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Please cite this article as:
Arribas Anta Julia, Cañete Ruiz Ángel, Álvarez-Nava Torrego Teresa, Piedracoba-Cadahía Carlos, Rafael de la Cruz Esteban David, Rodríguez Carrasco Marta, Romero Romero Esteban, del Pozo-García Andrés José, Rodríguez Muñoz Sarbelio, Díaz-Tasende José, Marín-Gabriel José Carlos. Long-term follow-up after endoscopic submucosal dissection of colorectal lesions in a Spanish cohort. Rev Esp Enferm Dig 2020. doi: 10.17235/reed.2020.6268/2019.

OR 6268 inglés

Long-term follow-up after endoscopic submucosal dissection of colorectal lesions in a Spanish cohort

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ABSTRACT

Introduction: ESD in the colon is an increasingly important technique in Occidental countries. There are few studies that include long term follow-up.

Aim: to analyze the long term recurrence free survival rate after ESD and to compare recurrence rates according to different variables.

Methods: this was a prospective observational study of patients with a planned ESD from September 2008 to December 2015. When it was not possible to achieve an ESD, hybrid ESD was performed, either en bloc or piecemeal. Kaplan-Meier survival curves were used to assess the five year local recurrence free survival rate and the recurrence rate. The results were compared according to different factors.

Results: of the 89 patients scheduled for ESD who were initially enrolled in the study, 69 were finally included for follow-up. ESD was performed in 31 (45%) patients, KAR in eleven (16%) and pKAR in 27 (39%). The median follow-up was 27 months (range 6-60). The five year disease free survival rate was 81%. The average number of endoscopies needed to eliminate recurrence was two (range 2-7) and no patient required surgery for this reason. The recurrence rate was significantly higher in piecemeal resections *vs* en bloc resections (27% *vs* 15%, p = 0.036) and R1 resections *vs* R0 resections (26% *vs* 0%, p = 0.034). The presence of affected or unknown lateral margins in en bloc resections without other poor prognosis factors had higher recurrence rates but the difference was not statistically significant (28% *vs* 0%, p = 0.09).

Conclusions: in our study, the five year disease free survival rate was 81% and no patient required surgery during follow-up. Piecemeal and R1 resections had significantly higher recurrence rates, as well as LM involvement, although this was not statistically significant.

Keywords: Endoscopic submucosal dissection. Colorectal neoplasia. Survival.

INTRODUCTION

Endoscopic submucosa dissection (ESD) is a technique frequently used in Asiatic countries for the resection of lesions in the digestive tract, with excellent results for en bloc and curative resections (R0). This technique is also becoming popular in occidental countries. However, it is difficult to perform and requires a great skill with a very long learning curve. Thus, the results obtained in Occidental countries have been very variable and not as favorable as those from Asia. A modification of the technique, known as knife-assisted resection (KAR), is sometimes used when the ESD is not technically feasible. In this procedure, a circumferential incision is performed around the lesion and then the resection is performed using a snare, either en bloc or piecemeal. There are very few studies focused on the long term follow-up after the performance of this kind of technique. The aim of this study was to evaluate the five year follow-up after the resection of colorectal lesions by ESD in a tertiary European center and to study the possible factors associated with a greater recurrence rate.

PATIENTS AND METHODS

Patients

This was a prospective observational study. All patients scheduled for ESD of colorectal lesions from January 2008 to December 2015, at the Hospital Universitario 12 de Octubre in Madrid, were consecutively included. ESD criteria were established beforehand according to the recommendations of the Japanese Colon ESD Standardization Implementation Working Group.

An informed consent was obtained from all patients (CEI 14/384; 29/9/2015), which was approved by the Ethics Committee of our center. The study was performed in accordance with the Declaration of Helsinki. The STROBE guidelines for cohort studies were followed when writing the manuscript.

Patients with a follow-up shorter than six months were excluded, as well as those who required surgery, either due to a perforation or technical difficulties, or because their histological specimen met poor prognosis criteria (lymphovascular invasion, poor differentiation, tumor budding or submucosal invasion > 1,000 microns from the muscularis mucosa) (2).

Disease-free survival at five years was analyzed as the primary endpoint, which was defined as the absence of local recurrence during post-ESD endoscopic follow-up.

Methods

Endoscopic assessment of lesions and ESD procedure

ESDs were performed using the following scalpels, according to the endoscopist's preference: Flush Knife® or Flush Knife BT® (Fujifilm, Tokyo, Japan) and IT Knife 2™ or IT Nano™ (Olympus, Tokyo, Japan). Knife-assisted snare resection was used, either en bloc (KAR) or piecemeal (pKAR), when technical difficulties arose. These included poor maneuverability or high perforation risk and when the procedure was excessively long (over 180 minutes in most cases). This procedure was not planned beforehand in any of the cases. Intraprocedural perforations were managed with endoclips.

All lesions were assessed before ESD using a magnification endoscope (EC 590 ZW or EC 600 ZW, Fujifilm, Tokyo, Japan). High-definition scopes, with or without

magnification, were used for endoscopic reviews including EG 590, EG 590 ZW, EG 600 or EG 600 ZW with EPX-4400, EPX-3500 HD or ELUXEO™ 7000 video processors (Fujifilm, Tokyo, Japan). Chromoendoscopy was performed with physical (0.4% indigo carmine) and/or virtual (Fuji Intelligent Chromo Endoscopy, FICE) staining of the post-ESD scar. A hot or cold polypectomy snare was used for the endoscopic management of recurrence, together with standard biopsy forceps and argon gas fulguration probes, according to recurrence characteristics and endoscopist judgement. The electrosurgical unit used was either the ICC 200 or VIO 300D model (ERBE, Tübingen, Germany). Resections were performed by four therapeutic endoscopy experts (JCMG, JDT, AdPG, and SRM).

Post-resection endoscopic follow-up was initially performed after three, six and 12 months, and subsequently on an annual basis. A recurrent lesion was considered as the development of dysplastic tissue at the post-ESD scar, identified by endoscopy or histology (per-protocol biopsies).

Lesions and histology

Lesion morphology was categorized according to the Paris classification (6) and the classification proposed by Kudo for lesions > 10 mm in lateral growth (7). The histopathological diagnosis was based on the Vienna classification (8). En bloc resection was considered when the lesion was removed in a single piece, otherwise it was described as a piecemeal resection. R0 resection was considered for en bloc excisions with negative lateral margins (LM) and vertical margins (VM) (at least 1 mm from the resection border). When no risk factors for lymphatic metastasis were identified by histology, the resection was deemed as curative R0. Resection was considered as R1 when a vertical or horizontal margin was affected by dysplasia or carcinoma (VM+ or HM+). When such involvement could not be ascertained in a margin, due to a diathermy artifact for example, the resection was described as Rx (VMx or HMx) (2,9).

Study variables

Baseline variables were collected from patients including age, sex, anti-platelet or anticoagulant medications and anesthetic risk score according to ASA. Data were collected on lesion location, size, morphology, crypt pattern according to Kudo (10), histopathological diagnosis according to the Vienna classification and procedure duration. Resection type was also collected including ESD, KAR or pKAR and both en bloc and R0 resection rates. These parameters were collected prospectively from the electronic medical records and from the endoscopy and pathology reports obtained during follow-up.

The number of delayed complications (perforation, bleeding) was also recorded during follow-up. Delayed bleeding was defined as a decrease in hemoglobin by > 2 g from the level prior to the procedure or obvious macroscopic evidence such as rectorrhagia or melena.

A subsequent retrospective analysis was performed of the data collected. Recurrence rate was assessed at 60 months and the results were compared according to various factors: ESD *vs* rescue knife-assisted snare resection (KAR or pKAR), en bloc (ESD or KAR) *vs* piecemeal (pKAR) resection, R0 *vs* R1 resection, negative horizontal margins (HM-) *vs* positive (HM+) or uncertain (HMx) margins in lesions with no risk factors for lymphatic metastasis. Results were also compared according to histology (Vienna score higher or lower than 5), size (greater or smaller than 3 cm) and rectal *vs* other colonic locations.

Statistical analysis

Data were collected using the MS-Access software (Microsoft Corp., Redmond, WA, USA). The statistical analysis was performed with the commercial software package IBM SPSS v. 23.0 for Windows (IBM Corp., Armonk, NY, USA). Discrete variables were expressed as percentages and continuous variables were expressed as mean, standard deviation (SD) and range. Data were stratified according to resection type and their distributions were compared using the Chi-squared test for qualitative variables, the Student's t-test for quantitative variables with a normal distribution or Wilcoxon's test for quantitative variables with a non-parametric distribution. Disease-free survival and

recurrence rates were analyzed with Kaplan-Meier curves and the results were compared according to several factors using the log-rank test. Differences were deemed statistically significant when p < 0.05. No specific sample size calculation was performed.

All authors could access the final results of the study, which were reviewed and approved for the final manuscript.

RESULTS

Of the 89 patients scheduled for ESD who were initially enrolled in the study, 20 (22.5%) were excluded. Nine (10%) were excluded as surgery was required; two (2%) due to technical difficulties, three (3%) due to delayed perforation and four (4%) due to poor prognosis histological criteria (deep submucosal invasion). Eleven (12%) were excluded due to a follow-up shorter than six months. Finally, 69 patients were included in the follow-up analysis. Of these, 31 (45%) underwent ESD, eleven (16%) en bloc KAR and 27 (39%) pKAR (Fig. 1).

The mean age was 66.5 ± 12.5 and 60.9% were male. A total of 65.3% of lesions were located in the rectum and mean size was 33.0 ± 17.8 mm. Baseline characteristics, overall and according to technique, are listed in table 1. Statistically significant differences according to type of procedure were only found for lesion size, which was significantly larger for lesions resected by pKAR (p = 0.03) (Table1).

The proportion of en bloc resections was 60.9% and 30.4% of R0 resections. Lesion histology according to the Vienna classification was: 33.4% Vienna 3, 65.2% Vienna 4 and 1.4% Vienna 5 (sm1). The overall delayed bleeding rate was 7.2%. Data concerning initial post-procedure results are listed in table 1. The median follow-up was 27 months (range, 6-60 months), with a mean of 32.2 ± 17.4 months. Thirty-two patients completed the five year follow-up.

Ten recurrences (14.5%) were detected during this period and disease-free survival, based on the Kaplan-Meier curve, was 81% (95% CI: 64-90%) (Fig. 2). When Kaplan-Meier curves were plotted to compare recurrence rates, a statistically significant lower number of recurrences was found for en bloc ESD *versus* piecemeal procedures (15% *vs* 27%; p = 0.04) and for R0 *versus* R1 (0% *vs* 26%; p = 0.03). Amongst en bloc

resections, specimens that were HM+ or HMx with no added poor prognosis factors had a higher recurrence rate, which did not reach statistical significance (28% *vs* 0%; p = 0.09) (Fig. 3). No significant differences were seen in recurrence rates according to type of technique when an en bloc resection was ultimately achieved (ESD or KAR, 17% *vs* 22%, p = 0.1) or a rectal location *versus* other colonic sites (21% *vs* 18%; p = 0.23). Furthermore, there were no significant differences in histology (Vienna < 4 *vs* Vienna 5: 26% *vs* 9%; p = 0.36), size (< 3 cm *vs* > 3 cm: 29% *vs* 14%; p = 0.71) or intraprocedural perforation (25% *vs* 16%; p = 0.5).

Ten recurrences developed during follow-up. Of these, two (3%) occurred after ESD, one (1.5%) after KAR and seven (10%) after pKAR. The latest recurrence occurred after 37 months during follow-up. The mean number of endoscopic procedures needed to eliminate recurrence was two (range, 1-7) and no patients required surgery on these grounds. The median size of recurring lesions was 28 mm (10-60 mm) and all of them were HM+ or HMx on the initial specimen.

DISCUSSION

Few studies are available with long-term follow-up after colorectal lesion resection by ESD and they have shown more favorable recurrence and disease-free survival rates in Asian countries (11-15). Our study showed a 14.5% recurrence rate, which falls within the range reported for other European countries, which range from 4% to 15%. This is a much higher figure than that obtained in Asian countries (3,9,16). Asian experts usually recommend that ESD training should start with gastric lesions before further proceeding to rectal and then colonic ones (17,18). However, the incidence of gastric lesions is lower in the West, hence such training is difficult (19). The results reported here correspond to dissection cases in our center, starting with the first resection with this technique, with no access to advice by *in situ* Asian experts. Furthermore, there were much fewer cases than those reported in Asia, and therefore a longer, more irregular learning curve.

When comparing the recurrence rates, we found that they were significantly higher for lesions resected in a piecemeal fashion as compared to en bloc resections (27% *vs* 15%) and for those where an R0 resection could not be achieved (26% *vs* 0%). Upon

analyzing en bloc resected lesions without risk factors for lymphatic metastasis, a trend towards higher recurrence rates was observed for lesions with either positive or uncertain horizontal margins as compared to those with negative margins (28% *vs* 0%). Although this was not statistically significant. This underscores the importance of free, assessable horizontal margins in order to achieve better outcomes during follow-up. These results are comparable to those reported in the literature (16,17).

As discussed above, the proportion of en bloc resections and R0 resection obtained was lower than reported in most studies (20-22). This is likely due to the fact that these were among the first cases managed at the start of the learning curve. Furthermore, the fact that some lesions had unassessable margins due to diathermy artifacts may have contributed to the small percentage of R0 resections. In a meta-analysis reported in 2017 of 109 studies (3), Western countries had a R0 rate of 71.3%, which was significantly lower than that reported in Asian countries (85.6%). Our data regarding en bloc and R0 resections are very similar to those reported in the study by Milano et al. (12). Hence, they are closer to those obtained in real life by endoscopists taking their first steps with this technique. There were 11% intraprocedural perforations endoscopically resolved and 3% delayed perforations that required surgery, all within the range of previously reported Western studies (23).

The majority of lesions in our study could be resected by ESD (45%); the remaining were managed with KAR (16%) or pKAR (39%) when technical difficulties were insurmountable with the experience gained. When comparing lesion and procedure characteristics, statistically significant differences were found only for lesion size. This was significantly larger for piecemeal resections (pKAR), likely due to their greater difficulty and the longer duration required when changing to a snare-assisted resection. Our team recently published a technical difficulty score for ESD (including the upper and lower GI tract) with the aim to predict the eventual need for snare-assisted resection (24).

In our series, the highest proportion of lesions were Vienna 4 (65.5%). The percentage of Vienna 3 lesions was 33.4%, which is similar to that reported by Asian series. In a 2010 prospective study of ESD for colorectal lesions by Saito et al. (25), the proportion of Vienna 3 and Vienna 4 lesions was similar to that seen in our study. This suggests

that our study intended to include a high proportion of lesions with advanced histological characteristics. These lesions would benefit more from an en bloc resection according to their likelihood of superficial submucosal invasion, even if it entails more technical difficulties for resection by endoscopists who are not experts in ESD. Our intention was that lesions with a greater likelihood of non-advanced histology (low-grade dysplasia) would not be selected for ESD. This selection considered lesion morphology factors, Paris classification and Kudo's LST, pit pattern and microvascular pattern classification using a magnification endoscope (data not included). Since complication risk early in the learning curve was foreseen to fall within the higher reported range, attempts were made to obtain a risk-benefit ratio as favorable and feasible according to definitive histology results (2). There were ten (14.5%) recurrences in our study, and most of them (70%) occurred after pKAR. The mean number of procedures performed to manage recurrence was two and all cases were resolved endoscopically with no need for surgery, which is consistent with other reported studies (16,20). This is another reason why our group decided to preferentially select those lesions with a higher risk of superficial submucosal invasion for ESD.

The strengths of our study are the inclusion of data from the early experience obtained with the first ESD cases in a European center, including hybrid dissections, and of data collected from long-term follow-up. The limitations include a limited number of patients from a single center. Furthermore, the decision of some patients to withdraw from follow-up due to multiple factors (age, comorbidities) contributed to a shortening of the median follow-up.

To conclude, our study provides the first long-term follow-up data after colorectal lesion resection using ESD in a single Spanish center. The disease-free survival rate was 81%, with recurrences occurring more significantly after ESD procedures that required conversion to piecemeal resection and those that failed to achieve an R0 resection. These data show an acceptable disease-free survival rate in the long term for these initial cases, but further studies are needed to validate our results.

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Table 1. Basal characteristics of patients and results after ESD

Variables		Total (%)	ESD (n = 31)	KAR (n = 11)	pKAR (n = 27)	p
Sex						0.17
	Female	27 (39.1)	10 (14.5)	7 (10.1)	10 (14.5)	
	Male	42 (60.9)	21 (30.4)	4 (5.9)	17 (24.6)	
Age (± SD)		66.5 (12.5)	67.06 (12.8)	62.80 (13.9)	67.50 (11.9)	0.93
ASA						0.91
	I-II	44 (63.8)	19 (27.5)	7 (10.1)	18 (26.0)	
	III-IV	25 (36.2)	12 (17.3)	4 (5.9)	9 (13.0)	
Antiplatelet		10 (14.4)	6 (8.7)	1 (1.4)	3 (4.3)	0.57
Anticoagulant		1 (1.4)	0 (0)	0 (0)	1 (1.4)	0.45
Location						0.31
	Colon	24 (34.7)	10 (14.4)	6 (8.7)	8 (11.6)	
	Rectum	45 (65.3)	21 (30.4)	5 (7.2)	19 (27.5)	
Median size (mm)		33 (10-100)	28 (11-50)	20 (10-65)	*40* (17-100)	*0.03*
Morphology						
	0-Is	16 (23.2)	10 (14.4)	1 (1.4)	5 (7.2)	
	LST-G mixed type	16 (23.2)	7 (10.1)	2 (2.9)	7 (10.1)	
	LST-G homogenous	19 (27.5)	9 (13.0)	1 (1.4)	9 (13.0)	
	LST NG type	18 (26.1)	5 (7.3)	6 (8.7)	7 (10.1)	
En bloc resection						0.00
	Yes	42 (60.9)	31 (45)	11 (16)	0 (0)	
	No	27 (39.1)	0 (0)	0 (0)	27 (39)	
R0 resection						0.00
	Yes	21 (30.4)	17 (24.6)	4 (5.7)	0 (0)	
	No	48 (69.6)	14 (20.2)	7 (10.1)	27 (39.1)	
Adverse events						
	Differed bleeding	5 (7.2)	3 (4.3)	0 (0)	2 (2.9)	0.56
	Endoscopic	4 (5.7)	2 (2.9)	0 (0)	2 (2.9)	0.66

treatment of bleeding					
Intraprocedural perforation	8 (11.6)	3 (4.3)	2 (2.9)	2 (4.3)	0.66
Duration of procedure	226.6 ± 75.7	225 (75-340)	194 (60-300)	270 (75-400)	0.71
Histology					0.81
Vienna 3	23 (33.4)	9 (13.0)	5 (7.2)	9 (13.0)	
Vienna 4	45 (65.2)	22 (31.8)	6 (8.7)	17 (24.6)	
Vienna 5 (sm1)	1 (1.4)	0 (0)	1 (1.4)	0 (0)	

ESD: endoscopic submucosal dissection; KAR: knife-assisted resection; PKAR: piecemeal knife-assisted resection; sm1: superficial submucosal invasion (< 1,000 micres); SD: standard deviation.

Table 2. Clinical-pathological characteristics of recurrences after ESD

Case	Age	Location	Size (mm)	Morphology	Histology (Vienna)	Technique	En bloc	R0	HM	VM	Recurr (mont
1	44	Rectum	10	LST NG	4	KAR	Yes	No	+	-	8
2	64	Sigmoid	25	Sesil (0-Is)	4	DSE	Yes	No	x	-	8
3	68	Rectum	20	LST-G h	3	DSE	Yes	No	+	-	37
4	67	Rectum	60	LST-G m	4	pKAR	No	No	x	-	6
5	64	Right	45	LST-G m	4	pKAR	No	No	x	-	6
6	72	Left	18	LST-NG	3	pKAR	No	No	x	-	7
7	84	Sigmoid	22	LST-G h	4	pKAR	No	No	x	-	11
8	45	Rectum	40	LST-G h	4	pKAR	No	No	x	-	12
9	73	Rectum	40	LST-NG	4	pKAR	No	No	x	-	13
10	71	Sigmoid	32	LST-NG	3	pkAR	No	No	x	-	3

HM: horizontal margin; VM: vertical margin; LST-NG: laterally spreading tumor non granular type; ST-G h: laterally spreading tumor granular type; LST-G m: laterally spreading tumor granular mixed type; EMR: endoscopic mucosal resection; x: unknown; Tt: treatment; APC: argon-plasma coagulation.

Fig. 1. Flow-chart of patients included in the study. ESD: endoscopic submucosal dissection; KAR: knife-assisted resection; pKAR: piecemeal knife-assisted resection; SMI: submucosal invasion; m: months. Resolution less than 300 dpi.

Fig. 2. Kaplan-Meier Curve of five-year disease free survival.

Fig. 3. Recurrences in resections with negative horizontal margins *vs* positive/unknown margins (en bloc resections).