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Evaluation of recurrence and surgical complementation rates after endoscopic resection of large colorectal non-pedunculated lesions

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ABSTRACT

Background and aim: the process that leads to the development of colorectal cancer takes many years and most tumors originate from polyps and non-polypoid lesions. Techniques of endoscopic resection are surgical treatment options, even in case of large lesions or with initial invasion. This study aimed to evaluate the recurrence and surgical complementation rates after endoscopic resection of large colorectal non-pedunculated lesions.

Methods: a retrospective, longitudinal and descriptive trial was performed via an analysis of colonoscopies with the resection of non-pedunculated lesions larger than 3 cm, performed between 2014 and 2017.

Results: sixty-two lesions were included from 61 patients and 32 (52.5 %) were female. The age ranged from 36 to 89 years, with a mean age of 60.5 years. Lesions had an average diameter of 40.08 mm, ranging from 30 to 80 mm. Regarding the location of the lesions, the most frequent colonic segments were the ascending and rectum, both accounting for 22.6 %. Considering the morphologic endoscopic classification, 67.7 % were granular laterally spreading tumors (LST), 38.8 % were homogeneous granular

and 29 % were mixed granular. The most frequent histological types were tubulovillous adenoma (30.7 %) and intramucosal adenocarcinoma (29 %). The resection technique was piecemeal mucosectomy in 85.5 %. Five lesions were removed by *en bloc* mucosectomy, two (3.2 %) by endoscopic submucosal dissection (ESD) and two (3.2 %) by a hybrid technique. The recurrence rate was 25.8 %. Three patients needed complementary surgical treatment and the clinical success of endoscopic treatment was 95.1 %.

Conclusion: recurrence rate after endoscopic resection of large colorectal lesions was 25.8 % and surgical complementation rate due to failure in the endoscopic treatment of recurrence was 4.8 %.

Keywords: Colorectal lesion. Laterally spreading tumor. Endoscopic resection. Local recurrence. Endoscopic mucosal resection.

INTRODUCTION

Colonoscopy is considered as the gold standard for colorectal cancer (CRC) screening because it allows not only a diagnosis, but also the resection of precursor lesions. The risk of progression of polyps to CRC is strongly dependent on their size. Small polyps (< 10 mm) rarely present high-grade dysplasia. However, the frequency of high-grade dysplasia and invasive carcinoma significantly increases in large colorectal polyps (1).

Large sessile polyps and laterally spreading tumors (LSTs) can be cured with endoscopic resection, even with superficial invasion of the submucosa. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) increase the therapeutic possibilities in large non-pedunculated lesions, reducing the number of patients referred for surgical treatment (2).

Incomplete endoscopic resection is one of the causes of interval cancer. In fact, adenomatous tissue is capable of rapid regeneration (3), thus, incomplete resection can result in local recurrence (4). Many studies have shown that an incomplete removal contributes to an increased incidence of subsequent CRC (5,6).

Local recurrence is not worrisome, particularly of non-pedunculated lesions that are generally removed by EMR. The problem of the persistence of residual lesions is more

pronounced in piecemeal resections, due to the difficulty of the endoscopic technique and the histological evaluation of the resection margins (7).

Local recurrence following endoscopic resection is not a significant clinical problem in the daily clinical practice, as it can be managed endoscopically with high success rates (7-11). However, recurrence should be monitored with care, as it can lead to a poorer prognosis of the patient, especially in advanced adenomas.

There has been a significant reduction in the number of surgeries for the treatment of colorectal cancer with the advances in endoscopic resection techniques. These are now limited to cases where endoscopic treatment has been unsuccessful, either because of an incomplete resection, histology of invasive cancer or recurrence. Studies have described complementary surgery rates between 4 % and 16 %, depending on the size, morphology and histology of the lesions evaluated (12-17).

The objective of this study was to evaluate the rate of recurrence after endoscopic resection of non-pedunculated lesions larger than 3.0 cm in diameter in the colon or rectum. Furthermore, the rate of complementary surgery for recurrence following endoscopic treatment of these lesions was also assessed.

MATERIALS AND METHODS

A longitudinal, retrospective descriptive study was performed of all colonoscopies with resections of non-pedunculated lesions larger than 3.0 cm in diameter in the endoscopy service of a tertiary hospital from 2014 to 2017. This study was approved by the Ethics Committee for Projects on May 11th, 2017.

Study population

Initially, 63 patients (64 lesions) were included. All patients had undergone an endoscopic resection of non-pedunculated lesions larger than 3.0 cm in diameter.

The following inclusion criteria were used:

- LSTs and sessile polyps removed by endoscopic technique *en bloc* or piecemeal (EMR and ESD).
- Lesions that were endoscopically confirmed as completely removed on examination.

– Colonoscopy control in the service.

The following exclusion criteria were used:

– Patients who did not meet endoscopy cure criteria for endoscopic resection. A resection was considered to be curative when the specimen presented a vertical tumor margin-negative, histologically complete resection, well or moderately differentiated histology, invasion up to 1,000 µg of the submucosa, absence of vascular invasion and budding grade I (18).

– Patients referred for surgical treatment for an initial unsuccessful endoscopic resection.

Two patients were excluded from the study. The endoscopic treatment could not completely remove the lesion in one case and the other presented a histology of invasive cancer. Sixty-one patients were finally included (62 lesions).

Description of endoscopic procedures.

The mucosectomies were performed in patients under sedation and continuous monitoring. ESDs and resections by hybrid techniques were performed under general anesthetic. The choice of the resection strategy was decided by the colonoscopist, according to their personal judgment and recommendations in the current literature. All patients signed a term of institutional consent before undergoing the procedure.

The examinations were performed by experienced physicians with at least three years of endoscopy practice, using the facilities of the sector. This included colonoscopy equipment from Olympus (GIF-TQ160, CF-H180-AL, CF-H190) and Fujinon (EPX 4400HD), snares of various sizes and formats and 23 gauge injecting needles (manufactured by Boston Scientific and Wilson Cook Medical, USA) (Fig. 1). In the case of ESDs and hybrid techniques, specific equipment were used such as the ITKnife (Olympus), Flush Knife (Fujifilm) and Needle Knife (Wilson Cook Medical).

In the classic form of ESD, the dissection of the submucosal layer was performed entirely with specific instruments (knives), without the use of polypectomy snares. In the hybrid technique, the submucosal layer was partially dissected and was completed with the aid of a polypectomy snare.

The wound bed was assessed using white-light and electronic chromoendoscopy (narrow-band imaging [NBI] or flexible spectral imaging color enhancement [FICE]) after the resection, in order to confirm the complete removal and detect signs of any complications (bleeding and perforation).

Hot-biopsy forceps, cold forceps and argon plasma were used to complement the resection in some patients, depending on the colonoscopist's indication. Hemostatic clips were used to prevent and treat bleeding, when necessary. Insufflation of the colon was performed with ambient air in the majority of examinations. From 2017, insufflation with CO_2 was used in almost all procedures. The scars were evaluated during follow-up colonoscopy with white-light and electronic chromoendoscopy and biopsies were performed in every suspicious finding.

Study variables

The demographic characteristics of patients (sex and age), characteristics of the lesions (size, location, morphological classification and histological findings), endoscopic resection technique, immediate complications, recurrence rate and complementary surgical treatment were evaluated. The recurrence rate of the lesions was defined after histological confirmation. A distinction was not made between residual or recurrent lesions. Intramucosal cancer was defined as a neoplastic lesion that involved the lamina propria or muscularis mucosa.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20. Categorical data were represented with the absolute frequency (n) and relative frequency (%) for the analysis of contingency matrices. Continuous variables were presented as the mean ± standard deviation (SD).

The independent samples t-test was performed to test the differences between the continuous variables in the two groups. Associations between categorical variables were tested using the Pearson's Chi-squared test. $p < 0.05$ was considered statistically significant.

RESULTS

Sixty-two lesions from 61 patients were included in the study, 32 females (52.5 %) and 29 males (47.5 %). The ages varied between 36 and 89 years, with a mean of 60.5 years. Lesions size were between 30 and 80 mm, with a mean of 40.08 mm (Table 1). With regard to the location of lesions, the ascendant colon and rectum were the most common topographies, both with a frequency of 22.6 %. Regarding the morphological classification of the lesions, 24 (38.7 %) were defined as homogeneous granular LST, 18 (29 %) as mixed granular LST, nine (14.5 %) as non-granular flat-elevated LSTs and eleven (17.7 %) as sessile polyps (Table 1). In relation to histology, 18 (29 %) lesions were intramucosal adenocarcinomas and 19 (30.7 %) were tubovillous adenomas. High degree dysplasia was found in 35.4 % of cases and low degree dysplasia in 19 % of lesions.

The resection technique used was piecemeal mucosectomy in 53 lesions (85.5 %). Five (8.1 %) were resected by *en bloc* mucosectomy, two (3.2 %) by ESD and two (3.2 %) by a hybrid technique. One of the hybrid technique resections as well as the piecemeal EMR were fragmented (Table 2). Five cases of bleeding occurred during EMR. The only perforation occurred during an *en bloc* mucosectomy of an LST. Complications were treated during the endoscopic procedure. No patient required surgical treatment due to complications.

Control colonoscopy was performed on average 5.6 months after resection. Endoscopic findings suggestive of recurrence were described in 23 (38.7 %) resection scars. These alterations were removed, although the anatomopathological examination confirmed recurrence in just 16 cases (25.8 %). Of the 16 lesions that presented recurrence, 15 (93.7 %) had been removed by the piecemeal technique (Table 3).

The second control colonoscopy was performed in 22 (36 %) of 61 patient. Recurrence was diagnosed in three cases (4.9 %), which had already presented recurrence in the first control colonoscopy. These lesions underwent endoscopic therapy again and had been endoscopically categorized as completely resected in the first control colonoscopy.

Complementary surgical resection due to an unsuccessful endoscopic treatment was necessary in three lesions (4.8 %). One of the patients was referred for surgery due to a continuing recurrence of the second control colonoscopy. A surgical treatment of recurrence was selected in the other two patients during the first control examination, as at the end of procedure the clinician thought that the lesion resection was incomplete. The clinical success of endoscopic treatment was 95.2 %.

DISCUSSION

The expansion of colonoscopy as a method of screening for CRC increases the detection of large colorectal lesions, which can be cured by endoscopic resection, even with superficial invasion of submucosa. However, they represent a constant challenge to the colonoscopist.

There was a predominance of lesions with advanced histology in this study, 29 % were intramucosal adenocarcinomas and 30.7 % tubovillous adenomas. Beyond this, a high degree dysplasia was present in 35.4 % of lesions. This finding is associated with the size of the lesions. Many findings in the literature corroborate this association between size and histology. In 1979, Shinya and Wolf (19) defined a risk of 10 to 20 % of developing invasive carcinoma for adenomas of more than 2 cm at the time of endoscopic resection. Those measuring between 1 cm and 2 cm had a 5 % risk and those smaller than 1 cm had less than a 1 % risk. Therefore, the histology is more advanced the larger the lesion (17).

In relation to the technique used for resection, piecemeal EMR was the most commonly used (85.5 %) in this study, as in the majority of studies in the Western world. Resection by mucosectomy *en bloc* was infrequently used due to the large size of the lesions, which make the procedure more technically difficult and high risk.

ESD and hybrid technique were used in only 6.4 % of patients. Endoscopic submucosal dissection is still infrequently used in Western countries. This is due to the associated higher costs, longer operating time, higher risk of perforation and longer learning curve (20,21).

Studies in Japan and Europe describe a high rate of perforation at the beginning of the learning curve for ESD. However, the rates of complication diminish with increasing

experience, achieving low values (1 to 2 %) in specialized centers in Japan (21).

ESD is often used for non-pedunculated lesions larger than 20 mm due to the benefits of resection *en bloc* in Asian countries, especially Japan and South Korea. This reduces local recurrence and ensures a precise histopathological analysis, via the possibility to assess lateral margins (2).

Mucosectomy of large non-pedunculated lesions have a high rate of recurrence, which is mainly associated with size (larger than 2 cm) and the piecemeal resection technique (9,16,22,23). Other factors for recurrence following EMR have been described, such as tubovillous histology and location in the right colon (24).

In this study, the control colonoscopy showed recurrence in 25.8 % of resections, probably related to the mean size of the lesions (40.08 mm) and fragmented resection, which occurred in 87.1 %. The rate of recurrence was larger in the piecemeal resections, as seen in table 3. There was no statistically significant difference after *en bloc* and piecemeal removal. However, the power of analysis was compromised due to the small size of the *en bloc* sample.

Endoscopic treatment was sufficient in 95.2 % of the lesions that fulfilled the criteria for cure with endoscopic treatment during the initial examination. Endoscopic therapy of large dimension non-pedunculated lesions with the piecemeal technique has a high rate of recurrence. However, this seems to be acceptable in the treatment of these lesions as further endoscopic therapy is possible to control this, despite the high rate of local recurrence. Almost all cases can be cured by an additional endoscopic resection.

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Table 1. Characteristics of patients and resected lesions

Variable	Description
Sex, n (%)	
Male	29 (47.5)
Female	32 (52.5)
Age (years)	
Mean ± SD	60.5 ± 11.12
Range	36-89
Size (mm)	
Mean ± SD	40.08 ± 12.33
Range	30-80
Localization, n (%)	
Cecum	6 (9.7)
Ascending	14 (22.6)
Transverse	11 (17.7)
Descending	7 (11.3)
Sigmoid	10 (16.1)
Rectum	14 (22.6)
Histology, n (%)	
Tubular adenoma	5 (8.2)
Tubular-villous adenoma	19 (30.7)
Intramucosal adenocarcinoma	18 (29)
Serrated traditional adenoma	10 (16.2)
Serrated sessile adenoma	9 (14.5)
Grade of dysplasia	
Low grade dysplasia	12 (19)
High grade dysplasia	22 (35.4)
Morphologic classification, n (%)	11 (17.7)
Sessile polyp	24 (38.7)
LST-GH	18 (29)
LST-NM	9 (14.5)

LST-NG FE

SD: standard deviation; LST-GH: LST granular homogenous; LST-NM: LST-granular nodular mixed; LST-NG FE: LST non-granular flat elevated.

Table 2. Characteristics of endoscopic procedures and complications

Variable	n (%)
Endoscopic technique	
Piecemeal EMR	53 (85.5)
En bloc EMR	5 (8.1)
ESD	2 (3.2)
Hybrid	2 (3.2)
Piecemeal resection	
Piecemeal	54 (87.1)
En bloc	8 (12.9)
Immediate complications	
Bleeding	6 (9.7)
Perforation	1 (1.6)

EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection.

Table 3. Rate of recurrence stratified by endoscopic technique

Endoscopic technique	Present recurrence n (%)	Absent recurrence n (%)	n	p
Piecemeal	15/54 (27.7)	39/54 (72.2)	54	0.668
En bloc	1/8 (12.5)	7/8 (87.5)	8	

	Present recurrence n (%)	Absent recurrence n (%)		

Fig. 1. Piecemeal mucosectomy. A and B. LST granular homogenous. C. Ch romoendoscopy with indigo carmine staining. D. Injection of saline solution into the submucosa. E-G. Piecemeal resection with a polipectomy snare. H. Hemostasia with hot-biopsy. I. Wound bed.