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ORIGINAL ARTICLE

A trial of radiofrequency ablation for anal intraepithelial neoplasia

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Abstract
Purpose Radiofrequency ablation (RFA) effectively treats esophageal high-grade dysplasia, but its efficacy in treating anal canal high-grade squamous intraepithelial lesions (HSILs) is unsubstantiated. This prospective study assessed the safety and efficacy of applying hemi-circumferential RFA to anal canal HSIL.
Methods Twenty-one HIV-negative participants with HSIL occupying ≤ half the anal canal circumference were treated with hemi-circumferential anal canal RFA. Participants were assessed every 3 months for 12 months with high-resolution anoscopy; recurrence in the treatment zone was re-treated with focal RFA.
Results Twenty-one participants with a mean of 1.7 lesions (range 1–4) enrolled and completed the trial. Six (29 %) participants had recurrent HSIL within the treated hemi-circumference within 1 year. Four participants (19 %) had persistence of an index lesion at 3 months. One (2.9 %) index HSIL persisted again at 12 months. No participants had more than two RFA treatments. KM curve-predicted HSIL-free survival within the treatment zone at 1 year was 76 % (95 % CI 52–89 %). Comparing the first 7 and last 14 participants, the predicted 1-year HSIL-free survivals are 43 % (95 % CI 10–73 %) and 93 % (95 % CI 59–99 %), respectively ($p = 0.008$), suggesting a learning curve with the treating physician. Multivariable analysis showed decreased recurrence in the last 14 participants (HR 0.02; 95 % CI 0.001–0.63) while increasing BMI increased recurrence (HR 1.43, 95 % CI 1.01–2.01). No participants had device or procedure-related serious adverse events, anal stricture, or heavy bleeding.
Conclusions Hemi-circumferential RFA yielded a high rate of anal HSIL eradication in HIV-negative patients at 1 year with minimal adverse events. Lesion persistence was probably related to incomplete initial ablation.

Keywords Anal cancer · High-grade squamous intraepithelial lesion · Radiofrequency ablation

Introduction

The incidence of anal squamous cell carcinoma (SCC) is rising, with approximately 8080 new cases predicted in the USA in 2016 [1]. Over the past decade, the rate of anal cancer cases has increased by approximately 2.2 % each year, while mortality has increased 3.8 % each year [2].

Both anal and cervical cancers result from oncogenic human papillomavirus (HPV) infection. HPV infection can cause high-grade squamous intraepithelial lesions (HSILs), the immediate invasive cancer precursor [3–6]. Cervical HSIL can be identified by colposcopy by using magnification, acetic acid, and Lugol's iodine solution. These techniques, adapted to the anal canal, are termed high-resolution anoscopy (HRA) [7]. Cervical HSIL is usually treated by complete excision of the squamocolumnar transformation zone with loop

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electrosurgical excision or cone biopsy [8, 9], but complete excision of the anal squamocolumnar transformation zone is contraindicated due to significant risk of anal stenosis, abscess formation, anal spasm, and dyschezia [10, 11]. Instead, current anal HSIL treatment focuses on targeted ablation by electrocautery, infrared coagulation, cryotherapy, laser ablation, or surgical excision [11–15].

Targeted ablation of anal HSIL decreased progression to invasive anal SCC to 1–2 % within 10 years [16, 17]. HSIL recurrence, however, remains persistently elevated with long-term follow-up studies reporting recurrence between 26 and 50 % at 1 year [17–21]. Patients require repeated follow-up examinations and treatment of recurrent HSIL to prevent cancer.

Esophageal adenocarcinoma is similar to anal SCC in several ways. Esophageal adenocarcinoma is preceded by high-grade glandular dysplasia within areas of intestinal metaplasia (Barrett's esophagus). Similar to the anus, complete esophageal mucosal resection presents significant risk for stenosis. Originally, high-grade dysplasia in Barrett's esophagus was managed with focal ablative therapies [22]. These methods, however, were not optimal for large lesions and were largely replaced with radiofrequency ablation (RFA) [23–25]. Radiofrequency energy delivered via electrodes creates a very superficial injury to the mucosa [26]. Circumferential RFA treatment of Barrett's esophagus, which has been established as the preferred endoscopic ablative method by gastroenterologists, resulted in zero esophageal perforations, significant stricture in only 5 % [27–29], and complete dysplasia eradication in >80 % of patients [23, 30–33].

RFA could potentially treat anal dysplasia. A phase I trial of hemi-circumferential anal RFA with one to three applications found the procedure safe and well tolerated [34]. In this prospective, pilot study, we endeavored to determine the efficacy and safety of hemi-circumferential RFA treatment of anal HSIL in HIV-negative participants.

Materials and methods

Trial design and objective

The trial was conducted at a single clinical site specializing in diagnosis and treatment of anal HSIL (SG). Participants were followed for 12 months. The trial was conducted according to Good Clinical Practice guidelines, and experimental protocols met US FDA guidelines and were approved by an institutional review committee. The study was registered with Clinicaltrials.gov (NCT01970787).

Trial participant eligibility and consent

All participants were screened for eligibility with HRA as previously described [7]. Informed consent was obtained from all individual participants included in the study. Biopsies of all lesions suspicious for HSIL were sent to local commercial pathology laboratories (Quest Diagnostics, Teterboro, NY, or Enzo Clinical Laboratories, Farmingdale, NY). Slides were interpreted in accordance with the LAST criteria [35] and reported as benign (including squamous metaplasia), low-grade squamous intraepithelial lesion (LSIL), or HSIL. Enrollment was open to men and women 18–75 years of age with HRA-identified, biopsy-proven HSIL (index lesions) involving ≤50 % circumference of the anal squamocolumnar junction occupying no more than two contiguous quadrants. The eligible treatment zone (ETZ) was defined as two contiguous quadrants containing the index HSIL. If only one quadrant had HSIL, the ETZ was extended to involve an adjacent quadrant (Fig. 1). Participants with prior HPV vaccination, prior treatment for anal HSIL within the ETZ or history of anal cancer, were excluded.

RFA device

We utilized the Barrx™ Flex RFA generator and Barrx™ 60 RFA catheters (Fig. 2) (Medtronic, Sunnyvale, CA). The catheter was modified by trimming away the latex endoscopy sleeve to make it less bulky. The electrode was not modified.

Trial procedure

After informed consent, all index lesions were re-identified by HRA. Participants were sedated intravenously, and 3–5 cm^3 of 0.5 % bupivacaine was injected to anesthetize the anal canal. The electrode was attached to a Kelly clamp and passed

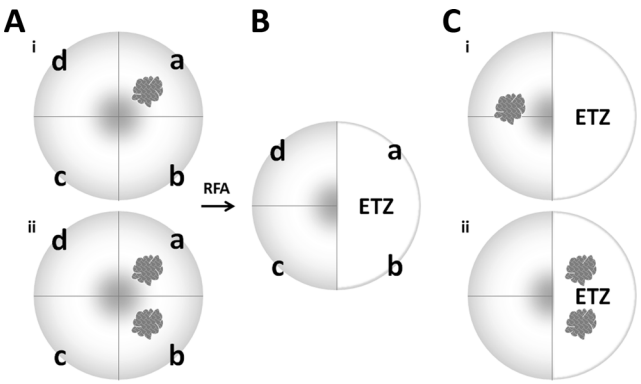

Fig. 1 Hemi-circumferential radiofrequency ablation method. **a** Diagrams showing lesions in one quadrant (*i*) or two quadrants (*ii*) but no more than half of the circumference of the anal canal. Quadrants *a*–*d* were designated clockwise. If HSIL was contained in only one quadrant, quadrant *a* was designated by situating the HSIL centrally within it. The eligible treatment zone (ETZ) was defined as quadrants *a* and *b*, regardless of lesion presence in quadrant *b*. **b** Post-RFA diagram showing the ETZ of hemi-circumferential ablation. **c** Diagrams depicting lesion recurrence (*i*) at a different location from the original HSIL site (metachronous) and lesion persistence (*ii*) at the same site as the original HSIL

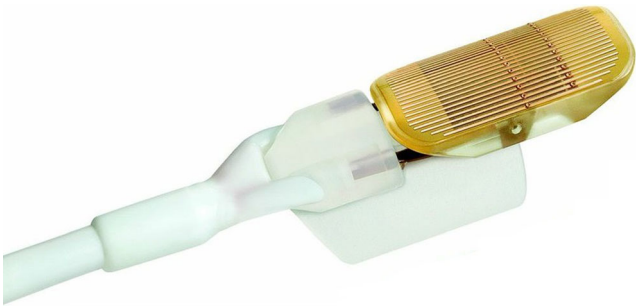

Fig. 2 RFA catheter used for ablation

through the anoscope and with gentle pressure, placed in contact with the mucosa. Three applications of energy were delivered in rapid succession at 12 J/cm^2/application. We ablated the entire ETZ in a non-overlapping, sequential fashion to cover the index lesions and adjacent normal tissue extending from 3 cm above the dentate line to the anal verge. We applied adequate pressure to open mucosal folds and achieve complete hemi-circumferential treatment. After three applications, the RFA catheter was removed and char collecting on its surface was wiped clean. The mucosa tended to blanche post treatment, and thicker lesions often sloughed (Fig. 3). Post-ablation, participants began fiber supplements, stool softeners, and sitz baths. Participants used ibuprofen or acetaminophen for pain with mild narcotics as needed.

Repeat HRA occurred at 3, 6, 9, and 12 months post-RFA, and HSIL-suspicious lesions were biopsied. Samples were also taken from normal-appearing quadrants that had been treated with RFA at the previous visit. Specimens were evaluated at local pathology labs. Recurrence could occur in two ways as previously described [18]. Persistent recurrence was a previously treated index lesion that recurred. Metachronous recurrence represented appearance of a new HSIL not identified at study initiation (Fig. 1c). Any HSIL identified within the ETZ at follow-up was retreated within 2–6 weeks by targeted RFA to the lesion and involved quadrant. Any HSIL outside the ETZ was treated with cautery, as previously described [19]. At 12 months, HRA was performed with biopsy of any lesions suspicious for HSIL and all normal-appearing quadrants.

Participants received diaries to self-record daily symptoms prior to and for 21 days after each RFA treatment. They reported anal pain on a visual scale ranging from 0 to 10 (0 = no pain; 10 = worst possible pain). Participants self-reported incontinence, defined as any feculent leakage, as mild (e.g., trace soiling of underwear), moderate (e.g., needing absorbent pad), or severe (e.g., needing adult diaper). Participants self-reported anal bleeding as mild (e.g., trace spotting in underwear), moderate (e.g., needing an absorbent pad), or severe (e.g., underwear or clothes ruined).

Pathology adjudication

All slides from index lesions and follow-up biopsies were sent for central pathology review at UCSF Department of Pathology (TD) after study completion. Diagnostic discrepancies were adjudicated by a third pathologist (AvZ). If a locally diagnosed HSIL was not confirmed by central pathology, the lesion was reclassified as non-HSIL.

Outcome measures

The primary endpoint was clearance of histological HSIL at 12 months defined as the percentage of participants and quadrants with no HSIL and the percentage of index lesions that cleared. Secondary outcomes included procedure tolerability assessed by post-RFA diary. Safety was evaluated by adverse events (AEs) reported throughout the trial. Efficacy calculations were based on the central pathology review. All RFA-treated participants were included in the safety analysis.

Statistics

Baseline and study outcomes were summarized by using descriptive statistics. Lesion-free survival was estimated by using the Kaplan-Meier method, and multivariate analysis on HSIL persistent recurrence was performed by using Cox's proportional hazard regression model. A p value <0.05 was considered statistically significant.

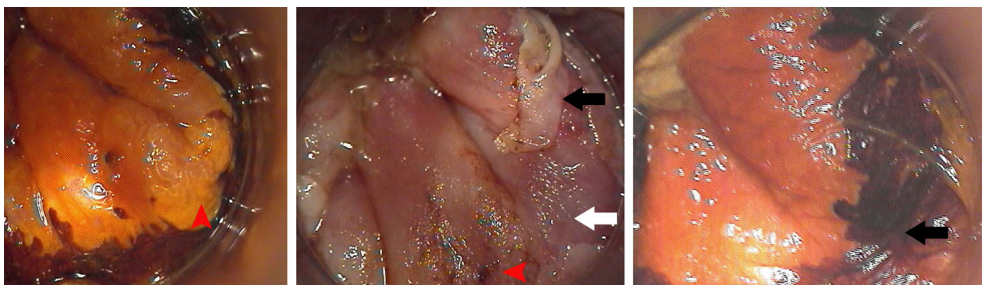

Fig. 3 RFA treatment of HSIL in a single patient. **a** Baseline image shows right anterior HSIL, negative for Lugol's staining, thick with mosaic pattern (*red arrowhead*). **b** Tissue immediately post-RFA with some coagulated vessels at the base (*red arrowhead*), minimal blanching (*white arrow*), and char lifting (*black arrow*). **c** Tissue at 12 months shows no sign of residual dysplasia (*arrow*) with excellent Lugol's uptake throughout and complete healing

Results

Participant demographics and procedure characteristics

Participant characteristics and flow are shown in Fig. 4 and Table 1. Twenty-five participants were screened for eligibility; 21 enrolled (including 3 women). One additional man initially enrolled was excluded from the efficacy but not safety analysis because HSIL was not confirmed on central pathology review. All participants completed the trial. Mean age was 45 (32–65) years, and BMI was 25 (19–32). At first RFA treatment, a mean of 1.7 HSILs (range 1–4) per participant were treated, with six (29 %) participants having HSIL in two quadrants. Mean duration of HRA and RFA procedures was 8 (5–13) and 4 (2–7) min, respectively.

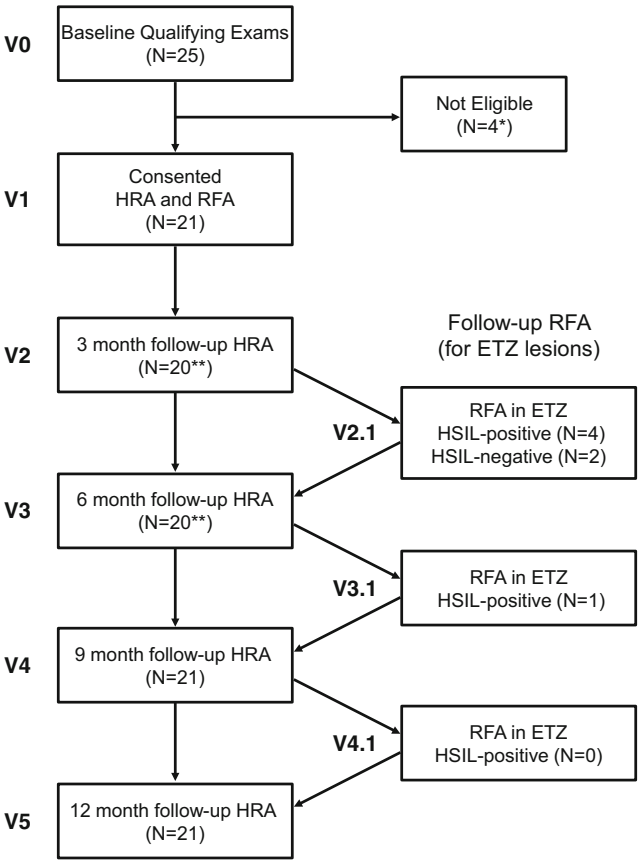

Fig. 4 Participant flow. The number of participants (*N*) is shown for each treatment visit and for each follow-up visit, excluding participants who missed the follow-up visit. *Asterisk* indicates that four participants were ineligible for the study: Three participants were screen failures, and one participant completed the trial but was found to have no biopsy-proven HSIL upon final pathology review and removed from efficacy analysis. *Double asterisk* indicates that one participant missed the 3 and 6 month follow-up appointments because he was undergoing drug rehabilitation out of state but returned at 9 and 12 months

Table 1 Participant demographics, baseline characteristics, and procedure characteristics

Parameter	Eligible participants enrolled (*N* = 21)
Age at consent	45 (32–65)
Gender	
Female	3 (14.3 %)
Male	18 (85.7 %)
BMI (kg/m^2)	25 (19–32)
Ethnicity	
Caucasian	17 (81.0 %)
Hispanic	2 (9.5 %)
African	1 (4.8 %)
Asian	1 (4.8 %)
Smoking (yes)	0
Initial HSIL lesions treated	
Total HSIL lesions treated with RFA	35
No. of HSIL lesions per participant	1.7 (1–4)
Participants with HSIL in contiguous quadrants	6 (29 %)
Procedure characteristics	
Duration of initial HRA (min)	8 (5–13)
Duration of initial RFA treatment (minu)	4 (2–7)

Data are expressed as *n*, *n* (%), or mean (range)

RFA efficacy

Participant follow-up assessments for persistent and metachronous HSIL appear in Table 2. Ten (48 %) total participants exhibited recurrent HSIL within the 1-year follow-up period: 3 (14 %) in the ETZ only, 3 (14 %) both inside and outside the ETZ, and 4 (19 %) outside the ETZ only. Four participants (19 %) had persistence of a single index lesion at 3 months post-initial RFA and were retreated with one lesion persisting a second time at 12 months. Three participants (14 %) developed metachronous lesions within the ETZ at 3, 6, and 12 months after initial treatment. Seven participants (33 %) developed metachronous HSIL outside of the ETZ (2 at 6 and 9 months and 3 at 12 months).

Kaplan-Meier-based predictions of lesion-free survival probability are shown in Fig. 5. Estimates for a participant being lesion-free within the ETZ at 3 months is 90.5 % (95 % CI [67.0–97.5 %]) and 76.2 % (95 % CI [51.9–89.3 %]) at 9 and 12 months.

The recurrence pattern suggested a treatment learning curve: Of the first 7 participants treated, 4 (57 %) had HSIL persistent or metachronous ETZ recurrence, while only 2 (14 %) of the remaining 14 participants had HSIL persistent or metachronous ETZ recurrence. Index lesion persistence in the first 7 and last 14 participants was 27 and 4 %, respectively. Kaplan-Meier-based predictions of lesion-free survival at

Table 2 Participant-level and lesion-level recurrences

	Participant and lesion assessments				
	3 Months	6 Months	9 Months	12 Months	Within 1 year
Participant recurrences					
Participants assessed	20[a]	20[a]	21	21	21
Participants with persistent or metachronous HSIL within ETZ	4 (20 %)	1 (5 %)	0 (0 %)	2 (10 %)[b]	6 (29 %)
Participants with persistent HSIL within ETZ	4 (20 %)	0 (0 %)	0 (0 %)	1 (5 %)[b]	4 (19 %)[b]
Participants with metachronous HSIL within ETZ	1 (5 %)	1 (5 %)[c]	0 (0 %)	1 (5 %)	3 (14 %)[d]
Participants with metachronous HSIL outside ETZ	0 (0 %)	2 (10 %)	2 (10 %)	3 (14 %)	7 (33 %)
Lesion recurrences					
Index HSIL assessed	34[a]	34[a]	35	35	
Index HSIL persistence	4 (12 %)	0	0	1 (2.9 %)[b]	

Data are expressed as *N* or *n* (%)

[a] One participant (with one index lesion) was unavailable to attend 3 and 6-month follow-up appointments but remained without persistent or metachronous HSIL at 9 and 12 months

[b] One participant had a single persistent HSIL that was retreated at 3 months but persisted again at 12 months

[c] One participant had two metachronous HSIL at 6 months

[d] One participant with metachronous HSIL at 3 months was also one of the four participants with persistent HSIL at 3 months

12 months for the first 7 and last 14 participants are 43 % (95 % CI [10–73 %]) and 93 % (95 % CI [59–99 %]) (p = 0.008 by log rank test) (Fig. 5). Early/late treatment groups did not demonstrate a statistically significant difference in metachronous recurrence outside the ETZ, indicating similar overall risk. There was no significant difference in demographics, extent of disease, or time for procedure between these two participant groups (data not shown).

Multivariate analysis (Table 3) showed that the last 14 participants had significantly less risk of recurrence than the first 7 (HR 0.02; 95 % CI 0.001–0.63). Increased BMI was associated with increased recurrence (HR 1.43, 95 % CI 1.01–2.01). Although each additional index HSIL increased recurrence risk, it was not statistically significant.

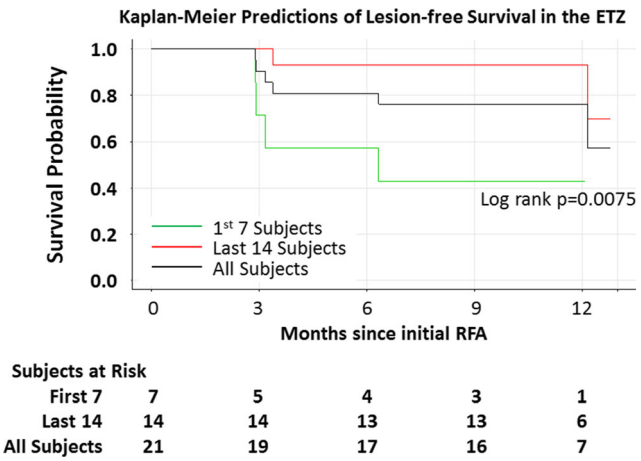

Fig. 5 Lesion-free survival following initial RFA. Kaplan-Meier curve of lesion-free survival for all participants (*black line*), the first 7 participants (*green line*), and the last 14 participants (*red line*)

Participant symptom diary of tolerability and pain

One participant failed to complete his diary post-initial RFA leaving 21 evaluable participant diaries (including the one participant treated but deemed ineligible for efficacy analysis after central pathology review). All except one experienced bleeding associated with defecation. Twelve (57 %) participants experienced anal bleeding without a bowel movement, mostly mild, for a median of 2 (0–16) days, with seven reporting moderate bleeding. One participant self-reported

Table 3 Multivariable analysis of risk factors for HSIL-free survival within the ETZ

Variable	Hazard ratio (95 % CI)	p value[a]
Last 14 participants (reference: first 7)	0.020 (0.001–0.626)	0.026*
Age	0.982 (0.841–1.147)	0.821
BMI	1.427 (1.014–2.007)	0.041*
Additional lesion	3.119 (0.686–14.182)	0.141

[a] p values are from multivariate Cox's proportional hazard regression model

*$p < 0.05$

severe bleeding associated with a bowel movement, but it resolved within a day without intervention. Median duration of moderate bleeding unassociated with defecation was 0 (0–10) days and 2 (0–12) days for mild bleeding. Two participants experienced moderate incontinence (4 and 7 days each), and two noted severe incontinence (1 day each). For one participant, severe incontinence lasted a single day (day 3) after which there was only trace soiling of underwear for 2 days (days 4 and 5 post-RFA). Median peak pain score was 3/10 (range 0–8) for the first 5 days post-RFA. Median pain resolved to less than 3 at 8 days post-RFA. Three participants reported a pain score ≥4 but ≤6 after day 15, but only one needed narcotics and took one dose of hydrocodone bitartrate and acetaminophen at day 17. Seven participants completed their diary again after subsequent focal lesion RFA, and only one participant experienced any bleeding (mild for 1 day), while two reported any incontinence (mild for 3 and 6 days each).

Adverse events

Four participants experienced seven AEs, and two participants had one serious AE (SAE) each (Table 4). Only two AEs were possibly device related. One participant experienced fever the night of the procedure. Another participant, who had healed well after RFA, developed granulation tissue at 9 months, and an anal pocket with a small amount of purulent discharge was identified at 12 months. On exploration, this area did not track and was successfully treated with silver nitrate. Although procedurally unrelated, one participant developed an anal fissure approximately 1 year after RFA, distal to the treatment area and related to anal sex. It healed without intervention. SAEs not attributed to the procedure were narcotic addiction related to an independent medical treatment and appendicitis. No participants developed anal stricture or required intervention for bleeding.

Table 4 Adverse events (AEs)

Variable	Participants enrolled ($N = 21$)	Device relationship?
Total AE (not including serious AE (SAE))	7	–
Anal fissure	1	No
Anal pocket with purulent discharge	1	Possible
Fever	1	Possible
Hypothyroidism	1	No
Knee tendon tear and meniscus tear	1	No
Low testosterone	1	No
Sleep apnea	1	No
Participants with at least one AE[a]	4 (19.0 %)	–
Total SAE	2	–
Narcotic pain medication addiction	1	No
Appendicitis	1	No
Participants with at least one SAE[a]	2 (9.5 %)	–

Data are expressed as *n* or *n* (%)

[a] Percentages are based on the number of participants in the full analysis set

Discussion

Although targeted ablation of anal HSIL most likely decreases progression to invasive anal SCC, recurrence is common and could be related to the fact that the majority of the oncogenic HPV-infected squamocolumnar transformation zone remains untreated [17–21, 36]. RFA represents a therapy that successfully treats diffuse mucosal dysplasia in Barrett's esophagus, with low incidence of complications, including stricture or perforation [23].

Our results demonstrate that RFA is an effective therapy for the management of anal HSIL. RFA appears to be as effective as targeted ablation at curing individual lesions. The individual lesion cure rate after one RFA treatment was 88 %. This result compares favorably with prior published results for individual lesion cure rates after targeted ablation ranging from 73 to 84 % [16]. It is interesting to note that of the four persistent HSIL lesions, all presented at 3-month follow-up, and only one recurred at 1 year. Thus, HSIL persistence is likely secondary to inadequate primary RFA treatment either because of insufficient depth or area of destruction. Based on gross visual appearance, we believe that the RFA does not ablate as deeply as electrocautery and could predispose to recurrence. The more limited depth of destruction, however, might result in less scarring and potential for stricture in circumferential ablation. While HRA is extremely helpful in identifying HSIL, the thickness of each lesion remains difficult to ascertain. Thus, thicker lesions may require multiple treatments for complete eradication. A second, more localized RFA to destroy residual HSIL improved individual lesion cure rate at 1 year to 97.1 % without stricture or undue side effects.

HRA is a challenging procedure, and HSIL identification improves with experience [37]. Even with extensive HRA experience, random biopsy during HRA was associated with increased detection of HSIL [38]. While targeted ablation only treats previously identified HSIL, large-field RFA potentially treats occult HSIL reducing recurrence over time. Moreover, during targeted ablation, non-condylomatous LSIL is typically not treated. Untreated LSIL could progress to HSIL causing additional recurrence. During large-field ablation, LSIL is also destroyed and could be another reason for reduction in recurrence. In this study, fewer participants developed metachronous HSIL within the ETZ than outside. Although

this difference does not reach statistical significance, likely secondary to small sample size, the data is encouraging and probably indicative of decreased overall recurrence through large-field ablation.

Large-field RFA could potentially eradicate a greater percentage of oncogenic HPV-infected cells than targeted ablation. Although in this study, participants only received hemi-circumferential ablation, the estimated 1-year lesion-free survival of 76.2 % within the treatment zone is superior to that of prior studies on targeted ablation that demonstrated HSIL-free survival rates of 50 to 74 % [17–21].

Like many new therapeutic interventions, our results strongly suggest a learning curve with improved results as experience grows. When compared to the first 7 participants, the last 14 demonstrated significantly decreased persistent and metachronous recurrence within the ETZ. The Kaplan-Meier prediction of nearly 93 % lesion-free survival at 1 year within the ETZ in the last 14 patients is far superior to what targeted ablation achieves [16–19].

This study also provides evidence that hemi-circumferential anal RFA is safe and well-tolerated. No participants developed a definite device or procedure-related SAE. As in the esophagus, all patients tolerated the procedure with sedation and local anesthetic. The median peak pain score of 3/10 throughout the first 5 days post-RFA indicates only mild pain among the majority of the participants. The majority did not experience significant post-operative bleeding, and among those who did, none required intervention other than stool softeners and fiber. Furthermore, no participants developed anal stenosis or failed to heal. While we identified one instance each of a fissure and small pocket developing, both occurred 9–12 months post-procedure, after complete healing had occurred.

When examining risk factors for recurrence, increased BMI significantly predicted recurrence. While there could be a biologic basis for this phenomenon, BMI could merely be an indication of difficulty optimizing the procedure in obese patients. Previous studies demonstrated that recurrence increases as a function of number of HSILs present at baseline [16]. Although each additional lesion increased risk of recurrence approximately threefold, this finding did not achieve significance. This could be related to small sample size and requiring limited disease for enrollment. A larger trial might answer whether increased number of lesions is a significant predictor of recurrence after RFA.

Our study has some limitations. First and foremost, our findings are limited by small sample size. We only had 21 evaluable participants which could impact generalizability of our findings. Additionally, participants in this study were all HIV-negative, a group known to have decreased HSIL recurrence and progression to anal SCC than HIV-positive populations [16, 19]. RFA will need to be studied on immunosuppressed patients to determine efficacy and safety in this higher risk population. This study only followed participants for 1 year post-RFA, and HIV-negative patients exhibit longer periods between treatment and recurrence after targeted ablation [18]. Our results, however, compare favorably with prior 1-year follow-up studies. Lastly, a prospective trial of RFA versus targeted ablation with a larger, multisite sample size is required to truly compare treatment outcomes.

Overall, this study demonstrates that hemi-circumferential RFA is well-tolerated, safe, and largely effective for management of anal dysplasia. Efficacy, however, may be impeded by only hemi-circumferential treatment and limited depth of ablation.

It is possible that circumferential RFA may provide superior disease-free survival through ablation of the majority of the squamocolumnar transformation zone. Circumferential RFA has been highly effective in the management of esophageal dysplasia and should be studied for treatment of anal dysplasia.

Conclusions

Hemi-circumferential RFA is an effective and safe treatment modality for the management of anal HSIL in HIV-negative patients. Future study of circumferential RFA is warranted.

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Author/coauthor contributions Author contributions include conception and study design (SEG, SRH, SD), study recruitment and data acquisition (SEG), study analysis and interpretation of the data (SEG, RNG, TMD, AvZ), drafting of the article (SEG, RNG), critical revision of the article for important intellectual content (SEG, RNG, SRH, SD, TMD, AvZ), and final approval of the article (SEG, RNG, SRH, SD, TMD, AvZ).

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of interest The study was sponsored and funded by Medtronic (Sunnyvale, CA). Medtronic provided medical writing assistance and statistical analysis support. SEG and TMD (or their institutions) received research support from Medtronic to conduct this trial. TMD has received supplies from Hologic. SRH and SD are employees and stockholders of Medtronic. SEG received consulting fees from Medtronic.

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