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HOW I DO IT

EndoVascular Occlusion and Tumor Excision (EVOTE): a Hybrid Approach to Small-Bowel Neuroendocrine Tumors with Mesenteric Metastases

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Abstract

Background Mesenteric metastases from small-bowel neuroendocrine tumors (SBNETs) present a surgical challenge due to encasement of mesenteric vessels. In this study, we evaluate the feasibility and safety of a new, hybrid surgical approach to these mesenteric masses, EndoVascular Occlusion and Tumor Excision (EVOTE).

Methods From 2014 to 2018, 13 patients underwent the EVOTE procedure after being referred to our institution for primary SBNETs with "unresectable" mesenteric metastases. During stage 1 of the hybrid EVOTE procedure, angiographic evaluation of the mesenteric mass is performed. If adequate collateralization is demonstrated, the encased mesenteric vessel(s) is embolized. Mass excision is performed the following day during stage 2 of the EVOTE procedure.

Results Preoperative embolization was successful in 86% of cases; 2 cases were aborted for persistent abdominal pain following occlusion testing. Complete surgical excision of the mesenteric mass was achieved in 86% of cases. The 30-day overall morbidity and mortality rate was 29% and 0%, respectively. There was one local recurrence at 31.8 months post-op; this patient underwent a repeat EVOTE procedure with successful complete excision.

Discussion EVOTE represents a new technique that aids in preoperative planning and surgical resection of SBNETs with mesenteric metastases.

Keywords Unresectable carcinoid · Metastatic carcinoid · Surgical management carcinoid · Mesenteric metastases

Introduction

Carcinoid tumors, now termed well-differentiated neuroendocrine tumors (NETs), are rare clinical entities, with an annual incidence of 30–50 cases per one million individuals.[1,2] Within the gastrointestinal tract, NETs are most commonly found in the small intestines, representing 37–44% of all gastrointestinal NETs.[1,3] For patients with small-bowel NETs (SBNETs), surgery is presently the only potentially curative treatment modality. While localized SBNETs have a favorable prognosis, regional and distant metastases result in 5-year overall survival rates ranging from 32 to 64%.[1,2]

Select patients with metastatic disease can experience an improved quality of life (QOL) and survival with resection or surgical debulking.[4,5] Additionally, patients with mesenteric nodal disease, found in up to 80% of patients at presentation, experience improved survival following resection of their mesenteric metastases, even in the presence of hepatic metastases.[5,6] Furthermore, resection ameliorates complications associated with mesenteric metastases such as abdominal pain, diarrhea, intestinal obstruction, and intestinal ischemia.[7] However, the morphology and location of mesenteric metastases from SBNETs make complete excision technically challenging. These mesenteric masses are classified based on their proximity to the primary SBNET: stage 1 nodes are adjacent to the SBNET, stage 2 nodes encase proximal segments of superior mesenteric artery (SMA) branches, stage 3 nodes encase the distal SMA and/or extend along the SMA trunk without encasement, and stage 4 nodes encase the proximal SMA and/or proximal superior mesenteric vein (SMV).[8]

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Vascular involvement is further complicated by the extensive desmoplastic reaction induced by local release of various vasoactive substances, resulting in dense mesenteric fibrosis.[9] Consequently, resection of these mesenteric masses is associated with a risk of short-bowel syndrome and significant intraoperative blood loss.[9]

In this study, we present the management of 13 patients with SBNETs with mesenteric metastases, which were previously deemed unresectable by the referring institutions due to stage 2 or 3 mesenteric nodal disease. These patients underwent a hybrid surgical approach termed EndoVascular Occlusion and Tumor Excision (EVOTE), which utilizes detailed, preoperative angiography and embolization to help facilitate complete surgical excision of mesenteric metastases. Herein, we provide a description of the technical details of the EVOTE procedure and the surgical outcomes of this approach.

Materials and Methods

Patients

From 2014 to 2018, 16 patients with SBNETs and mesenteric metastases, which were considered unresectable by the referring surgeons, presented to our institution for further management. The diagnosis of a NET with mesenteric metastases was confirmed by a combination of cross-sectional imaging (computed tomography (CT) or magnetic resonance imaging (MRI)), biochemical testing (serotonin and chromogranin A levels), and somatostatin receptor scintigraphy (octreoscan). Preoperative localization of the primary small-bowel NET was demonstrated in 46% of patients by imaging or prior exploratory surgery at the referring hospital. In the remaining patients, preoperative imaging studies were suggestive of a primary small bowel NET tumor based on the location of the nodal disease[9]; however, the primary tumor location was not definitely confirmed until surgical exploration and histopathologic evaluation of the surgical specimen. While preoperative localization is preferable, identifying the primary small-bowel NET(s) preoperatively is often not possible[10] and surgical outcomes are equivalent whether or not the primary tumor is definitely located preoperatively.[11] Eligible candidates for the EVOTE procedure required evidence of a likely SBNET(s) with stage 2 (encasement of proximal segments of SMA branches) or stage 3 (distal SMA encasement and/or proximal extension along the SMA trunk without encasement) mesenteric nodal disease, as demonstrated by CT angiography. Patients with distant metastases (distant nodal disease and/or hepatic metastases) were not excluded from this study, as control of local mesenteric disease may still confer a QOL and/or survival benefit.[5,6] Patients with severe comorbidities or stage 4 nodal disease (proximal SMA and/or proximal SMV encasement) were excluded from the study. Thirteen of the 16 referred patients (81%) were deemed candidates for the EVOTE procedure; the 3 unresectable patients were excluded for stage 4 nodal disease. Of note, one of the 13 patients underwent a repeat EVOTE procedure for a local recurrence. As such, our data reflect the outcomes from 13 patients who underwent 14 EVOTE procedures, representing 14 total cases. Data were collected prospectively for all patients following approval from the Icahn School of Medicine at Mount Sinai Institutional Review Board.

Hybrid Surgical Technique

For stage 1 of the two-stage EVOTE procedure, patients are admitted preoperatively for SMA angiography to assess the adequacy of arterial collateral flow around the mesenteric mass. This formal study assists in the preoperative determination of resectability; thus, in the case of sufficient collateralization, EVOTE facilitates a more aggressive attempt at complete surgical excision of the mesenteric mass while minimizing the risk of short bowel syndrome. The procedure is performed under minimal conscious sedation and local anesthesia. Upon identification of the involved SMA segment(s), balloon occlusion testing is performed to characterize the arterial collateralization and to monitor for the development of acute abdominal pain over a 20-min period, a technique described in certain cases prior to endovascular repair of thoracoabdominal aneurysms.[12,13] We define angiographic evidence of adequate arterial collateralization as rapid retrograde filling of the occluded vessel(s). If the patient remains asymptomatic and adequate collateralization is demonstrated angiographically, then a microvascular plug is deployed and the encased vessel is embolized. If the patient develops abdominal symptoms in the presence of adequate collateralization, then the vessel is not embolized, but the patient remains a candidate for surgical excision. However, if inadequate arterial collateralization is demonstrated, then the mass is considered unresectable. The procedure is repeated until all relevant feeding vessels have been tested. Importantly, only angiographic evidence of adequate arterial collateralization is required for the subsequent attempt at complete surgical excision; embolization is performed in patients with adequate arterial collateralization and no abdominal symptoms during balloon occlusion testing to aid in the dissection of the encased vessel(s) by allowing intraoperative palpation of the embolization plug. Embolization is accomplished by advancing a percutaneous 6F femoral sheath into the proximal SMA under fluoroscopic guidance. An AMPLATZER™ vascular plug (St. Jude Medical, St. Paul, MN) is then positioned over a 0.035-in. guidewire. SMA segment and/or branch occlusion is confirmed by contrast angiography.

The following day, the patient undergoes stage 2, an exploratory laparotomy followed by excision of the primary small bowel NET and mesenteric nodal disease. The patient is placed in the supine position for the operation. Following a midline incision, a table-fixed retractor is used for optimal exposure. The bowel is carefully examined from the ligament of Treitz

to the ileocecal valve for foci of NETs, manifesting as firm, plaque-like lesions, which should be marked with a silk stitch. The mesenteric mass is then exposed and carefully dissected circumferentially. Identification of the feeding SMA branch vessel(s) is facilitated by palpation of the microvascular embolization plug. The vessel is then controlled and ligated. The remainder of the mesenteric mass is then dissected free and completely excised with a macroscopically negative margin; a wide margin should be avoided so as to preserve important collateral blood vessels. A small bowel resection is then performed. The length of overriding bowel and the location(s) of the identified small bowel NET(s) determine the extent of the resection. Prior to the intestinal anastomosis, the bowel is closely monitored visually for evidence of arterial or venous insufficiency. In cases of equivocal bowel perfusion, indocyanine green (ICG) angiography (SPY Imaging, NOVADAQ, San Jose, CA) is utilized to assess the viability of the proximal and distal bowel ends. Subsequently, a standard, stapled small-bowel (or ileocolic) anastomosis between well-perfused bowel limbs is performed, which is followed by abdominal closure.

Results

The demographic and clinical characteristics of the 14 cases are summarized in Table 1. The mean age was 64. The average size of the mesenteric mass was 4.9 cm. Each tumor was found to encase either the distal SMA or a proximal segment of at least one SMA branch on CT angiography (Fig. 1a).

Twelve out of the 14 cases underwent successful preoperative embolization of the involved vasculature (Fig. 1b, Table 2). Embolization was aborted in 2 cases due to the development of persistent abdominal pain during balloon occlusion testing; however, robust, retrograde arterial collateralization was identified and the decision was made to attempt complete excision in these 2 cases.

Complete excision of the mesenteric mass was achieved in 12 out of 14 cases (86%). In the first case of partial mass excision (case 8), which occurred in a patient who did not tolerate preoperative embolization, the mass was discovered intraoperatively to involve the proximal SMV. In the second case (case 14), a rim of the tumor was incompletely resected off of the duodenum and proximal SMA. Additional intraoperative data is shown in Table 2. The average estimated blood loss (EBL) was 830 ml and the average length of resected small bowel was 105 cm. A representative image of the resected mesenteric mass is found in Fig. 2. The pathology in all 14 cases demonstrated well-differentiated primary small-bowel NETs with mesenteric metastases.

The 30-day overall morbidity rate was 29% and the 30-day mortality rate was 0% (Table 3). Of the 4 complications, 2 were minor (grades I and II based on the Clavien-Dindo classification) and 2 were severe (grade IIIa or greater).[14] The two minor complications included a prolonged post-operative ileus (case 3), which was managed conservatively, and a chyle leak (case 7), which resolved with a low-fat diet. Case 8 and case 13 experienced small-bowel anastomotic leaks. In case 8, the presence of a contained leak allowed for conservative management with CT-guided drainage and bowel rest, without reoperation. In case 13, the anastomotic leak required a reoperation during the same admission. There were no cases of short-bowel syndrome following the EVOTE procedure. Patients were

Table 1 Demographic and clinical characteristics

Case	Age	Gender	Presenting symptoms	BMI	Albumin (g/dl)	Mesenteric mass size	Encased vessel (s)	Distant metastases
1*	67	F	Bloating	32.6	4.5	5.9 cm	Distal SMA	–
2	56	M	Abd pain, diarrhea	25.1	3.5	8.4 cm	Ileal branches	–
3	41	M	Diarrhea	23.7	4.1	5.3 cm	Ileal branches	–
4	63	M	Flushing, diarrhea, palpitations	21.6	4.6	4 cm	Ileal branches	Liver
5	79	F	Abd pain, diarrhea	21.0	3.0	6.7 cm	Ileal branches	RPLNs
6*	69	F	Diarrhea	32.6	3.3	2.4 cm	Distal SMA	–
7	77	F	Abd pain, diarrhea	30.1	4.0	3.9 cm	ICA	RPLNs
8	65	M	Abd pain, diarrhea	21.6	3.0	4.1 cm	Ileal branches	RPLNs
9	48	F	Abd pain, diarrhea, flushing	21.7	4.1	6.6 cm	Ileal branches	–
10	53	M	Abd pain	35.4	3.5	2 cm	RCA, ICA	–
11	79	M	Abd pain, diarrhea	25.7	3.6	4.5 cm	ICA	–
12	65	M	Abd pain, diarrhea	22.1	4.2	4 cm	Distal SMA	Liver, bone
13	75	F	Abd pain	29.2	4.4	4.7 cm	Jejunal branches	Liver
14	59	F	Abd pain	26.3	4.4	6.2 cm	Distal SMA	RPLNs

BMI, body mass index; *Abd*, abdominal; *SMA*, superior mesenteric artery; *RCA*, right colic artery; *ICA*, ileocolic artery; *RPLNs*, retroperitoneal lymph nodes

*The patient required a repeat EVOTE procedure for a local recurrence

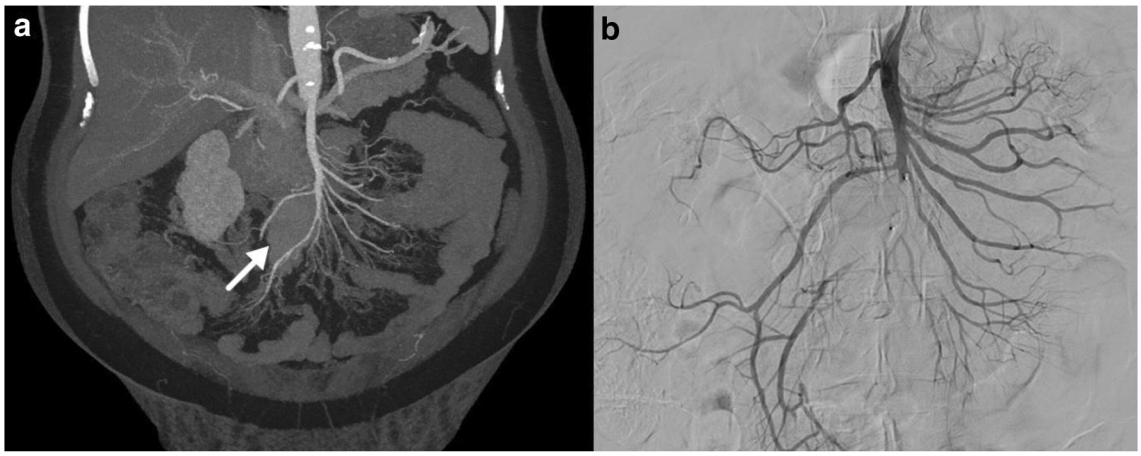

Fig. 1 **a** Reconstructed CT image reveals a 5.9 cm × 3.9 cm × 3.1 cm mass (arrow) at the root of the small-bowel mesentery just anterior to the third portion of the duodenum and encasing the distal SMA (case 1). **b** SMA angiogram demonstrates excellent retrograde flow via distal collaterals following embolization of the terminal trunk of the SMA with a microvascular plug (case 1)

followed for a mean of 15.1 months. One patient experienced a local recurrence after 31.8 months. This patient underwent a repeat EVOTE procedure of the secondary mesenteric tumor with a successful complete surgical resection (cases 1 and 6).

Discussion

Patients with SBNETs present with mesenteric metastases in up to 80% of cases.[5,6] The bulky, mesenteric nodal disease can cause intestinal obstruction and ischemia of the surrounding bowel in approximately 35% of patients as a result of carcinoid tumor-mediated mesenteric fibrosis and mesenteric vessel encasement, respectively.[15] Importantly, complications related to mesenteric metastases as well as survival can be improved with surgical excision or debulking.[4,5] This case series presents a novel management strategy, EVOTE, for patients with SBNETs complicated by mesenteric metastases that encase the distal SMA and/or proximal segments of SMA branches.

Patients undergoing the two-stage EVOTE procedure undergo preoperative angiographic evaluation and embolization of the encased mesenteric vasculature followed by complete surgical excision of the primary SBNET and mesenteric nodal disease. The primary goal of the preoperative angiography is to demonstrate adequate arterial collateralization during balloon occlusion testing of the encased arterial segments. Evidence of adequate arterial

Table 2 Perioperative data

Case	Pre-op embolization	Complete mass excision	EBL (ml)	Intra-op pRBC (units)	Length of bowel resection (cm)	Type of anastomosis
1*	+	+	250	0	60	SB-SB
2	+	+	500	2	45	SB-SB
3	Aborted	+	2000	3	110	SB-LB
4	+	+	400	0	135	SB-SB
5	+	+	1500	4	130	SB-LB
6*	+	+	1500	2	0	n/a
7	+	+	600	0	20	SB-LB
8	Aborted	–	1000	2	125	SB-SB
9	+	+	350	0	80	SB-SB
10	+	+	1000	0	100	SB-LB
11	+	+	300	0	150	SB-SB
12	+	+	200	0	100	SB-LB
13	+	+	1500	4	95	SB-SB
14	+	–	500	0	215	SB-LB

EBL, estimated blood loss; *pRBC*, packed red blood cell transfusion; *a (+)*, successful; *a (−)*, unsuccessful; *SB-SB*, small-bowel to small-bowel anastomosis; *SB-LB*, small-bowel to large-bowel anastomosis

*The patient required a repeat EVOTE procedure for a local recurrence

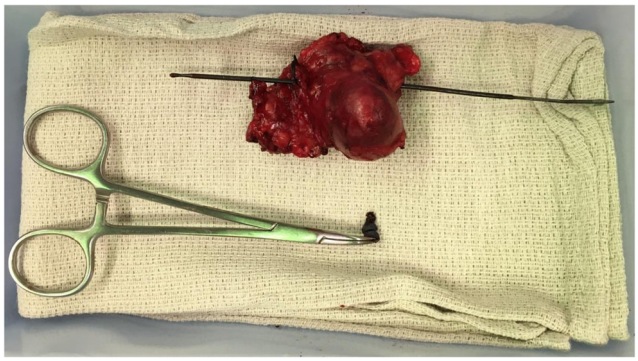

Fig. 2 The image shows a resected 4-cm mesenteric mass with its feeding vessel (right colic artery; as indicated by the surgical probe). The clamp highlights the microvascular plug that was used to embolize the right colic artery preoperatively (case 7)

collateralization aids in the preoperative decision-making of resectability, which ultimately facilitates a more aggressive attempt at complete surgical excision of the mesenteric mass while minimizing the risk of short-bowel syndrome. The secondary goal of the preoperative angiography is to embolize the encased mesenteric vessel(s), which assists in the intraoperative dissection of the mesenteric mass.

Although there are case reports utilizing preoperative embolization for thymic carcinoids, there are no reports describing this technique for SBNETs.[16] In one study of patients with advanced SBNETs, 12 of 82 (14.6%) patients had an overgrowth of the tumor into the mesentery with encasement of the vasculature.[17] Of those 12 patients, 6 were thought to be unresectable, but upon exploration, only 2 were ultimately unresectable, which demonstrates a tendency to overestimate the unresectability of these masses. Similarly, of the 16 patients with SBNETs and presumed, unresectable mesenteric metastases referred to our institution, 81% were determined to be candidates for the EVOTE procedure. Of the EVOTE candidates, 86% underwent a complete excision of the mesenteric nodal disease.

Of the 14 EVOTE procedures in this study, adequate arterial collateralization was demonstrated in all cases, while preoperative embolization, which was performed in asymptomatic patients with adequate collateralization during balloon occlusion testing, was performed in 12 of the 14 cases. In addition to improving intraoperative identification of the encased vessel, preoperative embolization has the additional potential benefit of reducing intraoperative blood loss; however, our study was not designed to make this assessment. Furthermore, even within the embolized group, we observed significant intraoperative bleeding (mean EBL 716 ml, $n = 12$ patients), confirming the surgical risks posed by an extensive dissection of a fibrotic mesentery.[9]

While our overall 30-day morbidity rate is consistent with the literature,[18] the small-bowel anastomotic leak rate was 14% in this study. Although our small sample size makes the leak rate difficult to interpret, both cases were likely a consequence of underappreciated ischemia while attempting to maximally preserve bowel length. Additionally, case 8 was complicated by SMV involvement that prevented a complete surgical excision of the mesenteric mass; the resultant venous

Table 3 Post-operative outcome data

Case	LOS (days)	Readmission	30-day morbidity	Management	30-day mortality	Local recurrence	Follow-up (months)
1*	6	–	–	.	–	+	44.6
2	9	–	–	.	–	–	7.2
3	6	+	PPOI	NGT for 2 days	–	–	27.8
4	5	–	–	.	–	–	17.7
5	8	–	–	.	–	–	26.6
6*	7	–	–	.	–	–	21.5
7	7	–	Chyle leak	Low-fat diet	–	–	12.6
8	11	+	Anastomotic leak	IR drainage, bowel rest	–	n/a**	6.2
9	10	–	–	.	–	–	17.1
10	8	–	–	.	–	–	6.8
11	7	–	–	.	–	–	4.0
12	8	–	–	.		–	8.3
13	85	–	Anastomotic leak	Washout, SBR	–	–	8.0
14	7	–	–	.	–	n/a**	2.4

LOS, length of stay; *IR*, interventional radiology; *PPOI*, prolonged post-operative ileus; *NGT*, nasogastric tube; *SBR*, small-bowel resection; *a (+)*, yes; *a (−)*, no.

*The patient required a repeat EVOTE procedure for a local recurrence

**Incomplete mass excision (see Table 2)

insufficiency may have further contributed to the anastomotic dehiscence. In response to these complications, we subsequently began using intraoperative ICG angiography prior to the anastomosis in cases of equivocal bowel perfusion assessed by visual inspection. While our initial experience and the colorectal surgery literature[19] are supportive of this technology, determining its efficacy in reducing small-bowel anastomotic complications after extensive mesentery resections, such as with the EVOTE procedure, will require further research. Importantly, regardless of the method of evaluation, a high index of suspicion for bowel ischemia is critical during these cases to minimize anastomotic complications.

The surgical management of patients with advanced SBNETs can be complex, requiring intensive, patient-specific planning using a multi-disciplinary approach that includes interventional radiology and general/vascular surgery. In this study, we demonstrate the feasibility of the EVOTE approach for SBNETs with mesenteric metastases as well as the potential for the EVOTE procedure to reduce the overestimation of unresectability of these mesenteric masses, ultimately improving patient access to beneficial, aggressive surgical management.

Authors' Contributions All authors contributed to the concept and design of the study, as well as drafting and revising of the manuscript. All authors gave final approval for the manuscript.

Compliance with ethical standards

Data were collected prospectively for all patients following approval from the Icahn School of Medicine at Mount Sinai Institutional Review Board.

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