



Endoscopic submucosal dissection to treat squamous cell carcinoma in situ of the anal canal

Michael Lajin, MD,¹ Mohamed O. Othman, MD,² Rokay Kamyar, MD,¹ Octavio Armas, MD¹

Background and Aims: The standard treatment for invasive squamous cell anal cancer is chemoradiation treatment. However, treatment options for high-grade dysplasia (squamous cell cancer in situ) are either surgical excision or topical treatment modalities. There are a few case reports, mainly from Japan, about resecting early squamous cell anal cancer (high-grade dysplasia/carcinoma in situ) by endoscopic submucosal dissection. We present a case series of 3 patients from a western hemisphere population with squamous carcinoma in situ of the anal canal resected with endoscopic submucosal dissection (ESD).

Methods: This is a retrospective series of 3 patients from a western hemisphere population with squamous carcinoma in situ of the anal canal resected with ESD. All patients were referred from the oncology team after declining surgical excision.

Results: Microscopically margin-negative en bloc resection was achieved in all patients. All patients were free from dysplasia or cancer on their latest endoscopic surveillance, ranging from 10 months to 26 months after ESD. One patient had a small lesion on follow-up 3 months after ESD that was removed by a curative EMR. There were no immediate or delayed adverse events.

Conclusions: ESD can be used to resect squamous cell carcinoma in situ of the anal canal. Larger studies with long-term follow-up are needed to evaluate the role of ESD in early squamous cell anal cancer and to compare it with other modalities of treatment. (VideoGIE 2022;7:235-9.)

INTRODUCTION

Squamous cell carcinoma is the most common cancer involving the anal canal, with an incidence of 1.8 per 100,000. It originates from squamous dysplastic lesions associated with human papillomavirus, particularly subtype 16. Risk factors include HIV, men who have sex with men, history of cervical cancer, and renal transplant patients.

The Lower Anogenital Squamous Terminology standardization project classifies squamous dysplastic lesions into 2 categories: low-grade squamous intraepithelial lesion, which correlates with anal intraepithelial neoplasia (AIN) 1 (anal condyloma), and high-grade squamous intraepithelial lesion (HSIL), which correlates with AIN 2-3.¹

Although chemoradiation therapy is the standard treatment for invasive squamous cell cancer of the anal canal,² there is significant controversy regarding the management of HSIL/AIN-3 lesions (squamous cell cancer in situ). Treatment modalities for HSIL/AIN-3 lesions include surgical excision and ablative/topical therapies.

Endoscopic submucosal dissection (ESD) is being increasingly used to manage precancerous and early cancerous lesions in the GI tract. Multiple case reports

from Japan have demonstrated the efficacy of ESD in treating HSIL/AIN-3 lesions.³⁻⁹

We present a case series of 3 patients from a Western population with HSIL/AIN-3 lesions managed with ESD.

PATIENTS AND METHODS

Patient 1

A 76-year-old woman with a history of diabetes was found to have a 3-cm, white, flat, elevated lesion involving the distal rectum and the anal canal (Fig. 1). Narrow-band imaging showed irregular vascular patterns (dilation, tortuosity, irregular shapes, and caliber changes). A biopsy specimen was consistent with “a high-grade squamous intraepithelial lesion (AIN-3).” She was evaluated by oncology and was referred for endoscopic resection after declining surgical excision.

The lesion was marked, and a submucosal injection was performed using ORISE Gel (Boston Scientific, Marlborough, Mass, USA). A circumferential mucosal incision was performed using a dual knife (endo cut current) (Olympus, Shinjuku City, Tokyo, Japan). Submucosal dissection was

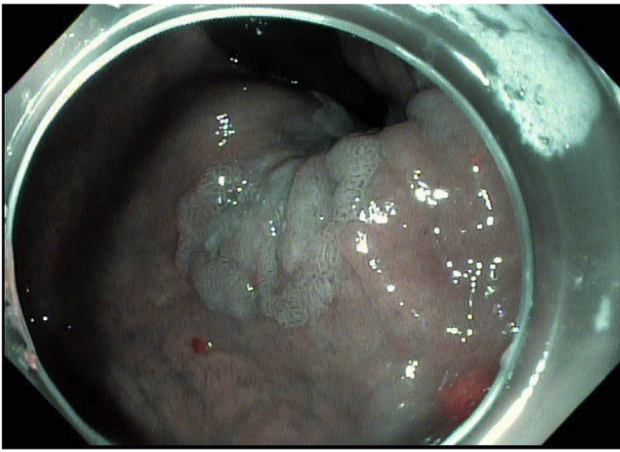


Figure 1. Case 1: Pre-endoscopic submucosal dissection narrow-band image of anal intraepithelial neoplasia-3 lesion.

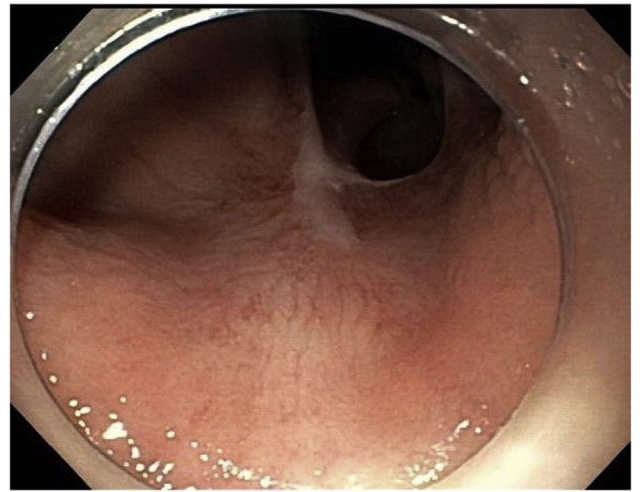


Figure 3. Case 1: Follow-up image after 10 months.

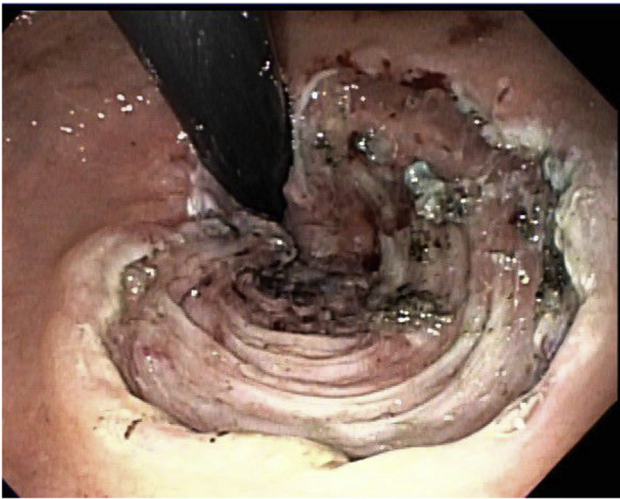


Figure 2. Case 1: Post-endoscopic submucosal dissection endoscopic image.

performed using the same knife with a forced coag current. The final submucosal dissection was facilitated by an IT knife (Olympus) with forced coag current (Fig. 2). The specimen was retrieved in 1 piece, measuring 4.7×2 cm. There were no immediate or delayed adverse events.

The final pathology was consistent with a high-grade squamous intraepithelial lesion (AIN-3). The margins were negative for dysplasia. Follow-up endoscopic evaluation at 3 months and then at 10 months (Fig. 3) showed no dysplasia/carcinoma.

Patient 2

A 71-year-old woman was found to have a 1.5-cm, white, flat, elevated lesion involving the distal rectum and anal canal (Fig. 4). A biopsy specimen was consistent with “fragments of squamous carcinoma in situ.” She was

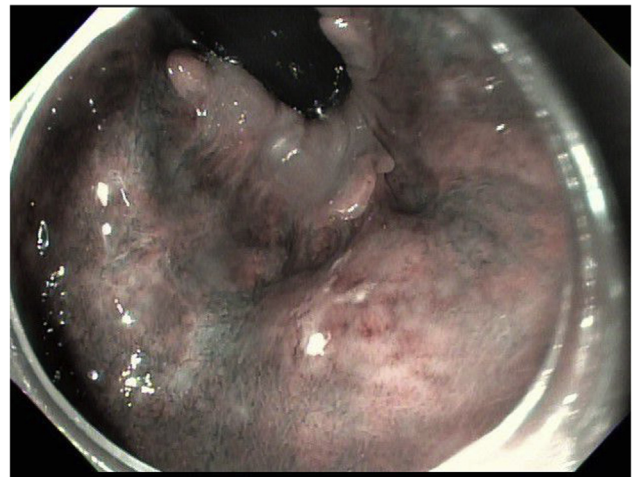


Figure 4. Case 2: Pre-endoscopic submucosal dissection narrow-band image of anal intraepithelial neoplasia-3 lesion.

evaluated by oncology and was referred for endoscopic resection after declining surgical excision.

The lesion was marked, and a submucosal injection was performed using ORISE Gel. The pocket technique was used. A mucosal incision was performed using a dual knife with endo cut current caudal to the lesion. The gastroscope entered a submucosal tunnel. Submucosal dissection was performed using the same knife with a forced coag current. After completing the dissection underneath the lesion, the circumferential mucosal incision was completed using an SB knife (Olympus) with endo cut current (Fig. 5). The specimen was retrieved in 1 piece, measuring 3.1×2.3 cm. There were no immediate or delayed adverse events.

The final pathology was consistent with squamous cell carcinoma in situ. The margins were free from carcinoma/dysplasia. Follow-up endoscopic evaluation at 4, 14, and 26 months (Fig. 6) after ESD showed no dysplasia/carcinoma.



Figure 5. Case 2: Post–endoscopic submucosal dissection endoscopic image.



Figure 7. Case 3: Pre–endoscopic submucosal dissection endoscopic image of anal intraepithelial neoplasia-3 lesion.



Figure 6. Case 2: Follow-up image after 26 months.



Figure 8. Case 3: Post–endoscopic submucosal dissection endoscopic image.

Patient 3

A 62-year-old man with a history of coronary artery disease and diastolic congestive heart failure was found to have a 3.5-cm, white, flat, elevated lesion involving the distal rectum and the anal canal (Fig. 7). Narrow-band imaging showed irregular vascular patterns (dilation, tortuosity, irregular shapes, and caliber changes). A biopsy specimen was consistent with “a high-grade squamous intraepithelial lesion (AIN-3).” He was evaluated by oncology and was referred for endoscopic resection after declining surgical excision.

The lesion was marked, and a submucosal injection was performed using ORISE Gel. The pocket technique was used. A mucosal incision was performed using a dual knife with endo cut current caudal to the lesion. The gastroscope entered a submucosal tunnel. Submucosal dissection was performed using the same knife with a forced

coag current. After completing the dissection underneath the lesion, the circumferential mucosal incision was completed using an SB knife with endo cut (Fig. 8). The specimen was retrieved in 1 piece, measuring 5.4 × 4.0 cm. There were no immediate or delayed adverse events.

The final pathology was consistent with a high-grade squamous intraepithelial lesion (AIN-3). The margins were negative for dysplasia. Follow-up endoscopic evaluation 3 months later showed an 8-mm lesion located outside the scar. The lesion was removed with band-assisted EMR. The pathology was consistent with AIN-3. The margins of resection were negative. Another endoscopic evaluation was performed 3 months after EMR and showed no residual dysplasia/carcinoma. Repeated endoscopic evaluation 15 months after initial ESD showed no residual cancer/dysplasia (Fig. 9).

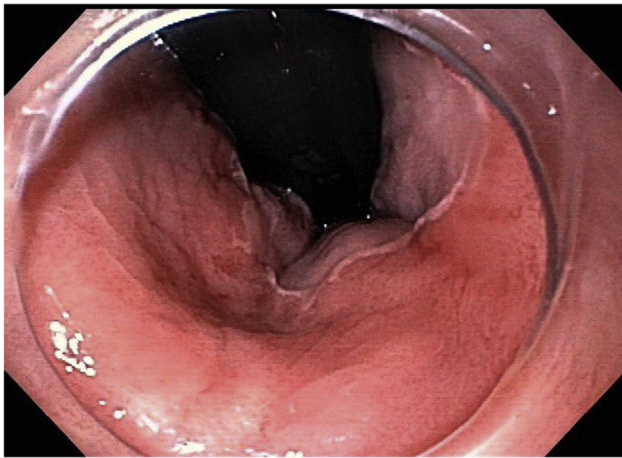


Figure 9. Case 3: Follow-up image after 15 months.

DISCUSSION

Preliminary studies estimate the rate of progression of HSIL/AIN-3 lesions to anal cancer to be 9% to 13% within 5 years.¹⁰

Surgical excision for these lesions was the preferred treatment in the past. However, the rate of recurrence/incomplete excision remains high at 9% to 63%.¹¹ Repeated surgical excisions increase the risk of stenosis or fecal incontinence. Topical treatments such as trichloroacetic acid, imiquimod, and 5-fluorouracil and ablative techniques such as fulguration with electrocautery or coagulation with infrared or laser are less invasive but carry a significant risk of recurrence.¹² Expectant management and watchful waiting by surveillance alone for HSIL/AIN-3 lesions expose patients to the risks of chemoradiation treatment if they convert to invasive anal cancer.

ESD uses the concept of dissecting the submucosal fibers underneath the lesion to achieve en bloc resection. It is now recognized as a preferred noninvasive treatment modality for premalignant and early malignant GI lesions. ESD allows resection of lesions in anatomically difficult locations such as the anal canal. En bloc resection provides accurate histological assessment to evaluate the adequacy of the treatment.

The key elements of ESD, such as using flexible endoscopy, distal attachment caps, smart electrosurgical units/knives, and accurate markings of borders combined with deep submucosal dissection, lead to a precise resection to decrease the chance of incomplete resection or recurrence. Multiple reports of curative ESD for HSIL/AIN-3 lesions have emerged from Asian countries such as Japan.

We present in this case series 3 patients from a western population who underwent ESD for HSIL/AIN-3 lesions. All 3 patients were referred by our oncology colleagues after declining surgical excision. Both the conventional method

and the pocket creation method¹³ were used in this case series.

The lesions in cases 2 and 3 were resected using the pocket creation method. This method allows preservation of the fluid in the submucosal space, resulting in an easier and more efficient dissection, particularly in difficult anatomical locations such as the anal canal. On the other hand, the lesion in case 1 was wider. The conventional method was selected in this case because it enables us to mark off the dissection endpoints at the borders of the lesion.

The initial mucosal incision was started at the anal side. This approach allowed us to perform the initial submucosal dissection with a straight rather than a retroflexed endoscope position. The incision at the anal side is more difficult. Thus, it is preferable to start with detaching that side first.¹⁴ ORISE Gel was the injection solution used in all cases because of its ability to provide a long-lasting submucosal fluid cushion.

All 3 procedures were performed with the patient under general anesthesia; as a result, lidocaine, which typically provides a transient numbing effect, was not used. Aside from minor rectal discomfort that was well controlled with oral acetaminophen, patients did not experience any significant rectal pain after all ESD procedures.

Successful en bloc resection was achieved in all patients. The ESD pathology was consistent with AIN-3 without invasive cancer. All patients had microscopically margin-negative resection with free margins. One patient was found to have an 8-mm AIN-3 lesion during 3-month follow-up surveillance, despite the negative margins achieved with the initial ESD. Multifocal AIN-3 lesions are reported in the literature.¹⁵ This lesion was located outside the scar of the previous ESD site; therefore, it is likely a separate focus of AIN-3. Given the small size of the lesion and the absence of scarring, it was removed safely with band-assisted EMR with clear margins.

Currently, all patients are clear from dysplasia/malignancy on their latest endoscopic surveillance ranging from 10 to 26 months after ESD. Because the pathology of the resected lesions is consistent with AIN-3 with free margins, all 3 patients are undergoing regular endoscopic surveillance, and no further treatment is warranted at this time. There were no immediate or delayed adverse events, such as bleeding, perforation, infection, stenosis, or fecal incontinence.

CONCLUSIONS

ESD is a promising noninvasive modality for treating HSIL/AIN-3 lesions. Larger studies with a longer follow-up are needed to assess its role in this clinical setting and to compare it with other modalities of treatment (Video 1, available online at www.giejournal.org).

DISCLOSURE

Dr Othman is a consultant for Olympus, Boston Scientific, Conmed, Lumendi, and Apollo and has received research grants from Abbvie, Conmed, and Lucid Diagnostic. All other authors disclosed no financial relationships.

Abbreviations: AIN, anal intraepithelial neoplasia; ESD, endoscopic submucosal dissection; HSIL, high-grade squamous intraepithelial lesion.

REFERENCES

- Darragh TM, Colgan TJ, Cox JT, et al. The lower anogenital squamous terminology standardization project for HPV-associated lesions: background and consensus recommendations from the College of American Pathologists and the American Society for Colposcopy and Cervical Pathology. *Arch Pathol Lab Med* 2012;136:1266-97.
- Shridhar R, Shibata D, Chan E, et al. Anal cancer: current standards in care and recent changes in practice. *CA Cancer J Clin* 2015;65:139-62.
- Tamaru Y, Oka S, Tanaka S, et al. Early squamous cell carcinoma of the anal canal resected by endoscopic submucosal dissection. *Case Rep Gastroenterol* 2015;9:120-5.
- Ito T, Morita S, Shimeno N, et al. The prospect of endoscopic submucosal dissection for early anal canal squamous cell carcinoma. *Clin J Gastroenterol* 2016;9:384-8.
- Tsuji S, Doyama H, Yamada S, et al. Endoscopic submucosal dissection of a squamous cell carcinoma in situ in the anal canal diagnosed by magnifying endoscopy with narrow-band imaging. *Clin J Gastroenterol* 2014;7:233-7.
- Uozumi T, Sumiyoshi T, Kondo H, et al. Endoscopic submucosal dissection for early squamous cell carcinoma in the anal canal and Lugol chromoendoscopy for assessment of the lateral margin. *Endosc Int Open* 2018;6:E1130-3.
- Chou YP, Saito Y, Matsuda T, et al. Novel diagnostic methods for early-stage squamous cell carcinoma of the anal canal successfully resected by endoscopic submucosal dissection. *Endoscopy* 2009;41:E283-5.
- Kasuga K, Saito Y, Wu SY, et al. Impact of endoscopic submucosal dissection of an anal squamous intraepithelial lesion with indistinct border. *Endoscopy* 2020;52:E75-7.
- Ozawa SI, Yasuda H, Sato Y, et al. A case of depressed-Type (O-IIc) squamous cell carcinoma in situ at the anal canal resected by endoscopic submucosal dissection as excisional biopsy. *Gastroenterol Endosc* 2015;57:2537-42.
- Scholefield JH, Castle MT, Watson NF. Malignant transformation of high-grade anal intraepithelial neoplasia. *Br J Surg* 2005;92:1133-6.
- Steele SR, Varma MG, Melton GB, et al. Practice parameters for anal squamous neoplasms. *Dis Colon Rectum* 2012;55:735-49.
- Siddharthan RV, Lanciault C, Tsikitis VL. Anal intraepithelial neoplasia: diagnosis, screening, and treatment. *Ann Gastroenterol* 2019;32:257-63.
- Sakamoto H, Hayashi Y, Miura Y, et al. Pocket-creation method facilitates endoscopic submucosal dissection of colorectal laterally spreading tumors, non-granular type. *Endosc Int Open* 2017;5:E123-9.
- Matsumoto S, Yoshida Y. Endoscopic submucosal dissection for colorectal tumors in the dentate line area and those adjacent to the dentate line. *Austin J Gastroenterol* 2015;2:1037.
- Weis SE. Current treatment options for management of anal intraepithelial neoplasia. *Onc Targets Ther* 2013;6:651-65.

SHARP health, San Diego, California (1), Baylor College Of Medicine, Houston, Texas (2).

If you would like to chat with an author of this article, you may contact Dr Lajin at mlajin@yahoo.com.

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<https://doi.org/10.1016/j.vgje.2022.02.011>

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