no individual patient information was revealed. Therefore this study was not previously reviewed by the Local Ethics Committee.

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

Conflict-of-interest statement: The authors declare that there is no conflict of interests regarding the publication of this paper.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at sara.s.o.monteiro@gmail.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

Manuscript source: Invited manuscript

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Received: July 11, 2016
Peer-review started: July 13, 2016
First decision: August 29, 2016
Revised: October 6, 2016
Accepted: November 1, 2016
Article in press: November 3, 2016
Published online: January 16, 2017

Abstract

AIM

To evaluate the role of small bowel capsule endoscopy (SBCE) on the reclassification of colonic inflammatory bowel disease type unclassified (IBDU).

METHODS
We performed a multicenter, retrospective study including patients with IBDU undergoing SBCE, between 2002 and 2014. SBCE studies were reviewed and the inflammatory activity was evaluated by determining the Lewis score (LS). Inflammatory activity was considered significant and consistent with Crohn's disease (CD) when the LS $\geqslant$ 135. The definitive diagnosis during follow-up (minimum 12 mo following SBCE) was based on the combination of clinical, analytical, imaging, endoscopic and histological elements.

RESULTS
Thirty-six patients were included, 21 females (58%) with mean age at diagnosis of 33 ± 13 (15-64) years. The mean follow-up time after the SBCE was 52 ± 41 (12-156) mo. The SBCE revealed findings consistent with significant inflammatory activity in the small bowel (LS $\geqslant$ 135) in 9 patients (25%); in all of them the diagnosis of CD was confirmed during follow-up. In 27 patients (75%), the SBCE revealed no significant inflammatory activity (LS < 135); among these patients, the diagnosis of Ulcerative Colitis (UC) was established in 16 cases (59.3%), CD in 1 case (3.7%) and 10 patients (37%) maintained a diagnosis of IBDU during follow-up. A LS $\geqslant$ 135 at SBCE had a sensitivity = 90%, specificity = 100%, positive predictive value = 100% and negative predictive value = 94% for the diagnosis of CD.

CONCLUSION
SBCE proved to be fundamental in the reclassification of patients with IBDU. Absence of significant inflammatory activity in the small intestine allowed exclusion of CD in 94% of cases.

Key words: Inflammatory bowel disease; Inflammatory bowel disease type unclassified; Capsule endoscopy; Crohn's disease; Lewis score; Reclassification

Core tip: This is a retrospective study to evaluate the role of small bowel capsule endoscopy (SBCE) on the reclassification of colonic inflammatory bowel disease type unclassified (IBDU). The SBCE revealed findings consistent with significant inflammatory activity in the small bowel, Lewis score (LS) $\geqslant$ 135, in 9 patients (25%); in all of them the diagnosis of Crohn's disease (CD) was confirmed during follow-up. In 27 patients (75%) without significant inflammatory activity (LS < 135), the diagnosis of ulcerative colitis was established in 16 cases (59.3%), CD in 1 case (3.7%) and 10 patients (37%) maintained a diagnosis of IBDU during follow-up.

Monteiro S, Dias de Castro F, Boal Carvalho P, Rosa B, Moreira MJ, Pinho R, Mascarenhas Saraiva M, Cotter J. Essential role of small bowel capsule endoscopy in reclassification of colonic inflammatory bowel disease type unclassified. *World J Gastrointest Endosc* 2017; 9(1): 34-40 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i1/34.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i1.34

INTRODUCTION

The differential diagnosis of Crohn's disease (CD) and ulcerative colitis (UC) relies on a combination of clinical, analytical, imaging, endoscopic and histologic data[1,2]. In 5% of patients with inflammatory bowel disease limited to the colon is not possible to establish a definitive diagnosis into CD or UC[3]. In 1978, Price introduced the concept of indeterminate colitis to describe cases in which colonic resections had been undertaken for chronic inflammatory bowel disease but a definitive diagnosis of either of UC and CD was not possible[4]. In 2005, the Montreal Working Party proposed that the term "indeterminate colitis" should be reserved for patients in whom surgical specimen is available and the term "colonic IBD type unclassified" (IBDU) for patients with no surgical specimen available and for whom the endoscopy is inconclusive and histology reveals chronic inflammation with absence of definite diagnostic features of either CD or UC[5]. Actually, for most patients, IBDU represents a temporary diagnosis, as it has been estimated that 80% of them will be reclassified to either CD or UC within 8 years[6].

The correct diagnosis of inflammatory bowel disease is extremely important to define prognosis, therapeutic orientation and surgical intervention[7,8]. Since Small Bowel Capsule Endoscopy (SBCE) enables a direct endoscopic visualization of throughout the small intestine with higher diagnostic yield compared to conventional endoscopy or imaging studies[9,10], it may be expected to contribute for the reclassification of IBDU. We report a multicenter study that aimed to evaluate the role of SBCE to reclassify patients with IBDU.

MATERIALS AND METHODS

We performed a multicenter study including consecutive patients undergoing SBCE between 2002 and 2014 for IBDU, ASCA negative/pANCA negative.

All patients had undergone an ileocolonoscopy prior to SBCE. Inclusion criteria were as follows: Patients with clinical features of chronic IBD, without previously known small bowel involvement, in whom endoscopic type and/or distribution of lesions did not allow a definite diagnosis of CD or UC, microscopy indicating active and patchy transmucosal chronic inflammation with minimal or moderate architectural distortion and absence of unequivocal diagnostic features for either CD or UC, after exclusion of infectious colitis[5]. Subjects were excluded from entering the study if they had nonsteroidal anti-inflammatory drugs intake within 4 wk prior to capsule endoscopy[11], clinical or imaging evidence of bowel stenosis or occlusion, or a follow-up of less than 12 mo.

Patients underwent SBCE with PillCam® SB1/SB2/

Table 1 Demographics and clinical characteristics of the inflammatory bowel disease type unclassified patients

No. of patients, *n* (%)	36 (100)
Gender	
Female	21 (58.3)
Male	15 (41.7)
Age (yr) (mean ± SD) at diagnosis	33.2 ± 13.1 (15-64)
Age (yr) (mean ± SD) at SBCE	35.9 ± 13.3 (18-64)
Device (no. patients), *n* (%)	
PillCam® SB1	13 (36.1)
PillCam® SB2	16 (44.4)
PillCam® SB3	1 (2.8)
Mirocam®	5 (13.9)
Endocapsule®	1 (2.8)
Gastric transit time (min)	38.6 ± 44.7 (2–257)
Small bowel transit time (min)	290.4 ± 101.5 (52-480)
Incomplete SBCE	1 (2.8)
Capsule retention	0
Follow-up (mo) before SBCE	30.2 ± 29.9 (1-108)
Follow-up (mo) after SBCE	51.9 ± 40.5 (12-156)

IBDU: Inflammatory bowel disease type unclassified; SB: Small bowel; SBCE: Small bowel capsule endoscopy.

SB3 (Given® Imaging, Yoqneam, Israel), Endocapsule® (Olympus Medical Systems Corporation, Tokyo, Japan) or Mirocam® (Intromedic Co., Ltd., Seoul, South Korea) receiving a clear liquid diet the day before capsule ingestion and an overnight 12 h fast. No bowel purge was administered prior to capsule ingestion.

SBCE videos were reviewed by two experienced gastroenterologists in each center. In case of disagreement, the findings were reviewed by investigators until a consensus was reached. Inflammatory activity was objectively assessed by determining the Lewis score (LS)[12]. Inflammatory activity was considered significant and consistent with CD when the LS $\geqslant$ 135[13].

The mean, SD, and range were calculated for continuous data. Categorical data analysis was conducted using the Fisher exact test. Data analysis was performed using SPSS version 20.0 (IBM, Armonk, New York, United States). Test characteristics were determined using a 2 × 2 table and calculating the sensitivity, specificity, positive predictive value and negative predictive value.

Statistical significance was considered when the *P* value was less than 0.05.

RESULTS

A total of 36 consecutive patients with IBDU underwent SBCE procedures between October 2002 and August 2014, with a mean follow-up before the exam of 30 mo (1-108 mo).

The mean age of patients at the time of diagnosis of IBDU and at time of SBCE was 33 years and 36 years, respectively, with 58% being of female gender.

Table 1 summarizes the demographic and clinical characteristics of the study population. The capsule was ingested without difficulty by all of the 36 subjects. There were no cases of capsule retention or reported adverse events in any of the subjects included in this study.

A complete small-bowel examination was achieved in 97.2% of studies. The mean follow-up after SBCE was 52 mo (12-156 mo).

At the moment of SBCE thirty four patients had clinically active disease and received anti-inflammatory treatment, as summarized in Tables 2 and 3. SBCE revealed small bowel lesions in 13 of patients (36.1%) and 23 (63.9%) patients had no lesions detected on SBCE. The distribution of the lesions in the small intestine were as follows: Two patients had multiple ulcerations ($n \geqslant 8$) throughout the entire small bowel, 1 patients had ulcerations in first and second tertiles, 1 patient had ulcerations only in the second tertile, 5 patients had multiples ulcerations in the third tertile. In 4 patients the capsule revealed subtle findings of focal edema in a single short segment of the small bowel (Table 2).

Nine patients (25%) had inflammatory lesions considered significant (LS $\geqslant$ 135) and consistent with a diagnosis of CD (Table 2). In 4 of those patients (44.4%) a subsequent ileocolonoscopy showed, by this occasion, lesions compatible with CD in the terminal ileum and histology of colonic lesions was unspecific. In the remaining 5 patients (55.6%), the histology of colonic lesions was unspecific and ileoscopy detected no lesions.

In 27 patients (75%), the SBCE revealed no significant inflammatory activity (LS < 135). Among these patients, no lesion was detected in 23 patients and subtle lesions were found in 4 cases (Tables 2 and 3).

One patient (4.3%) with no lesions at SBCE had on follow-up a subsequent ileoscopy which revealed lesions compatible with CD (Table 3).

In 12 of 23 patients (52.2%) with no lesions at SBCE, a diagnosis of UC was established on follow-up, on average 38.3 mo after SBCE (Table 3). Four patients (25%) with a final diagnosis of UC had subtle lesions (focal edema) on SBCE (Table 2). In all of these patients the endoscopic and histological findings were consistent with the diagnosis of UC, which remained in clinical and analytical remission on follow-up.

Ten patients (27.8%) remained with a diagnosis of IBDU after a mean follow-up of 42 mo (Table 3). Considering the endoscopic criterion of significant inflammatory activity to predict a diagnosis of CD, using a cut-off for LS $\geqslant$ 135[13], it would result in no false positive and only one false negative examinations, corresponding to a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 90%, 100%, 100% and 94%, respectively.

In 6 of 9 patients (66.7%) with significant inflammatory activity detected in SBCE, the treatment during the follow-up was escalated to immunosuppressive drugs or biological therapy (Table 2). In 3 of 16 (18.8%) patients with a definitive diagnosis of UC and in 4 of 10 (40%) patients who remained with a diagnosis of IBDU on follow-up, a new IBD medication was introduced during the follow-up.

The start of treatment with thiopurines and/or biologics in patients who were previously naïve to those medications

Table 2 Clinical characteristics and outcome of the patients with positive small bowel capsule

Case	Sex	Age	SBCE Findings	LS	Treatment pre-SBCE	Treatment post-SBCE	Diagnostic at follow-up
1	F	38	Multiple jejuno-ileal ulcerations	1404	5ASA	5 ASA + AZT	CD
2	F	18	Ulcer (n = 1) and edema of 3° tertile	143	AZT	Anti-TNF	CD
3	M	23	Ulcer (n = 1) and edema of 3° tertile	143	5ASA	5ASA	CD
4	F	20	Ulcerations (n = 2) and edema of 3° tertile	233	5ASA	5ASA	CD
5	F	33	Ulcer (n = 3) of 2° tertile	225	5ASA	5ASA	CD
6	F	19	Multiple ulcerations and edema of 3° tertile	908	5ASA	AZT	CD
7	M	60	Focal edema of 1° tertile	8	No treatment	5ASA	UC
8	M	22	Multiple jejuno-ileal ulcerations	2080	5ASA	5ASA + AZT	CD
9	F	32	Multiple ulcerations and edema of 3° tertile	908	5ASA	AZT	CD
10	F	27	Focal edema of 3° tertile	8	Prednisolone	anti-TNF	UC
11	F	47	Focal edema of 2° tertile	8	5ASA	5ASA	UC
12	F	31	Ulceration and edema of 1° (n = 5) and 2° tertile (n = 6)	879	5ASA+Prednisolone	AZT	CD
13	M	44	Focal edema of 3º tertile	8	5ASA	5ASA	UC

5ASA: Mesalamine; anti-TNF: Anti-tumor necrosis factor drug; AZT: Azathioprine; CD: Crohn's disease; SBCE: Small bowel capsule endoscopy; LS: Lewis score; UC: Ulcerative colitis.

Table 3 Clinical characteristics and outcome of the patients with negative small bowel capsule

Case	Sex	Age	Treatment pre-SBCE	Treatment post-SBCE	Diagnostic at follow-up
1	M	45	5ASA	5ASA	IBDU
2	F	15	Prednisolone, 5ASA	5ASA	UC
3	F	27	AZT, 5ASA	AZT	UC
4	F	26	5ASA	5ASA	UC
5	M	31	5ASA	5ASA	IBDU
6	F	34	5ASA	5ASA	IBDU
7	M	21	5ASA	5ASA	IBDU
8	F	22	5ASA	5ASA, AZT	IBDU
9	F	56	5ASA	5ASA	UC
10	F	27	AZT, anti-TNF	AZT, anti-TNF	UC
11	F	30	5ASA	5ASA	UC
12	M	24	5ASA	5ASA	CD
13	M	49	5ASA	5ASA	UC
14	M	43	5ASA	5ASA	UC
15	F	30	5ASA + AZT	Anti-TNF	IBDU
16	M	24	5ASA	5ASA	UC
17	F	20	5ASA	5ASA	UC
18	M	55	5ASA	5ASA	IBDU
19	F	31	5ASA	5ASA, AZT, Anti-TNF	UC
20	F	48	5ASA	5ASA, AZT	IBDU
21	M	64	5ASA	5ASA	UC
22	M	44	No treatment	5ASA	IBDU
23	M	53	5ASA	5ASA	IBDU

5ASA: Mesalamine; anti-TNF: Anti-tumor necrosis factor drug; AZT: Azathioprine; CD: Crohn's disease; IBDU: Colonic inflammatory bowel disease type unclassified; SBCE: Small bowel capsule endoscopy; UC: Ulcerative colitis.

occurred in 6/9 (66.7%) *vs* 5/27 (18.5%) patients with or without significant inflammatory activity detected at the SBCE, respectively (P = 0.012).

DISCUSSION

Ileocolonoscopy remains the first line exam to achieve the diagnosis in patients with suspected IBD[14]. Nonetheless, ileocolonoscopy can miss CD and result in false negative results due to skip lesions throughout the terminal ileum[15].

Upper endoscopy, SBCE, computed tomography enterography (CTE) and magnetic resonance enterography (MRE) can provide important information and may be useful to establish a definitive diagnosis[14].

In patients with suspected CD and negative ileocolonoscopy findings, recent European guidelines recommends SBCE as the next diagnostic exam for small bowel investigation, in the absence of obstructive symptoms or known stenosis[11].

SBCE has proven its superiority in identifying inflammatory lesions consistent with the diagnosis of CD in the small intestine when compared to CTE[9,16] or MRE[10], thus it has assumed an important role on the evaluation of patients with suspected CD[13,17-19], having a high negative predictive value for the absence of significant

inflammatory activity[13]. However, there is still limited evidence for the role of SBCE in patients with IBDU[11].

Most studies[20-22] used the non-validated diagnostic criteria for small-bowel CD proposed by Mow *et al*[23] (presence of more than three ulcerations).

Meanwhile, two scoring systems have been developed to standardize the quantification of inflammatory activity in the small bowel. The Capsule Endoscopy Crohn's Disease Activity Index (CECDAI) is based on evaluation of the following parameters: Inflammation, extent of disease and presence of a stricture, while the LS evaluates villous appearance, ulcers and strictures[12]. The LS has shown a better performance than the CECDAI at describing small-bowel inflammation[24].

Indeed, LS has been shown a strong interobserver agreement for the determination of the inflammatory activity, and it is validated for the reporting small-bowel inflammatory activity[25,26].

In our study, the findings revealed by SBCE were consistent with a diagnosis of CD, based upon LS ≥ 135, in 9 of 36 (25%) of the subjects with IBDU, which is in line with the 16%-50% range described in other previous series[20-22,27-29]. An even higher percentage has been reported in pediatric patients[14].

In the present study, 4 patients (25%) with final diagnosis of UC had subtle small bowel lesions, such as focal edema, without a significant inflammatory activity, LS < 135, and with clinical and analytical remission during follow-up. Indeed, previous studies already reported a significantly higher frequency of small-bowel lesions in UC patients as compared with that in the control healthy volunteers[30]. The significance of the presence of these lesions and the possible risk of misdiagnosis is still indeterminate[31].

Although a negative SBCE study did not allow to definitely exclude a future diagnosis of small bowel CD, as further investigation and biopsies on follow-up led to a diagnosis of CD in one patient, the absence of significant inflammatory activity (LS < 135) in the small intestine actually allowed exclusion of CD in 94% of cases.

Based on our findings, SBCE may lead to reclassification of disease from suspected IBDU to definitive CD in 25% of cases. Furthermore, treatment with thiopurines and/or biologics was initiated more often in patients with significant inflammatory activity detected on SBCE (66.7% *vs* 18.5%, $P = 0.012$). This association suggests that capsule findings may be helpful in the clinical management of these patients, as already been proven in other series[28,32-34].

There are some limitations of this study, including its retrospective design, a limited number of subjects, and no direct comparison of SBCE with alternative small bowel diagnostic imaging, however, the last was not an aim of this study.

Nevertheless, to our knowledge this is one of the studies with larger number of patients included to evaluate this particular issue[20-22,27-29].

There are no definite diagnostic criteria for IBDU, as it must be considered a provisional diagnosis until more information (clinical, endoscopic, radiologic or pathologic) or data on follow-up enable a definitive reclassification[35]. Mucosal biopsy samples before treatment can be useful to distinguish UC from CD, but this distinction is based primarily on the pattern, type and location (distribution) of the disease, rather than specific histological features, for which there is much overlap between the two diseases[36]. Therefore, SBCE has a valuable role in the reclassification of patients with IBDU, may also contribute to establish the strategy for clinical management, and should be performed in the undefined diagnosis, which IBDU represents, in order to contribute to a definite diagnosis.

COMMENTS

Background

Colonic inflammatory bowel disease type unclassified (IBDU) is defined as a chronic idiopathic inflammatory bowel disease limited to the colon, whose combination of clinical, analytical, imaging, endoscopic and histological elements does not allow a differential diagnosis between Crohn's disease (CD) and ulcerative colitis.

Research frontiers

In patients with suspected CD and negative ileocolonoscopy findings, small bowel capsule endoscopy (SBCE) is the next diagnostic exam for small bowel investigation, in the absence of obstructive symptoms or known stenosis. Since SBCE enables a direct endoscopic visualization of throughout the small intestine, it may be expected to contribute for the reclassification of IBDU. However, the role of SBCE in IBDU has not been clearly established. In this study, the authors evaluate the role of SBCE on the reclassification of IBDU.

Innovations and breakthroughs

In this study, inflammatory activity on SBCE was objectively assessed by determining the Lewis score (LS). SBCE lead to reclassification of disease from IBDU to definitive CD in 25% of cases. Although a negative SBCE study did not allow to definitely exclude a future diagnosis of small bowel CD, as further investigation and biopsies on follow-up led to a diagnosis of CD in one patient, the absence of significant inflammatory activity (LS < 135) in the small intestine actually allowed exclusion of CD in 94% of cases.

Applications

This study suggests that SBCE is useful in the reclassification of patients with IBDU. Facing a patient with IBDU, a SBCE should be performed in order to diagnosis or exclude a CD.

Peer-review

This manuscript "Essential role of small bowel capsule endoscopy in reclassification of colonic inflammatory bowel disease type unclassified" is well written.

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