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Pancreatoduodenectomy in Locally Advanced Right Colon Cancer

—Case Report and Literature Review

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Abstract

Background: Pancreatoduodenectomy (PD) associated with colectomy is an uncommon procedure accounting for 2% - 11.5% of all PD, and only 6.2% are due to ascending colon cancer. **Aim:** Report an uncommon presentation of locally advanced colon cancer meriting an en bloc multi-organic resection describing current recommendations for its treatment. **Case Presentation:** A 29-year-old woman with a locally advanced right-sided colon cancer with duodenal infiltration treated with an en bloc multi-organic resection by right hemicolectomy with pancreatoduodenectomy and adjuvant chemotherapy. **Conclusion:** The best therapeutic approach for these patients has not been defined; initial surgical treatment is the most recommended option whenever it is possible to achieve an R0 resection.

Keywords

Pancreatoduodenectomy, Right Hemicolectomy with Pancreatoduodenectomy, Locally Advanced Colon Cancer, Locally Advanced Right-Sided Colon Cancer, En Bloc Multi-Organic Resection

1. Introduction

Pancreatoduodenectomy (PD) associated with colectomy is an uncommon procedure accounting for 2% - 11.5% of all PD, the most frequent indications are periampullary malignant tumors, pancreatic head tumors, and duodenal tumors, which together account for 70.8% of cases [1]; other less frequent etiologies include neuroendocrine tumors (5.8%) and some benign pathologies (16.8%), and only 6.2% are due to ascending colon cancer, in which up to 54.7% of cases the tumor is located in the hepatic flexure [1] [2]. Likewise, of all colorectal cancers, only 5.2% - 23.6% invade neighboring organs, with the most common sites of the primary tumor being the descending colon and the rectosigmoid junction [3]-[8], and the most frequently invaded sites are the peritoneum (35%), the abdominal wall (25%), the jejunum/ileum (16%), the omentum (16%), and the ovaries (12%) [2] [9]. In right colon cancers an invasion of other organs is even less frequent with an incidence of 2.6% - 11%, and the duodenum and pancreas are the most commonly affected organs [1] [4] [6]-[8] [10].

Currently, few studies have focused on defining the ideal surgical approach that achieves the greatest increase in overall survival and recurrence free survival with the lowest possible morbidity and mortality for these patients [3] [5]; furthermore, most published studies on PD with associated colectomy include heterogeneous populations and few patients with variable indications of adjuvant and neoadjuvant treatments[1] [10].

Although in general for all cases of locally advanced colon cancer (LACC) with invasion of neighboring organs the first treatment option to consider is en bloc multi-organic resection to achieve negative resection margins (which in these patients includes right hemicolectomy with PD (RH + PD)) [3]-[5] [11] [12], few series have been published given the lack of knowledge about its oncological benefits [6] [13], and because both the intraoperative technical complexity and the high risk of postoperative complications may discourage surgeons to performing it limiting themselves only to partial duodenal resections with a high risk of residual disease, and/or to performing palliative procedures [2] [9] [10] [13]. We report a case with this uncommon presentation of locally advanced colon cancer meriting an en bloc multi-organic resection describing current recommendations for its treatment.

2. Case Presentation

A 29-year-old woman with no relevant medical history began one year prior to admission experiencing asthenia, adynamia, hyporexia, and weight loss. She was evaluated by a general practitioner who ordered laboratory tests which revealed persistent anemia that was treated with hematinics. Subsequently, the patient presented with early satiety accompanied by intermittent abdominal pain and constipation with exacerbation of the initial symptoms, further weight loss, and oral intolerance; therefore, a fecal occult blood test was performed which was positive, and an endoscopy revealed a tumor in the second portion of the duodenum that

occluded 80% of its lumen making it impossible to identify the ampulla of Vater due to its extent and active bleeding that was difficult to control endoscopically with the histopathological report of the biopsy as a moderately differentiated adenocarcinoma which is why she was sent to our hospital. A contrast-enhanced CT scan of the chest, abdomen, and pelvis was performed revealing a solid tumor in the hepatic flexure of the ascending colon which infiltrates the second portion of the duodenum and with striation of the pericolonic fat without distant metastasis (**Figure 1**), a colonoscopy revealed a tumor in the hepatic flexure with areas of necrosis and persistent bleeding that occluded 90% of the colonic lumen, and the reported carcinoembryonic antigen level was 85.4 ng/mL concluding the diagnosis of a LACC with duodenal infiltration. Given the patient's borderline nutritional status and the impossibility of establishing a non-surgical enteral feeding route (it was not possible to place a nasojejunal tube due to the obstruction of the duodenal passage), the persistent tumor bleeding as the patient only showed temporary improvements in hemoglobin levels after transfusions, and the imminent risks of intestinal obstruction and/or tumor perforation, a multidisciplinary team decided to admit her for in-hospital monitoring and to improve her condition with parenteral nutritional support and blood products for definitive surgical treatment given that imaging studies did not reveal suggestive findings of unresectability or a high risk of incomplete resection such as the presence of tumor invasion of superior mesenteric vessels or of the vessels of the hepatic hilum.

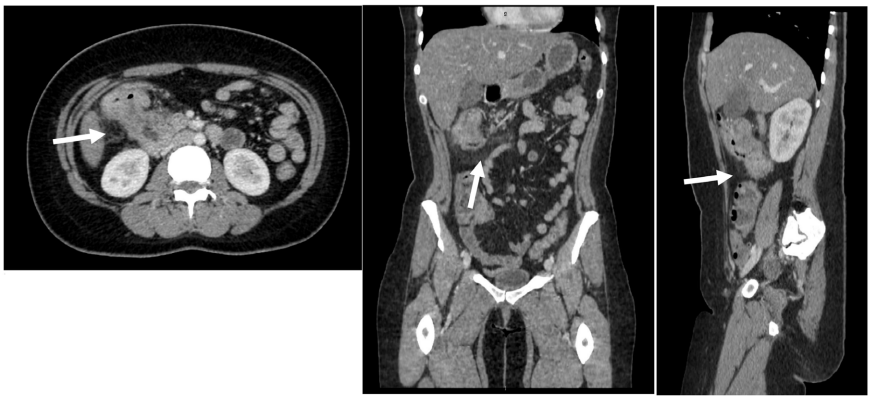

Figure 1. A solid tumor (white arrow) in the hepatic flexure of the ascending colon which infiltrates the second portion of the duodenum and with striation of the pericolonic fat.

She underwent an en bloc multi-organic resection which consisted of RH + PD with intraoperative findings of a tumor of the colonic hepatic flexure with a transmural infiltration of the second portion of the duodenum and traction of the pancreatic head, intraluminal blood in the jejunum and ileum, a distended ascending colon due to an imminent bowel obstruction, and without metastatic disease (**Figure 2(A)**, **Figure 2(B)**). The pancreas had a soft consistency and a pancreatic duct smaller than 2 mm and the diameter of the common bile duct was 5 mm. The patient had a satisfactory postoperative course, and the histopathological report concluded a moderately differentiated adenocarcinoma measuring 10 cm in di-

ameter with transmural duodenal invasion and adhesions with no infiltration to the pancreatic head, with the presence of lymphovascular invasion and moderate tumor budding, with 20 lymph nodes without metastasis, and negative resection margins, with a final staging of pT4bN0MO EC IIC (**Figures 3(A)-(D)**).

The expression of the mismatch repair (MMR) proteins MLH1, MSH2, MSH6 and PMS2 was determined by immunohistochemistry classifying the tumor as a pMMR (Mismatch Repair Proficient) colon cancer, so the patient was evaluated by clinical oncology who decided to administer the standard adyuvant chemotherapy according to the CAPOX scheme (Capecitabine 500 mg/m^2 plus Oxaliplatin 130 mg/m^2) for 6 months completing 8 cycles which were initiated 6 weeks after surgery evolving without incidents and with adequate gastrointestinal and hematological tolerance. Currently, the patient continues under oncological surveillance through serial imaging studies and colonoscopies with a disease-free survival of 2 years.

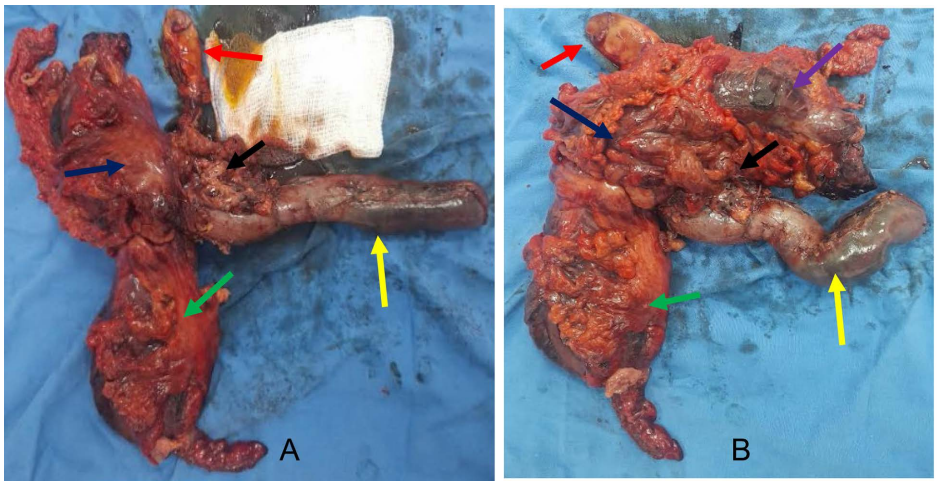

Figure 2. Hepatic flexure tumor of ascending colon with infiltration of the second portion of the duodenum and retraction of the pancreatic head. (A) Anterior view. (B) Posterior view. Tumor with duodenal infiltration (blue arrow), pancreatic head (black arrow), ascending colon (green arrow), transverse colon (purple arrow), proximal jejunum (yellow arrow) and gallbladder (red arrow).

3. Discussion

Turner first described partial duodenal resection for locally advanced right-sided colon cancer (LARCC) in 1929, and later in 1947 Calmenson and Black published a series of eight patients treated in the same way with a one-year survival rate of 0% and three of them dying in the immediate postoperative period [4] [14]. In 1953 Van Prohaska reported the first patient treated with RH + PD for LARCC and two years later Roux and Carcassonne proposed the en bloc multi-organic resection using RH + PD as the standard treatment for these patients [4] [8] [9] [11], however at that time morbidity, mortality, and recurrence rates were high due to insufficient equipment, lack of experience with the surgical technique, and high rates of incomplete resections [3] [5].

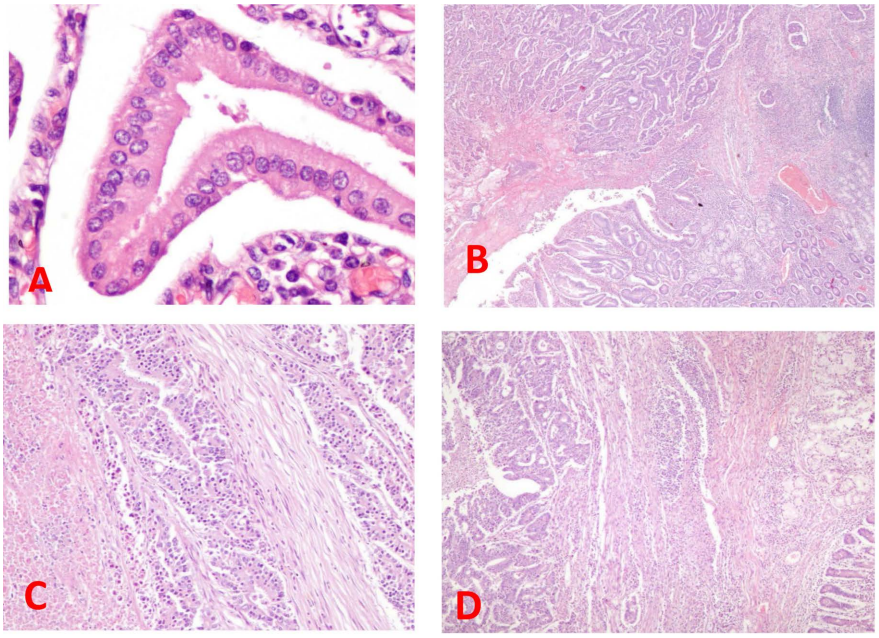

Figure 3. (A) A malignant lesion corresponds to a columnar cylindrical epithelium with loss of polarity and overlapping nuclei that reach the middle third, present moderate pleomorphism and evident nucleoli. (B) Duodenum, the upper half corresponds to a poorly differentiated ulcerated malignant lesion that infiltrates the duodenal tissue seen in the lower half. (C) Duodenum with ischemic necrosis at the far left, the rest corresponds to an epithelial neoplasm infiltrating the smooth muscle fibers of the wall. (D) On the right side duodenal mucosa with Brünner glands is observed and on the left, invasive adenocarcinoma with lymphatic vascular permeation.

Duodenal invasion by colon cancer is classified into three types: type I when it involves less than half of the circumference of the lateral duodenal wall, type II when it extends to more than half of the circumference away from the papilla, and type III if the invasion covers more than half of the circumference near the papilla [11]; our patient had a type III duodenal invasion. Currently, in the absence of metastatic disease, the first therapeutic option considered for these patients is an en bloc multi-organic by RH + PD with negative margins [3] [7] [8] [10] [11] [13] since evidence shows that these aggressive resections have acceptable morbidity and mortality [14] with better oncological results compared to limited resections possibly because they involve more extensive lymph node dissections as PD allows for more extensive lymphadenectomies [6] [7] [9] [10]. Only in cases of a limited invasion to the duodenum and ideally achieving a resection margin of at least 1 cm [10], an a sleeve resection of the duodenum and/or resection of the affected segment may be enough for types I and II duodenal invasion respectively [11] since the main factor in LARCC survival is an R0 [12]-[15] resection, as the presence of residual disease in adjacent organs is the main risk factor for recurrence and is associated with a poor prognosis [2] [6] [8] [11].

Distinguishing between inflammatory adhesions and malignant infiltration with sufficient accuracy is very difficult both in preoperative imaging studies and during surgical findings [1] [6] [8]-[11] [13]; furthermore, endoscopy only diag-

noses duodenal infiltration in the presence of mucosal invasion without being able to determine whether or not there is serosal invasion in the presence of intact mucosa [13]. Due to these facts all tumor adhesions should be considered as malignant invasion since the reported rate of tumor spread through the serosa to adjacent organs corroborated by histopathology is 53.4% - 84% [1] [2] [4] [6]-[9] [11] [13] [14] [16] and only a small percentage show inflammatory adhesions [10] [11]; in addition, the separation of these adhesions can increase the risk of tumor rupture and peritoneal dissemination increasing the local recurrence rate by up to 70% - 90% [1] [4]-[8] [10] [13]. In the vast majority of patients reported in the analyzed series, tumor invasion in firm adhesions was corroborated by histopathology [6] [13].

All these data combined with high R0 resection rates (greater than 90%) and overall (OS) and disease free survival (DFS) rates at 1, 3, and 5 years greater than 70%, 60%, and 50% respectively, may justify aggressive surgical treatment [1] [2] [5] [7] [8] [10] [11] [13], and therefore even advanced age and the presence of comorbidities are not absolute contraindications for multi-organ resections in these patients [4] [6] [9] [14] since although partial duodenal resections can be performed in patients with greater comorbidities if the ampulla of Vater is free of tumor invasion [4] [9], these procedures are associated with a higher risk of local recurrence [4] [6] [9] [11]. The largest systematic review of LARCC with invasion of neighboring organs included 11 studies from 2008 to 2021 with 117 patients, of whom 35 had duodenal invasion, 14 had pancreatic invasion, 18 had duodenal/pancreatic invasion, and 24 reported the presence of invasion of the pancreas and/or duodenum along with other sites including the mesentery, liver, gallbladder, kidney, superior mesenteric vein, and transverse colon [5]. Surgical treatments included eight partial duodenal resections and one local pancreatic resection for patients with duodenal and pancreatic invasion, respectively; the remaining patients including those with duodenal/pancreatic invasion and those with multi-organ invasion were treated with en bloc multi-organic resection by PD + RH and additional organ resections respectively [5]. The survival rates reported with en bloc multi-organic resections were 72% for patients with duodenal invasion, 71.4% for those with pancreatic invasion, and 55.56% for those with duodenal/pancreatic invasion; these rates were relatively higher than those achieved by RH with local resections because it was possible to achieve complete resection, consistent with previous reports from several studies [3] [5].

Similarly as in other reviews [2], after analyzing 15 previous studies Cirocchi *et al.* reported an overall survival rate of 52% with PD + RH and 0% - 25% with partial duodenal resections [7], and one of the series with the largest number of patients reported a morbidity rate of 53.8%, which is only slightly higher than that of standard PD which is 39.8% - 50% [1] [13]; this may be because an en bloc multi-organic resection involves longer surgery times and may be associated with greater bleeding, with a larger area of dissection which may increase the risk of developing collections and/or abscesses, and because in most patients there is a

soft pancreatic remnant with a small duct [1] [13], and a non-dilated common bile duct. Likewise, this series reported a mortality rate of 3.7%, which is similar to that of standard PD [13].

Another relevant point is the importance of establishing a timely diagnosis and treatment for these patients as they unfortunately present a high risk of local complications secondary to tumor progression including bowel obstruction, tumor perforation, and tumor bleeding; the latter is due to the fact that arterial embolizations have a low success rate given the high vascularity and multiple collateral vessels in the pancreatoduodenal region [12]. In these scenarios, a PD + RH in emergency surgical conditions presents even greater morbidity given the patient's condition and the indication for the procedure with a mortality rate of up to 40% [1] [12]. Fortunately our patient did not experience these complications although tumor bleeding was persistent, there was a likelihood of imminent bowel obstruction, and she already had oral intolerance due to duodenal obstruction.

Although the primary treatment for LACC is radical surgery which may involve en bloc multi-organic resections to achieve an adequate resection margin followed by adjuvant chemotherapy [17], certain factors related to local tumor extension may decrease the chances of achieving an R0 resection, and approximately 5% of patients with colon cancer present with locally advanced unresectable or borderline disease due to a high risk of positive resection margins and/or surgical morbidity or mortality [1] [17]. In these patients neoadjuvant treatment may offer benefits by reducing the tumor burden, eradicating micrometastatic disease, making surgical treatment more feasible and less extensive by favoring an R0 resection with preservation of other organs through downstaging, reducing the toxicity profile and the risks of delays of the adjuvant therapy, and could even select patients for non-surgical treatment with a watch-and-wait approach as in rectal cancer [1] [16]-[18].

The meta-analysis "Survival and safety after neoadjuvant chemotherapy or upfront surgery for locally advanced colon cancer" reported a 5-year OS and DFS of 79.9% and 73.1% respectively in patients treated with neoadjuvant therapy compared to OS and DFS of 72.6% and 64.5%, respectively in patients undergoing upfront surgery followed by adjuvant chemotherapy [18]. Similarly, neoadjuvant immunotherapy has demonstrated survival benefits in dMMR colon cancers with complete pathological response rates of 69% in patients treated with ipilimumab and nivolumab in the phase II NICHE study and no disease recurrence at 25 months of follow-up [18].

In terms of downstaging the phase III FoxTROT and OPTICAL studies (designed for T4 or T3 patients with invasion into the muscularis propria ≥ 5 mm) showed increases in R0 resection rates [17], higher degrees of tumor regression [16], higher rates of lymph node-negative disease (pN0), and greater reductions in T in patients with initial T3-T4 N0-2 M0 tumors treated with neoadjuvant FOLFOX and CAPOX [18], and even a small subgroup of patients had complete (3.8%) and near-complete (4.6%) tumor regression [16]; in addition, both trials showed

improvements in DFS rates and a decrease in colon cancer-specific mortality [17]. As previously mentioned, given the persistent tumor bleeding, the likelihood of imminent bowel obstruction, and the oral intolerance due to the duodenal obstruction, the patient was not considered a candidate for neoadjuvant treatment, and because imaging studies showed that the tumor was resectable with a highly likely to achieve an R0 resection, the decision was to improve her condition under close surveillance and proceed with definitive surgical treatment by a en bloc multi-organic resection.

As with other cancers, one of the main risks of neoadjuvant therapies is progression during treatment which can even complicate the disease through bowel obstruction or tumor perforation [18]. Likewise some patients may not complete the planned chemotherapy regimen due to toxicity and may even delay the optimal timing of surgery due to sustained bone marrow suppression [18]. Therefore, adequate T and N staging is extremely important to avoid overtreatment in low-risk patients [17] [18].

Other neoadjuvant treatment options include chemoradiotherapy, triplet neoadjuvant chemotherapy, neoadjuvant immunotherapy, and combinations of chemotherapy and immunotherapy. Although some studies have reported promising results, the optimal neoadjuvant strategy for LACC has not yet been established [17] [18]. The vast majority of patients reported in the series analyzed underwent initial surgery, and most subsequently reported completion of adjuvant chemotherapy, possibly because some patients were not in optimal condition to begin neoadjuvant therapy, as was the case with our patient.

Finally, although invasion of neighboring organs could be considered a sign of aggressive tumor biology [4], it is not associated with metastatic disease or greater lymph node dissemination, as it has been reported that 25% - 60% of colon cancers with duodenal or/and pancreatic invasion do not present lymph node metastases [4] [7]; likewise, when comparing organ invasion with the presence of lymph node disease, the prognosis appears to be similar [10]. Like our patient, several patients reported in our bibliographic review were staged as pN0 and did not present distant metastasis as an intraoperative finding that would contraindicate continuing with the surgical procedure [18].

4. Conclusion

Because LARCC with duodenal/pancreatic infiltration is a rare presentation the best therapeutic approach for these patients has not been defined; although an en bloc multi-organic resection is considered the initial treatment for LACC with infiltration of other organs, these resections generally do not carry the same morbidity as a multi-organ resection involving a PD. However, because many of these patients are not in optimal condition to begin neoadjuvant treatment and also have a high risk of developing local complications due to the likelihood of tumor progression, initial surgical treatment is the most recommended option whenever it is possible to achieve an R0 resection, and comparing local resections versus multi-organ resections, the latter appear to be associated with a higher rate of R0

resection and better oncological outcomes in terms of OS and DFS with an acceptable morbidity and mortality not very different to those of conventional PD. On the other hand, in patients with limited duodenal/pancreatic invasion and in good general condition, neoadjuvant treatment could be an acceptable therapeutic option.

Consent

Written informed consent was obtained from the patient for publication of this case report.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviation

Pancreatoduodenectomy (PD)
Locally advanced colon cancer (LACC)
Right hemicolectomy with pancreatoduodenectomy (RH + PD)
Locally advanced right-sided colon cancer (LARCC)
Overall survival (OS)
Disease free survival (DFS)