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Small as well as large colorectal lesions are effectively managed by endoscopic mucosal resection technique

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ABSTRACT – **Background** – Endoscopic mucosal resection (EMR) is an easy-to-use treatment option for superficial colorectal lesions, including lesions ≥20 mm. **Objective** – To evaluate the effectiveness of EMR. **Methods** – We evaluated 430 lesions removed by EMR in 404 patients. The lesions were analyzed according to their morphology, size, location, and histology. Lesions <20 mm were resected en bloc, whereas lesions ≥20 mm were removed by piecemeal EMR (p-EMR). Adverse events and recurrence were assessed. **Results** – Regarding morphology, 145 (33.7%) were depressed lesions, 157 (36.5%) were polypoid lesions and 128 (29.8%) were laterally spreading lesions, with 361 (84%) lesions <20 mm and 69 (16%) ≥20 mm. Regarding histology, 413 (96%) lesions were classified as neoplastic lesions. Overall, 14 (3.3%) adverse reactions occurred, most commonly in lesions removed by p-EMR (P<0.001) and associated with advanced histology (P=0.008). Recurrence occurred in 14 (5.2%) cases, more commonly in lesions removed by p-EMR (P<0.001). **Conclusion** – EMR is an effective technique for the treatment of superficial colorectal lesions, even of large lesions.

Keywords – Colonic polyps; adenoma; colonoscopy; endoscopic mucosal resection; large lesions; colorectal neoplasm.

INTRODUCTION

Endoscopic removal of colorectal lesions reduces the incidence and mortality of colorectal cancer (CRC), proving to be a decisive tool in its prevention[1]. A number of techniques have been proposed, ranging from a simple polypectomy to endoscopic submucosal dissection (ESD). Endoscopic mucosal resection (EMR) is considered the first-line treatment for most superficial lesions[2,3].

Inject-and-cut EMR is the most commonly used EMR technique. Currently, in addition to saline solution, colloid solutions are most commonly used.

It is important to recognize the individual characteristics of the lesions to be resected, as well as the predictive histological diagnosis in order to select the most appropriate approach. EMR represents a major advance in endoscopic treatment by allowing en bloc resection of superficial lesions <20 mm. Lesions ≥20 mm pose a greater challenge as they require a resection piece by piece, called piecemeal EMR (p-EMR). The main criticisms of p-EMR are higher recurrence or residual lesion rates. ESD is also an option for these lesions, allowing en bloc resection with lower recurrence; however, it is associated with a higher risk of perforation and requires a long learning curve[4].

For the management of large non-pedunculated colorectal neoplasms, the European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline suggests that most of these lesions can be treated with p-EMR[5]. To reduce this risk caused by local recurrence after EMR, it is recommended that the first follow-up be performed between two and six months after endoscopic resection[6,7].

The objective of the present study was to evaluate the effectiveness of EMR.

METHODS

Study design

This prospective cross-sectional study was conducted in the Department of Endoscopy at *Hospital Santa Casa de Caridade de Bagé*, Brazil. It was approved by the Research Ethics Committee of the institution and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all individual participants.

Patients

From January 2008 to December 2019, 430 EMRs of the colon and rectum were performed in 404 patients. Mean patient age was 62.4±10.4 years (range, 34–94 years), and 206 (51%) were men.

Equipment

After detection with white-light imaging, magnification chromoendoscopy with 0.4% indigo-carmine or image-enhancement endoscopy (IEE) were used for pit and capillary pattern analysis. High-definition colonoscopes were used, including LASEREO system since 2015.

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Lesions' characteristics

All lesions showed an endoscopic appearance that suggested the depth was limited to the mucosa or submucosa. The Paris classification was used to describe the morphology of the lesions[8]. According to Kudo et al.[9], LSLs were classified as granular (LSL-G), divided into homogeneous (LSL-G-H) and nodular mixed (LSL-G-N) subtypes and non-granular (LSL-NG), subclassified into flat elevated (LSL-NG-FE) and pseudo-depressed (LSL-NG-PD) subtypes.

Lesions subjected to EMR had pit and capillary patterns, according to the Kudo-Kimura and Teixeira classifications, respectively, suggestive of neoplastic lesion without massive submucosal invasion and were, therefore, amenable to endoscopic treatment[10-12]. All lesions were analyzed by an endoscopist with experience in IEE.

Advanced histology was defined as high-grade dysplasia or early carcinoma.

Endoscopic procedures

EMR was indicated in cases of superficial depressed lesions, sessile lesions ≥10 mm in diameter and LSLs. The inject-and-cut technique used a hypertonic saline solution – 4% sodium chloride. Lesion characteristics such as size, morphology, location, and histology were evaluated, as well as adverse events and recurrence of the endoscopic procedure. Lesion size was measured with open biopsy forceps. Location was divided into the right colon segment (from the transverse colon to the cecum) and the left colon segment (from the rectum to the descending colon).

For histological analysis, specimens were mounted on Styrofoam plates, fixed in 10% formalin, and then evaluated according to the World Health Organization classification for histopathology[13].

Lesions <20 mm were resected en bloc, whereas lesions ≥20 mm were removed by p-EMR (FIGURE 1) in a single session. Bleeding was divided into intraprocedural and delayed (after discharge from the endoscopy department). Prophylactic clipping was not performed to close the post-EMR defect.

Recurrence (or residual neoplasm) was defined as the presence of neoplastic tissue in the area of previous resection, as diagnosed by follow-up colonoscopy. Patients underwent follow-up at 3–6 and 12 months. Recurrent/residual mucosal lesions were treated with a second EMR and identified by the scar.

Argon plasma coagulation (APC) was used in the resection margin in 46 lesions ≥20 mm in a sequential, non-randomized manner. APC was not used in the first 23 lesions ≥20 mm.

Statistical analysis

Statistical analysis was performed using Stata, version 15.1. Categorical variables were expressed as absolute and relative frequencies and analyzed by Fisher's exact test. Numerical variables were expressed as mean and standard deviation and analyzed by analysis of variance (ANOVA). The significance level was set at 5% for two-tailed tests.

RESULTS

EMR was performed in 430 lesions, of which 145 (33.7%) were depressed lesions, 157 (36.5%) were polypoid lesions and 128 (29.8%) were LSLs. The mean lesion size was 12.2±9.8 mm; 361 (84%) lesions were <20 mm and 69 (16%) were ≥20 mm, removed en bloc and by p-EMR, respectively. Distribution of lesions' size is shown in TABLE 1. Regarding histology, 413 (96%) as neoplastic lesions (adenomas and early carcinomas) (TABLE 2). Advanced histology was more frequently observed in lesions removed by p-EMR than in lesions resected en bloc (50.7% vs 19.5%, P<0.001). Descriptive analysis of lesions with advanced histology is shown in TABLE 3.

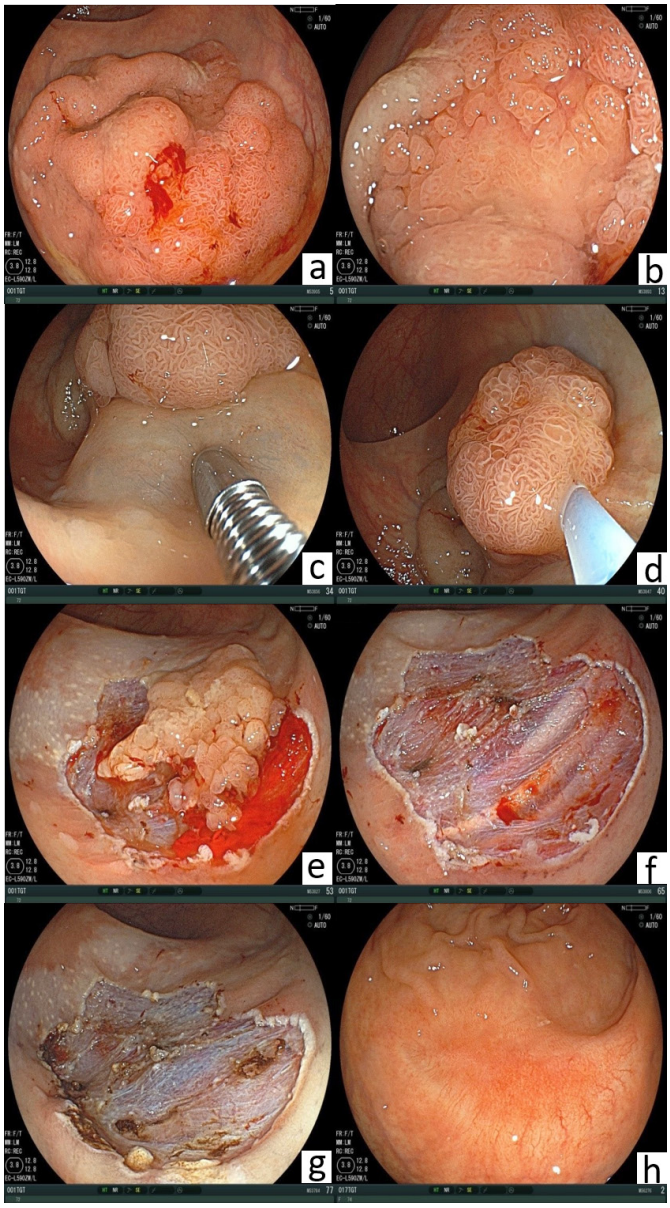

FIGURE 1. A) LSL-G-N subtype; **B)** Fibrosis area; **C)** Injection of 4% NaCl under the lesion; **D-E)** Piecemeal EMR; **F)** Post-resection; **G)** Post-resection and APC; **H)** Scar.

A total of 128 LSLs were removed endoscopically. Granular LSL-G-N subtype were significantly larger (P<0.001) and were more commonly subjected to p-EMR (P=0.003), with higher recurrence (P=0.02) and more adverse events (P=0.03). Advanced histology was more frequently observed in the pseudo-depressed (62.5%) and nodular mixed (53.9%) subtypes, with statistical significance in relation to the other subtypes (P<0.001) (TABLE 4).

TABLE 1. Distribution of lesion size.

Size (mm)	N	%
<10	146	33.9
10–19	215	50.0
20–29	39	9.1
39–39	13	3.0
≥40	17	4.0

TABLE 2. Descriptive analysis of colorectal lesions.

Characteristic	N	%
Sex (n=404)		
Female	198	49.0
Male	206	51.0
Age (mean; SD)	62.4	10.4
Age (years) (n=404)		
<50	41	10.2
≥50	363	89.8
Size (mean; SD)	12.2	9.8
Size (mm)		
<20	361	84.0
≥20	69	16.0
Morphology		
Depressed lesion	145	33.7
Polypoid	157	36.5
LSL	128	29.8
Location		
Left colon segment	196	45.6
Right colon segment	234	54.4
Pathology		
Non-neoplastic	17	4.0
Neoplastic	413	96.0
Technique		
En bloc	361	84.0
Piecemeal	69	16.0
Adverse reactions		
No	416	96.7
Yes	14	3.3
Follow-up		
No	158	36.7
Yes	272	63.3
Recurrence (n=272)		
No	258	94.8
Yes	14	5.2
Total	430	100

SD: standard deviation; LSL: laterally spreading lesion.

TABLE 3. Descriptive analysis of lesions with advanced histology.

Characteristic	% advanced histology	*P*-value
Sex (n=101)		<0.001
Female	17.2 (n=34)	
Male	32.5 (n=67)	
Age (years) (n=101)		0.257
<50	17.1 (n=7)	
≥50	25.9 (n=94)	
Size (mm)		<0.001
<20	19.4 (n=70)	
≥20	50.7 (n=35)	
Morphology		0.100
Depressed lesion	25.5 (n=37)	
Polypoid	28.7 (n=45)	
LSL	18.0 (n=23)	
Location		0.072
Left colon segment	28.6 (n=56)	
Right colon segment	20.9 (n=49)	
Technique		<0.001
En bloc	19.4 (n=70)	
Piecemeal	50.7 (n=35)	
Adverse events (n=105)		0.05
No	23.6 (n=98)	
Yes	50.0 (n=7)	
Follow-up		<0.001
No	5.7 (n=9)	
Yes	35.3 (n=96)	
Recurrence		0.259
No	34.5 (n=89)	
Yes	50.0 (n=7)	
Total	24.4 (n=105)	-

LSL: laterally spreading lesion.

TABLE 4. Characteristics of laterally spreading lesions.

Group	LSL-G-H (n=69)	LSL-G-N (n=13)	LSL-NG-PD (n=8)	LSL-NG-FE (n=38)	*P*-value
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	
Age (years)	62.9 (10.6)	67.2 (13.8)	61.0 (9.4)	63.0 (11.0)	0.5*
Size (mm)	18.3 (10.5) a	36.8 (15.3) b	15.8 (4.9) a	16.8 (7.9) a	<0.001*
	%	%	%	%	
Advanced histology					<0.001**
No	88.4	46.2	37.5	92.1	
Yes	11.6	53.9	62.5	7.9	
Technique					0.003**
En bloc	68.1	15.4	75.0	65.8	
Piecemeal	31.9	84.6	25.0	34.2	
Adverse reactions					
No	95.6	69.2	100.0	94.7	0.03**
Yes	4.4	30.8	0.0	5.3	
Recurrence					0.02**
No	91.3	61.5	1000	94.7	
Yes	8.7	38.5	0.0	5.3	

LSL-G-H: granular laterally spreading lesion of the homogeneous subtype; LSL-G-N: granular laterally spreading lesion of the nodular mixed subtype; LSL-NG-PD: non-granular laterally spreading lesion of the pseudo-depressed subtype; LSL-NG-FE: non-granular laterally spreading lesion of the flat elevated subtype. *Analysis of variance (b>a). **Fisher's exact test.

Overall, 14 (3.3%) adverse reactions occurred, most commonly in lesions removed by p-EMR (17.4% vs 0.6%, *P*<0.001) and associated with advanced histology (*P*=0.008). Intraprocedural bleeding occurred in 13 (3%) of all EMRs, with 11 cases of minor bleeding, controlled with injection therapy or APC. There were two cases of major bleeding. One occurred after p-EMR of a LSL-G-H subtype, measuring about 40 mm and located in the cecum, which was controlled with APC. After 36 hours, the patient developed pneumoperitoneum and was referred for surgery. The other case of major bleeding occurred after en bloc EMR of a polypoid intramucosal adenocarcinoma with superficial submucosal invasion, located in the rectum, and was controlled with the application of endoclips. There were no cases of delayed bleeding.

Post-EMR micro-perforation occurred in one case of a LSL-G-N subtype, measuring about 50 mm and located in the rectum. The case was managed conservatively with hospitalization, hydration, and antibiotics. There were no deaths.

A total of 272 (63.3%) lesions were followed up, with the first follow-up at 3–6 months, and then at 12 months after the index EMR, being 210 lesions (58.2% of lesions <20 mm) that were resected en bloc and 62 lesions (89.9% of lesions ≥20 mm) that were removed by p-EMR. Recurrence occurred in 14 (5.2%) cases, all detected at first follow-up, and was more common in lesions removed by p-EMR (17.4% vs 0.6%, *P*<0.001). Thirteen (92.9%) of the residual/recurrent lesions were successfully treated with a second EMR.

Of 69 lesions ≥20 mm, 46 received complementary APC in the resection margin. This group had a 15.2% recurrence rate, whereas the group that did not receive APC had a 21.7% recurrence rate (*P*=0.5).

DISCUSSION

EMR is a safe and effective tumor resection technique, even for large lesions. This approach offers an interesting alternative to surgery, including treatment of early carcinomas with superficial submucosal invasion. Chromoendoscopy and IEE are considered effectives resources in the characterization of colorectal lesions and in the risk stratification of submucosal invasion through pit and capillary pattern analysis[14-16]. Proficiency in the use of IEE techniques has been suggested and recommended for endoscopic recognition of submucosal invasion[5]. Kawaguti et al.[17] demonstrated 96.7% accuracy in the assessment of large lesions suspicious for submucosal invasion using pit pattern analysis for the predictive endoscopic diagnosis. In the present study, the endoscopist had expertise in IEE. Seventeen (4%) hyperplastic lesions with a type II-O pit pattern were resected, i.e., with high specificity for sessile serrated adenoma/polyp (SSA/P). The high variability that still exists among pathologists in the differential diagnosis of hyperplastic polyps and SSA/Ps may explain this difference in diagnosis.

Yandrapu et al.[18] demonstrated higher rates of en bloc resection (*P*=0.02) and lower rates of residual lesions (*P*=0.02) with the use of colloid solution compared with normal saline solution for lesions >20 mm. In the present study, hypertonic saline solution was used in all cases.

Advances in endoscopic resection techniques should reduce the rate of surgical indication in lesions amenable to endoscopic treatment, decreasing the rate of adverse events, and costs. Peery et al.[19] reported an increase in the incidence of surgery for non-malignant polyps from 5.9 to 9.4 per 100.000 adults. In a series of 262.843 surgical procedures for non-malignant colorectal polyps, the morbidity was 25.3%, and patients developing a postoperative adverse event had increase in mean hospital length of stay (*P*<0.0001) and in mean hospitalization costs (*P*<0.0001)[20]. Hassan et al.[21] showed that 14% of the patients were immediately referred for surgery before any attempt at endoscopic resection, mainly because of the endoscopic appearance suggestive of submucosal invasion. In the present study, one patient was referred for surgery, in whom bowel perforation was detected 36 hours after the use of APC to control post-EMR massive bleeding.

A meta-analysis showed that most large LSLs are non-invasive

(91.5%) and, therefore, can be treated with p-EMR. LSLs measuring 20–29 mm and ≥30 mm have a 9.2% and 16.5% risk of submucosal invasion, respectively, and that invasive lesions are more common in the pseudo-depressed (31.6%) and nodular mixed (10.5%) subtypes[22]. In the present study, advanced histology was more frequently observed in the pseudo-depressed (62.5%) and nodular mixed (53.9%) subtypes, with statistical significance (P<0.001). Overall, advanced histology was more noticeable in lesions that were resected by the piecemeal technique (P<0.001).

ESD presents significant adverse events in the initial training phase, and its use is limited to centers of excellence in Western countries. Russo et al.[23] showed similar results for EMR and ESD of LSLs in terms of complete resection and curative resection. Bleeding occurred in 9.6% of EMRs and 2.8% of ESDs, especially immediate minor bleeding. Bleeding was more frequent in the removal of LSL-G than LSL-NG (OR 2.46). The present study found a rate of 3.3% of adverse reactions, which were more frequent in lesions removed by p-EMR (P<0.001) and associated with advanced histology (P=0.008). EMR of LSL-G-N subtype resulted in more complications (P=0.03). Intraprocedural bleeding occurred in 3% of all EMRs, with minor bleeding in 11 of the 13 cases, controlled with endoscopic therapy. There were two cases of major bleeding, progressing to perforation after APC, and the other occurred after en bloc EMR of an invasive carcinoma and was controlled with the application of endoclips.

A recent meta-analysis concluded that routine use of prophylactic clipping does not reduce the overall risk of bleeding after polypectomy, but it showed a reduced risk of bleeding after resection of lesions ≥20 mm (P=0.02) or located in the proximal colon (P<0.001)[24]. Prophylactic clipping was not used in any of our patients.

Perforation is one of the most feared adverse events of endoscopic resection. In a recent meta-analysis, the risk of perforation was higher in ESD than in EMR (5.9% vs 1.2%)[23]. We had one case of micro-perforation in a giant LSL-G-N subtype, which was successfully treated conservatively.

The main criticism of EMR is the relatively high recurrence rate. In a meta-analysis, Belderbos et al.[25] identified a significantly higher risk of recurrence after p-EMR than after en bloc resection (P<0.0001). Most recurrences (88%) were found during the first follow-up colonoscopy, with a higher prevalence among carcinomas (P<0.001), and p-EMR was recognized as the only risk factor associated with recurrence. In previous studies by our group, we showed a significant association of the recurrence of lesions removed by p-EMR and with advanced histology[2,26]. In the present study, recurrence was 5.2% and associated with p-EMR (P<0.001). Although recurrence occurred often (almost a fifth of the cases) after p-EMR in larger lesions, they could be successfully managed by a new EMR during follow-up. When only LSLs were analyzed, recurrence was associated with the nodular mixed subtype (P=0.02), and in all cases the residual lesion was relatively small and amenable to successful endoscopic retreatment. There were no cases of late recurrence in the present study.

The use of APC remains controversial. A multi-center study showed lower recurrence at first follow-up in patients undergoing thermal ablation of the post-EMR mucosal defect than in controls receiving no additional treatment (P<0.001), which was directly related to the p-EMR (P<0.001) and lesion size ≥40 mm (P=0.001)[27]. In the present study, 69 lesions ≥20 mm were removed by p-EMR; of these, 46 received complementary APC of the post-EMR mucosal defect margin. Lower recurrence was observed in this group, but without significance (P=0.5).

The present study has some limitations. First, the study was conducted in a single endoscopy unit. Second, all procedures were performed by the same endoscopist. Third, the endoscopist had experience in EMR, which may have contributed to the low rate of serious complications. Fourth, the endoscopist had expertise in chromoendoscopy and IEE, correctly recognizing the lesions that had an indication for endoscopic resection.

In conclusion, this study showed that EMR is a safe and effective procedure for removing superficial neoplasms of the colon and rectum, remaining a viable option in the 21st century, and even allowing the curative resection of large lesions and early carcinomas with a low rate of serious adverse events.

Authors' contribution

Santos CEO: project management; Nader LA, Sanmartin IDA: formal analysis; Scherer C: conceptualization; Furlan RG: data preservation; Santos CEO: writing; Santos CEO, Pereira-Lima JC: review and editing.

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Santos CEO, Nader LA, Scherer C, Furlan RG, Sanmartin IDA, Pereira-Lima JC. Grandes e pequenas lesões colorretais são efetivamente tratadas pela técnica de mucosectomia. Arq Gastroenterol. 2022;59(1):16-21.

RESUMO – **Contexto** – Ressecção endoscópica da mucosa (REM) é uma opção fácil para o tratamento das lesões superficiais do cólon e reto, inclusive para as lesões ≥20 mm de diâmetro. **Objetivo** – Avaliar a efetividade da REM. **Métodos** – Este estudo prospectivo observacional avaliou 430 lesões ressecadas por REM em 404 pacientes. As lesões foram analisadas de acordo com a morfologia, tamanho, localização e histologia. Lesões <20 mm foram removidas em bloco, enquanto lesões ≥20 mm foram ressecadas em *piecemeal* REM (p-REM). Eventos adversos e recorrência foram avaliados. **Resultados** – Quanto à morfologia, 145 (33,7%) eram lesões deprimidas, 157 (36,5%) eram lesões polipoides e 128 (29,8%) eram lesões que se espalham lateralmente, com 361 (84%) lesões <20 mm e 69 (16%) ≥20 mm. Em relação à histologia, 413 (96%) foram classificadas como lesões neoplásicas. Globalmente tivemos 14 (3,3%) de reações adversas, mais presente nas lesões ≥20 mm removidas por p-REM (P<0,001) e associadas com histologia avançada (P=0,008). A recorrência ocorreu em 14 (5,2%) casos, sendo mais observada em lesões removidas por p-REM (P<0,001). **Conclusão** – REM é uma técnica efetiva para o tratamento das lesões colorretais superficiais, até mesmo para as grandes lesões.

Palavras-chave – Pólipos colônicos; adenoma; colonoscopia; ressecção endoscópica; grandes lesões; neoplasia colorretal.

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