

World Journal of *Gastrointestinal Pharmacology and Therapeutics*

World J Gastrointest Pharmacol Ther 2020 June 9; 11(2): 8-39





Contents

Irregular Volume 11 Number 2 June 9, 2020

REVIEW

- 8 Management of gastric outlet obstruction: Focusing on endoscopic approach
Jeong SJ, Lee J

ORIGINAL ARTICLE

Case Control Study

- 17 Gastrointestinal symptoms in acromegaly: A case control study
Inayet N, Hayat J, Bano G, Poullis A

Retrospective Cohort Study

- 25 Validation of American Joint Committee on Cancer 8th edition of TNM staging in resected distal pancreatic cancer
Yin F, Saad M, Xie H, Lin J, Jackson CR, Ren B, Lawson C, Karamchandani DM, Bernabeu BQ, Jiang W, Dhir T, Zheng R, Schultz CW, Zhang D, Thomas CL, Zhang X, Lai J, Schild M, Zhang X, Liu X

ABOUT COVER

Editorial Board Member of *World Journal of Gastrointestinal Pharmacology and Therapeutics*, Bang-Shun He, PhD, Associate Professor, General Clinical Research Center, Nanjing First Hospital, Nanjing 210006, Jiangsu Province, China

AIMS AND SCOPE

The primary aim of the *World Journal of Gastrointestinal Pharmacology and Therapeutics* (WJGPT, *World J Gastrointest Pharmacol Ther*) is to provide scholars and readers from various fields of gastrointestinal pharmacology and therapeutics with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJGPT mainly publishes articles reporting research results obtained in the field of gastrointestinal pharmacology and therapeutics and covering a wide range of topics including acid-related disorders, acute infectious gastrointestinal disease, chronic noninfectious inflammatory diseases, pharmacologic therapy for hepato-biliary diseases, drug assessment, functional gastrointestinal disorders, fundamentals of gastrointestinal pharmacology, gastrointestinal motility disorders, pain management in gastrointestinal disease, pharmacologic therapy for pancreatic disorders.

INDEXING/ABSTRACTING

The WJGPT is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR
THIS ISSUE**

Responsible Electronic Editor: *Li-Li Qi*
Proofing Production Department Director: *Xiang Li*
Responsible Editorial Office Director: *Jia-Ping Yan*

NAME OF JOURNAL

World Journal of Gastrointestinal Pharmacology and Therapeutics

ISSN

ISSN 2150-5349 (online)

LAUNCH DATE

May 6, 2010

FREQUENCY

Irregular

EDITORS-IN-CHIEF

Sin-Hyog Im, Emanuele Sinagra

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/2150-5349/editorialboard.htm>

PUBLICATION DATE

June 9, 2020

COPYRIGHT

© 2020 Baishideng Publishing Group Inc

INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Management of gastric outlet obstruction: Focusing on endoscopic approach

Su Jin Jeong, Jin Lee

ORCID number: Su Jin Jeong (0000-0003-2494-9117); Jin Lee (0000-0003-2404-385X).

Author contributions: All authors equally contributed to this paper with conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: February 27, 2020

Peer-review started: February 27, 2020

First decision: April 22, 2020

Revised: May 14, 2020

Accepted: May 29, 2020

Article in press: May 29, 2020

Published online: June 9, 2020

P-Reviewer: de Melo FF, Ng QX

Su Jin Jeong, Jin Lee, Division of Gastroenterology, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Busan 48108, South Korea

Corresponding author: Jin Lee, MD, Assistant Professor, Internal Medicine, Haeundae Paik Hospital, 875, Haeun-daero, Haeundae-gu, Busan 48108, South Korea. injemed76@naver.com

Abstract

Gastric outlet obstruction (GOO) is a medical condition characterized by epigastric pain and postprandial vomiting due to mechanical obstruction. The obstructions typically involved in GOO can be benign or malignant. Peptic ulcer disease is the most common cause of benign GOO, and malignant causes include gastric cancer, lymphoma, and gastrointestinal stromal tumor. With the eradication of *Helicobacter pylori* (*H. pylori*) and the use of proton pump inhibitors, the predominant causes have changed from benign to malignant diseases. Treatment of GOO depends on the underlying cause: Proton pump inhibitors, *H. pylori* eradication, endoscopic treatments including balloon dilatation or the placement of self-expandable stents, or surgery.

Key words: Gastric outlet obstruction; Balloon dilation; Metal stent

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The causes of gastric outlet obstruction are generally divided into benign and malignant. With the eradication of *Helicobacter pylori* and the use of proton pump inhibitors, the predominant causes have changed from benign to malignant diseases. Treatment of gastric outlet obstruction (GOO) depends on the underlying cause: Proton pump inhibitor, endoscopic techniques, or surgery. In this article, we review the etiology, diagnosis, and current treatment methods of GOO, especially endoscopic techniques.

Citation: Jeong SJ, Lee J. Management of gastric outlet obstruction: Focusing on endoscopic approach. *World J Gastrointest Pharmacol Ther* 2020; 11(2): 8-16

URL: <https://www.wjgnet.com/2150-5349/full/v11/i2/8.htm>

DOI: <https://dx.doi.org/10.4292/wjgpt.v11.i2.8>

S-Editor: Wang J
L-Editor: A
E-Editor: Qi LL



INTRODUCTION

Gastric outlet obstruction (GOO) occurs when gastric emptying is mechanically inhibited by various diseases, most of which involve obstruction of the gastric pylorus or proximal duodenum due to intrinsic or extrinsic factors. The precise incidence of GOO is unknown. Although GOO due to peptic ulcers has been common in the past, the use of proton pump inhibitors and identification of *Helicobacter pylori* (*H. pylori*) have reduced the incidence of peptic ulcer disease, and malignant diseases have become the main cause of GOO in recent decades, with about 50%-80% of GOO being caused by cancer^[1-5]. As the predominant cause of GOO shifts from benign to malignant diseases, treatment methods have also changed. In this article, we review the etiology, diagnosis, and current treatment methods of GOO, especially endoscopic techniques.

ETIOLOGY

Benign gastric outlet obstruction

Peptic ulcer disease is the most common cause of benign GOO, accounting for approximately 90% of cases^[6]. Caustic ingestion, inflammatory diseases such as Crohn's disease or tuberculosis, and non-steroidal anti-inflammatory drug-induced strictures may also result in GOO. Other rare benign causes are large gastric polyps, gallstone obstruction (Bouveret's syndrome), annular pancreas, pancreatic pseudocyst, and bezoars (Table 1)^[7]. Peptic ulcer disease was the leading cause of GOO in the past, with the use of proton pump inhibitors and identification of *H. pylori*, the incidence has declined significantly. Currently, GOO is the least common complication of peptic ulcer disease. Less than 5% of complicated duodenal ulcer disease and less than 1-2% of complicated gastric ulcer disease develop obstructive complications^[8,9].

Corrosive injury caused by caustic ingestion, including acid or alkali substances, can result in GOO by antral or pyloric scarring^[10,11]. The incidence rate of GOO by caustic ingestion varies from 20 to 60%^[10-12]. In a study of 41 cases of acid ingestion, 44.4% developed GOO^[10], and another study reported that 36.8% of the 31 alkali-ingestion patients developed GOO^[11].

Inflammatory causes, such as Crohn's disease or tuberculosis, also cause GOO. Crohn's disease mostly invades the distal gastrointestinal tract, and it rarely invades the upper gastrointestinal tract such as the stomach or duodenum alone. Clinically, severe gastroduodenal Crohn's disease is rare, in which case it continuously invades the antrum, pylorus, and proximal duodenum^[13]. Gastroduodenal tuberculosis is rare, occurring in only 0.3%-2.3% of patients with tuberculosis. GOO was identified in 61% of 23 patients with gastroduodenal tuberculosis which was confirmed by histopathological examination^[14].

Nonsteroidal anti-inflammatory drugs (NSAIDs) can also cause GOO. NSAIDs reduce prostaglandin E2 to induce pyloric edema and scarring, and increase histamine release to increase gastric secretion, reduce mucosal absorption, and cause gastric motility disturbances, leading to GOO^[15]. In a study of 10 cases of NSAID-induced GOO in 2011, the most common site of involvement was the duodenum, followed by the pylorus and duodenum, and then pylorus only^[16]. Most strictures were short web-like in nature, and endoscopic balloon dilation was successful in 90% of cases.

Malignant gastric outlet obstruction

In recent decades, malignancy has been the most common cause of GOO. The most common causes are pancreatic and gastric cancer, but lymphomas, duodenal carcinoma, biliary tract carcinoma, ampullary carcinoma, and metastatic malignancies can also cause malignant GOO. In pancreatic cancer, 15%-20% of patients have been reported to develop GOO^[17].

DIAGNOSIS

The diagnosis of gastric outlet obstruction is usually suggested by history and physical examination. Patients have suffered recurrent vomiting and show up electrolyte abnormalities including hypokalemia or hypochloremic metabolic alkalosis. The gastrin secretion due to gastric expansion increases serum gastrin levels (400-800 pg/mL range) and can be confused with Zollinger-Ellison syndrome^[18]. Tests such as endoscopy, and barium study are helpful for diagnosis. Plain radiography

Table 1 Causes of gastric outlet obstruction

Benign	Malignant
Peptic ulcer disease	Gastric cancer
Caustic ingestion	Gastric lymphoma
NSAID induced stricture	Pancreas cancer
Bouveret syndrome	Duodenal cancer
Hypertrophic pyloric stenosis	Cholangiocarcinoma
Iatrogenic	Gallbladder cancer
Post-surgical scar or anastomosis stricture	Metastatic cancer
Endoscopic submucosal dissection	
Endoscopic mucosal resection	
Inflammatory causes	
Crohn's disease	
Pancreatitis	
Inflammatory polyps	
Infectious causes	
Tuberculosis gastroenteritis	
CMV gastroenteritis	
Infiltrative causes	
Eosinophilic gastroenteritis	
Amyloidosis	

NSAID: Nonsteroidal anti-inflammatory drugs; CMV: Cytomegalovirus.

may show a large gastric shadow. Contrast studies with barium or water-soluble contrast agents may show an enlarged stomach and provide clues as to the underlying disease. The absence of any contrast passage in the small intestine suggests a complete GOO. CT scan is helpful, especially for evaluating the mural thickness of the pylorus or gastric wall, lymph node enlargement, pancreatic or biliary tract, and retroperitoneum^[9].

Endoscopy is the most useful examination to establish gastric outlet obstruction and obtain tissue specimens from obstructing areas for confirmation or exclusion of malignant GOO. Endoscopy should be performed after fasting for over 4 hours, and nasogastric tube suction is recommended before endoscopy to reduce the risk of aspiration.

TREATMENT

All patients with symptomatic GOO need to be hospitalized. Fluid resuscitation with normal saline and correction of electrolyte imbalance should be performed first. Nasogastric decompression should be initiated during hospitalization. This helps relieve discomfort and pain caused by gastric distension, clear the field during endoscopic procedure, and reduce the gastric capacity before surgery. In patients with benign gastric outlet obstruction due to acute peptic ulcer disease, patients showed improvement in symptoms due to reduced edema and spasm due to inflammation after 48-72 h with nasogastric decompression and proton pump inhibitors.

H. pylori eradication can be performed in patients with benign GOO with *H. pylori* infection. The prevalence of *H. pylori* in GOO varies from 33% to 90%^[19]. Kate *et al*^[20] reported a high prevalence of *H. pylori* infection in duodenal ulcers with GOO, even without active ulcers. Acute ulcers associated with *H. pylori* infection cause obstruction due to inflammation and edema, and antimicrobial treatment can help improve occlusion. Mohsina *et al*^[21] summarized reports on the role of *H. pylori* in GOO.

If GOO is irreversible with medical therapy, definitive treatment is required based upon the underlying cause (Table 2). Until the development of endoscopic procedures, surgery was the only treatment for these patients. In the past, 80%-90% of ulcer related GOO patients underwent surgery^[22], and the only treatment option for caustic GOO patients was surgery as well^[12]. Recent reports suggest that endoscopic balloon dilation is an effective treatment option, as an alternative to surgery in the

majority of peptic ulcer disease-related and caustic GOO patients^[23-31]. In benign GOO, intraluminal stent insertion is a poor treatment option. There are no commercial stents available for benign GOO, and if uncovered stents are used, stent removal is impossible, and long-term patency is not guaranteed, and stent migration occurs frequently when covered stents are used. On the other hand, if curative surgery is not possible in malignant GOO, there are palliative options such as endoscopic placement of self-expanding metal stents (SEMS), and bypass surgery such as gastrojejunostomy. Surgical gastrojejunostomy for palliative purposes has a high mortality of up to 10%^[32], and previous reports have shown that palliative SEMS insertion is more cost-effective, reduces the number of days of hospitalization, and improves symptoms rapidly^[33,34]. Endoscopic SEMS insertion is widely performed in malignant GOO.

ENDOSCOPIC MANAGEMENT

Endoscopic balloon dilation

Benjamin *et al*^[35,36] first reported the use of endoscopic balloon dilation (EBD) of the pylorus for the treatment of GOO using a through-the-scope 5-mm balloon with good clinical outcome. Subsequent reports have shown the safety and effectiveness of EBD for GOO management^[23-31]. Dilations can be performed with endoscopy and using balloon dilators inserted through the working channel of the endoscope, or using balloons placed over a guidewire under fluoroscopic guidance. If adequate dilation is achieved, the clinical response is maintained in 70%-80% of patients^[25,30]. Repeated recurrence of stricture after EBD may be an indication of surgery. If more than two sessions of dilations are required, they are highly associated with the probability of surgery^[28].

EBD may also be effective for GOO caused by caustic injury or endoscopic submucosal pylorus dissection^[37,38]. In a single-center study published by Kochhar *et al*^[39] recently, EBD had a clinical success of 97.3% and no recurrence during a 98-month follow-up period. Perforation occurred in 2 of 111 patients. However, the mean number of sessions was 2-13 times in caustic GOO, while only 1-3 times in PUD-induced GOO^[27,38]. GOO caused by other causes, such as Crohn's disease and tuberculosis, may also benefit with EBD^[26,40].

EBD is generally a safe procedure, with complications of bleeding and perforation in diameters less than 15 mm rare. Perforation occurred more often when the diameter was over 15 mm^[7,24,41,42]. Pain and minor bleeding are common during EBD procedures, but they are self-limited, whereas arterial bleeding is rarely reported^[40].

Intralesional steroids

A combination of balloon dilation and intralesional steroid injection could be performed to inhibit stricture formation. Triamcinolone blocks the cross-linking of collagen and prevents scar contracture^[43]. There are few reports on the treatment of pyloric strictures with intralesional steroids. Kochhar *et al*^[44] and Lee *et al*^[45] reported the efficacy of intralesional steroids.

Endoscopic incision

Endoscopic incision could be further performed after endoscopic balloon dilation in pyloric stenosis refractory to EBD. Boron *et al*^[46] reported an electrosurgical incision using sphincterotomy, and Hagiwara *et al*^[47] used a needle-knife radial electrosurgical incision in refractory anastomotic pyloric stenosis.

Endoscopic placement of self-expanding metal stents

SEMS insertion is used as a palliative treatment for malignant GOO and is used in cases of malignant gastrointestinal obstruction that cannot be surgically treated. The goal of SEMS insertion is to relieve obstruction symptoms. To evaluate the degree of symptom relief, the GOO score, which evaluates the severity of symptoms defined as satiety, nausea, and early vomiting, scoring based on the patient's oral intake level^[48].

Generally, the technical and clinical success rates are reported to be 89%-98% and 86%-89%, respectively, which is very good in terms of short-term success rates^[49-52]. SEMS insertions should be considered in patients with a short life expectancy (less than 2-6 mo)^[53]. In addition, there should be no other occlusion site in the distal part of the stent insertion site, and the presence of free perforation or peritonitis are contraindications to endoscopic stent placement^[54].

In malignant GOOs, biliary obstruction is often coexistent. Placement of the biliary metal stent should be considered before insertion of the duodenal stent. Since the endoscopic approach to the biliary tract is very limited after the duodenal stent is inserted, the percutaneous transhepatic approach is usually required^[54].

Table 2 Treatment of gastric outlet obstruction based upon the underlying cause

Underlying cause	Treatment
Benign	
Peptic ulcer disease	PPI ± HPE (1 st option) EBD or surgery (2 nd option)
Crohn disease	Corticosteroid (1 st option) EBD or surgery (2 nd option)
Caustic ingestion	EBD or surgery
Bouveret syndrome	Surgery or endoscopic removal
Large gastric polyp	Endoscopic resection
Malignant	
Palliative	Endoscopic stent (covered or uncovered) EUS-guided gastroenterostomy Surgical resection, surgical bypass (gastrojejunostomy) Radiation therapy
Curative	Surgery Chemotherapy (for lymphoma)

PPI: Proton pump inhibitor; HPE: Helicobacter pylori eradication; EBD: Endoscopic balloon dilatation; EUS: Endoscopic ultrasound.

Covered versus uncovered SEMS: Uncovered stents are widely used for the treatment of malignant GOO. It is less likely to migrate and more flexible, but the tumor can grow into the stent and result in stent obstruction. Covered stents are increasingly used in Europe because they provide the advantage of low tumor growth. However, they are more prone to migration and less flexible than uncovered stents^[55,56]. According to Kim *et al*^[57] stent migration rate was much higher in covered stents than in uncovered stents (28% *vs* 3%) within 8 weeks of stent insertion.

According to a systematic review by Yang *et al*^[58], there were no significant differences in technical or clinical success rate, long-term patency, or complications in three meta-analyses, in which comparison of efficacy and safety between covered or uncovered SEMS for malignant GOO were assessed.

Currently uncovered SEMS, rather than fully or partially covered stents, have been shown to be a standard treatment for managing malignant GOO, with low migration rates and better bile outflow^[55,56,59]. Tumor ingrowth/overgrowth has been reported in 17.2% of patients receiving bare metal stents and in 6.9% of patients with covered stents^[60,61]. This stent obstruction can be managed with a stent-in-stent technique, and stent occlusion rate was reported to be 10%-34% after the secondary SEMS insertion^[62,63]. The development of stents to compensate for the shortcomings of the existing stents continues, and recent new covered stents with anti-migration designs have been suggested to be superior in terms of stent patency and complications^[64].

SEMS *vs* surgery: The comparison of the effects and safety of surgical methods and endoscopic stents as palliative treatment for malignant GOO have been presented in various studies. Compared to surgery, the advantages of endoscopic stents are; shorter procedure time, less time to ingestion, and shorter hospitalization periods, but repeated procedures are often required due to frequent stent failures^[65-67]. According to one systematic study, patients treated with enteral stents showed shorter hospitalization periods (average 12 d) and faster oral intake (average 7 d) than those treated with gastrojejunostomy, and there was no significant difference in mortality, overall complications, and survival rates^[68]. Most studies have shown that there is no difference between both treatments in technical or clinical success rate of the procedure, but one meta-analysis reported that the success rate was higher in stent placement patients^[69,70]. There was no difference in the frequency of mild and severe complications in the early stage of complications after SEMS insertion or surgery, but it is known that the time of severe complications in the late stage is relatively earlier and more common in stent patients^[71]. Nevertheless, there was no difference in stent insertion or surgery-related mortality^[72]. In larger randomized trials with longer follow-up, late complications including recurrent obstruction and need for reoperation were more common in SEMS than gastrojejunostomy, which confirms the previous retrospective study, which reported that gastrojejunostomy surgery has more benefits and is associated with a longer life expectancy^[70,73,74].

Endoscopic ultrasound-guided gastroenterostomy

Endoscopic ultrasound-guided gastroenterostomy (EUS-GE) using lumen-apposing metal stents has emerged as a safe and effective alternative method. EUS-GE can allow sustained palliation of surgical bypass while maintaining a minimally invasive endoscopic approach^[75,76]. EUS-GE was first described by Binmoeller *et al*^[77] in 2012, and has shown significant efficacy in palliating malignant GOO in patients who are suitable for surgical bypass^[78]. In EUS-GE, a bypass is created by inserting a lumen-apposing metal stent from the stomach to the small bowel distal to the obstruction under EUS and fluoroscopic guidance.

EUS-GE can be used for palliative management of malignant GOO and can be a treatment option for benign GOO. Two recent case studies showed high technical (90%-92%) and clinical (85%-92%) success rates, with a variable percentage of adverse events (0-11.5%)^[79,80]. Tyberg *et al*^[79] showed there were fewer side effects (12% *vs* 41%) and similar technical success (88% *vs* 100%) with EUS-GE compared to surgical laparoscopic gastrojejunostomy. A retrospective study in 2020 by James *et al*^[81] reported EUS-GE as a bridge therapy for definitive treatment of benign gastric outlet obstruction. EUS-GE was performed in 22 patients with benign GOO, and 83.3% of patients were prevented from surgery. Lumen-apposing metal stents was maintained for a mean of 8.5 mo until GOO was resolved, and the low recurrence rate of GOO (5.6%) has been reported after lumen-apposing metal stents removal. Future prospective, large-scale, randomized studies comparing surgical gastroenterostomy and EUS-GE are needed.

SURGERY

Surgery is the preferred method of treatment in patients with refractory GOO, or for whom endoscopic treatment has not been indicated. In the past, open gastrojejunostomy was widely performed, but recently laparoscopic gastrojejunostomy has become the main treatment. The laparoscopic surgical approach is more effective than open surgery for rapid postoperative recovery and is associated with a shorter hospital stay^[82].

CONCLUSION

With the eradication of *H. pylori* and the use of proton pump inhibitors, the predominant causes of GOO have changed from benign to malignant diseases. Treatment of GOO depends on the underlying cause, and multiple treatment methods exist, including both endoscopic and surgical approaches. Therefore, determining the appropriate treatment for individual patients is important for treatment success and prognosis.

REFERENCES

- 1 Johnson CD. Gastric outlet obstruction malignant until proved otherwise. *Am J Gastroenterol* 1995; **90**: 1740 [PMID: 7572886]
- 2 Khullar SK, DiSario JA. Gastric outlet obstruction. *Gastrointest Endosc Clin N Am* 1996; **6**: 585-603 [PMID: 8803569 DOI: 10.1016/S1052-5157(18)30356-8]
- 3 Johnson CD, Ellis H. Gastric outlet obstruction now predicts malignancy. *Br J Surg* 1990; **77**: 1023-1024 [PMID: 2207566 DOI: 10.1002/bjs.1800770923]
- 4 Chowdhury A, Dhali GK, Banerjee PK. Etiology of gastric outlet obstruction. *Am J Gastroenterol* 1996; **91**: 1679 [PMID: 8759707]
- 5 Shone DN, Nikoomeanesh P, Smith-Meek MM, Bender JS. Malignancy is the most common cause of gastric outlet obstruction in the era of H2 blockers. *Am J Gastroenterol* 1995; **90**: 1769-1770 [PMID: 7572891]
- 6 Tringali A, Giannetti A, Adler DG. Endoscopic management of gastric outlet obstruction disease. *Ann Gastroenterol* 2019; **32**: 330-337 [PMID: 31263354 DOI: 10.20524/aog.2019.0390]
- 7 Kochhar R, Kochhar S. Endoscopic balloon dilation for benign gastric outlet obstruction in adults. *World J Gastrointest Endosc* 2010; **2**: 29-35 [PMID: 21160676 DOI: 10.4253/wjge.v2.i1.29]
- 8 Paimela H, Tuompo PK, Peräkylä T, Saario I, Höckerstedt K, Kivilaakso E. Peptic ulcer surgery during the H2-receptor antagonist era: a population-based epidemiological study of ulcer surgery in Helsinki from 1972 to 1987. *Br J Surg* 1991; **78**: 28-31 [PMID: 1671826 DOI: 10.1002/bjs.1800780110]
- 9 Ferzoco SJ, Soybel D. Gastric outlet obstruction, perforation and other complications of gastroduodenal ulcer. In: Gastric outlet obstruction, perforation and other complications of gastroduodenal ulcer. Therapy of digestive disorders: Elsevier Inc., 2006: 357-372 [DOI: 10.1016/b978-1-4160-0317-5.50028-5]
- 10 Zargar SA, Kochhar R, Nagi B, Mehta S, Mehta SK. Ingestion of corrosive acids. Spectrum of injury to upper gastrointestinal tract and natural history. *Gastroenterology* 1989; **97**: 702-707 [PMID: 2753330 DOI: 10.1016/0016-5085(89)90641-0]
- 11 Zargar SA, Kochhar R, Nagi B, Mehta S, Mehta SK. Ingestion of strong corrosive alkalis: spectrum of injury to upper gastrointestinal tract and natural history. *Am J Gastroenterol* 1992; **87**: 337-341 [PMID: 1311111 DOI: 10.1016/0016-5085(92)90641-0]

- 1539568]
- 12 **Chaudhary A**, Puri AS, Dhar P, Reddy P, Sachdev A, Lahoti D, Kumar N, Broor SL. Elective surgery for corrosive-induced gastric injury. *World J Surg* 1996; **20**: 703-706; discussion 706 [PMID: 8662156 DOI: 10.1007/s002689900107]
 - 13 **Nugent FW**, Roy MA. Duodenal Crohn's disease: an analysis of 89 cases. *Am J Gastroenterol* 1989; **84**: 249-254 [PMID: 2919581]
 - 14 **Miner PB**, Harri JE, McPhee MS. Intermittent gastric outlet obstruction from a pedunculated gastric polyp. *Gastrointest Endosc* 1982; **28**: 219-220 [PMID: 7129059 DOI: 10.1016/s0016-5107(82)73075-5]
 - 15 **Goldman G**, Tiomny E, Kahn PJ, Somjen D, Halpern Z, Gilat T, Wiznitzer T. Prostaglandin E2 in pyloric stenosis. *Arch Surg* 1989; **124**: 724-726 [PMID: 2730327 DOI: 10.1001/archsurg.1989.01410060096020]
 - 16 **Noor MT**, Dixit P, Kochhar R, Nagi B, Dutta U, Singh K, Poornachandra KS. NSAIDs-Related Pyloroduodenal Obstruction and Its Endoscopic Management. *Diagn Ther Endosc* 2011; **2011**: 967957 [PMID: 21747657 DOI: 10.1155/2011/967957]
 - 17 **Lopera JE**, Brazzini A, Gonzales A, Castaneda-Zuniga WR. Gastroduodenal stent placement: current status. *Radiographics* 2004; **24**: 1561-1573 [PMID: 15537965 DOI: 10.1148/rg.246045033]
 - 18 **Appasani S**, Kochhar S, Nagi B, Gupta V, Kochhar R. Benign gastric outlet obstruction--spectrum and management. *Trop Gastroenterol* 2011; **32**: 259-266 [PMID: 22696905]
 - 19 **Gisbert JP**, Pajares JM. Review article: Helicobacter pylori infection and gastric outlet obstruction - prevalence of the infection and role of antimicrobial treatment. *Aliment Pharmacol Ther* 2002; **16**: 1203-1208 [PMID: 12144568 DOI: 10.1046/j.1365-2036.2002.01275.x]
 - 20 **Kate V**, Ananthakrishnan N, Badrinath S, Amarnath SK, Ratnakar C. Helicobacter pylori infection in duodenal ulcer with gastric outlet obstruction. *Trop Gastroenterol* 1998; **19**: 75-77 [PMID: 9752759]
 - 21 **Mohsina S**, Muthusami A, Shankar G, Sureshkumar S, Kate V. Helicobacter pylori eradication in complicated peptic ulcer: Beneficial in most? *Int J Adv Med Health Res* 2016; **3**: 58 [DOI: 10.4103/2349-4220.195947]
 - 22 **Weiland D**, Dunn DH, Humphrey EW, Schwartz ML. Gastric outlet obstruction in peptic ulcer disease: an indication for surgery. *Am J Surg* 1982; **143**: 90-93 [PMID: 7053661 DOI: 10.1016/0002-9610(82)90135-0]
 - 23 **Lau JY**, Chung SC, Sung JJ, Chan AC, Ng EK, Suen RC, Li AK. Through-the-scope balloon dilation for pyloric stenosis: long-term results. *Gastrointest Endosc* 1996; **43**: 98-101 [PMID: 8635729 DOI: 10.1016/s0016-5107(06)80107-0]
 - 24 **Boylan JJ**, Gradzka MI. Long-term results of endoscopic balloon dilatation for gastric outlet obstruction. *Dig Dis Sci* 1999; **44**: 1883-1886 [PMID: 10505729 DOI: 10.1023/a:1018807125952]
 - 25 **Solt J**, Bajor J, Szabó M, Horváth OP. Long-term results of balloon catheter dilation for benign gastric outlet stenosis. *Endoscopy* 2003; **35**: 490-495 [PMID: 12783346 DOI: 10.1055/s-2003-39664]
 - 26 **Misra SP**, Dwivedi M. Long-term follow-up of patients undergoing balloon dilation for benign pyloric stenoses. *Endoscopy* 1996; **28**: 552-554 [PMID: 8911802 DOI: 10.1055/s-2007-1005553]
 - 27 **Kochhar R**, Sethy PK, Nagi B, Wig JD. Endoscopic balloon dilatation of benign gastric outlet obstruction. *J Gastroenterol Hepatol* 2004; **19**: 418-422 [PMID: 15012779 DOI: 10.1111/j.1440-1746.2003.03283.x]
 - 28 **Perng CL**, Lin HJ, Lo WC, Lai CR, Guo WS, Lee SD. Characteristics of patients with benign gastric outlet obstruction requiring surgery after endoscopic balloon dilation. *Am J Gastroenterol* 1996; **91**: 987-990 [PMID: 8633593]
 - 29 **Cherian PT**, Cherian S, Singh P. Long-term follow-up of patients with gastric outlet obstruction related to peptic ulcer disease treated with endoscopic balloon dilatation and drug therapy. *Gastrointest Endosc* 2007; **66**: 491-497 [PMID: 17640640 DOI: 10.1016/j.gie.2006.11.016]
 - 30 **Kozarek RA**, Botoman VA, Patterson DJ. Long-term follow-up in patients who have undergone balloon dilation for gastric outlet obstruction. *Gastrointest Endosc* 1990; **36**: 558-561 [PMID: 2279642 DOI: 10.1016/s0016-5107(90)71163-7]
 - 31 **Kuwada SK**, Alexander GL. Long-term outcome of endoscopic dilation of nonmalignant pyloric stenosis. *Gastrointest Endosc* 1995; **41**: 15-17 [PMID: 7698619 DOI: 10.1016/s0016-5107(95)70270-9]
 - 32 **Weaver DW**, Wiencek RG, Bouwman DL, Walt AJ. Gastrojejunostomy: is it helpful for patients with pancreatic cancer? *Surgery* 1987; **102**: 608-613 [PMID: 2443991]
 - 33 **Chandrasegaram MD**, Eslick GD, Mansfield CO, Liem H, Richardson M, Ahmed S, Cox MR. Endoscopic stenting versus operative gastrojejunostomy for malignant gastric outlet obstruction. *Surg Endosc* 2012; **26**: 323-329 [PMID: 21898024 DOI: 10.1007/s00464-011-1870-3]
 - 34 **Jeurnink SM**, Polinder S, Steyerberg EW, Kuipers EJ, Siersema PD. Cost comparison of gastrojejunostomy versus duodenal stent placement for malignant gastric outlet obstruction. *J Gastroenterol* 2010; **45**: 537-543 [PMID: 20033227 DOI: 10.1007/s00535-009-0181-0]
 - 35 **Benjamin SB**. Balloon dilation of the pylorus: therapy for gastric outlet obstruction. *Gastrointest Endosc* 1982; **28**: 253-255 [DOI: 10.1016/s0016-5107(82)73105-0]
 - 36 **Benjamin SB**, Glass RL, Cattau EL Jr, Miller WB. Preliminary experience with balloon dilation of the pylorus. *Gastrointest Endosc* 1984; **30**: 93-95 [PMID: 6714610 DOI: 10.1016/s0016-5107(84)72329-7]
 - 37 **Coda S**, Oda I, Gotoda T, Yokoi C, Kikuchi T, Ono H. Risk factors for cardiac and pyloric stenosis after endoscopic submucosal dissection, and efficacy of endoscopic balloon dilation treatment. *Endoscopy* 2009; **41**: 421-426 [PMID: 19418396 DOI: 10.1055/s-0029-1214642]
 - 38 **Kochhar R**, Dutta U, Sethy PK, Singh G, Sinha SK, Nagi B, Wig JD, Singh K. Endoscopic balloon dilation in caustic-induced chronic gastric outlet obstruction. *Gastrointest Endosc* 2009; **69**: 800-805 [PMID: 19136104 DOI: 10.1016/j.gie.2008.05.056]
 - 39 **Kochhar R**, Malik S, Reddy YR, Mallick B, Dhaka N, Gupta P, Sinha SK, Manrai M, Kochhar S, Wig JD, Gupta V. Endoscopic balloon dilatation is an effective management strategy for caustic-induced gastric outlet obstruction: a 15-year single center experience. *Endosc Int Open* 2019; **7**: E53-E61 [PMID: 30648140 DOI: 10.1055/a-0655-2057]
 - 40 **Kim JH**, Shin JH, Di ZH, Ko GY, Yoon HK, Sung KB, Song HY. Benign duodenal strictures: treatment by means of fluoroscopically guided balloon dilation. *J Vasc Interv Radiol* 2005; **16**: 543-548 [PMID: 15802456 DOI: 10.1097/01.RVI.0000150033.13928.D4]
 - 41 **DiSario JA**, Fennerty MB, Tietze CC, Hutson WR, Burt RW. Endoscopic balloon dilation for ulcer-induced gastric outlet obstruction. *Am J Gastroenterol* 1994; **89**: 868-871 [PMID: 8198096]
 - 42 **Lam YH**, Lau JY, Fung TM, Ng EK, Wong SK, Sung JJ, Chung SS. Endoscopic balloon dilation for benign gastric outlet obstruction with or without Helicobacter pylori infection. *Gastrointest Endosc* 2004; **60**: 229-233 [PMID: 15278050 DOI: 10.1016/s0016-5107(04)01569-x]
 - 43 **Ketchum LD**, Smith J, Robinson DW, Masters FW. The treatment of hypertrophic scar, keloid and scar

- contracture by triamcinolone acetonide. *Plast Reconstr Surg* 1966; **38**: 209-218 [PMID: 5919604 DOI: 10.1097/00006534-196609000-00005]
- 44 **Kochhar R**, Sriram PV, Ray JD, Kumar S, Nagi B, Singh K. Intralesional steroid injections for corrosive induced pyloric stenosis. *Endoscopy* 1998; **30**: 734-736 [PMID: 9865568 DOI: 10.1055/s-2007-1001400]
- 45 **Lee M**, Kubik CM, Polhamus CD, Brady CE, Kadakia SC. Preliminary experience with endoscopic intralesional steroid injection therapy for refractory upper gastrointestinal strictures. *Gastrointest Endosc* 1995; **41**: 598-601 [PMID: 7672557 DOI: 10.1016/s0016-5107(95)70199-0]
- 46 **Boron B**, Gross KR. Successful dilatation of pyloric stricture resistant to balloon dilatation with electrocautery using a sphinctertome. *J Clin Gastroenterol* 1996; **23**: 239-241 [PMID: 8899513 DOI: 10.1097/00004836-199610000-00020]
- 47 **Hagiwara A**, Sonoyama Y, Togawa T, Yamasaki J, Sakakura C, Yamagishi H. Combined use of electrosurgical incisions and balloon dilatation for the treatment of refractory postoperative pyloric stenosis. *Gastrointest Endosc* 2001; **53**: 504-508 [PMID: 11275897 DOI: 10.1067/mge.2001.113281]
- 48 **Adler DG**, Baron TH. Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: experience in 36 patients. *Am J Gastroenterol* 2002; **97**: 72-78 [PMID: 11808972 DOI: 10.1111/j.1572-0241.2002.05423.x]
- 49 **van den Berg MW**, Haijink S, Fockens P, Vleggaar FP, Dijkgraaf MG, Siersema PD, van Hooft JE. First data on the Evolution duodenal stent for palliation of malignant gastric outlet obstruction (DUOLUTION study): a prospective multicenter study. *Endoscopy* 2013; **45**: 174-181 [PMID: 23348890 DOI: 10.1055/s-0032-1326077]
- 50 **Dormann A**, Meisner S, Verin N, Wenk Lang A. Self-expanding metal stents for gastroduodenal malignancies: systematic review of their clinical effectiveness. *Endoscopy* 2004; **36**: 543-550 [PMID: 15202052 DOI: 10.1055/s-2004-814434]
- 51 **Mansoor H**, Yusuf MA. Outcomes of endoscopic pyloric stenting in malignant gastric outlet obstruction: a retrospective study. *BMC Res Notes* 2013; **6**: 280 [PMID: 23870091 DOI: 10.1186/1756-0500-6-280]
- 52 **Lee JE**, Lee K, Hong YS, Kim ER, Lee H, Min BH. Impact of Carcinomatosis on Clinical Outcomes after Self-Expandable Metallic Stent Placement for Malignant Gastric Outlet Obstruction. *PLoS One* 2015; **10**: e0140648 [PMID: 26465920 DOI: 10.1371/journal.pone.0140648]
- 53 **Jeurnink SM**, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, Kuipers EJ, Siersema PD; Dutch SUSTENT Study Group. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. *Gastrointest Endosc* 2010; **71**: 490-499 [PMID: 20003966 DOI: 10.1016/j.gie.2009.09.042]
- 54 **Baron TH**, Harewood GC. Enteral self-expandable stents. *Gastrointest Endosc* 2003; **58**: 421-433 [PMID: 14528223 DOI: 10.1067/s0016-5107(03)00023-3]
- 55 **Woo SM**, Kim DH, Lee WJ, Park KW, Park SJ, Han SS, Kim TH, Koh YH, Kim HB, Hong EK. Comparison of uncovered and covered stents for the treatment of malignant duodenal obstruction caused by pancreaticobiliary cancer. *Surg Endosc* 2013; **27**: 2031-2039 [PMID: 23288317 DOI: 10.1007/s00464-012-2705-6]
- 56 **van den Berg MW**, Walter D, Vleggaar FP, Siersema PD, Fockens P, van Hooft JE. High proximal migration rate of a partially covered "big cup" duodenal stent in patients with malignant gastric outlet obstruction. *Endoscopy* 2014; **46**: 158-161 [PMID: 24338240 DOI: 10.1055/s-0033-1359023]
- 57 **Kim CG**, Choi JJ, Lee JY, Cho SJ, Park SR, Lee JH, Ryu KW, Kim YW, Park YL. Covered versus uncovered self-expandable metallic stents for palliation of malignant pyloric obstruction in gastric cancer patients: a randomized, prospective study. *Gastrointest Endosc* 2010; **72**: 25-32 [PMID: 20381802 DOI: 10.1016/j.gie.2010.01.039]
- 58 **Yang Z**, Wu Q, Wang F, Ye X, Qi X, Fan D. A systematic review and meta-analysis of randomized trials and prospective studies comparing covered and bare self-expandable metal stents for the treatment of malignant obstruction in the digestive tract. *Int J Med Sci* 2013; **10**: 825-835 [PMID: 23794946 DOI: 10.7150/ijms.5969]
- 59 **Hamada T**, Hakuta R, Takahara N, Sasaki T, Nakai Y, Isayama H, Koike K. Covered versus uncovered metal stents for malignant gastric outlet obstruction: Systematic review and meta-analysis. *Dig Endosc* 2017; **29**: 259-271 [PMID: 27997723 DOI: 10.1111/den.12786]
- 60 **Song HY**, Shin JH, Yoon CJ, Lee GH, Kim TW, Lee SK, Yook JH, Kim BS. A dual expandable nitinol stent: experience in 102 patients with malignant gastroduodenal strictures. *J Vasc Interv Radiol* 2004; **15**: 1443-1449 [PMID: 15590803 DOI: 10.1097/01.RVI.0000142594.31221.AF]
- 61 **Jang JK**, Song HY, Kim JH, Song M, Park JH, Kim EY. Tumor overgrowth after expandable metallic stent placement: experience in 583 patients with malignant gastroduodenal obstruction. *AJR Am J Roentgenol* 2011; **196**: W831-W836 [PMID: 21606277 DOI: 10.2214/AJR.10.5861]
- 62 **Sasaki T**, Isayama H, Nakai Y, Takahara N, Hamada T, Mizuno S, Mohri D, Yagioka H, Kogure H, Arizumi T, Togawa O, Matsubara S, Ito Y, Yamamoto N, Sasahira N, Hirano K, Toda N, Tada M, Koike K. Clinical outcomes of secondary gastroduodenal self-expandable metallic stent placement by stent-in-stent technique for malignant gastric outlet obstruction. *Dig Endosc* 2015; **27**: 37-43 [PMID: 24995858 DOI: 10.1111/den.12321]
- 63 **Kim CG**, Choi JJ, Lee JY, Cho SJ, Kim SJ, Kim MJ, Park SR, Park YL. Outcomes of second self-expandable metallic stent insertion for malignant gastric outlet obstruction. *Surg Endosc* 2014; **28**: 281-288 [PMID: 24026566 DOI: 10.1007/s00464-013-3185-z]
- 64 **Lee H**, Min BH, Lee JH, Shin CM, Kim Y, Chung H, Lee SH. Covered metallic stents with an anti-migration design vs. uncovered stents for the palliation of malignant gastric outlet obstruction: a multicenter, randomized trial. *Am J Gastroenterol* 2015; **110**: 1440-1449 [PMID: 26372507 DOI: 10.1038/ajg.2015.286]
- 65 **Del Piano M**, Ballarè M, Montino F, Todesco A, Orsello M, Magnani C, Garello E. Endoscopy or surgery for malignant GI outlet obstruction? *Gastrointest Endosc* 2005; **61**: 421-426 [PMID: 15758914 DOI: 10.1016/s0016-5107(04)02757-9]
- 66 **Khashab M**, Alawad AS, Shin EJ, Kim K, Bourdel N, Singh VK, Lennon AM, Hutfless S, Sharaiha RZ, Amateau S, Okolo PI, Makary MA, Wolfgang C, Canto MI, Kalloo AN. Enteral stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction. *Surg Endosc* 2013; **27**: 2068-2075 [PMID: 23299137 DOI: 10.1007/s00464-012-2712-7]
- 67 **Roy A**, Kim M, Christein J, Varadarajulu S. Stenting versus gastrojejunostomy for management of malignant gastric outlet obstruction: comparison of clinical outcomes and costs. *Surg Endosc* 2012; **26**: 3114-3119 [PMID: 22549377 DOI: 10.1007/s00464-012-2301-9]
- 68 **Ly J**, O'Grady G, Mittal A, Plank L, Windsor JA. A systematic review of methods to palliate malignant

- gastric outlet obstruction. *Surg Endosc* 2010; **24**: 290-297 [PMID: [19551436](#) DOI: [10.1007/s00464-009-0577-1](#)]
- 69 **Hosono S**, Ohtani H, Arimoto Y, Kanamiya Y. Endoscopic stenting versus surgical gastroenterostomy for palliation of malignant gastroduodenal obstruction: a meta-analysis. *J Gastroenterol* 2007; **42**: 283-290 [PMID: [17464457](#) DOI: [10.1007/s00535-006-2003-y](#)]
- 70 **Jeurnink SM**, van Eijck CH, Steyerberg EW, Kuipers EJ, Siersema PD. Stent versus gastrojejunostomy for the palliation of gastric outlet obstruction: a systematic review. *BMC Gastroenterol* 2007; **7**: 18 [PMID: [17559659](#) DOI: [10.1186/1471-230X-7-18](#)]
- 71 **No JH**, Kim SW, Lim CH, Kim JS, Cho YK, Park JM, Lee IS, Choi MG, Choi KY. Long-term outcome of palliative therapy for gastric outlet obstruction caused by unresectable gastric cancer in patients with good performance status: endoscopic stenting versus surgery. *Gastrointest Endosc* 2013; **78**: 55-62 [PMID: [23522025](#) DOI: [10.1016/j.gie.2013.01.041](#)]
- 72 **Zheng B**, Wang X, Ma B, Tian J, Jiang L, Yang K. Endoscopic stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction. *Dig Endosc* 2012; **24**: 71-78 [PMID: [22348830](#) DOI: [10.1111/j.1443-1661.2011.01186.x](#)]
- 73 **Jeurnink SM**, Steyerberg EW, Hof Gv, van Eijck CH, Kuipers EJ, Siersema PD. Gastrojejunostomy versus stent placement in patients with malignant gastric outlet obstruction: a comparison in 95 patients. *J Surg Oncol* 2007; **96**: 389-396 [PMID: [17474082](#) DOI: [10.1002/jso.20828](#)]
- 74 **Jang S**, Stevens T, Lopez R, Bhatt A, Vargo JJ. Superiority of Gastrojejunostomy Over Endoscopic Stenting for Palliation of Malignant Gastric Outlet Obstruction. *Clin Gastroenterol Hepatol* 2019; **17**: 1295-1302.e1 [PMID: [30391433](#) DOI: [10.1016/j.cgh.2018.10.042](#)]
- 75 **Perez-Miranda M**, Tyberg A, Poletto D, Toscano E, Gaidhane M, Desai AP, Kumta NA, Fayad L, Nieto J, Barthet M, Shah R, Brauer BC, Sharaiha RZ, Kahaleh M. EUS-guided Gastrojejunostomy Versus Laparoscopic Gastrojejunostomy: An International Collaborative Study. *J Clin Gastroenterol* 2017; **51**: 896-899 [PMID: [28697151](#) DOI: [10.1097/MCG.0000000000000887](#)]
- 76 **Khashab MA**, Bukhari M, Baron TH, Nieto J, El Zein M, Chen YI, Chavez YH, Ngamruengphong S, Alawad AS, Kumbhari V, Itoi T. International multicenter comparative trial of endoscopic ultrasonography-guided gastroenterostomy versus surgical gastrojejunostomy for the treatment of malignant gastric outlet obstruction. *Endosc Int Open* 2017; **5**: E275-E281 [PMID: [28382326](#) DOI: [10.1055/s-0043-101695](#)]
- 77 **Binmoeller KF**, Shah JN. Endoscopic ultrasound-guided gastroenterostomy using novel tools designed for transluminal therapy: a porcine study. *Endoscopy* 2012; **44**: 499-503 [PMID: [22531985](#) DOI: [10.1055/s-0032-1309382](#)]
- 78 **Ge PS**, Young JY, Dong W, Thompson CC. EUS-guided gastroenterostomy versus enteral stent placement for palliation of malignant gastric outlet obstruction. *Surg Endosc* 2019; **33**: 3404-3411 [PMID: [30725254](#) DOI: [10.1007/s00464-018-06636-3](#)]
- 79 **Tyberg A**, Perez-Miranda M, Sanchez-Ocaña R, Peñas I, de la Serna C, Shah J, Binmoeller K, Gaidhane M, Grimm I, Baron T, Kahaleh M. Endoscopic ultrasound-guided gastrojejunostomy with a lumen-apposing metal stent: a multicenter, international experience. *Endosc Int Open* 2016; **4**: E276-E281 [PMID: [27004243](#) DOI: [10.1055/s-0042-101789](#)]
- 80 **Khashab MA**, Kumbhari V, Grimm IS, Ngamruengphong S, Aguila G, El Zein M, Kalloo AN, Baron TH. EUS-guided gastroenterostomy: the first U.S. clinical experience (with video). *Gastrointest Endosc* 2015; **82**: 932-938 [PMID: [26215646](#) DOI: [10.1016/j.gie.2015.06.017](#)]
- 81 **James TW**, Greenberg S, Grimm IS, Baron TH. EUS-guided gastroenteric anastomosis as a bridge to definitive treatment in benign gastric outlet obstruction. *Gastrointest Endosc* 2020; **91**: 537-542 [PMID: [31759034](#) DOI: [10.1016/j.gie.2019.11.017](#)]
- 82 **Al-Rashedy M**, Dadibhai M, Shareif A, Khandelwal MI, Ballester P, Abid G, McCloy RF, Ammori BJ. Laparoscopic gastric bypass for gastric outlet obstruction is associated with smoother, faster recovery and shorter hospital stay compared with open surgery. *J Hepatobiliary Pancreat Surg* 2005; **12**: 474-478 [PMID: [16365822](#) DOI: [10.1007/s00534-005-1013-0](#)]



Case Control Study

Gastrointestinal symptoms in acromegaly: A case control study

Nashiz Inayet, Jamal Hayat, Gul Bano, Andrew Poullis

ORCID number: Nashiz Inayet (0000-0002-2813-4161); Jamal Hayat (0000-0002-5461-2550); Gul Bano (0000-0003-0470-0461); Andrew Poullis (0000-0003-0703-0328).

Author contributions: Poullis A and Hayat J designed the project and reviewed the statistics and the manuscript; Bano G identified the cases and reviewed the manuscript; Inayet N collected the data, carried out the statistical analysis and wrote the manuscript.

Institutional review board

statement: The study protocol was approved by the South West-Central Bristol Research Ethics Committee and NHS Health Research Authority United Kingdom.

Informed consent statement: All patients had given informed consent for this study.

Conflict-of-interest statement: The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Data sharing statement: The questionnaire data used to support the findings of this study are available from the corresponding author upon request.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and

Nashiz Inayet, Jamal Hayat, Andrew Poullis, Department of Gastroenterology, St Georges Hospital and St Georges, University of London, London SW17 0QT, United Kingdom

Gul Bano, Department of Endocrinology, St Georges Hospital and St Georges, University of London, London SW17 0QT, United Kingdom

Corresponding author: Nashiz Inayet, BSc, CCST, MBBS, MD, MRCP, Doctor, Senior Lecturer, Department of Gastroenterology, St Georges Hospital and St Georges, University of London, Blackshaw Road, Tooting, London SW17 0QT, United Kingdom. n.inayet@nhs.net

Abstract

BACKGROUND

Acromegaly is a chronic disease caused by a pituitary somatotroph adenoma resulting in excess secretion of growth hormone, which leads to excess secretion of Insulin like growth factor 1 from the liver, causing abnormal soft tissue growth. There is increasing awareness that diseases affecting connective tissue are associated with an increase in functional gastrointestinal symptoms. Data was collected from patients with a confirmed diagnosis of acromegaly to evaluate the intensity, variety and impact of abdominal symptoms in comparison with a control group who were healthy participants recruited from the local fracture clinic.

AIM

To evaluate the frequency type and burden of abdominal symptoms in acromegaly in comparison with a control group.

METHODS

Medical documentation of patients with a diagnosis of acromegaly treated in one tertiary medical centre between 2010 and 2017 has been analysed. Data was collected from patients with confirmed acromegaly, using the Short Form Health Survey (SF36) and Rome IV Diagnostic questionnaire for Functional Gastrointestinal Disorders in Adults (R4DQ) and compared to a sex- and age-matched control group, to assess the burden of abdominal symptoms. Microsoft Excel and IBM SPSS v 25 were used for data analysis.

RESULTS

Fifty patients with acromegaly (24 male and 26 females; age range 23-64 years, mean 43) and 200 controls (96 male and 104 females; age range 18-84, mean 42.4) were recruited. 92% (46 out of 50) of patients with acromegaly reported abdominal symptoms and 78% (39 out of 50) had at least one functional gastrointestinal disorder according to the Rome IV diagnostic criteria, compared to 16% of controls (OR > 1, $P < 0.0001$). The most commonly reported symptom

fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See:

<http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: December 31, 2019

Peer-review started: December 31, 2019

First decision: January 19, 2020

Revised: April 25, 2020

Accepted: May 29, 2020

Article in press: May 29, 2020

Published online: June 9, 2020

P-Reviewer: Mari A, Wu KL

S-Editor: Dou Y

L-Editor: A

E-Editor: Qi LL



was constipation (69% acromegaly *vs* 21% of controls OR > 1, $P < 0.0001$, 95%CI: 4.4–15.8). 34 out of 50 (68%) respondents met the criteria for functional constipation according to Rome IV. Upper gastrointestinal disorders were also more prevalent in the acromegaly group. There was no statistically significant difference in the prevalence of biliary and anorectal symptoms between the two groups. Patients in acromegaly group scored lower on the mean scores of the eight parameters of SF36 Quality of Life questionnaire (mean scores 60.04 *vs* 71.23, 95%CI: -13.6829 to -8.6971, OR > 1, $P < 0.001$) as compared to the control group.

CONCLUSION

Upper and lower functional gastrointestinal tract disorders (defined by Rome IV diagnostic criteria) are significantly more prevalent in patients with acromegaly compared with healthy age and sex matched controls in our study. Functional constipation is the most commonly reported problem. Poorer quality of life may in part be attributable to the increased prevalence of abdominal symptoms.

Key words: Functional gastrointestinal disorders; Acromegaly; Constipation; Irritable bowel syndrome; Somatostatin; Pituitary

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: Irritable bowel syndrome is the commonest cause of gastrointestinal symptoms. The aetiology is thought to be multi-factorial but remains incompletely understood. Our group has previously identified that patients with connective tissue disorders have an increased incidence of functional gastrointestinal symptoms. Investigating for these symptoms in patients with acromegaly may give further insight into the pathogenesis of functional disorders and irritable bowel syndrome.

Citation: Inayet N, Hayat J, Bano G, Poullis A. Gastrointestinal symptoms in acromegaly: A case control study. *World J Gastrointest Pharmacol Ther* 2020; 11(2): 17-24

URL: <https://www.wjgnet.com/2150-5349/full/v11/i2/17.htm>

DOI: <https://dx.doi.org/10.4292/wjgpt.v11.i2.17>

INTRODUCTION

Acromegaly is caused by a pituitary somatotroph adenoma and characterised by excessive secretion of growth hormone (GH)^[1,2]. GH stimulates the liver to produce Insulin like growth factor 1 (IGF-1). In addition to the insulin-like effects, IGF-1 can also regulate cellular DNA synthesis and is an important signalling molecule with regards to cancer cell transformation and proliferation, including mitogenesis and apoptosis inhibition^[3].

A variety of complications have been reported in patients with acromegaly including cardiovascular diseases, such as hypertrophic cardiomyopathy, heart failure, hypertension, diabetes mellitus or respiratory disorders, obstructive sleep apnoea^[4] as well as increased risk of benign and malignant neoplasms including colon cancer^[5].

The organic gastrointestinal pathology associated with acromegaly such as increased risk of colonic cancer and an increased risk of cholelithiasis has been studied in detail^[6], however the issue of overall burden of gastrointestinal symptoms, particularly the functional disorders in acromegaly and the gastrointestinal effects of its treatment have not been well studied. We have previously identified how changes in connective tissue in hypermobility (in Marfan and Ehlers Danlos) are associated with an increase in functional gastrointestinal symptoms^[7]. The impact of soft tissue changes associated with over secretion of GH and gastrointestinal symptoms has not previously been studied.

Somatostatin analogues used in the treatment of acromegaly are also associated with a wide range of abdominal symptoms. Due to the higher risk of colon cancer, acromegaly patients are offered screening colonoscopy during which standard preparation for colonoscopy is often found inadequate, indicating functional and structural change^[5,8,9].

Our aim was to evaluate gastro-intestinal symptoms in a cohort of acromegaly patients. We assessed the frequency, character, severity and burden of abdominal symptoms in patients with acromegaly in comparison with a control group.

MATERIALS AND METHODS

Patients

Medical documentation of patients with acromegaly treated in one medical centre (Department of Endocrinology, St George's Hospital, London) between 2010 and June 2017 have been analysed in order to find the information about their diagnosis, treatment and presence of abdominal symptoms. Treatment information including Somatostatin analogues and other medicines with significant gastrointestinal effects were obtained from patients and controls. Selected patients were then asked to fill out Rome IV Diagnostic questionnaire for Functional Gastrointestinal Disorders in Adults (R4DQ) and SF36 questionnaire and were included as cases. Results were compared with sex- and age-matched group of controls.

Controls

Participants in the control group were recruited from people who were being discharged from fracture clinic who were otherwise healthy and did not report any other medical problems. Details of treatment history including drugs affecting the gastrointestinal system were obtained.

Statistical analysis

Microsoft Excel and IBM SPSS v 25 were used to analyse the data. A case-control ratio of 4:1 was used. Fisher's exact test was used to analyse the results of R4DQ and one-tailed Independent sample t test was used to analyse the mean scores of SF36. A *P*-value under 0.05 was considered statistically significant.

Screening protocol

All patients had a confirmed diagnosis of acromegaly and were either post treatment or undergoing treatment.

Ethics

The study protocol was approved by the South West-Central Bristol Research Ethics Committee and NHS Health Research Authority United Kingdom.

RESULTS

Fifty patients with acromegaly (24 male and 26 females; age range 23-64 years, mean 43) and 200 controls (96 male and 104 females; age range 18-84, mean 42.4) were recruited in a 1:4 Case:Control ratio. The mean age at diagnosis of acromegaly was 32.44 years and on average participants had their diagnosis confirmed 11.8 years prior to this study. All patients had trans-sphenoidal surgery and 21 (42%) had pituitary radiotherapy in addition. Thirty-seven (74%) patients were using somatostatin analogues (Table 1).

Ninety-two percent (46 out of 50) of patients with acromegaly reported abdominal symptoms (abdominal pain, diarrhoea or constipation) and 78% (39 out of 50) had at least one functional gastrointestinal disorder (FGID) according to the Rome IV diagnostic criteria, compared to 16% of controls (OR > 1, *P* < 0.0001). All female patients with acromegaly reported suffering from at least some abdominal symptoms as compared to 87% of male patients with acromegaly, however there was no statistically significant gender difference observed in the frequency and intensity of symptoms. The use of medicines (antacids, histamine receptor antagonists, proton pump inhibitors, laxatives) used to alleviate gastrointestinal symptoms was also higher and statistically significant in the acromegaly group (Table 2).

A few patients with acromegaly reported multiple abdominal symptoms and qualified for more than one FGID. The most commonly reported symptom was constipation (68% acromegaly group *vs* 7.5% of controls OR > 1, *P* < 0.0001, 95%CI: 4.4-15.8) followed by abdominal pain (22% acromegaly group *vs* 9.5% of controls OR > 1, *P* < 0.0001, 95%CI: 2.5-9.3). Thirty-four out of 50 (68%) respondents met the criteria for functional constipation according to Rome IV. The prevalence of constipation increased with increasing age and was often associated with bloating. All bowel symptoms showed statistically significant prevalence in the acromegaly group. Some oesophageal and gastroduodenal conditions such as functional heartburn, functional

Table 1 Acromegaly demographic and treatment data

	Controls	Acromegaly patients
<i>n</i>	200	50
M:F	96:104	24:26
Age at diagnosis (mean, yr)	33	32.44
Years since diagnosis (mean, yr)	-	11.8 yr
Transsphenoidal surgery	-	50 (100%)
Pituitary radiotherapy	-	21 (42%)
Somatostatin analogue	-	37 (74%)

dysphagia and functional dyspepsia also showed statistically significant prevalence in acromegaly group. There was no statistically significant difference of prevalence of biliary and anorectal symptoms between the acromegaly group and controls (Table 3).

Acromegaly patients scored lower than controls on the mean scores of all eight parameters measured by the SF36 quality of life index. These parameters include physical functioning levels, role limitations due to physical health, role limitations due to emotional health, energy/fatigue levels, emotional wellbeing, social functioning levels, perception of pain and general health (mean scores 60.04 *vs* 71.23, 95%CI: -13.6829 to -8.6971, OR > 1, *P* < 0.001) (Table 4).

DISCUSSION

Acromegaly is a rare and unique disease associated with abnormal soft tissue growth^[4] with a prevalence that is estimated at 40 per million in United Kingdom and an annual incidence rate ranging between 2 and 11 cases per million per year, with an equal distribution between genders^[10].

Acromegaly is associated with gastrointestinal complications, such as constipation, higher prevalence of colorectal polyps and cancer^[11] and higher prevalence of gallstones in patients treated with Somatostatin analogues^[12]. Somatostatin analogues used in the management of acromegaly are also associated with a wide range of abdominal symptoms in addition to the known association with gallstones.

The higher prevalence of lower gastrointestinal symptoms in acromegaly could partly be due to slow intestinal motility. Slow intestinal and colonic transit times have been attributed to both acromegaly and its treatment with Somatostatin analogues. Disease related slow gut motility may be worsened because of treatment with Somatostatin. Resmini *et al*^[13] demonstrated that patients with acromegaly have a prolonged small intestinal transit time and a prolonged colon transit time. The small bowel transit time calculated by standardized 10 g lactulose hydrogen breath test showed significantly slower oro-caecal transit in patients than in controls, without significant differences between patients treated with Somatostatin and untreated patients. These data suggest that acromegaly itself may cause motility alteration. However Thomas *et al*^[14] performed radiological tests to investigate colonic transit and found an increased transit time of colon (66% longer) in patients with acromegaly compared with controls, and it was even more increased during octreotide treatment. This may predispose to small intestinal bacterial overgrowth, which in turn can cause symptoms^[13]. Autonomic intestinal impairment due to vagal hypertonia, similar to that demonstrated previously in the cardiovascular system, has been proposed as a pathogenic mechanism^[15]. Another proposed pathogenic mechanism could be related to hormonal imbalance which can be influenced by the complex interaction between GH and ghrelin, as shown by Arosio *et al*^[16]. These gut motility disturbances in acromegaly increase circulating levels of IGF-1, which is a known mitogen^[17] that may stimulate the proliferation of intestinal epithelial cells by autocrine and paracrine actions^[11].

Our study has also showed a higher prevalence of upper gastrointestinal symptoms (functional heartburn, functional dysphagia and functional dyspepsia) in the acromegaly group. Sisman *et al*^[18] showed that the prevalence of gastritis, duodenitis, peptic ulcers or intestinal metaplasia were higher in patients with acromegaly than in healthy subjects; while the prevalence of hiatal hernia was lower. Ilhan *et al*^[19] demonstrated oesophageal dysmotility manifesting as profound reduction in the amplitude and duration of lower oesophageal sphincter relaxation even in acromegaly patients without any significant gastrointestinal symptoms. George *et al*^[20] described a rare case of megaduodenum without any distal obstruction in a patient

Table 2 Acromegaly abdominal symptoms and medicine use

	Controls (n = 200)	Acromegaly patients (n = 50)	P value (Fisher's exact test)
Gastrointestinal symptoms	32 (16%)	46 (92%)	
Abdominal pain	19 (9.5%)	11 (22%)	0.4905
Diarrhoea	8 (4%)	4 (8%)	0.2652
Constipation	15 (7.5%)	34 (68%)	< 0.00001 ^b
Medicines			
Regular use of anti-secretory (PPI/H2RA)/antacids	11 (6.5%)	31 (62%)	< 0.00001 ^b
Regular use of laxatives	6 (3%)	46 (92%)	< 0.00001 ^b
Regular use of opioid analgesics	11 (6.5%)	2 (4%)	Not statistically significant
Somatostatin analogues	-	37 (74%)	

^bP < 0.01, statistically significant. PPI: Proton pump inhibitor; H2RA: Histamine H2 receptor antagonists.

with acromegaly. Somatostatin analogues inhibitory effect on gut motility, particularly antral contractility may also produce or worsen symptoms in patients with delayed gastric emptying^[21].

Despite our study not showing any statistically significant difference in the prevalence of biliary symptoms in the two groups, other studies have shown an increased risk of gall stones in acromegaly^[22-24]. The increased risk of faecal anaerobic bacteria overgrowth associated with slow gut transit times, with the additional increased risk of impairment of bile acid metabolism may be responsible in part for gallstone development^[14]. Ultrasound studies have found increased gall bladder volume in both fasting and postprandial states in acromegaly. These are associated with profound suppression of released cholecystokinin, which is associated with Somatostatin administration. The incomplete gall bladder emptying may be the reason for higher incidence of gall bladder calculi in patients with acromegaly treated with Somatostatin^[12].

This study is the first study in our knowledge that looks into the prevalence of various abdominal symptoms in acromegaly. The burden of non-organic gastrointestinal symptoms, particularly the functional disorders in acromegaly and the gastrointestinal effects of its treatment have not been well studied. This study, along with our previous studies on Marfan and Ehlers Danlos^[7] gives insight into the possible link between connective tissue abnormalities and irritable bowel syndrome (IBS). IBS is the commonest final diagnosis in patients presenting with gastrointestinal symptoms. The aetiology is multifactorial. This study gives further evidence to the suggestion that connective tissue abnormalities may be the underlying pathology in some individuals with IBS.

The strengths of this study are that for a very rare condition this is a large patient cohort being looked after in one tertiary hospital, with a large control group for comparison. A weakness of this study is that cases were not clinically reviewed to ensure that symptoms had been fully investigated to ensure that the symptom complex was truly functional. Also, it was not possible to analyse for disease duration prior to diagnosis, treatment administered historically, on-going treatment and time since diagnosis were not possible.

The presence of FGIDs affecting both upper and lower gastrointestinal tract in patients with acromegaly is substantially higher than the controls in our study. The lower mean scores on quality of life indicators in the acromegaly group reflect the overall burden of disease on quality of life. The high prevalence of abdominal symptoms may in part explain this. This is likely to be multifactorial and factors such as delayed small intestinal and colonic transit times, treatment with Somatostatin analogues, increased bowel length may all play a part in this. A larger follow up international multi-centre study on the presence of abdominal symptoms in acromegaly and future clinical research focussing on the association of abdominal symptoms with connective tissue abnormalities may further help our understanding of IBS and other FGIDs.

Table 3 Gastrointestinal symptoms in acromegaly patients compared with controls

	Controls, <i>n</i> = 200 (%)	Acromegaly patients, <i>n</i> = 50 (%)	<i>P</i> value (Fisher's exact test)
Oesophageal disorders			
Functional chest pain	2 (1%)	3 (6%)	0.0561
Functional heartburn	22 (11%)	15 (30%)	0.0016 ^b
Globus	2 (1%)	2 (4%)	0.1796
Functional dysphagia	4 (2%)	6 (12%)	0.0053 ^b
Gastroduodenal disorders			
Functional dyspepsia	14 (7%)	12 (24%)	0.0013 ^b
Belching disorders	8 (4%)	5 (10%)	0.1441
Nausea and vomiting disorders	2 (1%)	2 (4%)	0.1796
Rumination syndrome	2 (1%)	1 (2%)	0.4895
Bowel disorders			
Irritable bowel syndrome	12 (6%)	10 (20%)	0.0041 ^b
Functional constipation	22 (11%)	34 (68%)	0.0006 ^b
Functional diarrhoea	10 (5%)	9 (18%)	0.0048 ^b
Functional abdominal bloating/distension	12 (6%)	11 (22%)	0.0015 ^b
Unspecified functional bowel disorder	44 (22%)	25 (50%)	0.0002 ^b
Centrally mediated Abdominal pain syndrome	6 (3%)	4 (8%)	0.1165
Functional Biliary pain	1 (0.5%)	3 (6%)	0.0261 ^a
Anorectal disorders			
Faecal incontinence	1 (0.5%)	2 (4%)	0.1028
Functional anorectal pain	2 (1%)	4 (8%)	0.0157 ^a

^a*P* < 0.05,^b*P* < 0.01, statistically significant.**Table 4** Quality of life scores in acromegaly patients

	Controls (mean scores)	Acromegaly (mean scores)	Independent sample <i>t</i> test
Physical functioning	100.0	80.0	0.80516
Role limitations due to physical health	100.0	50.0	0.001053 ^b
Role limitations due to emotional problems	100.0	100.0	1
Level of energy/fatigue	95.0	45.0	0.001053 ^b
Emotional wellbeing	100.0	68.0	0.002175 ^b
Social functioning	87.5	50.0	< 0.000076 ^b
Pain	77.5	67.5	0.1732
General health	100	30.0	< 0.0001 ^b

^b*P* < 0.01, statistically significant.

ARTICLE HIGHLIGHTS

Research background

Acromegaly results from an excess of growth hormone, which leads to excess secretion of Insulin like growth factor 1 from the liver, causing abnormal soft tissue growth. This is associated with an increase in a number of organic diseases. There is increasing awareness that diseases affecting connective tissue are associated with an increase in functional gastrointestinal symptoms. We are not aware of any other study that has looked into the burden of abdominal symptoms in acromegaly and the impact they have on patient's quality of life as a result of this.

Research motivation

This study is part of a larger study that is assessing the role and significance of connective tissue involvement in abdominal symptoms. We have previously described an increase in functional gastrointestinal symptoms in other diseases affecting connective tissue (Marfan and Ehlers Danlos). In this study we evaluate the frequency of abdominal symptoms in patients with acromegaly.

Research objectives

The main objective of this study was to evaluate if patients with acromegaly had more frequent and intense abdominal symptoms, as described by the Rome criteria, than controls and thus, as a result of this had poorer quality of life. Furthermore, other factors such as use of Somatostatin analogues, which in itself can cause abdominal symptoms, had to be taken into account. The next step in our research would be to carry out objective gastrointestinal physiological studies in larger groups of patients and controls to see if the presence of symptoms reflects actual physiological variations across different groups.

Research methods

Patients with acromegaly were identified from a clinical database at one tertiary medical centre (Department of Endocrinology, St George's Hospital, London). Identified patients were then asked to fill out previously validated questionnaires and results were compared with sex- and age-matched group of controls (recruited from fracture clinic who were otherwise healthy and did not report any other medical problems).

Research results

The results of this study showed that the presence of abdominal symptoms in acromegaly is significantly higher than controls. The results also show that the presence of these symptoms has an overall detrimental effect on quality of life or well being of the patient. This study also supports the increasing awareness in the scientific world regarding the association of connective tissue abnormalities and gastrointestinal or abdominal symptoms. It is yet to be seen if gastrointestinal physiological studies in these patients will be reflective of these results.

Research conclusions

The presence of abdominal symptoms is significantly higher in patients with acromegaly compared to controls and this may have a significant impact on their quality of life. Connective tissue abnormalities are associated with abdominal symptoms as has been shown by this study and other studies and may be one of the underlying reasons behind functional gastrointestinal disorders (FGIDs). Other studies have shown similar results in Ehlers-Danlos and Marfan syndromes and abnormalities of connective tissue such as elastin may be common to these disease processes. This needs to be studied further to see if minor variations in gut connective tissue the cause of FGIDs could be.

Research perspectives

Future research in this area will have to be pursued in an international and multicentre study as it is difficult for one centre to recruit a large number of patients in rare diseases. Gastrointestinal physiological studies would help to see if the variance in symptoms is reflected in physiological variance.

ACKNOWLEDGEMENTS

Thank you to the patients and controls who gave up their time to participate in this study.

REFERENCES

- 1 **Melmed S.** Medical progress: Acromegaly. *N Engl J Med* 2006; **355**: 2558-2573 [PMID: [17167139](#) DOI: [10.1056/NEJMr062453](#)]
- 2 **Nabarro JD.** Acromegaly. *Clin Endocrinol (Oxf)* 1987; **26**: 481-512 [PMID: [3308190](#) DOI: [10.1111/j.1365-2265.1987.tb00805.x](#)]
- 3 **Baserga R, Peruzzi F, Reiss K.** The IGF-1 receptor in cancer biology. *Int J Cancer* 2003; **107**: 873-877 [PMID: [14601044](#) DOI: [10.1002/ijc.11487](#)]
- 4 **Colao A, Ferone D, Marzullo P, Lombardi G.** Systemic complications of acromegaly: epidemiology, pathogenesis, and management. *Endocr Rev* 2004; **25**: 102-152 [PMID: [14769829](#) DOI: [10.1210/er.2002-0022](#)]
- 5 **Dworakowska D, Grossman AB.** Colonic Cancer and Acromegaly. *Front Endocrinol (Lausanne)* 2019; **10**: 390 [PMID: [31293513](#) DOI: [10.3389/fendo.2019.00390](#)]
- 6 **Ezzat S.** Hepatobiliary and gastrointestinal manifestations of acromegaly. *Dig Dis* 1992; **10**: 173-180 [PMID: [1611713](#) DOI: [10.1159/000171355](#)]
- 7 **Inayet N, Hayat JO, Kaul A, Tome M, Child A, Poullis A.** Gastrointestinal Symptoms in Marfan Syndrome and Hypermobile Ehlers-Danlos Syndrome. *Gastroenterol Res Pract* 2018; **2018**: 4854701 [PMID: [30151001](#) DOI: [10.1155/2018/4854701](#)]
- 8 **Renchan AG, Painter JE, Bell GD, Rowland RS, O'Dwyer ST, Shalet SM.** Determination of large bowel length and loop complexity in patients with acromegaly undergoing screening colonoscopy. *Clin Endocrinol (Oxf)* 2005; **62**: 323-330 [PMID: [15730414](#) DOI: [10.1111/j.1365-2265.2005.02217.x](#)]
Jenkins PJ, Fairclough PD, Richards T, Lowe DG, Monson J, Grossman A, Wass JA, Besser M.

- 9 Acromegaly, colonic polyps and carcinoma. *Clin Endocrinol (Oxf)* 1997; **47**: 17-22 [PMID: [9302367](#) DOI: [10.1046/j.1365-2265.1997.1911029.x](#)]
- 10 **Lavrentaki A**, Paluzzi A, Wass JA, Karavitaki N. Epidemiology of acromegaly: review of population studies. *Pituitary* 2017; **20**: 4-9 [PMID: [27743174](#) DOI: [10.1007/s11102-016-0754-x](#)]
- 11 **Rokkas T**, Pistiolas D, Sechopoulos P, Margantinis G, Koukoulis G. Risk of colorectal neoplasm in patients with acromegaly: a meta-analysis. *World J Gastroenterol* 2008; **14**: 3484-3489 [PMID: [18567075](#) DOI: [10.3748/wjg.14.3484](#)]
- 12 **Attanasio R**, Mainolfi A, Grimaldi F, Cozzi R, Montini M, Carzaniga C, Grotoli S, Cortesi L, Albizzi M, Testa RM, Fatti L, De Giorgio D, Scaroni C, Cavagnini F, Loli P, Pagani G, Ghigo E. Somatostatin analogs and gallstones: a retrospective survey on a large series of acromegalic patients. *J Endocrinol Invest* 2008; **31**: 704-710 [PMID: [18852531](#) DOI: [10.1007/BF03346419](#)]
- 13 **Resmini E**, Parodi A, Savarino V, Greco A, Rebora A, Minuto F, Ferone D. Evidence of prolonged oro-cecal transit time and small intestinal bacterial overgrowth in acromegalic patients. *J Clin Endocrinol Metab* 2007; **92**: 2119-2124 [PMID: [17405840](#) DOI: [10.1210/jc.2006-2509](#)]
- 14 **Thomas LA**, Veysey MJ, Murphy GM, Russell-Jones D, French GL, Wass JA, Dowling RH. Octreotide induced prolongation of colonic transit increases faecal anaerobic bacteria, bile acid metabolising enzymes, and serum deoxycholic acid in patients with acromegaly. *Gut* 2005; **54**: 630-635 [PMID: [15831907](#) DOI: [10.1136/gut.2003.028431](#)]
- 15 **Resmini E**, Casu M, Patrone V, Murialdo G, Bianchi F, Giusti M, Ferone D, Minuto F. Sympathovagal imbalance in acromegalic patients. *J Clin Endocrinol Metab* 2006; **91**: 115-120 [PMID: [16263819](#) DOI: [10.1210/jc.2005-1506](#)]
- 16 **Arosio M**, Ronchi CL, Gebbia C, Pizzinelli S, Conte D, Cappiello V, Epaminonda P, Cesana BM, Beck-Peccoz P, Peracchi M. Ghrelin administration affects circulating pituitary and gastro-entero-pancreatic hormones in acromegaly. *Eur J Endocrinol* 2004; **150**: 27-32 [PMID: [14713276](#) DOI: [10.1530/eje.0.1500027](#)]
- 17 **Benito M**, Valverde AM, Lorenzo M. IGF-I: a mitogen also involved in differentiation processes in mammalian cells. *Int J Biochem Cell Biol* 1996; **28**: 499-510 [PMID: [8697095](#) DOI: [10.1016/1357-2725\(95\)00168-9](#)]
- 18 **Sisman P**, Pekgoz M, Bayrakci I, Sisman M, Cander S, Oz Gul O, Erturk E, Ersoy C. Evaluation of upper gastrointestinal system in acromegaly. *Ann Endocrinol (Paris)* 2019; **80**: 196-201 [PMID: [31227172](#) DOI: [10.1016/j.ando.2019.03.001](#)]
- 19 **Ilhan M**, Danalioglu A, Turgut S, Karaman O, Arabaci E, Tasan E. Acromegaly can be associated with impairment of LES relaxation in the oesophagus. *Endokrynol Pol* 2015; **66**: 308-312 [PMID: [26323467](#) DOI: [10.5603/EP.2015.0039](#)]
- 20 **George B**, Vinay D, Moolechery J, Mathew V, Anantharaman R, Ayyar V, Bantwal G. Megaduodenum in a patient with acromegaly. *Indian J Endocrinol Metab* 2012; **16**: S324-S325 [PMID: [23565414](#)]
- 21 **Edmunds MC**, Chen JD, Soykan I, Lin Z, McCallum RW. Effect of octreotide on gastric and small bowel motility in patients with gastroparesis. *Aliment Pharmacol Ther* 1998; **12**: 167-174 [PMID: [9692691](#) DOI: [10.1046/j.1365-2036.1998.00289.x](#)]
- 22 **Rhodes M**, James RA, Bird M, Clayton B, Kendall-Taylor P, Lennard TW. Gallbladder function in acromegalic patients taking long-term octreotide: evidence of rebound hypermotility on cessation of treatment. *Scand J Gastroenterol* 1992; **27**: 115-118 [PMID: [1561523](#) DOI: [10.3109/00365529209165429](#)]
- 23 **Annamalai AK**, Gayton EL, Webb A, Halsall DJ, Rice C, Ibram F, Chaudhry AN, Simpson HL, Berman L, Gurnell M. Increased prevalence of gallbladder polyps in acromegaly. *J Clin Endocrinol Metab* 2011; **96**: E1120-E1125 [PMID: [21543430](#) DOI: [10.1210/jc.2010-2669](#)]
- 24 **Chakravarty AA**, Ajmani A, Manchanda S, Kulshreshtha B, Chopra S. Incidence of gall stone formation in acromegalic patients on octreotide therapy. *Indian J Endocrinol Metab* 2012; **16**: 406-408 [PMID: [22629508](#) DOI: [10.4103/2230-8210.95683](#)]



Retrospective Cohort Study

Validation of American Joint Committee on Cancer 8th edition of TNM staging in resected distal pancreatic cancer

Feng Yin, Mohammed Saad, Hao Xie, Jingmei Lin, Christopher R Jackson, Bing Ren, Cynthia Lawson, Dipti M Karamchandani, Belen Quereda Bernabeu, Wei Jiang, Teena Dhir, Richard Zheng, Christopher W Schultz, Dongwei Zhang, Courtney L Thomas, Xuchen Zhang, Jinping Lai, Michael Schild, Xuefeng Zhang, Xiuli Liu

ORCID number: Feng Yin (0000-0002-8444-1123); Mohammed Saad (0000-0002-8511-8897); Hao Xie (0000-0002-9640-4055); Jingmei Lin (0000-0003-2094-0262); Christopher R Jackson (0000-0003-1792-6726); Bing Ren (0000-0003-2374-7775); Cynthia Lawson (0000-0003-4200-7289); Dipti M Karamchandani (0000-0002-0351-2859); Belen Quereda Bernabeu (0000-0002-5770-0732); Wei Jiang (0000-0002-7874-3854); Teena Dhir (0000-0002-7674-9304); Richard Zheng (0000-0002-4743-5568); Christopher W Schultz (0000-0001-5932-805X); Dongwei Zhang (0000-0001-9168-7204); Courtney L Thomas (0000-0001-5888-7247); Xuchen Zhang (0000-0002-1484-4672); Jinping Lai (0000-0001-5365-2481); Michael Schild (0000-0003-3609-5649); Xuefeng Zhang (0000-0002-9069-4178); Xiuli Liu (0000-0001-5791-2017).

Author contributions: Liu X, Yin F, Lin J, Ren B, Karamchandani DM, Jiang W, Zhang D, Zhang X, Lai J, Schild M, Zhang X, and Xie H designed the research; Yin F, Saad M, Jackson CR, Lawson C, Bernabeu BQ, Dhir T, Zheng R, Schultz CW, and Thomas CL collected data; Yin F, Xie H, and Liu X analyzed the data; Yin F wrote the manuscript and Liu X, Xie H critically revised the manuscript.

Institutional review board

Feng Yin, Department of Pathology and Anatomical Sciences, University of Missouri, Columbia, MO 65212, United States

Mohammed Saad, Jingmei Lin, Department of Pathology, Indiana University, Indianapolis, IN 46202, United States

Hao Xie, Division of Medical Oncology, Mayo Clinic, Rochester, MN 55905, United States

Christopher R Jackson, Bing Ren, Department of Pathology, Dartmouth-Hitchcock Medical Center, Lebanon, PA 03766, United States

Cynthia Lawson, Dipti M Karamchandani, Department of Pathology, Pennsylvania State Health Milton S. Hershey Medical Center, Hershey, PA 17033, United States

Belen Quereda Bernabeu, Wei Jiang, Teena Dhir, Richard Zheng, Christopher W Schultz, Department of Pathology, Thomas Jefferson University Hospital, Philadelphia, PA 19107, United States

Dongwei Zhang, Department of Pathology and Lab Medicine, University of Rochester Medical Center, Rochester, NY 14642, United States

Courtney L Thomas, Xuchen Zhang, Department of Pathology, Yale University, New Haven, CT 06510, United States

Jinping Lai, Department of Pathology and Laboratory Medicine, Kaiser Permanente Sacramento Medical Center, Sacramento, CA 95825, United States

Michael Schild, Department of Pathology, Duke University, Durham, NC 27710, United States

Xuefeng Zhang, Department of Pathology, Cleveland Clinic, Cleveland, OH 44195, United States

Xiuli Liu, Department of Pathology, Immunology and Lab Medicine, University of Florida, Gainesville, FL 32610, United States

Corresponding author: Xiuli Liu, MD, PhD, Director, Professor, Department of Pathology, Immunology and Lab Medicine, University of Florida, 1345 Center Dr., Gainesville, FL 32610, United States. xiuliliu@ufl.edu

Abstract

statement: This study was reviewed and approved by the Institutional Review Board of University of Florida.

Informed consent statement:

Patients were not required to give informed consent to the study because our study was done retrospectively and data for study obtained after each patient agreed to treatment. Informed consent waiver was approved by Institutional review board of University of Florida.

Conflict-of-interest statement: The authors declare no competing interests in this study.

Data sharing statement: No additional data are available.

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

Open-Access: This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Received: December 30, 2019

Peer-review started: December 30, 2019

First decision: February 24, 2020

Revised: March 26, 2020

Accepted: May 12, 2020

Article in press: May 12, 2020

Published online: June 9, 2020

P-Reviewer: Liao R, Wang ZF, Zou J

S-Editor: Dou Y

L-Editor: A

E-Editor: Qi LL



BACKGROUND

In order to improve risk stratification and clinical management of the pancreatic ductal adenocarcinoma (PDAC), the American Joint Committee on Cancer (AJCC) has published its eighth edition staging manual. Some major changes have been introduced in the new staging system for both T and N categories. Given the rarity of resectable disease, distal pancreatic cancer is likely underrepresented in the published clinical studies, and how the impact of the staging system actually reflects on to clinical outcomes remain unclear.

AIM

To validate the AJCC 8th edition of TNM staging in distal PDAC.

METHODS

A retrospective cohort study was performed in seven academic medical centers in the United States. Clinicopathological prognostic factors associated with progression-free survival (PFS) and overall survival (OS) were evaluated through univariate and multivariate analyses.

RESULTS

Overall, 454 patients were enrolled in the study, and were divided into 2 subgroups: Invasive intraductal papillary mucinous neoplasms (IPMN) (115 cases) and non-IPMN associated adenocarcinoma (339 cases). Compared to invasive IPMN, non-IPMN associated adenocarcinomas are more common in relatively younger patients, have larger tumor size, are more likely to have positive lymph nodes, and are associated with a higher tumor (T) stage and nodal (N) stage, lymphovascular invasion, perineural invasion, tumor recurrence, and a worse PFS and OS. The cohort was predominantly categorized as stage 3 per AJCC 7th edition staging manual, and it's more evenly distributed based on 8th edition staging manual. T and N staging of both 7th and 8th edition sufficiently stratify PFS and OS in the entire cohort, although dividing into N1 and N2 according to the 8th edition does not show additional stratification. For PDAC arising in IPMN, T staging of the 7th edition and N1/N2 staging of the 8th edition appear to further stratify PFS and OS. For PDAC without an IPMN component, T staging from both versions fails to stratify PFS and OS.

CONCLUSION

The AJCC 8th edition TNM staging system provides even distribution for the T staging, however, it does not provide better risk stratification than previous staging system for distal pancreatic cancer.

Key words: Pancreatic cancer; Pancreatic ductal adenocarcinoma; Prognosis; Intraductal papillary mucinous neoplasms; Survival; American Joint Committee on Cancer

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: The American Joint Committee on Cancer 8th edition TNM staging system provides even distribution for the T staging, however, it does not provide better risk stratification than previous staging system for distal pancreatic cancer. This study also demonstrates the significant difference of clinical outcome and risk stratification between invasive intraductal papillary mucinous neoplasms and non-intraductal papillary mucinous neoplasms associated pancreatic ductal adenocarcinoma.

Citation: Yin F, Saad M, Xie H, Lin J, Jackson CR, Ren B, Lawson C, Karamchandani DM, Bernabeu BQ, Jiang W, Dhir T, Zheng R, Schultz CW, Zhang D, Thomas CL, Zhang X, Lai J, Schild M, Zhang X, Liu X. Validation of American Joint Committee on Cancer 8th edition of TNM staging in resected distal pancreatic cancer. *World J Gastrointest Pharmacol Ther* 2020; 11(2): 25-39

URL: <https://www.wjgnet.com/2150-5349/full/v11/i2/25.htm>

DOI: <https://dx.doi.org/10.4292/wjgpt.v11.i2.25>

INTRODUCTION

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive cancers. In the United States, PDAC is the fourth leading cause of cancer related deaths causing approximately 7% of all cancer mortalities, and has a dismal 5-year survival rate of less than 10%^[1,2]. A strong contributor to the low overall survival (OS) rate is a lack of early diagnostic symptoms, which results in PDAC frequently presenting at a late stage with locally advanced or metastatic disease^[3].

In order to improve risk stratification, staging, and clinical management of PDAC, the American Joint Committee on Cancer (AJCC) published its eighth edition staging manual for pancreatic cancer in October 2016^[4]. Some major changes have been introduced in the new staging system for both T and N categories. Of note, tumor size has become the only factor for the T staging except for pT4. pT1 is further subclassified into T1a (tumor 0.5 cm or less), T1b (tumor greater than 0.5 cm and less than 1 cm), and T1c (tumor greater than 1 cm but no more than 2 cm). The most important change was to replace the requirement of extra-pancreatic extension with tumor size (tumor greater than 4 cm) for a pT3 tumor. For the N category, N1 (regional lymph node metastasis) is subclassified into N1 (metastasis in 1-3 nodes) and N2 (metastasis in 4 or more nodes) in 8th edition staging system^[5]. Given the rarity of resectable disease, distal pancreatic cancer is likely underrepresented in the published clinical studies, and how the impact of the staging system actually reflects on to clinical outcomes remain unclear.

Intraductal papillary mucinous neoplasm (IPMN) is a pancreatic neoplasm with different epithelial types and histopathological grades^[6,7] that has the potential to progress into invasive carcinoma. The invasive IPMN and non-IPMN associated PDAC are likely derived through different molecular pathways^[8,9], and reports have suggested improved survival of patients with invasive IPMN as compared to patients with non-IPMN associated PDAC^[10,11]. However, whether invasive IPMN and non-IPMN PDAC share similar prognostic factors still remains unclear. So far, there is no specific staging system for invasive IPMN. Conventionally, it is staged using the AJCC system primarily developed and validated for non-IPMN associated PDAC. The size of the invasive component in invasive IPMN is subjective due to variability in sampling and measurement techniques and may not be a reliable parameter for staging.

Until now, the majority of validation studies for AJCC 8th edition were performed in patients with solely or predominantly PDAC in the head of pancreas^[5,12-16]. The current study was designed to validate the major T and N staging changes by the AJCC 8th edition of TNM staging manual in a cohort of patients with resected distal pancreatic carcinoma, as well as in a sub-cohort of patients with invasive IPMN or non-IPMN associated PDAC. Univariate and multivariable survival analyses were performed to identify prognostic factors in a multi-centered large-scale study.

MATERIALS AND METHODS

Patient characteristics

After approval from Institutional Review Boards from individual institutions, a retrospective cohort study was performed with cases collected from seven academic medical centers in the United States (University of Florida, Indiana University, Dartmouth-Hitchcock Medical Center, Penn State Health Hershey Medical Center, Thomas Jefferson University Hospital, University of Rochester Medical Center, and Yale University).

Clinicopathological data of resected distal PDAC cases were retrieved from year 2005 to 2018. Other tumor subtypes such as non-invasive IPMN, non-invasive mucinous cystic neoplasm, neuroendocrine neoplasm, and acinar cell carcinoma were excluded. Those cases which underwent preoperative neoadjuvant therapy were excluded from this study.

Histopathology review

Histopathological data were collected through reviewing pathology reports and glass slides. Oncological information was collected including tumor size, type, differentiation, margin status, splenic vasculature involvement, and lymph node status. All cases were re-staged based on the AJCC 7th and 8th edition, respectively. Splenic vein involvement was defined as tumor invading through the venous wall. Splenic artery involvement was defined as tumor invading into or through the arterial wall.

Clinical information review

Clinical information including patient's age, gender, radiographic studies, recurrence, metastasis, and survival status was collected through reviewing the medical records from the time of resection until September 2018. The progression free survival (PFS) is defined as the interval between the date of surgery and the date of initial recurrence and/or metastasis of tumor or death. The OS is defined as the interval between the date of surgery and the date of death.

Statistical analysis

Continuous variables were summarized as median and interquartile range (IQR) and compared with Wilcoxon rank sum test. Categorical variables were summarized as counts and percentages and compared with Fisher's exact test. PFS and OS were evaluated using Kaplan-Meier curves, and analyzed using log-rank analysis. Cox proportional hazards regression models were used in univariate and multivariable survival analyses to identify factors associated with PFS and OS. The proportionality assumption was assessed graphically using log (-log) plots and quantitatively using the Z statistic. All tests were two-sided and performed in R (version 3.5.3). A *P* value of < 0.05 was considered statistically significant.

RESULTS

Patient characteristics

The study enrolled 454 patients with resected distal pancreatic cancer. The age of the patients ranged from 27 to 91 years, with a mean age of 67.1 years, 53.5% of the patients were female (*n* = 243), and 46.5% were male (*n* = 211). Pathologic demographics and major pathologic features are summarized in [Table 1](#).

Stratification of patient survival in entire cohort

The majority of patients were categorized as stage pT3 per AJCC 7th edition staging manual, with 32 patients (7.0%), 50 patients (11.0%), and 351 patients (77.3%) being classified as pT1, pT2, and pT3, respectively. When categorizing based upon the AJCC 8th edition staging manual, the distribution was relatively more even, with 76 patients (16.7%), 202 patients (44.5%), and 166 patients (36.6%) classified as pT1, pT2, and pT3, respectively. T staging of both 7th and 8th systems sufficiently stratified PFS and OS in the entire cohort ([Figure 1A, B, E and F](#)).

Among the 237 patients with positive lymph nodes (pN1 per 7th edition), 180 patients (75.9%) were classified as pN1, and 57 patients (24.1%) were classified as pN2 based on AJCC 8th edition. N staging of both 7th and 8th systems sufficiently stratified PFS and OS in the entire cohort, although dividing into N1 and N2 according to the 8th edition did not show additional stratification ([Figure 1C, D, G and H](#)).

Invasive IPMN vs non-IPMN-associated adenocarcinoma

The diagnostic group (IPMN *vs* non-IPMN) is an important prognostic factor in resected distal pancreatic cancer. In the cohort, 115 patients (25.3%) and 339 patients (74.7%) were diagnosed as invasive IPMN and non-IPMN associated PDAC, respectively. There was no gender difference between the 2 groups, with a slight female predominance in both groups (53.0% female in IPMN group *vs* 53.7% in non-IPMN group). Compare to the invasive IPMN group, non-IPMN associated PDAC are more commonly seen in relatively younger patients (median age 66.7 years in non-IPMN group *vs* 70.0 years in IPMN group; *P* = 0.003), and have larger tumor size [median tumor size 3.6 cm (IQR: 2.5-5.2) in non-IPMN group *vs* median tumor size 3.0 cm (IQR: 2.0-4.5) in IPMN group; *P* = 0.012]. Non-IPMN associated PDAC are also associated with higher tumor (T) stage and nodal (N) stage, lymphovascular invasion (LVI), perineural invasion, tumor recurrence, as well as worse PFS and OS ([Table 1](#)).

Prognostic factors and stratification of patient survival with invasive IPMN

A total of 115 patients with invasive IPMN were included in the study. Sixty-one patients (54.0%) were female and fifty-four (47.0%) were male, with the median age of 70.0 years ([Table 1](#)).

In univariable analysis for invasive IPMN, tumor size, poor differentiation, pT3 stage (8th edition staging manual), positive lymph node, pN2 stage (8th edition staging manual), and pathologic splenic vein invasion were significantly associated with both poor PFS and poor OS. LVI, splenic artery invasion, and splenic parenchyma invasion were only associated with PFS. Positive resection margin and perineural invasion were only associated with OS. In multivariable analysis, only pT3 (8th edition staging manual) remained as independent prognosticator for OS ([Table 2](#)).

Table 1 Clinical and pathological characteristics of pancreatic ductal adenocarcinoma patients

Feature	Level	Total cohort	Subcohort		
			Invasive IPMN	Non-IPMN associated PDAC	P value
		Median (IQR)			
Age (in yr)		67.6 (60.0, 74.8)	70.0 (64.1, 75.5)	66.7 (59.4, 74.0)	0.003
Tumor size (in cm)		3.5 (2.5, 5.0)	3.0 (2.0, 4.5)	3.6 (2.5, 5.2)	0.012
		Median (95%CI)			
PFS (in mo)		21.0 (17.0, 27.0)	NR (47.0, NR)	17.0 (13.0, 22.0)	< 0.001
OS (in mo)		21.0 (19.0, 24.0)	60.0 (28.0, 69.0)	19.0 (18.0, 22.0)	< 0.001
		n (%)			
Gender (male/female)	Female	243 (53.5)	61 (53.0)	182 (53.7)	0.991
	Male	211 (46.5)	54 (47.0)	157 (46.3)	
Tumor differentiation	Well	41 (9.0)	15 (13.4)	26 (7.9)	0.103
	Moderate	271 (59.7)	71 (63.4)	200 (61.0)	
	Poor	128 (28.2)	26 (23.2)	102 (31.1)	
AJCC 8 th ed staging system	T1	76 (16.7)	32 (27.8)	44 (13.0)	0.003
	T2	202 (44.5)	46 (40.0)	156 (46.2)	
	T3	166 (36.6)	36 (31.3)	130 (38.5)	
AJCC 8 th ed staging system	N0	216 (47.6)	69 (60.0)	147 (43.4)	0.004
	N1	181 (39.9)	31 (27.0)	150 (44.2)	
	N2	57 (12.6)	15 (13.0)	42 (12.4)	
Lymphovascular invasion	Positive	219 (48.2)	44 (38.3)	175 (51.6)	0.011
	Negative	219 (48.2)	69 (60.0)	150 (44.2)	
	Indeterminant	16 (3.5)	2 (1.7)	14 (4.1)	
Perineural invasion	Positive	366 (80.6)	80 (69.6)	286 (84.4)	0.001
	Negative	82 (18.1)	34 (29.6)	48 (14.2)	
	Indeterminant	6 (1.3)	1 (0.9)	5 (1.5)	
Recurrence/metastasis	Present	218 (48.0)	43 (37.4)	175 (51.6)	0.015
	Absent	236 (52.0)	72 (62.6)	164 (48.4)	
Splenic parenchymal invasion	Present	25 (5.5)	2 (1.7)	23 (6.9)	0.067
	Absent	425 (93.6)	113 (98.3)	312 (93.1)	

AJCC: American Joint Committee on Cancer; IPMN: Intraductal papillary mucosal neoplasm; PDAC: Pancreatic ductal adenocarcinoma; PFS: Progression-free survival; OS: Overall survival; IQR: Interquartile range; NR: Not reached.

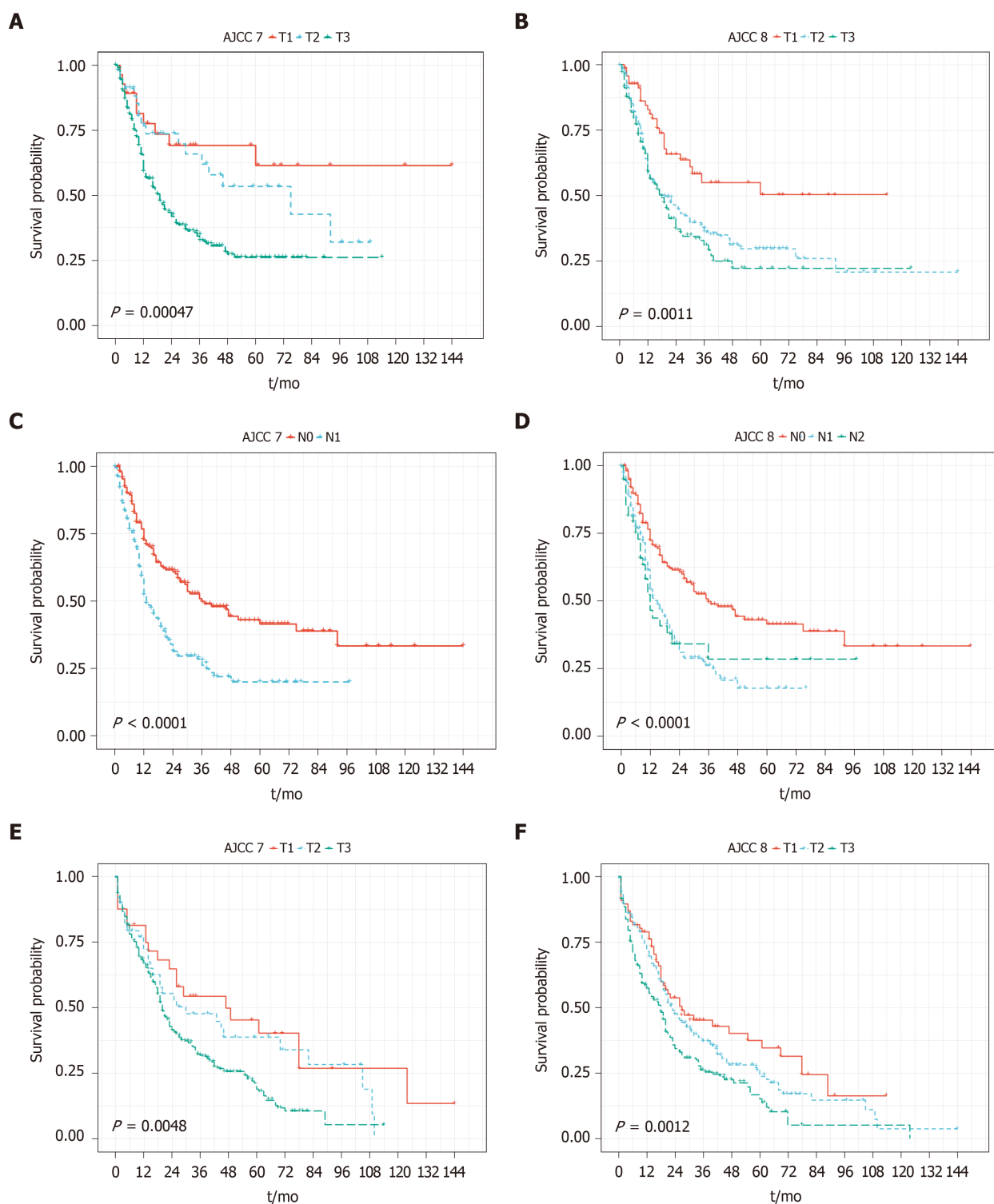
Per AJCC 7th edition staging manual, 13 patients (11.3%), 21 patients (18.3%), and 77 patients (67.0%) were classified as pT1, pT2, and pT3, respectively. Per AJCC 8th edition, 32 patients (27.8%), 46 patients (40.0%), and 36 patients (31.3%) were classified as pT1, pT2 and pT3, respectively. Among 46 patients with lymph node metastasis (pN1 per AJCC 7th edition), 31 patients and 15 patients were further diagnosed with pN1 and pN2 tumor according to AJCC 8th edition. T staging of the 7th system appeared to further stratify PFS and OS, however N1/N2 staging of the 8th edition appeared to further stratify PFS and OS (Figure 2).

Stratification of patient survival with non-IPMN associated PADC

A total of 339 patients with non-IPMN associated PDAC were included in the study. One hundred eighty-two patients (53.7%) were female and one hundred fifty-seven (46.3%) were male, with the median age of 66.7 years (Table 1).

In univariable analysis for non-IPMN associated PADC, nodal metastasis, pN1 stage (8th edition), and LVI were significantly associated with both PFS and OS. Tumor size, pathologic or radiographic evidence of splenic vein invasion, and adjuvant chemotherapy were all significantly associated with OS. In multivariable analysis, however, only pN1 (8th edition staging manual) remained as an independent prognosticator for both PFS and OS, while adjuvant chemotherapy remained as independent prognosticator for OS only (Table 3).

Per AJCC 7th edition staging manual, 19 patients (5.6%), 29 patients (8.6%), and 274



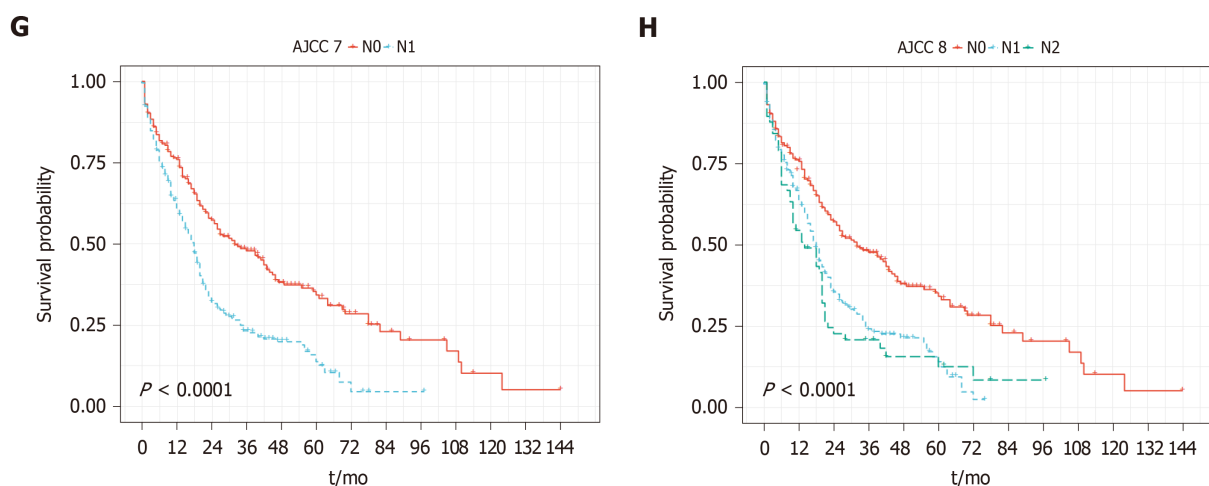


Figure 1 Kaplan-Meier curves for survival of the resected distal pancreatic cancer. A: PFS stratified according to AJCC 7th edition T staging; B: PFS stratified according to the AJCC 8th edition T staging; C: PFS stratified according to AJCC 7th edition N staging; D: PFS stratified according to the AJCC 8th edition N staging; E: OS stratified according to AJCC 7th edition T staging; F: OS stratified according to the AJCC 8th edition T staging; G: OS stratified according to AJCC 7th edition N staging; H: OS stratified according to the AJCC 8th edition N staging. PFS: Progression-free survival; AJCC: American Joint Committee on Cancer; OS: Overall survival.

patients (80.8%) were classified as pT1, pT2, and pT3, respectively. Per AJCC 8th edition staging manual, 44 patients (13.0%), 149 patients (44.0%), and 130 patients (38.3%) were classified as pT1, pT2 and pT3, respectively. Among 191 patients with lymph node metastasis (pN1 per AJCC 7th edition staging manual), 149 patients and 42 patients were further sub classified into pN1 and pN2 tumor according to AJCC 8th edition. For PDAC without IPMN component, T staging from both staging systems failed to stratify PFS and OS. N staging of both staging systems could stratify PFS and OS, although dividing N category into pN1 and pN2 as in the 8th edition staging manual did not add further value to this group (Figure 3).

DISCUSSION

In this study, we evaluated the prognostic relevance of the 8th edition AJCC TNM staging manual in a large United States cohort of distal pancreatic cancer. The new staging system recognizes tumor size as one of the most important prognostic factors for tumor staging. In practice, the vast majority of PDAC cases had spread into the peripancreatic soft tissue and were staged as pT3 even after the introduction of the 5th edition of the AJCC staging manual in 1997. By removing the diagnostic criteria of extra pancreatic extension for pT3, patients with PDAC are distributed more evenly using the new AJCC 8th staging system.

Even with relatively strict selection criteria, wide heterogeneity of diagnostic groups was still inevitable within our study subjects. To simplify this issue, we classified the cases as invasive IPMN and non-IPMN-associated adenocarcinoma. Consistent with previous reports^[10,11], invasive IPMN is associated with lower T stage and N stage, as well as better survival in our study. The study revealed multiple independent prognostic factors for patients with distal pancreatic cancer, such as poor differentiation, tumor size, pT3 stage (8th edition staging manual), positive lymph node, pN2 stage (8th edition staging manual), LVI, splenic artery or vein invasion, positive resection margin, and splenic parenchymal invasion. Interestingly, very limited overlap was observed among patients with invasive IPMN and non-IPMN associated PDAC. For invasive IPMN patients, pT3 is the only significant prognostic factor for OS upon multivariable analysis. On the other hand, lymph node metastasis (pN1 stage per 8th edition) appears to be the only independent prognosticator for both PFS and OS in non-IPMN-associated adenocarcinoma. The underlying mechanism account for these differences as well as their distinct clinical behavior and survival is not clear, but the molecular pathways underlying tumorigenesis for each entity might provide clues in the future.

Consistent with a recent study^[16], our study demonstrates that the AJCC 7th edition T staging better stratifies survival in patients with invasive IPMN. Tumor size alone is not an independent prognostic factor based on multivariable analysis^[16]. It's interesting to identify pT3 (8th edition) as the only significant risk factor for survival in

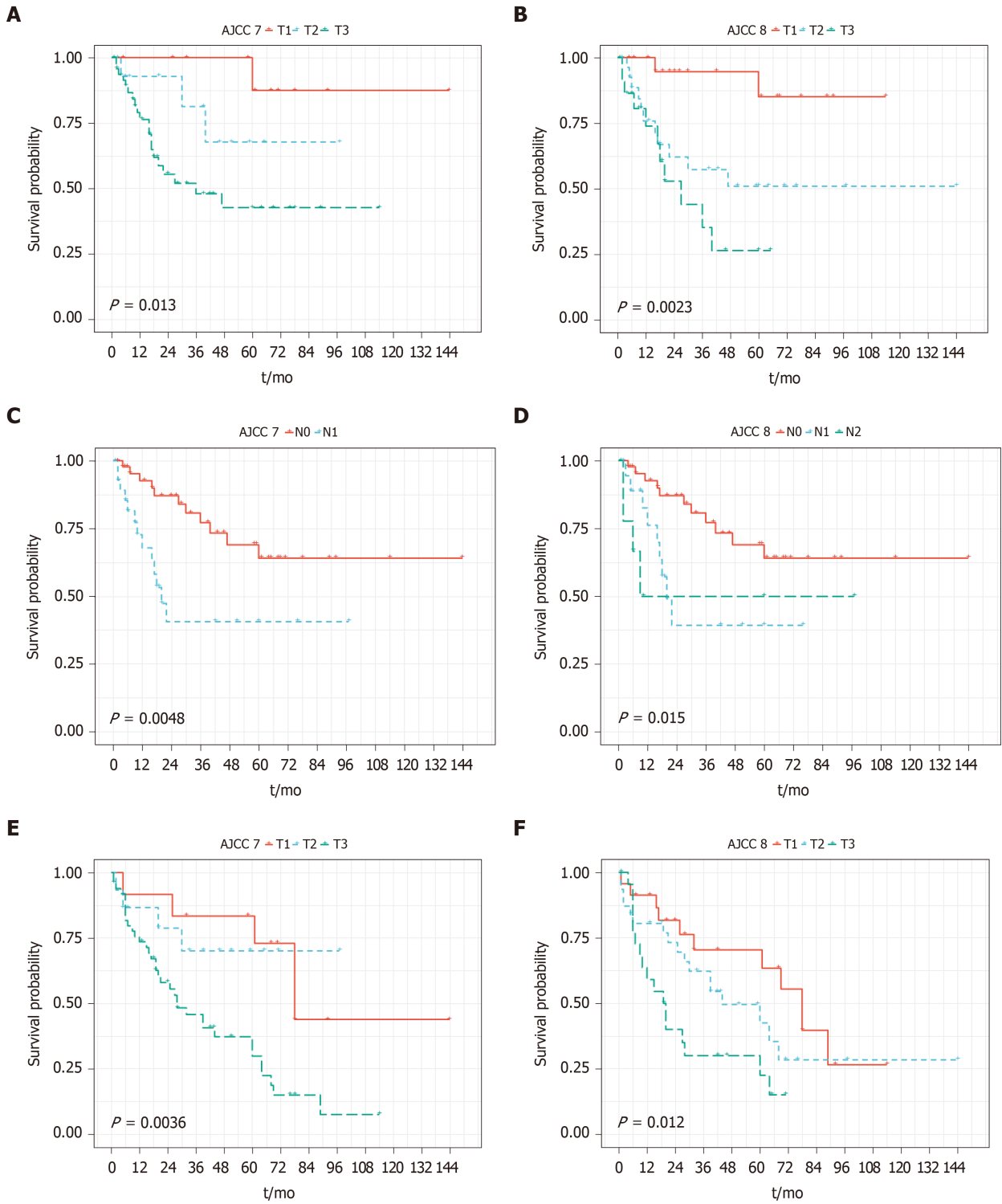
Table 2 Univariate and multivariable analysis for progression-free survival and overall survival in invasive intraductal papillary mucinous neoplasm

Feature	Level	PFS		OS	
		HR (95%CI), <i>P</i> value			
Gender		1.67 (0.91-3.05), <i>P</i> = 0.10	-	1.33 (0.85-2.08), <i>P</i> = 0.22	-
Age		0.99 (0.96-1.02), <i>P</i> = 0.52	-	1.01 (0.98-1.03), <i>P</i> = 0.54	-
Tumor size		1.18 (1.05-1.32), <i>P</i> = 0.01	-	1.10 (1.00-1.21), <i>P</i> = 0.04	-
Tumor differentiation	Well	-	-	-	-
	Moderate	2.71 (0.82-8.91), <i>P</i> = 0.10	12290265.82 (0.00-Inf), <i>P</i> = 1.00	1.04 (0.53-2.02), <i>P</i> = 0.92	1.62 (0.34-7.66), <i>P</i> = 0.55
	Poor	3.88 (1.06-14.27), <i>P</i> = 0.04	2274054.50 (0.00-Inf), <i>P</i> = 1.00	2.31 (1.10-4.86), <i>P</i> = 0.03	1.78 (0.15-20.67), <i>P</i> = 0.64
Positive lymph node		1.19 (1.05-1.35), <i>P</i> = 0.01	-	1.19 (1.07-1.31), <i>P</i> < 0.01	-
T stage (AJCC 8 th edition staging manual)	T1	-	-	-	-
	T2	2.69 (1.14-6.37), <i>P</i> = 0.02	0.81 (0.07-9.31), <i>P</i> = 0.87	1.65 (0.92-2.97), <i>P</i> = 0.09	0.89 (0.09-8.48), <i>P</i> = 0.92
	T3	3.48 (1.42-8.51), <i>P</i> = 0.01	5.29 (0.44-62.97), <i>P</i> = 0.19	2.28 (1.23-4.24), <i>P</i> = 0.01	26.22 (2.13-322.77), <i>P</i> = 0.01
N stage (AJCC 8 th edition staging manual)	N0	-	-	-	-
	N1	2.03 (1.03-4.02), <i>P</i> = 0.04	13.78 (1.15-165.63), <i>P</i> = 0.04	1.58 (0.93-2.67), <i>P</i> = 0.09	1.17 (0.24-5.70), <i>P</i> = 0.85
	N2	3.65 (1.60-8.34), <i>P</i> < 0.01	29.12 (0.87-979.78), <i>P</i> = 0.06	2.52 (1.36-4.65), <i>P</i> < 0.01	1.63 (0.10-27.11), <i>P</i> = 0.73
Lymphovascular invasion		2.12 (1.16-3.90), <i>P</i> = 0.02	0.31 (0.04-2.41), <i>P</i> = 0.26	1.43 (0.90-2.28), <i>P</i> = 0.13	-
Perineural invasion		1.99 (0.98-4.04), <i>P</i> = 0.06	-	2.45 (1.39-4.33), <i>P</i> < 0.01	2.67 (0.54-13.22), <i>P</i> = 0.23
Splenic artery invasion		5.30 (1.41-19.94), <i>P</i> = 0.01	2.44 (0.10-62.16), <i>P</i> = 0.59	1.70 (0.59-4.88), <i>P</i> = 0.32	-
Splenic vein invasion		18.69 (4.57-76.48), <i>P</i> < 0.01	5.28 (0.22-129.25), <i>P</i> = 0.31	2.66 (1.08-6.55), <i>P</i> = 0.03	5.62 (0.61-51.99), <i>P</i> = 0.13
Positive margin		1.25 (0.30-5.19), <i>P</i> = 0.76	-	3.14 (1.49-6.62), <i>P</i> < 0.01	0.00 (0.00-Inf), <i>P</i> = 1.00
Splenic parenchyma invasion		14.93 (1.83-121.81), <i>P</i> = 0.01	1.00 (1.00-1.00), <i>P</i> = NaN	1.23 (0.17-8.87), <i>P</i> = 0.84	-
Adjuvant radiation therapy		0.97 (0.52-1.81), <i>P</i> = 0.92	-	0.81 (0.48-1.37), <i>P</i> = 0.43	-
Adjuvant chemotherapy		2.50 (0.89-7.00), <i>P</i> = 0.08	-	0.69 (0.39-1.22), <i>P</i> = 0.20	-
Radiographic splenic artery invasion		2.12 (0.85-5.29), <i>P</i> = 0.11	-	1.45 (0.59-3.56), <i>P</i> = 0.41	-
Radiographic splenic vein invasion		2.27 (1.04-4.94), <i>P</i> = 0.04	2.88 (0.33-24.96), <i>P</i> = 0.34	1.46 (0.68-3.13), <i>P</i> = 0.33	-

AJCC: American Joint Committee on Cancer; PFS: Progression-free survival; OS: overall survival.

our study. One possible explanation is that majority of the pT3 tumor (> 4 cm per 8th edition staging manual) extend into peripancreatic soft tissue, and would also be staged as pT3 per the 7th edition staging manual^[17]. In contrast to the T staging, N1/N2 staging of the 8th edition staging manual appears to further stratify PFS and OS in invasive IPMN.

An unexpected finding in this study is that T staging from both staging systems failed to stratify PFS and OS in resected distal non-IPMN associated PDAC. Multiple studies have demonstrated the clinical relevance, reproducibility, and risk stratification of the AJCC 8th edition staging manual^[5,12-15]. However, due to the relative rarity, resected distal PDAC is likely underrepresented among those published studies. It should be noted that the stage-independent OS in distal pancreatic cancer is much worse as compared to its counterpart in the pancreatic head, and tumor location itself has been considered as a prognostic factor for survival in pancreatic cancer patients^[18,19]. Delay in diagnosis is likely the major reason for its poor prognosis, although other facts may also play a role. For example, distal pancreatic cancer patients are significantly older at the time of diagnosis, and less dissectible lymph nodes are present at the distal portion of the pancreas^[19]. Unlike invasive IPMN, lymph node metastasis is the most important prognostic factor for survival in non-IPMN associated PDAC. N staging of both 7th and 8th edition could stratify PFS and



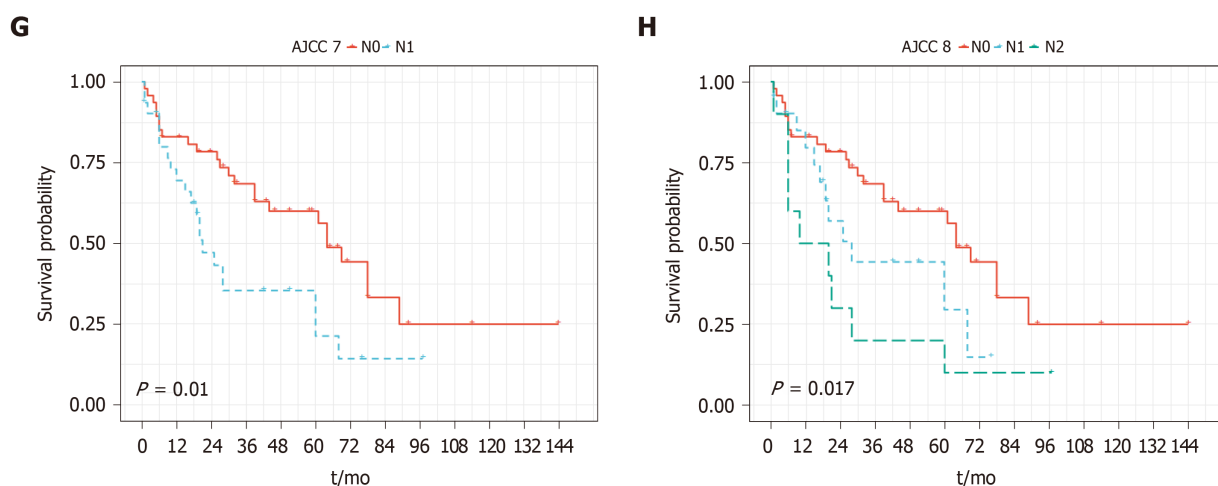


Figure 2 Kaplan-Meier curves for survival of the invasive intraductal papillary mucinous neoplasm. A: PFS stratified according to AJCC 7th edition T staging; B: PFS stratified according to the AJCC 8th edition T staging; C: PFS stratified according to AJCC 7th edition N staging; D: PFS stratified according to the AJCC 8th edition N staging; E: OS stratified according to AJCC 7th edition T staging; F: OS stratified according to the AJCC 8th edition T staging; G: OS stratified according to AJCC 7th edition N staging; H: OS stratified according to the AJCC 8th edition N staging. PFS: Progression-free survival; AJCC: American Joint Committee on Cancer; OS: Overall survival.

OS, although dividing N category into pN1 and pN2 in the 8th edition staging manual did not add further value in this group. The prognostic value of lymph node involvement has also been reported in a recent large scaled multi-institutional study. Morales-Oyarvide *et al.*^[20] demonstrated that the AJCC 8th edition staging system was a practical classification of lymph node involvement. Similar to other related validation studies^[5,12-16], predominant patient population in this study (74%) had PDAC in the head of pancreas, and only 14% of the patients had PDAC in the tail of pancreas. Notably, the prognostic value of lymph node involvement was weaker in patients with resected distal pancreatic cancer^[20].

This study has several strengths. It was a multicentered large-scale study designed to validate the major changes in the newer AJCC TNM staging system for resected distal pancreatic cancers. This study provides important insights for future revision of the AJCC staging system. Furthermore, all cases were re-staged according to the AJCC 7th or 8th edition and re-reviewed by pathologists subspecialized in gastrointestinal and pancreatic pathology. In addition, we included several potentially prognostic parameters such as radiographic evidence and histologic evidence of splenic vasculature and parenchymal invasion. In our study, we also compared the clinical behavior and risk stratification for invasive IPMN and non-IPMN associated PDAC.

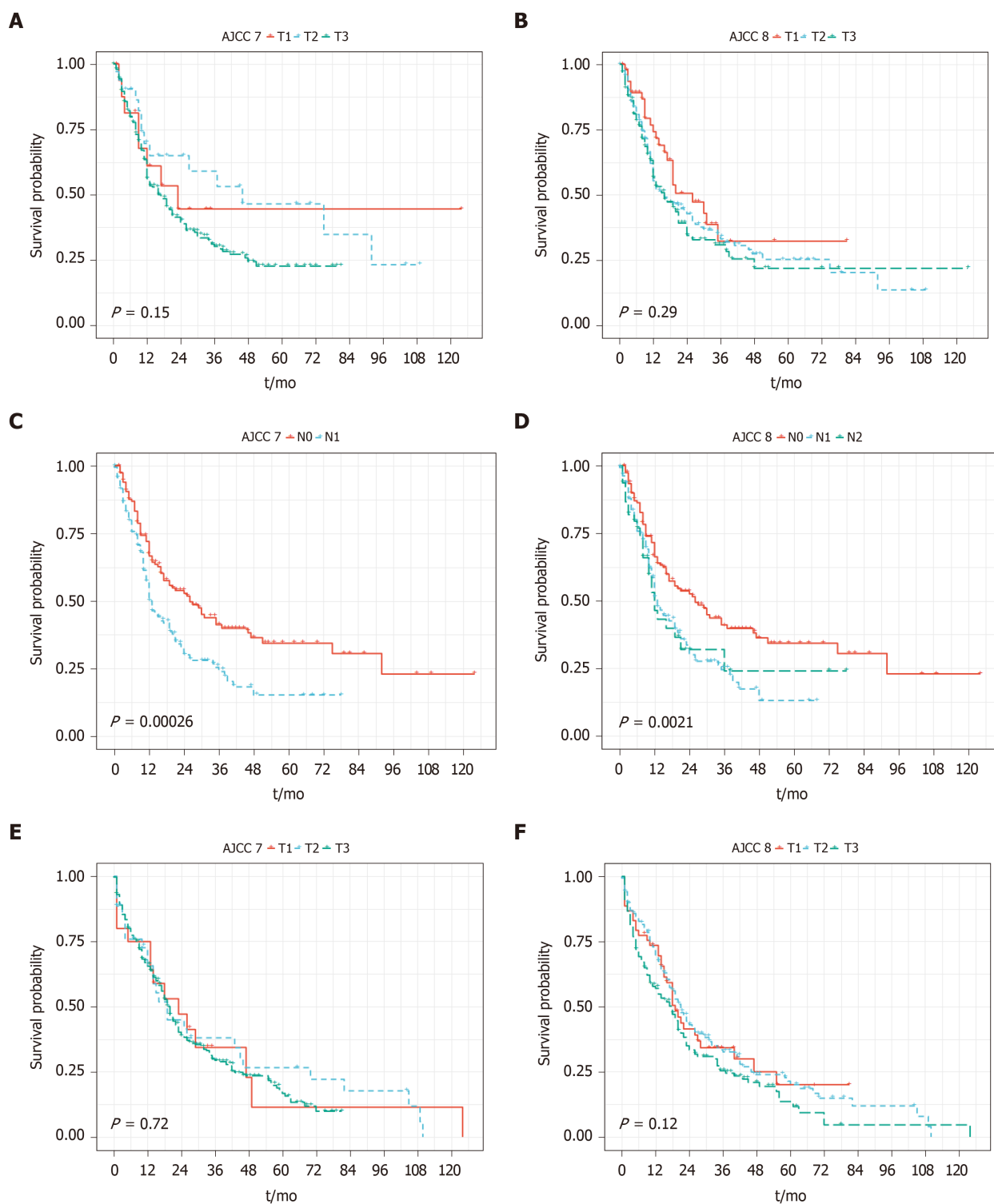
Our study also has some limitations. First, all cases were collected from major academic cancer centers that might have introduced selection bias. Second, the cases were collected from a 13-year period of time (2005-2018) during which multiple different AJCC staging editions (5th to 7th edition) had been applied for pancreatic cancer staging. However, all cases in this study were re-staged according to the 7th and 8th AJCC editions. The size of invasive IPMN was recorded from the surgical pathology report as this parameter is difficult to generate as it depends on the combination of macroscopic examination, sampling, and histology; histology review with measurement on slide alone does not provide an accurate assessment of this parameter.

In conclusion, our study demonstrates that the AJCC 8th edition TNM staging system provides even distribution for the T staging, however, it does not improve risk stratification when compared to previous staging system for resectable distal pancreatic cancers. Our study also demonstrates the significant difference of clinical outcome and risk stratification between invasive IPMN and non-IPMN associated PDAC. Our study indicates that tumor location and subtype are important factors to be considered in future revisions of the AJCC staging system for pancreatic cancer.

Table 3 Univariate and multivariable analysis for progression-free survival and overall survival in non-intraductal papillary mucinous neoplasm pancreatic ductal adenocarcinoma

Feature	Level	PFS		OS	
		HR (95%CI), <i>P</i> value			
Gender		0.89 (0.66-1.20), <i>P</i> = 0.43	-	1.05 (0.82-1.35), <i>P</i> = 0.69	-
Age		0.99 (0.98-1.01), <i>P</i> = 0.29	-	1.01 (1.00-1.03), <i>P</i> = 0.05	1.00 (0.98-1.02), <i>P</i> = 0.93
Tumor size		1.07 (0.99-1.15), <i>P</i> = 0.09	-	1.08 (1.02-1.16), <i>P</i> = 0.01	-
Tumor differentiation	Well	-	-	-	-
	Moderate	1.11 (0.64-1.91), <i>P</i> = 0.71	-	1.33 (0.78-2.27), <i>P</i> = 0.29	1.56 (0.65-3.78), <i>P</i> = 0.32
	Poor	1.21 (0.68-2.14), <i>P</i> = 0.52	-	1.72 (0.99-2.98), <i>P</i> = 0.05	2.23 (0.90-5.53), <i>P</i> = 0.08
Positive lymph node		1.06 (1.01-1.12), <i>P</i> = 0.03	-	1.08 (1.03-1.13), <i>P</i> < 0.01	-
T stage (AJCC 8 th edition staging manual)	T1	-	-	-	-
	T2	1.39 (0.83-2.31), <i>P</i> = 0.21	1.22 (0.73-2.05), <i>P</i> = 0.45	0.97 (0.64-1.46), <i>P</i> = 0.87	1.12 (0.57-2.20), <i>P</i> = 0.73
	T3	1.56 (0.92-2.62), <i>P</i> = 0.10	1.19 (0.68-2.07), <i>P</i> = 0.54	1.33 (0.88-2.03), <i>P</i> = 0.18	0.80 (0.39-1.64), <i>P</i> = 0.54
N stage (AJCC 8 th edition staging manual)	N0	-	-	-	-
	N1	1.73 (1.25-2.39), <i>P</i> < 0.01	1.59 (1.09-2.32), <i>P</i> = 0.02	1.75 (1.33-2.32), <i>P</i> < 0.01	2.54 (1.41-4.58), <i>P</i> < 0.01
	N2	1.57 (0.96-2.56), <i>P</i> = 0.07	1.47 (0.82-2.63), <i>P</i> = 0.20	1.83 (1.23-2.72), <i>P</i> < 0.01	2.45 (0.92-6.51), <i>P</i> = 0.07
Lymphovascular invasion		1.43 (1.05-1.95), <i>P</i> = 0.02	1.07 (0.73-1.56), <i>P</i> = 0.74	1.46 (1.12-1.89), <i>P</i> < 0.01	0.82 (0.45-1.49), <i>P</i> = 0.51
Perineural invasion		1.16 (0.76-1.78), <i>P</i> = 0.48	-	1.19 (0.83-1.73), <i>P</i> = 0.35	-
Splenic artery invasion		1.41 (0.71-2.80), <i>P</i> = 0.33	-	1.38 (0.81-2.36), <i>P</i> = 0.24	-
Splenic vein invasion		1.35 (0.82-2.23), <i>P</i> = 0.24	-	2.09 (1.44-3.03), <i>P</i> < 0.01	1.59 (0.83-3.02), <i>P</i> = 0.16
Positive margin		0.78 (0.43-1.40), <i>P</i> = 0.40	-	1.20 (0.78-1.82), <i>P</i> = 0.41	-
Splenic invasion		1.65 (0.95-2.85), <i>P</i> = 0.07	-	1.32 (0.82-2.11), <i>P</i> = 0.25	-
Adjuvant radiation therapy		0.93 (0.69-1.27), <i>P</i> = 0.66	-	0.85 (0.64-1.12), <i>P</i> = 0.25	-
Adjuvant chemotherapy		1.45 (0.90-2.34), <i>P</i> = 0.13	-	0.51 (0.37-0.71), <i>P</i> < 0.01	0.34 (0.20-0.58), <i>P</i> < 0.01
Radiographic splenic artery invasion		1.27 (0.87-1.84), <i>P</i> = 0.21	-	1.13 (0.81-1.59), <i>P</i> = 0.47	-
Radiographic splenic vein invasion		1.26 (0.88-1.80), <i>P</i> = 0.20	-	1.51 (1.10-2.07), <i>P</i> = 0.01	1.08 (0.65-1.80), <i>P</i> = 0.75

AJCC: American Joint Committee on Cancer; PFS: Progression-free survival; OS: Overall survival.



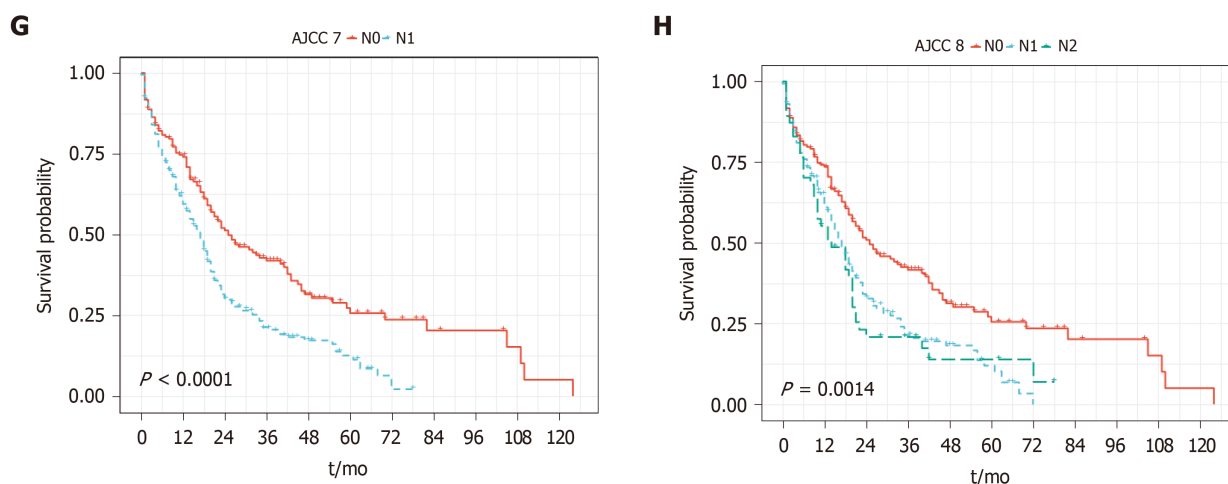


Figure 3 Kaplan-Meier curves for survival of the non-intraductal papillary mucinous neoplasm associated pancreatic ductal adenocarcinoma. A: PFS stratified according to AJCC 7th edition T staging; B: PFS stratified according to the AJCC 8th edition T staging; C: PFS stratified according to AJCC 7th edition N staging; D: PFS stratified according to the AJCC 8th edition N staging; E: OS stratified according to AJCC 7th edition T staging; F: OS stratified according to the AJCC 8th edition T staging; G: OS stratified according to AJCC 7th edition N staging; H: OS stratified according to the AJCC 8th edition N staging. PFS: Progression-free survival; AJCC: American Joint Committee on Cancer; OS: Overall survival.

ARTICLE HIGHLIGHTS

Research background

Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer related death worldwide. For the purpose of better risk stratification and clinical management, the American Joint Committee on Cancer (AJCC) published the eighth edition staging manual for pancreatic cancer that has introduced significant changes for both tumor (T) staging and nodal (N) staging. Notably majority of the validation studies were focused on PDAC in the head of pancreas, and the resected distal pancreatic adenocarcinoma was likely underrepresented due to its clinical rarity. Whether the AJCC 8th edition staging manual provides equal risk stratification for both invasive intraductal papillary mucinous neoplasm (IPMN) and non-IPMN associated PDAC is also unclear.

Research motivation

It's important to investigate whether the new AJCC staging system provides risk stratification in patients with distal pancreatic cancers. It's also important to investigate the clinical behavior and risk stratification for invasive IPMN and non-IPMN associated PDAC.

Research objectives

This study aims to validate the AJCC 8th edition staging manual in distal PDAC.

Research methods

Clinicopathological data of resected distal PDAC cases were retrieved. All cases were re-staged based on the AJCC 7th and 8th edition, respectively. Categorical variables were compared with Fisher's exact test. Progression-free survival (PFS) and overall survival (OS) were evaluated through Kaplan-Meier curves and univariate/multivariate analyses.

Research results

T and N staging of both 7th and 8th edition sufficiently stratify PFS and OS in the entire cohort, although dividing into N1 and N2 according to the 8th edition does not show additional stratification. For PDAC arising in IPMN, T staging of the 7th edition and N1/N2 staging of the 8th edition appear to further stratify PFS and OS. For PDAC without an IPMN component, T staging from both versions fails to stratify PFS and OS.

Research conclusions

The AJCC 8th edition TNM staging system provides even distribution for the T staging, however, it does not provide better risk stratification than previous staging system for distal pancreatic cancer. There is significant difference of clinical outcome and risk stratification between invasive IPMN and non-IPMN associated PDAC.

Research perspectives

Tumor location and subtype are important factors to be considered in future revisions of the AJCC staging system for pancreatic cancer.

ACKNOWLEDGEMENTS

We thank all participating institutions for the support of this study.

REFERENCES

- 1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34 [PMID: 30620402 DOI: 10.3322/caac.21551]
- 2 Cooperman AM, Bruckner H, Snady H, Hammerman H, Fader A, Feld M, Golier F, Rush T, Siegal J, Kasmin F, Cohen S, Wayne MG, Iskandar ME, Steele JG. Cancer of the Pancreas-Actual 5, 10, and 20+Year Survival: The Lucky and Fortunate Few. *Surg Clin North Am* 2018; **98**: 73-85 [PMID: 29191279 DOI: 10.1016/j.suc.2017.09.007]
- 3 Christein JD, Kendrick ML, Iqbal CW, Nagorney DM, Farnell MB. Distal pancreatectomy for resectable adenocarcinoma of the body and tail of the pancreas. *J Gastrointest Surg* 2005; **9**: 922-927 [PMID: 16137585]
- 4 Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, Sullivan DC, Jessup JM, Brierley JD, Gaspar LE, Schilsky RL, Balch CM, Winchester DP, Asare EA, Madera M, Gress DM, Meyer LR. American Joint Committee on Cancer. AJCC cancer staging manual. 8th ed. New York, NY: Springer; 2017
- 5 Kamarajah SK, Burns WR, Frankel TL, Cho CS, Nathan H. Validation of the American Joint Commission on Cancer (AJCC) 8th Edition Staging System for Patients with Pancreatic Adenocarcinoma: A Surveillance, Epidemiology and End Results (SEER) Analysis. *Ann Surg Oncol* 2017; **24**: 2023-2030 [PMID: 28213792 DOI: 10.1245/s10434-017-5810-x]
- 6 Adsay V, Mino-Kenudson M, Furukawa T, Basturk O, Zamboni G, Marchegiani G, Bassi C, Salvia R, Malleo G, Paiella S, Wolfgang CL, Matthaei H, Offerhaus GJ, Adham M, Bruno MJ, Reid MD, Krasinskas A, Klöppel G, Ohike N, Tajiri T, Jang KT, Roa JC, Allen P, Fernández-del Castillo C, Jang JY, Klimstra DS, Hruban RH; Members of Verona Consensus Meeting, 2013. Pathologic Evaluation and Reporting of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Other Tumoral Intraepithelial Neoplasms of Pancreatobiliary Tract: Recommendations of Verona Consensus Meeting. *Ann Surg* 2016; **263**: 162-177 [PMID: 25775066 DOI: 10.1097/SLA.0000000000001173]
- 7 Furukawa T, Hatori T, Fujita I, Yamamoto M, Kobayashi M, Ohike N, Morohoshi T, Egawa S, Unno M, Takao S, Osako M, Yonezawa S, Mino-Kenudson M, Lauwers GY, Yamaguchi H, Ban S, Shimizu M. Prognostic relevance of morphological types of intraductal papillary mucinous neoplasms of the pancreas. *Gut* 2011; **60**: 509-516 [PMID: 21193453 DOI: 10.1136/gut.2010.210567]
- 8 Fritz S, Fernandez-del Castillo C, Mino-Kenudson M, Crippa S, Deshpande V, Lauwers GY, Warshaw AL, Thayer SP, Iafate AJ. Global genomic analysis of intraductal papillary mucinous neoplasms of the pancreas reveals significant molecular differences compared to ductal adenocarcinoma. *Ann Surg* 2009; **249**: 440-447 [PMID: 19247032 DOI: 10.1097/SLA.0b013e31819a6e16]
- 9 Omori Y, Ono Y, Tanino M, Karasaki H, Yamaguchi H, Furukawa T, Enomoto K, Ueda J, Sumi A, Katayama J, Muraki M, Taniue K, Takahashi K, Ambo Y, Shinohara T, Nishihara H, Sasajima J, Maguchi H, Mizukami Y, Okumura T, Tanaka S. Pathways of Progression From Intraductal Papillary Mucinous Neoplasm to Pancreatic Ductal Adenocarcinoma Based on Molecular Features. *Gastroenterology* 2019; **156**: 647-661.e2 [PMID: 30342036 DOI: 10.1053/j.gastro.2018.10.029]
- 10 Woo SM, Ryu JK, Lee SH, Yoo JW, Park JK, Kim YT, Yoon YB. Survival and prognosis of invasive intraductal papillary mucinous neoplasms of the pancreas: comparison with pancreatic ductal adenocarcinoma. *Pancreas* 2008; **36**: 50-55 [PMID: 18192881 DOI: 10.1097/MPA.0b013e31812575df]
- 11 Yamada S, Fujii T, Hirakawa A, Takami H, Suenaga M, Hayashi M, Niwa Y, Hattori N, Iwata N, Kanda M, Tanaka C, Kobayashi D, Nakayama G, Koike M, Fujiwara M, Kodera Y. Comparison of the Survival Outcomes of Pancreatic Cancer and Intraductal Papillary Mucinous Neoplasms. *Pancreas* 2018; **47**: 974-979 [PMID: 30028445 DOI: 10.1097/MPA.0000000000001110]
- 12 Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, Lillemoe KD, Ferrone CR, Morales-Oyarvide V, He J, Weiss MJ, Hruban RH, Gönen M, Klimstra DS, Mino-Kenudson M. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. *Ann Surg* 2017; **265**: 185-191 [PMID: 27163957 DOI: 10.1097/SLA.0000000000001763]
- 13 Pu N, Li J, Xu Y, Lee W, Fang Y, Han X, Zhao G, Zhang L, Nuexiati A, Yin H, Wu W, Lou W. Comparison of prognostic prediction between nomogram based on lymph node ratio and AJCC 8th staging system for patients with resected pancreatic head carcinoma: a SEER analysis. *Cancer Manag Res* 2018; **10**: 227-238 [PMID: 29440932 DOI: 10.2147/CMAR.S157940]
- 14 Asano D, Nara S, Kishi Y, Esaki M, Hiraoka N, Tanabe M, Shimada K. A Single-Institution Validation Study of Lymph Node Staging By the AJCC 8th Edition for Patients with Pancreatic Head Cancer: A Proposal to Subdivide the N2 Category. *Ann Surg Oncol* 2019; **26**: 2112-2120 [PMID: 31037440 DOI: 10.1245/s10434-019-07390-z]
- 15 Kwon W, He J, Higuchi R, Son D, Lee SY, Kim J, Kim H, Kim SW, Wolfgang CL, Cameron JL, Yamamoto M, Jang JY. Multinational validation of the American Joint Committee on Cancer 8th edition pancreatic cancer staging system in a pancreas head cancer cohort. *J Hepatobiliary Pancreat Sci* 2018; **25**: 418-427 [PMID: 30118171 DOI: 10.1002/jhbp.577]
- 16 Fan Z, Cheng H, Jin K, Gong Y, Huang Q, Xu J, Ni Q, Yu X, Liu C, Luo G. AJCC 7th edition staging classification is more applicable than AJCC 8th edition staging classification for invasive IPMN. *World J Surg Oncol* 2019; **17**: 137 [PMID: 31387646 DOI: 10.1186/s12957-019-1682-9]
- 17 Saka B, Balci S, Basturk O, Bagci P, Postlewait LM, Maithel S, Knight J, El-Rayes B, Kooby D, Sarmiento J, Muraki T, Oliva I, Bandyopadhyay S, Akkas G, Goodman M, Reid MD, Krasinskas A, Everett R, Adsay V. Pancreatic Ductal Adenocarcinoma is Spread to the Peripancreatic Soft Tissue in the Majority of Resected Cases, Rendering the AJCC T-Stage Protocol (7th Edition) Inapplicable and Insignificant: A Size-Based Staging System (pT1: ≤2, pT2: >2-≤4, pT3: >4 cm) is More Valid and Clinically Relevant. *Ann Surg Oncol* 2016; **23**: 2010-2018 [PMID: 26832882 DOI: 10.1245/s10434-016-5093-7]
- 18 Birnbaum DJ, Bertucci F, Finetti P, Birnbaum D, Mamessier E. Head and Body/Tail Pancreatic

- Carcinomas Are Not the Same Tumors. *Cancers (Basel)* 2019; **11** [PMID: 30965637 DOI: 10.3390/cancers11040497]
- 19 **Artinyan A**, Soriano PA, Prendergast C, Low T, Ellenhorn JD, Kim J. The anatomic location of pancreatic cancer is a prognostic factor for survival. *HPB (Oxford)* 2008; **10**: 371-376 [PMID: 18982154 DOI: 10.1080/13651820802291233]
 - 20 **Morales-Oyarvide V**, Rubinson DA, Dunne RF, Kozak MM, Bui JL, Yuan C, Qian ZR, Babic A, Da Silva A, Nowak JA, Khalaf N, Brais LK, Welch MW, Zellers CL, Ng K, Chang DT, Miksad RA, Bullock AJ, Tseng JF, Swanson RS, Clancy TE, Linehan DC, Findeis-Hosey JJ, Doyle LA, Hornick JL, Ogino S, Fuchs CS, Hezel AF, Koong AC, Wolpin BM. Lymph node metastases in resected pancreatic ductal adenocarcinoma: predictors of disease recurrence and survival. *Br J Cancer* 2017; **117**: 1874-1882 [PMID: 28982112 DOI: 10.1038/bjc.2017.349]



Published by Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: <https://www.f6publishing.com/helpdesk>
<https://www.wjgnet.com>

