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EDITORIAL

Laparoscopic surgery for complex and recurrent Crohn's disease

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Abstract

Crohn's disease (CD) is a chronic inflammatory disease of digestive tract. Approximately 70% of patients with CD require surgical intervention within 10 years of their initial diagnosis, despite advanced medical treatment alternatives including biologics, immune suppressive drugs and steroids. Refractory to medical treatment in CD patients is the common indication for surgery. Unfortunately, surgery cannot cure the disease. Minimally invasive treatment modalities can be suitable for CD patients due to the benign nature of the disease especially at the time of index surgery. However, laparoscopic management in fistulizing or recurrent disease is controversial. Intractable fibrotic strictures with obstruction, fistulas with abscess formation and hemorrhage are the surgical indications of recurrent CD, which are also complicating laparoscopic treatments. Nevertheless, laparoscopy can be performed in selected CD patients with safety, and may provide better outcomes compared to open surgery. The common complication after laparoscopic intervention is postoperative ileus seems and this may strongly relate excessive manipulation of the bowel during dissection. But additionally, unsuccessful laparoscopic attempts requiring conversion to open surgery have been a major concern due to presumed risk of worse outcomes. However, recent data show that conversions do not to worsen the outcomes of colorectal surgery

in experienced hands. In conclusion, laparoscopic treatment modalities in recurrent CD patients have promising outcomes when it is used selectively.

Key words: Crohn's disease; Laparoscopic surgery; Complex disease management; Recurrent Crohn's disease

Core tip: Despite advanced medical treatment alternatives including biologics, immune suppressive drugs and steroids, approximately 70% of patients with Crohn's disease (CD) require surgical intervention within 10 years of their initial diagnosis. Forty percent to 50% of patients who had an index surgery for CD require a reoperation for recurrent disease in 10 years. Index surgical treatment type and medications used after index surgery appears to be factors related to recurrence risk of CD. In experienced hands, laparoscopic approach has promising outcomes in patients with recurrent CD when it is used selectively.

Sevim Y, Akyol C, Aytac E, Baca B, Bulut O, Remzi FH. Laparoscopic surgery for complex and recurrent Crohn's disease. *World J Gastrointest Endosc* 2017; 9(4): 149-152 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i4/149.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i4.149

Crohn's disease (CD) is a chronic inflammatory disease that can develop any part of the digestive tract. CD usually arises at the terminal ileum[1]. Despite advanced medical treatment alternatives including biologics, immune suppressive drugs and steroids, approximately 70% of patients with CD require surgical intervention within 10 years of their initial diagnosis[2,3]. Surgery is warranted for management of medically refractory CD. Surgical treatment overcomes emergent issues, improves symptoms and patient's quality of life. Unfortunately, there is no cure for CD and it tends to recur during the disease course. Recurrent CD is described based on treatment type including medical, endoscopic or surgical.

Endoscopically documented recurrent CD can be up to 93% within one year following intestinal resection[4], while clinically symptomatic recurrence is usually around 30% at first 3 years after surgery[5]. Forty percent to 50% of patients who had an index surgery for CD require a reoperation for recurrent disease in 10 years[6,7]. Index surgical treatment type and medications used after index surgery appears to be factors related to recurrence risk of CD[2,8-10]. CD patients can be good candidates for minimally invasive treatment modalities due to the benign nature of the disease especially at the time of index surgery. However, use of laparoscopy in patients with complex CD such as extensive fistulizing or recurrent disease requiring surgical treatment is controversial.

Majority of the surgical indications for recurrent CD are also the conditions complicating application of laparoscopic surgery such as intractable fibrotic strictures with obstruction, fistulas with abscess formation and hemorrhage[11,12]. Based on the extension and severity of disease, surgical options including strictureplasty, small bowel resection, ileocolectomy, internal bypass, partial/total colectomy and proctectomy may be performed laparoscopically[11,13]. In selected CD patients, laparoscopic surgery is safe, feasible and provides better outcomes compared to open surgery[14-17]. While operative times have decreased with increased experience, operative mortality is almost none and morbidity rates ranged from 10% to 40% in patients undergoing laparoscopic surgery for recurrent CD[17-19]. Postoperative ileus seems as the most common complication which may strongly relate excessive manipulation of the bowel during dissection[13]. Some surgeons believe that laparoscopic approach may also provide the well-known advantages of minimally invasive surgery such as reduced postoperative pain, lower morbidity, shorter hospital stay, earlier return to daily activity, and improved quality of life in patients with recurrent CD (Table 1).

Unsuccessful laparoscopic attempts requiring conversion to open surgery have been a major concern due to presumed risk of worse outcomes and conversion rates tend to be higher in laparoscopic operations for recurrent CD[20]. Conversion to open surgery rates varies between 6.7% and 42.3% in recurrent CD cases[21,22]. The most common cause of conversion was adhesions[13,23]. Having multiple resections, intraabdominal abscess and phlegmon are the other factors leading conversion in CD patients[22]. This clinical situation raises concerns on conversion related postoperative morbidity[24]. However, recent data show that conversions do not to worsen the outcomes of colorectal surgery in experienced hands[25]. The data regarding to operation type and disease characteristics especially related to index resection for CD are heterogeneous in the previous reports[26,27]. Outcomes after laparoscopic surgery for recurrent CD vary due to selection bias and experience of the surgeon[27,28]. Laparoscopic surgery showed better outcomes with shorter length of hospital stay compared to open surgery in selected cases[28], while laparoscopic approach did not provide expected benefits over open surgery in some series[13,27]. Although wound complications are reduced, the benefits of laparoscopic surgery in patients with a history of previous open intestinal resection through midline laparotomy seem questionable[13]. As an emerging technique, single incision laparoscopy can be performed for recurrent CD[29,30]. Single incision laparoscopy can be promising in complex cases by minimizing overall wound size, decreasing unnecessary adhesiolysis for secondary port placements and it affords the surgeon the opportunity to inspect the density of adhesions through port site and lead the surgeon to convert the operation preemptively if laparoscopic surgery seems unfeasible[31].

Table 1 Perioperative outcomes laparoscopy for complex and recurrent Crohn's disease

Ref.	Year	Patients surgery (*n*)	Conversion to open surgery (*n*)	Operative duration (min)	Hospital stay (d)
Wu *et al*[17]	1997	CL: 14	1	152	4.8
		RL: 10	2	144	3.9
		PL: 22	2	139	4.5
		O: 70	(-)	202[a]	7.9[a]
Hasegawa *et al*[28]	2003	RL: 16	2	210[a]	6.0
		PL: 45	3	180	8.0
Moorthy *et al*[22]	2004	RL: 26	11	118	8.0
		PL: 31	4	127	7.0
Goyer *et al*[32]	2009	Comp: 54[b]	20[a]	214[a]	8.0
		Uncomp: 70	10	191	7.0
Chaudhary *et al*[21]	2010	RL: 30	2	125[a]	3.0
		PL: 29	3	85	3.0
Brouquet *et al*[27]	2010	L: 29	9	215	9.0
		O: 33		226	9.0
Pinto *et al*[18]	2011	RL: 50	16	201	7.4
		PL: 80	15	182	6.7
Aytac *et al*[13]	2012	L: 26	3	169	6.4
		O: 26		158	6.9
Huang *et al*[20]	2012	RL: 48	10	100	ND
		PL: 82	14	106	ND

[a]Bold: Statistically significant; [b]27 of these patients had recurrent disease. CL: Laparoscopic surgery for complicated disease (phlegmon, abscess); PL: Laparoscopic surgery for primary disease; RL: Laparoscopic surgery for recurrent disease; L: Laparoscopic surgery; O: Open surgery; Comp: Complicated; Uncomp: Uncomplicated.

In experienced hands, laparoscopic approach has promising outcomes in patients with recurrent CD when it is used selectively. There is a need for new studies which focus on identification of proper patients who may benefit from laparoscopic surgery for recurrent and complex CD.

REFERENCES

1 **Longobardi T**, Jacobs P, Bernstein CN. Work losses related to inflammatory bowel disease in the United States: results from the National Health Interview Survey. *Am J Gastroenterol* 2003; **98**: 1064-1072 [PMID: 12809829 DOI: 10.1111/j.1572-0241.2003.07285.x]

2 **Bernell O**, Lapidus A, Hellers G. Recurrence after colectomy in Crohn's colitis. *Dis Colon Rectum* 2001; **44**: 647-654; discussion 654 [PMID: 11357022]

3 **Vind I**, Riis L, Jess T, Knudsen E, Pedersen N, Elkjaer M, Bak Andersen I, Wewer V, Nørregaard P, Moesgaard F, Bendtsen F, Munkholm P. Increasing incidences of inflammatory bowel disease and decreasing surgery rates in Copenhagen City and County, 2003-2005: a population-based study from the Danish Crohn colitis database. *Am J Gastroenterol* 2006; **101**: 1274-1282 [PMID: 16771949 DOI: 10.1111/j.1572-0241.2006.00552.x]

4 **Olaison G**, Smedh K, Sjödahl R. Natural course of Crohn's disease after ileocolic resection: endoscopically visualised ileal ulcers preceding symptoms. *Gut* 1992; **33**: 331-335 [PMID: 1568651]

5 **Sachar DB**. The problem of postoperative recurrence of Crohn's disease. *Med Clin North Am* 1990; **74**: 183-188 [PMID: 2404175]

6 **Nordgren SR**, Fasth SB, Oresland TO, Hultén LA. Long-term follow-up in Crohn's disease. Mortality, morbidity, and functional status. *Scand J Gastroenterol* 1994; **29**: 1122-1128 [PMID: 7886401]

7 **Aratari A**, Papi C, Leandro G, Viscido A, Capurso L, Caprilli R. Early versus late surgery for ileo-caecal Crohn's disease. *Aliment Pharmacol Ther* 2007; **26**: 1303-1312 [PMID: 17848181 DOI: 10.1111/j.1365-2036.2007.03515.x]

8 **Renna S**, Cammà C, Modesto I, Cabibbo G, Scimeca D, Civitavecchia G, Mocciaro F, Orlando A, Enea M, Cottone M. Meta-analysis of the placebo rates of clinical relapse and severe endoscopic recurrence in postoperative Crohn's disease. *Gastroenterology* 2008; **135**: 1500-1509 [PMID: 18823987 DOI: 10.1053/j.gastro.2008.07.066]

9 **Borley NR**, Mortensen NJ, Chaudry MA, Mohammed S, Warren BF, George BD, Clark T, Jewell DP, Kettlewell MG. Recurrence after abdominal surgery for Crohn's disease: relationship to disease site and surgical procedure. *Dis Colon Rectum* 2002; **45**: 377-383 [PMID: 12068198]

10 **Rutgeerts P**, Goboes K, Peeters M, Hiele M, Penninckx F, Aerts R, Kerremans R, Vantrappen G. Effect of faecal stream diversion on recurrence of Crohn's disease in the neoterminal ileum. *Lancet* 1991; **338**: 771-774 [PMID: 1681159]

11 **Jones DW**, Finlayson SR. Trends in surgery for Crohn's disease in the era of infliximab. *Ann Surg* 2010; **252**: 307-312 [PMID: 20585239 DOI: 10.1097/SLA.0b013e3181e61df5]

12 **Strong SA**, Koltun WA, Hyman NH, Buie WD. Practice parameters for the surgical management of Crohn's disease. *Dis Colon Rectum* 2007; **50**: 1735-1746 [PMID: 17690937 DOI: 10.1007/s10350-007-9012-7]

13 **Aytac E**, Stocchi L, Remzi FH, Kiran RP. Is laparoscopic surgery for recurrent Crohn's disease beneficial in patients with previous primary resection through midline laparotomy? A case-matched study. *Surg Endosc* 2012; **26**: 3552-3556 [PMID: 22648125 DOI: 10.1007/s00464-012-2361-x]

14 **Alabaz O**, Iroatulam AJ, Nessim A, Weiss EG, Nogueras JJ, Wexner SD. Comparison of laparoscopically assisted and conventional ileocolic resection for Crohn's disease. *Eur J Surg* 2000; **166**: 213-217 [PMID: 10755335 DOI: 10.1080/11024150750009302]

15 **Bemelman WA**, Slors JF, Dunker MS, van Hogezand RA, van Deventer SJ, Ringers J, Griffioen G, Gouma DJ. Laparoscopic-assisted vs. open ileocolic resection for Crohn's disease. A comparative study. *Surg Endosc* 2000; **14**: 721-725 [PMID: 10954817]

16 **Schmidt CM**, Talamini MA, Kaufman HS, Lilliemoe KD, Learn P, Bayless T. Laparoscopic surgery for Crohn's disease: reasons for conversion. *Ann Surg* 2001; **233**: 733-739 [PMID: 11371731]

17 **Wu JS**, Birnbaum EH, Kodner IJ, Fry RD, Read TE, Fleshman JW. Laparoscopic-assisted ileocolic resections in patients with Crohn's disease: are abscesses, phlegmons, or recurrent disease contraindications? *Surgery* 1997; **122**: 682-688; discussion 682-688 [PMID: 9347843]

18 **Pinto RA**, Shawki S, Narita K, Weiss EG, Wexner SD. Laparoscopy for recurrent Crohn's disease: how do the results compare with the results for primary Crohn's disease? *Colorectal Dis* 2011; **13**: 302-307 [PMID: 19912288 DOI: 10.1111/j.1463-1318.2009.02133.x]

19 **Tavernier M**, Lebreton G, Alves A. Laparoscopic surgery for complex Crohn's disease. *J Visc Surg* 2013; **150**: 389-393 [PMID: 24119432 DOI: 10.1016/j.jviscsurg.2013.09.004]

20 **Huang R**, Valerian BT, Lee EC. Laparoscopic approach in patients with recurrent Crohn's disease. *Am Surg* 2012; **78**: 595-599 [PMID: 22546134]

21 **Chaudhary B**, Glancy D, Dixon AR. Laparoscopic surgery for recurrent ileocolic Crohn's disease is as safe and effective as primary resection. *Colorectal Dis* 2011; **13**: 1413-1416 [PMID: 21087388 DOI: 10.1111/j.1463-1318.2010.02511.x]

22 **Moorthy K**, Shaul T, Foley RJ. Factors that predict conversion in patients undergoing laparoscopic surgery for Crohn's disease. *Am J Surg* 2004; **187**: 47-51 [PMID: 14706585]

23 **Holubar SD**, Dozois EJ, Privitera A, Cima RR, Pemberton JH, Young-Fadok T, Larson DW. Laparoscopic surgery for recurrent ileocolic Crohn's disease. *Inflamm Bowel Dis* 2010; **16**: 1382-1386 [PMID: 20027655 DOI: 10.1002/ibd.21186]

24 **Gonzalez R**, Smith CD, Mason E, Duncan T, Wilson R, Miller J, Ramshaw BJ. Consequences of conversion in laparoscopic colorectal surgery. *Dis Colon Rectum* 2006; **49**: 197-204 [PMID:

16328607 DOI: 10.1007/s10350-005-0258-7]
25 **Aytac E**, Stocchi L, Ozdemir Y, Kiran RP. Factors affecting morbidity after conversion of laparoscopic colorectal resections. *Br J Surg* 2013; **100**: 1641-1648
26 **Bandyopadhyay D**, Sagar PM, Mirnezami A, Lengyel J, Morrison C, Gatt M. Laparoscopic resection for recurrent Crohn's disease: safety, feasibility and short-term outcomes. *Colorectal Dis* 2011; **13**: 161-165 [PMID: 19888954 DOI: 10.1111/j.1463-1318.2009.02100.x]
27 **Brouquet A**, Bretagnol F, Soprani A, Valleur P, Bouhnik Y, Panis Y. A laparoscopic approach to iterative ileocolonic resection for the recurrence of Crohn's disease. *Surg Endosc* 2010; **24**: 879-887 [PMID: 19730944 DOI: 10.1007/s00464-009-0682-1]
28 **Hasegawa H**, Watanabe M, Nishibori H, Okabayashi K, Hibi T, Kitajima M. Laparoscopic surgery for recurrent Crohn's disease. *Br J Surg* 2003; **90**: 970-973 [PMID: 12905550 DOI: 10.1002/bjs.4136]
29 **Kawahara H**, Watanabe K, Ushigome T, Noaki R, Kobayashi S, Yanaga K. Single-incision laparoscopic right colectomy for recurrent Crohn's disease. *Hepatogastroenterology* 2010; **57**: 1170-1172 [PMID: 21410052]
30 **Moftah M**, Nazour F, Cunningham M, Cahill RA. Single port laparoscopic surgery for patients with complex and recurrent Crohn's disease. *J Crohns Colitis* 2014; **8**: 1055-1061 [PMID: 24589026 DOI: 10.1016/j.crohns.2014.02.003]
31 **Aytac E**, Stocchi L, Williams R, Remzi FH, Costedio MM. Single-port laparoscopic fecal diversion: more than cosmetic benefits? *Surg Laparosc Endosc Percutan Tech* 2014; **24**: e133-136
32 **Goyer P**, Alves A, Bretagnol F, Bouhnik Y, Valleur P, Panis Y. Impact of complex Crohn's disease on the outcome of laparoscopic ileocecal resection: a comparative clinical study in 124 patients. *Dis Colon Rectum* 2009; **52**: 205-210 [PMID: 19279413 DOI: 10.1007/DCR.0b013e31819c9c08]

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MINIREVIEWS

Non-functioning pancreatic neuroendocrine tumors: Surgery or observation?

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Abstract

Incidentally detected, sporadic, nonfunctional pancreatic neuroendocrine tumors are increasingly diagnosed on imaging studies performed for unrelated purposes. Although their resection is usually recommended, controversy still exists regarding their optimal management, due to their highly variable and difficult to predict biologic behavior. Recently, several studies and guidelines advocated an expectant management approach in small size, low grade, incidentally diagnosed nonfunctional pancreatic neuroendocrine tumors. The aim of this study is to review and summarize the available literature addressing nonfunctional pancreatic neuroendocrine tumors, with an emphasis on surgical management controversies.

Key words: Pancreatic neuroendocrine tumors; Nonfunctional; Incidental; Surgery; Observation

Core tip: Nonfunctional pancreatic neuroendocrine tumors are increasingly diagnosed. Controversy exists regarding their optimal management. Expectant management in small size, low grade, incidentally diagnosed nonfunctional pancreatic neuroendocrine tumors has been suggested as an optional treatment. The aim of this study is to review the available literature addressing nonfunctional pancreatic neuroendocrine tumors, with an emphasis on surgical management controversies.

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INTRODUCTION

Pancreatic neuroendocrine tumors (PNETs) are un-

common neoplasms that arise from the islet cells of the pancreas and represent 1%-2% of all pancreatic cancers[1]. PNETs are clinically classified as functional (F-PNETs) and non-functional (NF-PNETs) based on the existence or non-existence of symptoms caused by hormone hypersecretion[2]. F-PNETs can synthesize and produce hormones such as insulin, gastrin, glucagon, somatostatin, and vasoactive intestinal peptide (VIP) resulting in myriad clinical syndromes. NF-PNETs, on the other hand, may secret some peptides such as chromogranin, pancreatic polypeptide, and others, but without clinical syndromes of hypersecretion[3,4]. Historically, F-PNETs were reported to have increased incidence and earlier diagnosis as compared to NF-PNETs due to their symptoms of hypersecretion, although the later accounts for the majority of PNETs[5-7]. With the widespread use and improvement of cross-sectional imaging techniques, NF-PNETs are increasingly discovered incidentally in asymptomatic patients who undergo evaluation for unrelated conditions[8,9]. This has been accompanied by an increase preoperative histologic diagnosis through endoscopic ultrasonography (EUS) and EUS-guided fine needle aspiration[10]. While there is a unanimity consensus that favors surgical resection in F-PNETs, controversy exists among clinicians regarding the optimal management of asymptomatic, small, incidentally discovered NF-PNETs. This article provides an updated review and aims to address the controversies in the management of sporadic small NF-PNETs. In light of article scope limitations, management and treatment of advanced metastatic disease or familial related diseases will not be addressed in this review.

EPIDEMIOLOGY

PNETs are more common in Caucasian and in males, with an incidence that increases with age, reaching a pick in the fifth-sixth decades. Detection is increasing owing to the widespread use of axial imaging, with one retrospective study demonstrating more than 2-fold increase in the incidence of NF-PNETs compared to 16 years ago and that the increase is related to accidental detection of the tumors[8,11]. NF-PNETs are biologically diverse and account for 65% to 90% of PNETs[1,12,13].

While most of PNETs occur sporadically, 10%-30% of them are associated with various inherited disorders including MEN1, Von Hippel-Lindau syndrome, neurofibromatosis 1, tuberous sclerosis, and Mahvash disease[14,15]. The majority of PNETS related to MEN1 and VHL syndromes are non-functioning tumors[1].

CLINICAL PRESENTATION

Patients with F-PNETs have overt clinical symptoms due to their physiologic response to hormone hypersecretion. In contrast, NF-PNETs can remain asymptomatic before they reach a significant tumor burden. Thus, they often present later during the disease with symptoms of local compression or metastatic disease in 21% and 60%, respectively[1,6,16]. When symptomatic, the main complaints observed are abdominal pain (35%-78%), weight loss (20%-35%), and anorexia and nausea (45%). Less frequent signs include icterus (17%-50%), intraabdominal hemorrhage (4%-20%), or a palpable mass (7%-40%)[17]. Up to 50% of non-metastatic NF-PNETs will not show any symptoms being diagnosed incidentally on cross-sectional imaging performed for other indications[8,18].

DIAGNOSIS

The diagnostic approach of patients with NF-PNETs should be thorough and starts with detailed past medical and family history followed by complete physical examination. Then biochemical and imaging studies have uttermost importance for treatment strategy and are performed in order to evaluate the degree of local invasion, lymph node involvement, as well as the presence of metastatic disease.

IMAGING

High-resolution computerized tomography (CT) scan is the initial imaging modality at many institutions due to its noninvasiveness and availability. Studies have reported a sensitivity of more than 80%, with a direct correlation to tumor size[19,20].

Compared to CT, magnetic resonance imaging (MRI) has non-ionized radiation advantage and can be used as an alternative imaging modality. Furthermore, studies reported superiority of MRI over CT in detecting smaller pancreatic lesions and liver metastases[21,22]. One study reported a sensitivity and specificity of up to 85% and 100%, respectively[23].

EUS is an additional imaging modality, and has additional benefits in preoperative diagnosis[24]. Somatostatin receptor imaging (SRI) is a functional imaging modality of choice in the evaluation of neuroendocrine tumors. Besides its utility in the staging of these tumors, SRI may help to select the patients with advanced disease that are suitable for systemic somatostatin-based therapies[25,26].

While ^{111}Indium-DTPA-octreotide (Octreoscan) has been initially used, with the recent availability of the PET imaging technique, somatostatin analogues have been labeled with positron emitting isotopes, including Gallium-68, to image somatostatin receptor (SSR) expressing tumors[27]. The compounds often used in molecular imaging of NETs with PET are ^{68}Ga-DOTATOC, ^{68}Ga-DOTATATE, and ^{68}Ga-DOTANOC, with a varying affinity to different somatostatin receptors. It has been demonstrated that ^{68}Ga-DOTA-TATE PET CT scan has the highest affinity for SSR2 and can dramatically improve the spatial resolution in parallel with a significantly higher detection rate and accuracy compared to conventional Octreoscan[28,29].

BIOPSY

EUS-guided fine-needle aspiration biopsy can provide preoperative histologic information important for tumor grading. One meta-analysis reported a sensitivity of 87% and a specificity of 98%[30]. The utility of routine preoperative biopsy remains controversial. Some clinicians have argued that the theoretical risk of procedure complications outweighs the benefit, while others, including us, believe in routine biopsy given the importance of characterizing and grading the tumor. Dietrich *et al*[31] demonstrated in a large study the importance of preoperative diagnosis. Among 394 patients with incidental finding of lesions smaller than ⩽ 15 mm, all were diagnosed by imaging-guided biopsy and/or surgery, 156 (about 40%) were diagnosed with neuroendocrine tumors, 146 pancreatic ductal adenocarcinoma, and 92 with various other etiologies. Although retrospective, approximately 60% did not have pancreatic ductal adenocarcinoma and not necessarily require radical surgery that carries significant risks[31].

BIOCHEMICAL STUDIES

Chromogranin A (CgA) can be used as a nonspecific biochemical marker. It has an approximate sensitivity and specificity of 60% and 80%, respectively[32,33]. False positive elevations of CgA can present in many other conditions such as use of anti-acid drugs (*e.g.,* proton pump inhibitors, H2 blockers, *etc.*), atrophic gastritis, renal insufficiency, hepatic insufficiency, *ect*[34].

Pancreatic polypeptide (PP) and neuron specific enolase (NSE) are additional useful NF-PNET markers. As with CgA false positive elevations of pancreatic polypeptide can be postprandial and in renal insufficiency[16,32,35]. Preoperative increased levels of CgA or PP may potentially be helpful in evaluation of response, progression, or recurrence at an early stage[36].

Elevated NSE levels were exclusively associated with poor tumor differentiation[36].

GRADING AND STAGING

From histological point of view, the 2010 World Health Organization (WHO) classification system is the most used grading system. It identifies three categories: Grade 1 tumors (< 2 mitosis/10 HPF and Ki-67 index ⩽ 2%), grade 2 (2-20 mitosis/10 HPF and Ki-67 index 3%-20%), and grade 3 (> 20 mitosis/10 HPF and Ki-67 index of > 20%). This classification forms the basis for evaluating prognosis and predicting malignancy[2,37].

Two TNM based staging systems were developed for PNETs, one from the American Joint Committee on Cancer (AJCC) that covers both pancreatic exocrine and neuroendocrine malignancies and the other proposed by the European Neuroendocrine Tumor Society (ENETS) (Table 1)[38,39]. The difference between them is mainly expressed in the soft tissue involvement criteria. While the AJCC characterize T3-T4 using peripancreatic invasion of these tumors (sometimes difficult to assess due to the structure of the pancreas), the ENETS staging system relies on more assessable criteria such as tumor size[40,41]. Despite differences, both staging systems are highly prognostic validated and found to be useful for clinical practice[42-44].

One retrospective 11-year period report of 425 patients with PNETs demonstrated that the 5-year overall survival rates using the ENETS classification for patients treated in referral neuroendocrine tumor (NET) center for stages Ⅰ, Ⅱ, Ⅲ and Ⅳ disease were 100%, 88%, 85%, and 57%, respectively. The corresponding values using the AJCC classification were 92%, 84%, 81%, and 57%, respectively[44]. Another large cohort study of 1072 post-operative patients suggests the ENETS TNM staging system is superior to the AJCC and WHO 2010 TNM staging system and supports its use in clinical practice[42].

CURRENT GUIDELINES

Several guidelines for the management of PNETs have been established in order to help physicians treating these complex patients. The 2012 and 2016 European Neuroendocrine Tumor Society (ENETS) guidelines, the National Comprehensive Cancer Network 2016 (NCCN), North American Neuroendocrine Tumor Society-2013 (NANETS), and European Society of Medical Oncology-2012 (ESMO) have published diagnostic and therapeutic guidelines[3,12,45-47].

For initial biochemical workup the ENETS, ESMO, and NANETS guidelines all recommend measuring CgA and PP serum levels as a useful tool for reaching a diagnosis in a fraction of NF-PNETs.

The first imaging modality recommended is multiphasic CT/MRI with contrast agents imaging modality, while octreotide scintigraphy (planar and SPECT) but mainly ^{68}Ga-labeled somatostatin analogues with PET/CT are also recommended, if available.

All four guidelines recommend using the 2010 WHO grading system as the grading of choice and generally advocate surgical resection as the preferred option as long as there are no surgical limiting contraindications, highly diffuse metastatic disease, or selected cases that can be observed discussed in the next sections.

The surgical options for locoregional NF-PNETs mentioned in all guidelines range between simple enucleation, central pancreatectomy, distal pancreatectomy with or without splenectomy, and pancreatoduodenectomy (Whipple's operation). The extent and type of surgery mainly depends on the location of the primary tumor (head, body, or tail). Tumors larger than 2 cm that are locally invasive or have positive lymph node involvement in preoperative evaluation should all include regional lymph node dissection. In patients with smaller than 2 cm NF-PNETs, lymph node sampling is not always mandatory. While both NCCN and ENETS recognize the role of laparoscopic approach in PNETs resections, the EMCO guidelines do not recommend this approach due to the need for thorough intraoperative lymph node

Table 1 European Neuroendocrine Tumor Society and American Joint Committee on Cancer TNM grading systems for pancreatic tumors[38,39]

	ENETS	AJCC
T Grade (primary tumor)		
Tx	Primary tumor is not assessed	Primary tumor is not assessed
T0	No finding of primary tumor	No finding of a primary tumor
Tis		*In situ* carcinoma
T1	Tumor is limited to the pancreas and < 2 cm	Tumor is limited to the pancreas and ≤ 2 cm
T2	Tumor is limited to the pancreas and 2 to 4 cm	T2 tumor is limited to the pancreas and > 2 cm
T3	Tumor is limited to the pancreas and > 4 cm or with positive duodenum or biliary tract invasion	Tumor has progressed beyond the pancreas but there is no celiac or mesenteric artery involvement
T4	Tumor has invaded the neighboring organs (stomach, spleen, colon, adrenal gland) or walls of the large vessels (celiac artery or superior mesenteric artery)	Tumor shows celiac or superior mesenteric artery involvement
N-lymph node status		
Nx	Regional lymph nodes are not assessed	Regional lymph nodes are not assessed
N0	No regional lymph node metastasis	No regional lymph node metastasis
N1	Regional lymph node metastasis is positive	Regional lymph node metastasis is positive
M-distant metastasis		
Mx	Distant metastasis is not assessed	
M0	No distant metastasis	No distant metastasis
M1	Distant metastasis is positive	Distant metastasis is positive
Stage		
0		Tis, N0, M0
I	T1, N0, M0	
IA		T1, N0, M0
IB		T2, N0, M0
IIA	T2, N0, M0	T3, N0, M0; T1, N1, M0
IIB	T3, N0, M0	T2, N1, M0; T3,N1,M0
III		T4, Any N, M0
IIIA	T4, N0, M0	
IIIB	Any T, N1, M0	
IV	Any T, Any N, M1	Any T, Any N, M1

inspection.

Currently, updated ENETS and NCCN guidelines both acknowledge nonoperational options, with different tumor size-cutoff (NCCN < 1 cm, ENETS < 2 cm), as suitable for managing small NF-PNETs while taking into account factors such as incidental discovery, lack of clinical syndromes and radiological signs suspicious for malignancy, as well as patient's characteristics (surgical risk, comorbidities, and personal wishes)[12,45,47]. However, data supporting this non-operational option are controversial and will be reviewed in the next section. Figure 1 offers a suggested algorithm for patient management.

SURGICAL MANAGEMENT CONTROVERSY

In most cases surgery remains the curative modality of choice for NF-PNETs, with preliminary evidence demonstrating improved survival especially with localized disease[48,49]. However, as previously mentioned, during the last recent years there is a significant increase in the detection of small, incidentally discovered, asymptomatic NF-PNETs, that may be managed conservatively by observation. At present there are no RCTs or meta-analyses that can assist to outline the optimal approach for the management of such small NF-PNETs. Nevertheless, there are 12 retrospective series that may shed some light on this controversy.

Tumor size as criteria for treatment decision

Bettini *et al*[50] demonstrated a distinct correlation between tumor size and lower malignancy potential on 177 patients, who were divided into three groups depending on tumor size (≤ 2 cm, 2-4 cm, > 4 cm), all underwent curative resection. Patients with tumor ≤ 2 cm (n = 51) had higher frequency of incidental diagnosis compared with patients with > 4 cm (57% *vs* 32%, P = 0.014). Among those who were incidentally discovered, only 6% were malignant and none died from the disease. In addition, a correlation between tumor size and Ki67 was demonstrated. Patients with tumors ≤ 2 cm had lower Ki67 median values compared with patients with tumors > 2 cm ≤ 4 cm and > 4 cm (1% *vs* 2% and 3%, respectively). The authors suggested that nonsurgical management could be advocated in selected cases for low-grade tumors less than 2 cm, due to their indolent course. In an attempt to determine the prognostic value of indicators of malignancy in NF-PNETs ≤ 2 cm, Regenet *et al*[51] demonstrated, by using multivariate analysis, that tumor size is a significant indicator of malignancy, and

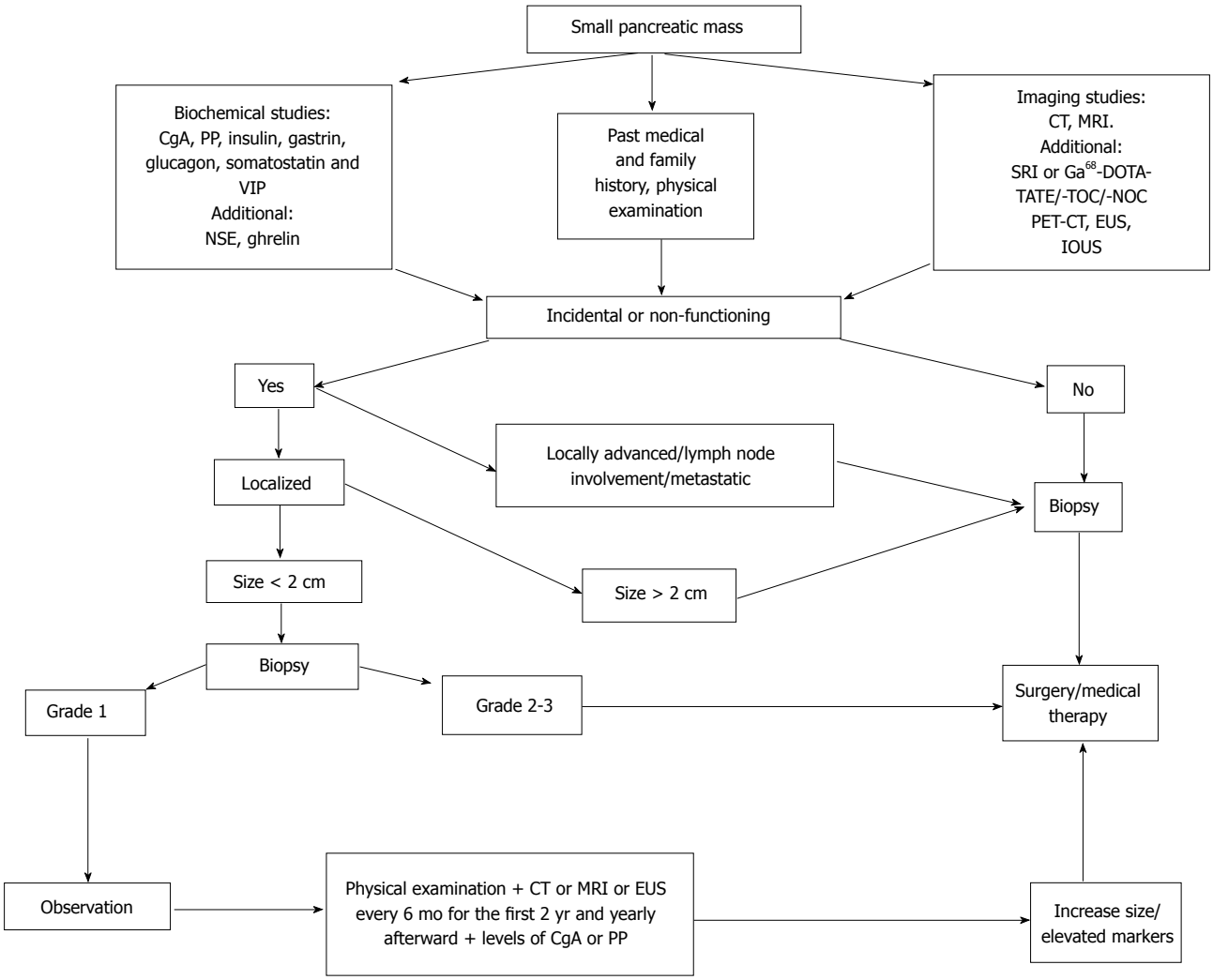

Figure 1 Suggested algorithm for the management of small pancreatic mass. CgA: Chromogranin A; PP: Pancreatic polypeptide; VIP: Vasoactive intestinal peptide; NSE: Neuron-specific enolase; CT: Computed tomography; MRI: Magnetic resonance imaging; SRI: Somatostatin-receptor imaging; EUS: Endoscopic ultrasonography; IOUS: Intraoperatively ultrasonography; PET: Positron emission tomography; Ga^{68}-DOTA-TATE/-TOC/-NOC: ^{68}Gallium-DOTA-TATE, ^{68}Gallium-DOTA-TOC^{68} and Gallium-DOTA-NOC respectively.

even proposed a new 1.7 cm cutoff as more accurate for prediction of malignancy potential with a sensitivity of 92% and specificity of 75%. Despite these findings, Ki67 was not found to be a significant indicator of malignancy probably due to large number of patients without complete histologic assessment and Ki67 evaluation[51]. In a larger population study by Gratian *et al*[52] among 1854 patients with NF-PNETs $\leqslant$ 2 cm, who were identified from the National Cancer Data Base (NCDB), 309 patients (29%) presented with regional lymph node involvement and 180 patients (10%) presented with distant metastases[52]. In contrast to Bettini *et al* findings, they conclude that tumors smaller than 2 cm have a significant risk of malignancy. It is worth mentioning that the study was limited by missing data of several variables, including Ki67.

Incidental vs non-incidental diagnosis as criteria for treatment decision

Different studies have recently tried to distinguish between incidental and non-incidental NF-PNETs, especially those discovered at early age, in terms of prognosis and treatment approach. Cheema *et al*[18] identified 143 nonmetastatic PNETs, 40% were diagnosed incidentally. They demonstrated that 5-year progression free survival (PFS) was significantly prolonged in patients with incidental diagnosed *vs* symptomatic tumors (86% *vs* 59%, $P = 0.007$).

Tumor grading as criteria for treatment decision

It should be noted that histopathologic grade was another statistically significant factor for progression on multivariate analysis (hazard ratio of 3.0 for Grade 2 *vs* Grade 1, $P = 0.007$), though Ki67 proliferation index was only evaluated in 25% of cases[18]. As opposed to Cheema *et al*[18], Haynes *at el*[53] described 139 patients who all underwent surgery and identified no large difference in tumor size (3.0 cm *vs* 3.5 cm, $P = 0.48$), frequency of malignant histopathologic findings (28% *vs* 30%), or 5-year PFS (83% *vs* 82%, $P = 0.27$)

Table 2 Retrospective studies regarding incidental discovery

Ref.	Study period	Patients (*n*)	Group	Number of patients *n* (%)	5-yr PFS rates (%)	*P* value	Median follow-up time (mo)
Cheema *et al*[18]	1999-2010	143	Incidental	56 (40)	86	0.07	67 (mean)
			Non-incidental	87 (60)	59		
Crippa *et al*[54]	1990-2009	355	Incidental	124 (35)	83	< 0.001	44
			Non-incidental	231 (65)	32		
Haynes *et al*[53]	1997-2009	139	Incidental	109 (82)	82.8	0.27	34.2
			Non-incidental	30 (18)	81.7		
Birnbaum *et al*[55]	1994-2010	108	Incidental	65 (61)	92	0.03	42
			Non-incidental	43 (39)	82		

between incidental and non-incidental groups[18,53]. Of the 39 patients with tumors ⩽ 2 cm, 3 patients (7.7%) had late metastases or recurrence. Though problematic due to lack of observational group, they concluded that all patients should undergo tumor resection, even in incidentally discovered NF-PNETs smaller than 2 cm. From a staging point of view Crippa *et al*[54] demonstrated in a larger (*n* = 355) retrospective study that NF-PNETs diagnosed incidentally have greater 5-year PFS rates in all stages than symptomatic tumors: Stage Ⅰ (97% *vs* 78%, *P* = 0.013), stage Ⅱ (93% *vs* 74%, *P* = 0.036), stage III (69% *vs* 27%, *P* < 0.0001), and stage Ⅳ (60% *vs* 17%, *P* = 0.112). On multivariate analysis Grade 2 NF-PNETs was found to be a predictor of PFS among 124 incidentally diagnosed patients, with a hazard ratio of 3.402 (95%CI: 0.92-12.57, *P* = 0.066). In addition, they reported that 12 excluded patients, who underwent non-operative management of incidental NF-PNETs and had no tumor progression after median follow up of 36 mo. In this small group of patients the median tumor size at diagnosis was 1.4 cm (range 1.0-2.9 cm), and was stable throughout the surveillance period. Similar PFS rates were demonstrated in another retrospective study by Birnbaum *et al*[55] that included 106 patients, 65 discovered incidentally. These patients demonstrated both higher incidence of tumors smaller than 2 cm (65% *vs* 42%, *P* = 0.019) and lower Ki67 proliferation index (1% *vs* 4%, *P* = 0.004) compared to symptomatic patients. The authors concluded that pancreas sparing surgery is recommended as an optional treatment for these incidental NF-PNETs, due to less aggressive characteristics compared with symptomatic tumors (Table 2).

Observation for selected patients

Several retrospectively designed studies tried to answer the question whether observational management is suitable for NF-PNETs smaller than 2 cm and to assess the risk-benefit balance of this approach. Gaujoux *et al*[56] published a series of 46 patients who were followed for at least 18 mo (median 34, range 24-52 mo) with an average of four (range 4-6) serial imaging sessions or followed up after resection[56]. Among the resection group (*n* = 8), all grade 1 and without lymph node involvement, 5 were resected upon initial diagnosis and only 3 were resected due to tumor enlargement under imaging observations. The remaining 38 patients, who were managed without surgery, did not show any significant characteristics of malignancy such as distant metastases, nodal involvement, or significant increase in tumor size. In this study the overall median tumor growth was 0.12 mm per year. Both Lee *et al*[57] and Rosenberg *et al*[58] published similar results where small NF-PNETs in either the operative or non-operative groups demonstrated no evidence of progression, with lower, though important, operational-morbidity related rates (46% and 35%, respectively)[57,58]. They both conclude that non-operative management may be advocated and safe in selected patients. In the Lee *et al*[57] study, both surgical and nonsurgical group's tumors had low or intermediate grade and Ki67 values smaller than 5%, in all patients with available results[57]. Rosenberg *et al*[58] published a 35 patients series divided into operative and non-operative groups as well: Ki67 proliferation index rates of < 2% and 3%-20% were 65% *vs* 0% and 30% *vs* 27%, respectively. Ki67 data was not available in 1 (5%) patient in the operative group *vs* 11 (73%) in the non-operative group[58].

The observational approach for certain tumors was reinforced by another recently published matched case-control study by Sadot *et al*[59] who demonstrated that 5-year PFS was 95% and 91% (*P* = 0.3) for observational and resection only groups, respectively. A quarter (*n* = 26) of the observation group crossed over to resection group, due to different reasons. After a median follow-up of 7 years, none of these patients developed malignant features (node involvement or metastases). These data imply that initially observational approach and delayed surgical intervention may not compromise long-term outcomes.

Contrary to this claim, Sharpe *et al*[60] performed a population based study and demonstrated that patients who were managed with observation had nearly three times the risk of mortality in comparison to those who underwent resection[60]. Their study was large and based on patients collected from NCDB, all with NF-PNETs smaller than 2 cm. The authors concluded that surgical resection provides a benefit regardless of tumor grade, though it wasn't statistically proven at poorly differentiated/undifferentiated tumor. A summary of the studies regarding surgical *vs* observational approach in NF-PNETs is presented in Table 3.

Table 3 Retrospective studies regarding surgery *vs* observational management

Ref.	Study period	Patients *n*	Group	Number of patients *n* (%)	Median follow-up time (mo)	Surgery morbidity rate (%)
Gaujoux *et al*[56]	2000-2011	46	Observational	38 (83)	> 18	62
			Surgery	8 (17)	27	
Lee *et al*[57]	2000-2011	133	Observational	77 (57)	44 (Mean)	46
			Surgery	56 (43)	52 (Mean)	
Rosenberg *et al*[58]	1999-2014	35	Observational	15 (42)	28	35
			Surgery	20 (58)	34	
Sharpe *et al*[60]	1998-2006	380	Observational	71 (19)	60	N/A
			Surgery	309 (81)	60	
Sadot *et al*[59]	1993-2013	181	Observational	104[2] (57)	44	N/A
			Surgery	77[1] (43)	57	

[1]Matched group; [2]Before cross over; N/A: Not available.

OBSERVATION PROTOCOL

History and physical examination, as well as biochemical markers and conventional trans-sectional high-resolution imaging should be used for both non-operative and postoperative surveillance. Postoperatively in patients with NF-PNETs grade 1 and 2, imaging is indicated every 3-9 mo (CT, MRI, or EUS), while more frequent imaging (up to 2-3 mo intervals periods) is indicated in Grade 3 or recurrent symptomatic patients, during the first year following surgery[12,45,47,61]. Either Octreoscan or PET/CT using ^{68}Ga-DOTA-TOC/-NOC/-TATE should be repeated every 18-24 mo for grades 1-2[61]. In non-surgical patients with less than 2 cm NF-PNETs, Gaujoux *et al*[56] recommend conventional contrast enhanced CT or MRI every 6 mo for the first 2 years and yearly afterward[56]. In patients who underwent surgical resection of the tumor, imaging at 6-12 mo intervals should be performed between one and ten years post resection, although the optimal duration surveillance time for either non-operative nor postoperative patients is unknown[46].

CONCLUSION

In the last two decades the incidence of small NF-PNETs neoplasms has been steadily increasing. Unfortunately, there are still no clear prognostic factors that can enable us to distinguish between tumors suitable for observation and tumors with greater malignant potential that should be treated more aggressively. Several retrospective population based studies were reviewed in this article in an attempt to reduce the uncertainty. However, issues of selection bias, small sampling, and lack of data that are inherent in this type of studies limit our ability to conclude valid recommendations. In our NET center, the decision on treatment approach (follow-up *vs* surgical excision) for incidental NF-PNETs patients is based on tumor size (less or more than 2 cm), tumor grading, intensity of uptake on functional imaging (^{68}GaDOTATATE-PET/CT), on the stage of the disease, as well as on patient's desire. Larger scale, preferably multicenter randomized control trials, are needed in order to clarify the optimal management strategy and treatment for these rare small incidentally discovered tumors.

REFERENCES

1 **Halfdanarson TR**, Rabe KG, Rubin J, Petersen GM. Pancreatic neuroendocrine tumors (PNETs): incidence, prognosis and recent trend toward improved survival. *Ann Oncol* 2008; **19**: 1727-1733 [PMID: 18515795 DOI: 10.1093/annonc/mdn351]

2 **Bosman FT**, Carneiro F, Hruban RH, Theise N. WHO Classification of Tumor of the Digestive System. Lyon, France: IARC Press, 2010

3 **Kulke MH**, Anthony LB, Bushnell DL, de Herder WW, Goldsmith SJ, Klimstra DS, Marx SJ, Pasieka JL, Pommier RF, Yao JC, Jensen RT. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. *Pancreas* 2010; **39**: 735-752 [PMID: 20664472 DOI: 10.1097/MPA.0b013e3181ebb168]

4 **Krampitz GW**, Norton JA. Pancreatic neuroendocrine tumors. *Curr Probl Surg* 2013; **50**: 509-545 [PMID: 24206780 DOI: 10.1067/j.cpsurg.2013.08.001]

5 **Bilimoria KY**, Tomlinson JS, Merkow RP, Stewart AK, Ko CY, Talamonti MS, Bentrem DJ. Clinicopathologic features and treatment trends of pancreatic neuroendocrine tumors: analysis of 9,821 patients. *J Gastrointest Surg* 2007; **11**: 1460-1467; discussion 1467-1469 [PMID: 17846854 DOI: 10.1007/s11605-007-0263-3]

6 **Franko J**, Feng W, Yip L, Genovese E, Moser AJ. Non-functional neuroendocrine carcinoma of the pancreas: incidence, tumor biology, and outcomes in 2,158 patients. *J Gastrointest Surg* 2010; **14**: 541-548 [PMID: 19997980 DOI: 10.1007/s11605-009-1115-0]

7 **Fraenkel M**, Kim MK, Faggiano A, Valk GD. Epidemiology of gastroenteropancreatic neuroendocrine tumours. *Best Pract Res Clin Gastroenterol* 2012; **26**: 691-703 [PMID: 23582913 DOI: 10.1016/j.bpg.2013.01.006]

8 **Vagefi PA**, Razo O, Deshpande V, McGrath DJ, Lauwers GY, Thayer SP, Warshaw AL, Fernández-Del Castillo C. Evolving patterns in the detection and outcomes of pancreatic neuroendocrine neoplasms: the Massachusetts General Hospital experience from 1977 to 2005. *Arch Surg* 2007; **142**: 347-354 [PMID: 17438169 DOI: 10.1001/archsurg.142.4.347]

9 **Fitzgerald TL**, Hickner ZJ, Schmitz M, Kort EJ. Changing incidence of pancreatic neoplasms: a 16-year review of statewide tumor registry. *Pancreas* 2008; **37**: 134-138 [PMID: 18665072 DOI: 10.1097/MPA.0b013e318163a329]

10 **Ashkar M**, Gardner TB. Role of endoscopic ultrasound in pancreatic diseases: a systematic review. *Minerva Gastroenterol Dietol* 2014; **60**: 227-245 [PMID: 25288203]

11 **Kuo JH**, Lee JA, Chabot JA. Nonfunctional pancreatic neuroendocrine tumors. *Surg Clin North Am* 2014; **94**: 689-708 [PMID: 24857584 DOI: 10.1016/j.suc.2014.02.010]

12 **Falconi M**, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, Kos-Kudla B, Kwekkeboom D, Rindi G, Klöppel G, Reed N, Kianmanesh R, Jensen RT. ENETS Consensus

Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. *Neuroendocrinology* 2016; **103**: 153-171 [PMID: 26742109 DOI: 10.1159/000443171]
13 **Lawrence B**, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; **40**: 1-18, vii [PMID: 21349409 DOI: 10.1016/j.ecl.2010.12.005]
14 **Ro C**, Chai W, Yu VE, Yu R. Pancreatic neuroendocrine tumors: biology, diagnosis,and treatment. *Chin J Cancer* 2013; **32**: 312-324 [PMID: 23237225 DOI: 10.5732/cjc.012.10295]
15 **Rhyu J**, Yu R. Mahvash disease: an autosomal recessive hereditary pancreatic neuroendocrine tumor syndrome. *International Journal of Endocrine Oncology* 2016; **3**: 235-243 [DOI: 10.2217/ije-2016-0005]
16 **Metz DC**, Jensen RT. Gastrointestinal neuroendocrine tumors: pancreatic endocrine tumors. *Gastroenterology* 2008; **135**: 1469-1492 [PMID: 18703061 DOI: 10.1053/j.gastro.2008.05.047]
17 **Falconi M**, Plockinger U, Kwekkeboom DJ, Manfredi R, Korner M, Kvols L, Pape UF, Ricke J, Goretzki PE, Wildi S, Steinmuller T, Oberg K, Scoazec JY. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. *Neuroendocrinology* 2006; **84**: 196-211 [PMID: 17312380 DOI: 10.1159/000098012]
18 **Cheema A**, Weber J, Strosberg JR. Incidental detection of pancreatic neuroendocrine tumors: an analysis of incidence and outcomes. *Ann Surg Oncol* 2012; **19**: 2932-2936 [PMID: 22350605 DOI: 10.1245/s10434-012-2285-7]
19 **Ichikawa T**, Peterson MS, Federle MP, Baron RL, Haradome H, Kawamori Y, Nawano S, Araki T. Islet cell tumor of the pancreas: biphasic CT versus MR imaging in tumor detection. *Radiology* 2000; **216**: 163-171 [PMID: 10887243 DOI: 10.1148/radiology.216.1.r00jl26163]
20 **Khashab MA**, Yong E, Lennon AM, Shin EJ, Amateau S, Hruban RH, Olino K, Giday S, Fishman EK, Wolfgang CL, Edil BH, Makary M, Canto MI. EUS is still superior to multidetector computerized tomography for detection of pancreatic neuroendocrine tumors. *Gastrointest Endosc* 2011; **73**: 691-696 [PMID: 21067742 DOI: 10.1016/j.gie.2010.08.030]
21 **Sundin A**, Vullierme MP, Kaltsas G, Plöckinger U. ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: radiological examinations. *Neuroendocrinology* 2009; **90**: 167-183 [PMID: 19077417 DOI: 10.1159/000184855]
22 **Dromain C**, de Baere T, Lumbroso J, Caillet H, Laplanche A, Boige V, Ducreux M, Duvillard P, Elias D, Schlumberger M, Sigal R, Baudin E. Detection of liver metastases from endocrine tumors: a prospective comparison of somatostatin receptor scintigraphy, computed tomography, and magnetic resonance imaging. *J Clin Oncol* 2005; **23**: 70-78 [PMID: 15625361 DOI: 10.1200/JCO.2005.01.013]
23 **Thoeni RF**, Mueller-Lisse UG, Chan R, Do NK, Shyn PB. Detection of small, functional islet cell tumors in the pancreas: selection of MR imaging sequences for optimal sensitivity. *Radiology* 2000; **214**: 483-490 [PMID: 10671597 DOI: 10.1148/radiology.214.2.r00fe32483]
24 **James PD**, Tsolakis AV, Zhang M, Belletrutti PJ, Mohamed R, Roberts DJ, Heitman SJ. Incremental benefit of preoperative EUS for the detection of pancreatic neuroendocrine tumors: a meta-analysis. *Gastrointest Endosc* 2015; **81**: 848-856.e1 [PMID: 25805462 DOI: 10.1016/j.gie.2014.12.031]
25 **Schillaci O**, Spanu A, Scopinaro F, Falchi A, Corleto V, Danieli R, Marongiu P, Pisu N, Madeddu G, Delle Fave G, Madeddu G. Somatostatin receptor scintigraphy with 111In-pentetreotide in non-functioning gastroenteropancreatic neuroendocrine tumors. *Int J Oncol* 2003; **23**: 1687-1695 [PMID: 14612942]
26 **Lebtahi R**, Cadiot G, Sarda L, Daou D, Faraggi M, Petegnief Y, Mignon M, le Guludec D. Clinical impact of somatostatin receptor scintigraphy in the management of patients with neuroendocrine gastroenteropancreatic tumors. *J Nucl Med* 1997; **38**: 853-858 [PMID: 9189129]
27 **Hofman MS**, Kong G, Neels OC, Eu P, Hong E, Hicks RJ. High management impact of Ga-68 DOTATATE (GaTate) PET/CT for imaging neuroendocrine and other somatostatin expressing tumours. *J Med Imaging Radiat Oncol* 2012; **56**: 40-47 [PMID: 22339744 DOI: 10.1111/j.1754-9485.2011.02327.x]
28 **Gabriel M**, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Von Guggenberg E, Bale R, Virgolini IJ. 68Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT. *J Nucl Med* 2007; **48**: 508-518 [PMID: 17401086]
29 **Yang J**, Kan Y, Ge BH, Yuan L, Li C, Zhao W. Diagnostic role of Gallium-68 DOTATOC and Gallium-68 DOTATATE PET in patients with neuroendocrine tumors: a meta-analysis. *Acta Radiol* 2014; **55**: 389-398 [PMID: 23928010 DOI: 10.1177/0284185113496679]
30 **Puli SR**, Kalva N, Bechtold ML, Pamulaparthy SR, Cashman MD, Estes NC, Pearl RH, Volmar FH, Dillon S, Shekleton MF, Forcione D. Diagnostic accuracy of endoscopic ultrasound in pancreatic neuroendocrine tumors: a systematic review and meta analysis. *World J Gastroenterol* 2013; **19**: 3678-3684 [PMID: 23801872 DOI: 10.3748/wjg.v19.i23.3678]
31 **Dietrich CF**, Sahai AV, D'Onofrio M, Will U, Arcidiacono PG, Petrone MC, Hocke M, Braden B, Burmester E, Möller K, Săftoiu A, Ignee A, Cui XW, Iordache S, Potthoff A, Iglesias-Garcia J, Fusaroli P, Dong Y, Jenssen C. Differential diagnosis of small solid pancreatic lesions. *Gastrointest Endosc* 2016; **84**: 933-940 [PMID: 27155592 DOI: 10.1016/j.gie.2016.04.034]
32 **Panzuto F**, Severi C, Cannizzaro R, Falconi M, Angeletti S, Pasquali A, Corleto VD, Annibale B, Buonadonna A, Pederzoli P, Delle Fave G. Utility of combined use of plasma levels of chromogranin A and pancreatic polypeptide in the diagnosis of gastrointestinal and pancreatic endocrine tumors. *J Endocrinol Invest* 2004; **27**: 6-11 [PMID: 15053236]
33 **Lawrence B**, Gustafsson BI, Kidd M, Pavel M, Svejda B, Modlin IM. The clinical relevance of chromogranin A as a biomarker for gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; **40**: 111-134, viii [PMID: 21349414 DOI: 10.1016/j.ecl.2010.12.001]
34 **Gut P**, Czarnywojtek A, Fischbach J, Bączyk M, Ziemnicka K, Wrotkowska E, Gryczyńska M, Ruchała M. Chromogranin A - unspecific neuroendocrine marker. Clinical utility and potential diagnostic pitfalls. *Arch Med Sci* 2016; **12**: 1-9 [PMID: 26925113 DOI: 10.5114/aoms.2016.57577]
35 **Vinik AI**, Silva MP, Woltering EA, Go VL, Warner R, Caplin M. Biochemical testing for neuroendocrine tumors. *Pancreas* 2009; **38**: 876-889 [PMID: 19855234 DOI: 10.1097/MPA.0b013e3181bc0e77]
36 **Oberg K**, Modlin IM, De Herder W, Pavel M, Klimstra D, Frilling A, Metz DC, Heaney A, Kwekkeboom D, Strosberg J, Meyer T, Moss SF, Washington K, Wolin E, Liu E, Goldenring J. Consensus on biomarkers for neuroendocrine tumour disease. *Lancet Oncol* 2015; **16**: e435-e446 [PMID: 26370353 DOI: 10.1016/S1470-2045(15)00186-2]
37 **Yang M**, Tian BL, Zhang Y, Su AP, Yue PJ, Xu S, Wang L. Evaluation of the World Health Organization 2010 grading system in surgical outcome and prognosis of pancreatic neuroendocrine tumors. *Pancreas* 2014; **43**: 1003-1008 [PMID: 24945681 DOI: 10.1097/MPA.0000000000000153]
38 **Edge S**, Byrd D, Compton C. AJCC Cancer Staging Manual, vol. 7th ed. New York: Springer, 2010
39 **Rindi G**, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Erikssson B, Falchetti A, Falconi M, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; **449**: 395-401 [PMID: 16967267 DOI: 10.1007/s00428-006-0250-1]
40 **Adsay NV**, Bagci P, Tajiri T, Oliva I, Ohike N, Balci S, Gonzalez RS, Basturk O, Jang KT, Roa JC. Pathologic staging of pancreatic, ampullary, biliary, and gallbladder cancers: pitfalls and practical limitations of the current AJCC/UICC TNM staging system and opportunities for improvement. *Semin Diagn Pathol* 2012; **29**:

127-141 [PMID: 23062420 DOI: 10.1053/j.semdp.2012.08.010]
41 **Reid MD**, Balci S, Saka B, Adsay NV. Neuroendocrine tumors of the pancreas: current concepts and controversies. *Endocr Pathol* 2014; **25**: 65-79 [PMID: 24430597 DOI: 10.1007/s12022-013-9295-2]
42 **Rindi G**, Falconi M, Klersy C, Albarello L, Boninsegna L, Buchler MW, Capella C, Caplin M, Couvelard A, Doglioni C, Delle Fave G, Fischer L, Fusai G, de Herder WW, Jann H, Komminoth P, de Krijger RR, La Rosa S, Luong TV, Pape U, Perren A, Ruszniewski P, Scarpa A, Schmitt A, Solcia E, Wiedenmann B. TNM staging of neoplasms of the endocrine pancreas: results from a large international cohort study. *J Natl Cancer Inst* 2012; **104**: 764-777 [PMID: 22525418 DOI: 10.1093/jnci/djs208]
43 **Strosberg JR**, Cheema A, Weber JM, Ghayouri M, Han G, Hodul PJ, Kvols LK. Relapse-free survival in patients with nonmetastatic, surgically resected pancreatic neuroendocrine tumors: an analysis of the AJCC and ENETS staging classifications. *Ann Surg* 2012; **256**: 321-325 [PMID: 22415420 DOI: 10.1097/SLA.0b013e31824e6108]
44 **Strosberg JR**, Cheema A, Weber J, Han G, Coppola D, Kvols LK. Prognostic validity of a novel American Joint Committee on Cancer Staging Classification for pancreatic neuroendocrine tumors. *J Clin Oncol* 2011; **29**: 3044-3049 [PMID: 21709192 DOI: 10.1200/JCO.2011.35.1817]
45 **Falconi M**, Bartsch DK, Eriksson B, Klöppel G, Lopes JM, O'Connor JM, Salazar R, Taal BG, Vullierme MP, O'Toole D. ENETS Consensus Guidelines for the management of patients with digestive neuroendocrine neoplasms of the digestive system: well-differentiated pancreatic non-functioning tumors. *Neuroendocrinology* 2012; **95**: 120-134 [PMID: 22261872 DOI: 10.1159/000335587]
46 **Kunz PL**, Reidy-Lagunes D, Anthony LB, Bertino EM, Brendtro K, Chan JA, Chen H, Jensen RT, Kim MK, Klimstra DS, Kulke MH, Liu EH, Metz DC, Phan AT, Sippel RS, Strosberg JR, Yao JC. Consensus guidelines for the management and treatment of neuroendocrine tumors. *Pancreas* 2013; **42**: 557-577 [PMID: 23591432 DOI: 10.1097/MPA.0b013e31828e34a4]
47 National Cancer Comprehensive Network (NCCN). NCCN neuroendocrine tumors version 2. 2016
48 **Keutgen XM**, Nilubol N, Glanville J, Sadowski SM, Liewehr DJ, Venzon DJ, Steinberg SM, Kebebew E. Resection of primary tumor site is associated with prolonged survival in metastatic nonfunctioning pancreatic neuroendocrine tumors. *Surgery* 2016; **159**: 311-318 [PMID: 26453135 DOI: 10.1016/j.surg.2015.05.042]
49 **Hill JS**, McPhee JT, McDade TP, Zhou Z, Sullivan ME, Whalen GF, Tseng JF. Pancreatic neuroendocrine tumors: the impact of surgical resection on survival. *Cancer* 2009; **115**: 741-751 [PMID: 19130464 DOI: 10.1002/cncr.24065]
50 **Bettini R**, Partelli S, Boninsegna L, Capelli P, Crippa S, Pederzoli P, Scarpa A, Falconi M. Tumor size correlates with malignancy in nonfunctioning pancreatic endocrine tumor. *Surgery* 2011; **150**: 75-82 [PMID: 21683859 DOI: 10.1016/j.surg.2011.02.022]
51 **Regenet N**, Carrere N, Boulanger G, de Calan L, Humeau M, Arnault V, Kraimps JL, Mathonnet M, Pessaux P, Donatini G, Venara A, Christou N, Bachelier P, Hamy A, Mirallié E. Is the 2-cm size cutoff relevant for small nonfunctioning pancreatic neuroendocrine tumors: A French multicenter study. *Surgery* 2016; **159**: 901-907 [PMID: 26590096 DOI: 10.1016/j.surg.2015.10.003]
52 **Gratian L**, Pura J, Dinan M, Roman S, Reed S, Sosa JA. Impact of extent of surgery on survival in patients with small nonfunctional pancreatic neuroendocrine tumors in the United States. *Ann Surg Oncol* 2014; **21**: 3515-3521 [PMID: 24841347 DOI: 10.1245/s10434-014-3769-4]
53 **Haynes AB**, Deshpande V, Ingkakul T, Vagefi PA, Szymonifka J, Thayer SP, Ferrone CR, Wargo JA, Warshaw AL, Fernández-del Castillo C. Implications of incidentally discovered, nonfunctioning pancreatic endocrine tumors: short-term and long-term patient outcomes. *Arch Surg* 2011; **146**: 534-538 [PMID: 21576607 DOI: 10.1001/archsurg.2011.102]
54 **Crippa S**, Partelli S, Zamboni G, Scarpa A, Tamburrino D, Bassi C, Pederzoli P, Falconi M. Incidental diagnosis as prognostic factor in different tumor stages of nonfunctioning pancreatic endocrine tumors. *Surgery* 2014; **155**: 145-153 [PMID: 24646958 DOI: 10.1016/j.surg.2013.08.002]
55 **Birnbaum DJ**, Gaujoux S, Cherif R, Dokmak S, Fuks D, Couvelard A, Vullierme MP, Ronot M, Ruszniewski P, Belghiti J, Sauvanet A. Sporadic nonfunctioning pancreatic neuroendocrine tumors: prognostic significance of incidental diagnosis. *Surgery* 2014; **155**: 13-21 [PMID: 24238123 DOI: 10.1016/j.surg.2013.08.007]
56 **Gaujoux S**, Partelli S, Maire F, D'Onofrio M, Larroque B, Tamburrino D, Sauvanet A, Falconi M, Ruszniewski P. Observational study of natural history of small sporadic nonfunctioning pancreatic neuroendocrine tumors. *J Clin Endocrinol Metab* 2013; **98**: 4784-4789 [PMID: 24057286 DOI: 10.1210/jc.2013-2604]
57 **Lee LC**, Grant CS, Salomao DR, Fletcher JG, Takahashi N, Fidler JL, Levy MJ, Huebner M. Small, nonfunctioning, asymptomatic pancreatic neuroendocrine tumors (PNETs): role for nonoperative management. *Surgery* 2012; **152**: 965-974 [PMID: 23102679 DOI: 10.1016/j.surg.2012.08.038]
58 **Rosenberg AM**, Friedmann P, Del Rivero J, Libutti SK, Laird AM. Resection versus expectant management of small incidentally discovered nonfunctional pancreatic neuroendocrine tumors. *Surgery* 2016; **159**: 302-309 [PMID: 26547726 DOI: 10.1016/j.surg.2015.10.013]
59 **Sadot E**, Reidy-Lagunes DL, Tang LH, Do RK, Gonen M, D'Angelica MI, DeMatteo RP, Kingham TP, Groot Koerkamp B, Untch BR, Brennan MF, Jarnagin WR, Allen PJ. Observation versus Resection for Small Asymptomatic Pancreatic Neuroendocrine Tumors: A Matched Case-Control Study. *Ann Surg Oncol* 2016; **23**: 1361-1370 [PMID: 26597365 DOI: 10.1245/s10434-015-4986-1]
60 **Sharpe SM**, In H, Winchester DJ, Talamonti MS, Baker MS. Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. *J Gastrointest Surg* 2015; **19**: 117-123; discussion 123 [PMID: 25155459 DOI: 10.1007/s11605-014-2615-0]
61 **Öberg K**, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-entero-pancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2012; **23 Suppl 7**: vii124-vii130 [PMID: 22997445 DOI: 10.1093/annonc/mds295]

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ORIGINAL ARTICLE

Case Control Study

Comparative study of outcomes following laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy in morbidly obese patients: A case control study

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Abstract

AIM

To compare the impact of laparoscopic Roux-en-Y gastric bypass (LRYGB) and laparoscopic sleeve gastrectomy (LSG) on weight loss and obesity related comorbidities over two year follow-up *via* case control study design.

METHODS

Forty patients undergoing LRYGB, who completed their two year follow-up were matched with 40 patients undergoing LSG for age, gender, body mass index and presence of type 2 diabetes mellitus (T2DM). Data of these patients was retrospectively reviewed to compare the outcome in terms of weight loss and improvement in comorbidities, *i.e.*, T2DM, hypertension (HTN), obstructive sleep apnea syndrome (OSAS), hypothyroidism and gastroesophageal reflux disease (GERD).

RESULTS

Percentage excess weight loss (EWL%) was similar in LRYGB and LSG groups at one year follow-up (70.5% *vs* 66.5%, P = 0.36) while it was significantly greater for LRYGB group after two years as compared to LSG group (76.5% *vs* 67.9%, P = 0.04). The complication rate after LRYGB and LSG was similar (10% *vs* 7.5%,

P = 0.99). The median duration of T2DM and mean number of oral hypoglycemic agents were higher in LRYGB group than LSG group (7 years *vs* 5 years and 2.2 *vs* 1.8 respectively, *P* < 0.05). Both LRYGB and LSG had significant but similar improvement in T2DM, HTN, OSAS and hypothyroidism. However, GERD resolved in all patients undergoing LRYGB while it resolved in only 50% cases with LSG. Eight point three percent patients developed new-onset GERD after LSG.

CONCLUSION

LRYGB has better outcomes in terms of weight loss two years after surgery as compared to LSG. The impact of LRYGB and LSG on T2DM, HTN, OSAS and hypothyroidism is similar. However, LRYGB has significant resolution of GERD as compared to LSG.

Key words: Bariatric surgery; Laparoscopic sleeve gastrectomy; Laparoscopic Roux-en-Y gastric bypass; Weight loss; Comorbidities

Core tip: Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) are the most popular bariatric procedures. Few studies have compared the outcomes of LSG *vs* LRYGB in terms of weight loss and comorbidity resolution, especially in India. Using case control design in a well-matched population of 40 patients each undergoing LSG and LRYGB, we found similar weight loss one year after surgery in both the groups but the weight loss was significantly higher in LRYGB group two years after surgery. The complication rate was similar in both groups. Regarding comorbidity resolution, both LRYGB and LSG had significant but similar impact on obesity related comorbidities except gastroesophageal reflux disease where LRYGB showed better improvement. This is also among the first few studies to study the impact of bariatric surgery on hypothyroidism.

Garg H, Priyadarshini P, Aggarwal S, Agarwal S, Chaudhary R. Comparative study of outcomes following laparoscopic Roux-en-Y gastric bypass and sleeve gastrectomy in morbidly obese patients: A case control study. *World J Gastrointest Endosc* 2017; 9(4): 162-170 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i4/162.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i4.162

INTRODUCTION

Bariatric surgery is an effective tool in the management of obesity and its associated comorbidities[1]. Laparoscopic Roux-en-Y-gastric bypass (LRYGB) is the current gold standard among the various bariatric procedures performed worldwide[2]. Studies have proven its excellent long term outcomes with low rate of morbidity[3]. Laparoscopic sleeve gastrectomy (LSG) was introduced as a first step procedure to reduce morbidity in high risk patients followed by either LRYGB or bilio-pancreatic diversion with duodenal switch (BPD-DS)[4]. With increasing experience, LSG has proved its efficacy as a stand-alone procedure in the management of morbid obesity. Compared to LRYGB, LSG has several advantages. LSG is relatively easier to perform, preserves pylorus and antrum resulting in less Dumping syndrome, avoids risk of internal hernia and complications due to gastro-jejunostomy or jejuno-jejunostomy, decreases the risk of nutritional deficiencies and provides accessibility of the remnant stomach via endoscopy, which is important especially in Asian population[5]. However, few studies have compared the effect of LRYGB with LSG on weight loss and obesity associated comorbidities, especially in Indian population[5-10].

This study is among the few studies, in the Indian population, to compare the impact of LSG *vs* LRYGB on weight loss and obesity related comorbidities in a matched cohort of morbid obese patients over a period of two years.

MATERIALS AND METHODS

Data of all patients who underwent LSG and LRYGB at our centre, between January 2008 and March 2015 and completed their two year follow up till March 2016, was retrospectively reviewed using a prospectively collected database. All the patients met the National Institute Health criteria for bariatric surgery. These patients include patients with morbid obesity, *i.e.*, body mass index (BMI) > 40 kg/m^2 or patients with BMI > 35 kg/m^2 with obesity associated comorbidities. The patients are counseled about the types of bariatric procedures - LSG and LRYGB and the benefits and complications associated with each of the procedures. The patients having severe gastroesophageal reflux disease (GERD), long-standing type 2 diabetes mellitus (T2DM) and with BMI > 50 kg/m^2 are preferred for LRYGB. The bariatric procedure for a particular patient is decided mutually based on patient's preference and surgeon's viewpoint. The patients undergoing revision surgery or two stage procedure were excluded from the study. Patients undergoing LSG and LRYGB were matched by age, gender, BMI and presence or absence of T2DM. All the procedures were performed by the same surgeon (SA) according to standard surgical protocol. The preoperative workup included blood tests, chest radiography, upper gastrointestinal endoscopy, electrocardiogram, abdominal ultrasound and hormonal and nutritional evaluation. The patients were kept on Very Low Calorie Diet (approximately 800 kcal, 60-70 g protein) for two weeks before surgery. The follow-up data upto 2 years was recorded in a study proforma.

Surgical procedure

LSG: The procedure was performed under general

anesthesia in Reverse Trendelenburg position. The sleeve was performed in a standard way. Four ports were used: Three 12 mm and one 5 mm. A self-retaining liver retractor was introduced through a 5-mm incision in the epigastrium. The greater omentum was detached from a point 4 cm from the pylorus up to the angle of His using either ultrasonic shears or a bipolar sealing device. The left crus was completely exposed up to the medial border. A sleeve was created over a 36F gastric calibration tube with sequential firings of a three-row stapler. Intraoperative leak test using methylene blue was done to check the staple line integrity. The remnant stomach was retrieved using one of the port site and port closure was done. A suction drain was placed as needed.

LRYGB: An antecolic and antigastric Roux-en-Y gastric bypass was done with an alimentary limb ranging 100-150 cm and bilio-pancreatic limb of 70 cm as measured from duodeno-jejunal flexure. The procedure was performed under general anesthesia in Reverse Trendelenburg position. A 30- to 50-cc vertical gastric pouch was created. End to side gastro-jejunostomy and side-to-side jejuno-jejunostomy was done using three row stapler. Mesentric defect was sutured in all cases. Intraoperative leak test using methylene blue was done to check for the staple line integrity. A suction drain was placed as needed.

The data collected included patient demographics, preoperative BMI, presence of medical comorbidities, intra- and postoperative complications, weight loss and status of comorbidities after surgery.

Weight loss

The weight of the patients in preoperative period and at annual follow up till two years was recorded. The yearly absolute weight loss and percentage excess weight loss (EWL%) was calculated as described by Deitel *et al*[11]. Failure of surgery was defined as % EWL < 50% as per Reinhold criteria[12].

Comorbidity outcome

T2DM, hypertension (HTN), obstructive sleep apnea (OSA), hypothyroidism and gastroesophageal reflux disease (GERD) were assessed so as to determine whether it was aggravated, unchanged, improved or resolved compared to preoperative period.

T2DM: Presence of T2DM was defined as glycosylated haemoglobin (HbA1c) level $\geqslant$ 6.5% or fasting blood glucose (FBG) $\geqslant$ 126 mg/dL. Remission was defined as FBG < 100 mg/dL in the absence of anti-diabetic medications, and improvement was defined as decrease in anti-diabetic medications to maintain normal FBG. HbA1c was not available for all the patients in follow up period and hence was not used in the criteria for remission.

HTN: Presence of HTN included both Stage 1 (blood pressure: 120-159/90-99 mmHg) and Stage 2 (> 160/100 mmHg). Remission was defined as normal blood pressure (< 120/80 mmHg) when off antihypertensive medications as reported by the patient. Improvement in HTN was considered if there was decrease in dosage or number of antihypertensive medications to maintain normal blood pressure.

Obstructive sleep apnea syndrome: Obstructive sleep apnea syndrome (OSAS) was defined as apnea hypopnea index (AHI) > 15 events/h or > 5 events/h with typical symptoms[13]. Patients with severe OSAS (AHI > 30 events/h) received night time Continuous Positive Airway Pressure (CPAP) for atleast 2 wk before surgery. Resolution in OSAS was defined as disappearance of symptoms with patient no longer receiving CPAP therapy. Improvement in OSAS was defined as decrease in the symptoms with no longer need of CPAP therapy. Polysomnography could not be done in all patients in post-operative period and hence AHI could not be used as criteria for remission of OSAS.

Hypothyroidism: Presence of hypothyroidism was defined as patients who were on thyroxine therapy for overt hypothyroidism in preoperative period. Remission was considered if patient showed normal thyroid function tests without any thyroxine therapy. Improvement in hypothyroidism was considered if there was decrease in dosage of thyroxine supplement to maintain normal thyroid function tests.

GERD: The presence of GERD symptoms using GERD severity symptom (GERD-SS) questionnaire[14] and proton pump inhibitors (PPI) intake was assessed preoperatively and at follow up visits. A GERD SS Score > 4 or regular intake of PPI was defined as GERD. The resolution of GERD was defined as disappearance of symptoms when patient was no longer taking PPIs, whereas improvement was defined as a decrease in or disappearance of symptoms with a lower PPI dosage. Worsening of GERD was defined as increase in the symptoms or increase in the dosage of PPI after LSG. *De novo* GERD was defined as the postoperative development of reflux symptoms in patients who had not experienced GERD before LSG.

Statistical analysis

Statistical analysis was performed using SPSS software version 20.0 (SPSS Inc., Chicago, IL, United States). Normality of the data was checked using Shapiro-Wilk Test. For continuous variables, results were presented as mean ± standard deviation (SD) or median (Interquartile range) as appropriate. Comparative analysis was performed using Student's *t* test or Mann-Whitney *U* test for continuous variables and χ^2 test for categorical variables. Correlation between data was assessed using Pearson or Spearman Rank Correlation Coefficient

Table 1 Baseline characteristics of study population (n = 80)

Parameter	LRYGB group (n = 40)	LSG group (n = 40)	P value
Age (yr)	44.6 ± 10.2	44.8 ± 10.2	NS
Gender			
Female, n (%)	29 (72.5%)	29 (72.5%)	NS
Male, n (%)	11 (27.5%)	11 (27.5%)	NS
Weight (kg)	109.9 ± 13.9	113.6 ± 15.2	NS
Body mass index (kg/m^2)	43.9 ± 5.5	45.8 ± 4.8	NS
Excess weight (kg)	46.9 ± 12.7	51.3 ± 12.2	NS
Comorbidities			
Type 2 diabetes mellitus, n (%)	27 (67.5%)	27 (67.5%)	NS
Patients on insulin	5 (18.5%)	5 (18.5%)	NS
[a]Number of OHA	2.2 ± 0.7	1.8 ± 0.7	
[a,b]Duration (yr)	7 (5-7)	5 (3-7)	
Hypertension, n (%)	25 (62.5%)	23 (57.5%)	NS
Number of AHA	1.7 ± 0.7	1.7 ± 0.8	NS
OSAS, n (%)	7 (17.5%)	2 (5%)	NS
Hypothyroidism, n (%)	11 (27.5%)	7 (17.5%)	NS
Thyroxine dosage (μg/d)	90.9 ± 25.7	89.9 ± 31.8	NS
GERD, n (%)	7 (17.5%)	4 (10%)	NS

All P values are non-significant except [a]P value < 0.05 as assessed by Student's t test; All data expressed as mean ± SD except [b]where data is presented as median (Interquartile range). AHA: Anti-hypertensive agents; GERD: Gastroesophageal reflux disease; OHA: Oral hypoglycemic agents; OSAS: Obstructive sleep apnea syndrome; LRYGB: Laparoscopic Roux-en-Y gastric bypass; LSG: Laparoscopic sleeve gastrectomy.

(SRCC) as appropriate. Statistical significance was identified as $P < 0.05$.

RESULTS

Four hundreds and seventy-six patients underwent LSG and 61 patients underwent LRYGB between January 2008 and March 2016 at our centre. Forty patients with primary LRYGB completed their two year follow up and were matched to 40 patients undergoing LSG who also completed this follow up period. Table 1 gives the baseline characteristics of both the groups.

Impact on weight and associated parameters

After one year follow-up, the mean BMI (± SD) decreased from 43.9 (± 3.7) kg/m^2 to 31.1 (± 4.8) kg/m^2 in LRYGB group while 45.8 (± 4.8) kg/m^2 to 32.5 (± 4.5) kg/m^2 in LSG group (Figure 1). The mean (± SD) %EWL at one year follow-up was 70.5% (± 21.5%) and 66.5% (± 18.6%) in LRYGB and LSG group respectively (Figure 2). Using Student's t test, there was no significant difference in mean BMI or %EWL one year after either LRYGB or LSG.

At two year follow up, the mean BMI (± SD) BMI declined to 29.9 (± 4.4) kg/m^2 and 31.9 (± 4.3) kg/m^2 in LRYGB and LSG group respectively (Figure 1). The %EWL at 2-year follow up was 76.7% (± 20.2%) and 67.9% (± 17.9%) in LRYGB and LSG group respectively (Figure 2). This difference was statistically significant with LRYGB having better outcome in terms of weight loss after two years. As per Reinhold's criteria of failure of surgery, there was 12.5% failure in LRYGB group compared to 20% failure in LSG group two years after the surgery. Figure 1 shows the decline in the weight and associated parameters after LSG and LRYGB.

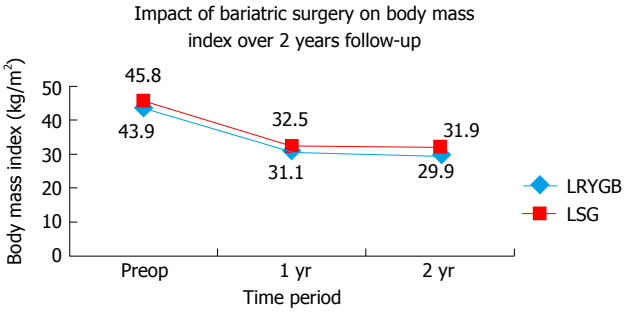

Figure 1 Impact of bariatric surgery on body mass index over two years follow-up: There was no significant difference in body mass index preoperatively (P = 0.11) and at 1 year post-op (P = 0.175). At 2 years follow-up however, patients who had undergone LSG had significantly higher BMI (P = 0.038) compared with those who had undergone LRYGB. Mean BMI were compared using Student's t test. LSG: Laparoscopic sleeve gastrectomy; LRYGB: Laparoscopic Roux-en-Y gastric bypass; BMI: Body mass index.

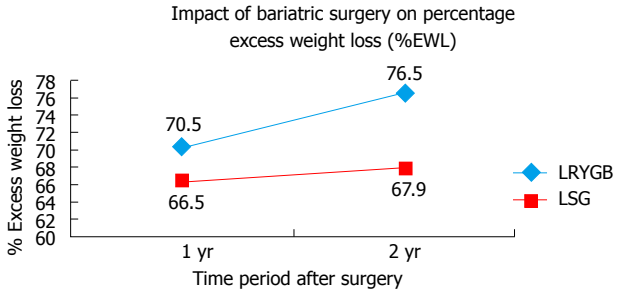

Figure 2 Impact of bariatric surgery on percentage excess weight loss over two years follow-up: There was no significant difference in percentage excess weight loss at 1 year post-op (P = 0.36). At 2 years follow-up however, patients who had undergone LRYGB had significantly greater excess weight loss (P = 0.044) compared with those who had undergone LSG. %EWL were compared using Student's t test. LSG: Laparoscopic sleeve gastrectomy; LRYGB: Laparoscopic Roux-en-Y gastric bypass; %EWL: Percentage excess weight loss.

Complication rate

In our experience of 476 LSG and 61 LRYGB, 6 (1.2%) patients in LSG group and no patient in LRYGB group had post-operative staple line leak. However, among the patients in the study cohort, none of the patient had staple line leak. In the LRYGB group, 2 (5%) patients underwent re-diagnostic laparoscopy and repair for internal hernia, one patient underwent laparoscopy adhesive intestinal obstruction eight months after primary surgery and one patient developed gastro-jejunostomy narrowing with edema which responded to conservative management. In the LSG group, 3 (8.3%) patients developed new-onset GERD in post-operative period managed with medical treatment. Overall, the complication rate in two groups was similar (10% in LRYGB *vs* 7.5% in LSG group, P = 0.99).

Impact on comorbidities

T2DM: Each of the LRYGB and LSG group had 27 patients with 5 patients each on insulin therapy. The

Table 2 Impact of bariatric surgery on comorbidities (n = 80)

Comorbidity	LRYGB			LSG			*P* value[1]
	Preoperative	Resolution	Improvement	Preoperative	Resolution	Improvement	
Type 2 diabetes mellitus	27	18	9	27	21	6	0.36
Hypertension	25	11	12	23	8	14	0.64
OSAS	7	7	0	2	2	0	-
Hypothyroidism	11	3	6	7	1	3	0.58

[1]All *P* values were calculated by applying χ^2 test for every comorbidity comparing LSG and LRYGB. OSAS: Obstructive sleep apnea syndrome; LRYGB: Laparoscopic Roux-en-Y gastric bypass; LSG: Laparoscopic sleeve gastrectomy.

Table 3 Impact of bariatric surgery on medications for various comorbidities (n = 80)

Medications	LRYGB		LSG		*P* value[1]
	Preoperative period	Postoperative period	Preoperative	Postoperative period	
Number of OHA	2.17 ± 0.7	0.3 ± 0.5	1.8 ± 0.7	0.3 ± 0.6	0.73
Number of AHA	1.7 ± 0.7	0.5 ± 0.5	1.7 ± 0.8	0.6 ± 0.6	0.78
Dosage of thyroxine (μg/d)	90.9 ± 25.7	45.5 ± 40.1	89.3 ± 31.8	53.6 ± 39.3	0.33

All data expressed as mean ± SD. [1]All *P* values were calculated using Student's *t* test separately for all comorbidities. AHA: Anti-hypertensive agents; OHA: Oral hypoglycemic agents; LRYGB: Laparoscopic Roux-en-Y gastric bypass; LSG: Laparoscopic sleeve gastrectomy.

median duration of T2DM differed significantly between LRYGB and LSG. The median (IQR) duration of T2DM and mean number of Oral Hypoglycemic Agents (OHA) were significantly higher in LRYGB group as compared to LSG group (Table 1).

On follow up, T2DM resolved in 66.7% (18 out of 27) patients while improved in 33.3% (9 out of 27) patients in LRYGB group. In the LSG group, DM resolved in 77.8% (21 out of 27) while improved in 22.2% (6 out of 27) patients. There was no new-onset T2DM noted in any of the groups. Both the procedures had significant impact on T2DM ($P < 0.001$). However, the impact of the two procedures on T2DM was comparable ($P = 0.544$) (Table 2).

In LRYGB group, all 5 patients, who were on insulin therapy pre-operatively, were off insulin therapy in post-operative period (100%) and the mean number (± SD) of OHA declined significantly from 2.17 (± 0.7) to 0.3 (± 0.5) in post-operative period. In LSG group, 3 out of 5 patients (60%), who were on insulin therapy, continued on insulin therapy with decreased dose in post-operative period and the mean number (± SD) of OHA declined from 1.8 (± 0.7) to 0.3 (± 0.6) in post-operative period. The decrease in number of OHA was similar in two groups ($P = 0.736$) (Table 3).

HTN: Twenty-five patients were hypertensive in LRYGB group and 23 patients were hypertensive in LSG group. After surgery, there was remission in 44% (11 out of 25) patients and improvement in 48% (12 out of 25) patients in LRYGB group. Similarly, there was remission in 34.8% (8 out of 23) patients and improvement in 60.8% (14 out of 23) patients in LSG group (Table 2). The mean number (± SD) of anti-hypertensive agents (AHA) declined from 1.7 (± 0.7) to 0.5 (± 0.5) in LRYGB group and 1.70 (± 0.8) to 0.57 (± 0.59) in LSG group. HTN, thus, improved significantly in both the groups ($P < 0.001$) but there was no significant difference in the outcome of either of the procedures (Table 3).

OSAS: Seventeen point five percent (7 out of 40) patients in LRYGB group and 5% (2 out of 40) patients in LSG group had severe OSA and were on CPAP therapy preoperatively. All the patients were off CPAP in postoperative period (100%) and showed improvement in symptoms of OSAS, irrespective of the procedure performed (Table 2).

Hypothyroidism: Twenty-seven point five percent (11 out of 40) and 17.5% (7 out of 40) patients were on thyroxine therapy for hypothyroidism in LRYGB and LSG group respectively. Twenty-seven point three percent (3 out of 11) patients in LRYGB group and 14.3% (1 out of 7) patients in LSG group maintained normal thyroid function tests without medications, 54.5% (6 out of 11) patients in LRYGB group and 42.8% (3 out of 7) patients in LSG group showed decrease in the dosage of thyroxine while 18.2% (2 out of 11) patients in LRYGB group and 42.8% (3 out of 7) patients in LSG group had no effect on medication for hypothyroidism (Table 2). The mean dosage of thyroxine decreased from 90.9 (± 25.7) μg to 45.5 (± 40.7) μg in LRYGB group and 89.2 (± 31.8) μg to 53.6 (± 39.3) μg in LSG group (Table 3). Both the procedures had significant impact on hypothyroidism but the impact was comparable ($P > 0.05$).

GERD: Based on GERD-SS questionnaire, 17.5% (7 out of 40) patients had GERD preoperatively in LRYGB group which resolved completely after surgery. In LSG group, 10% (4 out of 40) patients had GERD

preoperatively which resolved in 50% (2 out of 4) patients while remained same in rest of them. There was no new onset GERD in LRYGB group but 8.3% (3 out of 36 patients) developed new-onset GERD in LSG group.

DISCUSSION

In this study, we compared the outcomes of the two most commonly performed bariatric procedures-LSG and LRYGB in a well-matched morbidly obese population. We found the weight loss was similar at one year follow-up; however, weight loss was significantly higher in LRYGB group at two year follow-up. The complication rate was similar in both the groups. Regarding the impact on comorbidities, there was similar impact on T2DM, HTN, OSA and hypothyroidism. However, LRYGB led to better outcome in long-standing diabetics on insulin therapy.

The impact of LSG and LRYGB on BMI and weight associated parameters was significant over a follow-up of two years. We found %EWL for LRYGB *vs* LSG at 1-year and 2-year follow-up as 70.5% *vs* 66.5% (P = 0.36) and 76.7% *vs* 67.9% (P = 0.044) respectively. As per Reinhold's criteria[12], there was 20% failure in LSG group compared to 12.5% in LRYGB group. This suggests LRYGB had better outcome on weight loss over two years as compared to LSG. Similar results were reported by other studies. Lakdawala *et al*[10] reported similar weight loss at one year follow up in 100 patients undergoing LSG and LRYGB. El Chaar *et al*[9] found %EWL of 75% with LRYGB as compared to 60% with LSG over two year follow up period. Boza *et al*[6] also reported significantly higher %EWL with LRYGB (94% *vs* 84%) over two year follow-up in 786 patients undergoing LRYGB and 811 patients undergoing LSG. Such higher %EWL could be explained by lower initial BMI of 38 kg/m^2 in their study population. Nonetheless, there was lesser %EWL in LSG group. Li *et al*[7] in a meta-analysis involving 196 patients undergoing LRYGB and 200 patients undergoing LSG found significantly higher weight loss with LRYGB. The swiss multicentre bypass or sleeve study (SM-BOSS) - a prospective randomised controlled trial published its early results involving 107 patients undergoing LSG and 110 patients undergoing LRYGB[8]. They reported 77% and 73% excess BMI Loss (EBMIL) at one year follow-up and 73% and 63% EBMIL at three year follow-up after LRYGB and LSG respectively (P = 0.02)[8]. On the contrary, few studies have reported better outcome in weight loss with LSG at one year follow-up. Karamanakos *et al*[15] found %EWL of 69.7% in LSG group compared to 60.5% in LRYGB group, which they explained due to decreased ghrelin levels which suppressed appetite in initial period after surgery. Boza *et al*[6] also reported 10% and 5.4% failure rate of LSG and LRYGB at follow up of two years. As compared to our study, such lower failure rates could be due to involvement of less obese patients with mean BMI of 38 kg/m^2 in their study.

Both LRYGB and LSG had positive impact on T2DM. We found similar rate of improvement in both the groups. Unlike LSG, all patients on insulin therapy in LRYGB group were off insulin therapy in post-operative period. Buchwald et al reported 83% remission rate of T2DM with LRYGB in a meta-analysis involving more than 22000 patients[16]. Boza *et al*[6] found similar remission rate in LRYGB and LSG group (91% *vs* 87% respectively). Lakdawala *et al*[10] showed 100% and 98% remission rate of T2DM with LRYGB and LSG respectively. Inclusion of lower BMI patients with only 7 and 17 diabetics in LSG and LRYGB groups respectively and shorter duration of diabetes could be the possible reasons for such high rate of remission. They also explained the better results in Asian population could be due to decreased insulin resistance with decrease in central obesity which was more prevalent in Asian population. Other studies by Zhang *et al*[5] and Peterli *et al*[8] also showed similar remission rate of T2DM with LRYGB and LSG. On the contrary, Li *et al*[7] in a meta-analysis reported significantly better remission (Odds ratio = 9.08) of T2DM with LRYGB as compared to LSG. Similar results were reported by Lee *et al*[17].

Multiple mechanisms for remission of T2DM with LRYGB had been proposed. Foregut hypothesis, hindgut hypothesis, decreased ghrelin secretion and starvation followed by weight loss are among the major mechanisms[18]. The mechanism for remission of T2DM post LSG is still not completely understood. The possible mechanism include rise in post-prandial glucagon like peptide-1 due to increase in gastric emptying which lead to increase in insulin secretion. LSG also leads to decrease ghrelin and leptin levels which play role in glucose homeostasis after surgery[19].

The impact of LRYGB and LSG on HTN is variable. Sixty-two point five percent patients and 57.5% patients were hypertensive in LRYGB and LSG group respectively. We found remission rate of 44% and 35% and improvement in 48% and 60.8% in LRYGB and LSG groups respectively. Overall, both the procedures had similar impact on HTN. Similar results were shown by SM-BOSS[8]. Boza *et al*[6] showed 92% and 80% improvement in HTN with LRYGB and LSG respectively. In a study on Indian population, Lakadawala *et al*[10] showed 95% and 91% resolution in HTN. The possible mechanism for resolution of HTN would be decrease in the intra-abdominal pressure and Renin-Angiotension Aldosterone System activity after surgery[20].

Seventeen point five percent patients in LRYGB group and 50% patients in LSG group had severe OSA and were on CPAP therapy preoperatively. All the patients were off CPAP therapy with improvement in symptoms in post-operative period. Similar results were shown by other studies. Zhang *et al*[5] reported 82% and 91% resolution of OSA one year after LRYGB and LSG respectively. They found earlier resolution at 3-6 mo with LRYGB as compared to LSG.

The impact of bariatric surgery on hypothyroidism

is less studied. Both LRYGB and LSG had significant impact on need of thyroxine in post-operative period. Eighty-one point eight percent and 57.2% patients showed improvement in hypothyroidism. The improvement was similar in the two groups. Raftopoulos *et al*[21] reported 48% remission rate with complete resolution in 8% in 23 patients of hypothyroidism undergoing LRYGB. Ruiz-Tovar *et al*[22] found significant decrease in TSH level after LSG. Another study from our centre showed significant decrease in requirement of thyroxine after LSG[23]. Gkotsina *et al*[24] reported significant improvement in pharmacokinetic parameters of levo-T4 absorption after LSG while these remained same after LRYGB. Lips *et al*[25] compared restrictive and malabsorptive procedures and concluded that thyroid hormone regulation is directly proportional to the weight loss irrespective of the bariatric procedure. Hypothyroidism in obese individuals is partially mediated by increased leptin level and peripheral hormonal resistance. Weight loss leads to decrease in the hormone resistance and the need of thyroxine. However, certain subset of patients showed no effect of surgery on hypothyroidism probably because of other factors including autoimmune thyroid disorders[23].

GERD is commonly associated with obesity. While LRYGB led to resolution of GERD in all the patients, LSG led to improvement in GERD in only 50% cases. Importantly, 8.3% developed new onset GERD. Similar results were reported by Lakdawala *et al*[10]. They found 100% remission in GERD post LRYGB while reported rise in incidence in GERD from 5% to 9% after LSG. SM-BOSS trial also showed significantly higher remission in GERD with LRYGB as compared to LSG and reported 12.5% new onset GERD in LSG group[8]. Frezza *et al*[26] reported significant decrease in GERD-related symptoms over the 3-year study after LRYGB. Mechanisms of the anti-reflux effect of RYGB include promoting weight loss, lowering acid production in the gastric pouch, diverting bile from the Roux limb, rapid pouch emptying, and decreasing abdominal pressure over the LES[27]. The impact of LSG on GERD is still an unresolved issue. Multiple mechanisms have been proposed for the impact of LSG on GERD. The mechanisms for improvement of GERD after surgery include faster gastric emptying time, decreased gastric reservoir function, decrease intra-abdominal pressure, decreased acid production and alteration in neuro-hormonal mileu of gastrointestinal tract. Factors which may lead to exacerbation or new onset GERD include increased intraluminal pressure, modification in esophago-gastric junction, partial sectioning of sling fibres and presence of hiatus hernia[28].

Overall both LSG and LRYGB has similar effect on obesity related comorbidities over two year follow-up period, although GERD showed significantly better improvement with LRYGB.

The strengths of the study include well matched groups eliminating bias due to confounding factors and the standardized technique performed by same surgeon in all cases. The outcome of LSG in terms of weight loss and comorbidity resolution has been standardized. Our study is among the first few studies to compare the effect of LSG and LRYGB on thyroid disorder.

There are several limitations of this study. Retrospective nature of the study comes with inherent bias. Small sample size with short-term follow up is another limitation. The duration of T2DM and mean number of OHA were higher in LRYGB group than in LSG group, thereby, leading to a potential bias. The definition of comorbidities and its resolution were not optimally standardized. For T2DM, HbA1c was not available for all patients and hence could not be used in criteria for remission. For HTN, self-reporting of normal blood pressure by the patient was taken as remission or improvement. For OSAS, postoperative polysomnography was not available to objectively document the improvement in OSAS. For GERD, no objective measurement including pH-metry, impedance and high resolution manometry was done. Hyperlipidemia and cardiovascular risk factors could not be studied even knowing that myocardial infarction is the most common cause of mortality in this population.

In conclusion, our results indicate LRYGB has better outcomes in terms of weight loss two years after surgery as compared to LSG. The impact of LRYGB and LSG on T2DM, HTN and OSAS was similar. However, LRYGB had significant resolution of GERD as compared to LSG. Further comparative trials with large sample size and long term follow-up are needed to identify the ideal procedure of bariatric surgery.

COMMENTS

Background

Laparoscopic sleeve gastrectomy (LSG) and laparoscopic Roux-en-Y gastric bypass (LRYGB) are among the most frequently performed bariatric procedures worldwide. Compared to LRYGB, LSG is relatively easier to perform and is associated with less Dumping syndrome, avoids risk of internal hernia and complications due to gastro-jejunostomy or jejuno-jejunostomy, decreases the risk of nutritional deficiencies and provides accessibility of the remnant stomach *via* endoscopy, which is important especially in Asian population. However, few studies have compared the effects of LRYGB and LSG in well-matched Indian population.

Research frontiers

Few studies have compared the outcomes of LRYGB and LSG in a well matched Indian obese population undergoing bariatric surgery.

Innovations and breakthroughs

This study compared 40 patients undergoing LRYGB, who completed their 2-year follow-up with 40 patients undergoing LSG matched for age, gender, body mass index and presence of type 2 diabetes mellitus (T2DM). Data of these patients was retrospectively reviewed to compare the outcome in terms of weight loss and improvement in comorbidities, *i.e.*, T2DM, hypertension (HTN), obstructive sleep apnea syndrome (OSAS), hypothyroidism and gastroesophageal reflux disease. Using case control design , this study found similar weight loss one year after surgery in both the groups but the weight loss was significantly higher in LRYGB group two years after surgery. The complication rate was similar in both groups. Regarding comorbidity resolution, both LRYGB and LSG had significant but similar impact on obesity related comorbidities except gastroesophageal reflux disease where LRYGB showed better improvement. This is also among

the first few studies to study the impact of bariatric surgery on hypothyroidism, which improved significantly in both LSG and LRYGB groups.

Applications

This study compares the outcomes of LRYGB with LSG in a well-matched population over a period of two years follow-up. This is important in clinical practice as the impact of LRYGB and LSG on weight loss and obesity associated comorbidities is a casue of concern while selecting a particular bariatric procedure for a patient.

Terminology

Percentage excess weight loss (%EWL) is defined as [(Preoperative weight-current weight/preoperative weight-ideal weight] × 100%.

Peer-review

This is a retrospective study to compare the impact of LRYGB and LSG on weight loss and obesity related comorbidities. This is an important issue in clinics.

REFERENCES

1 **Rubino F**, Kaplan LM, Schauer PR, Cummings DE. The Diabetes Surgery Summit consensus conference: recommendations for the evaluation and use of gastrointestinal surgery to treat type 2 diabetes mellitus. *Ann Surg* 2010; **251**: 399-405 [PMID: 19934752 DOI: 10.1097/SLA.0b013e3181be34e7]

2 **Clinical Issues Committee of the American Society for Metabolic and Bariatric Surgery**. Updated position statement on sleeve gastrectomy as a bariatric procedure. *Surg Obes Relat Dis* 2010; **6**: 1-5 [PMID: 19939744 DOI: 10.1016/j.soard.2009.11.004]

3 **Nguyen NT**, Paya M, Stevens CM, Mavandadi S, Zainabadi K, Wilson SE. The relationship between hospital volume and outcome in bariatric surgery at academic medical centers. *Ann Surg* 2004; **240**: 586-593; discussion 593-594 [PMID: 15383786]

4 **Regan JP**, Inabnet WB, Gagner M, Pomp A. Early experience with two-stage laparoscopic Roux-en-Y gastric bypass as an alternative in the super-super obese patient. *Obes Surg* 2003; **13**: 861-864 [PMID: 14738671 DOI: 10.1381/096089203322618669]

5 **Zhang N**, Maffei A, Cerabona T, Pahuja A, Omana J, Kaul A. Reduction in obesity-related comorbidities: is gastric bypass better than sleeve gastrectomy? *Surg Endosc* 2013; **27**: 1273-1280 [PMID: 23239292 DOI: 10.1007/s0046401225957]

6 **Boza C**, Gamboa C, Salinas J, Achurra P, Vega A, Pérez G. Laparoscopic Roux-en-Y gastric bypass versus laparoscopic sleeve gastrectomy: a case-control study and 3 years of follow-up. *Surg Obes Relat Dis* 2012; **8**: 243-249 [PMID: 22285881 DOI: 10.1016/j.soard.2011.08.023]

7 **Li JF**, Lai DD, Ni B, Sun KX. Comparison of laparoscopic Roux-en-Y gastric bypass with laparoscopic sleeve gastrectomy for morbid obesity or type 2 diabetes mellitus: a meta-analysis of randomized controlled trials. *Can J Surg* 2013; **56**: E158-E164 [PMID: 24284156]

8 **Peterli R**, Borbély Y, Kern B, Gass M, Peters T, Thurnheer M, Schultes B, Laederach K, Bueter M, Schiesser M. Early results of the Swiss Multicentre Bypass or Sleeve Study (SM-BOSS): a prospective randomized trial comparing laparoscopic sleeve gastrectomy and Roux-en-Y gastric bypass. *Ann Surg* 2013; **258**: 690-694; discussion 695 [PMID: 23989054 DOI: 10.1097/SLA.0b013e3182a67426]

9 **El Chaar M**, Hammoud N, Ezeji G, Claros L, Miletics M, Stoltzfus J. Laparoscopic sleeve gastrectomy versus laparoscopic Roux-en-Y gastric bypass: a single center experience with 2 years follow-up. *Obes Surg* 2015; **25**: 254-262 [PMID: 25085223 DOI: 10.1007/s1169501413886]

10 **Lakdawala MA**, Bhasker A, Mulchandani D, Goel S, Jain S. Comparison between the results of laparoscopic sleeve gastrectomy and laparoscopic Roux-en-Y gastric bypass in the Indian population: a retrospective 1 year study. *Obes Surg* 2010; **20**: 1-6 [PMID: 19802646 DOI: 10.1007/s1169500999819]

11 **Deitel M**, Greenstein RJ. Recommendations for reporting weight loss. *Obes Surg* 2003; **13**: 159-160 [PMID: 12760387 DOI: 10.1381/096089203764467117]

12 **Reinhold RB**. Critical analysis of long term weight loss following gastric bypass. *Surg Gynecol Obstet* 1982; **155**: 385-394 [PMID: 7051382]

13 **Epstein LJ**, Kristo D, Strollo PJ, Friedman N, Malhotra A, Patil SP, Ramar K, Rogers R, Schwab RJ, Weaver EM, Weinstein MD. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med* 2009; **5**: 263-276 [PMID: 19960649]

14 **Vigneri S**, Termini R, Leandro G, Badalamenti S, Pantalena M, Savarino V, Di Mario F, Battaglia G, Mela GS, Pilotto A. A comparison of five maintenance therapies for reflux esophagitis. *N Engl J Med* 1995; **333**: 1106-1110 [PMID: 7565948 DOI: 10.1056/NEJM199510263331703]

15 **Karamanakos SN**, Vagenas K, Kalfarentzos F, Alexandrides TK. Weight loss, appetite suppression, and changes in fasting and postprandial ghrelin and peptide-YY levels after Roux-en-Y gastric bypass and sleeve gastrectomy: a prospective, double blind study. *Ann Surg* 2008; **247**: 401-407 [PMID: 18376181 DOI: 10.1097/SLA.0b013e318156f012]

16 **Buchwald H**, Estok R, Fahrbach K, Banel D, Jensen MD, Pories WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009; **122**: 248-256.e5 [PMID: 19272486 DOI: 10.1016/j.amjmed.2008.09.041]

17 **Lee SK**, Heo Y, Park JM, Kim YJ, Kim SM, Park do J, Han SM, Shim KW, Lee YJ, Lee JY, Kwon JW. Roux-en-Y Gastric Bypass vs. Sleeve Gastrectomy vs. Gastric Banding: The First Multicenter Retrospective Comparative Cohort Study in Obese Korean Patients. *Yonsei Med J* 2016; **57**: 956-962 [PMID: 27189291 DOI: 10.3349/ymj.2016.57.4.956]

18 **Thaler JP**, Cummings DE. Minireview: Hormonal and metabolic mechanisms of diabetes remission after gastrointestinal surgery. *Endocrinology* 2009; **150**: 2518-2525 [PMID: 19372197 DOI: 10.1210/en.20090367]

19 **Vigneshwaran B**, Wahal A, Aggarwal S, Priyadarshini P, Bhattacharjee H, Khadgawat R, Yadav R. Impact of Sleeve Gastrectomy on Type 2 Diabetes Mellitus, Gastric Emptying Time, Glucagon-Like Peptide 1 (GLP-1), Ghrelin and Leptin in Non-morbidly Obese Subjects with BMI 30-35.0 kg/m(2): a Prospective Study. *Obes Surg* 2016; **26**: 2817-2823 [PMID: 27185177 DOI: 10.1007/s11695-016-2226-9]

20 **Sugerman HJ**, Wolfe LG, Sica DA, Clore JN. Diabetes and hypertension in severe obesity and effects of gastric bypass-induced weight loss. *Ann Surg* 2003; **237**: 751-756; discussion 757-758 [PMID: 12796570 DOI: 10.1097/01.SLA.0000071560.76194.11]

21 **Raftopoulos Y**, Gagné DJ, Papasavas P, Hayetian F, Maurer J, Bononi P, Caushaj PF. Improvement of hypothyroidism after laparoscopic Roux-en-Y gastric bypass for morbid obesity. *Obes Surg* 2004; **14**: 509-513 [PMID: 15130228 DOI: 10.1381/096089204323013514]

22 **Ruiz-Tovar J**, Boix E, Galindo I, Zubiaga L, Diez M, Arroyo A, Calpena R. Evolution of subclinical hypothyroidism and its relation with glucose and triglycerides levels in morbidly obese patients after undergoing sleeve gastrectomy as bariatric procedure. *Obes Surg* 2014; **24**: 791-795 [PMID: 24347349 DOI: 10.1007/s1169501311505]

23 **Aggarwal S**, Modi S, Jose T. Laparoscopic sleeve gastrectomy leads to reduction in thyroxine requirement in morbidly obese patients with hypothyroidism. *World J Surg* 2014; **38**: 2628-2631 [PMID: 24844659 DOI: 10.1007/s0026801426464]

24 **Gkotsina M**, Michalaki M, Mamali I, Markantes G, Sakellaropoulos GC, Kalfarentzos F, Vagenakis AG, Markou KB. Improved levothyroxine pharmacokinetics after bariatric surgery. *Thyroid* 2013; **23**: 414-419 [PMID: 23110329 DOI: 10.1089/thy.2011.0526]

25 **Lips MA**, Pijl H, van Klinken JB, de Groot GH, Janssen IM, Van Ramshorst B, Van Wagensveld BA, Swank DJ, Van Dielen F, Smit JW. Roux-en-Y gastric bypass and calorie restriction induce comparable time-dependent effects on thyroid hormone function tests in obese female subjects. *Eur J Endocrinol* 2013; **169**: 339-347 [PMID: 23811187 DOI: 10.1530/EJE130339]

26 **Frezza EE**, Ikramuddin S, Gourash W, Rakitt T, Kingston A, Luketich J, Schauer P. Symptomatic improvement in gastroesophageal reflux disease (GERD) following laparoscopic Roux-en-Y gastric bypass. *Surg Endosc* 2002; **16**: 1027-1031 [PMID: 11984683 DOI: 10.1007/s0046400183135]

27 **Kawahara NT**, Alster C, Maluf-Filho F, Polara W, Campos GM, Poli-de-Figueiredo LF. Modified Nissen fundoplication: laparoscopic antireflux surgery after Roux-en-Y gastric bypass for obesity. *Clinics* (Sao Paulo) 2012; **67**: 531-533 [PMID: 22666803]

28 **Sharma A**, Aggarwal S, Ahuja V, Bal C. Evaluation of gastroesophageal reflux before and after sleeve gastrectomy using symptom scoring, scintigraphy, and endoscopy. *Surg Obes Relat Dis* 2014; **10**: 600-605 [PMID: 24837563 DOI: 10.1016/j.soard.2014.01.017]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Does serotonin reuptake inhibitor therapy increase the risk of post-sphincterotomy bleeding in patients undergoing endoscopic retrograde cholangio-pancreatography?

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Author contributions: Yadav D designed the research, collected data, performed the research and drafted the manuscript; Lopez R analyzed the data; Vargo J critically revised the manuscript for important intellectual content; Chahal P designed the research, supervised the study and critically revised the manuscript for important intellectual content.

Institutional review board statement: The study was reviewed and approved by the Institutional Review Board of the Cleveland Clinic.

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Abstract

AIM

To evaluate the risk of immediate and delayed bleeding following sphincterotomy procedure.

METHODS

This retrospective cohort study was conducted with all patients who underwent endoscopic sphincterotomy during January 2006 to September 2015 at a tertiary academic center. Patients were grouped according to pre procedural usage of serotonin reuptake inhibitors (SRIs). Both groups were matched for demographic and clinical characteristics. Patients with thrombocytopenia, increased international normalized ratio, or a history of bleeding or coagulation disorders, concurrent use of other antiplatelet/anticoagulants were excluded from the study.

RESULTS

A total of 447 patients were included, of which 219 (45.9%) used SRIs and 228 (54.1%) cases did not. There was no significant difference in acute or delayed bleeding during endoscopic sphincterotomy between the two groups. (8.2% *vs* 12.3%, $P = 0.16$).

CONCLUSION
The use of SRIs was not associated with an increased risk of post-sphincterotomy bleeding. To our best knowledge, this is the first study to explore this association.

Key words: Serotonin reuptake inhibitors; Post-sphincterotomy bleeding; Endoscopy; Endoscopic retrograde cholangiopancreatography; Gastrointestinal bleeding

Core tip: Serotonin reuptake inhibitors (SRIs) are a very commonly prescribed medication. The use of SRIs is reportedly associated with an increased risk for gastrointestinal bleeding in few studies. In this retrospective cohort study we analyzed the association between use of SRI and risk of post sphincterotomy bleeding with meticulous exclusion of all the confounders associated with increased risk of sphincterotomy bleeding. To our knowledge, this is a first study to assess the SRIs impact on post sphincterotomy bleeding.

Yadav D, Vargo J, Lopez R, Chahal P. Does serotonin reuptake inhibitor therapy increase the risk of post-sphincterotomy bleeding in patients undergoing endoscopic retrograde cholangio-pancreatography? *World J Gastrointest Endosc* 2017; 9(4): 171-176 Available from: URL: http://www.wjgnet.com/1948-5190/full/v9/i4/171.htm DOI: http://dx.doi.org/10.4253/wjge.v9.i4.171

INTRODUCTION

Since its earliest description in 1974, endoscopic sphincterotomy has become a commonly performed procedure for a variety of therapeutic indications during endoscopic retrograde cholangiopancreatography (ERCP)[1]. Including choledocholithiasis, placement of stents through malignant and benign strictures, as well as to treat dysfunction of the sphincter of Oddi. It is a technically difficult endoscopic procedure performed under visual and fluoroscopic guidance. It involves deep insertion of the cannula into the bile duct through the ampulla of Vater and the subsequent use of electrocautery to incise the sphincter of Oddi. Sphincterotomy has been associated with pancreatitis, hemorrhage, perforation and other complications most of which occur within the initial 24 h of procedure[2,3]. Hemorrhage is a well-known complication occurring in up to 2%-7% of all cases[1].

Serotonin reuptake inhibitors (SRIs) are considered to be a first-line pharmacologic therapy for depression, and are among the most commonly prescribed medications in the United States. The safety and side effect profile of these drugs have been well-described in the existing literature. In numerous studies, SRI therapy has been associated with an increased risk of gastrointestinal bleeding. Similarly, the use of non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants and aspirin has been associated with an increased risk of bleeding during sphincterotomy procedures[4]. These drugs are typically discontinued a week prior to the procedure date. Our aim was to evaluate the risk of immediate and delayed bleeding following sphincterotomy procedure. Our hypothesis was that SRIs medications increase the risk of post sphincterotomy bleeding.

Table 1 Complications of sphincterotomy and risk factors for hemorrhage

Complications of sphincterotomy	Risk factors for hemorrhage
Pancreatitis - 1.0%-15.7% (Most common complication)	Presence of coagulopathy
Hemorrhage - 2%-7%	Use of anti-coagulation
Cholangitis - 1% - (Fever, chills, elevated liver enzymes, and/or positive blood culture within 48 h after the procedure)	Cholangitis
Cholecystitis - (Clinical and radiographic evidence of an inflamed gallbladder)	Low endoscopist case volume

MATERIALS AND METHODS

Definitions

Immediate post endoscopic sphincterotomy (post-ES) bleeding is considered to be oozing of blood during ERCP. Delayed post ES bleeding occurs within 10 d after ERCP and manifested as melena, hematemesis or hematochezia (Table 1). Classification of bleeding according to Cotton *et al*[3] states mild bleeding is defined as hemoglobin drop of less than 3 g/dL without the need of transfusion, moderate bleeding is considered when blood transfusion of 4 units or less is required without any surgical intervention, severe bleeding is defined as blood transfusion of 5 units or more and surgical intervention is required (Table 2).

Patient selection

This retrospective cohort study was conducted after obtaining necessary approval from the Institution Review Board and patients consent. Patients who underwent ERCP with sphincterotomy at a tertiary referral center by a group of ten therapeutic endoscopists with a minimum of 5 years of experience during the study period of January 2006 - September 2015 were reviewed. One of the confounding factor of bleeding is low endoscopist case volume (Table 1). This study was conducted at a tertiary referral center with an average 2500 ERCP are performed in a year, in total 22500 during 2006-2015. SRI is a commonly prescribed drug in United States. Patients using either selective SRIs or serotonin-norepinephrine reuptake inhibitors (SNRIs) at the time of

Table 2 Bleeding grading system

Mild	Moderate	Severe
Transfusion is not required, with evidence of bleeding	Transfusion of 4 units or less is required	Transfusion of 5 units or more is required
Hemoglobin drop of less than 3 g/dL	No surgical intervention	Angiographic or surgical intervention
Immediate bleeding - seen in 30% patients (8) - endoscopic venous oozing which stopped with epinephrine		
Delayed bleeding - occur up to 2 wk after the procedure - hematemesis, melena, haematochezia		
Severe bleeding - 0.1%-0.5%		

Adapt from Cotton *et al*[3].

Table 3 Serotonin reuptake inhibitors medications included in the study

Serotonin reuptake inhibitors	Serotonin-norepinephrine reuptake inhibitors
Citalopram (Celexa)	Desvenlafaxine (Pristiq)
Escitalopram (Lexapro, Cipralex)	Duloxetine (Cymbalta)
Paroxetine (Paxil, Seroxat)	Levomilnacipran (Fetzima)
Fluoxetine (Prozac)	Milnacipran (Ixel, savella)
Fluvoxamine (Luvox)	Tofenacin (Elamol, tofacine)
Sertraline (Zoloft, lustral)	Venlafaxine (Effexor)

the procedure were included (Table 3). The patients were grouped according to whether they continued to take SRIs until the day of the procedure and patients who never had been on SRI's or SNRI's. Patients SRI dose wasn't included as the purpose of study was to analysis bleeding risk with SRI therapy. Patients with following risk factors that could independently increase the risk of bleeding (such as coagulopathies, liver disorders, and cholangitis), patients taking aspirin and NSAIDs, patients with abnormal lab values for PT-INR > 1.5, platelet count < 150000, and PTT > 25 s were excluded from the study (Figure 1). Data pertaining to the patient demographics (Tables 4 and 5), technical aspects of the procedure (Tables 6 and 7), medical co-morbidities including renal, cardiac, hepatic issues, coagulation disorder, bleeding disorder, history of alcohol intake, drug history, coagulation profile, platelet levels, recent antiplatelet or NSAID use was abstracted.

Statistical analysis

Continuous variables are presented as mean ± SD or median (25^{th}, 75^{th} percentiles) and categorical factors as frequency (percentage). A univariable analysis was performed to assess differences between subjects who used SRIs at the time of ERCP and those who did not. Analysis of variance or the non-parametric Kruskal-Wallis tests were used for continuous or ordinal variables and Pearson's χ^2 tests were used for categorical factors. In addition, univariable and multivariable logistic regression analyses were performed to assess factors associated with occurrence of post-sphincterotomy bleeding; factors seen in < 5 patients were not considered for this part of the analysis. An automated stepwise variable selection method performed on 1000 samples was used to choose the final model. The use of SRI was forced into the models and the additional three variables with highest inclusion rates were included in the final models. A P value < 0.05 was considered statistically significant. SAS version 9.4 (The SAS Institute, Cary, NC) was used to perform all analyses.

RESULTS

Out of 22500 who had undergone endoscopy, 447 subjects who underwent sphincterotomy were included in the study (Tables 5-7). At the time of the procedure, 219 patients were taking SRI therapy and 228 patients had never been on SRI therapy.

There was no evidence of a significant difference in the incidence of post-sphincterotomy bleeding between the groups 8.2% *vs* 12.3% (Table 8 and Figure 2). The absence of alcohol intake, depression, and lower PTT were significantly more common in subjects taking SRIs.

On univariable analysis, there was no evidence of an association between any of the assessed factors and post-sphincterotomy bleeding. The use of SRIs, demographic, BMI, clinical comorbidities including cardiovascular disorders, renal disease, indication of ERCP, and number of ERCPs were included in the final model but these did not reach statistical significance. None of the patients who experienced immediate post-sphincterotomy bleeding required blood transfusion therapy. Only two patients < 1% of the study group experienced delayed bleeding and did not require any transfusion. Patients who oozed blood were managed by injecting epinephrine.

DISCUSSION

It is a widely perceived, yet never before tested in patients undergoing sphincterotomy, theory that the use of SRI therapy is associated with an increased risk of gastrointestinal bleeding. In this retrospective cohort study, we found no significant association between the use of SRI and post-sphincterotomy bleeding. Moreover, no difference in estimated blood loss was observed in these two group. Association between percutaneous endoscopic gastrostomy and SRI's bleeding has been reported[5]; however, unlike our study, none of these studies excluded other confounding potential risk factors for bleeding. Our findings contradict the other studies that have found SRI to increase bleeding. The exact mechanism is unknown but the purported mechanism of SRI's on bleeding states that SRI's inhibits the serotonin transport protein and by blocking the uptake of synaptic serotonin into presynaptic neurons, it impairs the hemostasis function. SRI's act as a blocker and inhibit entry of serotonin from blood into platelets. Release of serotonin from platelets into the bloodstream during an injury is an important step platelet aggregation[9,11-13]. This

Table 4 Patient demographics *n* (%)

Factor	Overall (*n* = 447)		SRI (*n* = 219)		No SRI (*n* = 228)		*P* value
	n	Summary	*n*	Summary	*n*	Summary	
Age (yr)	445	64.4 ± 17.9	219	64.0 ± 16.8	226	64.7 ± 19.0	0.68[1]
Male	447	112 (25.1)	219	47 (21.5)	228	65 (28.5)	0.086[3]
BMI	442	29.5 ± 7.5	218	29.7 ± 7.6	224	29.3 ± 7.4	0.59[1]
Smoking	435	216 (49.7)	216	114 (52.8)	219	102 (46.6)	0.20[3]
Alcohol use	432	161 (37.3)	215	69 (32.1)	217	92 (42.4)	0.027[3]
Cardiovascular disorder	447	111 (24.8)	219	53 (24.2)	228	58 (25.4)	0.76[3]
Depression	445	160 (36.0)	219	99 (45.2)	226	61 (27.0)	< 0.001[3]
Renal disease	447	55 (12.3)	219	30 (13.7)	228	25 (11.0)	0.38[3]
Intestinal disease	447	66 (14.8)	219	29 (13.2)	228	37 (16.2)	0.37[3]
History of UGI bleed	389	1 (0.26)	207	0 (0.0)	182	1 (0.55)	0.47[4]

[1]ANOVA; [3]Pearson's χ^2 test; [4]Fisher's exact test. Intestinal diseases: Peptic ulcer, inflammatory bowel disease. Values presented as Mean ± SD or *n* (%). SRI: Serotonin reuptake inhibitor.

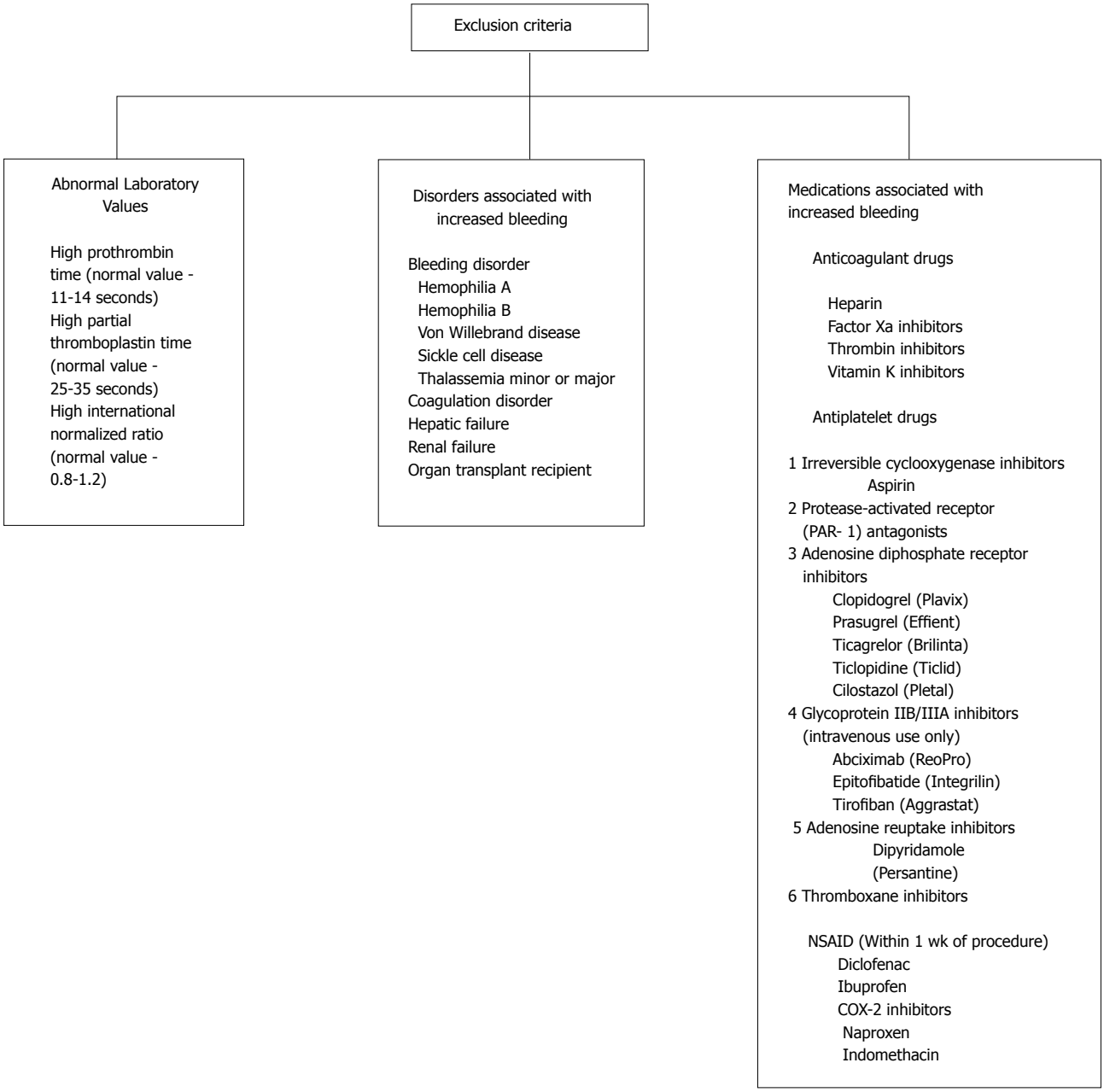

Figure 1 Exclusion criteria.

Table 5 Patients lab values

Factor	Overall (n = 447)		SRI (n = 219)		No SRI (n = 228)		P value
	n	Summary	n	Summary	n	Summary	
PPI	447	111 (24.8)	219	51 (23.3)	228	60 (26.3)	0.46[2]
Platelets	435		213		222		0.59[1]
140-400		432 (99.3)		212 (99.5)		220 (99.1)	
> 400		3 (0.69)		1 (0.47)		2 (0.90)	
INR	391		190		201		-
0.9-1.2		391 (100.0)		190 (100.0)		201 (100.0)	
PTT	361		171		190		-
24.7-32.7 s		361 (100.0)		171 (100.0)		190 (100.0)	

[1]Kruskal-Wallis test; [2]Pearson's χ^2 test. Values presented as Mean ± SD or n (%). SRI: Serotonin reuptake inhibitor.

Table 6 Number of endoscopic retrograde cholangiopancreatography

Number of ERCPs	Overall (n = 447)	SRI (n = 219)	No SRI (n = 228)	P value
1	432 (96.6)	214 (97.7)	218 (95.6)	0.23[1]
2	13 (2.9)	3 (1.4)	10 (4.4)	
3	2 (0.45)	2 (0.91)	0 (0.0)	

[1]Kruskal-Wallis test. Values presented as n (%). SRI: Serotonin reuptake inhibitor; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 7 Indications for endoscopic retrograde cholangiopancreatography

	Overall (n = 447)		SRI (n = 219)	No SRI (n = 228)	P value
	Summary		n (%)	n (%)	
Abnormal CT	16 (3.8)		9 (4.3)	7 (3.3)	0.57[1]
Abdominal pain	90 (21.2)		43 (20.6)	47 (21.9)	0.75[1]
Abnormal LFT	62 (14.6)		32 (15.3)	30 (14.0)	0.69[1]
Biliary dilation	8 (1.9)		6 (2.9)	2 (0.93)	0.17[2]
Bile duct stones	187 (44.1)		96 (45.9)	91 (42.3)	0.45[1]
Complications of prior biliary surgery	6 (1.4)		4 (1.9)	2 (0.93)	0.44[2]
Jaundice	49 (11.6)		16 (7.7)	33 (15.3)	0.013[1]
Cholangitis	9 (2.1)	209	4 (1.9)	5 (2.3)	0.99[2]

[1]Pearson's χ^2 test; [2]Fisher's exact test. Values presented as n (%). CT: Computed tomography; LFT: Lung function testing; SRI: Serotonin reuptake inhibitor.

Table 8 Bleeding and management

	Overall (n = 447)	SRI (n = 219)		No SRI (n = 228)		P value
	n (%)	n	Summary	n	Summary	
Post-sphincterotomy bleeding	46 (10.3)	219	18 (8.2)	228	28 (12.3)	0.16[1]
Injected with epinephrine	25 (54.3)	18	7 (38.9)	28	18 (64.3)	0.091[1]

[1]Pearson's χ^2 test;. Values presented n (%); SRI: Serotonin reuptake inhibitor..

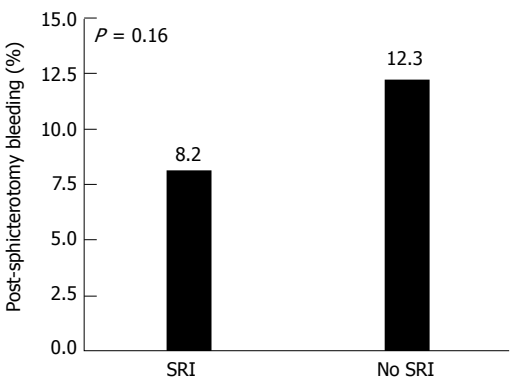

Figure 2 Post-sphincterotomy bleeding.

presumed mechanism can further predispose to bleeding disturbances. However, our finding did not show any evidence indicating SRI to increase bleeding.

Many studies suggest an association between SRI's and upper gastrointestinal bleeding. It's suggested that SRIs increase gastric acidity by targeting gastric mucosa which potentiates the risk of upper GI bleeding[9,11]. In a recent meta-analysis on risk for GI bleeds, it was noticed that patients on combined therapy such as NSAIDs, aspirin, SRIs were at higher risk for bleeding[8]. To our knowledge, only two studies have studied risk of post sphincterotomy bleeding with patients using NSAIDS and aspirin. The finding of the studies were equivocal:

Both found different results suggesting the safety of aspirin use during procedure[4,6] one study results showed that use of aspirin resulted in increased risk of bleeding[6], and the other study results showed aspirin and NSAIDs not associated with the risk bleeding[4].

Drugs that cause prolonged bleeding, such as aspirin and NSAIDS are advised to discontinue a week prior to surgery. Patients who experience bleeding during the procedure are injected with epinephrine around the sphincterotomy site. This is considered to be the most commonly used method to manage immediate bleeding.

Our usual approach is local therapy in the form of 1:10000 diluted epinephrine injection, either alone or in combination with cautery, hemoclips. Covered metal stents are placed in patients who are expected to resume therapeutic anticoagulation or have underlying coagulopathy.

While recognizing that no definite guidelines can be derived from this retrospective study, our result presented here provides novel knowledge about complex question of management of SRI's prior to therapeutic ERCP. We conclude if the confounding variables for bleeding are excluded, SRI's alone do not increase the risk of post-sphincterotomy bleeding. According to our knowledge, this is the first study to assess the SRI's impact on post sphincterotomy bleeding.

COMMENTS

Background

Since its earliest description in 1974, endoscopic sphincterotomy has become a commonly performed procedure for a variety of therapeutic indications during endoscopic retrograde cholangio-pancreatography. Including choledocholithiasis, placement of stents through malignant and benign strictures, as well as to treat dysfunction of the sphincter of Oddi.

Research frontiers

The authors hypothesis was that serotonin reuptake inhibitors (SRIs) medications increase the risk of post sphincterotomy bleeding.

Innovations and breakthroughs

The authors conclude if the confounding variables for bleeding are excluded, SRI's alone do not increase the risk of post-sphincterotomy bleeding. According to our knowledge, this is the first study to assess the SRI's impact on post sphincterotomy bleeding.

Peer-review

The paper of Yadav *et al* is original and well written. The interest to know there is no bleeding risk with SRI therapy is not so high but important to know.

REFERENCES

1 **Freeman ML**. Complications of endoscopic biliary sphincterotomy: a review. *Endoscopy* 1997; **29**: 288-297 [PMID: 9255535 DOI: 10.1055/s-2007-1004193]

2 **Ferreira LE**, Baron TH. Post-sphincterotomy bleeding: who, what, when, and how. *Am J Gastroenterol* 2007; **102**: 2850-2858 [PMID: 18042116 DOI: 10.1111/j.1572-0241.2007.01563.x]

3 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RCG, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: An attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [DOI: 10.1016/S0016-5107(91)70740-2]

4 **Onal IK**, Parlak E, Akdogan M, Yesil Y, Kuran SO, Kurt M, Disibeyaz S, Ozturk E, Odemis B. Do aspirin and non-steroidal anti-inflammatory drugs increase the risk of post-sphincterotomy hemorrhage--a case-control study. *Clin Res Hepatol Gastroenterol* 2013; **37**: 171-176 [PMID: 22677232 DOI: 10.1016/j.clinre.2012.04.010]

5 **Richter JA**, Patrie JT, Richter RP, Henry ZH, Pop GH, Regan KA, Peura DA, Sawyer RG, Northup PG, Wang AY. Bleeding after percutaneous endoscopic gastrostomy is linked to serotonin reuptake inhibitors, not aspirin or clopidogrel. *Gastrointest Endosc* 2011; **74**: 22-34.e1 [PMID: 21704806 DOI: 10.1016/j.gie.2011.03.1258]

6 **Hui CK**, Lai KC, Yuen MF, Wong WM, Lam SK, Lai CL. Does withholding aspirin for one week reduce the risk of post-sphincterotomy bleeding? *Aliment Pharmacol Ther* 2002; **16**: 929-936 [PMID: 11966501]

7 **Tavakoli HR**, DeMaio M, Wingert NC, Rieg TS, Cohn JA, Balmer RP, Dillard MA. Serotonin reuptake inhibitors and bleeding risks in major orthopedic procedures. *Psychosomatics* 2012; **53**: 559-565 [PMID: 23157994 DOI: 10.1016/j.psym.2012.05.001]

8 **Jiang HY**, Chen HZ, Hu XJ, Yu ZH, Yang W, Deng M, Zhang YH, Ruan B. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal bleeding: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2015; **13**: 42-50.e3 [PMID: 24993365 DOI: 10.1016/j.cgh.2014.06.021]

9 **Andrade C**, Sandarsh S, Chethan KB, Nagesh KS. Serotonin reuptake inhibitor antidepressants and abnormal bleeding: a review for clinicians and a reconsideration of mechanisms. *J Clin Psychiatry* 2010; **71**: 1565-1575 [PMID: 21190637 DOI: 10.4088/JCP.09r05786blu]

10 **Szary NM**, Al-Kawas FH. Complications of endoscopic retrograde cholangiopancreatography: how to avoid and manage them. *Gastroenterol Hepatol* (NY) 2013; **9**: 496-504 [PMID: 24719597]

11 **Loke YK**, Trivedi AN, Singh S. Meta-analysis: gastrointestinal bleeding due to interaction between selective serotonin uptake inhibitors and non-steroidal anti-inflammatory drugs. *Aliment Pharmacol Ther* 2008; **27**: 31-40 [PMID: 17919277 DOI: 10.1111/j.1365-2036.2007.03541.x]

12 **Dall M**, Schaffalitzky de Muckadell OB, Lassen AT, Hansen JM, Hallas J. An association between selective serotonin reuptake inhibitor use and serious upper gastrointestinal bleeding. *Clin Gastroenterol Hepatol* 2009; **7**: 1314-1321 [PMID: 19716436 DOI: 10.1016/j.cgh.2009.08.019]

13 **Dalton SO**, Johansen C, Mellemkjaer L, Nørgård B, Sørensen HT, Olsen JH. Use of selective serotonin reuptake inhibitors and risk of upper gastrointestinal tract bleeding: a population-based cohort study. *Arch Intern Med* 2003; **163**: 59-64 [PMID: 12523917 DOI: 10.1001/archinte.163.1.59]

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ORIGINAL ARTICLE

Retrospective Study

Does deep sedation with propofol affect adenoma detection rates in average risk screening colonoscopy exams?

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Author contributions: Thirumurthi S performed the research and wrote the paper; Raju GS and Lee JH provided clinical advice and reviewed the manuscript; Pande M performed the statistical analysis; Ruiz J, Carlson R and Hagan KB reviewed the manuscript; Ross WA designed the study, performed the research, reviewed and edited the manuscript.

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Institutional review board statement: This study was approved by the MD Anderson Cancer Center IRB.

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Abstract

AIM

To determine the effect of sedation with propofol on adenoma detection rate (ADR) and cecal intubation rates (CIR) in average risk screening colonoscopies compared to moderate sedation.

METHODS

We conducted a retrospective chart review of 2604 first-time average risk screening colonoscopies performed at MD Anderson Cancer Center from 2010-2013. ADR and CIR were calculated in each sedation group. Multivariable regression analysis was performed to adjust for potential confounders of age and body mass index (BMI).

RESULTS

One-third of the exams were done with propofol (n = 874). Overall ADR in the propofol group was significantly higher than moderate sedation (46.3% *vs* 41.2%, P =

0.01). After adjustment for age and BMI differences, ADR was similar between the groups. CIR was 99% for all exams. The mean cecal insertion time was shorter among propofol patients (6.9 min *vs* 8.2 min; $P < 0.0001$).

CONCLUSION

Deep sedation with propofol for screening colonoscopy did not significantly improve ADR or CIR in our population of average risk patients. While propofol may allow for safer sedation in certain patients (*e.g.*, with sleep apnea), the overall effect on colonoscopy quality metrics is not significant. Given its increased cost, propofol should be used judiciously and without the implicit expectation of a higher quality screening exam.

Key words: Sedation; Propofol; Adenoma detection rate; Cecal intubation rate; Colonoscopy; Quality metrics

Core tip: This is a retrospective study to evaluate the effect of propofol deep sedation *vs* opioid/benzodiazepine moderate sedation on adenoma detection rate (ADR) and cecal intubation rate (CIR) colonoscopy quality metrics. After adjusting for confounding variables of age, gender and body mass index, there was no difference seen in ADR or CIR between the two groups.

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INTRODUCTION

In the United States endoscopic procedures routinely utilize sedation to minimize patient discomfort. Today, moderate sedation is widely used, with a combination of opioid and benzodiazepine for amnestic and analgesic effects[1]. In recent years endoscopists have increasingly turned to deep sedation provided by anesthesiologists using propofol although significant regional differences in utilization exist[2]. Between 2008 and 2011, one third of colonoscopies were performed using anesthesia services[3]. Propofol provides sedative, amnestic and hypnotic effects but does not have analgesic properties.

Propofol is gaining popularity among United States endoscopists in part due to its rapid onset of action and faster patient recovery[4]. In a nationwide survey, physicians under age 65 used propofol in their practice more frequently and were more satisfied with propofol over moderate sedation compared to older physicians[5]. Half of the physicians in this survey favored propofol sedation for their own endoscopy as they felt that this would improve the quality of the exam[5]. However, the data on patient satisfaction compared with conscious sedation are mixed with a recent meta-analysis showing no difference[6].

Adenoma detection rate (ADR) is the premier quality indicator in screening colonoscopy and is inversely related to the risk of interval colorectal cancer development and death[7,8]. Since some gastroenterologists perceive that propofol sedation improves the quality of the exam, investigators have evaluated the effect of sedation on ADR. While multiple studies have compared varying levels of sedation to no sedation and found conflicting results in terms of exam quality[9,10] other studies have compared different levels of sedation to each other. However, these studies either did not utilize propofol[11], did not describe the level sedation achieved with various agents[12], or gave conflicting results[13]. Thus the question of whether deep sedation with propofol improves ADR when compared to moderate sedation with benzodiazepines/opioids remains unresolved.

Adenoma detection depends on the entire colon being examined, therefore cecal intubation rate (CIR) is another quality parameter in screening colonoscopy. The more comfortable the patient is, the higher likelihood that the cecum will be reached especially in technically difficult cases. In general, the use of any level of sedation has improved the rates of cecal intubation over unsedated exams[9,10]. In one study using propofol for sedation, CIR was 98% and incomplete exams were associated with patient history of constipation and poor bowel prep[14].

Given the recent trend toward increased anesthesia involvement in endoscopy and the added cost, the current emphasis on value in health care services makes it worthwhile to evaluate the relationship between deep sedation and colonoscopy quality metrics. Our primary outcome was to determine the effect of deep sedation with propofol (total intravenous anesthesia, TIVA) compared to moderate sedation on ADR in a population of average-risk patients presenting for their index screening colonoscopy. Our secondary aim was to determine any differences in cecal intubation rates between these two sedation groups.

MATERIALS AND METHODS

We performed a retrospective chart review of all average risk patients aged 50 to 75 undergoing initial screening colonoscopy between July 2010 and May 2013 at the University of Texas MD Anderson Cancer Center. Patients who have had prior exams often cannot recall the pertinent details (whether adenomas were removed, if the exam was complete, preparation quality, *etc.*) in addition the risk of adenomas increases with patient age. Therefore based on chart review, we excluded patients who had undergone a prior colonoscopy to get a homogenous group of patients to determine ADR. High-risk patients (*i.e.,* with a family history of colon cancer or genetic syndromes), diagnostic exams (done

for evaluation of symptoms) and patients who had undergone prior colon resection were excluded. Patients with a personal history of non-gastrointestinal cancers were included. In our group practice, the endoscopy time assigned to TIVA or moderate sedation use can vary between physicians. Endoscopists who performed less than 20 exams in either sedation group during the study period were excluded from analysis. This was done to evaluate a group of physicians who had contributed to both sedation groups to minimize bias and obtain accurate ADRs[15]. Full time faculty with endoscopic experience ranging from one year to 25 years post fellowship training performed all exams. All patients received a standard split dose bowel to optimize the quality of bowel prep[16]. Our Institutional Review Board approved this study. Informed consent was not required for this retrospective study, data was collected in a de-identified manner and in the course of usual patient management.

Patients are referred to our endoscopy unit for screening exams after being evaluated in a cancer prevention center, gastroenterology clinic, or by other MD Anderson clinics. These referrals are reviewed within our department and the patients are scheduled with moderate sedation or TIVA based on uniform criteria. Our criteria for TIVA mirror those of the American Society for Gastrointestinal Endoscopy and fall into three categories: (1) pulmonary (*e.g.,* increased risk of airway obstruction or aspiration, documented sleep apnea with use of continuous positive airway pressure device); (2) co-morbid conditions (*e.g.,* BMI $\geqslant$ 35, cardiac disease such as arrhythmia, pacemaker, decompensated heart failure, myocardial infarction within 6 mo*, etc.*); or (3) anticipated intolerance of moderate sedation (*e.g.,* scheduled use of narcotics or benzodiazepines or patient preference)[4]. Moderate sedation consisted of intravenous midazolam and either meperidine or fentanyl under the direction of the endoscopist with routine monitoring. Deep sedation was the target for TIVA patients. In addition to routine monitoring of blood pressure, EKG, and use of nasal cannula oxygen, TIVA patients were also monitored with end-tidal capnography.

Two investigators (WR and ST) performed data collection from the electronic medical record to identify patients for inclusion. Demographic information including age, gender, race and BMI were recorded for each patient. Transcribed clinic notes were reviewed to determine family history, presence of symptoms at the time of colonoscopy and reports of prior colonoscopy exams. Procedure notes and the endoscopy reporting software database (Endoworks Olympus Inc. Center Valley, PA, United States) were examined to determine method of sedation, insertion time to the cecum and scope withdrawal time (which are marked by the endoscopy technician during the procedure) as well as the number of polyps removed. The software system default for bowel prep quality is set to good/adequate and the physician must make the effort to change it. Since there is variability among our endoscopists in doing this, we did not specifically collect this data point. We used CIR as a surrogate marker for adequacy of bowel prep. Pathology reports were reviewed to record polyp histology (hyperplastic, adenoma, sessile serrated adenoma, or adenocarcinoma).

ADR was calculated for male and female patients by method of sedation. Statistical analysis was performed using the chi-square test for categorical variables and *t* test for continuous variables. Multivariable logistic regression analysis was performed to determine the effect of TIVA *vs* moderate sedation on ADR for male and female patients. The analyses were adjusted for potential confounders, namely BMI and age[17,18]. The relationship between the depths of sedation and CIR, as well as scope insertion times was evaluated. Pearson's correlation coefficient was calculated to assess for any relationship between ADR and the proportion of TIVA procedures performed by each endoscopist. We did not perform any additional provider-level analyses (such as ADR by years in clinical practice) because of unequal sub-group distribution of physicians in our practice.

RESULTS

A total of 2604 first-time screening colonoscopies were performed during the study period. The majority were done under moderate sedation (n = 1730, 66.4%; TIVA: n = 874, 33.6%). Female patients outnumbered male patients (n = 1681 and n = 926 respectively) and most patients were non-Hispanic whites (Table 1). Patients in the TIVA group had a significantly higher BMI and were older than the moderate sedation group as expected based on our allocation criteria. Adenomas were detected in 1118 exams while 1486 patients had negative exams. Of these, approximately 9% of patients had advanced adenomas and 6% had sessile serrated adenomas.

The overall ADR was higher in the TIVA group than the moderate sedation group (46.3% *vs* 41.2% P = 0.01). The ADR was significantly higher among female patients undergoing exams with TIVA compared to moderate sedation (42.4% *vs* 36.4% P = 0.03). There was no significant difference in ADR in male patients between the TIVA and moderate sedation groups (53.7% *vs* 50.4% P = NS). Detection of sessile serrated adenomas and advanced adenomas was similar between the two groups. Multivariate analysis was performed to adjust for potential confounders (*i.e.*, age and BMI)[17]. There was no significant difference in ADR in either male or female patients between the study groups after multivariable analysis (Table 2).

Cecal intubation rates were evaluated for the study group. CIR was 99.0% overall and similar between sedation groups (98.8% moderate sedation, 99.4% TIVA, P = 0.15). Failure to reach the cecum was more common among female patients (n = 15 of 19 incomplete exams). The most common reason for an incomplete colonoscopy was poor bowel prep,

Table 1 Patient characteristics by type of sedation

	Moderate sedation, *n* (%)	Propofol sedation, *n* (%)	*P* value
Total	1730 (66.4)	874 (33.6)	
Gender			0.16
Female	1133 (67.4)	548 (32.6)	
Male	597 (64.7)	326 (35.3)	
Race			< 0.0001
Non-Hispanic White	1190 (66.2)	607 (33.8)	
African American	166 (55.7)	132 (44.3)	
Hispanic	186 (65.5)	98 (34.5)	
Asian	172 (83.9)	33 (16.1)	
Unknown	16 (80.0)	4 (20.0)	
BMI			< 0.0001
< 25	617 (81.8)	137 (18.2)	
25-30	645 (76.0)	204 (24.0)	
> 30	451 (45.8)	533 (54.2)	
Missing	17 (100)	0 (0)	
Mean age (SD)	55.4 (5.3)	56.7 (5.9)	< 0.0001
Adenoma			0.01
No	1017 (58.8)	469 (53.7)	
Yes	713 (41.2)	405 (46.3)	
Mean insertion time, min (SD)	8.2 (6.5)	6.9 (4.7)	< 0.0001
Mean scope withdrawal time, min (SD)	12.8 (6.3)	12.6 (6.6)	0.75
Advanced adenoma detection rate (SD)	134 (7.8)	95 (10.4)	0.065
Sessile serrated adenoma detection rate (SD)	106 (6.1)	54 (5.9)	0.52

followed by technical difficulty (adhesions, fixed angulations, redundant colon). Three patients in the moderate sedation group had an incomplete exam due to inadequate sedation (pain during the procedure, paradoxical reaction to medication). In these cases, examination of the colon was completed by CT colonography or repeat colonoscopy with TIVA.

The mean scope insertion time to the cecum was calculated for complete exams and was significantly shorter among patients in the TIVA group compared to moderate sedation (6.9 min *vs* 8.2 min; $P < 0.0001$). Within the TIVA group, mean insertion times were longer for female patients compared to male patients (7.3 min *vs* 6.3 min; $P = 0.003$). Use of TIVA was associated with a significantly shorter scope insertion time to cecum among both females (OR = 0.96, 95%CI: 0.94-0.97, $P < 0.001$) and males (OR = 0.96, 95%CI: 0.60-0.99, $P = 0.02$) and remained significant even after adjusting for age and BMI (Table 2). Scope withdrawal times were similar for the TIVA and moderate sedation groups for exams done without polypectomy ($P = 919$, mean 12.6 min *vs* 12.8 min respectively, $P = 0.75$). The proportion of TIVA procedures performed by each endoscopist had no correlation with the ADR the physician achieved (R = 0.11).

DISCUSSION

Our group aimed to evaluate the effect of deep sedation with propofol compared to moderate sedation on ADR and CIR in our clinical setting. The overall ADR for our group was 40.9% for moderate sedation and 46.1% for TIVA cases, higher than commonly reported rates and higher than the recently modified national society performance targets of 20% ADR for women and 30% for men[8]. Although our reported ADR is higher than generally expected, comparable rates are seen in high performers[19]. Our initial analysis found a significantly higher ADR among female patients having exams with TIVA but no difference among male patients. After adjusting for age and BMI, there was no difference in ADR among male or female patients regardless of the type of sedation. CIR was 99% in both sedation groups.

Although previous investigators have studied the effect of sedation on colonoscopy quality metrics, there are several important distinctions in our study[9-11]. One of our strengths is that we specifically compare propofol for deep sedation *vs* an opioid/benzodiazepine combination to achieve moderate sedation and is reflective of clinical practice. The depth of sedation achieved with this cocktail can be variable while propofol reliably induces deep sedation. Another strength is our homogenous patient population best suited to evaluate ADR among average-risk patients undergoing their first screening colonoscopy. Other studies were performed among higher risk patients presenting for colonoscopy by virtue of positive symptoms, prior adenoma, older age, positive family history, *etc*. which influence adenoma prevalence[10-12]. Our group had more female than male patients presenting for screening colonoscopy which supports existing literature[20].

The decision to perform colonoscopy with moderate *vs* deep sedation is often left to a practitioner's clinical judgment and this variability can affect study outcomes. We consistently applied our department's criteria in selecting patients for exams with TIVA, to ensure uniform patient selection for the sedation groups. While we recognize that our specific criteria are not used universally, we feel that they are fairly generalizable (age, comorbidity, BMI) and done with the patients' safety in mind. While random assignment is ideal, it does not reflect clinical practice.

We realize that our study has limitations. This was a retrospective study with the limitations inherent in that design. While we are a tertiary care center, MD Anderson has a Cancer Prevention and Screening clinic. As a result, over half of our colon cancer screening practice consists of patients without a prior cancer history. While we included patients with a prior history of cancer, we excluded those with a prior gastrointestinal malignancy in order to reduce bias. We feel that survivors of non-gastrointestinal malignancies and are representative of the patients seen in general clinical practice. In addition, we have previously demonstrated that there was no difference in the ADR between patients without a cancer history and those with a history of non-gastrointestinal malignancy[21]. There may be additional unmeasured confounders or selection bias present. Sedation may have an effect on detection of right sided *vs* left sided lesions but our database did not allow us to investigate

Table 2 Multivariable analysis: Association of type of sedation (propofol *vs* moderate) with adenoma detection rate and scope insertion time

	Variable	Propofol, *n* (%)	Crude odds ratio (95%CI)	*P* value	Adjusted odds ratio[1] (95%CI)	*P* value
Adenoma detection						
Gender	Female	548 (32.6)	1.27 (1.03-1.56)	0.03	1.07 (0.84-1.35)	0.60
	Male	326 (35.3)	1.14 (0.87-1.49)	0.34	1.16 (0.87-1.55)	0.32
Scope insertion time, mean (SD)						
Gender	Female	7.3 (5.0)	0.96 (0.94-0.97)	< 0.001	0.97 (0.95-0.99)	0.02
	Male	6.3 (4.2)	0.96 (0.60-0.99)	0.02	0.97 (0.93-1.00)	0.05

[1]Adjusted for patient age and body mass index.

this further.

Ease of scope insertion to the cecum and performing a deliberate exam during scope withdrawal are important factors for a quality exam[22]. In addition to overall CIR, we also evaluated mean scope insertion times and scope withdrawal times. The mean insertion time to the cecum was significantly shorter in our TIVA group. Investigators have shown that scope insertion to the cecum takes longer for female patients than male patients and this was confirmed in our study[23-26]. Increasing patient age and BMI are other well-recognized factors that independently prolong scope insertion time[23-26]. When adjusted for these factors, the scope insertion times were shorter with deep sedation compared to moderate sedation only in females. Our scope withdrawal times were similar between the two sedation groups for normal exams. One limitation is that polyp removal time was not separately recorded from insertion or withdrawal time. We assume that the endoscopist's preference of polypectomy during insertion or withdrawal would be performed consistently regardless of the method of sedation. Reaching the cecum more quickly could allow for additional time for inspection and increased polyp detection in the deep sedation group, but this was not seen. Apart from patient and procedure-related factors that affect ADR, the endoscopist themselves may have a greater impact on ADR than patient age or gender[27]. Therefore we wanted to determine if there was a correlation between the proportion of TIVA procedures performed by an individual endoscopist and their ADR. No such correlation was seen in our study.

Although the majority of propofol sedation is done safely, some have reported increased complications with deep sedation[3,28]. This may be a reflection of patient selection as regions of the country with more selective use of propofol show the highest complication rates compared to moderate sedation[3]. In areas where propofol is used indiscriminantly, the complication rates are more modest. While the participation of anesthesiologists can expand the population that can undergo endoscopy safely, the use of propofol for routine procedures and, in some centers, without specific medical justification, contributes to escalating healthcare costs[2]. We were not able to demonstrate an improvement in screening colonoscopy quality metrics with the use of propofol sedation. The additional expense of propofol may not be fully mitigated by enhanced efficiency[29]. In these times of heightened concern for value in health care expenditures, the effect of propofol use for endoscopic sedation on patient outcomes deserves further study.

COMMENTS

Background

Screening colonoscopy exams are being performed with deep sedation using propofol with increasing frequency in the United States. The authors aimed to determine if there was any effect of deep sedation (compared to moderate sedation) on colonoscopy quality metrics, specifically adenoma detection rates and cecal intubation rates.

Research frontiers

Although previous investigators have studied the effect of sedation on colonoscopy quality metrics, there are several important distinctions in this study. One of the strengths of this study is that we specifically compare propofol for deep sedation to opioid/benzodiazepine combination for moderate sedation which is reflective of clinical practice. This study inclusion criteria allowed us to identify average risk patients undergoing first-time screening colonoscopy, a homogenous group to evaluate adenoma detection rate.

Applications

Physicians using anesthesia services for propofol administration during elective screening colonoscopy should not have the expectation that this will improve the quality of their exam. Deep sedation with propofol did not affect adenoma detection rate in this retrospective study.

Peer-review

This is a retrospective study looking at a single institution's experience with colonoscopy using deep sedation with propofol or moderate sedation, and its impact on adenoma detection rate and other colonoscopy metrics such as completion rate, insertion time, and withdrawal time.

REFERENCES

1 **Childers RE**, Williams JL, Sonnenberg A. Practice patterns of sedation for colonoscopy. *Gastrointest Endosc* 2015; **82**: 503-511 [PMID: 25851159 DOI: 10.1016/j.gie.2015.01.041]

2 **Liu H**, Waxman DA, Main R, Mattke S. Utilization of anesthesia services during outpatient endoscopies and colonoscopies and associated spending in 2003-2009. *JAMA* 2012; **307**: 1178-1184 [PMID: 22436958 DOI: 10.1001/jama.2012.270]

3 **Wernli KJ**, Brenner AT, Rutter CM, Inadomi JM. Risks Associated With Anesthesia Services During Colonoscopy. *Gastroenterology* 2016; **150**: 888-894; quiz e18 [PMID: 26709032 DOI: 10.1053/j.gastro.2015.12.018]

4 **Lichtenstein DR**, Jagannath S, Baron TH, Anderson MA, Banerjee S, Dominitz JA, Fanelli RD, Gan SI, Harrison ME, Ikenberry SO, Shen B, Stewart L, Khan K, Vargo JJ. Sedation and anesthesia in GI endoscopy. *Gastrointest Endosc* 2008; **68**: 815-826 [PMID:

18984096 DOI: 10.1016/j.gie.2008.09.029]
5 **Cohen LB**, Wecsler JS, Gaetano JN, Benson AA, Miller KM, Durkalski V, Aisenberg J. Endoscopic sedation in the United States: results from a nationwide survey. *Am J Gastroenterol* 2006; **101**: 967-974 [PMID: 16573781 DOI: 10.1111/j.1572-0241.2006.00500.x]
6 **Wang D**, Chen C, Chen J, Xu Y, Wang L, Zhu Z, Deng D, Chen J, Long A, Tang D, Liu J. The use of propofol as a sedative agent in gastrointestinal endoscopy: a meta-analysis. *PLoS One* 2013; **8**: e53311 [PMID: 23308191 DOI: 10.1371/journal.pone.0053311]
7 **Corley DA**, Jensen CD, Marks AR, Zhao WK, Lee JK, Doubeni CA, Zauber AG, de Boer J, Fireman BH, Schottinger JE, Quinn VP, Ghai NR, Levin TR, Quesenberry CP. Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014; **370**: 1298-1306 [PMID: 24693890 DOI: 10.1056/NEJMoa1309086]
8 **Rex DK**, Schoenfeld PS, Cohen J, Pike IM, Adler DG, Fennerty MB, Lieb JG, Park WG, Rizk MK, Sawhney MS, Shaheen NJ, Wani S, Weinberg DS. Quality indicators for colonoscopy. *Gastrointest Endosc* 2015; **81**: 31-53 [PMID: 25480100 DOI: 10.1016/j.gie.2014.07.058]
9 **Bannert C**, Reinhart K, Dunkler D, Trauner M, Renner F, Knoflach P, Ferlitsch A, Weiss W, Ferlitsch M. Sedation in screening colonoscopy: impact on quality indicators and complications. *Am J Gastroenterol* 2012; **107**: 1837-1848 [PMID: 23147522 DOI: 10.1038/ajg.2012.347]
10 **Radaelli F**, Meucci G, Sgroi G, Minoli G. Technical performance of colonoscopy: the key role of sedation/analgesia and other quality indicators. *Am J Gastroenterol* 2008; **103**: 1122-1130 [PMID: 18445096 DOI: 10.1111/j.1572-0241.2007.01778.x]
11 **Paspatis GA**, Tribonias G, Manolaraki MM, Konstantinidis K, Chainaki I, Theodoropoulou A, Vardas E, Chlouverakis G. Deep sedation compared with moderate sedation in polyp detection during colonoscopy: a randomized controlled trial. *Colorectal Dis* 2011; **13**: e137-e144 [PMID: 21564466 DOI: 10.1111/j.1463-1318.2011.02555.x]
12 **Metwally M**, Agresti N, Hale WB, Ciofoaia V, O'Connor R, Wallace MB, Fine J, Wang Y, Gross SA. Conscious or unconscious: the impact of sedation choice on colon adenoma detection. *World J Gastroenterol* 2011; **17**: 3912-3915 [PMID: 22025879 DOI: 10.3748/wjg.v17.i34.3912]
13 **Wang A**, Hoda KM, Holub JL, Eisen GM. Does level of sedation impact detection of advanced neoplasia? *Dig Dis Sci* 2010; **55**: 2337-2343 [PMID: 20411420 DOI: 10.1007/s10620-010-1226-1]
14 **Hsu CM**, Lin WP, Su MY, Chiu CT, Ho YP, Chen PC. Factors that influence cecal intubation rate during colonoscopy in deeply sedated patients. *J Gastroenterol Hepatol* 2012; **27**: 76-80 [PMID: 21649720 DOI: 10.1111/j.1440-1746.2011.06795.x]
15 **Do A**, Weinberg J, Kakkar A, Jacobson BC. Reliability of adenoma detection rate is based on procedural volume. *Gastrointest Endosc* 2013; **77**: 376-380 [PMID: 23211748 DOI: 10.1016/j.gie.2012.10.023]
16 **Saltzman JR**, Cash BD, Pasha SF, Early DS, Muthusamy VR, Khashab MA, Chathadi KV, Fanelli RD, Chandrasekhara V, Lightdale JR, Fonkalsrud L, Shergill AK, Hwang JH, Decker GA, Jue TL, Sharaf R, Fisher DA, Evans JA, Foley K, Shaukat A, Eloubeidi MA, Faulx AL, Wang A, Acosta RD. Bowel preparation before colonoscopy. *Gastrointest Endosc* 2015; **81**: 781-794 [PMID: 25595062 DOI: 10.1016/j.gie.2014.09.048]
17 **Ben Q**, An W, Jiang Y, Zhan X, Du Y, Cai QC, Gao J, Li Z. Body mass index increases risk for colorectal adenomas based on meta-analysis. *Gastroenterology* 2012; **142**: 762-772 [PMID: 22245665 DOI: 10.1053/j.gastro.2011.12.050]
18 **Corley DA**, Jensen CD, Marks AR, Zhao WK, de Boer J, Levin TR, Doubeni C, Fireman BH, Quesenberry CP. Variation of adenoma prevalence by age, sex, race, and colon location in a large population: implications for screening and quality programs. *Clin Gastroenterol Hepatol* 2013; **11**: 172-180 [PMID: 22985608 DOI: 10.1016/j.cgh.2012.09.010]
19 **Rex DK**, Helbig CC. High yields of small and flat adenomas with high-definition colonoscopes using either white light or narrow band imaging. *Gastroenterology* 2007; **133**: 42-47 [PMID: 17631129 DOI: 10.1053/j.gastro.2007.04.029]
20 **Wallace PM**, Suzuki R. Regional, racial, and gender differences in colorectal cancer screening in middle-aged African-Americans and Whites. *J Cancer Educ* 2012; **27**: 703-708 [PMID: 22791544 DOI: 10.1007/s13187-012-0396-2]
21 **Ross WA**, Thirumurthi S, Lynch PM, Rashid A, Pande M, Shafi MA, Lee JH, Raju GS. Detection rates of premalignant polyps during screening colonoscopy: time to revise quality standards? *Gastrointest Endosc* 2015; **81**: 567-574 [PMID: 25583558 DOI: 10.1016/j.gie.2014.07.030]
22 **Lee TJ**, Blanks RG, Rees CJ, Wright KC, Nickerson C, Moss SM, Chilton A, Goddard AF, Patnick J, McNally RJ, Rutter MD. Longer mean colonoscopy withdrawal time is associated with increased adenoma detection: evidence from the Bowel Cancer Screening Programme in England. *Endoscopy* 2013; **45**: 20-26 [PMID: 23254403 DOI: 10.1055/s-0032-1325803]
23 **Anderson JC**, Messina CR, Cohn W, Gottfried E, Ingber S, Bernstein G, Coman E, Polito J. Factors predictive of difficult colonoscopy. *Gastrointest Endosc* 2001; **54**: 558-562 [PMID: 11677470 DOI: 10.1067/mge.2001.118950]
24 **Bernstein C**, Thorn M, Monsees K, Spell R, O'Connor JB. A prospective study of factors that determine cecal intubation time at colonoscopy. *Gastrointest Endosc* 2005; **61**: 72-75 [PMID: 15672059 DOI: 10.1016/S0016-5107(04)02461-7]
25 **Hsieh YH**, Kuo CS, Tseng KC, Lin HJ. Factors that predict cecal insertion time during sedated colonoscopy: the role of waist circumference. *J Gastroenterol Hepatol* 2008; **23**: 215-217 [PMID: 18289354 DOI: 10.1111/j.1440-1746.2006.04818.x]
26 **Lee HL**, Eun CS, Lee OY, Jeon YC, Han DS, Sohn JH, Yoon BC, Choi HS, Hahm JS, Lee MH, Lee DH, Moon W, Kim SY. Significance of colonoscope length in cecal insertion time. *Gastrointest Endosc* 2009; **69**: 503-508 [PMID: 19152904 DOI: 10.1016/j.gie.2008.06.006]
27 **Chen SC**, Rex DK. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. *Am J Gastroenterol* 2007; **102**: 856-861 [PMID: 17222317 DOI: 10.1111/j.1572-0241.2006.01054.x]
28 **Cooper GS**, Kou TD, Rex DK. Complications following colonoscopy with anesthesia assistance: a population-based analysis. *JAMA Intern Med* 2013; **173**: 551-556 [PMID: 23478904 DOI: 10.1001/jamainternmed.2013.2908]
29 **Vargo JJ**, Bramley T, Meyer K, Nightengale B. Practice efficiency and economics: the case for rapid recovery sedation agents for colonoscopy in a screening population. *J Clin Gastroenterol* 2007; **41**: 591-598 [PMID: 17577116 DOI: 10.1097/01.mcg.0000225634.52780.0e]

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic balloon catheter dilatation *via* retrograde or static technique is safe and effective for cricopharyngeal dysfunction

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Abstract

AIM

To evaluate the safety and efficacy of upper esophageal sphincter (UES) dilatation for cricopharyngeal (CP) dysfunction. To determine if: (1) indication for dilatation; or (2) technique of dilatation correlated with symptom improvement.

METHODS

All balloon dilatations performed at our institution from over a 3-year period were retrospectively analyzed for demographics, indication and dilatation site. All dilatations involving the UES underwent further review to determine efficacy, complications, and factors that predict success. Dilatation technique was separated

into static (stationary balloon distention) and retrograde (brusque pull-back of a fully distended balloon across the UES).

RESULTS

Four hundred and eighty-eight dilatations were reviewed. Thirty-one patients were identified who underwent UES dilatation. Median age was 63 years (range 27-81) and 55% of patients were male. Indications included dysphagia (28 patients), globus sensation with evidence of UES dysfunction (2 patients) and obstruction to echocardiography probe with cricopharyngeal (CP) bar (1 patient). There was evidence of concurrent oropharyngeal dysfunction in 16 patients (52%) and a small Zenker's diverticula ($\leqslant$ 2 cm) in 7 patients (23%). Dilator size ranged from 15 mm to 20 mm. Of the 31 patients, 11 had dilatation of other esophageal segments concurrently with UES dilatation and 20 had UES dilatation alone. Follow-up was available for 24 patients for a median of 2.5 mo (interquartile range 1-10 mo), of whom 19 reported symptomatic improvement (79%). For patients undergoing UES dilatation alone, follow-up was available for 15 patients, 12 of whom reported improvement (80%). Nineteen patients underwent retrograde dilatation (84% response) while 5 patients had static dilatation (60% response); however, there was no significant difference in symptom improvement between the techniques (P = 0.5). Successful symptom resolution was also not significantly affected by dilator size, oropharyngeal dysfunction, Zenker's diverticulum, age or gender (P > 0.05). The only complication noted was uvular edema and a shallow ulcer after static dilatation in one patient, which resolved spontaneously and did not require hospital admission.

CONCLUSION

UES dilatation with a through-the-scope balloon by either static or retrograde technique is safe and effective for the treatment of dysphagia due to CP dysfunction. To our knowledge, this is the first study evaluating retrograde balloon dilatation of the UES.

Key words: Cricopharygeal dysfunction; Cricopharyngeal bar; Dysphagia; Esophageal dilatation; Endoscopic balloon dilation

Core tip: Cricopharyngeal dysphagia can be treated with endoscopic balloon dilatation. In this series, a novel dilatation technique of pulling a fully inflated 15-20 mm balloon dilator in a retrograde manner across the upper esophageal sphincter was safe and effective for the treatment of cricopharyngeal dysphagia.

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INTRODUCTION

The upper esophageal sphincter, comprised of the cricopharyngeus, or the cricopharyngeal (CP) muscle, inferior pharyngeal constrictor, and proximal cervical esophagus serves a pivotal role in the act of deglutition. The CP muscle normally remains in a contracted state and relaxes during swallowing prior to penetration of a food bolus into the cricopharyngeal region. Cricopharyngeal dysfunction (CPD) refers to incoordination of the cricophyngeal muscle either due to a primary functional disorder or as a result of an underlying neurological or medical condition[1]. Symptoms of CPD can range from a globus sensation to oropharyngeal dysphagia manifested by regurgitation, coughing, choking and recurrent aspiration.

The diagnosis of CPD can be difficult to make and often requires a meticulous history and physical examination. Videofluoroscopy is often helpful for the diagnosis of CPD with the typical appearance of a shelf in the posterior column of barium at the level of the cricoid cartilage, more commonly described as a cricopharyngeal bar[2]. The incidence of CP bars is variable in the reported literature, ranging from 5% to 22% in patients who undergo videofluoroscopic swallow studies for dysphagia[2-4]. CP bars are frequently detected in asymptomatic individuals and therefore other modalities such as esophageal manometry and upper endoscopy must be performed to exclude other etiologies of dysphagia.

Endoscopic treatment for CPD has not been well studied and remains controversial. Historically, management has relied upon surgical CP myotomy[5-7]. Endoscopic dilatation poses an attractive option, given the risks associated with myotomy; however, published case series to date have included very small numbers of patients with varying dilatation techniques[8-13]. The aim of our study was to determine the efficacy and safety of through-the-scope (TTS) balloon dilatation of the upper esophageal sphincter (UES) in patients with CPD and to compare the traditional static technique of sequential distention of the balloon with a brusque "pull-back" retrograde approach across the UES.

MATERIALS AND METHODS

The study was approved by the Johns Hopkins Medicine institutional review board. The medical records of all patients that underwent esophageal dilatation with a through-the-scope balloon dilator at the Johns Hopkins Hospital over a consecutive 3-year period were reviewed. Patients were included in the study cohort if they had CPD that was treated with TTS balloon dilatation of the UES, including those with a Zenker's diverticulum. Patients were excluded if they were under the age of 18 years old and if balloon dilatation of the UES was not performed. Patient demographics, prior radiographic data, procedural indications, test results, complications and follow-up clinical outcomes were recorded.

Data was analyzed using Stata version 9 (StataCorp,

Table 1 Patient demographics *n* (%)

Patients undergoing UES dilatation	*n* = 31
Age, yr, median (range)	63 (27-81)
Sex	
Male	17 (55)
Female	14 (45)
Indications	
Radiographic CP hypertrophy with dysphagia	22 (71)
Endoscopic UES tightness with dysphagia	3 (10)
Inclusion body myositis with dysphagia and prominent cricopharyngeus	3 (10)
Globus sensation with evidence of UES dysfunction	2 (6)
Obstruction to echocardiography probe with CP bar, but otherwise asymptomatic	1 (3)
Presence of oropharyngeal dysfunction	16 (52)
Presence of Zenker's diverticulum	7 (23)

UES: Upper esophageal sphincter; CP: Cricopharyngeal.

College Station, TX) on a per-patient basis. Descriptive statistics were calculated for all covariates and outcomes including *t* test, χ^2 test, and Fisher's exact test, where appropriate.

Procedural technique

Balloon dilatation of the upper esophageal sphincter was performed using two different techniques: Static and retrograde. With the traditional "static" technique, a through-the scope balloon dilation catheter (Boston Scientific Corporation, Natick, MA) is positioned across the upper esophageal sphincter under visual guidance without the use of a guidewire or fluoroscopy. The balloon is then sequentially inflated, holding the balloon in position for 30 to 60 s with each distention to a maximum diameter of 15 mm to 20 mm at the discretion of the endoscopist.

The retrograde approach across the UES is a newly described technique for the management of CPD. The actual technique has been used for mucosal disruption and treatment of esophageal rings, but has not been described in the management of CPD[14]. In this approach, the TTS balloon is inflated to the maximal desired diameter under visual guidance in the proximal esophagus, distal to the UES. The fully distended balloon is then brought back to the tip of the endoscope. Both the endoscope and distended balloon are then withdrawn across the UES into the oropharynx as one unit, usually with moderate resistance.

In all cases, individuals were sedated for the procedure. After dilatation was performed, the UES and the surrounding structures were closely inspected for evidence of mucosal damage.

RESULTS

Over a consecutive three-year period 488 esophageal TTS balloon dilatations were performed at our institution, of which 31 patients had dilatation of the UES for CPD. The median age at time of UES dilatation was 63 years and 55% of the patients were male (Table 1). Indications for UES dilatation are summarized in Table 1. Twenty-eight patients (90%) were experiencing dysphagia symptoms. In addition to CPD, 16 patients (52%) had evidence of concurrent oropharyngeal dysfunction and 7 patients (23%) were also found to have a Zenker's diverticulum.

Table 2 Balloon dilatation procedural details *n* (%)

	Enrolled (*n* = 31)
Number of procedures per patient, median (range)	1 (1-3)
Type of initial dilatation	
Retrograde (brusque pull-back)	24 (77)
Static (sequential distention)	7 (23)
UES dilatation alone	20 (65)
Concurrent dilatation of the UES and other portions of the esophagus	11 (35)
Maximal diameter size, median (range)	20 mm (15-20 mm)
Total Number of complications	1 (3)
Serious complications requiring hospitalization	0

UES: Upper esophageal sphincter.

Each individual underwent a median of 1 dilatation (range, 1-3), with 24 individuals (77%) receiving a retrograde approach (Table 2). The majority of individuals (26) underwent only 1 dilatation session. Four individuals underwent two dilatation sessions and one patient had three dilatation sessions. Eleven individuals had dilatation of other esophageal segments concurrently with UES dilatation and 20 patients had UES dilatation alone. Of those with multiple sites of esophageal dilatation, nine were for a Schatzki ring, one was for a peptic stricture and one was for subjective stenosis at the esophagogastric junction. The median maximal diameter for UES balloon dilatation was 20 mm, ranging from 15 to 20 mm. Three individuals were dilated with a 15 mm balloon, nine individuals were dilated with an 18 mm balloon, and nineteen individuals were dilated with a 20 mm balloon.

Follow-up was available for 24 of the 31 patients, 19 of whom underwent retrograde brusque technique. The median duration of follow-up was 2.5 mo (interquartile range: 1-10 mo), of whom 19 (79%) reported symptomatic improvement. Sixteen patients (84%) patients with the retrograde approach responded to dilatation, whereas 3 patients (60%) with the static dilatation approach responded to treatment. However, there was no statistically significant difference in symptom improvement between the two techniques (P = 0.5). Successful symptom resolution was also not significantly affected by dilator size, presence of oropharyngeal dysfunction, presence of a Zenker's diverticulum, age or gender (Table 3). Of those patients undergoing UES dilatation alone, follow-up was available for 15 patients, 12 of whom (80%) reported symptom improvement.

One patient developed uvular edema and a shallow ulcer after static dilatation of the UES that spontaneously resolved in the recovery room and did not require hospitalization. A second patient initially underwent dilatation of the GE junction that resulted in a

Table 3 Predictors of clinical response *n* (%)

Characteristic	Clinical response		*P* value
	Y (19)	N (5)	
Age, mean ± SD	61.9 ± 11.9	66.4 ± 22.4	0.48
Sex, Male	10 (53)	2 (40)	0.68
Technique			
Retrograde	16	3	0.49
Static	3	2	
Maximal dilator size (mean ± SD, mm)	19.2 ± 1.4	19.6 ± 0.9	0.25
Oropharyngeal dysfunction	11 (58)	2 (40)	0.68
Zenker's diverticulum	4 (21)	2 (40)	0.45

small mucosal tear that was adequately treated with placement of a single endoclip. During the same endoscopy, subsequent to endoclip placement, the patient underwent retrograde dilatation of the UES without complication. There were no adverse events associated with the retrograde brusque technique of the UES.

DISCUSSION

Oropharyngeal dysphagia can be associated with significant morbidity and treatments to date are imperfect and limited. Since first used for treatment of post-poliomyelitis dysphagia in 1951[15], surgical myotomy has been the traditional approach for dysphagia related to cricopharyngeal prominence or dysfunction[16-18]. However, efficacy remains controversial and this procedure is not without risk - particularly in elderly patients in whom cricopharyngeal bars are more common[18-20]. Botulinum toxin injection has also been studied as a potential therapy and has been shown to be of benefit in several series[21-23]. Reported complications have stemmed from diffusion of Botox to adjacent muscles leading to aspiration, worsened dysphagia, vocal cord paralysis and at least one recorded death[24-26]. Moreover, the average duration of effect appears to be approximately 4 mo and waning efficacy may be observed with repeated therapy[25].

Endoscopic dilatation of the upper esophageal sphincter poses an attractive therapeutic alternative for dysphagia related to CPD. Data, however, is limited to small case series - most of which contained less than 10 patients. The published data suggest that endoscopic dilatation may be a safe and effective option for carefully selected patients. A small series reported clinical improvement in 7 of 12 patients (58%) after dilatation with a Savary dilator (17 mm)[8]. Another limited series reported higher rates of symptomatic improvement in 9 of 10 patients (90%) with similar dilatation techniques (18-20 mm)[9]. Patel *et al*[13] recently reported a larger experience with 31 patients undergoing Savary dilation with 45 French to 60 French size dilators. In this study, 65% of patients had significant improvement for at least 6 mo using a functional outcome swallow score.

One study of 5 patients undergoing static balloon dilation of the UES to a maximal diameter of 20 mm achieved 100% success rate[10]. Another study reported complete success in 6 patients undergoing dilatation of CP bars, but this study only included one patient with balloon dilation to 20 mm and the five others underwent Savary dilation[12]. In these series and reports, there have been no recorded major complications. There has been one report of superficial mucosal injury after dilatation that was self-limited and did not require treatment or hospitalization[10]. The recent systematic review on management of CPD reported comparable success rates of endoscopic dilation and myotomy; however, the authors comment that there were significantly fewer studies investigating endoscopic dilatation (6 studies involving 113 patients) and therefore the data were insufficient to make a strong recommendation on the role of endoscopic dilatation for CPD[1].

Our series represents the largest published series to date looking at endoscopic balloon dilatation of the upper esophageal sphincter for dysphagia related to CPD. When compared to reported success rates for cricopharyngeal myotomy[18,20], the results for endoscopic dilatation appear equivalent. Moreover, the safety profile of this approach appears to be excellent. In our series, the only reported complication was uvular edema and a shallow ulcer after balloon dilatation using a static technique in 1 patient that did not require admission and spontaneously improved over time. To our knowledge, there have been no perforations reported in the literature with this approach and certainly no fatalities.

At our institution, the preference has been to utilize endoscopic balloon dilatation via either a static or retrograde technique for CPD. The idea behind the static approach is to maximize radial forces while avoiding any sheering movements, whereas the concept for the retrograde approach is to combine radial and sheering forces with directed attention to the upper esophageal sphincter. As opposed to a Savary dilatation, the retrograde balloon technique may allow a more rapid increase in diameter and, with experience, a better subjective gauge of sphincter resistance. To our knowledge, this technique has not been previously reported in the literature for the management of CPD but has been used frequently at our institution for disruption of Schatzki rings, mucosal webs and upper esophageal sphincter dysfunction. While the safety of this approach has not been directly compared to conventional static dilatation, it has been our subjective opinion that the safety of these two approaches is equivalent. The one patient who developed a shallow ulcer in our series did so in the context of a static dilatation.

Traditionally, the presence of a Zenker's diverticulum has often been felt to represent a relative contraindication to endoscopic dilatation; however, mechanistically, these diverticula often arise in the context of elevated intrabolus pressure and/or upper esophageal sphincter dysfunction and for this reason may actually portend a better prognosis[27]. Certainly in our series, response rates seemed equivalent between patients with and without a diverticulum and there did not appear to be any safety concerns. Likewise, oropharyngeal

dysfunction has been hypothesized to be a potential issue that may limit efficacy. However, this group may actually be more sensitive to minor mechanical alterations in outflow resistance and the presence of oropharyngeal dysfunction in our series did not affect or predict response.

Our study does have several limitations worth noting. To begin with, it is a retrospective evaluation and clinical response was determined subjectively through review of medical records. A prospective study with validated dysphagia questionnaires would have been ideal and this certainly is worth future consideration. Second, 11 of our patients had dilatation of other esophageal segments other than the upper esophageal sphincter and it is unclear if the symptom response was due to dilatation of the cricopharyngeus or the other segment of the esophagus. However, even without including these patients, this remains the largest published experience with endoscopic balloon dilatation for CPD. Third, the indications for dilatation in our series were heterogeneous and it is possible (and indeed likely) that certain subsets have significantly varied responses. For example, it is our subjective opinion that patients with inclusion body myositis likely have a greater response to dilatation; however, given the total number of patients in our study there is no way to statistically address that question. Finally, our median follow-up was 2.5 mo and given the underlying mechanisms of upper esophageal sphincter dysfunction a longer evaluation period would have been ideal.

In summary, UES dilatation with a TTS balloon by either static or retrograde technique is safe and effective for the treatment of dysphagia in the context of CP dysfunction. As suggested in prior smaller series, this appears to be a safe and effective approach. Our series, however, is the first to describe retrograde balloon dilatation of the UES. Given this data is tandem with the reported complications of surgical myotomy and Botulinum toxin injection, we suggest that endoscopic dilatation of the upper esophageal sphincter should be the first therapy offered for patients with oropharyngeal dysphagia in the context of upper esophageal sphincter dysfunction. In addition, our experience would suggest that balloon dilatation *via* a retrograde technique is at least as safe and effective as conventional methods with either Savary or static balloon dilatation.

COMMENTS

Background

Cricopharyngeal dysfunction (CPD) is associated with a variety of symptoms including globus sensation, oropharyngeal dysphagia, regurgitation, coughing, choking and recurrent aspiration. While a variety of treatment options have been proposed, endoscopic dilatation by pulling a fully inflated 15-20 mm balloon dilator in a retrograde manner across the upper esophageal sphincter appears to be safe and effective for the treatment of cricopharyngeal dysphagia.

Research frontiers

Optimal management of cricopharyngeal dysphagia is not clear. Endoscopic dilatation appears to be safe with immediate relief of symptoms. Several small series have demonstrated benefit with endoscopic dilatation using a variety of techniques. Additional research into the durability of the procedure and objective parameters of relief are needed.

Innovations and breakthroughs

This represents the largest endoscopic experience for managing CPD. In this series, a novel dilatation technique of pulling a fully inflated 15-20 mm balloon dilator in a retrograde manner across the upper esophageal sphincter was safe and effective for the treatment of cricopharyngeal dysphagia.

Applications

The retrograde dilatation technique provides another method for effective dilatation and disruption of the upper esophageal sphincter complex to relieve symptoms associated with cricopharyngeal dysphagia. Many endoscopists are more comfortable with balloon dilatation and this technique may allow them to better treat CPD using this technique.

Terminology

CPD - refers to incoordination of the cricophyngeal muscle either due to a primary functional disorder or as a result of an underlying neurological or medical condition.

Peer-review

This is a study assessing the efficacy of endoscopic balloon catheter dilatation for treatment of criocopharyngeal dysfunction. The authors retrospectively reviewed all UES dilatations performed during a three year period. Thirty-one patients were included although follow-up was only available for 24. A symptomatic improvement was confirmed for 80% of patients. The manuscript is well written and describes a large series of cases.

REFERENCES

1 **Kocdor P**, Siegel ER, Tulunay-Ugur OE. Cricopharyngeal dysfunction: A systematic review comparing outcomes of dilatation, botulinum toxin injection, and myotomy. *Laryngoscope* 2016; **126**: 135-141 [PMID: 26360122 DOI: 10.1002/lary.25447]

2 **Baredes S**, Shah CS, Kaufman R. The frequency of cricopharyngeal dysfunction on videofluoroscopic swallowing studies in patients with dysphagia. *Am J Otolaryngol* 1997; **18**: 185-189 [PMID: 9164621 DOI: 10.1016/S0196-0709(97)90080-6]

3 **Cook IJ**, Kahrilas PJ. AGA technical review on management of oropharyngeal dysphagia. *Gastroenterology* 1999; **116**: 455-478 [PMID: 9922328 DOI: 10.1016/S0016-5085(99)70144-7]

4 **Dantas RO**, Cook IJ, Dodds WJ, Kern MK, Lang IM, Brasseur JG. Biomechanics of cricopharyngeal bars. *Gastroenterology* 1990; **99**: 1269-1274 [PMID: 2210235]

5 **Ross ER**, Green R, Auslander MO, Biller HF. Cricopharyngeal myotomy: management of cervical dysphagia. *Otolaryngol Head Neck Surg* 1982; **90**: 434-441 [PMID: 6817273 DOI: 10.1177/019459988209000413]

6 **Herberhold C**, Walther EK. Endoscopic laser myotomy in cricopharyngeal achalasia. *Adv Otorhinolaryngol* 1995; **49**: 144-147 [PMID: 7653350 DOI: 10.1159/000424359]

7 **Lawson G**, Remacle M. Endoscopic cricopharyngeal myotomy: indications and technique. *Curr Opin Otolaryngol Head Neck Surg* 2006; **14**: 437-441 [PMID: 17099353 DOI: 10.1097/MOO.0b013e3280106314]

8 **Ali GN**, Wallace KL, Laundl TM, Hunt DR, deCarle DJ, Cook IJ. Predictors of outcome following cricopharyngeal disruption for pharyngeal dysphagia. *Dysphagia* 1997; **12**: 133-139 [PMID: 9190098 DOI: 10.1007/PL00009527]

9 **Hatlebakk JG**, Castell JA, Spiegel J, Paoletti V, Katz PO, Castell DO. Dilatation therapy for dysphagia in patients with upper esophageal sphincter dysfunction--manometric and symptomatic response. *Dis Esophagus* 1998; **11**: 254-259 [PMID: 10071809]

10 **Solt J**, Bajor J, Moizs M, Grexa E, Horváth PO. Primary cricopharyngeal dysfunction: treatment with balloon catheter dilatation. *Gastrointest Endosc* 2001; **54**: 767-771 [PMID: 11726859

DOI: 10.1067/mge.2001.118442]
11 **Zepeda-Gómez S**, Montaño Loza A, Valdovinos F, Schmulson M, Valdovinos MA. Endoscopic balloon catheter dilation for treatment of primary cricopharyngeal dysfunction. *Dig Dis Sci* 2004; **49**: 1612-1614 [PMID: 15573914]
12 **Wang AY**, Kadkade R, Kahrilas PJ, Hirano I. Effectiveness of esophageal dilation for symptomatic cricopharyngeal bar. *Gastrointest Endosc* 2005; **61**: 148-152 [PMID: 15672078 DOI: 10.1016/S0016-5107(04)02447-2]
13 **Patel BJ**, Mathur AK, Dehom S, Jackson CS. Savary dilation is a safe and effective long-term means of treatment of symptomatic cricopharyngeal bar: a single-center experience. *J Clin Gastroenterol* 2014; **48**: 500-504 [PMID: 24231933 DOI: 10.1097/MCG.0000000000000026]
14 **Chung RS**. Retrograde dilation of esophageal strictures with balloon dilators. *Surg Endosc* 1991; **5**: 68-69 [PMID: 1948616 DOI: 10.1007/BF00316839]
15 **Kaplan S**. Paralysis of deglutition, a post-poliomyelitis complication treated by section of the cricopharyngeus muscle. *Ann Surg* 1951; **133**: 572-573 [PMID: 14819998 DOI: 10.1097/00000658-195104000-00021]
16 **Berg HM**, Jacobs JB, Persky MS, Cohen NL. Cricopharyngeal myotomy: a review of surgical results in patients with cricopharyngeal achalasia of neurogenic origin. *Laryngoscope* 1985; **95**: 1337-1340 [PMID: 4058211 DOI: 10.1288/00005537-198511000-00008]
17 **Bonavina L**, Khan NA, DeMeester TR. Pharyngoesophageal dysfunctions. The role of cricopharyngeal myotomy. *Arch Surg* 1985; **120**: 541-549 [PMID: 3921004 DOI: 10.1001/archsurg.1985.01390290023004]
18 **Kelly JH**. Management of upper esophageal sphincter disorders: indications and complications of myotomy. *Am J Med* 2000; **108** Suppl 4a: 43S-46S [PMID: 10718451 DOI: 10.1016/S0002-9343(99)00334-4]
19 **Leonard R**, Kendall K, McKenzie S. UES opening and cricopharyngeal bar in nondysphagic elderly and nonelderly adults. *Dysphagia* 2004; **19**: 182-191 [PMID: 15383948 DOI: 10.1007/s00455-004-0005-6]
20 **Buchholz DW**. Cricopharyngeal myotomy may be effective treatment for selected patients with neurogenic oropharyngeal dysphagia. *Dysphagia* 1995; **10**: 255-258 [PMID: 7493506 DOI: 10.1007/BF00431418]
21 **Murry T**, Wasserman T, Carrau RL, Castillo B. Injection of botulinum toxin A for the treatment of dysfunction of the upper esophageal sphincter. *Am J Otolaryngol* 2005; **26**: 157-162 [PMID: 15858769 DOI: 10.1016/j.amjoto.2004.11.010]
22 **Kim DY**, Park CI, Ohn SH, Moon JY, Chang WH, Park SW. Botulinum toxin type A for poststroke cricopharyngeal muscle dysfunction. *Arch Phys Med Rehabil* 2006; **87**: 1346-1351 [PMID: 17023244 DOI: 10.1016/j.apmr.2006.06.018]
23 **Alfonsi E**, Merlo IM, Ponzio M, Montomoli C, Tassorelli C, Biancardi C, Lozza A, Martignoni E. An electrophysiological approach to the diagnosis of neurogenic dysphagia: implications for botulinum toxin treatment. *J Neurol Neurosurg Psychiatry* 2010; **81**: 54-60 [PMID: 19762326 DOI: 10.1136/jnnp.2009.174698]
24 **Zaninotto G**, Marchese Ragona R, Briani C, Costantini M, Rizzetto C, Portale G, Zanetti L, Masiero S, Costantino M, Nicoletti L, Polidoro A, Feltrin G, Angelini C, Ancona E, Guidolin D, Parenti AR. The role of botulinum toxin injection and upper esophageal sphincter myotomy in treating oropharyngeal dysphagia. *J Gastrointest Surg* 2004; **8**: 997-1006 [PMID: 15585387 DOI: 10.1016/j.gassur.2004.09.037]
25 **Moerman MB**. Cricopharyngeal Botox injection: indications and technique. *Curr Opin Otolaryngol Head Neck Surg* 2006; **14**: 431-436 [PMID: 17099352 DOI: 10.1097/MOO.0b013e328010b85b]
26 **Cook IJ**. Treatment of Oropharyngeal Dysphagia. *Curr Treat Options Gastroenterol* 2003; **6**: 273-281 [PMID: 12846936 DOI: 10.1007/s11938-003-0019-4]
27 **Ferreira LE**, Simmons DT, Baron TH. Zenker's diverticula: pathophysiology, clinical presentation, and flexible endoscopic management. *Dis Esophagus* 2008; **21**: 1-8 [PMID: 18197932 DOI: 10.1111/j.1442-2050.2007.00795.x]

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ORIGINAL ARTICLE

Retrospective Study

Analysis of the risk factors for severity in post endoscopic retrograde cholangiopancreatography pancreatitis: The indication of prophylactic treatments

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Abstract

AIM

To determine the risk factors of severe post endoscopic retrograde cholangiopancreatography pancreatitis (sPEP) and clarify the indication of prophylactic treatments.

METHODS

At our hospital, endoscopic retrograde cholangiopancreatography (ERCP) was performed on 1507 patients from May 2012 to December 2015. Of these patients, we enrolled all 121 patients that were diagnosed with post endoscopic retrograde PEP. Fourteen of 121 patients diagnosed as sPEP were analyzed.

RESULTS

Forty-one patients had contrast media remaining in the pancreatic duct after completion of ERCP. Seventy-

one patients had abdominal pain within three hours after ERCP. These were significant differences for sPEP ($P < 0.05$). The median of Body mass index, the median time for ERCP, the median serum amylase level of the next day, past histories including drinking and smoking, past history of pancreatitis, sphincter of Oddi dysfunction, whether emergency or not, expertise of ERCP procedure, diverticulum nearby Vater papilla, whether there was sphincterotomy or papillary balloon dilation, pancreatic duct cannulation, use of intraductal ultrasonography enforcement, and transpapillary biopsies had no significant differences with sPEP.

CONCLUSION
Contrast media remaining in the pancreatic duct and the appearance of abdominal pain within three hours after ERCP were risk factors of sPEP.

Key words: Pancreatic duct stent; Post endoscopic retrograde cholangiopancreatography pancreatitis; Prophylactic treatment; Risk factor; Severe acute pancreatitis

Core tip: Post endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is a typical endoscopy-related accident in the biliopancreatic field. Since PEP is a predictable pathology, and if discovered and appropriately treated early many patients rapidly recover. However, some cases aggravate to a severe state and become fatal. Therefore, it is important to identify factors leading PEP to a severe state. In our study, significant differences were noted in residual enhancement of the pancreatic duct and development of abdominal pain showing that these were independent risk factors of severe PEP. The presence of these findings is an indication of therapeutic intervention for severe PEP.

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INTRODUCTION

Post endoscopic retrograde cholangiopancreatography pancreatitis (PEP) is a typical endoscopy-related accident in the biliopancreatic field, and there are many reports on its risk factors[1-4]. Many researchers reported methods to prevent PEP[5-17]. However, treatment to prevent PEP in all endoscopic retrograde cholangiopancreatography (ERCP) patients is not recommended in consideration of accidents caused by the addition of preventive techniques, adverse reactions of preventive drug administration, and cost[13]. Since PEP is a predictable pathology, and if discovered and appropriately treated early many patients rapidly recover. However, some cases aggravate to a severe state and become fatal. Therefore, it is important to identify factors leading PEP to a severe state, and when such risk factors are observed, therapeutic intervention, such as the addition of preventive techniques and preventive drug administration, should be performed. The objective of this study was to retrospectively clarify risk factors aggravating PEP to a severe state and determine the indications to prevent and treat PEP.

MATERIALS AND METHODS

Patients

Between May 2012 and October 2015, 1507 patients were examined by ERCP at our hospital. PEP was diagnosed in 121 of them (8.02%), and 14 of them were diagnosed with severe PEP (sPEP) and analyzed. Patients accompanied by acute pancreatitis at the time of undergoing ERCP were excluded (Figure 1). The study was performed in conformity with the Declaration of Helsinki and registered at UMIN-CTR (000022086).

ERCP procedure

For ERCP, a side-view duodenoscope was used. The endoscope used was JF260V (Olympus Medical, Tokyo, Japan). For the cannula, for contrast medium, a 0.035-inch V system (Olympus Medical, Tokyo, Japan) was used. For the guide wire, Jagwire (0.035inch; Boston scientific Corporation, Tokyo, Japan) or Visigride (0.025 inch; Olympus Medical, Tokyo, Japan) was used. Replacement fluid (2000 mL) was intravenously administered within 24 h before and after ERCP. Patients received protease inhibitor (nafamostat mesilate, 20 mg/d) and prophylactic antibiotic administration (sulbactam/cefoperazone, 2 g/d) for 2 d. Vitals were checked 3 h after completion of ERCP. For patients in whom abdominal pain developed before this, 25 or 50 mg of indomethacin suppositories were administered. When PEP was diagnosed, sufficient fluid replacement including protease inhibitor and antibiotics was continued so as to maintain the urinary volume at 1 mL/min under monitoring of circulatory dynamics.

Diagnoses and grading of PEP

PEP was diagnosed following the Cotton's criteria[16]: When abdominal pain developed on the day following ERCP and the serum amylase level was 3 times or higher than the normal upper limit, the patient was diagnosed with PEP. sPEP was defined as PEP with 10 d or longer prolongation of inpatient treatment, hemorrhagic pancreatitis, phlegmon, and pseudocyst.

Risk factors for sPEP

Clinical data of PEP patients were retrospectively

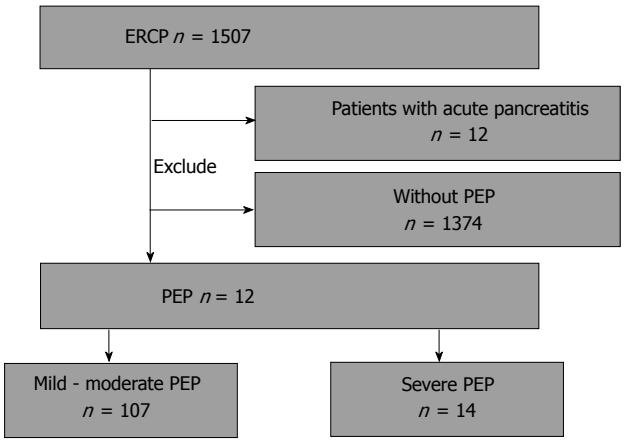

Figure 1 Patients' flow chart. ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis.

extracted from their clinical records. As sPEP risk factors, age, gender, Body mass index (BMI), past medial history including cigarette smoking and alcohol drinking and acute pancreatitis, the presence or absence of the sphincter of Oddi dysfunction (SOD), diverticulum nearby Vater papilla and common bile duct (CBD) diameter of patient with CBD stones, whether or not it was emergency ERCP, whether or not EST or EPBD was performed, pancreatography, the presence or absence of residual contrast medium in the pancreatic duct after completion of ERCP, the use of IDUS and transpapillary biopsy, treatment time, experience of operators, development of abdominal pain within 3 h after completion of ERCP, and serum amylase level, white blood cell count, and C-reactive protein on the day following ERCP were surveyed (Tables 1 and 2). The time from insertion to removal of a scope was defined as the ERCP treatment time. Experience of operators was defined based on the total and recent numbers of ERCP performed. Operators with a total number of ERCP performed of 200 or fewer and/or a recent number of ERCP performed of 40 or fewer per year were regarded as non-expert. Unfortunately, no study has examined role of sphincterotomy and number of pancreatic cannulation except our following conference paper.

Statistical analysis

In the univariate analysis, the difference between the two groups of categorical parameters were analyzed using Pearson's χ^2 test. The Kruskal-Wallis test was used for continuous parameters. The stepwise logistic regression model (forward selection) was used to calculate the odds ratio (OR) with 95%CI. Significant predictors in the univariate analysis were then included in a forward stepwise multiple logistic regression model. All tests were two-sided and *P* values of < 0.05 were considered significant. Analyses were performed using IBM SPSS statistical software (version 21; SPSS Japan Inc., Tokyo, Japan).

Table 1 Characterization of patients with post endoscopic retrograde cholangiopancreatography pancreatitis

Variables	Mild-moderate PEP	Severe PEP
Age (yr) (*n* = 121)		
Median	73.7	76.5
(range)	(18-93)	(32-88)
Gender (*n* = 121)		
Male/female	57/50	7/7
BMI (kg/m^2) (*n* = 121)		
Median	21.6	23.2
(range)	(13.97-35.20)	(14.79-29.5)
Smoking status (*n* = 121)		
Non-smoker/Ex- or current smoker	83/24	7/7
Drinking status (*n* = 121)		
Absent/present	67/40	12/2
Past history (*n* = 121)		
Absent/present	31/76	4/10
Malignant disease (*n* = 121)		
Absent/present	84/23	10/4
History of pancreatitis (*n* = 121)		
Absent/present	106/1	1/13
SOD (*n* = 121)		
Absent/present	101/6	1/13
Diverticulum nearby vater papilla (*n* = 121)		
Absent/present	70/37	11/3
CBD diameter of patient with CBD stones (*n* = 41)		
$\geqslant$ 10 mm/< 10 mm	21/16	2/2

PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; BMI: Body mass index; SOD: Sphincter of Oddi dysfunction; CBD: Common bile duct.

RESULTS

Patient characteristics in the PEP

The median age of the 121 PEP patients was 76 (18-91) years old, and there were 64 male (52.9%) and 57 female (47.1%) patients. The median BMI was 21.2 (14.0-35.2) kg/m^2. Thirty-one and 42 patients were cigarette smokers and habitual alcohol drinkers, respectively. The past medical history was heart disease in 21 patients, diabetes in 24, chronic kidney disease in 41, malignant disease in 27, and acute pancreatitis in 2. SOD was suspected in 7. Diverticulum nearby Vater papilla was noted in 40. Forty-one patients had CBD stones (Table 3).

Clinical data and ERCP intervention in the PEP

ERCP was performed urgently in 17 patients. EST and EPBD were performed in 31 and 14 patients, respectively. Pancreatography was performed in 74 patients, and residual enhancement of the pancreatic duct was noted at completion of ERCP in 41 patients. IDUS and transpalillary biopsy were performed in 26 and 35 patients, respectively. The median treatment time was 50 (12-170) min. Experts and non-experts performed ERCP in 50 and 71 patients, respectively. Abdominal pain developed within 3 h after completion of ERCP in 71 patients. The median serum amylase level, WBC count, and serum CRP on the day following ERCP

Table 2 Clinical data and endoscopic retrograde cholangiopancreatography intervention of patients with post endoscopic retrograde cholangiopancreatography pancreatitis

Variables	Mild-moderate PEP (n = 107)	Severe PEP (n = 14)
ERCP procedure		
Not emergency/emergency	91/16	13/1
EST	29	2
EPBD	12	2
Pancreatography		
No/yes	38/69	9/5
Contrast media remained in the pancreatic duct		
No/yes	75/32	5/9
IDUS		
No/yes	86/21	9/5
Transpapillary biopsies		
No/yes	76/31	10/4
Time for ERCP procedure (min)		
Median	50	56
(range)	(12-170)	(26-150)
Expertise of ERCP procedure		
Not expert/expert	62/45	9/5
Abdominal pain within three hours after ERCP		
No/yes	49/58	1/13
Serum amylase level of the next day (IU/mL)		
Median	1001	1543
(range)	(83-3604)	(258-2969)
White blood cell of the next day (/μL)		
median	8040	8790
(range)	(3240-26320)	(6270-13410)
C-reactive protein of the next day (mg/dL)		
Median	2.08	3.1
(range)	(0.04-32.55)	(0.20-38.31)

ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; EST: Endoscopic sphincterotomy; EPBD: Endoscopic papillary balloon dilation; IDUS: Intraductal ultrasonography.

were 1065 (83-3604) IU/mL, 8050 (3240-26320)/μL, and 2.1 (0.04-38.31) mg/dL, respectively (Table 4). No patients died during the study.

Risk factors of sPEP

On univariate analysis, residual enhancement of the pancreatic duct at completion of ERCP and development of abdominal pain within 3 h after completion of ERCP were significant risk factors of sPEP (Tables 3 and 4). On multivariate analysis, significant differences were noted in residual enhancement of the pancreatic duct (OR = 4.254, 95%CI: 1.238-14.616) and development of abdominal pain (OR = 11.881, 95%CI: 1.400-100.784), showing that these were independent risk factors of sPEP (Table 5).

DISCUSSION

It has been reported that the incidence of PEP in all patients examined by ERCP was about 3.5%, and PEP aggravated to a severe state (sPEP) in 0.4%[17]. Therefore, the indication of ERCP should be carefully judged. It has become possible to refrain from performing diagnostic ERCP as low-invasive examination techniques, such as MDCT, MRI, and EUS, have improved. However, ERCP is still essential as a therapeutic measure to diagnose the advancement of biliary tract malignancy and obstructive disease of the pacreaticobiliary duct, and ERCP has to be inevitably performed although there is a risk of causing PEP. There are many previous reports on risk factors of PEP, but risk factors of sPEP are unclear. Generally admitted risk factors of PEP include female gender, pancreatic sphincterotomy, difficulty in cannulation, 3 times or more applications of ERP, ERP reaching the tail of the pancreas even if it was performed once, excess contrast pressure, contrast imaging of the pancreatic acinus, brushing pancreatic juice cytology, and SOD[1-4]. These were risk factors of PEP, but not risk factors of sPEP in our study.

In our study, the residual contrast medium in the pancreatic duct at completion of ERCP was an independent risk factor of sPEP, suggesting that reduction of intraductal pressure of the pancreas at completion of ERCP may prevent sPEP, which may lead to a method to effectively avoid sPEP. Akashi *et al*[5] compared groups with and without the addition of EST and observed that the incidence of sPEP was lower in the group with EST. They hypothesized that reduction of intraductal pressure of the pancreas by the addition of EST reduced the incidence of sPEP. However, EST may accidentally perforate the digestive tract and it is contraindicated for patients treated with oral antithrombin. Thus, not all patients should be treated with EST. On the other hand, Nakahara *et al*[6] reported that when the pancreatic duct guide wire method is employed for a patient with difficult bile duct cannulation, pancreatic duct stenting should be performed even though EST was added. In addition, Ito *et al*[7] reported that preventive pancreatic duct stenting contributes to reducing the incidence of PEP, excluding IPMN patients not accompanied by pancreatic duct dilatation in the pancreatic head. The European Society of Gastrointestinal Endoscopy Guideline[18] and the American Society for Gastrointestinal Endoscopy Guideline[19] recommend pancreatic duct stenting in patients with a risk factor, and Sofuni *et al*[8] reported that the use of a spontaneous dislodgment pancreatic duct stent prevented PEP regardless of the presence or absence of a risk factor. However, the frequency of cannulation for stenting increases as a problem with preventive pancreatic duct stenting. We also consider that pancreatic duct stenting reported by many researchers[6-12,15], is an effective method to prevent PEP including sPEP, but no patients with pancreatic duct stenting were included in our study. The appropriate conditions for pancreatic duct stenting in ERCP patients have not been established, but, based on the results of our study, conduct of a large-scale clinical study on the addition of preventive EST and pancreatic duct

Table 3 Univariate analyses of characterization for severe post-endoscopic retrograde cholangiopancreatography pancreatitis

Variables	No. of patients	Median of patients (range)	Univariate analysis *P* value
Age (yr) (n = 121)		76 (18-91)	0.874
Gender (n = 121)			0.818
Male/female	64/57		
BMI (kg/m^2) (n = 121)		21.2 (14.0-35.2)	0.379
Smoking status (n = 121)			0.201
Non-smoker/Ex- or current smoker	90/31		
Drinking status (n = 121)			0.302
Absent/present	79/42		
Past history (n = 121)			0.967
Absent/present	35/86		
Malignant disease (n = 121)			0.550
Absent/present	94/27		
History of pancreatitis (n = 121)			0.606
Absent/present	119/7		
SOD (n = 121)			0.644
Absent/present	114/7		
Diverticulum nearby vater papilla (n = 121)			0.325
Absent/present	81/40		
CBD diameter of patient with CBD stones (n = 41)			0.796
⩾ 10 mm/< 10 mm	23/18		

BMI: Body mass index; SOD: Sphincter of Oddi dysfunction; CBD: Common bile duct.

Table 4 Univariate analyses of clinical data and endoscopic retrograde cholangiopancreatography intervention for post-endoscopic retrograde cholangiopancreatography pancreatitis

Variables	No. of patients (n = 121)	Median of patients (range)	Univariate analysis *P* value
ERCP procedure			0.429
Not emergency/emergency	104/17		
EST	31		0.302
EPBD	14		0.736
Pancreatography			0.798
No/yes	47/74		
Contrast media remained in the pancreatic duct			0.011
No/yes	80/41		
IDUS			0.168
No/yes	95/26		
Transpapillary biopsies			0.975
No/yes	86/35		
Time for ERCP procedure (min)		50 (12-170)	0.343
Expertise of ERCP procedure			0.65
Not expert/expert	71/50		
Abdominal pain within three hours after ERCP			0.006
No/yes	50/51		
Serum amylase level of the next day (IU/mL)		1065 (83-3604)	0.184
White blood cell of the next day (/μL)		8050 (3240-26320)	0.668
C-reactive protein of the next day (mg/dL)		2.1 (0.04-38.31)	0.601

ERCP: Endoscopic retrograde cholangiopancreatography; EST: Endoscopic Sphincterotomy; EPBD: Endoscopic papillary balloon dilation; IDUS: Intraductal ultrasonography.

Table 5 Multivariate analyses of risk factors for severe post-Endoscopic retrograde cholangiopancreatography pancreatitis

Variables	Multivariate analysis	
	Odds ratio (95%CI)	*P* value
Contrast media remained in the pancreatic duct		
No	1	
Yes	4.254 (1.238-14.616)	0.021
Abdominal pain within three hours after ERCP		
No	1	
Yes	11.881 (1.400-100.784)	0.023

ERCP: Endoscopic retrograde cholangiopancreatography.

stenting in patients with residual contrast medium in the pancreatic duct at completion of ERCP is expected.

In addition, development of abdominal pain within 3 h after completion of ERCP was a strong risk factor of sPEP. In our facility, cannulation is intended to be followed by 25-50 mg dose of rectal indomethacin only when abdominal pain exceeded restraining pain. Elmunzer *et al*[14] reported that rectal indomethacin significantly reduced the incidence of PEP in patients with a PEP risk factor. On the other hand, Levenick *et al*[13] reported that the preventive rectal indomethacin does not always inhibit PEP in all ERCP-applied cases. They mentioned that the rectal indomethacin can prevent PEP only in patients with a risk factor of PEP, and its indication should be reconsidered. Moreover, 100 mg of indomethacin is excessive for Japanese with a relatively small physique, and not all ERCP cases are treated with rectal indomethacin at our facility. Furthermore, this treatment inhibited some cases of PEP, but it did not prevent the progression to sPEP in our study. This might have been due to differences in the indication of the rectal indomethacin.

There are several limitations in this study. No diagnosis by exclusion based on the indication and intervention was established. Since it was a retrospective study performed at a single institution, the sample size was small. However, risk factors of sPEP were clarified and these may contribute to demonstrate appropriate conditions and methods to prevent sPEP. As discussed with many PEP-inhibitory methods, the addition of preventive techniques, such as EST and pancreatic duct stenting, and preventive drug administration, such as rectal indomethacin, should be performed after clarifying risk factors of sPEP.

Residual contrast medium in the pancreatic duct at completion of ERCP and development of abdominal pain within 3 h after completion of ERCP are risk factors of sPEP. The presence of these findings is an indication of therapeutic intervention for sPEP, and a method to avoid it should be considered.

COMMENTS

Background

Cholangiopancreatography pancreatitis (PEP) is an unavoidable endoscopic complication for pancreatobiliary systems. Since PEP is a predictable pathology, and if discovered and appropriately treated early many patients rapidly recover. However, some cases aggravate to a severe state and become fatal. Therefore, it is important to identify factors leading PEP to a severe state.

Research frontiers

There are many reports about risk factors of PEP; however, there are few reports to assess the risk factors of severe PEP (sPEP).

Innovations and breakthrough

Significant differences were noted in residual enhancement of the pancreatic duct and development of abdominal pain showing that these were independent risk factors of sPEP.

Applications

The presence of residual contrast medium in the pancreatic duct at completion of endoscopic retrograde cholangiopancreatography (ERCP) and development of abdominal pain within 3 h after completion of ERCP is an indication of therapeutic intervention for sPEP, and a method to avoid it should be considered.

Terminology

PEP is one of the major adverse events of ERCP. Some PEP aggravate to severe state as sPEP. sPEP sometimes results in the death, so that it has been the most concern still now.

Peer-review

This is a unique single center retrospective study with a significant number of patients investigating an important topic, the risk factors of severe PEP and clarify the indication of prophylactic treatments. The results have a clinical impact on detecting the patients in need for therapeutic intervention for preventing severe PEP; patients with residual contrast medium in the pancreatic duct at completion of ERCP and development of abdominal pain within 3 h after completion of ERCP. This is a well-written article; the manuscript is concise, clear, comprehensive, and convincing.

REFERENCES

1 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434 [PMID: 11577302 DOI: 10.1067/mge.2001.117550]

2 **Loperfido S**, Angelini G, Benedetti G, Chilovi F, Costan F, De Berardinis F, De Bernardin M, Ederle A, Fina P, Fratton A. Major early complications from diagnostic and therapeutic ERCP: a prospective multicenter study. *Gastrointest Endosc* 1998; **48**: 1-10 [PMID: 9684657 DOI: 10.1016/S0016-5107(98)70121-X]

3 **Masci E**, Toti G, Mariani A, Curioni S, Lomazzi A, Dinelli M, Minoli G, Crosta C, Comin U, Fertitta A, Prada A, Passoni GR, Testoni PA. Complications of diagnostic and therapeutic ERCP: a prospective multicenter study. *Am J Gastroenterol* 2001; **96**: 417-423 [PMID: 11232684 DOI: 10.1111/j.1572-0241.2001.03594.x]

4 **Williams EJ**, Taylor S, Fairclough P, Hamlyn A, Logan RF, Martin D, Riley SA, Veitch P, Wilkinson ML, Williamson PR, Lombard M. Risk factors for complication following ERCP; results of a large-scale, prospective multicenter study. *Endoscopy* 2007; **39**: 793-801 [PMID: 17703388 DOI: 10.1055/s-2007-966723]

5 **Akashi R**, Kiyozumi T, Tanaka T, Sakurai K, Oda Y, Sagara K. Mechanism of pancreatitis caused by ERCP. *Gastrointest Endosc* 2002; **55**: 50-54 [PMID: 11756914 DOI: 10.1067/mge.2002.118964]

6 **Nakahara K**, Okuse C, Suetani K, Michikawa Y, Kobayashi S, Otsubo T, Itoh F. Need for pancreatic stenting after sphincterotomy in patients with difficult cannulation. *World J Gastroenterol* 2014; **20**: 8617-8623 [PMID: 25024617 DOI: 10.3748/wjg.v20.i26.8617]

7 **Ito K**, Fujita N, Kanno A, Matsubayashi H, Okaniwa S, Nakahara K, Suzuki K, Enohara R. Risk factors for post-ERCP pancreatitis in high risk patients who have undergone prophylactic pancreatic duct stenting: a multicenter retrospective study. *Intern Med* 2011; **50**: 2927-2932 [PMID: 22185981 DOI: 10.2169/internalmedicine.50.6235]

8 **Sofuni A**, Maguchi H, Mukai T, Kawakami H, Irisawa A, Kubota K, Okaniwa S, Kikuyama M, Kutsumi H, Hanada K, Ueki T, Itoi T. Endoscopic pancreatic duct stents reduce the incidence of post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients. *Clin Gastroenterol Hepatol* 2011; **9**: 851-858; quiz e110 [PMID: 21749851 DOI: 10.1016/j.cgh.2011.06.033]

9 **Tarnasky PR**, Palesch YY, Cunningham JT, Mauldin PD, Cotton PB, Hawes RH.Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. *Gastroenterology* 1998; **115**: 1518-1524 [DOI: 10.1016/S0016-5085(98)70031-9]

10 **Fazel A**, Quadri A, Catalano MF, Meyerson SM, Geenen JE. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. *Gastrointest Endosc* 2003; **57**: 291-294 [PMID: 12612504 DOI: 10.1067/mge.2003.124]

11 **Harewood GC**, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. *Gastrointest Endosc* 2005; **62**: 367-370 [PMID: 16111953 DOI: 10.1016/j.gie.2005.04.020]

12 **Tsuchiya T**, Itoi T, Sofuni A, Itokawa F, Kurihara T, Ishii K, Tsuji S, Kawai T, Moriyasu F. Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center, randomized controlled trial. *J Hepatobiliary Pancreat Surg* 2007; **14**: 302-307 [PMID: 17520207 DOI: 10.1007/s00534-006-1147-8]

13 **Levenick JM**, Gordon SR, Fadden LL, Levy LC, Rockacy MJ, Hyder SM, Lacy BE, Bensen SP, Parr DD, Gardner TB. Rectal Indomethacin Does Not Prevent Post-ERCP Pancreatitis in Consecutive Patients. *Gastroenterology* 2016; **150**: 911-917; quiz e19 [PMID: 26775631 DOI: 10.1053/j.gastro.2015.12.040]

14 **Elmunzer BJ**, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, Hayward RA, Romagnuolo J, Elta GH, Sherman S, Waljee AK, Repaka A, Atkinson MR, Cote GA, Kwon RS, McHenry L, Piraka CR, Wamsteker EJ, Watkins JL, Korsnes SJ, Schmidt SE, Turner SM, Nicholson S, Fogel EL. A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. *N Engl J Med* 2012; **366**: 1414-1422 [PMID: 22494121 DOI: 10.1056/NEJMoa1111103]

15 **Takenaka M**, Fujita T, Sugiyama D, Masuda A, Shiomi H, Sugimoto M, Sanuki T, Hayakumo T, Azuma T, Kutsumi H. What is the most adapted indication of prophylactic pancreatic duct stent within the high-risk group of post-endoscopic retrograde cholangiopancreatography pancreatitis? Using the propensity score analysis. *J Hepatobiliary Pancreat Sci* 2014; **21**: 275-280 [PMID: 24039185 DOI: 10.1002/jhbp.24]

16 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]

17 **Andriulli A**, Loperfido S, Napolitano G, Niro G, Valvano MR, Spirito F, Pilotto A, Forlano R. Incidence rates of post-ERCP complications: a systematic survey of prospective studies. *Am J Gastroenterol* 2007; **102**: 1781-1788 [PMID: 17509029 DOI: 10.1111/j.1572-0241.2007.01279.x]

18 **Dumonceau JM**, Andriulli A, Deviere J, Mariani A, Rigaux J, Baron TH, Testoni PA. European Society of Gastrointestinal Endoscopy (ESGE) Guideline: prophylaxis of post-ERCP pancreatitis. *Endoscopy* 2010; **42**: 503-515 [PMID: 20506068 DOI: 10.1055/s-0029-1244208]

19 **Anderson MA**, Fisher L, Jain R, Evans JA, Appalaneni V, Ben-Menachem T, Cash BD, Decker GA, Early DS, Fanelli RD, Fisher

DA, Fukami N, Hwang JH, Ikenberry SO, Jue TL, Khan KM, Krinsky ML, Malpas PM, Maple JT, Sharaf RN, Shergill AK, Dominitz JA. Complications of ERCP. *Gastrointest Endosc* 2012; **75**: 467-473 [PMID: 22341094 DOI: 10.1016/j.gie.2011.07.010]

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ORIGINAL ARTICLE

Observational Study

Endoscopic assessment and management of sporadic duodenal adenomas: The results of single centre multidisciplinary management

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Abstract

AIM

To review the role of multidisciplinary management in treating sporadic duodenal adenomas (SDA).

METHODS

SDA managed at North Shore Hospital between 2009-2014 were entered into a prospective database. Pathology, endoscopic and surgical management as well as follow up were reviewed.

RESULTS

Twenty-eight patients (14 male: Median age 68 years) presented with SDA [18 were classified as non ampullary location (NA), 10 as ampullary location (A)]. All SDA were diagnosed on upper gastrointestinal endoscopy and were imaged with a contrast enhanced CT scan of the chest, abdomen and pelvis. Of the NA adenomas 14 were located in the second part, 2 in the first part and 2 in the third part of the duodenum. Two patients declined treatment, 3 patients underwent surgical resection (2 transduodenal resections and 1 pancreaticoduodenectomy), and 23 patients were treated with endoscopic mucosal resection (EMR). The only complication with endoscopic resection was mild pancreatitis post procedure. Patients were followed with gastroduodenoscopy for a median of 22 mo (range: 2-69 mo). There were 8 recurrences treated with EMR with one

patient proceeding to pancreaticodeuodenectomy because of high grade dysplasia in the resected specimen and 2 NA recurrences were managed with surgical resection (distal gastrectomy for a lesion in the first part of the duodenum and a transduodenal resection of a lesion in the third part of the duodenum).

CONCLUSION

SDA can be treated endoscopically with minimal morbidity and piecemeal resection results in eradication in nearly three quarters of patients. Recurrent SDA can be treated with endoscopic reresection with surgical resection indicated when the lesions are large (> 4 cm in diameter) or demonstrate severe dysplasia or invasive cancer.

Key words: Duodenal adenoma; Endoscopic resection; Surgical resection; Pancreaticoduodenectomy; Endoscopic surveillance; Dysplasia

Core tip: Sporadic duodenal adenomas can be treated endoscopically with minimal morbidity and even piecemeal resection results in eradication in nearly three quarters of patients. Optimal surveillance strategies include re-endoscopy 6 mo after the initial resection is a satisfactory starting point. Recurrent sporadic adenomas can be treated with endoscopic re-resection with surgical resection indicated when the lesions are large (> 3 cm in diameter) or demonstrate severe dysplasia or invasive cancer.

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INTRODUCTION

Sporadic duodenal adenomas (SDA) are rare lesions with a prevalence of 0.3%-1.5%[1]. Due to this rarity, the natural history of SDA is not well understood although it is known to follow an adenoma to carcinoma sequence similar to colorectal cancer[2]. The reported rate of malignant transformation of SDA ranges from 25% to 85% and this provides a rationale for preventative intervention and surveillance[2-4]. The majority of sporadic adenomas are sessile and occur in the second part of the duodenum[5,6] and can be divided into those with an ampullary location (A) or non ampullary location (NA)[1,2].

Currently there is no consensus on the optimal management of SDA and, in particular, the choice of surgical or endoscopic resection remains controversial since surgical resection involves either local resection by the transduodenal approach or by pancreaticoduodenectomy with the risk of significant morbidity and mortality. In contrast endoscopic mucosal resection (EMR) was first described in 1992 and has become increasingly favoured as the first line treatment modality[6-8].

This investigation describes the multidisciplinary management strategy for SDA as used at a single unit and involves contributions from surgery, endoscopy and gastroenterology. The specific aims of this study were to: (1) define the role of EMR of SDA; (2) define the role of whole *vs* piece meal endoscopic resection; (3) define an optimal surveillance strategy following endoscopic resection; and (4) define the optimal treatment for recurrence SDA following endoscopic resection.

MATERIALS AND METHODS

Consecutive cases of duodenal adenoma diagnosed at North Shore Hospital (NSH) between 2009 and 2014 were reviewed. The pathology findings from all patients was entered into a prospective database. Demographic, diagnostic, biopsy, treatment and follow up information was then reviewed as well as details pertaining to local recurrence rate and salvage treatments.

This project was logged with the Awhina Research and Knowledge Centre at NSH and ethics approval was obtained from the Regional Ethics Committee.

RESULTS

Thirty-four patients were diagnosed with duodenal adenomas between 2009 and 2014 of which six patients were excluded because of an underlying diagnosis of familial adenomatous polyposis. Data from 28 patients was analysed for the investigation of whom 18 were classified as NA and 10 as A.

Demographics, presentation and investigation

A summary of patient demographics, polyp morphology and investigations utilized in the management of the reported patients with SDA are presented in Table 1. All patients were New Zealand European with no Maori or Pacific Island patients presenting with SDA. Five patients (50%) with ampullary lesions presented with adenoma specific symptoms (iron deficiency anaemia 3, obstructive jaundice 2), while five (28%) of the NA patients presented with iron deficiency anaemia. The remaining patients with ampullary lesions underwent investigation for non-specific abdominal pain or following an incidental finding on ERCP for choledocolithiasis. In patients with NA upper gastrointestinal endoscopy was also undertaken for non-specific pain (4 patients), peptic ulcer disease or reflux (4 patients), and one patient each for globus, dysphagia, incidental finding during ERCP and investigation of Crohn's disease and incidentally noted raised carcino-embryonic antigen. All SDA were diagnosed on upper gastrointestinal endoscopy and were biopsied (Table 1). All patients

Table 1 Summary of patient demographics, adenoma morphology and investigations utilized *n* (%)

	Non-ampullary (*n* = 18)	Ampullary (*n* = 10)
Demographics		
Median age, yr (range)	69 (47-88)	67 (48-80)
Male: female	9:9	5:5
Morphology		
Pedunculated	3 (17)	1 (10)
Sessile	15 (83)	9 (90)
Median size, mm (range)	15 (9-24)	20 (10-35)
Number ⩾ 20 mm	7 (39)	6 (60)
Investigations		
Biopsy	7 (39)	8 (80)
EUS	3 (17)	0
ERCP	0	10 (100)

ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound.

were imaged with a contrast enhanced CT scan of the abdomen to define signs of invasion or metastases. Of the non-ampullary adenomas 14 were located in the second part of the duodenum, two in the first part and two in the third part of the duodenum. Endoscopic ultrasound (EUS) was used selectively to locoregionally stage lesions that were large, ulcerated or had high grade dysplasia on biopsy (5 of 8 ampullary adenomas and 8 of 15 non-ampullary adenomas). EUS permitted detailed assessment of lesional size and depth and location of further biopsy specimens[4,5,7].

Treatment

Patient management is summarised in Figure 1 and Table 2. All endoscopically treated patients had an EMR. All endoscopic procedures were undertaken in a specialist endoscopy suite with conscious sedation administered intravenously followed by recovery and same day discharge. Endoscopic resection was undertaken after submucosal injection of saline, epinephrine or methylene blue depending on the endoscopist's preference. The median number of endoresections per patient was 1 and was higher for ampullary (median 2.5) than non-ampullary adenomas (median 1). Endoscopic *en bloc* resection was aimed for in all cases but, due to the size of the lesions, 11 NA and 6 A underwent piecemeal resection (Table 2). The only complication of endoscopic resection was one episode of mild pancreatitis post-procedure which was self-limiting.

Once removed specimens were orientated and sent for pathological examination. Overall biopsies were concordant with final pathology in 4 of 7 NA and 7 of 8 A (Table 2).

Two non-ampullary adenomas underwent surgical resection: Two patients underwent transduodenal resection of lesions in the second and third parts of the duodenum and one patient with a large ampullary adenoma, was treated with a pancreaticoduodenectomy. In addition, two elderly patients declined any treatment.

Table 2 Summary of treatment, biopsy and final pathology and recurrence

	Non-ampullary (*n* = 18)	Ampullary (*n* = 10)
Endoscopic treatment	15	8
Stenting		
Biliary	0	2
Pancreatic	0	5
Specimen removal		
Piecemeal	11	6
En bloc	4	2
Complications	0	1
Surgical resection	2	1
No treatment	1	1
Histology		
	1 no dysplasia 13 low grade dysplasia 3 high grade dysplasia	7 low grade dysplasia 1 high grade dysplasia 1 adenocarcinoma
Concordance with biopsy	4/7	7/8
Recurrence	5	5

Surveillance

All patients had follow up gastroscopies although five patients declined follow up and one patient had undergone a pancreaticoduodenectomy (*n* = 1). The average time taken for the first endoscopic surveillance post resection was 7.9 mo for NA and 5.9 mo for A. The median follow up period was 22 mo (range 2-69 mo).

Recurrence

Details on recurrence rate in the 20 cases actively followed up are presented in Table 3 in addition to salvage therapy employed. EMR was used to treat 8 recurrences. Endoscopic ultrasound was used in two ampullary recurrences to rule out transmural invasion. One of eight patients treated with endoscopic resection was shown to be a high grade dysplastic lesion and was subsequently treated with a pancreaticoduodenectomy (final pathology T_1N_0 adenocarcinoma). Two non-ampullary recurrences were managed with surgical resection (distal gastrectomy for a lesion in the first part of the duodenum and a transduodenal resection of a lesion in the third part of the duodenum).

DISCUSSION

This investigation was undertaken to review multidisciplinary management of SDA and confirms that the majority of SDA are not symptomatic and are found incidentally[6-9]. Endoscopically SDA tend to be large, sessile and located in the second part of the duodenum[6,10-13] and this series also confirms that most SDA harbour dysplasia[14-19]. Kim *et al*[13] found that all of their 17 non ampullary adenomas were dysplastic while a larger series from Japan[14] demonstrated that dysplasia was presented in all 233 non-ampullary adenomas assessed. The rate of low grade dysplasia

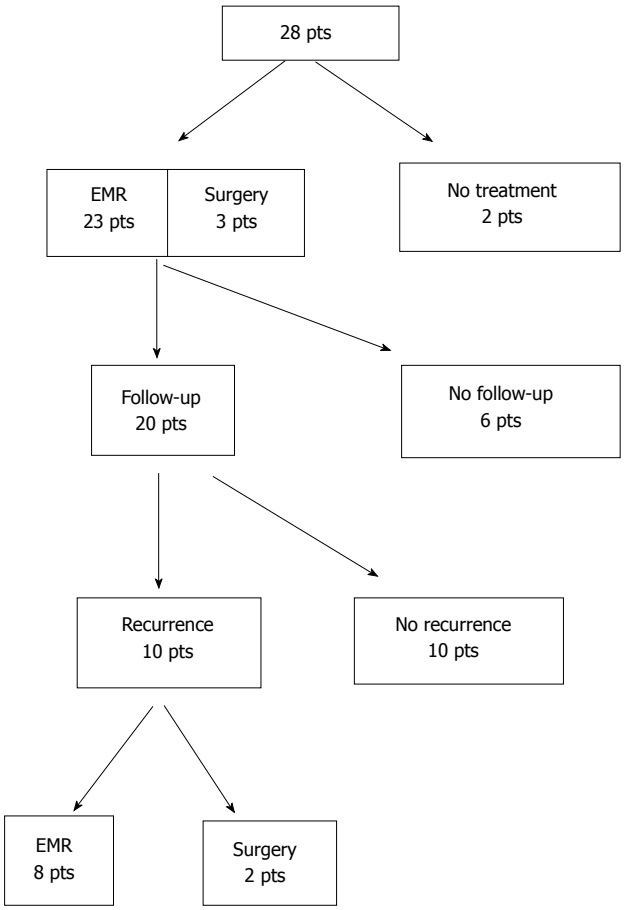

Figure 1 Summary of treatment of ampullary and non-ampullary adenomas. EMR: Endoscopic mucosal resection.

in non-ampullary adenomas in our series was 73.3%, which was within range (52%-84%) of recently published series[13-15,19], while the rate of low grade dysplasia in our ampullary adenomas (78%) was higher than 53%-66% previously reported[16-18]. The processes responsible for the high rates of dysplasia in SDA are not clear however Rubio[19] suggested that the duodenum of those patients may exhibit gastric duodenal metaplasia and bile acids and pancreatic juices may provide a milieu that encourages the metaplasia to proceed onto the adenoma-carcinoma sequence. It is possible that SDA progress to dysplasia faster than other adenomas in the gastrointestinal tract[19].

Strategy for investigations

The variable investigations performed during patient workup is a reflection of the lack of guidelines available in managing this rare entity.

Role of biopsy: There are no clear guidelines regarding the absolute need to biopsy all lesions and therefore the decision is often left to the discretion of the endoscopist. However a pre resection biopsy for SDAs may compromise a subsequent safe "lift off" technique of EMR and may increase the risk of perforation especially in the setting of a thin duodenal wall or a large duodenal

Table 3 Comparison of characteristics of recurrences (n = 10) *vs* no recurrence (n = 10)

	Recurrence (n = 10)	No recurrence (n = 10)
Non-ampullary/ ampullary	5:5	7:3
Median size (mm)	20 mm	10 mm
Treatment		
Endoscopic resection	10	8
Surgical resection	0	2
Specimen retrieval		
Piecemeal	8	6
En bloc	2	4
Margin positivity	9 (90%)	6 (60%)
Salvage therapy		
Endoscopic resection	8	
Surgical resection	2	

tumour. Moreover morphological changes after biopsy may give the false impression of submucosal infiltration of a superficial lesion[20,21]. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines suggests that all suspicious lesions should be biopsied[22]. Although biopsy concordance with final pathology is commonly around 75%, as in this investigation[23-25], and the non-concordant biopsies usually fail to sample a small focus of malignancy within the SDA particularly ampullary adenomas[26]. Elek suggests taking large, multiple biopsies (up to 6) or doing papillectomies to improve the diagnostic yield[27].

Role of EUS: We pursued a selective policy of EUS prior to resection to define invasion or pancreatic ductal involvement in large SDA that were suspicious (large size, ulceration or the presence of high grade dysplasia on biopsy)[8,27-29]. However SDA size is a variable determinant of high grade dysplasia or malignant change with authors quoting a size > 10 mm[30], > 20 mm[8,27,28,31], and > 30 mm[29]. ASGE guidelines suggest the use of EUS in lesions > 2 cm in non-ampullary and > 1 cm in ampullary adenoma[22]. Currently the role of intraductal ultrasound is not well defined. Menzel *et al*[32] suggested it was more useful than EUS in tumour diagnosis but a recent prospective study suggested that it could overstage tumours[33].

Role of ERCP: This is the least controversial investigational tool for ampullary adenomas and was performed in all our patients since it provides an accurate means of assessing ductal involvement[34-36].

Treatment

Most of the SDAs were resected endoscopically, which is in line with contemporary management[37].

Role for EMR: The factors affecting the suitability for a lesion to undergo endoscopic resection include size, presence of malignant signs, extension along the wall

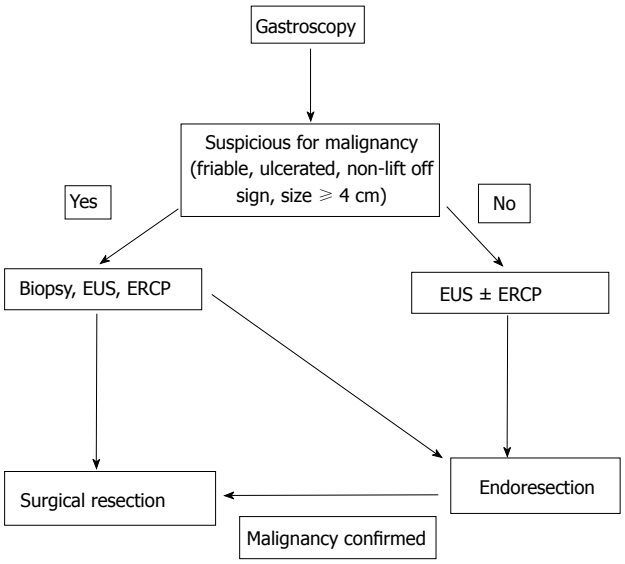

Figure 2 Management of ampullary adenomas. ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound.

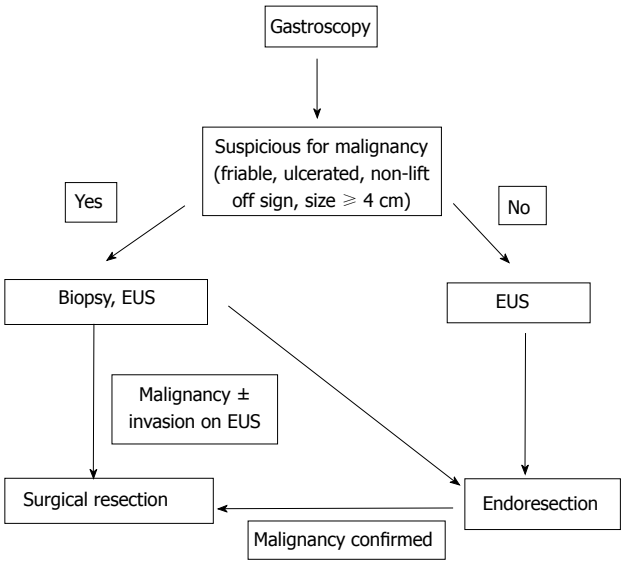

Figure 3 Management of non-ampullary adenomas. EUS: Endoscopic ultrasound.

of the duodenum and extension into biliary/pancreatic ducts[37]. There is no consensus regarding the absolute size that would make a lesion suitable for endoscopic resection although a maximum size of 4-5 cm for an endoscopic ampullectomy has been suggested, due to the increased risk of malignancy. Large adenomas can be challenging to resect *en bloc* although Irani had a success rate of 84%, with a mean lesion size of 2.4 cm[38].

There has been a significant shift with respect to size criteria for non ampullary lesions. In 2003 Perez *et al*[8] suggested that lesions more than 2 cm ought to be resected surgically. In 2009 Alexander *et al*[7] showed that lesions with mean size of 27.6 mm could be resected endoscopically. Apart from size, the physical appearance of the lesion is important. If the depressed segment is < 10 mm and non-depressed segment < 50 mm then it will be suitable for endoscopic resection and the non-lift sign is a strong sign of malignancy[39].

Role for endoscopic submucosal dissection: In our institution we have favoured EMR as a method of endoscopic resection. In general it has a success rate of 79%-100% with ability to deal with any lesion in only one session in 80%. The complication rate been quoted as 0.6% for perforation and up to 9% for non-fatal bleeding. Endoscopic submucosal dissection has recently been trialled in duodenal adenomas and electrosurgical dissection with an endoscopic knife achieves a better *en bloc* resection of the lesion[11]. However the complication rate is higher with perforation rates of 31%, 15% for post-procedural bleeding and a longer procedural duration.

***En bloc vs* piecemeal resection:** We have more commonly resorted to piecemeal resection for both types of adenoma. Ideally *en bloc* resection would allow an oncologically better resection of the tumour but this can be challenging for lesions > 2 cm[7,40]. Piecemeal resection allows tumours of larger size to be resected endoscopically with reduced risk of perforation, reduces resection time and uses less electrocautery. Unfortunately it does predispose to repeated subsequent resections[22] as there is increased risk of recurrence[7] especially when the lesion is > 20 mm[7,22].

Role of pancreatic stenting following ampullectomy: Pancreatic duct stenting has been shown to reduce the risk of post procedural pancreatitis in a prospective randomised trial[41], although the study only included 19 patients. A meta-analysis of five studies involving 481 patients showed that patients in the no stent group had a 3-fold increased risk of post-ERCP pancreatitis[42]. Our pancreatic stenting rate is only 62.5%, without however any trend towards significant pancreatitis post resection. There is no strong evidence regarding prophylactic biliary stenting, although it has a role should biliary drainage post procedure be a concern[33].

Complications

We reported a 4.3% complication rate. This was a single patient with self-limiting mild pancreatitis after a papillectomy. The rate of specific complications associated with endoscopic resections include pancreatitis (8%-15%), perforation (up to 4%), cholangitis (up to 2%), papillary stenosis (0%-8%)[22]. A recent prospective study showed a risk of minor bleeding of 18% and 6.5% for major bleeding[43]. The low rate of bleeding at our institution could be due to meticulous hemostasis being achieved once resection is completed.

Surveillance and recurrence

In our series of cases, recurrences in ampullary

adenomas occurred earlier and more often than in non ampullary SDA. The inherent risk of recurrence after endoscopic resection has been investigated separately in both subgroups of adenomas. Two series on ampullary adenomas showed a recurrence rate of 19% on follow-up[43,44] while a published case series of endoscopic resection of non-ampullary adenomas showed an average recurrence rate of 19.9%[31]. However subset analysis shows that the recurrence rate of 37% can go up to 63% if lesion of > 2 cm diameter are analysed separately[6]. Currently there is no accepted standardized follow up regime. Most commonly it is suggested that patients should have annual endoscopic follow up for first 2 years after complete resection[6], while Apel *et al*[10] suggests 3 monthly endoscopy for 1 year, increasing to 6 monthly for 2 years followed by annual endoscopy.

Best salvage therapy

A treatment plan for recurrences should be devised by all units offering endoscopic therapy of duodenal adenomas as recurrences are common, especially if there has been more than one endoresection, the lesion was large or the resection was incomplete. Unfortunately there is no consensus on the optimal salvage therapy. As more experience is being gathered with endoresection it is increasingly becoming an attractive tool to treat recurrences, often coupled with ablative therapy such as argon beam coagulation (APC). Alexander *et al*[7] noted 5 recurrences after treating 23 patients with NA by EMR, with median size of 20 mm. Those were cleared with a further session of APC ± EMR with a mean follow up of 13 mo. Similarly a series of 54 patients with non-ampullary adenomas (mean size 15 mm)[45] had 16 recurrences of which 15 were eradicated with a further session of EMR ± APC. However, the median follow up period was only 10.8 mo.

Very few series have assessed ablation therapy in isolation. Lienert *et al*[46] assessed 16 cases of NA treated with APC ± polypectomy where 3 of the 4 recurrences were successfully treated with ablative therapy. Apel *et al*[10] had assessed 18 cases of non-ampullary adenoma, with a median size of 27.5 mm, treated with a combination of serial sessions of polypectomy and APC (33 sessions) carried out over 3 wk to achieve a 55% success rate although 6 cases could not be eradicated despite multimodal endoscopic therapy.

Recently Schneider *et al*[47] addressed the role of surgery to treat recurrences after failed endoscopic treatment of ampullary adenomas. Forty-four cases were referred for transduodenal surgical ampullectomy following a median of 3 endoscopic treatments before referral. The surgical cure rate was 84% with a post-operative morbidity of 24%, the majority being mild (Clavien-Dindo grade I/II). This was comparable to morbidity associated with endoresection (8%-27%).

Proposed management algorithm

Based on this information a management algorithm for sporadic non-ampullary and ampullary adenomas is summarised in Figures 2 and 3 respectively. However, management does depend on the experience of the endoscopist (*e.g.*, with respect to size of polyp), the availability of investigative tools (*e.g.*, EUS) and the fitness of the patient to tolerate the treatment offered.

In conclusion, this investigation has confirmed that SDA can be treated endoscopically with minimal morbidity and that piecemeal resection results in eradication in nearly three quarters of patients. Optimal surveillance strategies following resection are not clearly established but re-endoscopy 6 mo after the initial resection is a satisfactory starting point. Recurrent SDA can be treated with endoscopic reresection with surgical resection indicated when the lesions are large (> 3 cm in diameter) or demonstrate severe dysplasia or invasive cancer.

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COMMENTS

Background

The optimal treatment strategy for sporadic duodenal adenomas (SDA) is not yet established although it is clear that this involves contributions from both advanced endoscopy and upper gastrointestinal surgery.

Research frontiers

Developing algorithms to accurately predict the optimal treatment (endoscopic or surgical resection) based on morphology and pathology of both primary and recurrent SDA will assist in their multidisciplinary management.

Innovations and breakthrough

Most SDA can be treated endoscopically with even piecemeal resection resulting in eradication in three quarters of patients. Surgical resection can be reserved for lesions > 4 cm in diameter or with malignant change.

Applications

With multidisciplinary review, endoscopic resection can be the primary treatment modality for SDA.

Terminology

SDA is a management challenge due to their anatomical position and the often comorbid status of patients.

Peer-review

This manuscript is interesting due to the paucity of precise international guidelines regarding the topic.

REFERENCES

1 **Jepsen JM**, Persson M, Jakobsen NO, Christiansen T, Skoubo-Kristensen E, Funch-Jensen P, Kruse A, Thommesen P. Prospective study of prevalence and endoscopic and histopathologic characteristics of duodenal polyps in patients submitted to upper endoscopy. *Scand J Gastroenterol* 1994; **29**: 483-487 [PMID: 8079103 DOI: 10.3109/00365529409092458]

2 **Seifert E**, Schulte F, Stolte M. Adenoma and carcinoma of the duodenum and papilla of Vater: a clinicopathologic study. *Am J*

Gastroenterol 1992; **87**: 37-42 [PMID: 1728122]
3 **Spigelman AD**, Talbot IC, Penna C, Nugent KP, Phillips RK, Costello C, DeCosse JJ. Evidence for adenoma-carcinoma sequence in the duodenum of patients with familial adenomatous polyposis. The Leeds Castle Polyposis Group (Upper Gastrointestinal Committee). *J Clin Pathol* 1994; **47**: 709-710 [PMID: 7962621 DOI: 10.1136/jcp.47.8.709]
4 **Hirota WK**, Zuckerman MJ, Adler DG, Davila RE, Egan J, Leighton JA, Qureshi WA, Rajan E, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO. ASGE guideline: the role of endoscopy in the surveillance of premalignant conditions of the upper GI tract. *Gastrointest Endosc* 2006; **63**: 570-580 [PMID: 16564854 DOI: 10.1016/j.gie.2006.02.004]
5 **El Hajj II**, Coté GA. Endoscopic diagnosis and management of ampullary lesions. *Gastrointest Endosc Clin N Am* 2013; **23**: 95-109 [PMID: 23168121 DOI: 10.1016/j.giec.2012.10.004]
6 **Abbass R**, Rigaux J, Al-Kawas FH. Nonampullary duodenal polyps: characteristics and endoscopic management. *Gastrointest Endosc* 2010; **71**: 754-759 [PMID: 20363416 DOI: 10.1016/j.gie.2009.11.043]
7 **Alexander S**, Bourke MJ, Williams SJ, Bailey A, Co J. EMR of large, sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome (with videos). *Gastrointest Endosc* 2009; **69**: 66-73 [PMID: 18725157 DOI: 10.1016/j.gie.2008.04.061]
8 **Perez A**, Saltzman JR, Carr-Locke DL, Brooks DC, Osteen RT, Zinner MJ, Ashley SW, Whang EE. Benign nonampullary duodenal neoplasms. *J Gastrointest Surg* 2003; **7**: 536-541 [PMID: 12763412 DOI: 10.1016/S1091-255X(02)00146-4]
9 **Takahashi T**, Ando T, Kabeshima Y, Kawakubo H, Shito M, Sugiura H, Omori T. Borderline cases between benignancy and malignancy of the duodenum diagnosed successfully by endoscopic submucosal dissection. *Scand J Gastroenterol* 2009; **44**: 1377-1383 [PMID: 19821793 DOI: 10.3109/00365520903287551]
10 **Apel D**, Jakobs R, Spiethoff A, Riemann JF. Follow-up after endoscopic snare resection of duodenal adenomas. *Endoscopy* 2005; **37**: 444-448 [PMID: 15844023 DOI: 10.1055/s-2005-861287]
11 **Honda T**, Yamamoto H, Osawa H, Yoshizawa M, Nakano H, Sunada K, Hanatsuka K, Sugano K. Endoscopic submucosal dissection for superficial duodenal neoplasms. *Dig Endosc* 2009; **21**: 270-274 [PMID: 19961529 DOI: 10.1111/j.1443-1661.2009.00908.x]
12 **Lépilliez V**, Chemaly M, Ponchon T, Napoleon B, Saurin JC. Endoscopic resection of sporadic duodenal adenomas: an efficient technique with a substantial risk of delayed bleeding. *Endoscopy* 2008; **40**: 806-810 [PMID: 18828076 DOI: 10.1055/s-2008-1077619]
13 **Kim HK**, Chung WC, Lee BI, Cho YS. Efficacy and long-term outcome of endoscopic treatment of sporadic nonampullary duodenal adenoma. *Gut Liver* 2010; **4**: 373-377 [PMID: 20981216 DOI: 10.5009/gnl.2010.4.3.373]
14 **Goda K**, Kikuchi D, Yamamoto Y, Takimoto K, Kakushima N, Morita Y, Doyama H, Gotoda T, Maehata Y, Abe N. Endoscopic diagnosis of superficial non-ampullary duodenal epithelial tumors in Japan: Multicenter case series. *Dig Endosc* 2014; **26** Suppl 2: 23-29 [PMID: 24750144 DOI: 10.1111/den.12277]
15 **Kedia P**, Brensinger C, Ginsberg G. Endoscopic predictors of successful endoluminal eradication in sporadic duodenal adenomas and its acute complications. *Gastrointest Endosc* 2010; **72**: 1297-1301 [PMID: 20970793 DOI: 10.1016/j.gie.2010.07.039]
16 **Boix J**, Lorenzo-Zúñiga V, Moreno de Vega V, Domènech E, Gassull MA. Endoscopic resection of ampullary tumors: 12-year review of 21 cases. *Surg Endosc* 2009; **23**: 45-49 [PMID: 18398649 DOI: 10.1007/s00464-008-9866-3]
17 **Jeanniard-Malet O**, Caillol F, Pesenti C, Bories E, Monges G, Giovannini M. Short-term results of 42 endoscopic ampullectomies: a single-center experience. *Scand J Gastroenterol* 2011; **46**: 1014-1019 [PMID: 21492053 DOI: 10.3109/00365521.2011.571711]
18 **Laleman W**, Verreth A, Topal B, Aerts R, Komuta M, Roskams T, Van der Merwe S, Cassiman D, Nevens F, Verslype C, Van Steenbergen W. Endoscopic resection of ampullary lesions: a single-center 8-year retrospective cohort study of 91 patients with long-term follow-up. *Surg Endosc* 2013; **27**: 3865-3876 [PMID: 23708714 DOI: 10.1007/s00464-013-2996-2]
19 **Rubio CA**. Gastric duodenal metaplasia in duodenal adenomas. *J Clin Pathol* 2007; **60**: 661-663 [PMID: 16837629 DOI: 10.1136/jcp.2006.039388]
20 **Uno Y**, Munakata A. The non-lifting sign of invasive colon cancer. *Gastrointest Endosc* 1994; **40**: 485-489 [PMID: 7926542 DOI: 10.1016/S0016-5107(94)70216-0]
21 **Han KS**, Sohn DK, Choi DH, Hong CW, Chang HJ, Lim SB, Choi HS, Jeong SY, Park JG. Prolongation of the period between biopsy and EMR can influence the nonlifting sign in endoscopically resectable colorectal cancers. *Gastrointest Endosc* 2008; **67**: 97-102 [PMID: 18155430 DOI: 10.1016/j.gie.2007.05.057]
22 **Chathadi KV**, Khashab MA, Acosta RD, Chandrasekhara V, Eloubeidi MA, Faulx AL, Fonkalsrud L, Lightdale JR, Salztman JR, Shaukat A, Wang A, Cash BD, DeWitt JM. The role of endoscopy in ampullary and duodenal adenomas. *Gastrointest Endosc* 2015; **82**: 773-781 [PMID: 26260385]
23 **Elek G**, Gyôri S, Tóth B, Pap A. Histological evaluation of preoperative biopsies from ampulla vateri. *Pathol Oncol Res* 2003; **9**: 32-41 [PMID: 12704445 DOI: 10.1007/BF03033712]
24 **Bellizzi AM**, Kahaleh M, Stelow EB. The assessment of specimens procured by endoscopic ampullectomy. *Am J Clin Pathol* 2009; **132**: 506-513 [PMID: 19762527 DOI: 10.1309/AJCPUZWJ8WA2IHBG]
25 **Rodríguez C**, Borda F, Elizalde I, Jiménez Pérez FJ, Carral D. How accurate is preoperative diagnosis by endoscopic biopsies in ampullary tumours? *Rev Esp Enferm Dig* 2002; **94**: 585-592 [PMID: 12647408]
26 **Pandolfi M**, Martino M, Gabbrielli A. Endoscopic treatment of ampullary adenomas. *JOP* 2008; **9**: 1-8 [PMID: 18182736]
27 **Ahmad NA**, Kochman ML, Long WB, Furth EE, Ginsberg GG. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. *Gastrointest Endosc* 2002; **55**: 390-396 [PMID: 11868015 DOI: 10.1067/mge.2002.121881]
28 **Min YW**, Min BH, Kim ER, Lee JH, Rhee PL, Rhee JC, Kim JJ. Efficacy and safety of endoscopic treatment for nonampullary sporadic duodenal adenomas. *Dig Dis Sci* 2013; **58**: 2926-2932 [PMID: 23695872 DOI: 10.1007/s10620-013-2708-8]
29 **Lim GJ**, Devereaux BM. EUS in the assessment of ampullary lesions prior to endoscopic resection. *Tech Gastrointest Endosc* 2010; **12**: 49-52 [DOI: 10.1016/j.tgie.2010.01.008]
30 **Baillie J**. Endoscopic ampullectomy. *Am J Gastroenterol* 2005; **100**: 2379-2381 [PMID: 16279887 DOI: 10.1111/j.1572-0241.2005.00332.x]
31 **Basford PJ**, Bhandari P. Endoscopic management of nonampullary duodenal polyps. *Therap Adv Gastroenterol* 2012; **5**: 127-138 [PMID: 22423261 DOI: 10.1177/1756283X11429590]
32 **Menzel J**, Hoepffner N, Sulkowski U, Reimer P, Heinecke A, Poremba C, Domschke W. Polypoid tumors of the major duodenal papilla: preoperative staging with intraductal US, EUS, and CT--a prospective, histopathologically controlled study. *Gastrointest Endosc* 1999; **49**: 349-357 [PMID: 10049419 DOI: 10.1016/S0016-5107(99)70012-X]
33 **Ito K**, Fujita N, Noda Y, Kobayashi G, Horaguchi J, Takasawa O, Obana T. Preoperative evaluation of ampullary neoplasm with EUS and transpapillary intraductal US: a prospective and histopathologically controlled study. *Gastrointest Endosc* 2007; **66**: 740-747 [PMID: 17905017 DOI: 10.1016/j.gie.2007.03.1081]
34 **Norton ID**, Gostout CJ, Baron TH, Geller A, Petersen BT, Wiersema MJ. Safety and outcome of endoscopic snare excision of the major duodenal papilla. *Gastrointest Endosc* 2002; **56**: 239-243 [PMID: 12145603 DOI: 10.1016/S0016-5107(02)70184-3]
35 **Catalano MF**, Linder JD, Chak A, Sivak MV, Raijman I, Geenen JE, Howell DA. Endoscopic management of adenoma of the major duodenal papilla. *Gastrointest Endosc* 2004; **59**: 225-232 [PMID: 14745396 DOI: 10.1016/S0016-5107(03)02366-6]
36 **Norton ID**, Geller A, Petersen BT, Sorbi D, Gostout CJ. Endoscopic surveillance and ablative therapy for periampullary adenomas. *Am J Gastroenterol* 2001; **96**: 101-106 [PMID: 11197237 DOI: 10.1111/j.1572-0241.2001.03358.x]
37 **Moon JH**, Choi HJ, Lee YN. Current status of endoscopic

papillectomy for ampullary tumors. *Gut Liver* 2014; **8**: 598-604 [PMID: 25368746 DOI: 10.5009/gnl14099]
38 **Irani S**, Arai A, Ayub K, Biehl T, Brandabur JJ, Dorer R, Gluck M, Jiranek G, Patterson D, Schembre D, Traverso LW, Kozarek RA. Papillectomy for ampullary neoplasm: results of a single referral center over a 10-year period. *Gastrointest Endosc* 2009; **70**: 923-932 [PMID: 19608181 DOI: 10.1016/j.gie.2009.04.015]
39 **Kahaleh M**, Shami VM, Brock A, Conaway MR, Yoshida C, Moskaluk CA, Adams RB, Tokar J, Yeaton P. Factors predictive of malignancy and endoscopic resectability in ampullary neoplasia. *Am J Gastroenterol* 2004; **99**: 2335-2339 [PMID: 15571579 DOI: 10.1111/j.1572-0241.2004.40391.x]
40 **Desilets DJ**, Dy RM, Ku PM, Hanson BL, Elton E, Mattia A, Howell DA. Endoscopic management of tumors of the major duodenal papilla: Refined techniques to improve outcome and avoid complications. *Gastrointest Endosc* 2001; **54**: 202-208 [PMID: 11474391 DOI: 10.1067/mge.2001.116564]
41 **Harewood GC**, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. *Gastrointest Endosc* 2005; **62**: 367-370 [PMID: 16111953 DOI: 10.1016/j.gie.2005.04.020]
42 **Singh P**, Das A, Isenberg G, Wong RC, Sivak MV, Agrawal D, Chak A. Does prophylactic pancreatic stent placement reduce the risk of post-ERCP acute pancreatitis? A meta-analysis of controlled trials. *Gastrointest Endosc* 2004; **60**: 544-550 [PMID: 15472676 DOI: 10.1016/S0016-5107(04)02013-9]
43 **Aschmoneit-Messer I**, Richl J, Pohl J, Ell C, May A. Prospective study of acute complication rates and associated risk factors in endoscopic therapy for duodenal adenomas. *Surg Endosc* 2015; **29**: 1823-1830 [PMID: 25380706 DOI: 10.1007/s00464-014-3871-5]
44 **Zádorová Z**, Dvofák M, Hajer J. Endoscopic therapy of benign tumors of the papilla of Vater. *Endoscopy* 2001; **33**: 345-347 [PMID: 11315897 DOI: 10.1055/s-2001-13693]
45 **Navaneethan U**, Lourdusamy D, Mehta D, Lourdusamy V, Venkatesh PG, Sanaka MR. Endoscopic resection of large sporadic non-ampullary duodenal polyps: efficacy and long-term recurrence. *Surg Endosc* 2014; **28**: 2616-2622 [PMID: 24695983 DOI: 10.1007/s00464-014-3512-z]
46 **Lienert A**, Bagshaw PF. Treatment of duodenal adenomas with endoscopic argon plasma coagulation. *ANZ J Surg* 2007; **77**: 371-373 [PMID: 17497979 DOI: 10.1111/j.1445-2197.2007.04063.x]
47 **Schneider L**, Contin P, Fritz S, Strobel O, Büchler MW, Hackert T. Surgical ampullectomy: an underestimated operation in the era of endoscopy. *HPB* (Oxford) 2016; **18**: 65-71 [PMID: 26776853 DOI: 10.1016/j.hpb.2015.07.004]

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