

Underwater endoscopic mucosal resection for non-pedunculated colorectal lesions. A prospective single-arm study

Luciano LENZ^{1,2}, Bruno MARTINS^{1,2}, Fabio Shiguehisa KAWAGUTI^{1,2}, Alexandre TELLIAN³, Caterina Maria Pia Simoni PENNACHI¹, Mauricio SORBELLO^{1,3}, Carla GUSMON¹, Gustavo Andrade de PAULO^{1,4}, Ricardo UEMURA¹, Sebastian GEIGER¹, Marcelo Simas de LIMA¹, Adriana SAFATLE-RIBEIRO^{1,3,5}, Elisa BABA¹, Claudio Lyoiti HASHIMOTO^{3,5}, Fauze MALUF-FILHO¹ and Ulysses RIBEIRO JR¹

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ABSTRACT – Background – Underwater endoscopic mucosal resection (UEMR) has emerged as a revolutionary method allowing resection of colorectal lesions without submucosal injection. Brazilian literature about this technique is sparse. **Objective** – The aim of this study was to evaluate the efficacy and safety of UEMR technique for removing non-pedunculated colorectal lesions in two Brazilian tertiary centers. **Methods** – This prospective study was conducted between June 2016 and May 2017. Naïve and non-pedunculated lesions without signs of submucosal invasion were resected using UEMR technique. **Results** – A total of 55 patients with 65 lesions were included. All lesions, except one, were successfully and completely removed by UEMR (success rate 98.5%). During UEMR, two cases of bleeding were observed (3.0%). One patient had abdominal pain on the day after resection without pneumoperitoneum. There was no perforation or delayed bleeding. **Conclusion** – This study supports the existing data indicating acceptable rates of technical success, and low incidence of adverse events with UEMR. The results of this Brazilian study were consistent with previous abroad studies.

HEADINGS – Intestinal polyps. Colorectal neoplasms. Endoscopic mucosal resection. Immersion. Prospective studies.

INTRODUCTION

Colorectal cancer is a leading cause of cancer mortality worldwide⁽¹⁾. The endoscopic removal of polyps reduces the incidence of colorectal cancer by up to 90%⁽²⁾. Ninety percent of polyps are small and can be easily treated with conventional polypectomy⁽³⁾. However, larger non-pedunculated lesions pose a technical challenge⁽²⁾.

Advanced endoscopic therapeutic options for colorectal lesions have been developed. Conventional endoscopic mucosal resection (CEMR) is the current accepted standard modality. CEMR utilizes submucosal injection of a solution to separate the superficial layers from the deep submucosa and the muscularis propria⁽⁴⁾. Theoretically, it decreases the risk of thermal injury to the deeper tissue layers and iatrogenic perforation. However, submucosal injection may paradoxically make snare capture of a flat polyp more difficult⁽⁵⁾.

An alternative technique, endoscopic submucosal dissection (ESD), has also been developed to remove lesions that were previously removed only by surgical means. This technique has the ability to obtain en bloc resection of large lesions, but it is complex, technically demanding and time consuming. In addition, ESD is associated with high risk of perforation and has a long learning curve⁽⁴⁾.

Developed by Binmoeller et al.⁽⁵⁾ in 2012, and later described as the “third way” by Amato et al.⁽⁶⁾, underwater endoscopic mu-

cosal resection (UEMR) has emerged as a revolutionary method allowing resection without submucosal injection. Recent studies demonstrated that UEMR safely removes large lesions due to natural separation of the submucosa from the muscularis propria when air insufflation is not used. Additionally, they showed high technical success with few adverse events^(1,4-13).

The overwhelming majority of studies have been published about overseas UEMR experience^(1,4-14). Only two South American studies, both Brazilian, were published regarding the underwater technique for colorectal lesions. The first Brazilian study included four patients, one with a pedunculated lesion⁽¹³⁾. The other one included 14 lesions, all of which were sessile serrated adenomas⁽⁷⁾.

This prospective single-arm study evaluated the safety and efficacy of a UEMR for removing non-pedunculated colorectal lesions using the snare for marking and using three different electrosurgical settings in two Brazilian referral centers.

METHODS

Patients

Between June 2016 and May 2017, a prospective non-controlled trial was conducted with consecutive patients undergoing UEMR in two university tertiary hospitals. The inclusion criteria were: (1)

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¹ Universidade de São Paulo, Faculdade de Medicina, Departamento de Gastroenterologia, Instituto do Câncer do Estado de São Paulo, São Paulo, SP, Brasil. ² Fleury Medicina e Saúde, São Paulo, SP, Brasil. ³ Universidade de São Paulo, Faculdade de Medicina, Departamento de Gastroenterologia, Divisão de Gastroenterologia e Hepatologia Clínica, Centro de Diagnóstico em Gastroenterologia, São Paulo, SP, Brasil. ⁴ Hospital Israelita Albert Einstein, Serviço de Endoscopia, São Paulo, SP, Brasil. ⁵ Hospital Sírio-Libanês, São Paulo, SP, Brasil.

Corresponding author: Luciano Lenz. E-mail: luciano88lenz@gmail.com

non-pedunculated lesions; (2) size between 10 and 40 mm; (3) naïve lesions; (4) no signs of invasive disease (ulceration, spontaneous bleeding, indurations, or non-floating sign). The study protocol was approved in 10th June 2016 by our Institutional Review Board (*Núcleo de Pesquisa*) as a part of a pilot study before a clinical trial comparing CEMR and UEMR (NCT03021135). This study protocol conforms to the ethical guidelines of Helsinki Declaration. A written, informed consent was obtained from all patients included in this study.

METHODS

All procedures were performed on an outpatient basis and under sedation. Miniprobe EUS examination not used. A high definition colonoscope (GIF-H180 or 190, Olympus Medical, Center Valley, Pa) without a distal cap was used. Intravenous hyoscine was administered (if no contra-indications) to arrest peristalsis. The endoscopists, who performed the procedures, learned UEMR watching internet videos, and reading the available articles about the technique, however, they had never performed UEMR before this study.

Two types of snares were used: 13 mm Captivator II® (Boston Scientific, Marlborough, USA) or 25 mm Snare Master® (Olympus, Center Valley, USA). The snare was chosen according to the lesion size and at the discretion of the endoscopist. The electrosurgical unit used was the VIO 300 D (ERBE Elektromedizin, Tübingen, Germany).

The lesions were examined by white light, virtual chromoscopy (NBI - Narrow Band Image), and conventional chromoscopy (0.4% indigo carmine solution) without magnification. After identifying the target lesion, UEMR was started by marking the perimeter with the tip of snare (soft coagulation, 50–80W) under air insufflation (FIGURE 1). Next, the intestinal lumen was decompressed. The lumen was then filled with room temperature water using an irrigation pump (OFP-2, Olympus). A torque-crimp method was used to maximize tissue ensnaring (FIGURE 2). One of three electrosurgical settings chosen (DRYCUT – effect 5, power 60W; AUTOCUT – effect 5, power 80W or ENDOCUT Q – effect 3, interval cut 6, time cut 1). Adjacent parts of the lesion were resected in a piecemeal way, taking care not to leave any pathological “island”. Remnant tissue too small to snare was removed by cold forceps biopsy. Neither argon plasma coagulation nor hot biopsy forceps were used. All specimens were retrieved for histopathologi-



FIGURE 1. Marks made with snare tip.



FIGURE 2. Lesion ensnaring underwater.

cal examination. Endoclips were employed for the management of hemorrhage, or according to the operator’s judgment, e.g., for deep wounds or in patients with higher risk of bleeding (aspirin use or coagulopathy). The procedure was timed, beginning with the marking of the edges until the resection of the last fragment. Tattooing was done to facilitate localization of the resection site. It was performed 3 cm distal, on the same wall of the lesion after saline bleed with 0.5 mL of India ink.

Follow-up

We called the patients at least 10 days after the procedure to assess delayed adverse events. Surveillance colonoscopies were scheduled 6 months later. The scars were inspected by white light, NBI and conventional chromoscopy followed by biopsies. Recurrences were defined as histologically-proven adenomas at the resection site. We did not consider procedural minimal bleeding without need of intervention as an adverse event. Adverse events were categorized as early (intraprocedural or within 24 hours) or delayed (after one day).

RESULTS

Patient and lesion characteristics

Over 11 months, a total of 55 patients – 34 female (60%), mean age 67 years, range 53–87) with 65 lesions (mean size 16.67 mm, range 10–40 mm) underwent UEMR. The patient and lesion characteristics (gender, age, location, size, morphology, and histopathology) are listed in TABLE 1.

For seven lesions, we selected DRYCUT mode; for sixteen AUTOCUT; and for forty-two the ENDOCUT mode. Forty lesions were removed en bloc (61.5%) and 25 (38.5%) in piecemeal. The procedure time was recorded in 36 lesions (mean time 12 minutes; range 4–40). Of the 65 colorectal lesions, 64 (98.5%) were successfully removed by UEMR (TABLE 2). The exception was a lesion in the sigmoid that was 80% removed by UEMR. However, the remaining part of the lesion was located behind a fold and could not be reached by this route. The submucosal injection was then used, achieving complete resection. Despite buoyancy and adequate elevation with submucosal injection, histopathological examination revealed massive submucosal infiltration (SM3), and the patient was referred for surgical treatment. However, she died due to primary lung cancer before colonic surgery. Two more patients with deep submucosal invasion (SM2) were also referred to colectomy. No

TABLE 1. Patient and lesion characteristics.

Gender (%)	
Male	21 (38.2)
Female	34 (61.8)
Age, y	
Median (range)	67 (53–87)
Total n. of lesions	65
Lesion size, mm	
Median (range)	16.67 (10–40)
Lesion localization n.	
Cecum	7
Ascending	25
Transverse	11
Descending	8
Sigmoid	6
Rectum	8
Paris classification	
Is	10
II a	44
Is + II a	11
Histology n. (%)	
Sessile serrated	19 (29.2)
Tradicional serrated	1 (1.5)
Tubular adenoma	22 (33.8)
Tubulovillous adenoma	15 (23.1)
Intramucosal carcinoma	4 (6.2)
Submucosal carcinoma	4 (6.2)

TABLE 2. Procedures and outcomes.

Setting – n. of lesions (%)	
Auto cut	16 (24.6%)
Dry cut	7 (10.8)
Endo cut	42 (64.6)
Resection	
En bloc n. (%)	40 (61.5)
Piecemeal n. (%)	25 (38.5)
Procedure time, min*	
Median (range)	12 (4–40)
Success n. (%)	64 (98.5)
Complications	
Total n. of patients	3 (5.4)
Bleeding	2 (3.6)
Post-polypectomy syndrome	1 (1.8)
Perforation	0
Follow-up, n. patients (%)	41 (74.5)
Mean of follow-up – months (range)	6.8 (1–17)
Residual at follow-up, n. lesions (%)	3 (6)

*Recorded in 36 procedures.

residual cancers were found in the surgical specimens in both cases. Additionally, one patient with superficial submucosal invasion (SM1) could not have endoscopic follow-up due to comorbidities.

During UEMR AUTOCUT mode, spurting bleeding was observed in two patients (5.45%). Hemostasis was easily achieved in both cases by clipping. Neither required blood transfusion. One patient had severe abdominal pain on the day after the procedure, without signs of pneumoperitoneum by tomography. The patient was treated conservatively with antibiotics. There was no delayed hemorrhage or perforation (TABLE 2).

Fourteen patients did not have the endoscopic evaluation for recurrence. Four patients died before the follow-up (one of them with deep SM invasion). The two other patients with deep submucosal invasion (SM2/3) were submitted for surgical treatment. Two additional patients were lost to follow-up. Five patients, due to severe comorbidities, were not in suitable clinical condition to undergo the new colonoscopy. In one patient, the resection site could not be evaluated due to poor bowel preparation. Follow-up colonoscopy was performed in 41 patients (74.54%) with 50 lesions (76.92%). Local recurrence was detected at three resection sites (6%) (TABLE 2). All recurrences were smaller than 5 mm and were easily removed with cold forceps biopsy.

DISCUSSION

Developed by Binmoeller in 2012⁽⁵⁾, UEMR is a relatively new technique with few articles published in the literature so far^(4,10,12,13,15-17). In our study, we have shown that UEMR is effective, easy-to-learn and with low risk of adverse events.

Marking the margins is optional. However, it is recommended because sometimes it is more difficult to define the edges underwater. The marks can be made with an argon catheter^(5,6) or with the snare tip⁽¹⁾. In this study we used the snare tip (FIGURE 1), which is kept in the working channel while the lumen is filled with water. In addition, we saved time and resources by replacing the argon catheter with the snare.

Electrosurgical settings are determined by trial and error and personal preference⁽¹¹⁾. In the literature, the effect ranged from 2 to 5 and the maximum power, between 30 and 120 W. DRYCUT was the most commonly selected mode^(1,5,8,17). ENDOCUT mode was favored in two studies^(6,10), whilst only Binmoeller et al. in 2015 used AUTOCUT setting⁽¹²⁾. In our study, we initially used the DRYCUT mode, but due to the occurrence of minor, non-clinically significant bleeding, we changed to AUTOCUT mode. However, patients in this group had significant bleeding demanding endoscopic management. Finally, we used ENDOCUT mode, which was used for most patients, with no bleeding experienced. Our sample size does not allow conclusions to be drawn as to which mode is safer. However, we suggest, until trials comparing the different modes are performed, that the endoscopist tests the three modes and verifies which one is of his or her preference.

In the literature, the technical success rate is also high (90%–100%)^(1,4-14,16). In the meta-analysis, the pooled resection of UEMR on 508 colorectal lesions was 96.36%⁽¹⁴⁾. In our study, only one of the 65 lesions (resection rate of 98.5%) was not completely resected by the underwater technique alone. This was a 3 cm lesion in the sigmoid, the most distal part of which was resected underwater. The remainder of the lesion was then completely removed after saline submucosal injection with adequate lifting. This case was considered therapeutic failure. However, there may be cases like

this in which CEMR can be complementary to UEMR and vice versa. Despite the floatage and lifting, this lesion had deep submucosal invasion (SM3). In addition to this described case, there were two more lesions with submucosal invasion (SM2). And in all cases (even those with deep invasion) there was good buoyancy. Although not yet discussed in the literature, it would be expected that invasive lesions will not float; being a rational analogy between the “lifting-sign” and the “floating-sign”. However, even the reliability of the “lifting-sign” in predicting invasive malignancy has been questioned. A multicenter study found around 40% of lesions with invasion beyond 1000 µm with a false negative non-“lifting-sign”, and the endoscopic evaluation to be more reliable than the “lifting-sign”⁽¹⁸⁾.

The rate of submucosal invasion in our study was 6.2% which is similar to the recent UEMR meta-analysis (5.9%)⁽¹⁴⁾ and slightly smaller to the 8% reported in conventional EMR and/or polypectomy meta-analysis⁽¹⁹⁾.

The procedure time in our study ranged from 4 to 40 minutes, with a mean time of 12 minutes. Similar to the mean time described by Curcio et al.⁽¹⁾ (11.8 minutes). Most of the time was spent on the marking of the lesion rather than on the submerged phase itself (subjective analysis), and unfortunately the time was only recorded in just over half of the procedures (55%).

Safety is an aspect that draws attention with the underwater technique. There is a relatively low incidence of adverse events, and the vast majority of them had a conservative management^(1,4-14). The total incidence of adverse events in our study was 5.4%. There were two immediate bleeding episodes (3.6%), both successfully treated endoscopically with clips. The hemorrhage rate after UEMR in the literature ranged from 0% to 18%, with only a few cases of delayed bleeding described⁽¹⁾. According to Spadaccini et al.⁽¹⁴⁾ meta-analysis, the during-UEMR procedure bleeding rate was 3.14% and post procedural hemorrhage rate occurred in 2.85%⁽¹⁴⁾. Also worthy of mention is the bleeding post resection treatment when the intestine is filled with water, as the bleeding point can accurately be identified when using water irrigations⁽⁵⁾. A peculiar aspect with our work is that major bleeds only occurred with the use of AUTOCUT mode. However, without further investigation, it is impossible to draw any conclusion between the electrosurgical setting and the incidence of bleeding. In this study, there was one case of post-polypectomy syndrome. To our knowledge, this is the first case of post-polypectomy syndrome described in the literature. In our study, as in others, there were no cases of perforation. As far as we know, only two cases of perforation post UEMR have been described. One case was in a retroflexion maneuver that may be related to this adverse event⁽²⁰⁾. The other case occurred when it was injected into the submucosa before the UEMR (hybrid technique)⁽¹⁶⁾. The authors of this paper also suggest that stretching of the colonic wall by the submucosal injection is probably to be the cause. Therefore, until further studies are conducted about the relation between retroflexion and hybrid technique with the perforation after underwater resection, we recommend that UEMR should be performed only in forward view and without submucosal injection.

The incidence of recurrence after UEMR in the literature varied between null and 20%, being 8.82% in UEMR systematic review⁽¹⁴⁾. In our study, the recurrence rate was 6%, comparable to that described by Schenck et al.⁽⁴⁾ (7.3%). Unfortunately, a lower-than-expected number of patients had endoscopic surveillance (74.54%),

with a significant percentage of patients who died or were too ill to undergo colonoscopy. In addition, endoscopic surveillance in our study was performed with white light, virtual chromoscopy (NBI), conventional (indigo carmine), and biopsy of the scars, which may increase the sensitivity⁽²¹⁾.

The number of patients underwent to UEMR in our cohort was surpassed only by Curcio et al.⁽¹⁾, Binmoeller et al.⁽¹²⁾, Siau et al.⁽¹⁵⁾ and Yamashina et al.⁽⁹⁾; being the Brazilian study about UEMR with more patients.

In summary, UEMR seems to be safe and effective. Taken together, our results and the data in the literature encourage the dissemination of the method. A natural issue is the comparison with the submucosal injection technique. In a retrospective study, Schenck et al.⁽⁴⁾ observed similar safety with both methods (CEMR and UEMR), however, there was superiority in terms of complete resection indexes, and a lower frequency of recurrence with the underwater technique. In a recent prospective randomized study, the en bloc resection rate was higher with UEMR than CEMR, without significant difference with adverse events⁽⁹⁾. More trials with a larger casuistry and with long-term follow-up are needed for more consistent conclusions. We hope that we can finalize our randomized study (NCT03021135) soon to help answer these questions.

Authors' contribution

Data curation: Lenz L, Martins B, Kawaguti FS, Tellian A, Pennachi CMPS, Sorbello M, Gusmon C, Paulo GA, Uemura R, Geiger S, Lima MS, Safatle-Ribeiro A, Baba E, Hashimoto CL, Maluf-Filho F, Ribeiro Jr U. Resources: Martins B. Investigation: Kawaguti FS, Lima MS, Geiger S, Baba E, Hashimoto CL, Maluf-Filho F. Conceptualization: Lenz L, Martins B, Paulo GA, Safatle-Ribeiro A, Hashimoto CL, Maluf-Filho F, Ribeiro Jr U. Formal analysis: Lenz L, Maluf-Filho F. Methodology: Lenz L, Martins B, Paulo GA, Baba E, Hashimoto CL, Maluf-Filho F, Ribeiro Jr U. Visualization: Lenz L, Kawaguti FS, Paulo GA, Lima MS, Safatle-Ribeiro A, Hashimoto CL, Maluf-Filho F. Writing-original draft: Lenz L, Kawaguti FS, Safatle-Ribeiro A, Maluf-Filho F. Writing-review & editing: Lenz L, Martins B, Safatle-Ribeiro A, Maluf-Filho F. Project administration: Lenz L, Martins B, Paulo GA, Maluf-Filho F, Ribeiro Jr U. Supervision: Lenz L, Maluf-Filho F, Ribeiro Jr U. Validation: Safatle-Ribeiro A, Maluf-Filho F.

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Luciano Lenz: 0000-0002-7945-8158.
Bruno Martins: 0000-0002-0282-0753.
Fabio Shiguehisa Kawaguti: 0000-0002-6709-9979.
Alexandre Tellian: 0000-0002-2279-6623.
Caterina Maria Pia Simoni Pennachi: 0000-0001-6963-8211.
Mauricio Sorbello: 0000-0002-4021-6573.
Carla Gusmon: 0000-0003-3803-3417.
Gustavo Andrade de Paulo: 0000-0002-7926-9373.
Ricardo Uemura: 0000-0002-2970-7136.
Sebastian Geiger: 0000-0001-6626-9131.
Marcelo Simas de Lima: 0000-0002-4601-7276.
Adriana Safatle-Ribeiro: 0000-0001-7686-8859.
Elisa Baba: 0000-0001-7261-9054.
Claudio Lyoiti Hashimoto: 0000-0002-5763-339X.
Fauze Maluf-Filho: 0000-0001-8875-420X.
Ulysses Ribeiro Jr: 0000-0003-1711-7347.

Lenz L, Martins B, Kawaguti FS, Tellian A, Pennachi CMPS, Sorbello M, Gusmon C, Paulo GA, Uemura R, Geiger S, Lima MS, Safatle-Ribeiro A, Baba E, Hashimoto CL, Maluf-Filho F, Ribeiro Jr U. Ressecção da mucosa endoscópica sob imersão d'água para lesões colorretais não pediculadas. Um estudo prospectivo de braço único. *Arq Gastroenterol.* 2020;57(2):193-7.

RESUMO – Contexto – A ressecção endoscópica da mucosa sob imersão d'água (REMS) surgiu como um método revolucionário que permite a ressecção de lesões colorretais sem injeção submucosa. A literatura brasileira sobre essa técnica é escassa. **Objetivo** – A finalidade deste estudo foi avaliar a eficácia e segurança da técnica REMS na remoção de lesões colorretais não pediculadas em dois centros terciários brasileiros. **Métodos** – Este estudo prospectivo foi realizado entre junho de 2016 e maio de 2017. As lesões sem tentativa de ressecção prévia, não pediculadas e sem sinais de invasão submucosa foram ressecadas pela técnica REMS. **Resultados** – Um total de 55 pacientes com 65 lesões foram incluídos. Todas as lesões, exceto uma, foram removidas com sucesso e completamente por REMS (taxa de sucesso de 98,5%). Durante a REMS, foram observados dois casos de sangramento (3,0%). Uma paciente apresentou dor abdominal no dia seguinte à ressecção sem pneumoperitônio. Não houve perfuração ou sangramento tardio.

Conclusão – Este estudo apoia os dados existentes, indicando taxas aceitáveis de sucesso técnico e baixa incidência de eventos adversos com a REMS. Os resultados deste estudo brasileiro foram consistentes com estudos internacionais prévios.

DESCRITORES – Pólipos intestinais. Neoplasias colorretais. Ressecção endoscópica de mucosa. Imersão. Estudos prospectivos.

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