Enterocutaneous Fistula Associated with Malignancy and Prior Radiation Therapy

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ABSTRACT

Enterocutaneous fistula (ECF) associated with cancer or radiation injury increases the complexity of normal management. Factors such as timing of additional adjuvant therapy or palliative care, technical considerations for operating on irradiated bowel, poor wound healing, increased risk of additional ECF, and decreased likelihood of spontaneous ECF closure all need to be considered in this scenario. Here the authors focus specifically on the management of ECF associated with cancer and/or radiation-induced injury to the bowel.

KEYWORDS: Enterocutaneous fistula, cancer, radiation injury, management

Objectives: After reading this article, the reader should have an understanding of the management of ECF in the setting of malignancy or radiation injury to the bowel.

Enterocutaneous fistula (ECF) is defined as an anomalous communication between the bowel and the skin.¹ Surgical procedures involving the gastrointestinal tract (GI), Crohn disease, neoplasia, and radiation are responsible for the majority of ECF². The initial management of ECF may be complex and includes resuscitation, eradication of associated infections, control of ECF effluent, protection of the surrounding skin, and nutritional support. Ultimately, most ECF will require surgical repair.

In cases of ECF associated with cancer or radiation injury, the complexity of management is only further increased. ECF in cancer patients will often delay or prevent additional adjuvant therapy or palliative care, resulting in markedly poor quality of life and survival.³ Patients who have received radiotherapy to organs in the abdomen or pelvis are at risk for radiation-induced damage to the intestinal microvasculature, which may result in enteritis, strictures, abscess, or

fistula.⁴ Surgery on irradiated bowel is associated with poor healing, increased risk of ECF, and decreased likelihood of spontaneous ECF closure.⁵

Currently, multimodality therapy with chemotherapy, radiotherapy, and surgery is the standard of care for a variety of intraabdominal malignancies.^{6–9} It follows that the incidence of cancer and radiation-associated ECF will be on the rise. However, there are few recent data regarding the natural history and associated mortality of ECF in cancer patients.³ Here we focus specifically on the management of ECF associated with cancer and/or radiation-induced injury to the bowel.

ETIOLOGY AND CLINICAL PRESENTATION

ECFs typically occur after operative procedures and, therefore, can often be considered as iatrogenic.² Missed injuries to the bowel that occurred during surgery,

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disruption of repaired enterotomies, or anastomotic leak are the main causes of surgery-related ECF.¹⁰ Adherence to good surgical practice, with gentle handling of the bowel, avoidance of tension or ischemia in the bowel anastomosis, and the appropriate use of end or defunctioning ileostomies are generally thought to be helpful in avoiding ECF after small bowel and colorectal surgery.^{11,12} In addition, preoperative anemia, malnutrition, and undrained abdominal infections should, when possible, be dealt with *prior* to surgery with the aim of optimizing the patient for an event-free operation and recovery. Use of preoperative percutaneous drainage, antibiotics, and supplemental nutrition may be invaluable with helping to minimize morbidity.

Yet even with the most diligent of care, ECF associated with malignancy may result from a variety of settings as well as varying physiological states of the patient. Cancer-associated ECF may unfortunately result from a perforated cancer, where the patient may be in extremis and urgent operative intervention is required. On the other hand, ECF may result following elective surgical resection of the cancer complicated by a bowel injury or anastomotic leak, or even as a delayed presentation from collateral damage to the bowel that occurs with the radiation therapy or drug therapy that is used to treat the primary cancer.

Radiotherapy

Up to 75% of patients undergoing abdominal or pelvic radiation will suffer some degree of radiation enteritis.¹³ In most cases this manifests as either bleeding or stricture; however, a small percentage may develop fistulous complications. In this subset of patients who develop a radiation-related ECF, it may take 6 months or more for the fistula to become apparent.^{10,14} Strategies to minimize radiation enteritis include the surgical placement of a mesh prosthesis or omental flap to isolate small bowel from the planned radiation field (e.g., the pelvis) and the use of modern radiotherapy techniques such as three-dimensional preprocedural evaluation and focused external beam therapy that are aimed at limiting collateral radiation damage. In addition, appropriate use of neoadjuvant radiation therapy may minimize small bowel exposure to radiation. Yet, despite these maneuvers, no major reduction in ECF occurrence has been observed in recent studies.^{11,12}

Bevacizumab

Bevacizumab, a humanized monoclonal antibody to vascular endothelial growth factor (Avastin; Genentech, San Francisco, CA) has become widely used for a variety of neoplasias. This drug is generally well tolerated, but it has an adverse affect on the healing process and is associated with spontaneous GI perforation rates of 1

to 2%.^{15–19} Some of these patients will require emergent surgical treatment and some may be managed without surgery. In either scenario, ECF may occur, and with it a particularly difficult problem in the setting of metastatic cancer and often a nutritionally depleted and generally weakened patient.^{20,21} Additionally, the underlying negative effects of the agent on proper wound healing can have a dramatic impact on ultimate outcome even with the most diligent of operative or nonoperative care.

Cytoreductive Surgery and Intraperitoneal Hyperthermic Chemotherapy

Recently, the use of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (C-HIPC) for the treatment of peritoneal carcinomatosis has gained increased interest.^{22,23} The aim of this multimodality therapy is to surgically remove all gross tumor deposits from the peritoneal cavity and then use chemotherapy to destroy any residual malignant cells. In most cases this involves prolonged operative times, hemodynamic changes during the heated intraperitoneal chemotherapy portion, and extensive surgical resections that may include large and small bowel, liver, peritoneum, omentum, uterus, and spleen. On the positive side, for colorectal cancer patients undergoing this procedure, 5-year overall survival rates of 11 to 32% have been reported.²³

Despite the potential benefits of C-HIPC, it is fraught with the potential for major postoperative complications and death. Several authors have reported increased rates of ECF after C-HIPC, though limited widespread use of this procedure make rates variable.^{24–26} In some cases, these patients will present with multiple ECF or ECF with an open abdomen, the so-called enteroatmospheric fistula, a truly complex management problem for everyone who is involved in the care of the patient.²

DIAGNOSTIC STUDIES

Once the patient with ECF is stabilized, resuscitated, and the ECF is controlled, the next steps are to determine if an abdominal or pelvic abscess is present, and then to define the anatomy of the fistula. This is especially important in the setting of a malignancy. Focus should be placed on determining the origin of the fistula and whether this may represent tumor perforation or local versus remote complication of prior therapy. Computed tomography (CT) scan or magnetic resonance imaging (MRI), contrast studies of the bowel, fistulography, and endoscopy may be required to achieve these objectives. CT and MRI are both useful to demonstrate intestinal and extraintestinal pathology including residual cancer, abscess, adjacent organ involvement (e.g., hydronephrosis or carcinomatosis), and sometimes

the anatomy of the fistula.^{27–29} Although CT is more generally available, less costly, and often easier for surgeons to interpret than MRI, the ability of CT to define the fistulous tract may not be as good as MRI.^{27,30} Whereas MRI has been recommended for the preoperative assessment of complex perianal fistulas,^{31,32} the accuracy of MRI in evaluating the proximal origin of ECF remains unclear, with limited evidence to support its use in the setting of malignant ECF.^{3,33–36}

In cases of ECF in which an abdominal abscess is detected, treatment with intravenous (IV) antibiotics and image-guided percutaneous drainage need to be considered. When it is desirable to know the precise anatomy of the ECF, fistulography may be required.³⁷ With this study, injection of water-soluble contrast into the external opening of the ECF is performed and then plain radiographs or fluoroscopy are used to delineate the fistula pathway. The information obtained from a fistulogram may complement the findings of CT and MRI and may be helpful in planning surgical repair of the ECF; therefore, this test should be used selectively—when the information obtained will be useful in the care of the patient.

TREATMENT

General Approach

In 1964, Chapman et al³⁸ described the four cardinal principles in the initial care of patients with ECF: correction of intravascular volume deficit, drainage of abdominal abscess, control of fistula effluent, and skin protection. These principles, described more than 40 years ago and covered in detail in other sections of this issue, apply to all ECFs regardless of their etiology. In patients with ECFs associated with cancer or radiation injury, additional diagnostic or treatment approaches may be required. In this regard, collaboration with specialists in radiation therapy and chemotherapy will often be necessary.

Surgical Approach

The first consideration in the surgical approach to ECF is the appropriate timing for surgical intervention. One scenario to consider is the patient who underwent a curative resection for colon cancer who then develops an ECF in the early postoperative period. The cause of the ECF in this scenario is most often an anastomotic leak or a missed enterotomy. The treatment options depend on the timing of ECF presentation, the physiological condition of the patient, and the complexity of the surgery that was performed.

When an ECF develops in the first 10 to 12 days after surgery, a return to the operating room to address the problem surgically may be the best option for the patient. In our practice, reoperation in these cases most

often involves washout of the peritoneal cavity, repair of the defect in the anastomosis, when possible, and creation of a defunctioning loop ileostomy. In some cases, inflammation around the leaking anastomosis or difficult access to the anastomosis (e.g., low pelvic) precludes safe repair and diversion alone is performed. Most often, we use a defunctioning loop ileostomy with preservation of the colon for possible future use in a redo colorectal or coloanal anastomosis. In cases with extensive peritoneal soiling, an ischemic anastomosis, or an unstable patient, it may be necessary to take apart the anastomosis, close or drain the distal bowel, and create an end ileostomy or colostomy. With either approach, the patient with an ECF is usually able to quickly resume oral intake and is faced with an easily pouchable loop ostomy rather than an ECF. Nevertheless, advocates of surgical treatment of early postoperative ECF should also consider the potential of spontaneous healing of the ECF.

After 3 months of diversion a water-soluble contrast enema is performed to evaluate the anastomosis. If the anastomosis has healed then reversal of the enterostomy can be performed. If a stricture is detected, an endoscopic evaluation and possible stricture dilatation is indicated prior to takedown of the diverting stoma to avoid the situation of a distal obstruction. If the contrast study reveals a persistent leak then we typically have the patient wait another 3 months and perform the contrast study again. At that point, if the leak persists then resection and reconstruction of the anastomosis, with or without proximal diversion, is required.

We will perform a simple reversal of the loop enterostomy as early as 2 to 3 months after it is made (so long as healing is confirmed); however, we will wait at least 6 months, and preferably 9 to 12 months, before repeating a laparotomy. The reasons for this are multifold, though include foremost the dense adhesions or “obliterative peritonitis” that is often present as early as after postoperative day 10 to 12 and may persist for several months until the fibrous adhesion become softer, less vascular, and more manageable by adhesiolysis.^{2,39,40}

Clinical signs that may help the surgeon determine the appropriate timing for reoperation include prolapse of the fistulating loops of bowel and mobility of the peritoneal contents that can be appreciated by palpation and “rocking” of the abdominal contents while the patient is laying supine.^{41,42} Other considerations in the timing of surgery for ECF are the nutritional and functional status of the patient. Ideally, nutritional optimization, with weight gain and normalization of serum albumin, correction of anemia, and physical rehabilitation are completed before reoperation is performed.

In patients in whom an ECF develops early in the postoperative period who are not good candidates for early reoperation (dense adhesions encountered at the first operation or comorbid conditions that preclude safe

reoperation), nonoperative management of the ECF can be performed as described in other section of this issue.

ENTEROCUTANEOUS FISTULA ASSOCIATED WITH A CANCER

In the patient with a small bowel or colon cancer that has evolved into an ECF, the first step in surgical treatment is careful planning of the operation. In terms of timing of the operation, the surgeon is usually not faced with the obstacles created by a recent laparotomy. Rather, the patient with a perforated cancer and malignant ECF most likely did not have a recent laparotomy, and depending on the patient's physiological condition and control of the fistula, operative management can be performed in a semielective or elective manner. In that case, cancer staging and identification of collateral organ involvement (ureter, bladder, vagina, major vessels, bone) are evaluated before going to the operating room. Consultation with a medical oncologist and/or radiation oncologist is indicated. Depending on the type of tumor, nonsurgical therapy may be the first or only line of treatment.⁴³⁻⁴⁷

Once the decision is made to perform surgery, the following should be considered: the need for ureteral stents; the availability of a urologist, vascular surgeon, or plastic surgeon; the availability of blood products; and the need for preoperative ostomy education and stoma marking. For malignant fistulas that involve the terminal ileum or colon or rectum, preoperative colonoscopy is needed to exclude synchronous colorectal cancers.

At surgery, the aim is curative resection of the cancer. This will involve en bloc removal of the tumor along with the fistula tract and any structures that are attached or invaded by the tumor or traversed by the fistula tract. Depending on the location of the tumor and ECF, the patient is positioned on the operating table either supine or in a modified lithotomy position. Our preference is to tuck the patient's arms to maximize accessibility to the abdomen. A midline incision is made several centimeters cephalad to the ECF so that the peritoneal cavity may be entered in an area that may be less "hostile." The surgeons' finger can then be inserted into the peritoneal cavity, alongside the ECF, and the electrocautery is used to incise the surrounding skin, muscle, and fascia with at least a 1-cm margin. Once the ECF is encircled, the next step is to mobilize the mass of bowel and mesentery that comprises the ECF. It is during this stage of the operation that the surgeon will identify the ureters and determine if there are other organs or vessels that are involved. The next step is to identify the loops of bowel that can be preserved and the loops that must be resected with the ECF. Care must be taken in patients with prior surgery to assess as much as possible the remaining length and type (e.g., proximal/distal) of bowel remaining to avoid overaggressive resection and resultant short bowel syndrome. The bowel and mesenteric resection is performed in the usual manner

and either bowel continuity is restored or an end ostomy is created. When the decision is made to reconstruct the bowel, a defunctioning proximal loop ileostomy or jejunostomy is made in nearly all cases to ensure the best chance of an event and recurrent ECF-free recovery.

Closure of the abdomen is often quite difficult in the patients as there is typically a large fascial defect that results, in part, from lateral retraction of the fascia, and, in part, from the wide excision of the fascia that was performed during the initial encirclement of the tumor and ECF. When primary closure of the rectus fascia is not possible, our preference is to use a biological mesh prosthesis as a fascial bridge, knowing full well that a subsequent hernia may develop and require definitive repair once the cancer is under control and the patient has fully recovered from the major stress of ECF repair.

In the patient with a malignant ECF that is not amenable to resection, either due to inability to perform a curative resection or medical frailty of the patient, either a palliative bypass or diverting ostomy creation may be considered. Palliative bypass of a malignant ECF may be appropriate for the patient with a malignant ECF that involves either the small bowel or colon. The operative technique for this usually involves a sutured side-to-side anastomosis between proximal and distal segments of uninvolved bowel. The aim of this operation is palliation with control of ECF output, relief of obstruction, and avoidance of the need for an ostomy. The use of a palliative ostomy may be best suited for malignant ECF associated with the distal small bowel, colon, or rectum, as the ostomy should be distal enough to allow adequate nutritional support via the enteral route and also to avoid a high-output ostomy with its resultant fluid and electrolyte abnormalities.

POSTRADIOTHERAPY

Radiation enteritis is often a severe and irreversible condition. Irradiation results in damage to the intestinal microvascular endothelium,⁴ which may lead to fibrotic strictures, full-thickness necrosis with free perforation or abscess, and fistula formation.⁴⁸ Surgery for radiation injury is typically performed for stricture but may also be required for ECF. The type of fistula encountered in irradiated patients is determined by the position of the original lesion requiring radiotherapy. Therefore, the incidence of radiation-induced rectovaginal or colovesical fistulas related to radiotherapy are much higher than radiation-induced ECF.^{49,50}

Patients suffering from radiation-induced ECF are likely to have other lesions present at the same time. In one study, Cooke et al⁵¹ found that, 6 of 28 patients with rectovaginal fistula, had another associated fistula. In another review, Galland et al⁵² found that these patients also have an increased risk for metachronous radiation-induced pathology. For these reasons, it is important to exclude synchronous fistulae before

attempting a definitive surgical procedure and to follow these patients after they undergo surgical treatment.

As for cancer-associated ECF, the surgical options for radiation-associated ECF are resection, bypass, or diversion. Although resection may be the ideal therapy, it can be difficult or even impossible in some cases due to “matting” together of adjacent bowel loops, the ureters, nearby organs, or major vessels. In these situations, bypass of the pathology (as described above) or formation of a diverting ostomy may be the only surgical options.⁵⁰ In patients who are unfit for definitive resection or have disease that cannot be removed with curative intent, the diverting ostomy may also be a satisfactory definitive measure.¹²

When resection of the radiation-induced ECF can be performed, the preoperative planning and surgical steps are in general similar to those that were described for cancer-associated ECF. However, for radiation-associated ECF, the surgeon must also consider that radiation injury may be present in nearby normal-appearing small or large bowel. In patients who received irradiation to the pelvis, the terminal ileum, cecum, ascending colon, and sigmoid colon may look and feel normal but have in fact been compromised by radiation injury. The use of these bowel segments for an anastomosis will increase the risk of leak and should therefore be avoided.⁵³

As with cancer-associated ECF, those that are related to radiation are also typically associated with large abdominal defects that require major abdominal wall reconstruction when the abdomen is closed. The complexity of abdominal wall closure may be increased in patients with radiation ECF due to compromise of the blood flow to the surrounding skin and soft tissues and major soft tissue flaps may be required to improve the chances of a successful abdominal closure. In these cases, the assistance of a plastic surgeon and wound management team will likely improve the chances for success.⁵⁴

CONCLUSION

ECFs are a challenge no matter what the cause. The addition of cancer or radiation injury only increases the challenge. The principles of ECF management in these patients are the same as they are for benign ECF: resuscitation, control of ECF output, eradication of infection, nutritional optimization, and the appropriate timing for definitive repair. However, unique to cancer-associated ECF, the involvement of both the radiation oncologist and medical oncologist is often required before surgery is performed. For both cancer-related and radiation-related ECF, the surgical options are resection, bypass, or diversion, with en bloc resection the ideal option in most circumstances. Similar to the preoperative management, the operative management of these patients often requires a multidisciplinary team of specialists to ensure the best possible outcome.

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