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Ablative therapies for the treatment of anal high-grade squamous intraepithelial lesions

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A B S T R A C T

Anal HSIL is the precursor lesion of anal squamous cell carcinoma. The exact rate of cancer progression from HSIL is not clear, but likely approaches 10% in immunocompromised individuals. Just as excision and destruction of cervical dysplasia has been shown to significantly decrease the risk of cervical cancer, several studies have shown a reduced incidence of anal cancer after targeted ablation of HSIL. Given the morbidity of anal mapping and wide local excision, we cannot justify this treatment method, especially since recurrence is common. Except for the most severe cases, anal and perianal lesions are very amenable to office-based treatments. Topical therapies have a role in treating anal and perianal HSIL, especially in the setting of wide-spread disease. However, ablation has been shown to be more effective and better tolerated compared to topical treatments. Recurrence is to be expected following treatment of HSIL, highlighting the need for close long-term follow-up.

Introduction

While the anal high-grade squamous intraepithelial lesion (HSIL) is the accepted squamous cell carcinoma (SCC) precursor, the rate of progression to cancer of untreated HSIL is unknown. Most accept that progression is slower in the anal canal than cervix, where rates of progression approximate 31% by 30 years.[1] Surgeons have long accepted that untreated Bowen's disease of the anal margin has up to a 20% progression to invasive cancer and Bowen's disease is identical to HSIL.[2,3] In a meta-analysis estimating risk of progression to cancer of untreated HSIL, the authors calculated a progression rate of 1 in 377 HIV-positive MSM/year.[4] However, another large prospective series from Australia calculated a much higher rate of progression of untreated HSIL to cancer of 1.2 per 100 person-years (95% CI: 0.31–4.95).[5] Devaraj and Cosman[6] published their results of expectant management of anal dysplasia in a population of 40 consecutive HIV-positive patients with at least 1 year of follow-up. Three patients (9.7%) developed invasive SCC during the study period. Scholefield reported that three of six (50%) HIV-negative patients taking immunosuppressants developed invasive anal SCC after a mean of 5 years after initial AIN3 diagnosis.[7] Weis et al.[8] followed 22 patients with untreated HSIL and 2 (9.1%) progressed to cancer at 9 and 28 months while none of the 102 treated patients progressed.

Treatment of anal HSIL can be categorized as either topical therapy or surgical destruction of high-grade lesions. Anal mapping with wide local excisions of Bowen's disease, as initially described by Strauss and Fazio in 1979,[9] developed at a time when we lacked an understanding that this disease was related to infection with oncogenic strains of HPV and that dysplastic lesions could be identified before they became grossly visible or palpable. Moreover, the disease was most often well localized and present in immune competent women. Although the American Society of Colon and Rectal surgeons still describes mapping and wide local excision as acceptable practice, we would rather it be viewed as of historical significance only since this method was associated with significant morbidity that cannot be justified given the high recurrence rates.[10]

Anal and cervical HSIL are histologically identical and both primarily affect the squamous columnar transformation zone, but can spread to the keratinized epithelium. In the female genital track these lesions are categorized as vulvar or vaginal intraepithelial neoplasia (VIN or VaIN). In women, high-grade cervical intraepithelial neoplasia (CIN) is most often treated with excision of the squamous columnar transformation zone (LEEP or conization). More distal lesions of the vulva or vagina can be excised or ablated. In the anal canal, the transformation zone cannot be excised as there would be unacceptable high rates of morbidity including pain, bleeding, and stricture. As such, therapy relies largely on HRA guided targeted ablation of biopsy-proven HSIL.

Ablative therapies

Goldstone et al.[11] first described HRA guided targeted ablation of intra-anal HSIL in 2005 in a retrospective review of

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68 HIV-positive patients with 165 primary HSILs. The technique involved first performing HRA to identify and biopsy areas of potential HSIL. Most procedures were performed in an office setting with local anesthetic. The procedure was first performed in a knee-chest position, but lateral decubitus or lithotomy positions also provide adequate exposure. Once histology was confirmed, patients returned for ablative therapy of HSIL. HRA is repeated and lesions are relocalized and infiltrated with local anesthetic (lidocaine or bupivacaine with or without epinephrine). Unless the lesion is large and very thick, it is best to avoid injecting directly into the lesion as this can cause architectural distortion of thin, small lesions from the fluid or resultant bleeding. We typically use a 25 gauge, 1.5 inch needle attached to a 1 cc syringe passed under direct visualization down the barrel of the anoscope. Unfortunately, needles and syringes equipped with protective devices to prevent needle sticks should be avoided as they are too wide to pass through the anoscope without obscuring visualization. We insert the needle just to a point where the bevel disappears below the mucosal surface and inject just enough anesthetic to cause a very slight swelling of the tissue. If you can target a point just proximal to the dentate line, the patient will have far less discomfort. If the lesion extends distal to the dentate line, first injecting proximal and waiting 30–60 sec before injecting more distally will also improve patient tolerance. Although most HSIL occurs above the dentate line and biopsies can be performed without local anesthetic, ablation produces heat that will diffuse distally through the tissues causing pain, making adequate anesthesia crucial. We typically inject 0.1–0.3 mL/lesion and can sometimes inject more than one lesion without withdrawing the needle and syringe from the anoscope. Once, however, we withdraw the needle to reposition the anoscope and identify additional lesions, we never reinsert a needle that has already been used for injecting. Any needle that has pierced the patient is immediately placed into a sharps container once it is withdrawn from the anoscope to prevent needle sticks during reinsertion. You must take your eyes from the colposcope anytime you insert a sharp object into an anoscope, watching until the needle/instrument has passed into the anoscope to prevent inadvertent injury to your hand or the patient. We also prefer to identify and anesthetize all areas requiring treatment at the start of the procedure, so we can rapidly move from one to the next in a sequential fashion once we begin the actual ablation. As with biopsy we prefer to start with the most dependent lesion to prevent any oozing from obscuring visualization.

Infrared coagulation (IRC) (Redfield Corporation, Rochelle Park, NJ) involves a light source that generates infrared light transmitted down a rigid light-guide covered in a protective Teflon tipped sleeve.[11] The end of the guide is placed in contact with the tissue and can be used to flatten folds to best target the lesion. The pulse is typically set for 1.5 sec, which generally causes a 1.5 mm depth of tissue necrosis. This is visualized as blanching of the tissue. After we treat the entire lesion surface we debride the eschar by moving the anoscope in and out for blunt dissection or with a biopsy forceps for sharper debridement. We believe it is best to ablate to the level of the submucosal vessels to achieve adequate depth of destruction and ensure that you have destroyed the full thickness of the HSIL. Hemostasis is easily achieved with the IRC or Monsel's solution and suturing is not required.

Typically, patients are placed on fiber supplements, increased fluids and stool softeners to promote easier bowel movements postprocedure. Pain can most often be controlled with over the counter analgesics or NSAIDs with or without *sitz* baths. When treating more extensive disease we prescribe mild narcotic analgesics as well.

As initially described in our first series, patients were followed at 3–6 month intervals with cytology and HRA and biopsy of lesions suspicious for HSIL.[11] Recurrence was described as either persistence if HSIL recurred in a previously treated area, or metachronous if HSIL developed in a previously untreated location. Metachronous and persistent HSIL were retreated with IRC. During the follow-up period, we identified a 28% persistence rate per lesion. Thus, the initial cure rate per lesion was 72%, which did not change with retreatment. In this series, overall recurrence of any type after initial ablation was 65% within a median time of 217 days. HSIL recurrence decreased consistently with repeated treatments and significantly increased with each additional baseline HSIL. No patient developed SCC during the follow-up period. We did, however, note decreased recurrence as we gained experience over 3 years with the IRC.

In 2007, Goldstone et al.[12] reported the results of a similarly designed retrospective analysis of IRC ablation of intra-anal HSIL in 75 HIV-negative patients. We treated 113 HSILs with an initial cure rate of 81% per lesion. Overall recurrence after the first treatment was 53% driven largely by metachronous disease. When comparing the two studies, we determined that HIV-positive individuals were almost twice as likely to develop recurrent disease when compared with HIV-negative individuals. No patient developed SCC during the follow-up period.

Other series have also looked at the efficacy of IRC ablation of intra-anal HSIL. In a retrospective review of 68 HIV-positive MSM with 74 HSILs, Cranston et al.[13] demonstrated a 64% efficacy per lesion with IRC. In 2013, Sirera et al.[14] reported a retrospective cohort study of 69 HIV-positive men and women with biopsy-proven HSIL. Treatment success, defined as no cytologic or histologic evidence of dysplasia during the follow-up period (mean time = 25 months, range: 12–60 months), was 87.5%. The mean time to recurrence was 30 months (range: 18–43 months). No serious events were reported and none of the patients developed SCC during the follow-up period.

Weis et al.[8] were the first to prospectively compare the efficacy of infrared coagulation (IRC) treatment to expectant management in 124 HIV-positive men and women with biopsy-proven HSIL. While all 124 patients were advised to have their HSIL treated, 82 patients were treated immediately, 20 received delayed treatment, and 22 were never treated. By 28 months of follow-up, 37 (88%) of the untreated patients had persistent HSIL and 2 (5%) developed SCC. In contrast, 25 (26%) of treated patients had recurrent HSIL and none developed SCC.

Electrocautery ablation

A little more than a decade ago, we began to transition from treating HSIL with IRC to electrocautery.[16] Many types of electrosurgical devices are commonly used in offices and operating rooms. Essentially, the technique is almost identical to what we described for IRC ablative therapy. Lesions are first identified and biopsied with HRA and patients with confirmed HSIL return for ablative therapy at a subsequent visit. Lesions are reidentified with HRA, local anesthetic is injected, and the lesion is ablated to the depth of the submucosal vessels (Fig. 1). We use a low-energy hyfrecator in office because it does not require patient grounding and is far less expensive than the typical electrosurgical unit found in operating rooms. Typically we use 15 W delivered through a long insulated probe with a spatulated tip that easily passes down the barrel of the anoscope. The end of the tip is placed in gentle contact with the HSIL and the current is delivered to the tissue. We employ a gentle “paintbrush” sweeping over the lesion as we continuously deliver current rather than very short pulses of current. It is important to maintain contact with the tissue to prevent arcing. The char can often be removed during the actual application of current with a sweeping motion of the blade. For thicker lesions, char can be removed with biopsy forceps or vigorous scraping with the blade without current flowing. As with IRC, we ideally want to treat the full extent of the lesion to the depth of submucosal vessels.