

# Pancreaticobiliary Reconstruction Limb Ulcers Following Transarterial Radioembolization in Post-Pancreaticoduodenectomy Anatomy

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<b>Background</b>	Yttrium-90 ( <sup>90</sup> Y) transarterial radioembolization (TARE) is a safe and effective treatment for liver malignancies, including hepatocellular carcinoma (HCC) and metastatic neuroendocrine tumors (NET) not amenable to resection or ablation. While gastric and duodenal ulcers are known, albeit rare, complications of <sup>90</sup> Y TARE, there are no reports in the literature to our knowledge of jejunal or pancreaticobiliary reconstruction limb ulcers following <sup>90</sup> Y TARE treatment.
<b>Summary</b>	We report a case of perforated jejunal ulcers in the pancreaticobiliary reconstruction limb following <sup>90</sup> Y TARE treatment of metastatic gastrinoma recurrence in a patient with post-pancreaticoduodenectomy surgical anatomy. These ulcers ultimately required jejunal resection and were distinct from prior jejunal ulcers near the duodenojejunosomy (DJ) anastomosis caused by acid hypersecretion associated with gastrinoma recurrence.
<b>Conclusion</b>	We present the first known case of ulcer formation in the pancreaticobiliary reconstruction limb following <sup>90</sup> Y TARE in a patient who is post-pancreaticoduodenectomy. When considering <sup>90</sup> Y TARE, patients with aberrant anatomy such that a segment of the small bowel is directly adjacent to the <sup>90</sup> Y treatment bed warrant special attention.
<b>Key Words</b>	yttrium-90; transarterial radioembolization; neuroendocrine tumor; pancreaticoduodenectomy; jejunal resection; jejunal ulcer; pancreaticobiliary reconstruction limb

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## Case Description

A 66-year-old woman who had undergone pylorus-preserving pancreaticoduodenectomy sixteen years earlier for a pancreatic head gastrinoma had a solitary segment V hepatic recurrence treated with highly selective  $^{90}\text{Y}$  TARE. She then presented four months post-treatment with severe, acute abdominal pain, later found to be from a perforated jejunal ulcer in the pancreaticobiliary reconstruction limb.

The patient initially presented at age 50 with a history of worsening diarrhea, with work-up revealing a pancreatic head mass and elevated serum gastrin levels to 585 pg/mL. She underwent pylorus-preserving pancreaticoduodenectomy for a 1.6 cm malignant gastrinoma, involving one of eight lymph nodes (pT1N1). The configuration of the alimentary tract reconstruction, from proximal to distal, consisted of: the jejunal staple line, then 5 cm to the pancreaticojejunostomy, then 5 cm to the hepaticojejunostomy (HJ), and finally 10 cm to the duodenojejunostomy (DJ) anastomosis. Postoperatively, the patient had a prolonged ileus requiring TPN but ultimately recovered well. Oncologic surveillance examinations demonstrated no evidence of local, regional, or distant recurrent disease, and interval serum gastrin and chromogranin A levels were normal when measured off of proton pump inhibitor (PPI).

Eight years after surgery, the patient (age 58) presented to the emergency department with severe abdominal pain. Work-up was unrevealing, the symptoms were self-limited, and she was discharged home on a PPI trial, a result which replayed two years later (age 60), with a similar course. It was not until sixteen years after surgery (age 66) that the patient was admitted to the hospital with acute-onset, severe, unrelenting epigastric and right upper quadrant abdominal pain associated with bilious emesis, non-bloody diarrhea, focally peritoneal abdominal examination, and worsening leukocytosis and lactatemia, with computed tomography (CT) scan demonstrating segmental jejunal hypoperfusion. She was taken emergently to the operating room for exploration due to concern for bowel ischemia. After extensive lysis of adhesions, findings included a 30 cm segment of dilated and thickened but viable jejunum starting 10 cm proximal to the DJ anastomosis, without evidence of perforation, ischemia, or internal herniation. Upper endoscopy during this hospitalization noted multiple non-bleeding cratered ulcers in the jejunum bordering the DJ, in the efferent more so than the afferent limb (Figure 1). This finding raised concern for gastrinoma recurrence, causing acid hypersecretion and resultant ulcer formation. Given adherent clot, a visible vessel, and concern for bleeding, three clips were placed, although two days later, these dislodged, and the patient had an upper gastrointestinal bleed requiring transfusion. She was managed conservatively and subsequently discharged on a PPI, with plans for outpatient workup of ulcer etiology.

**Figure 1.** Endoscopy. Published with Permission

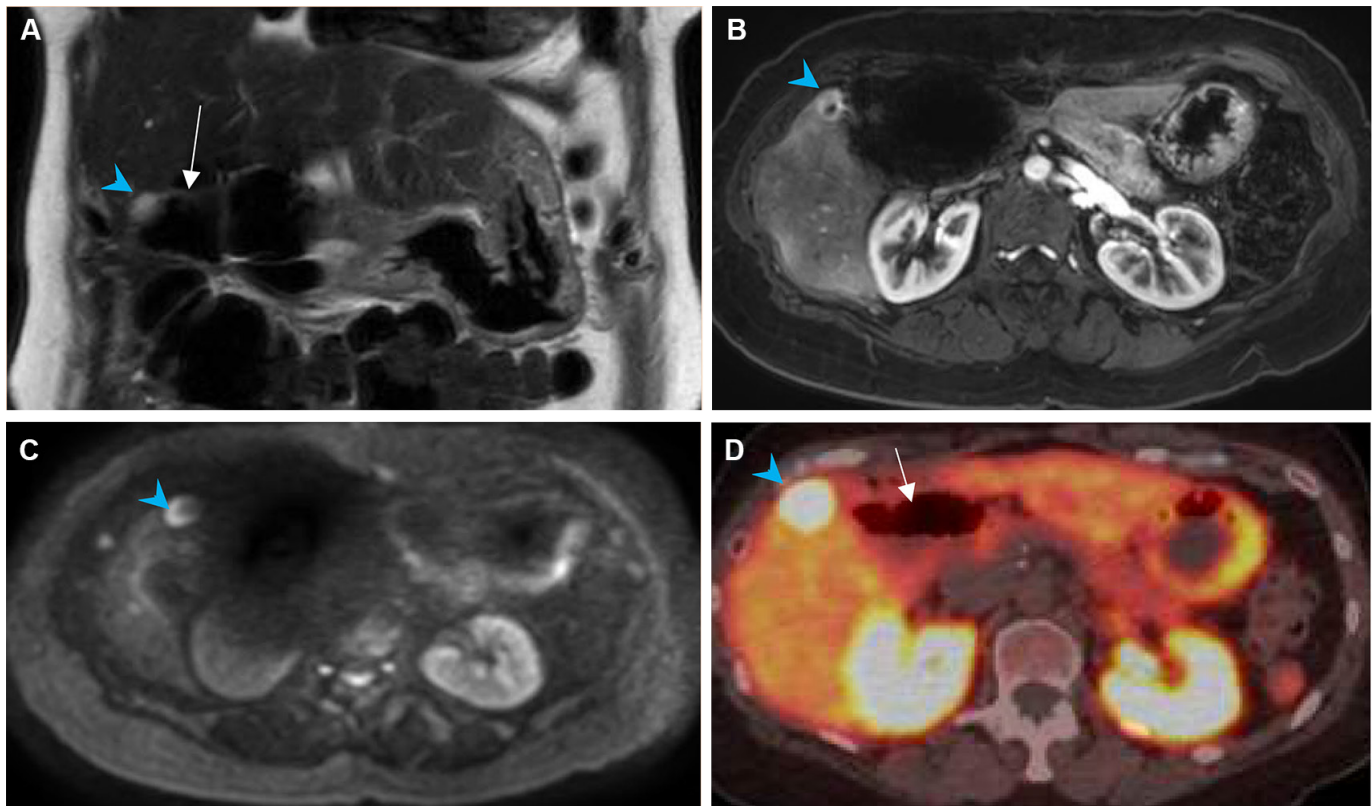


A) Diffuse Ulceration at Duodenojejunostomy Anastomosis; B, C) Efferent Jejunal Limb

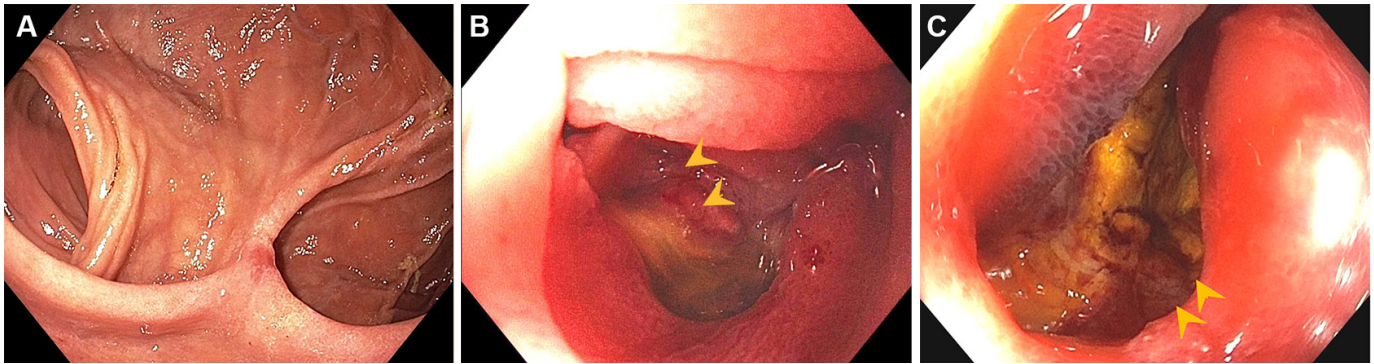
Two weeks after the patient's hospitalization, serum chromogranin A levels were found to be elevated to 1502 ng/mL (reference range <93 ng/mL). Serum gastrin levels were not obtained due to lab error. Subsequent magnetic resonance imaging (MRI) revealed a hypervascular, diffusion-restricting 1.2 cm lesion in liver segment V with focal uptake on gallium-68 ( $^{68}\text{Ga}$ ) DOTATATE positron emission tomography, confirming metastatic recurrence (Figure 2). Four months following this hospitalization, the patient successfully underwent superselective  $^{90}\text{Y}$  TARE with microsphere delivery through an arterial branch solely supplying the segment V tumor. There was no evidence of extrahepatic radiotracer uptake on a post-embolization single-photon emission computed tomography (SPECT) scan. She experienced mild fatigue from post-embolization syndrome in the months following the procedure but otherwise recovered well. A repeat MRI showed the segment V treatment zone with minimal peripheral enhancement and no evidence of residual or recurrent disease.

Four months after  $^{90}\text{Y}$  TARE, the patient presented to the emergency department with abdominal pain, CT exhibiting a perihepatic fluid collection, and possible small bowel obstruction versus ileus. She was admitted for nonoperative management and small bowel follow-through confirmed ileus. Endoscopy during this admission demonstrated resolution of the previously visualized jejunal ulcers bordering the DJ anastomosis but identified two new, deep, 1 cm ulcers just distal to the HJ anastomosis (Figures 3A and 3B). Biopsy noted enteritis but no evidence of malignancy, ischemia, or presence of  $^{90}\text{Y}$  microspheres. Serum gastrin and chromogranin A levels from the month prior were both normal. She was managed conservatively and discharged on twice-daily PPI and sucralfate.

**Figure 2.** Magnetic Resonance Imaging. Published with Permission



A) Segment V liver lesion (blue arrowhead) hyperintense on T2 and directly adjacent to bowel (white arrow); B) enhancing on arterial phase; C) and with restricted diffusion on diffusion-weighted imaging; D) gallium-68 DOTATATE positron emission tomography/computed tomography demonstrating intense focal uptake (May 2019)

**Figure 3.** Endoscopy Demonstrating Healthy Jejunal Mucosa. Published with Permission

A) Duodenojejunosotomy anastomosis; B) two new ulcers adjacent to hepaticojejunosotomy anastomosis (yellow arrowheads); and C) increased size of ulcers on follow-up endoscopy.

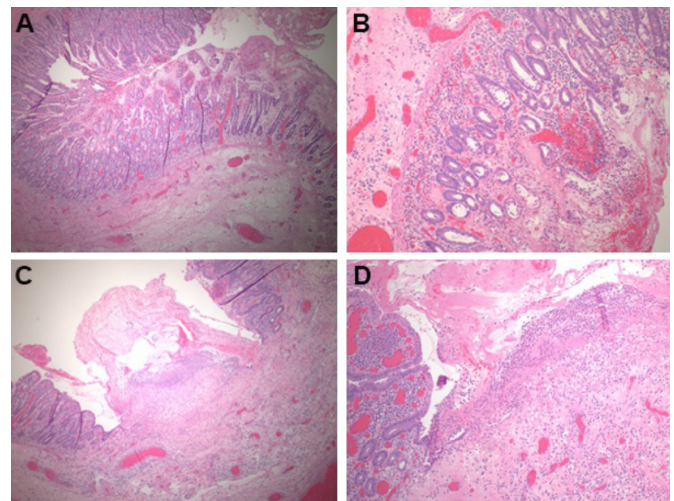
The patient continued to experience severe, stabbing abdominal pain, and follow-up endoscopy one month later revealed increased size of the jejunal ulcers adjacent to the HJ anastomosis (Figure 3C). She was admitted to the hospital, and a CT scan was obtained, with findings suggestive of erosion between the liver and an adjoining segment of the jejunum. On exploratory laparotomy, after extensive lysis of adhesions, a 1 cm jejunal segment distal to the HJ anastomosis was adherent to the liver with a contained jejunal perforation and fistulous tract into the radiated segment V lesion. The HJ and DJ anastomoses were noted to be intact, and the remainder of the visible jejunal mucosa appeared healthy. The jejunal perforation and 1 cm of bowel on either side were resected, and an end-to-end jejunojunction was matured. Surgical pathology showed small bowel mucosa with erosion, ulceration, fistula formation, edema, and serosal adhesions but was negative for neoplasm or evidence of  $^{90}\text{Y}$  microspheres<sup>1</sup> (Figure 4).

Our detailed pathologic findings included the following details:

- On gross examination, serosal surfaces of the resected jejunum were variegated, diffusely hemorrhagic, and focally shaggy.
- The mucosal surfaces were congested and attenuated with a few normal intestinal folds.
- There were no masses or lesions.
- On histological examination, the small intestinal mucosa was ulcerated, with denuded epithelium, extensive mixed inflammatory infiltrates, and areas of erosion.
- There were prominent, congested blood vessels in the submucosa, with stromal edema.

- The serosal surface of the small intestine had dense fibroconnective tissue, consistent with serosal adhesions.
- $^{90}\text{Y}$  microspheres or neoplasm were not identified.

The patient recovered uneventfully and had significant improvement in her symptoms. Of note, she recently underwent genetic testing, which found a variant of uncertain significance in the *POLE* gene, but the remainder of the panel, including MEN, was negative.

**Figure 4.** Hematoxylin and Eosin Stains. Published with Permission

Small intestinal mucosa with partially denuded epithelium, reactive epithelial changes, and admixed acute and chronic inflammatory infiltrates, A) 40x magnification and B) 100x magnification; ulcerated small intestinal mucosa with neutrophilic and lymphoplasmacytic inflammation in background of stromal edema and prominent congested blood vessels, C) 40x magnification and D) 100x magnification

## Discussion

Yttrium-90 (<sup>90</sup>Y) transarterial radioembolization (TARE), a form of intra-arterial brachytherapy, is a notable option in the treatment armamentarium for liver malignancies, including hepatocellular carcinoma (HCC) and metastatic neuroendocrine tumors (NET). First used in the 1960s to manage primary HCC and metastatic NET not amenable to surgical resection, <sup>90</sup>Y TARE has demonstrated favorable tumor response and patient survival that stands the test of time.<sup>1-6</sup> Overall, <sup>90</sup>Y TARE is considered a safe therapy. In a recent meta-analysis comprising 870 patients with NET liver metastases treated with <sup>90</sup>Y TARE, complications were reported in less than 1 percent of patients.<sup>7</sup> Complications may result from collateral radiation damage or nontarget deposition of the <sup>90</sup>Y radioactive microspheres, and include radiation pneumonitis, gastritis, cholecystitis, duodenal ulceration, post-procedure hepatic insufficiency, and liver failure.<sup>8-10</sup> Although rare, non-neoplastic gastric and duodenal ulcers have been described following <sup>90</sup>Y TARE of hepatic tumors; however, there are no reports of jejunal or pancreaticobiliary reconstruction limb ulcers to our knowledge.<sup>10,11</sup> Here, we report a case of a perforated jejunal ulcer in a patient with post-pancreaticoduodenectomy surgical anatomy and metastatic gastrinoma recurrence treated by <sup>90</sup>Y TARE.

We describe a case of pancreaticobiliary reconstruction limb ulcers that occurred after <sup>90</sup>Y TARE to an adjacent liver segment in a patient with post-pancreaticoduodenectomy surgical anatomy. In our literature review, this is the first report of ulceration in the jejunum of the pancreaticobiliary reconstruction limb following <sup>90</sup>Y TARE.

<sup>90</sup>Y TARE is a widely utilized therapeutic modality for treating liver malignancies not amenable to resection or ablation, including NET metastases as in our patient.<sup>9,11,12</sup> With over 50 years of data available, <sup>90</sup>Y TARE has demonstrated effective locoregional tumor control and beneficial long-term oncologic outcomes for both primary and metastatic hepatic malignancies.<sup>1,6,7</sup> For NET metastases specifically, <sup>90</sup>Y TARE has been associated with symptom relief, favorable disease control, and improved survival, with 78 percent of patients exhibiting tumor response or stable disease and a 72.5 percent one-year survival rate.<sup>7,14</sup>

The toxicity of radioembolization derives from what also provides its therapeutic effect: radiation.<sup>15</sup> The interventional radiologist must select the appropriate hepatic arterial inflow for radioembolization to minimize this toxicity

to adjacent normal tissue. Improvements in technology, technique, and experience have enabled more selective administration, thus minimizing adverse events.<sup>11,16</sup> However, there are still complications from radiation-induced collateral liver damage, with up to 77 percent of patients exhibiting grade II or III liver toxicity one year after treatment, based on National Cancer Institute Common Toxicity Criteria for Acute Events.<sup>8</sup> While gastric and duodenal ulcers are the most commonly reported extrahepatic complications of <sup>90</sup>Y TARE, they are rare, with recent literature indicating a prevalence of less than 5 percent.<sup>17-19</sup> These are thought to be caused by nontarget microsphere accumulation in the gastrointestinal submucosa resulting in tissue and small vessel damage.<sup>10,11,20</sup> In this patient's case, a subsegmental arterial branch supplying the segment V tumor was specifically identified and targeted to deliver the <sup>90</sup>Y microspheres, with no evidence of nontarget delivery.

The development of the jejunal ulceration in our patient was a result of a "perfect storm": the segment V hepatic recurrence was located in a superficial, subcapsular location; a dedicated branch of the hepatic artery was identified to be supplying the tumor on the mapping angiogram made this lesion amenable to super-selective, high-dose delivery of the <sup>90</sup>Y microspheres; and the patient's altered post-pancreaticoduodenectomy anatomy placed the affected jejunal segment directly adjacent to the radiated liver. The jejunal ulceration thus resulted not from nontarget microsphere deposition but an ablative radiation dose close to the small bowel, described at our institution as "shine-through radiation." The average tissue penetration of the beta energy from <sup>90</sup>Y TARE is 2 mm to 3 mm, up to a maximum of 11 mm. To this end, a retrospective study of 97 patients undergoing non-ablative, conventional radioembolization to the left hepatic lobe demonstrated the safety of the therapy when delivered near the gastric wall.<sup>21</sup>

In our patient's case, the ulcerated jejunum was not just close to the liver metastasis but was found intraoperatively to be adherent to it. Of note, there is limited experience regarding special considerations for <sup>90</sup>Y TARE in patients after pancreaticoduodenectomy. In a cohort of 33 patients receiving <sup>90</sup>Y treatment for liver metastases from pancreatic adenocarcinoma, there were no reports of gastrointestinal ulceration in ten patients who had undergone prior pancreatic resection. However, whether these patients had undergone pancreaticoduodenectomy or the location of the liver metastases was not specified.<sup>22</sup>

Furthermore, a higher radiation dose than conventional TARE was used in this case to perform an ablative radioembolization, or radiation segmentectomy, in which increased doses administered to two or fewer liver segments are considered curative.<sup>23</sup> In short, the patient's post-pancreaticoduodenectomy anatomy placing the jejunum directly adjacent to the superficial liver tumor, combined with the high radiation dose afforded by ablative TARE, is the likely cause of this unique complication.

Our patient developed two sets of jejunal ulcers in succession from distinct etiologies. She initially formed jejunal ulcers adjacent to the DJ anastomosis due to her gastrinoma recurrence and its associated acid hypersecretion, which improved with PPI and ultimately resolved with <sup>90</sup>Y TARE treatment of the recurrence. She subsequently developed new ulcers adjacent to the HJ anastomosis following <sup>90</sup>Y TARE therapy, when serum chromogranin A and gastrin levels were low. It is unlikely that the segment of jejunum affected had been previously damaged by stomach acid hypersecretion as it was in the afferent limb, considerably distant relative to the DJ anastomosis. Of note, there was a low threshold for performing endoscopy in this patient given concern for recurrent cancer, which may have led to earlier, serendipitous detection of the post-<sup>90</sup>Y ulcers.

## Conclusion

We present the first known case of a perforated pancreaticobiliary reconstruction limb ulcer following <sup>90</sup>Y TARE and requiring segmental jejunal resection in a post-pancreaticoduodenectomy patient. When considering <sup>90</sup>Y therapy follow-up, patients like ours with aberrant anatomy such that a segment of the small bowel is directly adjacent to the <sup>90</sup>Y treatment bed warrant special attention.

## Lessons Learned

While gastrointestinal ulceration is a rare complication of ablative, yttrium-90 transarterial radioembolization for treating liver malignancies, patients with altered intestinal anatomy present a unique challenge. Pancreaticobiliary reconstruction limb ulceration is a potential complication of <sup>90</sup>Y radiation segmentectomy in patients with prior pancreaticoduodenectomy.

*LKD, KPL, and JOP contributed to the conception of the work. All authors contributed to the interpretation of the patient information, including laboratory values, endoscopic images, radiologic images, operative findings, and histopathology findings. LKD, KPL, CW, WM, and JOP drafted the article and/or substantively revised it. All authors read and approved the final version to be submitted.*

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