ORIGINAL CONTRIBUTION

# Sphincter-Sparing Anal Fistula Repair: Are We Getting Better?

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***BACKGROUND:*** Sphincter-sparing repairs are commonly used to treat anal fistulas with significant muscle involvement.

***OBJECTIVE:*** The current study evaluates the trends and efficacy of sphincter-sparing repairs and determines risk factors for fistula recurrence.

***DESIGN AND SETTINGS:*** A retrospective review was performed at 3 university-affiliated teaching hospitals.

***PATIENTS:*** All 462 patients with cryptoglandular anal fistulas who underwent 573 sphincter-sparing repairs between 2005 and 2015 were included. Patients with Crohn's disease were excluded.

***MAIN OUTCOME MEASURES:*** The primary outcome was the rate of fistula healing defined as cessation of drainage with closure of the external opening. Risk factors for nonhealing were also analyzed.

***RESULTS:*** Five hundred three sphincter-sparing repairs were analyzed, whereas 70 were lost to follow-up. Two hundred twenty sphincter-sparing repairs (44%) resulted in healing, 283 (56%) resulted in nonhealing with a median follow-up of 9 (range, 1–125) months. The median time to fistula recurrence was 3 (range, 0–75) months with 79% and 91% of recurrences noted within 6 and 12 months. Patients treated with a dermal advancement flap, rectal advancement flap, or ligation of the intersphincteric tract procedure were less likely to have a recurrence than patients treated with a fistula plug or fibrin glue ($p < 0.001$). Over time, there was a significantly increased use of the ligation of the intersphincteric tract procedure ($p < 0.001$) and a significantly decreased use of fistula plugs and fibrin glue ($p < 0.001$); healing rates improved accordingly. There were no significant differences in healing rates with respect to patient demographics, comorbidities, or fistula characteristics.

***LIMITATIONS:*** This study was limited by its retrospective design.

***CONCLUSIONS:*** Healing rates following sphincter-sparing repairs of cryptoglandular anal fistulas are modest, but have improved over time with the use of better surgical techniques. In this study, ligation of the intersphincteric fistula tract and flaps were superior to fistula plugs and fibrin glue; the former procedures are therefore favored. See **Video Abstract** at http://links.lww.com/DCR/A391.

***KEY WORDS:*** Advancement flap; Anal fistula; Fibrin glue; Fistula plug; LIFT; Sphincter-sparing repair.

An anal fistula is a common anorectal ailment with an estimated incidence in the United States of 20 000 to 25 000 cases per year.[1] Over 90% of anal fistulas are cryptoglandular in origin and arise from anorectal abscesses.[2] Fistulotomy is the gold standard for the treatment for anal fistulas with a healing rate of >90%.[3–5] However, patients treated with fistulotomy are at risk of developing postoperative anal sphincter dysfunction, especially females or patients with complex fistulas, preoperative incontinence, recurrent disease, or previous anorectal surgeries.[5,6] Therefore, there has been a considerable interest to develop sphincter-sparing repair (SSR) procedures that attempt to treat anal fistulas without dividing sphincter muscle.

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Various SSRs have been described and evaluated including rectal advancement flaps (RAFs), dermal advancement flaps (DAFs), fibrin glue (FG), anal fistula plugs (AFPs), and, most recently, ligation of the intersphincteric fistula tract (LIFT). Rectal advancement flaps are one of the oldest and best known techniques with healing rates reported between 66% and 87%.[7] However, their appeal as a first-line SSR option is limited by the fact that internal sphincter muscle may be included in the flap. This can cause mild to moderate incontinence reported in 13% of patients.[8] There is less literature on DAFs, but most series report healing rates between 70% and 80%.[9–12] Although there is no division of the anal sphincter muscles, DAFs may still be associated with decrement in continence.[12–14] Fibrin glue and AFPs carry essentially no risk of postoperative incontinence, but are relatively ineffective, with healing rates <50% in more recent studies.[7] Last, the LIFT procedure was first described in 1993,[15] and has been rapidly adopted as a first-line SSR by many surgeons since being simplified in 2007.[16] Recent systematic reviews report promising healing rates between 61% and 94% with only rare disturbance of fecal continence.[17,18]

The purpose of this study was to evaluate the trends in the use of various SSRs over time and their efficacy at 3 large academic institutions in the Chicago area. An additional goal was to identify predictors of healing following a SSR.

## PATIENTS AND METHODS

All patients who underwent an operation for treatment of an anal fistula between January 2005 and December 2015 were identified from prospectively maintained databases at 3 large Chicago-area academic institutions and reviewed retrospectively. Patients with IBD, traumatic, malignant, or radiation-induced fistulas were excluded along with patients in whom a SSR was never attempted (Fig. 1).

The electronic medical records of patients who met the study criteria were thoroughly reviewed and the following data collected: patient demographics (age, sex, BMI), comorbidities (history of smoking, diabetes mellitus, HIV, ASA classification, and Charlson Comorbidity Index[19]), and fistula characteristics (location, length, duration of symptoms, Parks classification,[20] depth of the internal opening, associated abscess at time of repair, use of a draining seton before repair, placement of a drain in the external opening, history of prior attempts at repair), type of repair performed, and length of follow-up. Descriptive fistula characteristics, such as location and Parks classification,[20] were recorded as documented from examination under anesthesia before the repair. The tract length was determined by measuring the distance from the external opening to the anal verge. The cutoff for data collection was November 7, 2016.

The primary outcome was the rate of fistula healing after a SSR. A fistula was considered healed when there was cessation of drainage, as reported by the patient and

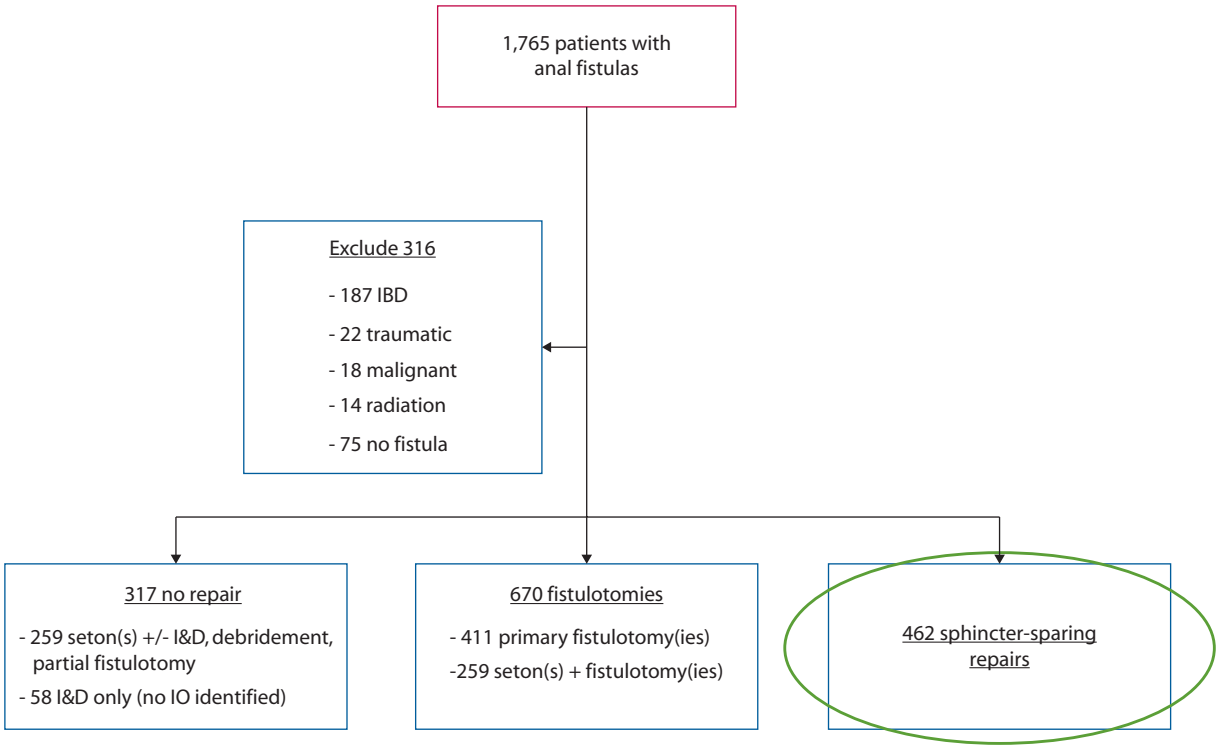


**FIGURE 1.** All patients who underwent operative treatment for an anal fistula between January 2005 and December 2015. I&D = incision and drainage; IO = internal opening.

confirmed on examination, and closure of the external opening on last follow-up. Fistulas that required additional surgery or that failed to meet healed criteria beyond 1 month of follow-up, whether persistent or recurrent, were considered nonhealed. Fistulas were classified as lost to follow-up if the patient either failed to follow-up after the repair or if the last follow-up visit occurred within 1 month of the repair without meeting healed criteria. Patient demographics, comorbidities, and fistula characteristics were compared between patients with healed and nonhealed anal fistulas to identify predictors of healing. To assess if there was improvement over time, outcomes were compared before and after January 1, 2010. This date was chosen as a dividing point, because it roughly divided the data set in half. Patient demographics, comorbidities, and fistula characteristics were also compared between the different types of SSR to identify any factors that may have led a surgeon to choose 1 type of repair over another. This study protocol was approved by the institutional review boards at all 3 study sites.

Data analyses were conducted using SPSS version 24 (IBM Corp, Armonk, NY). Descriptive statistics were reported as median (range) for continuous variables and n (%) for categorical variables. Differences between groups on continuous variables were tested by using the Mann-Whitney *U* test or Kruskal-Wallis test and on categorical variables using a $\chi^2$ test or Fisher exact test. Binary logistic regression was used to compare univariate predictors of healing. A time to fistula recurrence analysis was performed by using the Kaplan-Meier method. Observed differences were considered statistically significant if $p < 0.05$.

## RESULTS

Four hundred sixty-two patients underwent 573 SSRs during the study period. Five hundred three SSRs were analyzed, whereas 70 were lost to follow-up. Two hundred twenty SSRs (44%) resulted in healing, 283 (56%) resulted in nonhealing with a median follow-up of 9 (range, 1–125) months. The median time to fistula recurrence was 3 (range, 0–75) months with 79% and 91% of recurrences noted within 6 and 12 months (Fig. 2). There were no significant differences in patient demographics or comorbidities between the healers and nonhealers (Table 1).

The vast majority of the fistulas were transsphincteric (n = 478, 95%), and patients reported symptoms over a median time of 15 (range, 1–422) months before repair. Three hundred five fistulas (61%) were treated with a draining seton before SSR, and 159 (32%) had failed a previous attempt at repair. Most fistulas had internal openings located at or distal to the dentate line (88%), and 198 fistulas (39%) had internal openings in the posterior midline. There was a trend that fistulas with an internal opening at or distal to the dentate line were more likely to heal

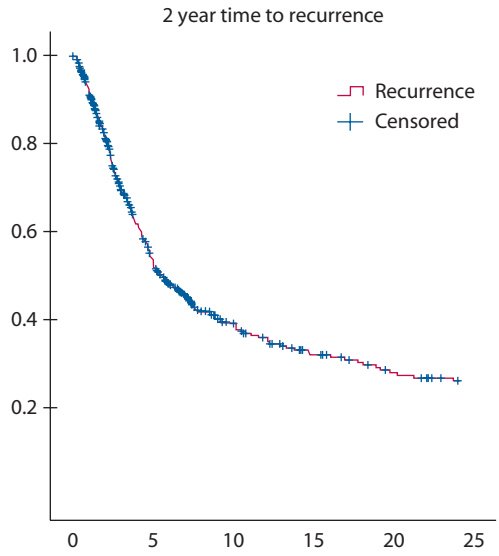


**FIGURE 2.** Time to fistula recurrence. Overall healing rate following a sphincter-sparing repair was 44%. However, because disproportionate censoring of healers, the estimated healing rate at 2 years is lower.

compared with those with an internal opening above the dentate line ($p = 0.1$). There were no other differences in fistula characteristics between the healers and nonhealers (Table 2).

Univariate predictors of healing included type of repair performed ($p < 0.001$) and date of operation before or after 2010 ($p = 0.005$). The various types of SSRs utilized in the study period, their frequency of use, and their healing rates are summarized in Figure 3. Patients treated with a RAF, DAF, or LIFT procedure were significantly more likely to heal compared with patients treated with an AFP or FG ($p < 0.001$). Over time, there was a significantly increased use of the LIFT procedure ($p < 0.001$) and a significantly decreased use of AFPs and FG ($p < 0.001$); healing rates improved accordingly (Fig. 4). On multivariate analysis, only type of repair performed remained a sig-

**TABLE 1.** Patient characteristics

| *Characteristic* | *Healers (n = 220)* | *Nonhealers (n = 283)* | *p* |
|---|---|---|---|
| Age, y | 46 (20–78) | 46 (18–74) | 0.21[a] |
| Male | 132 (65) | 185 (65) | 0.85[b] |
| BMI | 29 (16–58) | 29 (16–55) | 0.97[a] |
| ASA classification | | | |
| I | 86 (39) | 111 (40) | 1.0[c] |
| II | 115 (53) | 147 (52) | |
| III | 18 (8) | 23 (8) | |
| Diabetics | 26 (12) | 23 (8) | 0.18[b] |
| HIV[c] | 4 (2) | 6 (2) | 1.0[b] |
| Smokers | 64 (29) | 76 (27) | 0.62[b] |
| Charlson Comorbidty Index | 0 (0–6) | 0 (0–7) | 0.63[a] |

Data reported as median (range) or n (%).
[a]Mann-Whitney *U* test,
[b]Fisher exact test,
[c]$\chi^2$ test

**TABLE 2.** Fistula characteristics

| Characteristic | Healers (n = 220) | Nonhealers (n = 283) | p |
|---|---|---|---|
| Parks classification | | | |
| Intersphincteric | 6 (3) | 5 (2) | |
| Transphincteric | 209 (95) | 269 (96) | 0.62[a] |
| Suprasphincteric | 3 (1) | 4 (2) | |
| Extrasphincteric | 1 (1) | 0 | |
| Symptom duration, mo | 16 (1–422) | 15 (1–369) | 0.47[b] |
| Draining seton before repair | 134 (61) | 171 (60) | 0.93[c] |
| Failed prior attempt at repair | 64 (29) | 95 (34) | 0.29[c] |
| Depth of IO | | | |
| Distal to dentate line | 15 (14) | 12 (8) | |
| At dentate line | 86 (78) | 111 (76) | 0.1[a] |
| Proximal to dentate line | 9 (8) | 23 (16) | |
| Tract length, cm | 3 (1–10) | 3 (1–10) | 0.69[b] |
| Posterior midline IO | 86 (39) | 112 (40) | 0.93[c] |
| Abscess cavity at time of repair | 10 (5) | 11 (4) | 0.82[c] |
| Placement of drain into EO | 26 (12) | 24 (8) | 0.23[c] |

Data reported as median (range) or n (%).
IO = internal opening; EO = external opening.
[a]$\chi^2$ test.
[b]Mann-Whitney *U* test.
[c]Fisher exact test.

nificant predictor of fistula healing ($p < 0.001$). There was a significant difference in the median length of follow-up between healers and nonhealers: 6 (range 1–121) versus 14 (range, 1–125) months. Most patient and fistula characteristics were similar across the type of repair performed, although differences were noted in sex, Parks classification, and history of failed prior repair (Table 3).

## DISCUSSION

These data demonstrate an evolution in use of various SSRs in the Chicago region. The LIFT procedure has become the most popular SSR over the past 6 years, essentially replacing AFPs and FG. As a result, the healing rates have improved. There was a steady use of DAFs and RAFs both before and after 2010, although they were never the most utilized SSR at any time period in the study. This may be explained by the notion that flaps are more prone to cause postoperative continence disturbances compared with LIFT, FG, and AFPs.[8,12–14] The most utilized SSRs at present, LIFT, RAF, and DAF, were also shown to be the most efficacious. This practice is supported by the 2016 American Society of Colon and Rectal Surgeons clinical practice guidelines that favor RAFs and LIFTs over AFPs and FG because the latter are relatively ineffective.[7]

To our knowledge, this is the first study that has attempted to identify predictors of fistula healing following any type of SSR. Aside from type of repair performed, there were no predictors of fistula healing found. A few large series that have attempted to identify risk factors for fistula recurrence did so by examining a cohort of patients that were treated with a fistulotomy most commonly. Garcia-Aguilar et al[5] reviewed a 375-patient cohort, 300

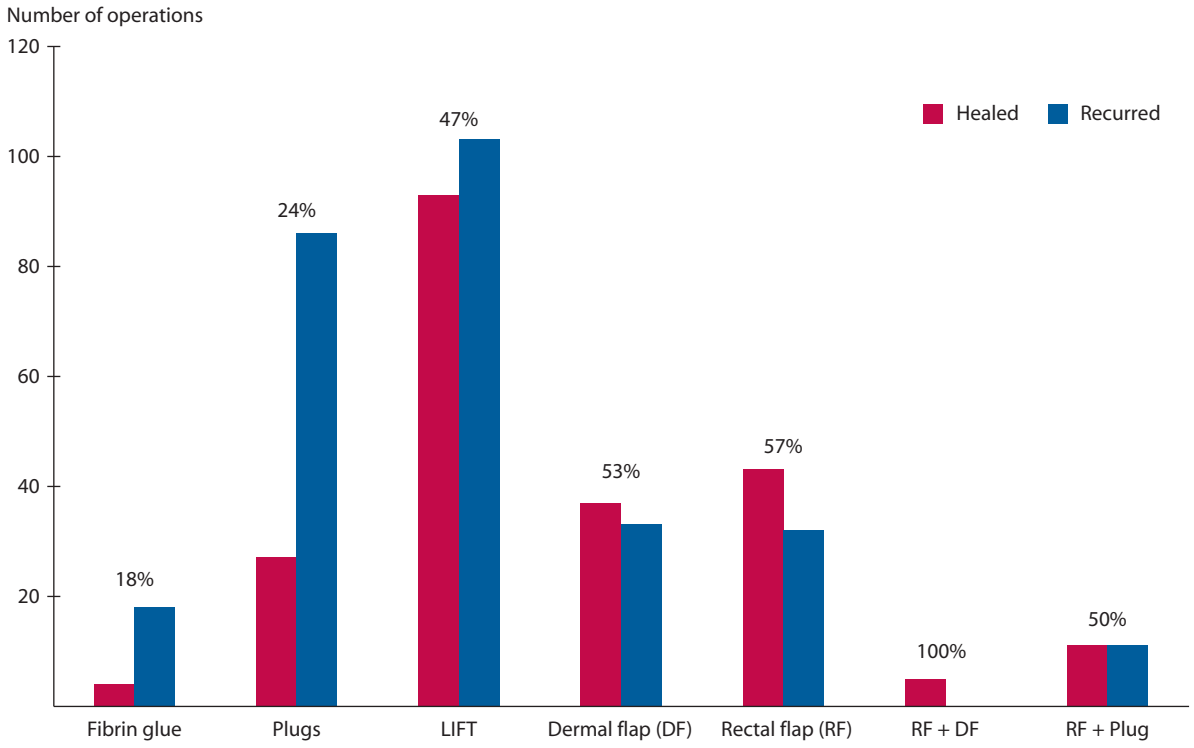


**FIGURE 3.** Types of sphincter-sparing repairs and their outcomes. DF = dermal flap; LIFT = ligation of the intersphincteric fistula tract; RF = rectal flap.

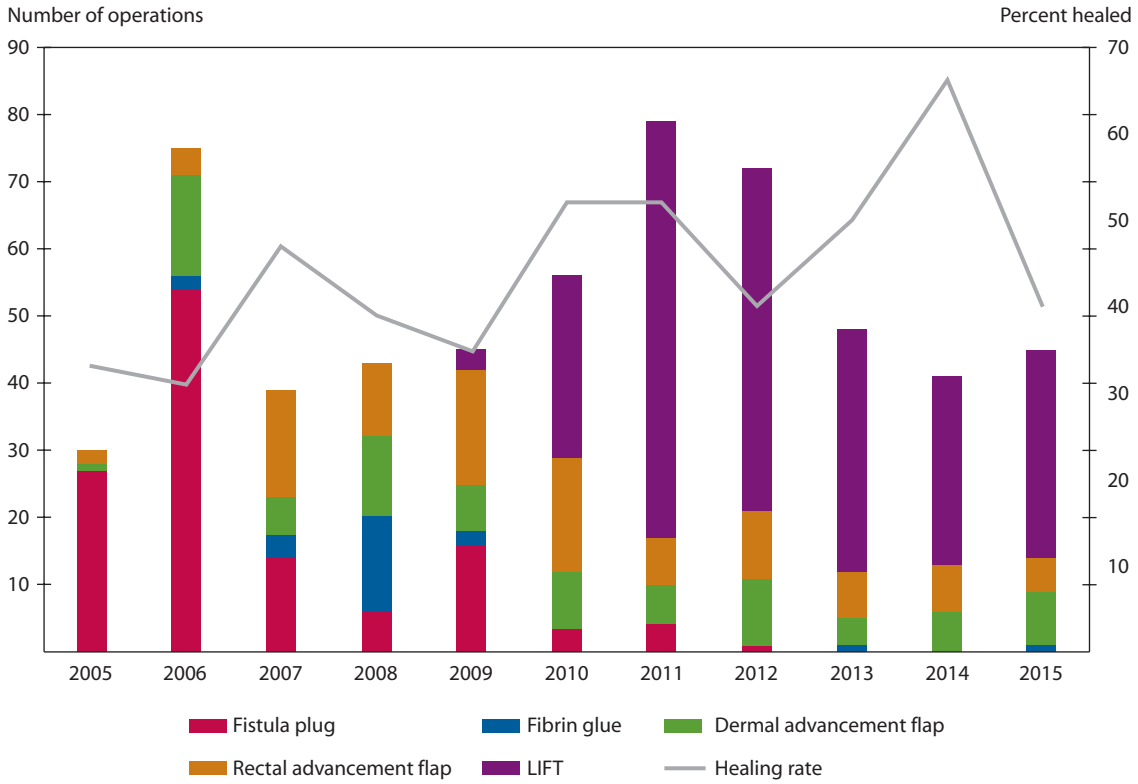


**FIGURE 4.** Sphincter-sparing repair outcomes over time. LIFT = ligation of the intersphincteric fistula tract.

of which were treated with a fistulotomy, and found that risk factors associated with recurrence were complex type of fistula, horseshoe extension, lack of identification of internal opening, lateral internal opening, previous fistula surgery, and operating surgeon. In contrast, van Koperen et al[21] examined a 179-patient cohort, 109 of which were treated with a fistulotomy, and found no risk factors for recurrence. Similar to the present study, Abbas et al[22] found that use of an AFP compared with fistulotomy or RAF was an independent risk factor for failure.

Many studies have looked at both clinical and fistula-related factors that may predict the outcomes following individual SSRs. In terms of patient factors, older patients may have better outcomes with RAFs,[23,24] and patients with a high BMI may do worse with LIFTs.[25] Also, there is some evidence that women do better with DAFs,[14] which could explain why a higher portion of women underwent flap procedures in the current study. Smoking has been shown to be a risk factor for recurrence following a RAF,[26,27] DAF,[27] AFP,[28] and LIFT,[29] but was not shown to predict recurrence in the present study. Similarly, patients with a history of prior fistula repair have been shown to have worse outcomes,[10,27–30] but this was not a significant predictor of failure in this study. However, it remained a confounding variable when comparing the efficacy of the various SSRs because patients treated with an AFP, FG, RAF, or DAF were more likely to have had a prior repair than patients treated with a LIFT. Other fistula factors that have been shown to impact outcomes of SSRs include tract length,[31,32] complexity,[22,33,34] and posterior location,[28] but none of which were significant in the present study. However, there was a trend that fistulas with internal openings proximal to the dentate line tended to have worse outcomes. Overall, reasons for SSR failure are not well-understood and may extend beyond clinical and anatomical factors.

Many surgeons routinely place draining setons before repairing an anal fistula. Setons are thought to help reduce inflammation in the acute setting by draining sepsis and causing a fibrotic reaction that matures the fistula tract.[35] There is some evidence that prior seton placement lowers recurrence rates following a SSR.[36] The majority of patients in this study (61%) received a draining seton before SSR; however, no difference was noted in healing rates. The question therefore remains if routine use of draining setons before SSR is necessary in all patients.

There are several limitations to these data. Although most patient and fistula characteristics were similar across the type of repair performed (Table 3), there may be other factors that influenced the surgeon's choice of SSR. This selection bias is inherent due to the retrospective design of the study. Also, the nonhealers had significantly longer follow-up than the healers. Although this may seem intuitive, it also has the potential to add bias to the data, because it is known that fistula recurrence rates increase with longer follow-up.[37] The median length of follow-up was relatively

**TABLE 3.** Patient demographics, comorbidities, and fistula characteristics compared across the types of sphincter-sparing repairs

| *Characteristic* | *Plugs and glue (n = 148)* | *Flaps (n = 187)* | *LIFTs (n = 238)* | *p* |
|---|---|---|---|---|
| Age, y | 47 (18–78) | 46 (20–78) | 45 (18–73) | 0.78[a] |
| Males | 103 (70) | 110 (59) | 172 (72) | 0.01[b] |
| BMI | 29 (20–58) | 30 (16–51) | 28 (18–55) | 0.24[a] |
| ASA classification | | | | |
| I | 60 (42) | 71 (38) | 98 (41) | 0.87[b] |
| II | 70 (49) | 101 (54) | 122 (52) | |
| III | 13 (9) | 15 (8) | 17 (7) | |
| Diabetics | 15 (10) | 18 (10) | 19 (8) | 0.74[b] |
| HIV+ | 4 (3) | 1 (1) | 8 (3) | 0.14[b] |
| Smokers | 37 (25) | 64 (34) | 61 (26) | 0.09[b] |
| Charlson Comorbidity Index | 0 (0–7) | 0 (0–7) | 0 (0–6) | 0.74[a] |
| Parks classification | | | | |
| Intersphincteric | 4 (3) | 8 (4) | 0 | 0.028[b] |
| Transphincteric | 141 (96) | 170 (93) | 234 (99) | |
| Suprasphincteric | 0 | 1 (1) | 0 | |
| Extrasphincteric | 1 (1) | 4 (2) | 2 (1) | |
| Symptom duration, mo | 18 (1–422) | 16 (1–394) | 13 (1–210) | 0.19[a] |
| Draining seton prior to repair | 81 (55) | 117 (63) | 145 (61) | 0.32[b] |
| Failed prior attempt at repair | 54 (36) | 77 (41) | 43 (18) | <0.001 |
| Depth of IO | | | | |
| Distal to dentate line | 7 (11) | 11 (12) | 13 (9) | 0.82 |
| At dentate line | 54 (82) | 68 (77) | 111 (79) | |
| Proximal to dentate line | 5 (7) | 10 (11) | 17 (12) | |
| Tract length, cm | 4 (1–10) | 3 (1–9) | 3 (1–10) | 0.74[a] |
| Posterior midline IO | 67 (45) | 74 (40) | 82 (34) | 0.1[b] |
| Abscess cavity at time of repair | 3 (2) | 9 (5) | 13 (5) | 0.26[b] |

Data reported as median (range) or n (%).
LIFT = ligation of intersphincteric fistula tract; IO = internal opening.
[a]Kruskal-Wallis test.
[b]$\chi^2$ test.

short at 9 months. The number and timing of follow-up visits were not standardized. No data were collected on changes in fecal continence because of the lack of standardized reporting in the electronic medical records.

## CONCLUSION

Healing rates following SSRs of cryptoglandular anal fistulas are modest, but have improved over time with the use of better surgical techniques. LIFT and flap procedures are currently favored and they were more efficacious than AFPs and FG in this study. There were no other patient and fistula characteristics that predicted healing following a SSR. Future directions include evaluating the trends and efficacy of fistula repairs as a whole inclusive of fistulotomy, fistulectomy, and cutting setons, and examination of molecular and cellular factors in the fistula tissue that may contribute to the pathogenesis of nonhealing anal fistulas.[38]

## ACKNOWLEDGMENTS

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## REFERENCES

1. Nelson R. Anorectal abscess fistula: what do we know? *Surg Clin North Am.* 2002;82:1139–51, v.
2. Sainio P. Fistula-in-ano in a defined population. Incidence and epidemiological aspects. *Ann Chir Gynaecol.* 1984;73:219–224.
3. Hall JF, Bordeianou L, Hyman N, et al. Outcomes after operations for anal fistula: results of a prospective, multicenter, regional study. *Dis Colon Rectum.* 2014;57:1304–1308.
4. Abramowitz L, Soudan D, Souffran M, et al; Groupe de Recherche en Proctologie de la Société Nationale Française de Colo-Proctologie and the Club de Réflexion des Cabinets et Groupe d'Hépato-Gastroentérologie. The outcome of fistulotomy for anal fistula at 1 year: a prospective multicentre French study. *Colorectal Dis.* 2016;18:279–285.
5. Garcia-Aguilar J, Belmonte C, Wong WD, Goldberg SM, Madoff RD. Anal fistula surgery. Factors associated with recurrence and incontinence. *Dis Colon Rectum.* 1996;39:723–729.
6. Jordán J, Roig JV, García-Armengol J, García-Granero E, Solana A, Lledó S. Risk factors for recurrence and incontinence after anal fistula surgery. *Colorectal Dis.* 2010;12:254–260.
7. Vogel JD, Johnson EK, Morris AM, et al. Clinical Practice Guideline for the Management of Anorectal Abscess, Fistula-in-Ano, and Rectovaginal Fistula. *Dis Colon Rectum.* 2016;59:1117–1133.
8. Soltani A, Kaiser AM. Endorectal advancement flap for cryptoglandular or Crohn's fistula-in-ano. *Dis Colon Rectum.* 2010;53:486–495.

9. Jun SH, Choi GS. Anocutaneous advancement flap closure of high anal fistulas. *Br J Surg*. 1999;86:490–492.
10. Nelson RL, Cintron J, Abcarian H. Dermal island-flap anoplasty for transsphincteric fistula-in-ano: assessment of treatment failures. *Dis Colon Rectum*. 2000;43:681–684.
11. Sungurtekin U, Sungurtekin H, Kabay B, et al. Anocutaneous V-Y advancement flap for the treatment of complex perianal fistula. *Dis Colon Rectum*. 2004;47:2178–2183.
12. Robertson WG, Mangione JS. Cutaneous advancement flap closure: alternative method for treatment of complicated anal fistulas. *Dis Colon Rectum*. 1998;41:884–886.
13. Hossack T, Solomon MJ, Young JM. Ano-cutaneous flap repair for complex and recurrent supra-sphincteric anal fistula. *Colorectal Dis*. 2005;7:187–192.
14. Zimmerman DD, Briel JW, Gosselink MP, Schouten WR. Anocutaneous advancement flap repair of transsphincteric fistulas. *Dis Colon Rectum*. 2001;44:1474–1480.
15. Matos D, Lunniss PJ, Phillips RK. Total sphincter conservation in high fistula in ano: results of a new approach. *Br J Surg*. 1993;80:802–804.
16. Rojanasakul A, Pattanaarun J, Sahakitrungruang C, Tantiphlachiva K. Total anal sphincter saving technique for fistula-in-ano; the ligation of intersphincteric fistula tract. *J Med Assoc Thai*. 2007;90:581–586.
17. Sirany AM, Nygaard RM, Morken JJ. The ligation of the intersphincteric fistula tract procedure for anal fistula: a mixed bag of results. *Dis Colon Rectum*. 2015;58:604–612.
18. Hong KD, Kang S, Kalaskar S, Wexner SD. Ligation of intersphincteric fistula tract (LIFT) to treat anal fistula: systematic review and meta-analysis. *Tech Coloproctol*. 2014;18:685–691.
19. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.
20. Parks AG, Gordon PH, Hardcastle JD. A classification of fistula-in-ano. *Br J Surg*. 1976;63:1–12.
21. van Koperen PJ, Wind J, Bemelman WA, Bakx R, Reitsma JB, Slors JF. Long-term functional outcome and risk factors for recurrence after surgical treatment for low and high perianal fistulas of cryptoglandular origin. *Dis Colon Rectum*. 2008;51:1475–1481.
22. Abbas MA, Jackson CH, Haigh PI. Predictors of outcome for anal fistula surgery. *Arch Surg*. 2011;146:1011–1016.
23. Sonoda T, Hull T, Piedmonte MR, Fazio VW. Outcomes of primary repair of anorectal and rectovaginal fistulas using the endorectal advancement flap. *Dis Colon Rectum*. 2002;45:1622–1628.
24. Gustafsson UM, Graf W. Randomized clinical trial of local gentamicin-collagen treatment in advancement flap repair for anal fistula. *Br J Surg*. 2006;93:1202–1207.
25. Sirikurnpiboon S, Awapittaya B, Jivapaisarnpong P. Ligation of intersphincteric fistula tract and its modification: results from treatment of complex fistula. *World J Gastrointest Surg*. 2013;5:123–128.
26. Zimmerman DD, Delemarre JB, Gosselink MP, Hop WC, Briel JW, Schouten WR. Smoking affects the outcome of transanal mucosal advancement flap repair of trans-sphincteric fistulas. *Br J Surg*. 2003;90:351–354.
27. Ellis CN, Clark S. Effect of tobacco smoking on advancement flap repair of complex anal fistulas. *Dis Colon Rectum*. 2007;50:459–463.
28. Ellis CN, Rostas JW, Greiner FG. Long-term outcomes with the use of bioprosthetic plugs for the management of complex anal fistulas. *Dis Colon Rectum*. 2010;53:798–802.
29. Abcarian AM, Estrada JJ, Park J, et al. Ligation of intersphincteric fistula tract: early results of a pilot study. *Dis Colon Rectum*. 2012;55:778–782.
30. Gisbertz SS, Sosef MN, Festen S, Gerhards MF. Treatment of fistulas in ano with fibrin glue. *Dig Surg*. 2005;22:91–94.
31. Patrlj L, Kocman B, Martinac M, et al. Fibrin glue-antibiotic mixture in the treatment of anal fistulae: experience with 69 cases. *Dig Surg*. 2000;17:77–80.
32. Liu WY, Aboulian A, Kaji AH, Kumar RR. Long-term results of ligation of intersphincteric fistula tract (LIFT) for fistula-in-ano. *Dis Colon Rectum*. 2013;56:343–347.
33. Cintron JR, Park JJ, Orsay CP, et al. Repair of fistulas-in-ano using fibrin adhesive: long-term follow-up. *Dis Colon Rectum*. 2000;43:944–949.
34. van Onkelen RS, Gosselink MP, Thijsse S, Schouten WR. Predictors of outcome after transanal advancement flap repair for high transsphincteric fistulas. *Dis Colon Rectum*. 2014;57:1007–1011.
35. Abcarian H. *Anal Fistula: Principles and Management*. New York: Springer; 2014.
36. Mushaya C, Bartlett L, Schulze B, Ho YH. Ligation of intersphincteric fistula tract compared with advancement flap for complex anorectal fistulas requiring initial seton drainage. *Am J Surg*. 2012;204:283–289.
37. Mizrahi N, Wexner SD, Zmora O, et al. Endorectal advancement flap: are there predictors of failure? *Dis Colon Rectum*. 2002;45:1616–1621.
38. van Onkelen RS, Gosselink MP, van Meurs M, Melief MJ, Schouten WR, Laman JD. Pro-inflammatory cytokines in cryptoglandular anal fistulas. *Tech Coloproctol*. 2016;20:619–625.