Surgical Endoscopy (2021) 35:536–561
https://doi.org/10.1007/s00464-020-08040-2

REVIEW ARTICLE

# Evaluation and management of a pancreatic rest noted during pre-bariatric surgery screening endoscopy

Galen Leung[1] · John Mills[2] · Juan Carlos Bucobo[1] · Salvatore Docimo[3]

Received: 6 June 2020 / Accepted: 22 September 2020 / Published online: 1 October 2020


## Abstract

**Introduction** Pancreatic rest (PR) is an ectopic pancreatic lesion that is usually found incidentally on endoscopy or surgery. While most lesions do not have clinical significance, some patients are symptomatic and rarely, PR can predispose to malignancy. With the growing popularity of bariatric surgery, it has been unclear how to manage PR found on screening endoscopies, prior to bariatric surgery. Through review of the current literature, we propose an algorithm for clinicians to evaluate and manage PR found on screening endoscopies prior to bariatric surgery.

**Methods** We performed a literature search in PubMed pertaining to PR, clinical characteristics, risk of malignant transformation, endoscopic characteristics, histological descriptions, and resection techniques. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), we found 33 published articles from 2001 to 2019, including case reports, case series, retrospective cohorts, and a review paper.

**Results** PR is commonly found incidentally in the gastric antrum. Larger lesions have a higher risk of being symptomatic or predisposing to malignant transformation. Endoscopic ultrasound (EUS) can assist in the diagnosis of PR and guide resection technique. Certain histological characteristics, such as Heinrich class, grading of neoplasia, and genetic alterations, can determine malignancy risk of PR. Resection technique, either endoscopically or surgically, should be based on lesion size, depth of wall invasion, and the endoscopists' level of skill in endoscopic resection.

**Conclusions** Proper evaluation and treatment of PR should be considered because of the risk for symptoms and malignant transformation. Symptomatic lesions and those at risk for malignant transformation should be considered for resection. EUS can guide the diagnosis and type of resection, either endoscopically through EMR or ESD or surgically through sleeve gastrectomy or Roux-en-Y gastric bypass (RYGB).

**Keywords** Pancreatic rest · Bariatric surgery · Endoscopy · Endoscopic mucosal resection · Endoscopic submucosal dissection · Endoscopic ultrasonography

Pancreatic rest (PR), or heterotopic pancreas, is an uncommon finding of an ectopic pancreatic lesion that is usually found incidentally on endoscopy or surgery, or between 2 and 15% of all autopsies [1]. There is a slight male predominance (64% males), can occur in all age groups, and are predominantly found in the gastric antrum [2]. In the majority of cases, they pose no clinical significance as most patients are asymptomatic [2]. However, they can predispose to complications, such as pancreatitis, gastrointestinal obstruction, bleeding, anemia, abdominal pain, and nausea. In addition, there is a rare risk of malignant transformation of about 0.7 to 1.8% [3, 4].

With the increase in morbid obesity rates worldwide, bariatric surgery has been shown to be the most effective treatment in terms of weight loss and improving obesity-related comorbidities [5]. Sleeve gastrectomy (SG) has increased from 0 to 37% of all bariatric surgeries

**Electronic supplementary material** The online version of this article (https://doi.org/10.1007/s00464-020-08040-2) contains supplementary material, which is available to authorized users.

✉ Galen Leung
leung.galen@gmail.com

[1] Department of Medicine, Stony Brook University Hospital, 101 Nicolls Road, Stony Brook, NY 11794, USA

[2] Department of Surgery, University of Pittsburgh Medical Center Pinnacle, 4300 Londonderry Road, Harrisburg, PA 17109, USA

[3] Department of Surgery, Stony Brook University Hospital, 101 Nicolls Road, Stony Brook, NY 11794, USA

worldwide from 2003 to 2013 [5], and RYGB comprises of 45% of bariatric surgeries worldwide in 2013 [5]. In addition, PR can be found in 0.6% of bariatric surgeries [6]. After bariatric surgery, the potential complications and risk of malignant transformation in this population with PR is much more significant and difficult to manage given the need for repeat surgery and difficulty in surveillance or endoscopic resection in the setting of altered anatomy. Screening esophagogastroduodenoscopies (EGDs) are typically performed prior to bariatric surgery in order to evaluate for ulcers, erosions, hiatal hernias, or any other concerning lesions [7].

Currently, there is no guidance on how to evaluate patients with potential PR lesions prior to bariatric surgery. This manuscript performs a thorough analysis of the most current literature regarding incidence, diagnostic characteristics, potential complications, risk of malignant transformation, and resection techniques of PR. We aim to create an algorithm for clinicians to evaluate when PR should be resected and if so, what resection method should be utilized.

## Methods

We performed a literature search in PubMed using keywords, "pancreas rest," "heterotopic pancreas," "pancreatic heterotopias," "ectopic pancreas," "pancreatic intraepithelial neoplasia," "pancreatic ductal adenocarcinoma," "Henreich system." Given the limited studies published on heterotopic pancreas, we included case reports, case series, systematic reviews, retrospective reviews, and prospective studies in a list of eligible publications. We also identified articles from the references of the articles from our search results in order to expand our list of publications. IRB approval was not needed, so was not obtained because the study is a review of existing literature and does not involve participation of patients or patient chart review.

We filtered the publications which described the endoscopic, imaging, and histological features of HP, the clinical manifestations and risk of malignant transformation, as well as articles that describe various resection techniques for PR. For articles that include pancreatic ductal adenocarcinoma, we only considered them if the malignancy was attributed to heterotopic pancreas.

We extracted data on demographics of patients with pancreatic rests, endoscopic, histological, and genetic/molecular characteristics, features at risk for malignant transformation, and outcomes of various resection endoscopic and surgical techniques. Supplementary Table 1 contains the compilation of all studies used in the review with descriptions of key points.

## Results

### Literature search

Figure 1 shows our Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. For our inclusion criteria, we searched for studies that were published in the year 2000 and afterwards. We searched for publications which discussed gastric PR, contained English text, were case reports, review papers, retrospective studies, and prospective studies. We excluded publications which were image reports, video reports, editorials, and contained pediatric cases. We also did not include studies which the full text was not available. Studies were reviewed by a single reviewer. Based on the literature search, we initially found 51 relevant published articles through literature search and 34 published articles from references among the literature search. After removing duplicate articles, we found 70 articles, which we removed 12 articles due to various reasons, such as not being able to find the full text or that the text was in a non-English language. Then we read through the full text and excluded 18 articles that did not pertain to gastric PR, were image or video reports, or small case reports which did not contribute much relevant information to our review. There were 7 articles which were referenced in our review but were not included in analysis for our algorithm.

Finally, we found 33 published articles relating to PR, published from 2001 to 2019. These included 7 case reports, 6 case series, 19 retrospective cohorts, and 1 review paper. 20 articles contained data on demographics and clinical characteristics of HP. 20 articles studied endoscopic ultrasonographic diagnosis. 15 articles discussed histological features. 25 articles discussed various resection techniques. There were no prospective studies given the rarity of PR. The grading of evidence is low given the lack of prospective randomized studies and the limited evidence on the topic of PR.

### Demographics, endoscopic appearance, and clinical symptoms

Table 1 lists the demographic, endoscopic, and clinical characteristics of PR from the literature search. The pathogenesis of PR is unknown and there are no studied risk factors for its development. PR can be found from 0.25% of surgical explorations to 14% of autopsies [8]. One third of PR are found incidentally during procedures [9]. It can be seen in 0.6% of cases of bariatric surgeries [8] and 0.9% of gastrectomies [10]. Given the low incidence of PR found during surgery compared to those found during autopsies,

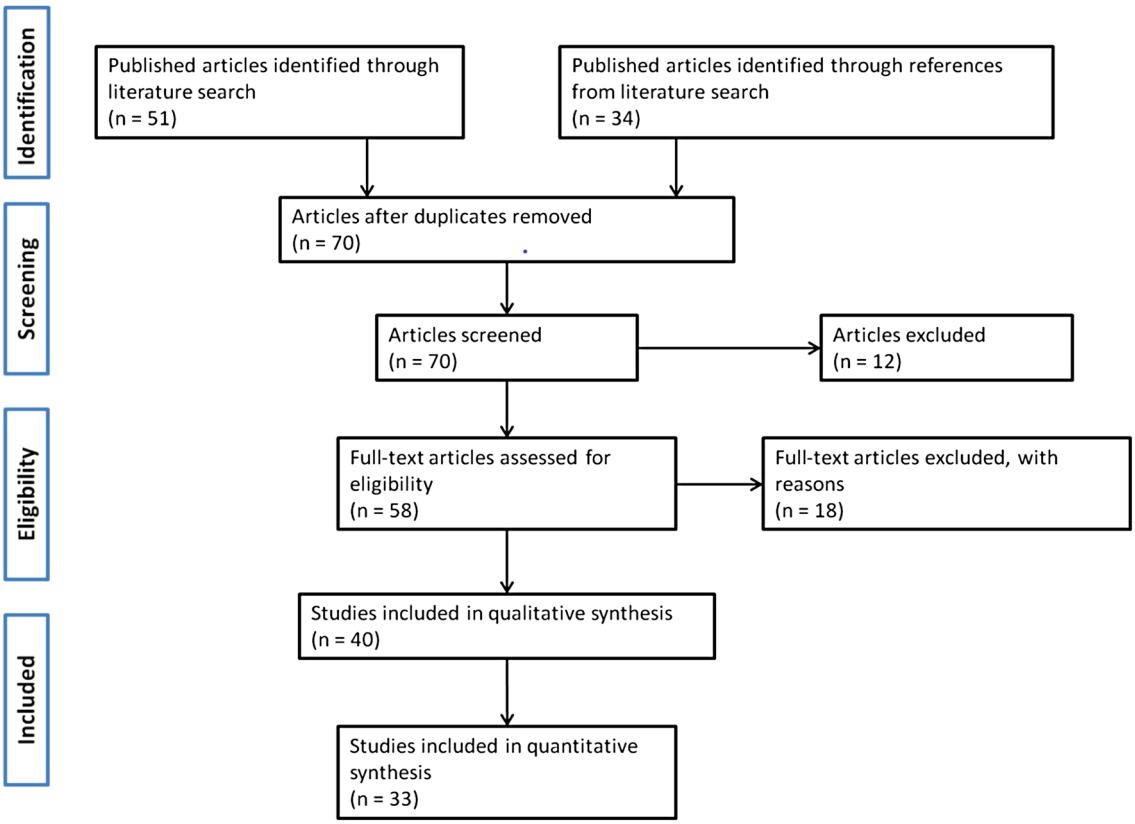


**Fig. 1** PRISMA flow diagram

a majority of PR may be missed, but exact numbers have not been discussed in existing literature. They are usually found in the stomach in 25–38% of cases, especially in the antrum, followed by the duodenum [10]. It can affect any age range, but is more common in ages 30 to 50 years and predominantly affects males [10]. Most patients are asymptomatic [8], but patients with symptoms usually had larger lesions [10]. However, when symptomatic, they can commonly present with nausea, vomiting, epigastric pain, and weight loss [11]. Rarely can it cause a gastric outlet obstruction [12]. In addition, malignant transformation can occur in 0.7% to 1.8% of cases [13–15], which demonstrates that it may be important to evaluate PR when noted.

## Endoscopic ultrasonography characteristics

The endoscopic ultrasonographic characteristics of PR, as described in the literature, is listed in Table 2. Endoscopically, PR often appear as subepithelial lesions, primarily in the gastric antrum, followed by gastric body, then duodenum [10]. Size ranges from under 1 cm to over 4 cm [16–18]. Central dimpling, or umbilication, can sometimes be seen, which corresponds to the opening of the HP duct [19]. However, central dimpling is not found frequently and is usually seen in larger lesions [20]. Figure 2 demonstrates a typical PR lesion found on endoscopy.

However, endoscopic mucosal forceps biopsies are limited in diagnostic yield, often showing normal overlying mucosa [16, 21, 22], and EUS can help distinguish benign from malignant subepithelial lesions, which would guide endoscopic resection [23]. PR is a subepithelial lesion that mostly commonly arises from the submucosa (15 to 70%), followed by the muscularis propria (3 to 60%), then subserosa (0 to 10%) [18, 19, 24–27]. EUS can be helpful for diagnosis, given certain features. Typical ultrasound features include heterogeneous echogenicity with hypoechoic acinous tissue and anechoic ductal features [24], as well as indistinct borders [20]. However, lesions originating from the muscularis propria, as compared to those arising from the submucosa, may contain more of a homogenous pattern with hypoechoic features [19]. With added FNA, the sensitivity and specificity of cytological diagnosis can be 83.3% and 100%, respectively [12]. In addition, EUS can guide resection by determining risk of bleeding, extent of resection needed [28].

**Table 1** Demographics, characteristics, and complications

| Year | References | Number of patients | Age, Gender | Endoscopic appearance | Clinical symptoms |
|---|---|---|---|---|---|
| 2004 | Eisenberger [11] | 11 | NA | NA | Majority asymptomatic. Symptomatic patients with nausea, vomiting, epigastric pain, weight loss |
| 2007 | Christodoulidis et al. [10] | 1 | 40, F | Sessile polypoid gastric antral mass. 5 cm. Umbilicated submucosal lesion can also be seen | Epigastric pain, but also risk of pancreatitis, bleeding, ulcers, obstruction, malignant transformation. Lesions greater than 1.5 cm more likely to be symptomatic |
| 2017 | Jun et al. [13] | 165 | Mean age 52.2 years, Male/Female 1.4 | Mean size 14.0 ± 8.5 mm. 34.6% located in stomach, 33.9% in duodenum | Abdominal pain, nausea, vomiting. Symptomatic mostly with larger size, younger patients, gastric location |
| 2016 | Zhang et al. [9] | 184 | Median 49 years, Male/Female 0.94 | 52.7% stomach, 26% small intestine. 35.3% smaller than 0.5 cm, 34.8% 0.5 to 1 cm, 29.9% larger than 1.1 cm. Well-circumscribed, broad-based submucosal nodule, sometimes with central mucosal surface dimple, no mucosal changes. Can also appear as broad-based or pedunculated polyp with submucosal origin | Abdominal pain, distension, nausea, vomiting, malaise, anorexia, anemia, weight loss, melena, jaundice (ampulla of Vater lesion) |
| 2008 | Chen et al. [22] | 39 | Mean 46 years, 21 F, 18 M | 33% in stomach, the rest in small bowel. Median diameter 1.1 cm. Well-circumscribed, soft, rubbery, yellow, intramural mass with central umbilication | Abdominal pain, bleeding, abdominal distension. Gastric lesions more likely to be symptomatic |
| 2019 | Cazacu et al. [4] | 54 malignant lesions | 3–86 years (mean 55.6), 51.8% males | Malignant lesions most common in stomach (35.2%), then duodenum (22.2%). Endoscopically, has subepithelial tumor-like appearance, stenotic or ulcerated. Mean size 4.8 cm (most malignant lesions greater than 4 cm) | Most were middle-aged. 83% with clinical symptoms of abdominal pain, dyspepsia, bleeding, obstruction<br>35.2% of malignant tumors involved the stomach |
| 2004 | Emerson et al. [1] | 1 | M, 52 | Stomach. Ulcerated mucosa | Abdominal pain |
| 2013 | Endo et al. [17] | 2 | 2 M, 73, 75 | One case with a duodenal stenotic submucosal lesion with mucosal redness. Endoscopic mucosal biopsies inconclusive<br>Another lesion with 4 cm gastric antral submucosal tumor | Abdominal pain, melena |
| 1999 | Matsushita et al. [24] | 12 | 24–77 (mean 50.3), 5 M, 7 F | Gastric (body, antrum, prepylorus) PR. 10 patients had EGD with biopsies with unsuccessful diagnosis | Asymptomatic |
| 2014 | Chou et al. [19] | 13 | Mean 40.8 years (range 20–77) | Gastric PR. Size 10 to 23 mm (mean 16 ± 5 mm). 53.8% with central dimpling | Symptomatic with abdominal pain |
| 2011 | Park et al. [20] | 26 | 18–71 (mean 42), 12 M, 14 F | 10 lesions in antrum, 16 lesions in body<br>34.6% had umbilication. 61.5% had mural growth pattern | 9 patients had abdominal pain. 17 patients asymptomatic |

**Table 1** (continued)

| Year | References | Number of patients | Age, Gender | Endoscopic appearance | Clinical symptoms |
|---|---|---|---|---|---|
| 2011 | Bain et al. [16] | 35 | Median 53 (range 28–89), 11 F, 8 M | 14 suspected PR with mucosal forceps biopsies but 36% were diagnostic with majority being benign mucosa. 21 suspected PR underwent successful endoscopic band ligation snare polypectomy without complications with 90% able to have diagnosis of PR. Median endoscopic size of 10 mm (range 6–10 mm). 58% with central umbilication | Asymptomatic |
| 2008 | Ormarsson et al. [34] | 30 | Mean 42.5, 15 F, 15 M | 14 cases in stomach, 1 in duodenum. 3 cases with central umbilication. 8 cases with polyp, knot, mucosal thickening or mucosal defect. Only 40% of biopsies led to correct diagnosis | 53% of cases were symptomatic, mostly with abdominal pain. 1 case with obstructive symptoms |
| 2013 | Zhong et al. [18] | 60 | Median 39 (15–62), 28 F, 32 M | All gastric lesions with 85% in the antrum. 38.8% with central umbilication. Mean size of 1.4 cm (range 0.4–3.5 cm) | 26.7% with abdominal pain, 13.3% with abdominal distension, 10% with black stools, and rest were incidentally found |
| 2013 | Liu et al. [12] | 9 | Mean 48.3, 6 F, 3 M | 11.1% cases diagnosed by endoscopic biopsy | All with post-prandial fullness, bloating. 67% with epigastric pain. 44.4% with nausea. 44% with epigastric burning. 11% with vomiting from pyloric obstruction |
| 2009 | Khashab et al. [21] | 2 | 49, 15; 2 F | One case with small, firm, umbilicated subepithelial antral mass with endoscopic mucosal biopsy showing chronic gastritis<br>2nd case with small subepithelailantral mass with normal overlying mucosa and endoscopic mucosal biopsies showing mild gastritis | One case symptomatic with abdominal bloating, constipation, anemic, heme occult positive stools<br>2nd case with abdominal pain |
| 2001 | Faigel et al. [35] | 1 | 34, F | 10 mm smooth submucosal nodule with central umbilication in gastric antrum. Non-diagnostic mucosal biopsy | Dyspepsia, nausea |
| 2010 | Ryu et al. [36] | 8 | Mean 36 (range 18–57), 7 F, 1 M | 5 lesions found in antrum. 3 lesions found in gastric body. No signs of umbilication. All mucosal biopsies non-diagnostic | 4 patients with abdominal pain. 4 patients were asymptomatic |
| 2016 | Xin et al. [28] | 52 | Mean 47.5 (range 21–78), 31 F, 21 M | Gastric antrum. 67.3% with umbilication | 28.8% with upper abdominal pain, 13.5% with abdominal distension, 13.5% with black stools, rest were asymptomatic |
| 2017 | Vitiello et al. [14] | 29 | NA | NA | 37.9% had symptoms (abdominal pain, upper GI bleed, perforation/obstruction). 6.9% with pancreatitis |

**Table 1** (continued)

| Year | References | Number of patients | Age, Gender | Endoscopic appearance | Clinical symptoms |
|---|---|---|---|---|---|
| 2015 | Attwell et al. [25] | 10 | Median 52 (range 26–64), 7 F, 3 M | 60% gastric antrum, 30% gastric body, 10% duodenum. 60% with mucosal dimple. Mean size of 17 mm (8-25 mm). 70% had superficial biopsies, but showed normal gastric mucosa | 10% symptomatic with epigastric pain. 90% asymptomatic |
| 2002 | Huang et al. [15] | 2 | 41, 53; 2 M | One case with a 2.5 cm prepyloric submucosal tumor with central dimple<br>Another case with 2 cm intramural mass with mucosal antrum in distal antrum | Gastric outlet obstruction, abdominal pain, tarry stool |
| 2008 | Chen et al. [26] | 20 | Mean 39 (range 19–58) years, 9 F, 11 M | 95% located in antrum, 5% in duodenum. 90% with central umbilication. 10% of mucosal forceps biopsy diagnosed as HP | 33.3% with epigastric pain or dyspepsia |
| 2002 | Jeong et al. [37] | 1 | 64 years, 1 M | 3 cm protruding submucosal mass in prepyloric antrum | Dyspepsia, gastric outlet obstruction |
| 2006 | Galvez-Valdovinos et al. [38] | 2 | 28, 32 years, 2 F | One case with a firm, round sessle nodular lesion with central umbilication in the antrum<br>Another case with a intraluminal protrusion in the prepyloric area | Epigastric pain, hematemesis |

## Histopathology and genetic/molecular marker characteristics

Table 3 details the histopathologic characteristics of PR from a review of the literature. Histolopathological examination of PR contains a mixture of pancreatic acini, ducts, and islets of Langerhans with normal overlying gastric mucosa and can involve the submucosa, muscularis propria, or subserosa [10]. The growth pattern can be either pushing or infiltrative, and there can be mucosal erosion, atrophy, as well as interstitial fibrosis or lymphoid cuffs [13].

Heinrich in 1909, then Gaspar-Fuentes in 1973 classified PR into three categories. Type 1 heterotopia consisted of normal pancreatic tissue with acini, ducts, and islet cells. Type II heterotopias showed pancreatic ducts only, and Type III only contained acinar tissue. Type IV is comprised of only islet cells [10]. The most common type is Type II heterotopia [22]. Most studied malignancies (42 to 58%) arose from Type I heterotopias, with the most common type being adenocarcinoma [1, 4].

Guillou, et al. proposed criteria for carcinoma to be arising from PR: (1) presence of neoplasm located in/or in the proximity of the PR site; (2) concurrent presence and continuity of normal ectopic pancreatic tissue and adenocarcinoma; (3) PR tissue with normal histological structure [29]. Most malignant transformation occurs with gastric PR and lesions were mostly greater than 4 cm [4]. Reported cases of adenocarcinomas arising from PR showed histological signs of desmoplastic stroma with most moderately differentiated, a few poorly differentiated [13].

Histopathological grading of neoplasia can be graded from Pancreatic Intraepithelial Neoplasia-1 (PanIN-1) to PanIN-3. Having PanIN or IPMN is associated with larger lesions, deeper wall involvement, and infiltrative growth. While low-grade PanINs can occur in normal pancreas tissue, high-grade PanINs contain higher number or genetic alterations, such as KRAS mutation, p53 accumulation, cyclin D1 overexpression, and loss of p16 expression, predisposing to malignancy [30]. In addition, KRAS mutation shows good evidence that the malignancy did arise from PR, so it may be helpful to perform KRAS mutational and SMAD4/DPC4 immunohistochemical studies in order to determine malignancy risk of PR [13]. Regarding IPMNs, which are usually larger or equal to 1 cm, progressive genetic alterations of KRAS, CDKN2A, TP53 may cause changes from low-grade to high-grade IPMN, then to pancreatic adenocarcinoma [13].

**Table 2** Endoscopic ultrasonography characteristics

| Year | References | Number of patients | Age, Gender | Endoscopic appearance | EUS appearance | FNA/FNB performed |
|---|---|---|---|---|---|---|
| 2016 | Zhang et al. [18] | 184 | Median 49 years, male/female 0.94 | 52.7% stomach, 26% small intestine. 35.3% smaller than 0.5 cm, 34.8% 0.5 to 1 cm, 29.9% larger than 1.1 cm. Well-circumscribed, broad-based submucosal nodule, sometimes with central mucosal surface dimple, no mucosal changes. Can also appear as broad-based or pedunculated polyp with submucosal origin | May involve submucosa, muscularis propria, or entire GI tract wall | NA |
| 2013 | Endo et al. [17] | 2 | 73, 75; 2 M | One case with duodenal stenotic submucosal lesion with mucosal redness. Endoscopic mucosal biopsies inconclusive<br>Another lesion with a 4 cm gastric antral submucosal tumor, but endoscopic mucosal biopsies inconclusive | Duodenal lesion showed submucosal origin. FNA showed adenocarcinoma of uncertain origin<br>Gastric lesion showed hypoechoic mass with cystic component primarily in muscularis propria<br>Typical PR EUS features show involvement from submucosa to musclaris propria, poorly defined low echoic mass with area of spotty high echo inside, spindle-shaped, thickened muscularisproprianeighboring the lesion | FNA for duodenal lesion |
| 1999 | Matsushita et al. [24] | 12 | 24–77 (mean 50.3), 5 M, 7 F | Gastric (body, antrum, prepylorus) PR. 10 patients had EGD with biopsies with unsuccessful diagnosis | 50% of lesions located in the submucosa and muscularis propria. 50% located in submucosa. 80% with indistinct margins with lobular acinous tissue. Heterogeneous from hypoechoic acinous tissue. Anechoic areas correlated with duct dilatation and hypertrophy of muscularis propria | NA |

**Table 2** (continued)

| Year | References | Number of patients | Age, Gender | Endoscopic appearance | EUS appearance | FNA/FNB performed |
|---|---|---|---|---|---|---|
| 2016 | Dias de Castro et al. [39] | 55 | NA | NA | 17% (55) of EUS procedures for subepithelial lesions had presumptive diagnosis of HP based on EUS features. Overall, 66% failure rate of obtaining adequate sample for histology by EUS-FNA, contributed to mean lesion size < 25 mm | FNA |
| 2014 | Chou et al. [19] | 13 | Mean 40.8 years (range 20–77) | Gastric PR. Size 10 to 23 mm (mean 16 ± 5 mm). 53.8% with central dimpling | 69% with hypoechoic echogenicity, 30% with mixed echoic echogenicity. 53% were homogenous. 76% with distinct borders. 7.6% with anechoic tubular structures. 54% originated from muscularispropria, 31% from muscularis mucosa, 15% from both muscularis mucosa and submucosa. Muscularispropria lesions had higher frequency of hypoechoic echogenicity and more likelyhomogeneous, and exhibit both hypoechoic and homogeneous features than those involving other layers | NA |
| 2011 | Park et al. [20] | 26 | 18–71 (mean 42), 12 M, 14 F | 10 lesions in antrum, 16 lesions in body<br>34.6% had umbilication. 61.5% had mural growth pattern | 92.3% showed hypoechoic echogenicity. 50.0% heterogeneous. 61.5% with indistinct borders. 61.5% with lobulated margins. 65.4% with anechoic cystic or tubular structures. 76.9% involved 2 or more layers. Mean size of 14 mm (range 6–37 mm). 6 lesions involved submucosa. 23.1% involved muscularis mucosa and submucosa. 30.7% involved submucosa and muscularispropria, 53.8% involved submucosa, muscularispropria, serosa 12 were S type, 14 were D type | NA |

**Table 2** (continued)

| Year | References | Number of patients | Age, Gender | Endoscopic appearance | EUS appearance | FNA/FNB performed |
|---|---|---|---|---|---|---|
| 2011 | Bain et al. [16] | 35 | Median 53 (range 28–89), 11 F, 8 M | 14 suspected HP and mucosal forceps biopsies but 36% were diagnostic with majority being benign mucosa. 21 suspected HP underwent successful endoscopic band ligation snare polypectomy without complications with 90% able to have diagnosis of HP. Median endoscopic size of 10 mm (range 6–10 mm). 58% with central umbilication | Mean EUS size of 7 mm by 4 mm. Submucosa. Hypoechoic or heterogeneous | NA |
| 2013 | Zhong et al. [18] | 60 | Median 39 (15–62), 28 F, 32 M | All gastric lesions with 85% in the antrum. 38.8% with central umbilication. Mean size of 1.4 cm (range 0.4–3.5 cm) | 3.3% involvement of muscularis mucosa, 70% of submucosa, 26.7% of muscularis propria. 63.6% with hypoechoic changes, 6.7% with medium echo, 3.3% hyperchoic, 26.7% heterogeneous echo | NA |
| 2013 | Liu et al. [12] | 9 | Mean 48.3, 6 F, 3 M | 11.1% cases diagnosed by endoscopic biopsy | Submucosal involvement. 22.2% involved muscularis mucosa, submucosa, and muscularis-propria. 5 cases diagnosed by EUS-FNA. 83.3% sensitivity and 100% specificity of cytology | FNA |
| 2009 | Khashab et al. [21] | 2 | 49, 15;, 2 F | One case with small, firm, umbilicated subepithelial antral mass with endoscopic mucosal biopsy showing chronic gastritis<br>2nd case with small subepithelailantral mass with normal overlying mucosa and endoscopic mucosal biopsies showing mild gastritis | One case showed a well-defined hypoechoic lesion from deep mucosa/submucosa, measuring 8 mm × 6 mm<br>2nd case with well-defined 9 mm × 7 mm hypoechoic lesion from deep mucosa and submucosa | No |
| 2001 | Faigel et al. [35] | 1 | 34, F | 10 mm smooth submucosal nodule with central umbilication in gastric antrum. Non-diagnostic mucosal biopsy | 9 mm poorly circumscribed mass from submucosa. Mixed echogenicity, both hyperechoic and hypoechoic foci. No ductal structure | No |

**Table 2** (continued)

| Year | References | Number of patients | Age, Gender | Endoscopic appearance | EUS appearance | FNA/FNB performed |
|---|---|---|---|---|---|---|
| 2010 | Ryu et al. [36] | 8 | Mean 36 (range 18–57), 7 F, 1 M | 5 lesions found in antrum. 3 lesions found in gastric body. No signs of umbilication. All mucosal biopsies non-diagnostic | Lesions mainly located in deep mucosa or submucosa. Mean size 8 mm (range 6 to 12 mm). Hypoechoic. 5 lesions homogeneous. 3 lesions heterogeneous. 62.5% with distinct borders. Anechoic cystic or tubular structures in 37.5% | No |
| 2015 | Iwamuro et al. [40] | 1 | 32, M | Sessile submucosal tumor about 10 mm in diameter in gastric antrum. No umbilication. Endoscopic mucosal biopsy non-diagnostic | 11.8 mm solid tumor located in the deep mucosa and submucosa. Homogeneous and hypoechoic echogenicity, similar to echogenicity of deep mucosa. No anechoic duct-like structure | No |
| 2016 | Xin et al. [28] | 52 | Mean 47.5 (range 21–78), 31 F, 21 M | Gastric antrum. 67.3% with umbilication | 7.7% involve muscularis mucosa, 65.4% involve submucosa, 26.9% involve muscularis propria. 63.5% showed hypoechoic changes. 5.8% with medium echo. 3.8% hyperechoic, 26.9^ heterogeneous echo. EUS-Doppler can predict risk of intraoperative bleeding, safety of ESD, procedure time, risk of muscle layer injury, use of clips | No |
| 2014 | Zhang et al. [31] | 42 | Median 41 (range 21–68), 13 F, 29 M | Mean size of 15.2 (10–28)mm. All gastric lesions. Smooth mucosal surface and 26.2% with central dimpling | 78.6% with clear border. 14.3% with low-level echo, 64.3% with medium echo, 21.4% with high-level echo. 76.2% with uneven echo. 42.9% suspected to be gastric PR, 19% suspected GIST, 16.7% suspected polyp, 21.4% unknown | NA |

**Table 2** (continued)

| Year | References | Number of patients | Age, Gender | Endoscopic appearance | EUS appearance | FNA/FNB performed |
|---|---|---|---|---|---|---|
| 2015 | Attwell et al. [25] | 10 | Median 52 (range 26–64), 7 F, 3 M | 60% gastric antrum, 30% gastric body, 10% duodenum. 60% with mucosal dimple. Mean size of 17 mm (8-25 mm). 70% had superficial biopsies, but showed normal gastric mucosa | Mean size 17 (8–25)mm. 70% involved submucosa. 60% involved muscularis propria. 10% involved muscularis mucosa. 10% involved subserosa. 50% involved more than 1 layer. 90% hypoechoic, 10% isoechoic. 50% homogenous, 50% heterogenous. 50% had presence of ductal structure. 10% developed mild acute ectopic pancreatitis after FNA | 90% with FNA. 89% had successful aspiration of cellular material. 88% showed acini with adequate cytology, occasional ductal structures. 1 EUS-FNA developed ectopic acute pancreatitis. 1 out of 2 had diagnostic deep, tunneling biopsy |
| 2002 | Huang et al. [15] | 2 | 41, 53, 2 M | One case with a 2.5 cm prepyloric submucosal tumor with central dimple<br>Another case with 2 cm intramural mass with mucosal antrum in distal antrum | One case with EUS showing 2.5 cm isoechoic tumor with blurring of mucosal and submucosal layers and some hypoechoic components | No |
| 2008 | Kim et al. [27] | 71 (18 HP) | Mean 49 (range 35–63) years, 38 F, 33 M | For PR: 55.5% in gastric body, 38.9% in antrum, 5.6% un cardia. Mean size of 26.3 mm (15.1–37.5) | 11.1% from muscularis mucosa, 66.7% from submucosa, 11.1% from muscularis propria, 11.1% indeterminate. 88.8% with homogenous internal echo. 77.8% with intermediate echogenecity. 22.2% with focal anechoic portions | NA |
| 2008 | Chen et al. [26] | 20 | Mean 39 (range 19–58) years, 9 F, 11 M | 95% located in antrum, 5% in duodenum. 90% with central umbilication. 10% of mucosal forceps biopsy diagnosed as HP | Size 8-20 mm (mean 12 mm). 95% with heterogenous, hypoechoic, or mixed echogenic lesions. 5% with homogenous echogenic lesion. 65% with indistinct borders. 35% with anechoic cystic or tubular structures. 15% originated in muscularis mucosa, 25% from submucosa, 5% from muscularispropria, 50% involved muscularis mucosa and submucosa, 5% involved muscularis mucosa, submucosa, muscularispropria | No |

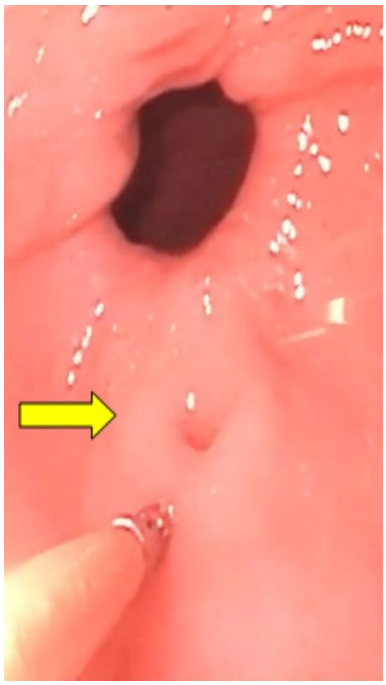

**Fig. 2** Gastric pancreatic rest. Arrow points to PR with central umbilication located at the gastric antrum, found endoscopically

## Endoscopic and surgical resection techniques

Table 4 reviews endoscopic and surgical resection modalities for PR. Usually asymptomatic lesions can be surveyed, but with the risk of malignancy and development of minimally invasive surgery and therapeutic endoscopy, it would be reasonable to resect lesions, which may develop into malignancy. It may be reasonable to resect concerning incidental lesions, such as high-risk PR, during bariatric procedures without increasing the post-operative complication rate [8]. Resection can serve as a diagnostic approach [4].

It may be reasonable to endoscopically resect gastric PR lesions given the low complication rate of EMR/ESD and difficulty of surveillance for post-bariatric surgery patients [18]. Park, et al. classified lesions that were of superficial type, which originate from the deep mucosa and/or submucosa, and those of the deep type, which originate from the submucosa and muscularis propria with or without extension into the subserosal or serosal layer, and proposed that superficial type lesions were appropriate for endoscopic resection [20]. In high-volume ESD centers, ESDs have been performed for small gastric lesions ($\leq 20$ mm) that originate from the muscularis propria with en bloc curative resection and no complications [19]. ESD with en bloc resection have also been performed for PR less than 3.5 cm in diameter [31]. The AGA Institute Clinical Practice states that indications for gastric ESD include moderately and well-differentiated superficial cancers $\leq 3$ cm with ulceration or contain early submucosal invasion [32]. However, if lesions contained more vessels, this may result in longer procedure time and higher risk of muscle layer injury [28]. More superficial lesions, such as those originating from the submucosa, have been successful resected by standard EMR [12] or by endoscopic band ligation snare polypectomy without complications [16, 21]. It has been proposed that if the lesion is larger than 1 cm and there is no muscularis propria involvement on EUS, then EMR can be performed [18].

Surgical wedge resection has been reportedly used to curatively resect large, over 3 cm, gastric and small bowel PR, which can involve the muscularis propria and subserosa, without any complications [8, 10]. It has been recommended that smaller sized lesions, located in the stomach, superficial lesions, more pushing than infiltrative growth can be endoscopically resected [13]. Lesions that are larger in size, with deeper wall involvement, more infiltrative growth, with interstitial fibrosis should be resected surgically [13]. Pushing growth pattern refers to a well-demarcated pushing border with surrounding fibro adipose tissue, and an infiltrative growth pattern refers to an irregular infiltrating pattern into smooth muscle [13]. For patients with obesity, a laparoscopic wedge, followed by a RYGB, has been performed without complications for large (4 cm) submucosal PR [33]. In addition, for larger muscularis propria lesions, subtotal gastectomy with Billroth II anastomosis has also been performed without complications [15].

**Table 3** Histopathology and genetic/molecular marker characteristics

| Year | References | Number of patients | Age, Gender | Pathology characteristics | IPMN or PANIN | Malignancy | Henreich Class | Molecular/genetic characteristics |
|---|---|---|---|---|---|---|---|---|
| 2007 | Christodoulidis et al. [10] | 1 | 40, F | Mixture of pancreatic acini, ducts, islets of Langerhans with normal overlying gastric mucosa<br>Involves submucosa (73%), muscularis propria (17%), subserosa (10%) | NA | No | NA | NA |
| 2017 | Jun et al. [13] | 165 | NA | Mixed acinar, ductal, and islet cells. Pushing growth or infiltrative pattern. Mucosal erosion, atrophy. Interstitial fibrosis, lymphoid cuffs | 42.4% with PanINs/IPMNs. 98.5% of those with low-grade PanIN. PanIN/IPMN associated with larger lesions, deeper wall involvement, infiltrative growth, lymphoid cuffs. PanIN-1 has low rate of progression to PDA, but high-grade PanIN/IPMN may be marker for invasion. Gastric and jejunal PR associated with PanIN/IPMN | No | 66.1% Type 1, 27.3% Type 2, 3.0% Type 3, 3.6% unclassifiable. Type 1 and 2 more commonly seen in cases with PDA | NA |
| 2007 | Zhang et al. [30] | 32 PR, 6 with PDA of pancreatic head | 5 males, 1 female, 57–80 | All patients with pancreatic head adenocarcinoma who presented for surgery: 1 gastric PR, 5 duodenal HP. For those without pancreatic adenocarcinoma, 2 PR with PanIN-1A, none with high-grade PanIN. Progression from PanIN to PDA occurs in PR. Lobular acinar tissue, fibrous septa, interlobular ducts | 6 with PanIN-1A, 5 with anIN-2, 1 with PanIN-3. PR of patients with PDA of pancreas contained PanIN lesions with similar genetic alterations | No | NA | High-grade PanIN in PR with similar KRAS mutation, p53 accumulation, cyclin D1 overexpression, loss of p16 expression as in PDA of pancreas. Low-grade PanIN with genetic alterations may be maintained in more advanced lesions |

**Table 3** (continued)

| Year | References | Number of patients | Age, Gender | Pathology characteristics | IPMN or PANIN | Malignancy | Henreich Class | Molecular/genetic characteristics |
|---|---|---|---|---|---|---|---|---|
| 2016 | Zhang et al. [9] | 184 | Median 49 years, male/female 0.94 | Acini with pyramidal exocrine epithelial cells, ducts, islet of Langerhans. Most lesions only with acini. 40% in lamina propria and submucosa. 43.5% in muscularis propria or all wall layers | NA | No | NA | NA |
| 2008 | Chen et al. [22] | 39 | Mean 46 years, 21 F, 18 M | NA | NA | 1 with gastric adenocarcinoma | 56.3% mixed Type II and III, 31.3% type II, 6.3% type I | NA |
| 2019 | Cazacu et al. [4] | NA | Slight predominance of males over females | NA | NA | Adenocarcinoma most common malignant transformation. Others include anaplastic carcinoma, mucinous cystadenocarcinoma, acinar cell carcinoma, solid pseudopapillary tumors, pancreatoblastoma, perivascular epithelioid cell tumor, neuroendocrine tumors | 58.4% of all malignancy from Type I. One case from Type III | 57% of adenocarcinoma had elevated CA 19–9 (lower than in primary pancreatic cancer) |
| 2004 | Emerson et al. [1] | 1 | M, 52 | Circumferential 4.0×2.5×1.5 cm mass. Adenomyomatous proliferation of muscularispropria, duct structures, cysts. Cysts and ducts lined by bland-appearing columnar to cuboidal cells, occasionally with mucin-rich cytoplasm. Rare collection of islet cells in muscularis propria. Antibodies against synaptophysin. Neoplastic proliferation infiltration into muscularis propria and serosal surface. Malignant ducts extended to distal (duodenal) margin | NA | Adenocarcinoma | Type III. Literature review shows 42% of adenocarcinoma from Type I, then type II (33%) | NA |

**Table 3** (continued)

| Year | References | Number of patients | Age, Gender | Pathology characteristics | IPMN or PANIN | Malignancy | Henreich Class | Molecular/genetic characteristics |
|---|---|---|---|---|---|---|---|---|
| 2013 | Endo et al. [17] | 2 | 2 M, 73, 75 | Duodenal case with 2.2 × 2.1 × 1.2 cm elastic hard tumor involving duodenum, common bile duct, proximal pancreas with focal ulceration in duodenal mucosa, positive for CK7 and neg for CK20<br>Gastric casewith 4.5 × 3.0 × 2.5 cm elastic hard tumor involving stomach and duodenum, located between submucosa and serosa, and containing mucinous tumor cells overlapping ectopic pancreatic tissue with acinar cells, duct cells, islets of Langerhans, stained positive for CK7 and CK20 | NA | Both cases showed adenocarcinoma, | Type I (both cases) | Elevated CEA and CA 19–9<br>Duodenal adeniocarcinoma positive stain for CK7, negative for CK20<br>Gastric adenocarcinoma positive stain for CK7, marginally positive for CK20 |
| 1999 | Matsushita et al. [24] | 12 | 24–77 (mean 50.3), 5 M, 7 F | Gastric submucosa or muscularis propria involvement. Dilated ducts, hypertrophy of muscularispropria. Densely gathered acinous tissue predominantly in muscularis propria | NA | No | Type I (41.7%), Type II (41.7%), Type III (16.7%) | NA |
| 2008 | Ormarsson et al. [34] | 30 | Mean 42.5, 15 F, 15 M | Gastric HP showed exocrine tissue and tubular structures. Small intestinal lesions showed endocrine islets. Localized to submucosa in 50% of lesions, serosa in 23.3%. Average size less than 9 mm (range 1 to 16 mm) | NA | No | NA | NA |

**Table 3** (continued)

| Year | References | Number of patients | Age, Gender | Pathology characteristics | IPMN or PANIN | Malignancy | Henreich Class | Molecular/genetic characteristics |
|---|---|---|---|---|---|---|---|---|
| 2013 | Liu et al. [12] | 9 | Mean 48.3, 6 F, 3 M | All cases had acini. 3 cases with anechoic cystic or tubular structures | NA | No | 33.3% Type I, 44.4% Type II, 11.1% Type III | NA |
| 2001 | Faigel et al. [35] | 1 | 34, F | Normal gastric antral mucosa overlying submucosal complex of ecstatic ductal structures, surrounded by variable thick layer of smooth muscle. Ductal structures lined by columnar cell with mucus-producing features | NA | No | NA | NA |
| 2015 | Iwamuro et al. [40] | 1 | 32, M | Pancreatic tissue with acini, ducts, islets of Langerhans | NA | No | NA | NA |
| 2017 | Vitiello et al. [14] | 29 | NA | Tumor size 0.5 to 4.8 cm | 10.3% had pre-neoplastic changes (PanIN 1) Lesions with PanIN were 0.5 to 1.6 cm in diameter | 3.4% had pancreatic adenocarcinoma (small bowel) | NA | NA |
| 2015 | Attwell et al. [25] | 10 | Median 52 (range 26–64), 7 F, 3 M | 88% showed acini with adequate cytology, occasional ductal structures | NA | No | NA | NA |
| 2002 | Jeong, et al. [37] | 1 | 64 years, 1 M | Malignant change in the glands of ectopic pancreas in the muscle layer. Moderately differentiated adenocarcinoma arising from heterotopic pancreas | NA | Adenocarcinoma | NA | NA |

**Table 4** Endoscopic and surgical resection techniques

| Year | References | Number of patients | Age, gender | Type of resection | Location | Size of lesion | Depth of invasion | Curative resection | Pathological diagnosis | Post-procedure complications |
|---|---|---|---|---|---|---|---|---|---|---|
| 2007 | Christodoulidis et al. [10] | 1 | 40, F | Wedge resection | Gastric antrum | 5 cm | Muscularis propria | Yes | PR | None |
| 2017 | Jun et al. [13] | 184 | NA | 87.3% radical surgery, 21% endoscopic resection. Surgery for larger size, deeper wall layer involvement, more infiltrative growth pattern, interstitial fibrosis. Endoscopic resection for smaller size, gastric, superficial lesions, more pushing type growth, surface mucosal change. Endoscopic resection usually for lesions in stomach, associated with surface mucosal change | Gastric, duodenal, omental, jejunal | Mean 14.0 ± 8.5 mm | Mucosa, submucosa, muscularis propria, subserosa | NA | PR | NA |
| 2008 | Chen et al. [22] | 39 | Mean 46 years, 21 F, 18 M | 20.5% subtotal gastrectomy for suspected malignancy (only 1 had adenocarcinoma) | Gastric | NA | NA | NA | PR. 1 with pancreatic adenocarcinoma | NA |

**Table 4** (continued)

| Year | References | Number of patients | Age, gender | Type of resection | Location | Size of lesion | Depth of invasion | Curative resection | Pathological diagnosis | Post-procedure complications |
|---|---|---|---|---|---|---|---|---|---|---|
| 2019 | Cazacu et al. [4] | NA | Slight predominance of males over females | 87% surgical resection (also diagnostic approach) | Stomach, duodenum, jejunum | NA | Average size 4.1 cm. Most over 4 cm | 27.7% died from cancer-related complications. 36.1% developed metastasis. 39% of patients with follow-up alive and without disease at least 1 year after resection | Adenocarcinoma, anaplastic carcinoma, mucinous cystadenocarcinoma, acinar cell carcinoma, solid pseudopapillary tumors, pancreatoblastoma, perivascular epithelioid cell tumor, neuroendocrine tumor | NA |
| 2004 | Emerson et al. [1] | 1 | M, 52 | 50% gastrectomy with vagotomy and duodenal resection | Gastric pylorus | 4.0×2.5×1.5 cm | Serosa | Disease free at 9 months | Adenocarcinoma | None |
| 2013 | Endo et al. [17] | 2 | 2 M, 73, 75 | Subtotal stomach-preserving pancreatoduodenectomy for duodenal adenocarcinoma<br>Gastric lesion with EMR, but was unresectable on diagnosis, then eventually chemotherapy and distal gastrectomy | One lesion in duodenum<br>Another lesion in gastric antrum | 2.2×2.1×1.2 cm (duodenum)<br>4.5×3.0×2.5 cm (gastric antrum) | Submucosa (duodenum)<br>Serosa (gastric antrum) | No recurrence at 5 years | Adenocarcinoma | None |
| 1999 | Matsushita et al. [24] | 12 | 24–77 (mean 50.3), 5 M, 7 F | 4 had endoscopic resection. 8 had gastrectomy, when endoscopic snaring unsuccessful, invasive gastric carcinoma, large gastric neurinoma | Gastric (body, antrum, prepylorus) | 19.1 (9-40 mm) | Submucosa, Muscularis propria | NA | PR, ulcer, cancer, neurinoma | None |

**Table 4** (continued)

| Year | References | Number of patients | Age, gender | Type of resection | Location | Size of lesion | Depth of invasion | Curative resection | Pathological diagnosis | Post-procedure complications |
|---|---|---|---|---|---|---|---|---|---|---|
| 2014 | Chou et al. [19] | 13 | Mean 40.8 years (range 20–77) | 2 ESDs for muscularis propria layer lesions. ESD appeared safe for complete resection of small lesions (≤20 mm) originating form mucularis propria layer | Gastric | ≤20 mm | Muscularis propria | Curative resection | PR | None |
| 2011 | Park et al. [20] | 26 | 18–71 (mean 42), 12 M, 14 F | 30.8% with laparoscopoic wedge resection. 34.6% with endoscopic resection | 38.5% in antrum. 61.5% in gastric body<br>50% of gastric body lesions underwent surgical resection | Mean 14 mm (range 6 to 37 mm) | Muscularis mucosa, submucosa, muscularispropria, serosa<br>All surgical resection lesions were D type | NA | PR | NA |
| 2011 | Bain et al. [16] | 35 | Median 53 (range 28–89), 11 F, 8 M | 21 suspected PR underwent successful endoscopic band ligation snare polypectomy without complications with 90% able to have diagnosis of PR | Gastric antrum | Mean 10 mm (range 6–10 mm) | Submucosa | NA | 90% PR, 5% leiomyoma, 5% inflamed fibroid polyp | None |
| 2008 | Ormarsson et al. [34] | 30 | Mean 42.5, 15 F, 15 M | 3 resected by open wedge resection, 3 by laparoscopic wedge resection, 1 by sling resection, 1 by open excision, 1 by laparoscopic excision | Stomach (14), small intestine (6), Meckel's diverticulum (7), duodenum (1), gallbladder (2) | Average less than 9 mm (range 1 to 16 mm) | Mucosa, submucosa, subserosa | NA | PR | NA |

**Table 4** (continued)

| Year | References | Number of patients | Age, gender | Type of resection | Location | Size of lesion | Depth of invasion | Curative resection | Pathological diagnosis | Post-procedure complications |
|---|---|---|---|---|---|---|---|---|---|---|
| 2013 | Zhong et al. [18] | 60 | Median 39 (15–62), 28 F, 32 M | 23.3% underwent EMR. 51.7% of initially planned EMR converted to ESD due to inadequate lift with saline. Median EMR procedure time of 12 min with en block resection of 64.3%. In 5 cases, tumor adherent to muscularis propria and in 3 of those cases, resected by hook knife. No perforations or delayed hemorrhage. Median hospital stay 1 day<br>76.7% underwent ESD. 15 involved submucosa with diameter greater than 1 cm and 16 cases involved muscularis propria. Median procedure time 20 min. En block resection of 97.8% No delayed bleeding or perforation. Median hospital length of stay of 2 days<br>If diameter larger than 1 cm and no muscularis propria involvement on EUS, then EMR | Gastric antrum (85%), gastric body (10%), gastric angle (5%) | Mean size 1.4 + 0.1 cm | Muscularis mucosa (3.3%), submucosa (70%), muscularispropria (26.7%) | 98.3% | PR | None |

**Table 4** (continued)

| Year | References | Number of patients | Age, gender | Type of resection | Location | Size of lesion | Depth of invasion | Curative resection | Pathological diagnosis | Post-procedure complications |
|---|---|---|---|---|---|---|---|---|---|---|
| 2013 | Liu et al. [12] | 9 | Mean 48.3, 6 F, 3 M | EMR if originated from mucosa and/or submucosa. ESD if originated from submucosa or musclarispropria EMR for 1 patient. ESD for 8 patients | Gastric antrum (77.8%), gastric body (22.2%) | Mean 16.2×15.9 mm (range 9–22×10-24 mm) | Submucosal involvement. 22.2% involved muscularis mucosa, submucosa, and muscularis propria | No symptom recurrence at 8–10 weeks | PR | None |
| 2009 | Khashab et al. [21] | 2 | 49, 15;, 2 F | Both cases resected by ligator-assisted EMR | Gastric antrum | 7 mm x 6 mm, 8 mm x 7 mm | Submucosa | None | PR | None |
| 2001 | Faigel et al. [35] | 1 | 34, F | Cap-assisted endoscopic submucosal resection | Gastric antrum | 1.2×1.0×0.7 cm | Submucosa | None at 6 months | PR | None |
| 2010 | Ryu et al. [36] | 8 | Mean 36 (range 18–57), 7 F, 1 M | Attempted EMR first, but in 4 cases, lesions became flattened, so ESD performed | Gastric antrum (6.25%), gastric body (3.75%) | 6 to 12 mm | Deep mucosa to submucosa | No recurrence at median follow-up of 30 months | PR | None |
| 2015 | Iwamuro et al. [40] | 1 | 32, M | ESD en bloc resection | Gastric antrum | 11.8 mm | Deep mucosa and submucosa | NA | PR | None |
| 2016 | Xin et al. [28] | 52 | Mean 47.5 (range 21–78), 31 F, 21 M | High-volume ESD center. All en block resection. Lesions with more vessels required longer procedure time, more at risk for muscle layer injury, clip use | Gastric antrum | 14.4.4 ± 5.6 mm, 15.7 ± 7.7 mm | Mucosa, Submucosa, Muscularis-propria | No recurrence at 18-month follow-up | PR | 7.78% muscle layer injury in lesions rich with vessels. No perforation or delayed bleeding |
| 2014 | Zhang et al. [31] | 42 | Median 41 (range 21–68), 13 F, 29 M | High-volume ESD center. ESD with 95.2% en block resection. 2 lesions resected piecemeal due to tight adhesion to muscularis propria | Gastric antrum (81.0%), gastric incisura (7.1%), gastric body (9.5%), gastric fundus (2.4%) | Mean 15.2 mm (range 10–28 mm) | Submucosa, muscularis propria | No recurrence at median follow-up of 30 months | PR | No massive bleeding, delayed bleeding, perforation, or other severe complications |

**Table 4** (continued)

| Year | References | Number of patients | Age, gender | Type of resection | Location | Size of lesion | Depth of invasion | Curative resection | Pathological diagnosis | Post-procedure complications |
|---|---|---|---|---|---|---|---|---|---|---|
| 2006 | Otani et al. [41] | 60 (12 HP) | Median 59 (range 32–86), 23 F, 37 M | Laparoscopic wedge resection | Gastric | Mean/Median 25 mm (range 15–35 mm) | Submucosa | NA | GIST, PR | None |
| 2011 | Kakeji et al. [42] | 18 (1 HP) | 39, F (for HP) | Laparoscopic resection | Gastric body | 3.8 cm | Submucosa | NA | HP | None |
| 2017 | Vitiello et al. [14] | 29 | NA | Robotic-assisted laparoscopic gastrectomy (wedge or partial) | Gastric (24.1%), duodenum (31.0%), small bowel (27.6%), Meckel's diverticulum (10.3%), gallbladder (3.4%), colon (3.4%) | 2.5×2.09×1.5 cm; 1.0×0.5 cm | Submucosa | No recurrence after 18 and 24 months | HP | None |
| 2019 | Haidar et al. [33] | 30 | 30, F | Laparoscopic resection, then conversion to RYGB for obesity | Gastric body (less curvature) | 4 cm | Submucosa | None at 6 months | PR | None |
| 2015 | Attwell et al. [25] | 10 | Median 52 (range 26–64), 7 F, 3 M | 2 patients underwent wedge resection | 1 case was located in gastricantrum. Other lesion was gastric (unspecified) | NA | NA | NA | PR | None |
| 2002 | Huang et al. [15] | 2 | 41, 53, 2 M | 2 subtotal gastrectomy with Billroth II anastomosis | Gastricprepylorus (along greater curvature), gastric antrum | 2.5 cm, 2 cm | Muscularis propria | NA | PR | None |
| 2002 | Jeong et al. [37] | 1 | 64 years, 1 M | Distal gastrectomy with Roux-en-Y esophagojejunostomy, Braun anastomosis | Gastric antrum | 3 cm | Muscularis propria | None | Moderately differentiated adenocarcinoma from PR | None |
| 2006 | Galvez-Valdovinos et al. [38] | 2 | 28, 32 years, 2 F | 2 laparoscopic resections | Gastric antrum, prepylorus | 2 cm, 2 cm | NA | Long-term follow-up EGDs were normal | PR | None |

## Discussion

### Algorithm

Currently, there are no guidelines in managing PR during screening EGD prior to bariatric surgery. While most PR are asymptomatic and benign, there is a possibility of symptom development and malignant transformation. In addition, endoscopic surveillance after bariatric surgery may be difficult. Figure 3 presents a guideline on how to diagnose PR on a pre-bariatric surgery EGD and how to decide on resection, depending on symptoms, size, EUS characteristics, and histopathological findings. Once resection is determined, Fig. 4 guides clinicians on choice of resection, either endoscopic or surgical.

### Screening EGD

A screening EGD prior to bariatric surgery is important in identifying concerning lesions that may require management prior to surgery. On pre-bariatric surgery screening EGD, PR is often seen in the gastric antrum as a subepithelial lesion without mucosal changes. Central umbilication or dimpling may be seen in larger lesions, which corresponds an opening of a PR duct [19, 20]. Mucosal forceps biopsies are usually non-diagnostic, so do not need to be done [1, 21, 26].

### Further work-up with EUS

EUS provides further characterization of the subepithelial lesion and can distinguish between benign and malignant lesions. Most PR lesions are heterogeneous, with hypoechoi cacinous tissue and anechoic ductal features [24]. The borders may be distinct [19] or indistinct [20]. However, not all PR lesions may follow these characteristic features, as some may be more homogenous, depending on the wall layer they originate from. If the lesion is characteristic of other types of subepithelial lesions, then appropriate management should follow the appropriate guidelines. PR lesions may originate from the muscularis mucosa, submucosa, muscularispropria, serosa, or a combination, which will help determine the appropriate form of resection, if needed [20].

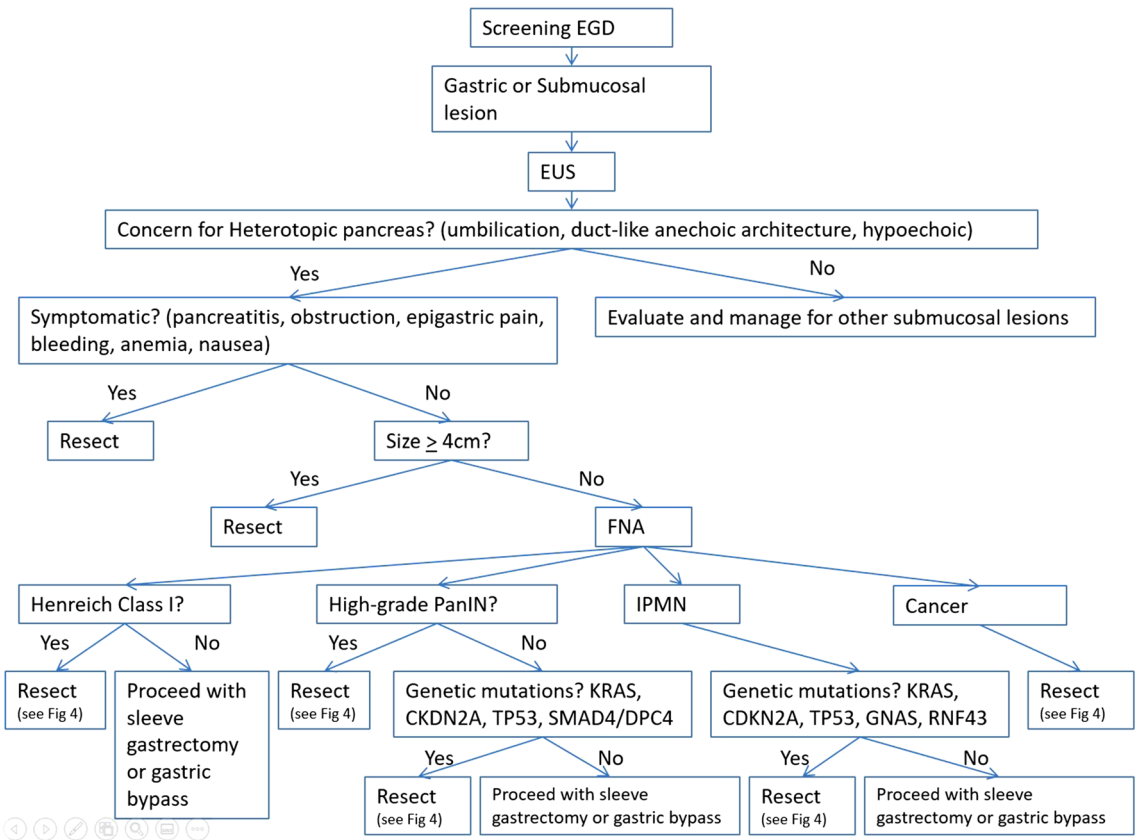


**Fig. 3** Diagnosis and management algorithm

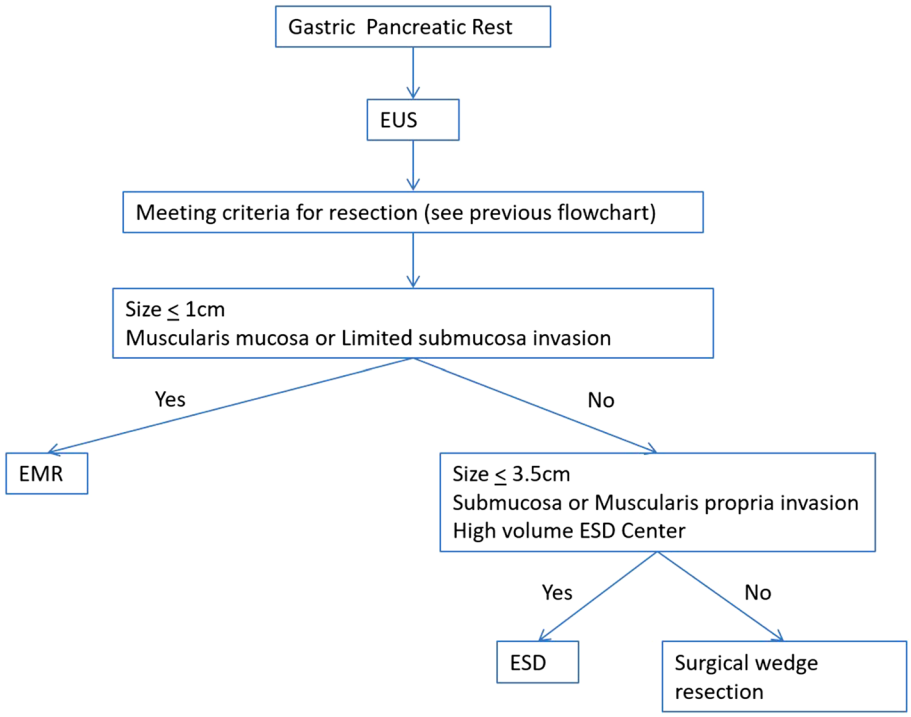


**Fig. 4** Resection management algorithm

## Symptomatology and size

Once there is suspicion for an PR lesion, the clinical characteristics of the patient must be taken into consideration. While most patients are asymptomatic, PR can cause or predispose to various symptoms, such as abdominal pain, obstruction, nausea, anemia, or pancreatitis [11, 12]. If the patient is symptomatic from PR, we recommend resection for clinical symptoms.

If the patient is not symptomatic, but the lesion is large, there is a possibility that the lesion may become symptomatic later on, as larger lesions are usually symptomatic [10]. In addition, PR has a risk of malignant transformation occurs in gastric PR when they are larger than 4 cm in diameter [4]. Therefore, we propose that asymptomatic lesions that are greater or equal to 4 cm in diameter should be resected.

## Histopathological guidance

If the patient with suspected PR is asymptomatic and the lesion is smaller than 4 cm in diameter, then further work-up with histopathological analysis should help determine if resection is warranted. EUS-FNA can be used to obtain cytological diagnosis with a high sensitivity and specificity [12]. Most malignant transformation has occurred from Henreich Type I heterotopias [1, 4], classified as normal pancreatic tissue containing acini, ducts, and islet cells [10]. As a result, those lesions with Henreich Class I should proceed with resection, while patients with Type II to IV lesions may reasonably proceed to bariatric surgery.

Those PR lesions with high-grade PanIN have more infiltrative growth and higher risk of progression towards malignancy [30], so they should be considered for resection. If there are no signs of high-grade PanIN, then genetic/molecular analysis should be performed to evaluate for mutations that may predispose to malignant transformation. Genetic alterations, such as KRAS mutation, p53 accumulation, cyclin D1 overexpression, loss of p16 expression [30], and SMAD4/DPC4 mutation [13] may provide a stepwise progression to adenocarcinoma, so these PR lesions should be resected. Low-grade PanIN without those mutational alterations may not need to be resected because of the negligible risk of malignant transformation.

For IPMN lesions, then genetic/molecular testing should be performed to evaluate for alterations to KRAS, CDKN2A, TP53, which may predispose to progression to high-grade IPMN and then to pancreatic adenocarcinoma (Jun et al.). For these lesions, resection should be considered. Otherwise, it may be reasonable to proceed with bariatric surgery.

Histopathological findings of cancer should appropriately be managed.

## Size and the choice of resection

Once the PR lesion has been decided for resection, then there are various methods which can be used. Endoscopic methods include EMR and ESD, and surgical resection is

another option. Endoscopically, current technology allows for resection of early gastric cancers and small luminal lesions with limited wall layer infiltration through either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). When compared to ESD, EMR can only allow en bloc resection of smaller lesions, although still limited to superficial submucosal lesions [32].

Based on size, if the lesion is equal or less than 1 cm in diameter, then EMR is appropriate [18]. These lesions can be removed either by standard lift and resect EMR [12], but it also has been successfully removed by endoscopic band ligation snare polypectomy [16, 21]. Endoscopic resection, through EMR or ESD, has had a low complication rate [18], but for ESD, the studies have been at high-volume ESD centers [18, 19]. If the lesion is greater than 1 cm but equal or less than 3.5 cm in diameter and the center is a high-volume ESD center, then ESD with en bloc resection can be considered [31, 32]. If the center is not a high-volume ESD center or if the lesion is greater than 3 cm or 3.5 cm, then surgical resection should be considered [8, 10]. This can be in the form of a laparoscopic wedge resection, followed by a RYGB [33] or by a laparoscopic sleeve gastrectomy.

Depth of invasion or wall layer involvement is another important factor to consider in terms of resection options. Based on EUS characteristics, if there is only involvement of the muscularis mucosa or limited involvement of the submucosa, then EMR can be attempted through standard techniques or band-snare polypectomy [12, 16, 18, 21]. If there is significant involvement of the submucosa or if there is involvement of the muscularis propria, then ESD can be considered if it is performed at a high-volume ESD center [12, 18, 19]. Otherwise, surgical resection would be another option [8, 10, 15]. If subserosal involvement is suspected on EUS, then surgical resection should be attempted.

Surgical resection can be in the form of a wedge resection, followed by a RYGB [33] or laparoscopic sleeve gastrectomy. If the lesion is in the lesser curvature of the stomach, then it would be appropriate to perform a subtotal gastrectomy and RYGB [33]. If the lesion is in the antrum, which is the most common location, then a subtotal gastrectomy with Billroth II anastomosis, followed by a RYGB may be considered. For lesions along the greater curvature of the stomach, then a sleeve gastrectomy may be performed to resect the lesion. If a PR is noted during a screening EGD for bariatric surgery, we would recommend the surgeon follow the appropriate algorithm as noted in Figs. 3 and 4. If the bariatric patient is intended to undergo a RYGB, we recommend the PR is appropriately treated prior to the RYGB considering the PR will likely be excluded from proper follow-up using upper endoscopy.

Given the limited evidence on the diagnosis and management of PR, there are inherently limitations to our review study. Given the single reviewer methodology of selecting publications, there is a risk of bias. Given the rarity of PR and its malignant transformation, our review paper referenced existing literature on PR consisting of mostly case reports and retrospective cohorts, which unavoidably limits the level of evidence of our algorithm to a low level of evidence. However, most of the case reports and retrospective studies are consistent in the description of PRs, their malignant potential, and the endoscopic, ultrasonographic, and pathological findings. Nonetheless, our review paper is the first to create an algorithm on management of PR before bariatric surgery.

With the rising incidence of obesity and popularity of bariatric surgery, screening EGDs will demonstrate more findings of PR. Patients with these lesions may be symptomatic, become symptomatic, and there is a possibility of malignant transformation. What to do about these lesions prior to bariatric surgery has not been discussed previously. Based on extensive literature search, we created an algorithm to guide clinicians on the approach and management of patients with PR. Symptomatic lesions should be considered for resection and those at risk for malignant transformation, such as greater size, high degree of neoplasia, and genetic mutations. EUS can aid in extent of wall layer involvement in order to determine the type of resection, either endoscopically through EMR or ESD, or by surgery, either sleeve gastrectomy or RYGB. We also recommend proper treatment evaluation and treatment of the PR if a patient is destined for a RYGB.

Funding No sources of funding.

## Compliance with ethical standards

**Disclosures** Salvatore Docimo—Consultant, Boston Scientific. Galen Leung, John Mills, Juan Carlos Bucobo declares that they have no conflict of interest.

## References

1. Emerson L, Layfield LJ, Rohr LR et al (2004) Adenocarcinoma arising in association with gastric heterotopic pancreas: a case report and review of the literature. J Surg Oncol 87:53–57
2. Dolan RV, Remine WH, Dockerty MB (1974) The fate of heterotopic pancreatic tissue. A study of 212 cases. Arch Surg 109:762–765
3. Yan ML, Wang YD, Tian YF et al (2012) Adenocarcinoma arising from intrahepatic heterotopic pancreas: a case report and literature review. World J Gastroenterol 18(22):2881–2884
4. Cazacu IM, Chavez AAL, Gonzalez GMN et al (2019) Malignant transformation of ectopic pancreas. Dig Dis Sci 64:655–668
5. Angrisani L, Santonicola A, Iovino P et al (2015) Bariatric surgery worldwide 2013. Obes Surg 25:1822–1832
6. Finnell CW, Madan AK, Temovits CA (2007) Unexpected pathology during laparoscopic bariatric surgery. Surg Endosc 21:867–869

7. Loewen M, Giovanni J, Barba C (2008) Screening endoscopy before bariatric surgery: a series of 448 patients. Surg Obes Relat Dis 4(6):709–712
8. Montalvo D, Hernandez P, Larrazaba A (2016) Unexpected ectopic pancreatic tissue during laparoscopic bariatric surgery. Case report and literature review. Surg Obes Relat Dis 12:E87–e88
9. Zhang Y, Sun X, Gold JS et al (2016) Heterotopic pancreas: a clinicopathological study of 184 cases from a single high-volume medical center in China. Hum Pathol 55:135–142
10. Christodoulidis G, Zacharoulis D, Barbanis S et al (2007) Heterotopic pancreas in the stomach: a case report and literature review. World J Gastroenterol 13(45):6098–6100
11. Eisenberger CF, Gocht A, Knoefel WT et al (2004) Heterotopic pancreas—clinical presentation and pathology with review of literature. Hepatogastroenterology 51(57):854–858
12. Liu X, Wang G, Ge N et al (2013) Endoscopic removal of symptomatic gastric heterotopic pancreas: a report of nine cases. Surg Innov 20(6):NP40–NP46
13. Jun SY, Son D, Kim MJ et al (2017) Heterotopic pancreas of the gastrointestinal tract and associated precursor and cancerous lesions: systematic pathologic studies of 165 cases. Am J Surg Pathol 41:833–848
14. Vitiello GA, Cavnar MJ, Haidu C et al (2017) Minimally invasive management of ectopic pancreas. J Laparoendosc Adv Surg Technol 27(3):277–282
15. Huang YC, Chen HM, Jan YY et al (2002) Ectopic pancreas with gastric outlet obstruction: report of two cases and literature review. Chang Gung Med J 25(7):485–490
16. Bain AJ, Owens DJ, Tang RS et al (2011) Pancreatic rest resection using band ligation snare polypectomy. Dig Dis Sci 56:1884–1888
17. Endo S, Saito R, Ochi D et al (2013) Effectiveness of an endoscopic biopsy procedure using EUS-FNA and EMR-C for diagnosing adenocarcinoma arising from ectopic pancreas: two case reports and a literature review. Intern Med 53:1055–1062
18. Zhong YS, Shi Q, Yao LQ et al (2013) Endoscopic mucosal resection/endoscopic submucosal dissection for gastric heterotopic pancreas. Turk J Gastroenterol 24(4):322–329
19. Chou JW, Cheng KS, Ting CF et al (2014) Endosonographic features of histologically proven gastric ectopic pancreas. Gastroenterol Res Pract 2014:160601
20. Park SH, Kim GH, Park DY et al (2011) Endosonographic findings of gastric ectopic pancreas: a single center experience. J Gastroenterol Hepatol 26(9):1441–1446
21. Khashab MA, Cummings OW, DeWitt JM (2009) Ligation-assisted endoscopic mucosal resection of gastric heterotopic pancreas. World J Gastroenterol 15(22):2805–2808
22. Chen HL, Chang WH, Shih SC et al (2008) Changing pattern of ecotopic pancreas: 22 years of experience in a medical center. J Formos Med Assoc 107(12):932–936
23. Cantor MJ, Davila RE, Faigel D (2016) Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. Gastrointest Endosc 65:29–34
24. Matsushita M, Okazaki HK, Takakuwa H (1999) Gastric aberrant pancreas: EUS analysis in comparison with the histology. Gastrointest Endosc 49(4):493–497
25. Attwell A, Sams S, Fukami N (2015) Diagnosis of ectopic pancreas by endoscopic ultrasound with fine-needle aspiration. World J Gastroenterol 21(8):2367–2373
26. Chen SH, Huang WH, Feng CL et al (2008) Clinical analysis of ectopic pancreas with endoscopic ultrasonography: an experience in a medical center. J Gastrointest Surg 12(5):877–881
27. Kim JH, Lim JS, Lee YC et al (2008) Endosonographic features of gastric ectopic pancreases distinguishable from mesenchymal tumors. J Gastroenterol Hepatol 23(8):e301–e307
28. Xin L, Jun LQ, Hua XL et al (2016) Endoscopic color Doppler ultrasonography in predicting the safety of endoscopic submucosal dissection for antral heterotopic pancreas. Saudi J Gastroenterol 22:380–384
29. Guillou L, Nordback P, Gerber C et al (1994) Ductal adenocarcinoma arising in a heterotopic pancreas situated in a hiatal hernia. Arch Pathol Lab Med 118(5):568–571
30. Zhang L, Sanderson SO, Lloyd RV et al (2014) Pancreatic intraepithelial neoplasia in heterotopic pancreas: evidence for the progression model of pancreatic ductal adenocarcinoma. Am J Surg Pathol. 31:1191–1195
31. Zhang Y, Huang Q, Zhu LH et al (2014) Endoscopic excavation for gastric heterotopic pancreas: an analysis of 42 cases from a tertiary center. Wien KlinWochenschr 126:509–514
32. Draganov PV, Wang AY, Othman MO et al (2019) AGA Institute clinical practice update: endoscopic submucosal dissection in the United States. Clin Gastroenterol Hepatol 17(1):16–25
33. Haidar AH, Saliba C, Nicolas G et al (2019) Unexpected gastric ectopic pancreas during sleeve gastrectomy: a case report. Am J Case Rep 30(20):1966–1968
34. Ormarsson OT, Gudmundsdottir I, Marvik R (2008) Diagnosis and treatment of gastric heterotopic pancreas. World J Surg 30:1682–1689
35. Faigel DO, Gopal D, Weeks DA et al (2001) Cap-assisted endoscopic submucosal resection of a pancreatic rest. Gastrointest Endosc 54(6):782–784
36. Ryu DY, Kim GH, Park DY et al (2010) Endoscopic removal of gastric ectopic pancreas: an initial experience with endoscopic submucosal dissection. World J Gastroenterol 16(36):4589–4593
37. Jeong HY, Yang HW, Seo SW et al (2002) Adenocarcinoma arising from an ectopic pancreas in the stomach. Endoscopy 12:1014–1017
38. Galvez-Valdovinos R, Mendoza-Rodriguez A, Coronado-Perez JH et al (2006) Laparoscopic treatment of heterotopic pancreas in the prepyloric region. J Minim Access Surg 2(4):224–226
39. Dias de Castro F, Magalhaes J, Monteiro S et al (2016) The role of endoscopic ultrasound in the diagnostic assessment of subepithelial lesions of the upper gastrointestinal tract. GE Port J Gastroenterol 23(6):287–292
40. Iwamuro M, Tsuzuki T, Ohya S et al (2015) Ectopic pancreas in the stomach successfully resected by endoscopic submucosal dissection. Case Rep Med 2015:147927
41. Otani Y, Furukawa T, Saikawa Y et al (2006) Operative indications for relatively small (2–5cm) gastrointestinal stromal tumor of the stomach based on analysis of 60 operated cases. Surgery 139(4):484–492
42. Kakeji Y, Nakanoko T, Yoshida R et al (2012) Laparoscopic resection for gastrointestinal stromal tumors in the stomach. Surg Today 42:554–558