Diseases of the Colon & Rectum

Infrared Coagulator™: A Useful Tool for Treating Anal Squamous Intraepithelial Lesions

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PURPOSE: The incidence of invasive anal squamous carcinoma in men who have sex with men is rising, particularly in those with human immunodeficiency virus. As in the cervix the high-grade squamous intraepithelial lesion is thought to be an invasive squamous cell carcinoma precursor. Cervical high-grade squamous intraepithelial lesions are treated by removing the squamocolumnar transition zone. This is not possible in the anus, where treatment is often surgical and is accompanied by significant pain and morbidity. Better office-based techniques to treat anal high-grade squamous intraepithelial lesions are needed. We employed the infrared coagulator™ in an office setting to ablate high-grade squamous intraepithelial lesions. METHODS: A retrospective review of medical records was performed on 68 human immunodeficiency virus-positive men who have sex with men who underwent infrared coagulator™ ablation of biopsy-proven high-grade dysplasia from the time we began using the procedure in 1999. All patients have had at least six months of follow-up. Procedures were performed with local anesthesia on patients with discrete high-grade squamous intraepithelial lesions. Follow-up consisted of anal cytology with high-resolution anoscopy and biopsy of suspicious areas every three to six months. New or recurrent high-grade dysplasia was retreated. Patients with circumferential or bulky disease were treated in the operating room and were excluded from the study. RESULTS: Altogether, 68 patients met the enrollment criteria. The median patient age was 41 years (range 29–62 years). A total of 165 lesions were treated (mean 1.6 lesions, range 1–5) and only 46 (28 percent) persisted. However, 44 patients (65 percent) developed a new or persistent high-grade squamous intraepithelial lesion within a median time of 217 days (range 27–566 days) after infrared coagulation. The remaining 24 patients (35 percent) were free of high-grade dysplasia for a median of 413 days (range 162–1313 days) after infrared coagulation. When patients were treated a second or third time, the incidence of new or persistent high-grade dysplasia dropped to 58 percent and 40 percent, respectively. The probability of curing a retreated lesion was 72 percent. Using generalized estimating equations, the incidence of high-grade dysplasia decreased with repeated infrared coagulator™ treatments. No patient developed squamous-cell carcinoma, had a serious adverse event, or developed anal stenosis. CONCLUSIONS: The infrared coagulator™ is a safe, office-based modality for treating anal high-grade squamous intraepithelial lesion in human immunodeficiency virus-positive men who have sex with men. Successive treatments led to decreased recurrence rates. [Key words: Anal high-grade dysplasia; Anal cancer; Neoplasia; HIV; Homosexual; Men who have sex with men; Human papillomavirus]

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The incidence of invasive anal squamous cell carcinoma (SCC) is rising among men who have sex with men (MSM) to the point where it now approximates the rates of cervical cancer found in women before routine use of the cervical papanicolaou (Pap) smear as a screening tool.[1,2] Human immunodeficiency virus (HIV)-positive MSM experience a twofold increased risk of developing SCC compared to their HIV-negative counterparts.[3,4] Cress and Holley recently reported on the striking rise in anal cancer among men in California. Although they did not report the data based on sexual orientation, they showed that in San Francisco the rise in anal cancer

was particularly dramatic in all men ages 40 to 64, among whom rates increased from 3.7 cases per 100,000 during 1973 to 1978, to 8.6 cases per 100,000 during 1984 to 1990, to 20.6 cases per 100,000 during 1996 to 1999. The authors concluded that although the rise in anal cancer rates in San Francisco men predated the acquired immunodeficiency syndrome (AIDS) epidemic, the introduction of highly active antiretroviral therapy (HAART) with longer survival of patients allowed more frequent progression to SCC and the dramatic increased prevalence seen during the late 1990s. Before HAART, most of these men would have died from AIDS before developing anal cancer.[5]

Intraepithelial neoplasia in the anus, as it is in the cervix, is thought to be the precursor to SCC and is more common in MSM than in the average population.[6,7] These men experience an increased incidence due to associated HIV infection, advancing immunosuppression (associated with a declining CD4 count), the presence of high-risk oncogenic human papillomavirus (HPV) infection, and epidemiologic factors such as smoking and alcohol consumption.[8,9] HPV is closely associated with the development of both cervical (CIN) and anal (AIN) intraepithelial neoplasia and invasive cancer.[10,11] Although cervical dysplasia and the malignant potential of CIN have been well described, the temporal relation between the development of HPV infection, AIN, and anal cancer has not been definitively proven. Given the increasingly evident similarities between AIN and CIN, the anatomic similarities between the cervix and anus, and the role of HPV infection in these two diseases states, one can conclude that anal carcinoma evolves in a manner similar to its cervical cancer counterpart, with worsening dysplasia progressing to invasive carcinoma. Moreover, eradication of dysplasia leads to a decreased incidence of invasive cancer.[12,13] It does not appear that introduction of HAART in HIV-positive MSM has led to regression of AIN, once present, or clearance of anal HPV infection.[14,15]

The hallmark of CIN treatment has been removal of some or all of the cervical squamocolumnar transition zone, local destruction of lesions, or both. Procedures such as the loop electrosurgical excision procedure (LEEP), cone biopsy, surgical excision, and ablation are frequently used to destroy CIN and prevent recurrence or progression to cancer.[16] Although the histopathology of the anus is similar to that of the cervix, physicians are restricted to locally ablative procedures and surgery to eliminate AIN and prevent progression to SCC. The squamous columnar transition zone between the anus and rectum is a common site for AIN and cannot be removed.[17] Chang *et al.* presented the only published series analyzing the success of treating AIN and preventing recurrence. They utilized electrocautery to ablate high-grade squamous intraepithelial lesions (HSILs), but the procedures were performed in an operating room with anesthesia.[18]

Figure 1. Infrared Coagulator™ (IRC2100; Redfield Corporation, Rochelle Park, NJ).

We explored the use of the Infrared Coagulator™ (IRC 2100; Redfield Corporation, Rochelle Park, NJ) as an alternative surgical modality for the in-office treatment of AIN (Fig. 1). Infrared photocoagulation (IRC) is an appealing treatment modality because it can be performed in an outpatient clinical setting with local anesthesia. It provides excellent hemostasis without the vapor plume found with laser surgery or electrocautery. The device uses a beam of far-infrared light delivered through a light guide covered with a disposable plastic sheath to ablate tissue and coagulate blood in the immediate surface area in contact with the tip. The IRC beam can be pulsed at 0.5- to 3.0-second intervals, thereby preventing trauma to deeper tissues. The depth of tissue coagulation (in millimeters) is roughly equal to the length of the pulse applied. Thus a one-second pulse penetrates the tissue to a depth of approximately 1 mm. Pulse duration longer than three seconds produces char with burning of surrounding tissue.[19,20]

Infrared coagulation therapy has been used successfully to treat a variety of lesions, including internal hemorrhoids, condylomas, and benign cervical disease.[20–23] To date, there are no published reports on the efficacy of IRC for the treatment of AIN. In this

study, we describe both the technique for, and the results of, IRC treatment of intra-anal HSIL in HIV-positive MSM.

MATERIALS AND METHODS

A retrospective review of medical records was performed on HIV-positive MSM who had undergone IRC ablation of biopsy-proven intra-anal HSILs from the time we instituted the procedure in 1999. To be eligible for inclusion in this series, patients had to have had at least six months of postprocedure follow-up. All patients had a thorough history and physical examination including digital rectal examination, standard anoscopy, and anal cytology utilizing standard techniques.[17] Patients provided a verbal report of their most recent CD4 cell count, but new laboratory values were not obtained. Patients with abnormal cytology (atypia of squamous cells of undetermined significance (ASCUS), low-grade squamous intraepithelial lesion (LSIL), or HSIL or visible lesions on standard anoscopy underwent high-resolution anoscopy (HRA) in accordance with the technique described by Jay *et al.*[24] Lesions suspicious for HSIL were biopsied and photographed. It is not proper to assume that a lesion with visual characteristics of HSIL is indeed HSIL. Squamous metaplasia often appears similar to HSIL on HRA and is a nonpathologic condition not requiring ablation. Biopsy specimens were immediately fixed in 10 percent formalin and sent to Quest Diagnostic Laboratories (Teterboro, NJ) for routine histopathologic examination, and the diagnosis was reported in accordance with the Bethesda system.[25] Only subjects who had biopsy-proven HSIL and no evidence of microscopic invasion or history of anal cancer were eligible for inclusion.

Figures 2 through 5 are photographs of an HSIL lesion viewed through a clear anoscope under magnification during HRA and treatment with IRC. Office-based IRC ablation was performed only on lesions where pathologic confirmation of HSIL had been achieved and prevented unnecessary treatment of non-high-grade lesions that had the HRA appearance of being neoplastic. Patients returned to the office without any bowel preparation. They were placed in the knee-chest position on a standard sigmoidoscopy table. HRA was again performed, and high-grade lesions were reidentified with the aid of previously obtained photographs and written descriptors of lesion location (Fig. 2). Although most lesions were above the dentate line, local anesthesia was required to prevent pain from distal diffusion of heat from the IRC. Local anesthesia was achieved with 1 percent lidocaine with epinephrine in a 1-cc syringe and 30-gauge needle passed down the barrel of the anoscope. Anesthetic was first instilled above the dentate line in

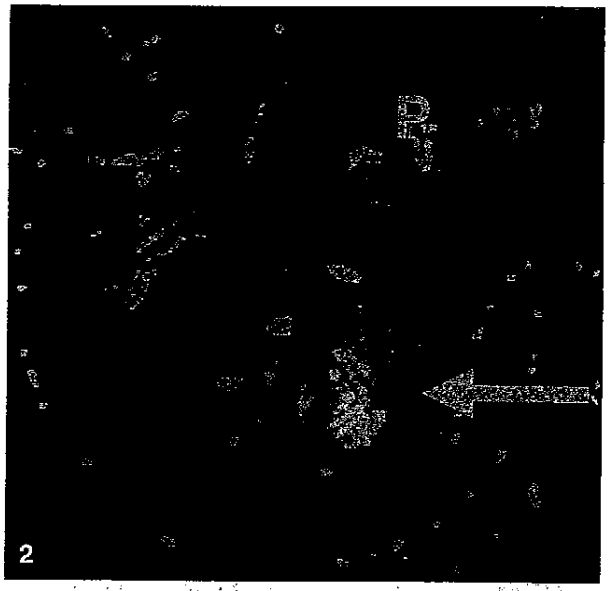


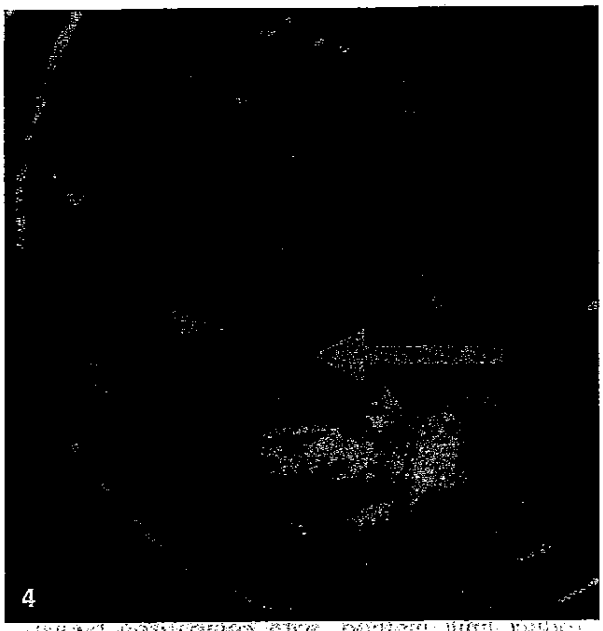
Figure 2. Note the well circumscribed high-grade lesion (arrow) that appears mustard-colored after Lugol's staining of the surrounding squamous epithelium turns normal tissue and low-grade squamous intraepithelial lesions (LSILs) black. P = hypertrophic papilla.

Figure 3. Blunt dissection was used to separate the eschar after successful desiccation of the high-grade intraepithelial lesion (HSIL) (arrow). The base can then be débrided with sharp dissection to ensure destruction of the full thickness of the lesion.

what was often a pain-free injection. After waiting one minute, a more distal injection below the dentate line could occur with minimal discomfort. We utilized as little anesthetic as possible (often far less than 1 ml per lesion) to prevent distortion of landmarks and architecture. After achieving adequate anesthesia, the IRC light guide was applied to the lesion with gentle pressure and fired in 1.5-second pulses. Successful coagulation was marked by tissue blanching as desiccation occurred. The light guide was then repositioned over another portion of the lesion, and we fired the IRC again. We repeated this procedure until the entire lesion had been treated. We utilized the end of the anoscope or a cotton swab to débride the eschar bluntly (Fig. 3). A baby Tischler biopsy forceps proved optimal for sharp débridement of eschar that did not separate easily. To ensure complete destruction of lesions, retreatment with the IRC and débridement of eschar was repeated until we reached a depth of the submucosal vessels. These vessels were readily apparent, bulging into the wound as tissue was removed layer by layer (Fig. 4). We coagulated these vessels with the IRC before terminating the procedure (Fig. 5). All areas of HSIL were treated in a single session. No patients received intravenous anesthesia, and antibiotics were prescribed only for patients at risk for endocarditis.

Patients were discharged from the office back to work or home. They were instructed to take over-the-counter analgesics or a prescription-strength mild narcotic if necessary. Patients were advised to expect minor bleeding for one to two weeks as healing occurred and were told to contact the office should severe pain, bleeding, or signs of infection develop.

Follow-up evaluation occurred three months posttreatment unless a palpable lesion developed sooner. At three months patients typically underwent repeat examination including digital rectal and standard anoscopy. If a lesion was visualized, they were referred for HRA. If no lesion was identified grossly, patients were to return six months posttreatment for a similar examination, but this time anal cytology would also be performed. If the cytology was benign and no visible lesions were present, the patient would be scored at that point as being without HSIL. If the cytology revealed any abnormality or if a visible lesion was identified, however, the patient would undergo HRA with biopsy of suspicious areas. We also biopsied the site(s) of prior HSIL to ensure that the lesion was gone. If patients had a negative biopsy (normal, squamous metaplasia, or LSIL) and if the pap smear did not show high-grade dysplasia, the patient was scored as not having HSIL at that time. If the biopsy or pap smear identified HSIL, however, the patient was classified as having recurrent HSIL. We divided the category of "recurrence" into two subgroups. If the HSIL was present at the same site as the prior treat-



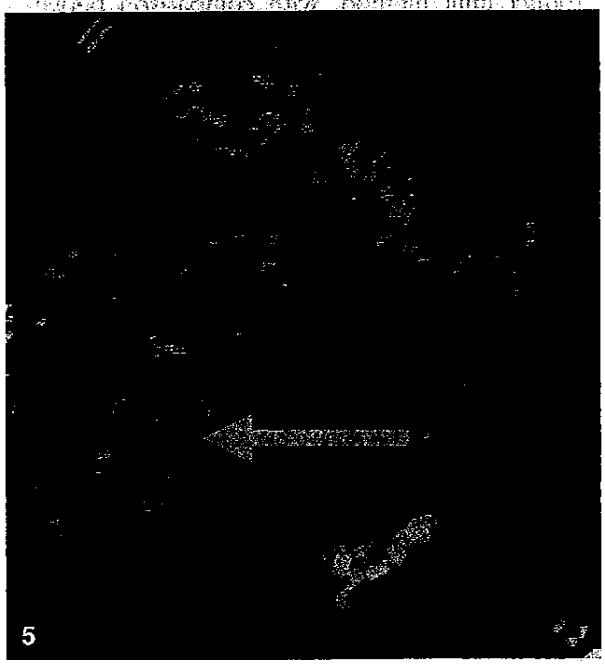


Figure 4. A bulging vein (arrow) is visible after the lesion has been systematically coagulated and débrided to a depth of the submucosal vessels.

Figure 5. The coagulated submucosal vessel with a dark thrombus is visible (arrow). The lesion has been successfully ablated through its entire thickness.

ment area, we viewed it as a persistent lesion. If a new area that had not been previously treated with IRC showed HSIL, the lesion was classified as metachronous.

New or persistent HSILs were retreated with IRC ablation, and these areas were followed for recurrence as well. If at follow-up no HSIL was seen or the patient had a benign pap smear, the patient returned at three- to six-month intervals for examination and anal cytology with HRA as indicated in the algorithm previously described by Goldstone et al.[17] Patients with circumferential or bulky disease were treated in an operating room and excluded from this analysis.

Statistical analyses were performed with SAS software (SAS Institute, Cary, NC). Chi-squared ($\chi 2$) tests were used to compare proportions and Student's *t*-tests to compare means, as appropriate. Probabilities of recurrence were computed using the Kaplan-Meier product limit method, with comparison between groups evaluated by the Wilcoxon test statistics. Cox regression was used to compute risk ratios (equivalent of odds ratios) and confidence intervals and to determine significance after adjusting for other covariates.

In addition, a statistical method known as general estimating equations (GEE) was used to assess whether the number of internal HSILs diagnosed per visit diminished over time following IRC treatments. Because the number of lesions for each patient at any one visit is correlated with the number of lesions for the same patient at another visit, GEE, a statistical method that accommodates correlated count data, was used. A compound symmetrical covariance structure was assumed, and the data were assumed to follow a Poisson distribution.

RESULTS

Sixty-eight patients met enrollment criteria. The median patient age was 41 years (range, 29–62 years). A total of 165 primary lesions were treated in these 68 MSM over the course of the follow-up period after IRC, which was as long as 1313 days but not less than 162 days. The maximum number of visits per patient was eight, and the minimum was two. Average number of lesions treated with IRC at any given visit was 1.03 (range, 1–5). The first treatment visit averaged 1.56 treated lesions (range 1–5) (Table 1). The median time from HSIL diagnosis (date of biopsy) to IRC treatment was 22 days (range 4–380 days). Altogether, 90 percent of subjects underwent IRC treatment within 57 days of their initial HSIL biopsy; 36 patients underwent a second IRC ablation for persistent or metachronous HSIL (or both), and 15 patients underwent a third treatment. No patient underwent more than three IRC treatments. Not all patients who developed HSIL after their first treatment consented to further therapy.

Table 1.
High-Grade Lesions Present in Subjects at their First IRC Treatment

Lesion	No. of Subjects
1 HSIL	1
2 HSIL	40
3 HSIL	20
4 HSIL	7
5 HSIL	0

IRC = infrared coagulation; HSIL = high-grade squamous intraepithelial lesion.

Table 2 illustrates the recurrence rates for HSIL in patients after each treatment and includes those with persistence of treated lesion(s) as well as those with metachronous lesions. If multiple lesions were treated and one or more persisted, or if one or more metachronous lesions developed, the patient was scored as having a recurrence. Following the initial treatment (visit 1), persistent or metachronous HSIL developed in 44 of the 68 subjects (65 percent) within a median time of 203 days posttreatment (range, 27–566 days). The remaining 24 subjects (35 percent) never developed HSIL again during the trial period for a median of 413 days (range of 162–1313 days). Although 44 patients developed HSIL after their first IRC treatment, only 36 underwent a second treatment. Of these subjects, 21 (58 percent) redeveloped HSIL with a median time to recurrence of 217 days (range, 56–924 days), and 15 (42 percent) were disease-free for a median of 594 days (range, 292–903 days). Although only 15 patients underwent a third IRC treatment for HSIL, 6 (40 percent) redeveloped HSIL within a median of 91 days (range, 54–224 days), whereas 9 (60 percent) did not redevelop a lesion within a median 645 days (range, 392–1155 days). The difference between time to recurrence and time without recurrence for each IRC treatment was highly significant ($P < 0.0001$). The difference between patients who redeveloped HSIL and those who did not with respect to age and baseline CD4 cell count was not statistically significant.

Table 3 examines the incidence of metachronous lesions developing in patients who had undergone IRC for primary HSIL. After their first IRC ablation of

Table 2.
Recurrence Rates*

HIV-Positive Patients	HSIL (no.)	No HSIL (no.)	*P** (for Difference between HSIL and No HSIL); Mean Difference ± SE	Total No.
After 1st IRC treatment				
No. of patients	44 (65%)	24 (35%)	$p = 0.0153$	68 (100%)
Days after IRC†				
Mean	246.5	474.4	−227.94 ± 53.7; $p < 0.0001$	326.9
Median	202.5	413	n/a	228.50
Range	27–566	162–1313	n/a	27–1313
Age at diagnosis				
Mean	41.4	42.2	−0.89 ± 1.8; $p = 0.6261$	41.7
Median	40.9	41.6	n/a	40.9
Range	28.8–62.2	29.1–59.9	n/a	28.8–62.2
T-cell count at baseline				
Mean	402.2	377.5	24.71 ± 62.9; $p = 0.6956$	393.7 (n = 64)
Median	390.5 (n = 42)	358 (n = 22)	n/a	380.5 (n = 64)
Range	8–1200 (n = 42)	70–800 (n = 42)	n/a	8–1200 (n = 64)
After 2nd IRC treatment				
No. of patients	21 (58%)	15 (42%)	$p = 0.3173$	36‡ (100%)
Days after IRC†				
Mean	254	627	−373.00 ± 65.2; $p < 0.0001$	409.4
Median	217	594	n/a	318.5
Range	56–924	292–903	n/a	56–924
Age at diagnosis				
Mean	43.0	39.9	3.11 ± 2.5; $p = 0.2280$	41.7
Median	42.4	38.6	n/a	41.2
Range	29.6–62.9	28.8–50.9	n/a	28.8–62.9
T-cell count at baseline				
Mean	358.2	459.8	−101.6 ± 92.1; $p = 0.2777$	400.6
Median	300	497	n/a	356
Range	8–1200	40–800	n/a	8–1200
After 3rd IRC treatment				
No. of patients	6 (40%)	9 (60%)	0.4386	15§ (100%)
Days after IRC†				
Mean	105.8	738.8	−632.9 ± 109.3; $p < 0.0001$	485.6
Median	90.5	645	n/a	483
Range	54–224	392–1155	n/a	54–1155
Age at diagnosis				
Mean	42.2	40.0	2.14 ± 3.5; $p = 0.5517$	40.9
Median	42.8	38.9	n/a	42.0
Range	30.0–51.9	32.7–50.9	n/a	30–52
T-cell count at baseline				
Mean	498.5	306.9	191.6 ± 176.8; $p = 0.2982$	383.5
Median	450	298	n/a	300
Range	44–1200	8–914	n/a	8–1200

IRC = infrared coagulation; HSIL = high-grade squamous intraepithelial lesion; SE = standard error.

*A patient is counted as having a recurrence if there is a diagnosis of internal HSIL following IRC, whether it is in the same location (persistent lesion) or a new location (metachronous lesion).

†For those who relapsed, this is the number of days from IRC to the time of new HSIL(s); and for those who did not relapse, it is the follow-up time in days.

‡Of the 44 patients, 4 had their first relapse on their last visit and thus could not be followed up for relapse; 4 of the 44 never received their second course of IRC.

§Five of the 21 patients, 5 had their second relapse on their last visit; 1 of the 21 patients never received the third course of IRC.

HSIL, 40 patients (59 percent) developed a metachronous lesion(s), and 28 (41 percent) did not. The median time for development of this new HSIL was 217 days (range, 27–636 days), whereas the median follow-up in those who did not develop metachronous HSIL was 413 days (range, 162–1313 days; $P = 0.0003$).

Table 3.
Metachronous Lesions*

HIV-Positive Patients	HSIL (no.)	No HSIL (no.)	*P* (for Difference between HSIL and No HSIL); Mean Difference ± SE	Total No.
After 1st IRC treatment				
No. of patients	40 (59%)	28 (41%)	0.1456	68 (100%)
Days after IRC†				
Mean	259.9	464.0	−204.1 ± 53.7; $p = 0.0003$	344.0
Median	216.5	413	n/a	251.5
Range	27–636	162–1313	n/a	27–1313
Age at diagnosis				
Mean	41.6	41.8	−0.13 ± 1.8; $p = 0.9402$	41.7
Median	41.2	40.5	n/a	40.9
Range	28.8–62.2	29.1–59.9	n/a	28.8–62.2
T-cell count at baseline				
Mean	385.7 (n = 25)	406.2 (n = 39)	−20.5 ± 61.2; $p = 0.7391$	393.7 (n = 64)
Median	380 (n = 25)	395 (n = 39)	n/a	380.5 (n = 64)
Range	8–1200 (n = 25)	70–800 (n = 39)	n/a	8–1200 (n = 64)
After 2nd IRC treatment				
No. of patients	15 (45%)	18 (55%)	0.6015	33‡ (100%)
Days after IRC†				
Mean	221.9	331	−109.13 ± 55.5; $p = 0.0581$	281.4
Median	203	335	n/a	279
Range	56–667	64–607	n/a	56–667
Age at diagnosis				
Mean	41.9	42.0	−0.15 ± 2.8; $p = 0.9582$	42.0
Median	42.7	40.9	n/a	42.4
Range	30.0–59.3]	28.8–62.2	n/a	28.8–62.2
T-cell count at baseline				
Mean	378.7	388.3	−9.7 ± 96.7; $p = 0.9210$	383.9
Median	300	402	n/a	350
Range	39–1200	8–700	n/a	8–1200
After 3rd IRC treatment				
No. of patients	3 (30%)	7 (70%)	0.2059	10¶ (100%)
Days after IRC†				
Mean	287	258.4	28.6 ± 123.5; $p = 0.8228$	267
Median	184	265	n/a	224.5
Range	62–615	91–409	n/a	62–615
Age at diagnosis				
Mean	46.8	36.5	10.3 ± 3.3; $p = 0.0137$	39.6
Median	45.0	36.4	n/a	39.6
Range	43.0–52.5	30.0–43.3	n/a	30.5–52.5
T-cell count at baseline				
Mean	230.3	502.7	−272.4 ± 262.3; $p = 0.3295$	421
Median	247	350	n/a	325
Range	44–400	50–1200	n/a	44–1200

IRC = infrared coagulation; HSIL = high-grade squamous intraepithelial lesion; SE = standard error.

*Development of a metachronous HSIL lesion occurs when an individual is diagnosed with at least one internal HSIL lesion after prior treatment with IRC; the lesion must occur in a different/new location to qualify as metachronous.

†For those who relapsed, this is the number of days from IRC to the time to new HSIL(s); and for those who did not relapse, it is the follow-up time in days.

‡Of the 40 patients who had a metachronous lesion, 7 never received their second course of IRC.

¶Four of the 15 patients had their second relapse on their last visit. of the 15 patients, 1 never received his third course of IRC.

Among the 33 subjects with metachronous lesions who were treated a second time with IRC, the incidence of another metachronous HSIL was 45 percent within a median of 203 days (range, 56–667 days). Ten subjects with metachronous lesions were treated a third time with IRC; and although the numbers are small, 30 percent developed another metachronous lesion.

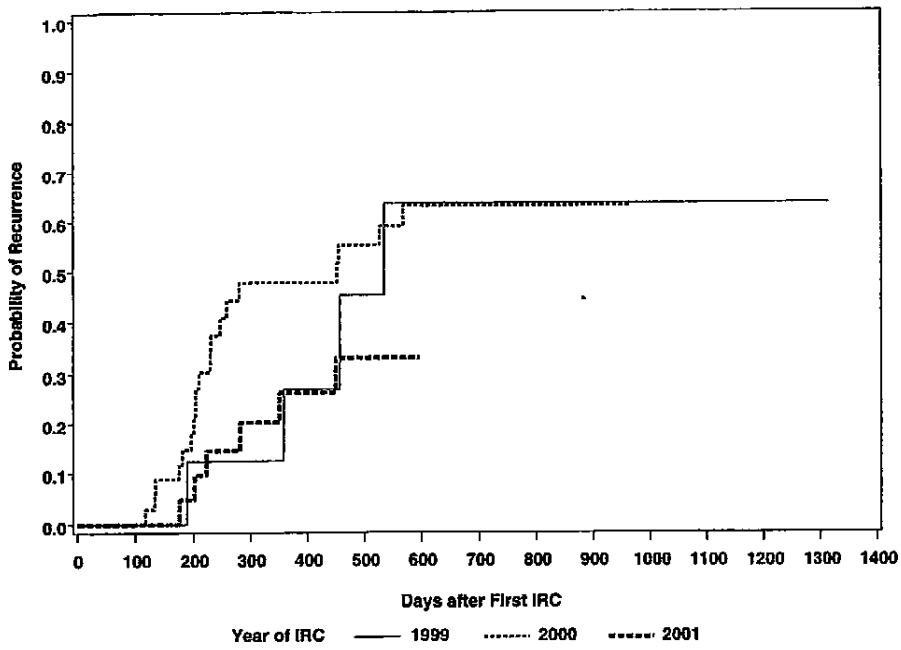


Figure 6. Recurrence rates after first infrared coagulation (IRC) treatment as a function of the years 1999, 2000, and 2001.

Because many patients in this series had multiple areas of dysplasia, it is important to examine the success rates for ablating individual high-grade lesions with IRC. During the course of the follow-up period, 165 individual lesions were treated a first time in these 68 patients, and 29 patients (43 percent) demonstrated persistence of at least one of these areas. When analyzing ablation success for each treated HSIL by itself, we found that 46 lesions (28 percent) persisted during the follow-up period. Thus the probability of destroying an individual HSIL lesion with its first IRC treatment was 72 percent. Of the 46 HSIL lesions that persisted after the first attempt at ablation with IRC, 39 were treated a second time and 11 recurred (28 percent). Thus the probability of successfully ablating a recurrent high-grade lesion with a second IRC treatment was again 72 percent.

Figure 6 represents the Kaplan-Meier estimated recurrence curves of HSIL for subjects after the first IRC treatment for each of the three years during the study period. Although it appears that those patients treated in 2001 have a consistently lower probability of recurrence after 180 days than those treated in 2000, the difference is not statistically significant ($P = 0.1509$). Similarly, the estimated curves representing the probability for developing metachronous lesions after their first IRC exposure was consistently lower for patients treated in 2001 and 2000 than for those treated in 1999; however, the difference was not statistically significant ($P = 0.2597$; data not shown).

Figure 7 represents the Kaplan-Meier estimated recurrence curves of HSIL for subjects after their first IRC treatment stratified by the number of lesions treated. The difference between the curves is significant (Wilcoxon, $P = 0.0078$) and shows that the probability of recurrence among patients with two or more lesions is consistently higher than in patients who had only one lesion treated after 200 days.

In Table 4 we used Cox's regression to estimate the risk for recurrence of HSIL following IRC while adjusting for the covariates CD4 cell count, age, and treatment year. We found that the risk for recurrence after the first IRC for patients with a CD4 cell count less than 200 was 1.3 times the risk for patients with a CD4 cell count of 200 or more; however, the risk ratio was not significantly different from 1 ($P = 0.5753$). The risk for recurrence after the first IRC for patients over 30 years of age was 1.4 times the risk for those under 30 years; but again the risk ratio was not significantly different from 1 ($P = 0.7575$). The risk for recurrence after the first IRC exposure for patients who underwent their first IRC in 2002 or 2001 was 39 percent of the risk for patients who underwent their IRC in 2000 or 1999, and the difference was of borderline significance ($P = 0.0606$).

Finally, using generalized estimating equations, the

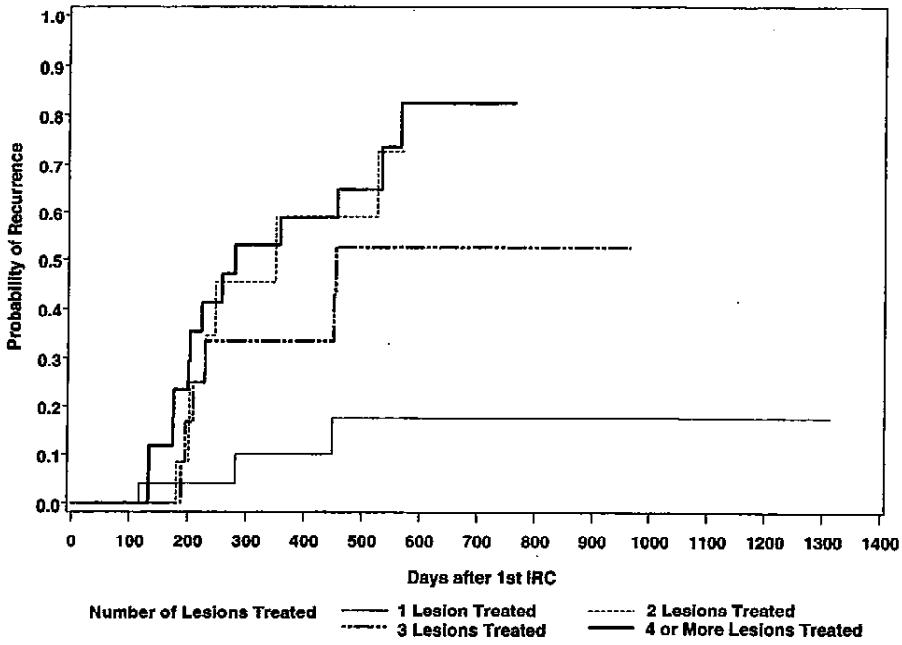


Figure 7. Recurrence rates after the first infrared coagulation (IRC) treatment as a function of the number of lesions treated.

Table 4.
Cox Regression for Recurrence After First IRC (Adjustment for Covariates of Age, CD4 Count, and Year of Treatment)

IRC Treatment and Prognostic Factors	Crude Risk Ratio (95% CI)	Adjusted Risk Ratio (95% CI)
CD4 cell count: <200 *vs.* 200 cells/mm	1.435 (0.607, 3.388); $P = 0.4106$	1.281 (0.539, 3.048); $P = 0.5753$
Age: 30 *vs.* <30 years	1.610 (0.218, 11.906); $P = 0.6410$	1.373 (0.183, 10.291); $P = 0.7575$
IRC year: 2002 and 2001 *vs.* 2000 and 1999	0.422 (0.171, 1.037); $P = 0.060$	0.394 (0.149, 1.042); $P = 0.0606$*

IRC = infrared coagulation; CI = confidence interval.

incidence of HSIL was shown to decrease consistently with repeated IRC treatments ($P < 0.0001$).

Patient records were also analyzed for significant postprocedure complications. After treatment, no patient developed severe bleeding, experienced pain that could not be controlled with oral analgesics, had an anal stricture, or developed infection that required antibiotic therapy. No patient who desired to resume anal sex was prevented from doing so after recovery. No patient developed SCC during the follow-up period.

DISCUSSION

The recent increased incidence of SCC of the anus, especially among HIV-positive MSM needs to be addressed. Although no definitive progression of HSIL to anal SCC has been proven, the wealth of accumulating evidence seems to support this conclusion. Moreover, surgeons have long supported the prophylactic removal of Bowen's lesions to prevent SCC, and this lesion is histologically identical to HSILs found elsewhere in the anal canal.[26,27] If we apply what we have learned from the cervical cancer model to the anal canal, it follows that removal of high-grade intraepithelial neoplasia can prevent progression to cancer. To date, however, only one series has reported on the treatment of anal HSIL; these surgeons utilized electrocautery in an intraoperative setting to ablate the lesions. We present the first report of a new technique for treating HSILs in the anal canal utilizing IRC in an office setting with only local anesthesia.

Our results document that IRC treatment of biopsy-proven HSIL under local anesthesia is a safe, effective office procedure. None of the 68 treated patients developed a serious complication. We were able to treat multiple lesions during a single session. After IRC, however, patients were at risk for both persistence of

HSIL at treatment sites and developing new lesions elsewhere in the anal canal. In our series, HSIL was diagnosed after treatment in 65 percent of patients; the other 35 percent remained disease-free for as long as almost 3 years. Although on the surface the fact that only 35 percent of patients were disease-free may seem discouraging, it must be evaluated in light of several factors. Most patients had multiple lesions treated and were scored as having persistent disease if even one lesion persisted. Moreover, because we could not remove the squamocolumnar transition zone, patients were at risk for developing new lesions during the follow-up period. These two factors combined to make the overall response rate for each patient seem low (35 percent). However, we demonstrated a per-individual lesion ablation success rate of 72 percent, which we believe is an excellent response given the fact that all patients were, by diagnosis, immunosuppressed.

Our data also compare quite favorably with those of Chang *et al.*, who utilized electrocautcry ablation of HSILs in an operating room setting and reported a 79 percent recurrence rate in a much smaller series over similar follow-up periods. That study also demonstrated that almost one-half of all subjects complained of uncontrolled postoperative pain lasting a mean of 2.9 weeks.[18] Given the similarity in recurrence rates between these two series, it does not appear that the more extensive intraoperative ablation of HSILs with electrocautery is warranted if the disease can be ablated in the office with IRC. Although we did not specifically measure postprocedure pain, it is our experience that the level of discomfort after IRC was far less than what is typically reported after an operative procedure.

If we accept the cervical cancer model as a corollary for anal cancer, it is important to compare the effectiveness of IRC ablation of AIN with standard treatment methods for CIN. Although removal of the squamocolumnar transition zone or targeted ablation of CIN in the cervix produces excellent control of disease in HIV-negative women, the results have not been nearly as good in HIV-positive women with multiple series reporting recurrence rates of 62 to 73 percent.[16,28,29] Our recurrence rate of 65 percent compares favorably with the data in these series. Moreover, most women in these series underwent complete excision of the transition zone, whereas our patients underwent ablation of only individual lesions. Tate and Anderson showed that among HIV-positive women who had local ablation of cervical lesions with either a laser or cryotherapy, recurrence rates were 83 and 100 percent, respectively.[16] Fruchter *et al.* found that among HIV-positive women treated a second or third time for recurrent CIN the recurrence rate remained at 50 percent.[28] In our series, the recurrence rates in HIV-positive MSM treated a second and third time were 58 percent and 40 percent, respectively. Although the numbers in each series are small, they appear to compare favorably. It therefore appears that our results after IRC ablation of anal HSILs in HIV-positive MSM are comparable to, if not better than, the results achieved when treating CIN in HIV-positive women using standard therapy.

It is also clear from our results that with time patients are likely to develop new areas of HSIL. These metachronous lesions were seen in 59 percent of patients following their first treatment, in 45 percent of patients following a second treatment, and in only 30 percent of patients after a third IRC treatment. We also showed that successful ablation of individual lesions was 72 percent after the first IRC treatment. Persistent lesions that were treated a second time again produced a 72 percent ablation success rate. Although recurrent HSIL is frustrating to both physicians and patients, our findings coupled with the results from the GEE analysis that showed a decreased incidence of HSIL with repeated IRC treatments are cause for hope. Our data predict that periodic follow-up on a three- to six-month basis and IRC ablation of new or persistent HSILs should lead to a decreased incidence of disease over time. It also stands to reason that if, with time, fewer lesions persist or develop,the subsequent IRC treatments can be less extensive and hopefully even better tolerated. Further analysis of disease-free survival over longer periods of time will help predict whether follow-up intervals can be safely extended as patients remain disease-free.

Our data clearly show that patients with multiple high-grade lesions have higher recurrence rates than those with just one lesion. Although the cause remains to be determined, there are several possible explanations. Those with multiple lesions could be infected with more aggressive HPV types; they could have poorer immune responses to the HPV and dysplasia, allowing progression; or the infection could merely be longer-standing and more difficult to treat. These factors could work alone or in synergy to make eradication more difficult. There could also be other factors at play that we have yet to elucidate. Although our data seem to suggest an increased risk of recur-

rence rates in patients with CD4 counts of less than 200 and age over 30 years, the ratios were not significantly different than 1. Moreover, the CD4 counts were reported by patients and not confirmed, nor were they rechecked over the course of the follow-up period. Furthermore, larger studies may help determine whether these variables play a significant role in treatment outcome.

Clinicians have employed many modalities to ablate HPV-related disease in the office setting, including electrocautery and the use of trichloroacetic acid, imiquimod, and liquid nitrogen.[30-32] To date, no series has published results utilizing these methods specifically for the treatment of HSIL in the office setting. Although there is no reason to suspect that these methods would be inferior to IRC ablation, it is our opinion that IRC may provide several advantages over alternative treatments. Both cryotherapy and chemical topical ablative therapy can destroy dysplasia, but the depth of tissue destruction cannot be accessed at the time of treatment. Patients must return for frequent follow-up with repeat HRA to determine if the lesion has been completely destroyed. Moreover, thicker lesions require multiple treatments, which are not without discomfort and other side effects. With IRC, we can safely ablate the full thickness of the lesion by working to the level of the submucosal vessels in a single session. We are confident that patients can return less frequently for evaluation.

Electrocautery can also be used to ablate HSIL safely.[18] It is our opinion that IRC is as effective and does not produce the plume that cautery does. If a physician is more comfortable using electrocautery to ablate HSIL, there might be little advantage in switching to IRC. Clearly, a comparison study between IRC and other modalities would better determine if one treatment method is superior to another.

We have chosen a posttreatment follow-up period of three to six months, as described previously, and admit that although it is somewhat arbitrary a number of considerations factored into this decision. We believe that this is a safe interval as the likelihood that a missed or recurrent HSIL will progress to invasive cancer during this short time frame is negligible. More frequent HRA without definitive evidence of disease can become overly burdensome to the patient and lead to loss of follow-up. With time and more experience treating HSIL, we may adjust the follow-up interval.

This study is the first report of its kind detailing office-based treatment of HSIL in HIV-positive MSM, and many questions remain to be answered. It is unclear whether longer follow-up with treatment of subsequent lesions will continue to show diminishing recurrence rates. Moreover, our patients underwent a maximum of three treatments, and longer follow-up might identify patients who require many more procedures. It remains to be determined if more treatments will be well tolerated or if as-yet unseen complications such as scarring, infection, or bleeding will develop. We also did not treat LSIL, and it remains to be seen whether treating these lesions as well as HSIL will be well tolerated and if this more aggressive approach will further diminish recurrence rates. This series also did not evaluate IRC treatment of HSIL in HIV-negative MSM. It remains to be seen whether it will prove to be a more effective treatment modality in immunocompetent individuals. Our series was comprised only of MSM, and it is clear that women also develop AIN and SCC.[15] It remains to be determined whether women undergoing IRC ablation of anal HSIL will respond in a fashion similar to that of men. Although no patient in our series developed SCC, it remains to be seen whether IRC ablation of HSIL will continue to prevent this complication over much longer periods of time. A large, prospective study of longer duration including both HIV-positive and HIV-negative patients of both sexes could help answer these questions.

We have shown that IRC ablation of HSIL is safe, but it still requires a surgical procedure with its inherent risks, and the lesion has a high incidence of recurrence. As with the treatment of CIN, this modality is not optimal and we should not become complacent. AIN is a growing problem, and it remains to be determined whether other therapies will be developed that improve rates and diminish patient morbidity. A recent report of activity of HPV-16-derived vaccine therapy against condyloma could hopefully show activity against HSIL as well, but to date studies have not been published.[33] Routine cervical cytology screening for women with detection and treatment of cervical HSIL has played a large role in reducing the incidence of cervical SCC over the last 60 years. Progression to invasive cervical cancer has been shown to occur in 36 percent of untreated women over a 20-year period.[34] It remains to be seen whether screening MSM for HSIL and treating lesions with IRC can decrease the incidence of SCC. Our ultimate goal should be the diminution of anal cancer rates in MSM.

CONCLUSIONS

Infrared coagulation is a safe, office-based modality for treating anal HSIL in HIV-positive MSM. Although recurrence rates are high, they are comparable to results seen in the cervix and in another surgical series. Successive treatments led to decreased recurrence rates, but patients should continue to be followed for disease.

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