

GI PERSPECTIVES 01

STRATEGIES FOR COMPLETE ENDOSCOPIC MUCOSAL RESECTIONS



FEATURED CLINICIAN

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Colorectal cancer (CRC) is the second leading cause of cancer-related deaths in the United States for cancers that affect both men and women.¹ Although the overall incidence of CRC has been declining for decades, mostly due to increased colorectal screening, it is rising in younger patients.² Endoscopic CRC screening is critical to reducing CRC-related mortality.³ Approximately 90% of patients live 5 or more years when their CRC is found early through screening.⁴ The American College of Gastroenterology Guidelines recommend colonoscopy, with the highest level of detection for precancerous lesions, as the preferred cancer screening test to be offered first to patients ≥ 50 years of age.⁵

Among the estimated 15 million colonoscopies that are performed in the United States annually, the polyp detection rate is approximately 50%.^{4,6} However, the benefit of colonoscopy on cancer prevention is dependent both on effective polyp detection and on successful removal.³ Complete resection is critical, as incomplete resections may contribute to the development of colon cancers after colonoscopy, also known as interval cancers.^{3,7,8} The Complete Adenoma Resection (CARE) study estimated the overall incomplete resection rate to be 10.1%, though that percentage increased for both large and sessile serrated adenomas/polyps (SSA/P).⁸

Polyp Morphology and Removal: The Role of EMR

Colorectal polyps can be classified by both morphology and cancer risk. Morphologically, polyps can be pedunculated or flat, the latter of which usually require submucosal injection before resection. The 2 main types of polyps with malignant potential are adenomas and SSA/P (**Figure 1**).^{9,10}

Figure 1: Classification of Colorectal Polyps

	Adenomas ^{9,10}	Serrated ^{9,10}
Pedunculated ⁹	Low-grade dysplasia	SSA/P without dysplasia
Flat ⁹	High-grade dysplasia	SSA/P with dysplasia

Images courtesy of Dr Qiang Cai.

Endoscopic techniques for polyp removal have eliminated the need for surgery for minimally invasive lesions, particularly for the removal of large polyps.¹¹ Endoscopic mucosal resection (EMR), which was developed for the removal of minimally invasive sessile or flat polyps (which could not be removed by snare polypectomy) confined to the superficial layers (mucosa and submucosa) of the colon, esophagus, stomach, and duodenum can be performed on polyps ≥ 20 mm.^{11,13} In EMR, a submucosal injection creates a cushion for the polyp, which can then be snared either en bloc or piecemeal.¹¹ The advantage of en bloc removal is that it allows for full histological assessment of the complete resection.⁷

Before beginning an EMR procedure, it is important to define the margins of the lesion to be resected, which includes visual inspection and marking the margins. Close visual inspection is required in order to define the margins of the lesion, which is especially important for flat lesions because manipulation of the lesion may obscure landmarks. Furthermore, marking the margins of the lesion with wider superficial cautery marks may be helpful to delineate the margins.^{7,12} Clinically, complete resection with EMR is associated with lower rates of recurrence and interval cancer.^{3,7}

“EMR is an important tool in endoscopic resection of relatively large, flat lesions in the colon. A submucosal injection agent is used during EMR to lift the mucosa and submucosa, to make the margins of the lesion easily visualized, and to make the resection safer to perform.” –Dr Qiang Cai

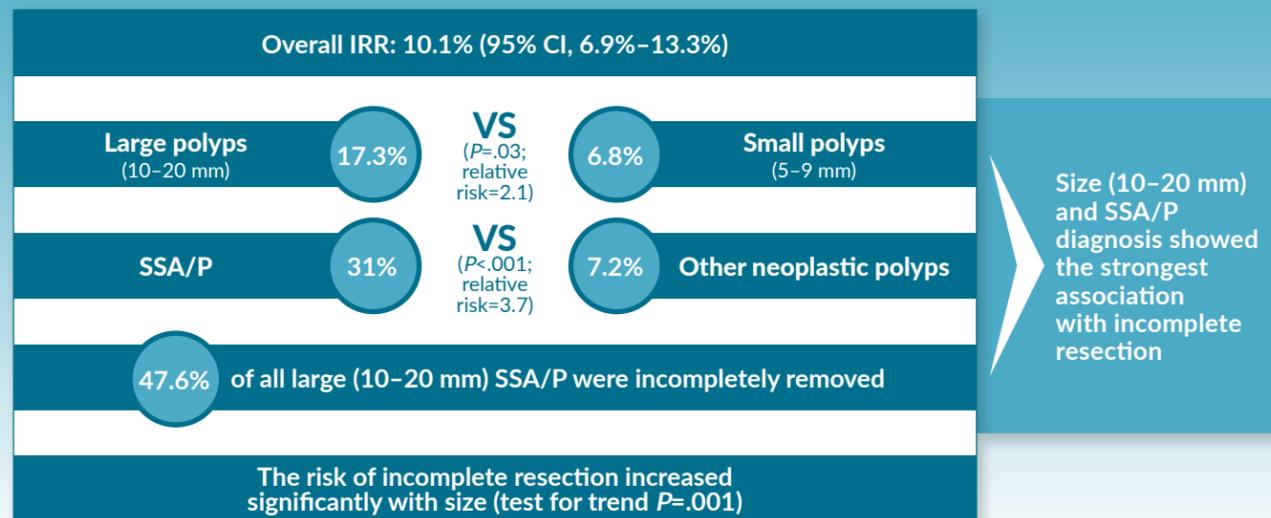
The CARE Study Defined Risk Factors for Incomplete Resections

The CARE study was a prospective study on 1427 patients aged 40 through 85 years who underwent colonoscopy at 2 academic medical centers and had at least 1 nonpedunculated polyp (5–20 mm) detected during colonoscopy. After polyp removal was considered macroscopically complete, biopsies were obtained from the resection margin. The primary outcome was the percentage of incompletely resected neoplastic polyps (incomplete resection rate, or IRR), determined by the presence of neoplastic tissue in postpolypectomy

biopsies. Associations between the IRR and polyp size, morphology, histology, and endoscopist were assessed by regression analysis.⁸

The results of the study yielded significant risk factors for incomplete resections, which included polyp size (10–20 mm) and a diagnosis of SSA/P (**Figure 2**). In addition, the IRR for endoscopists with at least 20 polypectomies ranged from 6.5% to 22.7%; there was a 3.4-fold difference between the highest and lowest IRR after adjusting for size and sessile serrated histology.⁸

Figure 2: Significant Risk Factors for Incomplete Resections From the CARE Study^{8,*}



*The CARE study showed incomplete resection rates among 269 patients with neoplastic polyps (N=418; mean age 63.4 years).

Overall, this study demonstrated the role of polyp size and sessile morphology in incomplete resections. Because incomplete resections contribute to interval cancers, it is important for endoscopists to keep these risk factors in mind when performing EMR.

The Role of Submucosal Injection to Ensure a Successful EMR

The use of submucosal injection is essential for a successful EMR. There are multiple benefits associated with this technique, which can help improve procedural feasibility and reduce complications, including^{14–16}:

- Cushioning and isolating the target tissue
- Delineating tissue margins
- Reducing complication risks, including perforation, bleeding, and thermal injury (postpolypectomy syndrome)
- Enabling complete (en bloc) or extended (piecemeal) resections

“Neoplastic polyps are often incompletely resected, and the rate of incomplete resection varies broadly among endoscopists. Incomplete resection might contribute to the development of colon cancers after colonoscopy (interval cancers). Efforts are needed to ensure complete resection, especially of larger lesions.”

–Dr Qiang Cai

The Role of Submucosal Injection to Ensure a Successful EMR (continued)

Ideal submucosal injection agents should, at minimum, provide sufficient elevation to facilitate en bloc resections. Other optimal attributes of an ideal submucosal injection agent that can help to enable en bloc resections include^{12,14,15}:

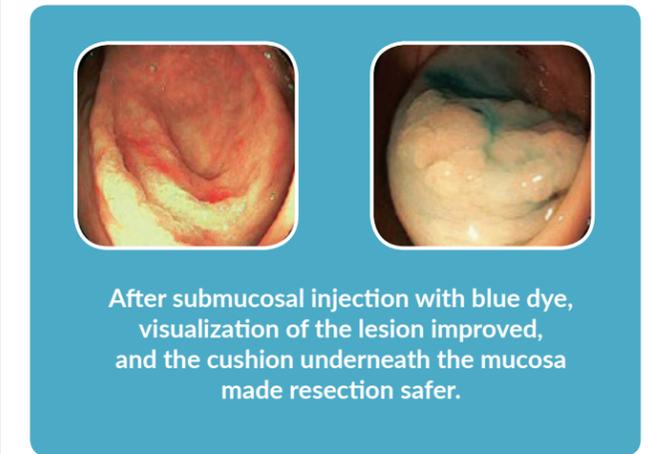
- Easy to inject
- Provides a long-lasting cushion of sufficient height
- Maintains cushion lift throughout the procedure
- Facilitates the visualization of the margins of the lesions
- Preserves tissues for pathological staging

Submucosal injection with blue dye facilitates complete resection. The addition of dye to the submucosal injection agent can improve both the visualization of lesion margins and the overall safety of the procedure (**Figure 3**).¹²

The use of viscous solutions can also lead to a higher rate of successful en bloc resection. One meta-analysis of 5 prospective, randomized trials demonstrated that the use of viscous solutions led to significantly higher odds of en bloc resection (OR, 1.91; 95% CI, 1.11–3.29; $I^2=0\%$; $P=.02$) and significantly lower odds of residual lesions (OR, 0.54; 95% CI, 0.32–0.91; $I^2=0\%$; $P=.02$) versus the normal saline preparations.¹⁷

Overall, effective polyp detection and removal is essential for CRC prevention. Complete resection with EMR—facilitated by a submucosal injection that enables an easy and safe resection procedure—is critical to prevent the development of interval cancers.

Figure 3: Submucosal Injection With Blue Dye Facilitates Complete Resection¹²



Images courtesy of Dr Qiang Cai.

Eleview™: A US Food and Drug Administration (FDA) 510(k) Cleared Submucosal Injection Agent

Eleview™ is a new commercially available submucosal injectable composition intended for use in gastrointestinal (GI) endoscopic procedures for submucosal lift of polyps, adenomas, early-stage cancers, and other GI lesions, prior to excision with a snare or an endoscopic device. The benefits of Eleview™ include^{18,19}:

- Long-lasting cushion-forming duration of up to 45 minutes
- Sterile and ready to use
- Contains methylene blue to improve visibility of lesion margins
- Can be used with commercially available endoscopic injection needles or more sophisticated systems
- Cleared in the United States (510[k]) and in the European Union as a medical device

Randomized, Double-Blind Trial of Eleview™ for EMR of Large Sessile Polyps of the Colon

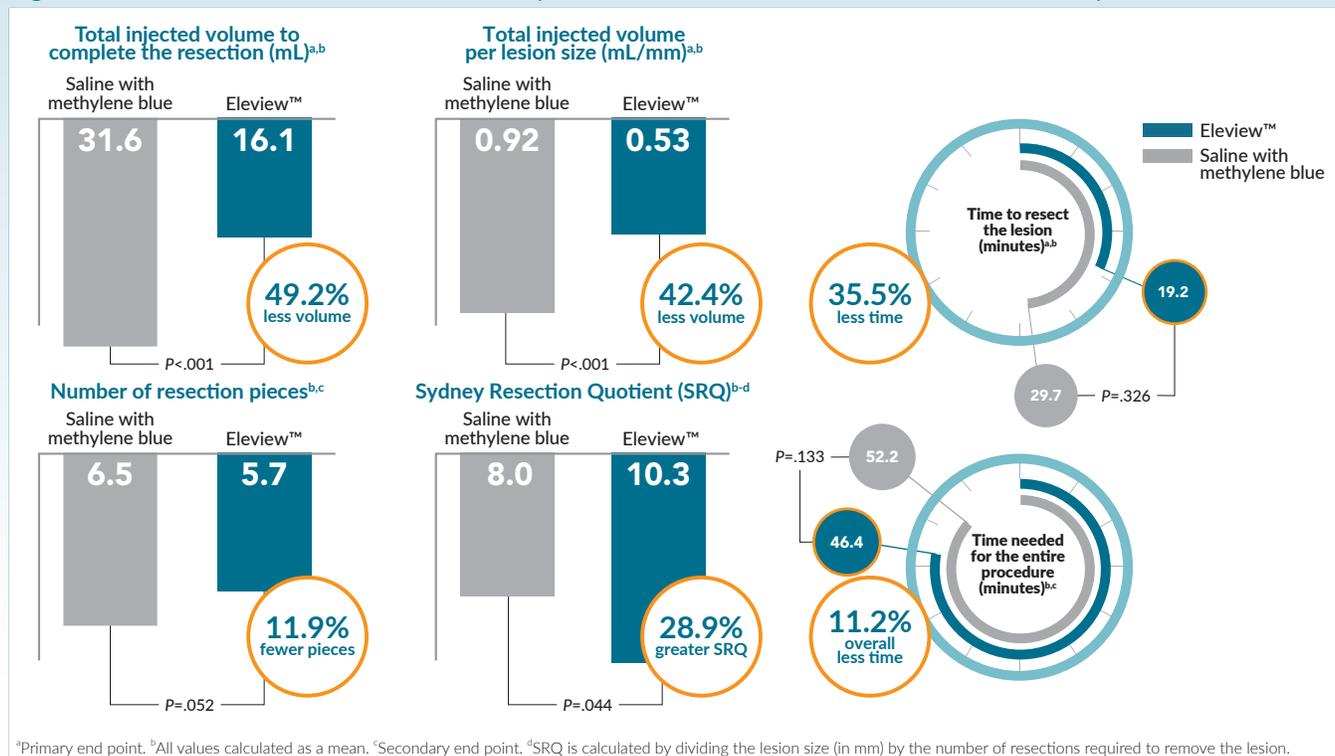
This multicenter trial conducted at select sites in the United States and the European Union assessed the effectiveness and safety of Eleview™ versus standard of care. The trial included 211 patients undergoing EMR for excision of treatment-naïve, laterally spreading sessile or flat colonic polyps/adenomas ≥ 20 mm in largest dimension. Primary end points included total injected volume needed to complete the EMR procedure, total injected volume per lesion size, and time to resect the lesion completely.²⁰ As depicted in the efficacy results, this was the first in-human study to demonstrate relative improvement with Eleview™ versus sites' standard of care in select effectiveness measures (**Figure 4**).²⁰



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Randomized, Double-Blind Trial of Eleview™ for EMR of Large Sessile Polyps of the Colon (continued)

Figure 4: Eleview™ Demonstrated Relative Improvement for All End Points in the Human Study²⁰



Furthermore, the safety analysis demonstrated no difference between Eleview™ and the comparator in the number of adverse events (AEs) and serious AEs.²⁰ In the interim analysis, AEs were essentially identical and rare. Subjects with at least 1 complication included: Eleview™ 17 (15.0%); comparator 17 (15.2%). These data are interim until final patient analysis is completed after the 60-day postprocedure follow-up period.²¹

While the study was not powered to show statistical significance, several end points were statistically significant in favor of Eleview™. Overall, this study demonstrated relative improvement with Eleview™ for all primary and secondary efficacy measures, and no difference in the number of AEs between Eleview™ and the comparator.

“An optimal submucosal agent like Eleview™ should be safe, easy to inject, and deliver long-lasting cushion-forming duration to avoid repeating the injection.”

—Dr Qiang Cai

Important Safety Information

WARNINGS AND PRECAUTIONS

- The safety of Eleview™ has not been established in pregnant or lactating women, or in children under 18 years of age.
- The endoscopist injecting Eleview™ must be experienced in the administration technique.

ADVERSE REACTIONS

- Rarely, local bleeding and/or inflammatory reaction could occur which may or may not be associated with Eleview™.

CONTRAINDICATIONS

- Patients with known sensitivity to any of the components contained in Eleview™.



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Eleview is a trademark of Cosmo Technologies Ltd.
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References: 1. Centers for Disease Control and Prevention. Colorectal cancer statistics. <https://www.cdc.gov/cancer/colorectal/statistics/>. Updated June 7, 2017. Accessed June 20, 2017. 2. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974-2013. *J Natl Cancer Inst*. 2017;109(3):1-6. 3. von Renteln D, Pohl H. Polyp resection—controversial practices and unanswered questions. *Clin Transl Gastroenterol*. 2017;8(3):e76. 4. Centers for Disease Control and Prevention. Colorectal cancer screening capacity in the United States. https://www.cdc.gov/cancer/dccp/research/articles/crc_screening_model.htm. Accessed June 20, 2017. 5. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastrointest Endosc*. 2017;86(1):18-33. 6. Boroff ES, Gurudu SR, Hentz JG, Leighton JA, Ramirez FC. Polyp and adenoma detection rates in the proximal and distal colon. *Am J Gastroenterol*. 2013;108(6):993-999. 7. Bujanda L, Cosme A, Gil I, Arenas-Mirave JJ. Malignant colorectal polyps. *World J Gastroenterol*. 2010;16(25):3103-3111. 8. Pohl H, Srivastava A, Bensen SP, et al. Incomplete polyp resection during colonoscopy—results of the complete adenoma resection (CARE) study. *Gastroenterology*. 2013;144(1):74-80.e1. 9. Simon K. Colorectal cancer development and advances in screening. *Clin Interv Aging*. 2016;11:967-976. 10. Jass JR, Baker K, Zlobec I, et al. Advanced colorectal polyps with the molecular and morphological features of serrated polyps and adenomas: concept of a ‘fusion’ pathway to colorectal cancer. *Histopathology*. 2006;49(2):121-131. 11. Fyock CJ, Draganov PV. Colonoscopic polypectomy and associated techniques. *World J Gastroenterol*. 2010;16(29):3630-3637. 12. Hwang JH, Konda V, Abu Dayyeh BK, et al. for ASGE Technology Committee. Endoscopic mucosal resection. *Gastrointest Endosc*. 2015;82(2):215-226. 13. Steele SR, Johnson EK, Champagne B, et al. Endoscopy and polyps—diagnostic and therapeutic advances in management. *World J Gastroenterol*. 2013;19(27):4277-4288. 14. Uraoka T, Saito Y, Yamamoto K, Fujii T. Submucosal injection solution for gastrointestinal tract endoscopic mucosal resection and endoscopic submucosal dissection. *Drug Des Devel Ther*. 2009;2:131-138. 15. Jung YS, Park DI. Submucosal injection solutions for endoscopic mucosal resection and endoscopic submucosal dissection of gastrointestinal neoplasms. *Gastrointest Interv*. 2013;2(2):73-77. 16. Ferreira AO, Moleiro J, Torres J, Dinis-Ribeiro M. Solutions for submucosal injection in endoscopic resection: a systematic review and meta-analysis. *Endosc Int Open*. 2016;4(1):E1-E16. 17. Yandrapu H, Desai M, Siddique S, et al. Normal saline solution versus other viscous solutions for submucosal injection during endoscopic mucosal resection: a systematic review and meta-analysis. *Gastrointest Endosc*. 2017;85(4):693-699. 18. Eleview™ Instructions for Use. San Diego, CA: Aries Pharmaceuticals, Inc.; 2017. 19. Data on file. Aries Pharmaceuticals, Inc.; 2015. 20. Rex D, Wallace M, Sharma P, et al. A randomized double-blind trial of a new injectable solution (SIC 8000) for endoscopic resection of colonic polyps larger than 2 centimeters: an interim report. Presentation at: Digestive Disease Week 2017; May 6-9, 2017; Chicago, Illinois. 21. Wallace MB. Endoscopic removal of polyps in the gastrointestinal tract. *Gastroenterol Hepatol*. 2017;13(6):371-374.