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ORIGINAL ARTICLE

Endorectal Advancement Flaps for Perianal Fistulae in Crohn's Disease: Careful Patient Selection Leads to Optimal Outcomes

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Abstract

Background Anorectal fistulae resultant from Crohn's disease (CD) is a clinical challenge. The advent of immune therapy (IT) has altered the way in which fistulae have responded to treatment. Endorectal advancement flap (ERAF) is a surgical procedure that is used to treat complex fistulae. We have employed ERAF as our second stage treatment of choice in this patient population. Our aim was to determine the success of ERAF in treating perianal fistulas in patients with CD in an era of IT.

Methods Multicenter retrospective review from 2007 to 2017 of all patients with CD and a perianal fistulae who underwent ERAF.

Results Forty-one flaps were performed in 39 patients with perianal CD with an average follow-up of 797 days. There were no significant differences in patient demographics; however, all patients who were diverted at the time of surgery had successful healing. Of patients, 73.2% were on IT at an average of 380 days prior to surgery. The duration of single-agent therapy was associated with better healing rates ($p = 0.03$). The overall failure rate was 19.5% ($n = 8$). Six patients underwent secondary techniques for fistulae closure; five were successful. In combination with the patients who did not initially fail, the overall healing rate was 92.6%.

Conclusions This study demonstrates several factors that may improve fistulae closure for CD patients. Patients who were diverted prior to surgery did not have a fistulae recurrence. Patients who were on IT longer prior to ERAF were more likely to achieve successful closure.

Keywords Crohn's disease · Immune therapy · Perianal fistulae · Endorectal advancement flaps

Introduction

Perianal fistulae from Crohn's disease (CD) occur in approximately one third of patients and can be the only manifestation of the disease in roughly 5% of patients.[1,2] The presence of perianal fistulae can be the initial manifestation of CD in up to 10% of patients.[3] Perianal fistulae cause significant morbidity, are associated with an overall decreased quality of life, and have been demonstrated to be risk factors for both anxiety and depression.[4] Fistulae associated with CD usually require multiple surgical treatments to achieve healing, with a median of six procedures for complex fistulae and three for simple fistulae.[5] The inflammatory nature of CD leads to high rates of recurrences and incomplete closure as simple fistulotomy will often leave the patient with nonhealing perianal wounds and more advanced repairs are prone to failure.

The advent of immune therapy (IT) in the treatment of CD has significantly improved the symptoms and flares associated with the disease, including the healing of perianal fistulae. Prospective studies have demonstrated that 30–50% of patients have complete resolution of Crohn's associated fistulae solely with the use of infliximab of which one third will continue to demonstrate complete closure at 1 year and up to 50% at 5 years.[6–8] Other studies have demonstrated that the combination of infliximab and seton placement have better outcomes in regard to healing CD fistulae as compared with the

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use of infliximab alone.[9,10] However, up to 38% of CD patients will have complex fistulae that do not respond to standard medical or surgical management and thus require a more extensive sphincter preserving procedure for the definitive management of their perianal fistulae.[5]

Endorectal advancement flap (ERAF) is a surgical procedure that is commonly used to treat chronic and complex fistulae, especially in patients who may have a high transsphincteric fistulae or are undergoing repeat fistulae surgery where it is felt the patient's continence is at risk. It involves creating a mucosal flap within the rectum, which then covers the ligated internal opening of the fistulae. Success rates of utilizing ERAF for the definitive management of CD perianal fistulae vary and are reported to be anywhere from 33 to 83%.[11] The literature on evaluating ERAF in healing perianal fistulae in CD patients is largely limited by the small sample sizes of reports, most of which only review 5–30 cases.[11–15] Many of these studies also largely represent patients from the 1990s to early 2000s when corticosteroids were the mainstay of treatment and the widespread adoption of newer immunomodulatory therapies was just starting.

There are limited studies looking at the effects of IT and the closure rates of fistulae in patients with CD. For this study, we examine the outcomes of patients undergoing ERAF for the treatment of anorectal fistulae in CD and report our outcomes in 41 cases across two high volume institutions. This is the largest series reported to date.

Methods and Materials

The surgical databases of eight colorectal surgeons at the University of California in San Diego and Icahn School of Medicine at Mount Sinai in New York were queried for patients with Crohn's disease who underwent ERAF for the closure of perianal fistulae from 2007 to 2017. Inclusion criteria were patients 18 years or older who had a previous tissue diagnosis of CD or were actively being treated by a Gastroenterologist for the management of CD and underwent an ERAF for the definitive management of anorectal fistulae. Patients who underwent multiple ERAFs for separate fistulae were considered separately whereas patients who underwent multiple ERAFs for the same fistulae were considered failures to heal. We excluded patients under the age of 18, pregnant women, or patients who did not have a diagnosis of CD or were not actively being treated for CD at the time of surgery.

Charts were retrospectively reviewed for patient demographics, the presence of CD, use and duration of IT, fistulae characteristics, surgical treatments and postsurgical outcomes to include fistulae recurrence, failure to heal, or incontinence. The reviewed data was then analyzed to compare patients whose fistulae healed vs. those who did not heal after ERAF. The primary end point was fistulae healing as defined by complete closure of the external opening of the fistulae per physician examination and cessation of previous symptoms related to the fistulae. Secondary end points included 30-day perioperative complications and long-term incontinence rates. Averages are reported as means. Significance was determined using the Student's t test and chi-square analysis with a P value of < 0.05. This study was approved by the IRBs of the participating institutions.

Surgical Technique

The appropriate time to perform an ERAF was determined by the individual surgeon and was largely based upon evidence that the patient did not have active CD in the small bowel, colon, or rectum. Both recent colonoscopy and MR enterography were used to assess for active disease within the ileum and colon while physical exam with anoscopy, if not flexible sigmoidoscopy, was largely used to determine evidence of proctitis. IT was not held prior to ERAF and there was not a specific waiting time to perform ERAF after a dose of IT was administered. All procedures were performed under general anesthesia and patient positioning depended upon the location of the fistulae. Patients were placed in the lithotomy position for posteriorly located fistulae while the prone-jackknife position was used for anteriorly located fistulae. The use of preoperative bowel preparation and antibiotics was at the discretion of the surgeon. If a bowel preparation was used, it was a fleet enema. Seton placement prior to ERAF was done in most cases to control perianal sepsis at the discretion of the surgeon.

The procedure begins by identifying the fistulous tract based on the location of the noncutting seton or physical exam (Fig. 1a). An anal probe is then inserted into the tract with care to avoid creating a new tract and the seton is removed (Fig. 1b). Once the tract is identified, local anesthetic with epinephrine is injected submucosally to elevate the tissue and a wide-based trapezoidal shaped mucosal flap is created around the internal opening of the fistulae using a scalpel (Fig. 1c). The flap is dissected approximately 1–2 mm caudal to the internal opening of the fistulae with the base being at least twice as wide as the height. A thick mucosal flap is then sharply raised, down to the internal sphincter muscle (Fig. 1d). The creation of the flap with a sharp instrument may create a small amount of bleeding, which can be controlled with direct pressure. The authors purposefully avoid electrocautery during this portion of the procedure to prevent any potential deleterious effects of thermal injury to the anal sphincter or flap.

After the flap is created, the internal tract opening is closed with multiple figure of eight 0-vicryl sutures through the muscular layer until an anal probe can no longer be passed through the tract or until there is no passage of hydrogen peroxide into the lumen when it is injected via

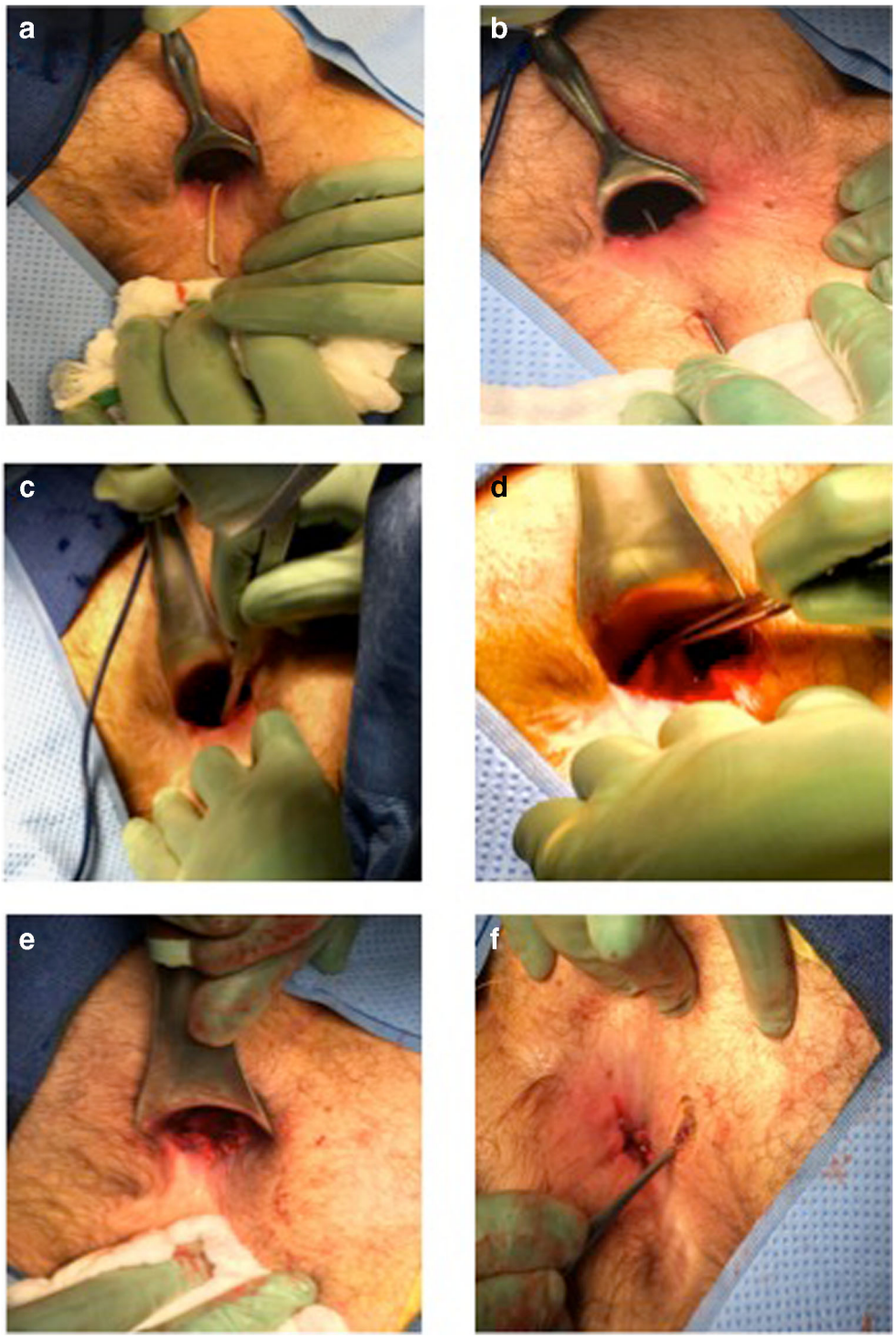

Fig. 1 Surgical technique for creating an endorectal advancement flap. **a** Identify the fistulae. **b** Insert an anal probe through the fistulae. **c** Create a wide-based trapezoidal shaped mucosal flap with a scalpel. **d** Raise a thick mucosal flap down to the internal sphincter muscle. **e** Ligate the internal opening with absorbable sutured, advance the flap over the internal opening and suture the flap to the anal mucosa. **f** Curette the external opening and allow to heal by secondary intent

an angiocath into the external opening. The distal end of the flap is trimmed back to healthy tissue and the flap is advanced to fully cover the previous opening and sutured to the anal mucosa with multiple interrupted 3–0 vicryl sutures (Fig. 1e). Once the flap has been adequately sutured to the anal mucosa and perfusion appears adequate, the external fistulae tract opening is curetted with electrocautery and left to heal by secondary intent (Fig. 1f).

Results

A total of 557 ERAFs were performed over a 10-year period. Forty-one (7.4%) of ERAFs were performed in 39 patients with perianal CD and were followed up for an average of 27 months postoperatively (1–256 months). The overall failure rate after ERAF was 19.5% ($n = 8$). Of the eight patients who failed, five underwent a variety of salvage procedures to

successfully achieve fistulae closure. One patient achieved closure solely after starting anti-TNF therapy while two patients had a repeat, successful ERAF, one of which was started on biologic IT prior to their second procedure. The final two patients healed after fecal diversion, one of which was started on biologics. Both patients eventually underwent stoma reversals at 198 and 69 days after placement. Of the three patients who did not undergo a salvage procedure, two were lost to follow-up. The remaining patient who did not attempt salvage procedures was unsuccessful in healing of the fistulae after 10+ seton placements and is continuing IT treatment. Given the total primary healing rate of 80.5% ($n = 33$) and the five fistulae that were healed with a salvage procedure, the overall healing rate was 92.6% ($n = 38$).

Patient demographics are shown in Table 1. In comparing patients who failed to those who healed, there were no significant differences in age, gender, or presence of small bowel disease, which included ileocolic disease. In regard to fistulae, there were no differences in patients who previously had an IPAA, pouchvaginal or rectovaginal fistulas, the average number of fistulae, complexity of fistulae or location in relation to the dentate line. Complex fistulae in this study were defined as multiple fistulae, those that did not originate at the dentate line, or pouch/rectovaginal fistulae. While there were no differences between the number of prior seton placements or prior surgical procedures for fistulae disease, patients who had setons in place for a longer duration of time prior to ERAF had statistically significant higher rates of fistulae healing ($p = 0.04$; 344 vs. 161 days). Although there was not a statistical significance for those who had fecal diversion at the time of ERAF ($p = 0.12$), all patients who were diverted ($n = 8$) had successful healing of their fistulae.

Analysis was then performed to evaluate if there was a relationship between IT and failure of fistulae to heal after ERAF (Table 2). There were no patients in the study on steroids or methotrexate prior to surgery, while 73.2% of patients were on IT starting an average of 381 days prior to surgery. The percentages of patients taking zero agents, a single agent, and double agents prior to surgery were 26.8%, 43.9%, and 29.3%. The average number of days patients were on single and double agents prior to surgery was 456 and 244 days. There were no differences in failure rates for patients taking double or single agents; however, patients who underwent successful closure in the single-agent group were taking these agents for a statistically longer duration of time prior to surgery (531 vs 262 days; $p = 0.03$). This suggests that the longer a patient was on IT prior to surgery, the higher the likelihood they would have a successful fistulae closure after ERAF.

Further subset analysis was performed for each individual IT as compared to no agents. Table 3 demonstrates the use of the individual single agents, either biologics or

Table 1 Patient Demographics

	All Patients ($n = 41$)	Healed Fistulae ($n = 33$)	Failure ($n = 8$)	p-value
Average age (years)	33.7 (+/− 11.9)	33.3 (+/− 12.4)	35.5 (+/− 10.2)	0.61
Female	58.5% ($n = 24$)	57.6% ($n = 19$)	62.5% ($n = 5$)	0.8
Small bowel disease	68.3% ($n = 28$)	69.7% ($n = 23$)	62.5% ($n = 5$)	0.69
IPAA	4.9% ($n = 2$)	3.0% ($n = 1$)	12.5% ($n = 1$)	n/a
PVF/RVF	26.8% ($n = 11$)	27.3% ($n = 9$)	25% ($n = 2$)	0.90
Average # of Fistulae	1.22 (+/− 0.5)	1.24 (+/− 0.5)	1.12 (+/− 0.4)	0.45
Complex fistulae	41.5% ($n = 17$)	36.4% ($n = 12$)	62.5% ($n = 5$)	0.18
Orifice at dentate line	41.5% ($n = 17$)	42.4% ($n = 14$)	37.5% ($n = 3$)	0.8
Preoperative seton	76% ($n = 31$)	76% ($n = 25$)	75% ($n = 6$)	0.96
Average no. of days seton in place prior to ERAF	308 (+/− 123.2)	344 (+/−123.2)	161 (+/−111.8)	0.04
No. of Setons	1.1 (+/− 1.0)	1.1 (+/−0.9)	1.4 (+/-1.4)	0.56
Diverted	19.5% ($n = 8$)	24.2% ($n = 8$)	0	0.12
Prior procedure	87.5% ($n = 36$)	90.9% ($n = 30$)	75% ($n = 6$)	0.22
Prior definitive repair	26.8% ($n = 11$)	24.2% ($n = 8$)	37.5% ($n = 3$)	0.44
No. of prior procedures	2.4 (+/− 2.1)	2.5 (+/− 2.1)	1.9 (+/− 2.0)	0.43
Preoperative antibiotics	51.2% ($n = 21$)	51.5% ($n = 17$)	50% ($n = 4$)	0.94
Postoperative antibiotics	34.1% ($n = 14$)	36.4% ($n = 12$)	25% ($n = 2$)	0.55

IPAA ileal pouch-anal anastomosis, *PVF* pouch-vaginal fistulae, *RVF* rectovaginal fistulae, *ERAF* endorectal advancement flap

Table 2 Overall use of immune therapy

	All patients ($n = 41$)	Healed fistulae ($n = 33$)	Failure ($n = 8$)	p value
Immune modulation	73.2% ($n = 30$)	72.7% ($n = 24$)	75% ($n = 6$)	0.9
Average no. of days	381	399.6	288.7	0.24
No agents	26.8% ($n = 11$)	27.3% ($n = 9$)	25% ($n = 2$)	n/a
Single agents	43.9% ($n = 18$)	39.4% ($n = 13$)	62.5% ($n = 5$)	0.56
Average no. of days	456	531	262	0.03
Double agents	29.3% ($n = 12$)	33.3% ($n = 11$)	12.5% ($n = 1$)	0.48
Average no. of days	244	257	110	*

*Too small sample size to calculate p value

thiopurines. Although not statistically significant, there is a similar trend of fewer failures in patients taking a single biologic medication for longer duration prior to surgery (infliximab, adalimumab, certolizumab, ustekinumab, vedolizumab; 550 vs 268 days; $p = 0.07$). There were no other differences appreciated with the type of single agent used or the duration of use prior to surgery. The trends in use and duration of double agents were unable to be determined due to small sample size; however, it is worth mentioning that all patients ($n = 6$) who were on a combination of infliximab + thiopurines at an average of 301 days had successful healing of their fistulae. Table 4 demonstrates the use of all immune therapies, regardless if used as a single agent or in combination, as compared to no agents. There were no statistical differences appreciated in this category.

The overall 30-day perioperative complication rate was 4.9% ($n = 2$). One patient developed a superficial cellulitis that was treated with postoperative antibiotics and another patient required an incision and drainage for a postoperative abscess. Neither of these complications led to a fistulae recurrence. There were no patients who reported issues with incontinence after surgery; however, one physical examination description mentioned "sphincter weakness" postoperatively.

Discussion

To our knowledge, this is the first study to evaluate the impact of IT on ERAF outcomes and their combined effect in healing perianal fistulae in patients with CD. The healing rate of perianal fistulae in our study was 80.5% after the initial ERAF and 92.6% after secondary adjunctive therapies, with an average follow-up of 27 months. We purposefully chose to define "fistulae healing" as a complete closure of the external opening of the fistulae per physician examination and

Table 3 Single-agent analysis

	All patients ($n = 41$)	Healed fistulae ($n = 33$)	Failure ($n = 8$)	p value
All biologics	31.7% ($n = 13$)	27.3% ($n = 9$)	50% ($n = 4$)	0.48
Average no. of days	436	550	268	0.07
Infliximab	4.9% ($n = 2$)	0	25% ($n = 2$)	*
Average no. of days	143	0	143	*
Adalimumab	14.6% ($n = 6$)	15.2% ($n = 5$)	12.5% ($n = 1$)	0.93
Average no. of days	475.7	510.8	300	*
Certolizumab	7.3% ($n = 3$)	6.1% ($n = 2$)	12.5% ($n = 1$)	*
Average no. of days	587	638	485	*
Vedolizumab	4.8% ($n = 2$)	6.1% ($n = 2$)	0	*
Average no. of days	562	562	0	*
All thiopurines	12.2% ($n = 5$)	12.1% ($n = 4$)	12.5% ($n = 1$)	0.93
Average no. of days	437	487	240	*
6-MP	7.3% ($n = 3$)	6.1% ($n = 2$)	12.5% ($n = 1$)	*
Average no. of days	342	394	240	*
Azathioprine	4.8% ($n = 2$)	6.1% ($n = 2$)	0	*
Average no. of days	580	580	0	*

6-MP mercaptopurine

*Too small sample size to calculate p value

Table 4 Immune therapy use

	All patients ($n = 41$)	Healed fistulae ($n = 33$)	Failure ($n = 8$)	p value
Infliximab	22% ($n = 9$)	21.2% ($n = 7$)	25% ($n = 2$)	0.67
Average no. of days		329.1	143	0.29
Adalimumab	22% ($n = 9$)	21.2% ($n = 7$)	25% ($n = 2$)	0.52
Average no. of days		438.1	205	0.23
Certolizumab	9.8% ($n = 4$)	9.1% ($n = 3$)	12.5% ($n = 1$)	0.66
Average no. of days		593.3	485	*
Vedolizumab	4.9% ($n = 2$)	6.1% ($n = 2$)	$n = 0$	0.52
Average no. of days		561.5	n/a	*
Ustekinumab	4.9% ($n = 2$)	6.1% ($n = 2$)	$n = 0$	0.52
Average no. of days		357	n/a	*
6-MP	26.8% ($n = 11$)	27.3% ($n = 9$)	25% ($n = 2$)	0.88
Average no. of days		396.4	420	*
Azathioprine	12.2% ($n = 5$)	15.2% ($n = 5$)	$n = 0$	0.31
Average no. of days		285.8	n/a	*

6-MP mercaptopurine

*Too small sample size to calculate p value

cessation of previous symptoms related to the fistulae because in our experience, the routine use of post operative MRI tends to demonstrate a residual fibrous band of scar tissue that is not always indicative of a fistulae recurrence. The success rate in our study is higher than previously described by Soltani et al.[11] Their meta-analysis demonstrated the majority of healing rates were 60–70%. There are a few studies that report higher rates of fistulae healing; however, these primarily include fistulae of cryptoglandular origin and do not separate their outcomes for patients with CD. These series are also are much smaller than the current one.[15–18] The largest case series by Makowiec et al. evaluated 36 ERAFs in patients with fistulizing CD and demonstrated an initial 89% success rate; however, approximately 50% of patients had a recurrence at 2-year follow-up.[15] We were able to demonstrate, with similar follow-up to the previously mentioned studies, a much lower failure rate and believe this is likely due to better long-term management with IT. We believe that IT is synergistic with surgical intervention in that it is able to effectively minimize the impact of disease, therefore ensuring the success and durability of surgical repair. It is well recognized that treatment with IT is associated with improvement or even complete healing of mucosal ulcerations in the small intestines and colon. The SONIC trial was able to demonstrate this with the use of infliximab and azathioprine, and more recently, the DIAMOND study reviewed this with adalimumab and azathioprine. Both studies demonstrated endoscopic evidence of mucosal healing at 26 weeks after IT.[19,20] Another factor that may have contributed to our higher success rate was the use of a thick mucosal flap during ERAF.

Given the retrospective nature of this study, the patients were on a variety of medications preoperatively without controls for this and, although a specific medication regimen for the healing of perianal fistulae in CD cannot be determined, there are several noticeable trends that may serve as guides for future management. As mentioned, the majority of the studies described previously were performed in the 1990s and early 2000s, before IT was in widespread use and corticosteroids were the cornerstone of treatment. Infliximab alone has not only demonstrated to have a significant improvement in healing rates of perianal fistulae as compared to placebo but has also demonstrated a reduction in hospitalizations, surgeries, and procedures in fistulizing CD.[7,8,21] A retrospective review comparing infliximab vs. adalimumab in the treatment of perianal fistulae in CD demonstrated cumulative rates of healing or nonaggravation of fistulae to be 83.9% and 62.5% at 24 months. These results trended towards, but never achieved significance.[22] We believe the use and long-term maintenance of IT in patients with CD is critical to the success of ERAF in healing perianal fistulae. We are able to demonstrate that patients who were on a single agent for a longer duration of time are more likely to have successful surgery ($p = 0.03$). Although not statistically significant, there was also a trend in improved healing rates in patients who were taking any single biologic agent for a longer period of time prior to ERAF ($p = 0.07$). It is unclear exactly how long a patient should be on IT prior to surgery; however, those who were taking a single agent were on them for an average of 531 days while those on a single biologic agent were on them for an average of 550 days prior to ERAF. A patient who can be maintained on a stable dose of IT for a longer period of time is more likely to have well-controlled disease compared to those who have not been afforded an opportunity to fail therapy. The significant finding of improved rates of healing in patients who had setons in place for a longer duration of time prior to ERAF ($p = 0.04$) is likely a result of the waiting period

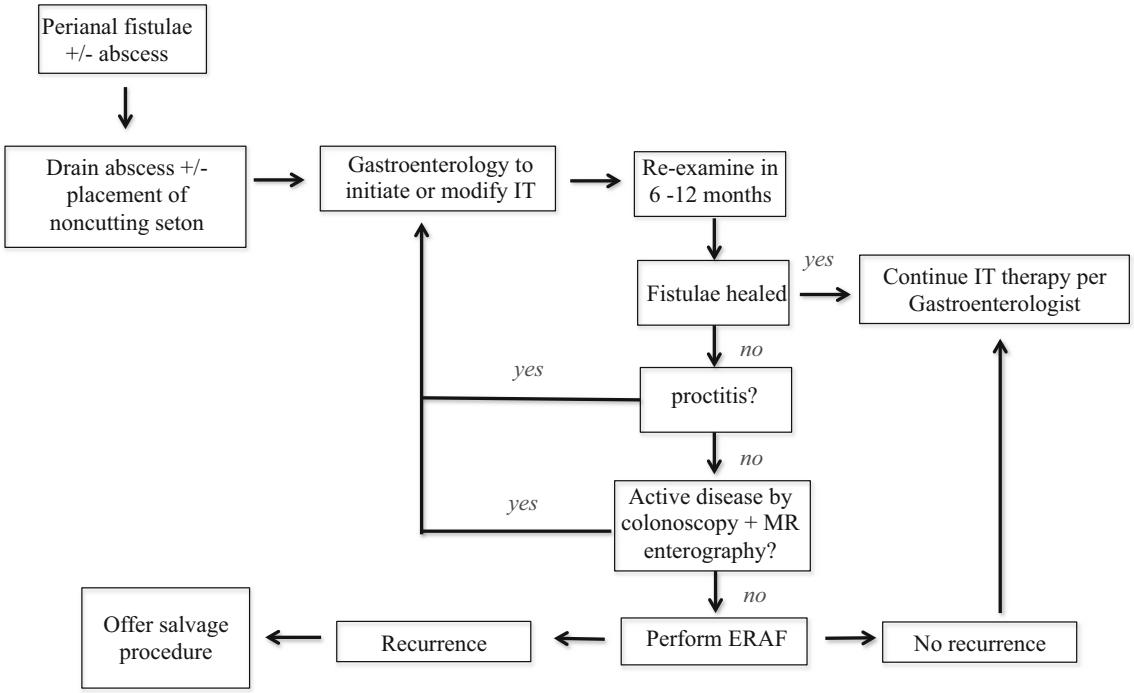

Fig. 2 Algorithm for treating perianal fistulas in patients with Crohn's disease

required to achieve well-controlled disease. It is also important to note that none of the patients in this study were taking corticosteroids at the time of surgery.

Another important trend in this study was that although not found to be statistically significant, all eight patients who had fecal diversion at the time of ERAF had successful healing of their fistulae and were diverted for an average of 359 days prior to ERAF. This finding is consistent with the study performed by Rehg et al. who demonstrated an 85% resolution of fistulas in patients who had a fecal diversion prior to surgical therapy as compared to 19% of patients who only underwent surgical therapy for the management of perirectal fistulizing CD.[23] Fecal diversion was also utilized as a salvage procedure in two of our initial failures and in both cases, lead to successful fistulae closure. Both of these patients eventually underwent stoma reversal and have not demonstrated fistulae recurrence. Of the patients who had a diversion prior to ERAF, three have had stoma reversals at an average of 75 days post-ERAF and have not demonstrated a fistulae recurrence at an average follow-up of 41 months. In regard to the other five patients, one is in the process of being reversed, one was lost to follow-up, two currently have active disease, and one has elected to withhold reversal for the time being despite having well-controlled disease. While we do not believe every patient should have a fecal diversion prior to the surgical management of fistulizing CD, it should always be a consideration, especially in patients with severe perianal disease where seton placement alone may not control perianal sepsis.

The overall 30-day perioperative complication rate in this study was 4.9% ($n = 2$), which is comparable to previously described studies.[11,14] One patient developed a superficial cellulitis that was treated with a short course of oral antibiotics and the other developed a perirectal abscess that was treated with incision and drainage. Fortunately, neither of these complications resulted in failure of the fistulae to heal. There were no patients who complained of incontinence after ERAF.

Finally, a limitation to this study is the small sample size; however, this was largely due to the strict selection criteria for patients undergoing this procedure. Although we did not enforce a specific duration of IT prior to ERAF, there was a period of watchful waiting at each individual surgeon's discretion to ensure patients remained in remission while on IT. In addition to the prerequisite of the absence of active proctitis on physical exam, patients were also required to demonstrate there was no ileal or colonic inflammation immediately prior to ERAF. This was confirmed by both a recent colonoscopy and MR enterography. The rationale for this was that active disease in the small bowel or colon may be an indicator that anorectal disease was also poorly controlled, even in the absence of visibly active proctitis, and thus lead to failure of healing after ERAF. An overview of our management algorithm for the treatment of perianal fistulae in CD is demonstrated in Fig. 2.

Conclusion

In conclusion, utilizing ERAF as the surgical procedure for the definitive management of perianal fistulae in patients with CD is a safe and effective technique given the appropriate patient selection. The continued use and advances in IT play a

significant role in the success of this procedure, and future research is still needed to further identify optimal medical and surgical management.

Authors' Contributions Michelle T. Roper: Contributions to the design of the work, acquisition, analysis and interpretation of data for the work, drafting the work and revising it critically, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Stephen M. Trinidad: Contributions to the design of the work, acquisition, analysis and interpretation of data for the work, drafting the work and revising it critically, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sonia L. Ramamoorthy: Contributions to the conception and design of the work, critically revising the work, final approval of the version to be published and agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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