Digestive Endoscopy

Cost analysis and outcome of endoscopic submucosal dissection for colorectal lesions in an outpatient setting

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ABSTRACT

Background and study aims: Endoscopic submucosal dissection (ESD), a minimally invasive treatment for early gastrointestinal (GI) cancer, is considered challenging and risky in the colorectum. As such, most patients undergoing ESD are hospitalized due to the perceived increased risk of adverse events. The aim of this study was to compare the costs, safety and efficacy of colorectal-ESD in an outpatient *vs* inpatient setting in a tertiary level center.
Methods: This is a retrospective study on consecutive patients admitted for colorectal-ESD. Patients were divided into outpatients (Group-A, same-day discharge), and inpatients (Group-B, admitted for at least one night). Data on overall costs, outcomes and adverse events were assessed for each group.
Results: A total of 136 patients were considered. Fourteen were excluded because ESD was not performed due to intraprocedural suspicion of invasive cancer. Eighty-three patients were treated as outpatients (Group-A, 68%) and 39 (Group-B, 32%) were hospitalized. R0-rate was 90.4% in Group-A and 89.7% in Group-B ($P=0.98$). One perforation occurred in Group-A (1.2%) and 2 in Group-B (5.1%, $P=0.2$). Mean Length of stay (LOS) was 1 day for outpatients and 3.3 days for inpatients. Management of Group-A as outpatients produced a cost savings of 941€ on average per patient.
Conclusions: Outpatient colorectal-ESD is a feasible, cost-effective strategy to manage superficial colorectal tumors with outcomes comparable to inpatient colorectal-ESD. By using proper selection criteria, outpatient ESD could be considered the first-line approach for most patients.

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1. Introduction

Colorectal endoscopic submucosal dissection (ESD) is recommended for superficial neoplastic lesions at high risk of submucosal invasion, such as non-granular or mixed-type lateral spreading tumors (LSTs) and depressed/irregular lesions [1]. Despite its high efficacy in achieving *en bloc* resection of large lesions, some concerns have been raised in relation to its relatively increased risk of adverse events, namely perforation or bleeding, compared to endoscopic mucosal resection (EMR) [2]. On the other hand, most of these adverse events can be treated endoscopically, as evidenced by the very low risk of post-ESD surgery, which provides reassurance on the overall safety of the procedure [2].

Further concerns have been raised about the relatively high costs of colorectal ESD, especially in countries without specific reimbursement for this procedure. As ESD is considered to have a high rate of adverse events, it is common practice to admit these patients for two or more days, as shown by both Western and Eastern series [3,4]. Inpatient admission is likely to affect the imple-
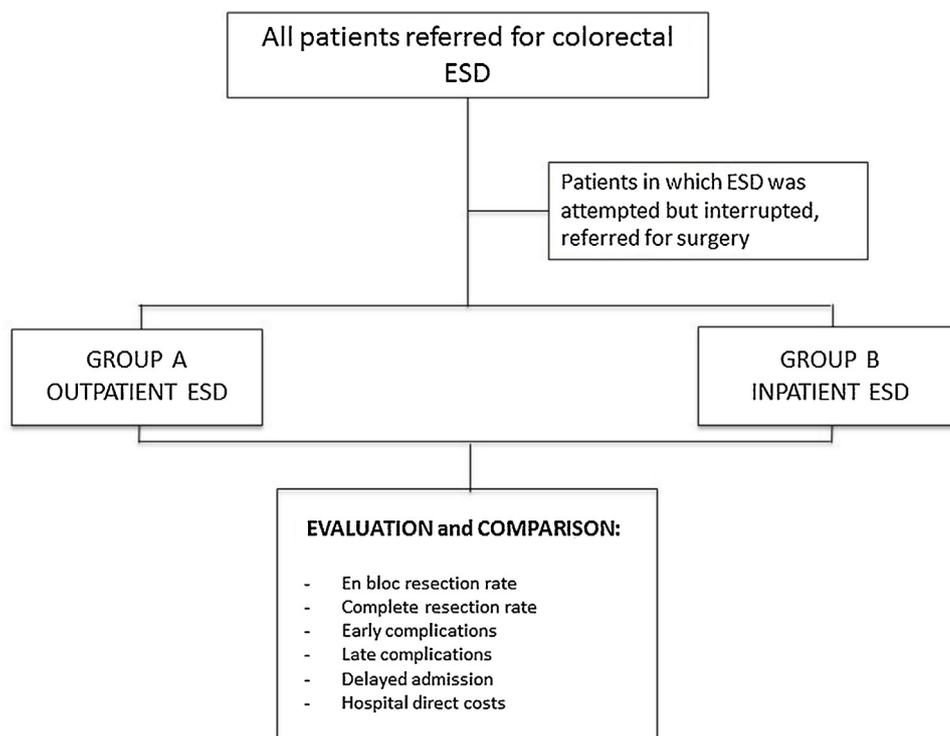
Fig. 1. Study design.

mentation of ESD in Western countries [5], as reimbursement for endoscopic resection is relatively low. In contrast, most EMRs are now performed as an outpatient procedure, even when dealing with very large or complex lesions. The economic savings of EMR also represents one of the main reasons why the more costly and invasive surgical approach for superficial colorectal neoplasia has been replaced by more convenient, minimally invasive endoscopic treatments [6–9].

If we combine the high efficacy of ESD on one hand with the reassuring minimal rate of post-ESD surgery on the other, an outpatient approach would make it possible to substantially reduce the economic burden of ESD, improving its attractiveness as a cost-effective alternative to piecemeal EMR, which in turn would seem to be suboptimal when dealing with lesions at high risk of submucosal invasion.

The aim of this study, therefore, was to assess the economic resources when performing colorectal ESD in an outpatient setting as compared to an inpatient setting, as well as to investigate its feasibility, efficacy and safety.

2. Material and methods

2.1. Study design and patients

From May 2014 to June 2016, consecutive patients admitted to Humanitas Research Hospital (Milan, Italy) for colorectal ESD were enrolled in a prospective registry. Before May 2014, it was common policy to admit these patients for at least one night after the procedure. Based on the reassuring safety data of colorectal ESD observed in our center, a decision was made to replace this policy with a more flexible approach based on a simple triage system. Specifically, all patients undergoing colorectal ESD who were in a relatively healthy state (i.e. ≤79 years and ASA I/II [10]) were treated as outpatients and discharged the same day of the procedure. Patients ≥80 years or > ASA III continued to be hospitalized for at least one night.

For the purpose of this study, we compared the clinical and economic outcomes between these two groups of patients: Group-A represented by outpatient ESD, and Group-B by inpatient ESD. Patients for whom ESD was planned but not performed or was interrupted due to the intraprocedural suspicion of deeply invasive cancer were excluded from our analysis. Data were extracted from a prospectively maintained database on ESD procedures approved by the IRB of our institution (n.11/14, April 2014). The following data were collected and compared between the two groups: (a) mean size of resected specimens, (b) *en bloc* resection rate, (c) complete resection rate (R0), (d) adverse event rate, (e) management costs, and (f) delayed hospital admission.

Colorectal lesions were morphologically classified using the Paris Classification [11] as polypoid (0–I) or non-polypoid (0–II) lesions (laterally spreading tumor, granular type = LST-G, or non-granular type = LST-NG).

In accordance with current guidelines, resection was considered complete (R0) when the tumor was removed *en bloc* with tumor-free lateral and vertical margins. Resection was considered incomplete in two cases: when lateral or vertical margins were positive for tumor invasion (R1) and when the margins were not evaluable because of artefactual burn effects (Rx) [1]. The histological classification was made according to the Vienna Classification [12]. Surgery was recommended when the final diagnosis included lympho-vascular invasion, infiltration deeper than sm1, positive/non-evaluable vertical margin, or poorly differentiated tumor with submucosal invasion [1].

Adverse events included bleeding and perforation. Bleeding was defined as a drop in hemoglobin of ≥2 g/dL with clinical evidence of bleeding (melena or hematochezia) that required endoscopic hemostasis, either on the day of the procedure (early bleeding) or up to 14 days after the procedure (delayed bleeding) [13]. Intraprocedural perforation was defined as a deep muscle layer injury and/or observation of mesenteric fat, intraperitoneal organs or muscle sparing [4,13] during the ESD procedure. Delayed perforation was defined as the finding of free air on abdominal

computed tomography or plain X-ray in symptomatic patients after completion of the ESD procedure. Finally, the management of complications (endoscopic or surgical) was recorded.

Delayed hospital admission was defined as any hospital readmission after discharge, including any passage through the emergency room. The study design is shown in Fig. 1.

2.2. ESD procedures

Throughout the study period, there were no significant technical changes in the colorectal ESD technique as previously described [12]. All procedures were performed by two endoscopists (AR, RM) and with CO_2 insufflation. After submucosal injection, the procedures were performed using a monopolar needle knife: HybridKnife (ERBE Elektromedizin GmbH) or DualKnife (Olympus Medical, Tokyo, Japan). As the final step, hemostasis of the ESD bed was achieved (Fig. 2). Specimens were sent for histopathological examination [11]. Patients with histologic features of high-risk submucosal or deeply invasive cancer in the ESD specimen were referred for surgery.

2.3. Post-ESD management and follow-up

Following the ESD procedure, Group-A patients were monitored in the endoscopy recovery room where they received IV fluids, analgesics and antiemetic medications as needed; all variations in clinical status (temperature, blood pressure, pulse) as well as signs of bleeding (melena or hematochezia) were evaluated. After a minimum of 6 h, patients were discharged as dictated by clinical evaluation. Each patient received a structured telephone call after 24 and 48 h in order to re-evaluate clinical symptoms.

Inpatients (Group-B) received daily clinical evaluations to determine readiness for discharge from the hospital. All patients were called again on day 7 and day 14 in order to re-evaluate clinical symptoms.

2.4. Economic analysis

Considering that the direct costs of the ESD procedures (cost of service, cost of sedation and consumables) were the same for both the inpatient and outpatient group, these costs were not computed, as they did not affect the inter-group comparison. Thus, the comparison of ESD costs was restricted to the setting in which the procedure was performed: same-day surgery (without overnight stay) vs. ordinary admission (one or more nights of stay) in terms of hospital stay, post-procedure visits (defined as medical personnel time = number of hours per patient per length of stay), post-procedure examinations (blood tests, radiological exams), and adverse event management (delayed admissions, surgery). Analytical cost data were automatically available from the patient-specific electronic clinical charts in the hospital database. Costs were reported in Euro currency. The economic analysis was used to calculate the opportunity cost related to an inpatient ESD procedure, defined as the benefit that can be gained from an alternative use of the same resources.

2.5. Statistical analysis

All analyses were performed using PRISM version 6.0 (Graphpad Software Inc., La Jolla, USA). Data were collected and analysed by means of descriptive statistics (mean and standard deviation) using the Fisher's exact test for categorical variables. The Student't test was used to compare the distribution of continuous variables by outcome. All differences were considered significant at two-sided P-values <0.05.

Table 1
Patient and lesion characteristics.

	Group A outpatients	Group B inpatients	P
n	83	39	
Gender (M/F)	54/29	24/15	
Age (yy, range)	67.3 ± 8.05(44–79)	71.6 ± 8.2 (62–91)	0.02
ASA status			
ASA I	40/83 (48.2%)	–	0.0001
ASA II	43/83 (51.8%)	26/39 (66.7%)	0.01
ASA III	–	13/39 (33.3%)	0.0001
Lesion size (mm, range)	38.7 ± 15.9 (20–90)	41.7 ± 18.9 (20–120)	0.36
Lesion site (n/%)			
Rectum	51 (61.5%)	24 (61.5%)	1.0
Left Colon	11 (13.3%)	4 (10.3%)	0.77
Transverse	6 (7.2%)	5 (12.8%)	0.32
Right Colon	15 (18%)	6 (15.4%)	0.80
Lesion morphology (n/%)			
Is	14 (16.7%)	6 (15.4%)	1.0
Isp	4 (4.8%)	1 (0.73%)	1.0
LST-G	32 (38.5%)	15 (38.4%)	0.98
LST-NG	33 (40%)	17 (43.6%)	0.70

3. Results

3.1. Patients, lesion characteristics

Between May 2014 and July 2016, colorectal ESD was planned on 136 lesions in 136 patients (M/F 88/48, mean age 67.9 years, range 44–91). ESD was initially attempted but suspended because of suspected deeply invasive cancer in 14 patients. These patients were referred for surgery and not considered in the final evaluation.

Overall, 83 (68%) patients were treated as outpatients (Group-A; M/F 54/29; mean age 67.3 years; lesion size 38.7 mm, range 20–90 mm), whereas 39 patients (32%) were hospitalized (Group-B; M/F 24/15; mean age 75.2 years; lesion size 41.2 mm, range 20–120). Median operation time was 85.4 (range 15–293) minutes. The clinical characteristics of the patients and lesions are shown in Table 1. There was a significant difference in age and comorbidities between the two groups, as these were the main criteria used to determine whether a patient was admitted following ESD. The location, size, and morphology of the colorectal lesions, which were similar between the two groups, are also reported in Table 1.

3.2. ESD clinical outcomes

En bloc and R0 resections were achieved in 80/83 (96.4%) and 75/83 (90.4%) cases in Group-A, and in 37/39 (94.9%) and 35/39 (89.7%) cases in Group-B, respectively, with no statistically significant difference between the two groups ($P = 0.5$ and $P = 0.9$). Despite having successful ESDs, twelve patients (9.8%) were referred for surgery due to unfavorable histopathology (Group A: 8/83 patients; Group B: 4/39 patients).

A total of 3 early adverse events were reported. Perforations occurred in 3 cases (2.5%): 1/83 (1.2%) in the outpatient group and 2/39 (5.1%) in the inpatient group ($P = 0.2$). All of them were intraprocedural perforations treated endoscopically and did not require subsequent surgery. In particular, the perforation that occurred in the outpatient was a tiny defect, which was successfully closed by a clip and did not require any additional examination or hospitalization. No postoperative bleeding or delayed perforations occurred in either group. No patients who were supposed to be discharged after the procedure were admitted; similarly, there where no patients discharged home as outpatients who were originally scheduled to be admitted to the hospital. These results are summarized in Table 2. Histopathology revealed submucosal cancer in 21 (25.3%) and 10 (25.6%) lesions in Group-A and -B, respectively, while intramucosal carcinomas were found in 18 (21.7%) and 11
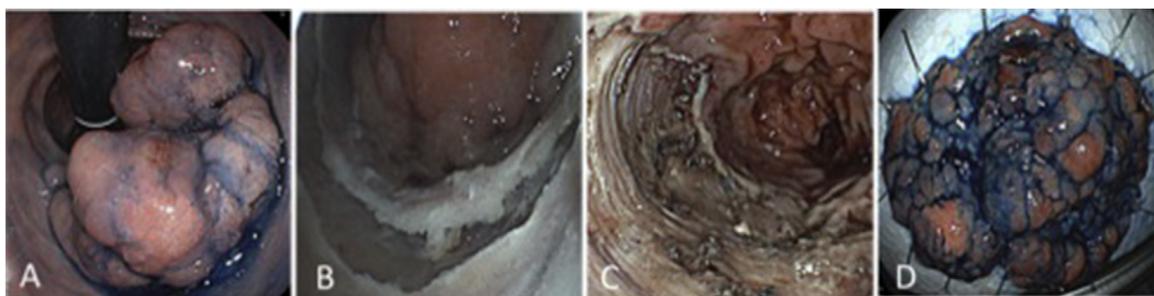
Fig. 2. (A) Sessile lesion (type Is) located in the rectum, after indigo carmine dye spraying. Estimated size of this lesion was 80 mm in diameter. (B) After injection (saline + adrenaline + indigo carmine) into the submucosal layer, ESD was performed by DualKnife. (C) ESD bed after en bloc resection. (D) Resected specimen (80 × 60 mm in diameter).

Table 2
ESD outcomes.

	Group A outpatients	Group B inpatients	P
ESD outcomes (n/%)			
en bloc resection rate	80 (96.4%)	37 (94.9%)	0.65
R0 resection rate	75 (90.4%)	35 (89.7%)	0.98
Bleeding		–	
Early bleeding	–		
Delayed bleeding	–	–	
Perforation	1 (1.2%)	2 (5.1%)	0.24
Immediate			
Delayed			
Delayed admission	–	–	

Table 3
Histopathology results.

Histopathology	Group A outpatients N (%)	Group B inpatients N (%)
LGD adenomas	20 (24.1%)	9 (23.1)
HGD adenomas	24 (28.9%)	9 (23.1%)
Intramucosal carcinomas	18 (21.7%)	11 (28.2%)
Submucosal invading carcinomas	21 (25.3%)	10 (25.6%)
sm1	16	7
sm2	3	2
sm3	2	1

(28.2%) lesions, respectively. Histopathology results are detailed in Table 3.

3.3. Economic analysis

Resource utilization (length of stay, medical personnel time, diagnostic exams during stay) was lower for Group-A (average cost €437.30) as compared to Group-B (average cost €1378.20). The monetary value of the resources saved using the same-day surgery regimen in our hospital was 941€ per patient (805€ per day of stay). Considering the opportunity cost, every patient undergoing ESD as an outpatient freed up a mean of 2.3 days of stay and 1.1 h of medical time. If the hospital was actually able to re-use these freed up resources for the benefit of other patients, the corresponding monetary value of the opportunity cost would again be 941€ per patient. Resources directly involved in the ESD treatment are listed in Table 4.

4. Discussion

According to our study, colorectal ESD is feasible, safe and effective in an outpatient setting, providing a mean cost savings of €941 per patient. The results of our study are significant for several reasons. First, we adopted inpatient ESD as the comparator, which is the current standard in both Eastern and Western areas [3,4,11–14]. When comparing the main outcome of efficacy, namely R0 resection rate, no difference between the outpatient and inpatient setting was found. Thus, the shift between the two settings was not associated with any loss of efficacy. Of note, there were no differences in the main characteristics of the lesions, such as size, location and morphology between the two groups, excluding any selection bias.

Second, the mean R0 resection rate in both groups was approximately 90%, with a mean size of approximately 40 mm. This is similar to the corresponding value achieved in a large Japanese series [4], showing that Western colorectal ESD may achieve outcomes for large lesions similar to those achieved in Eastern countries, despite a much lower volume of gastric ESD. Third, the outpatient setting was not associated with a higher risk of adverse events or delayed admission. This was related on one hand to the overall low risk of perforation or major bleeding, and on the other hand to the possibility to diagnose and successfully treat adverse events during the same endoscopic procedure or early during the post-procedure observation time.

Fourth, the prevalence of submucosal cancer in our series was approximately 25%, which is nearly 3 times higher than in previous EMR series [15]. This may be consistent with the quite large size of the resected lesions as well as with the significant group of LST-NGs considered for ESD in the present series. Of note, less than 10% of patients eventually required surgery for invasive cancer, further supporting the surgery-sparing role of ESD for superficially invasive submucosal cancer. Fifth, we adopted a very simple triage system, based on age and comorbidities. Although not prospectively validated in the ESD setting, these variables appear to be strong predictors of post-colorectal cancer surgical morbidity and mortality [16]. Thus, we can assume that what really makes the difference in selecting the correct approach (inpatient vs. outpatient) is the general status of the patient rather than the type or location of the lesion. Further studies are needed to assess the safety of an outpatient ESD setting for high-risk patients.

Our study carefully assessed the economic resources potentially saved by the shift from an inpatient to outpatient setting for ESD. According to our Italian health system, there was an absolute savings of €941, which was mainly explained by the 2-day difference in hospital stay. It could be argued that the setting-related savings in this ESD analysis are nearly 5 times lower as compared with the estimated savings obtained when comparing surgery with endoscopic resection for large colorectal lesions [7,8]. However, the €941 savings shown in our analysis should be added to the savings related to the additional surgery-sparing role of ESD vs EMR, as shown by the very low rate of post-ESD surgery for invasive cancer in our series. In addition, the 2-day difference in hospitalization between the two groups in our study is of the same magnitude as the 2.8-night difference in hospitalization when comparing surgery with endoscopic resection [6]. This shows that the savings in terms

Table 4
ESD resources directly involved in the one-day regimen vs. ordinary admission.

	Unit of measueament	Resources used		Delta resource (Group B-Group A) per patient	Average cost in €		Delta resources (group B-group A) per patient
		Group B	Group A		Group B	Group A	
Patients	Number	39	83				
Length of stay (LOS)	Average days	3.3	1.0	−2.3	1155	350	−805
Medical personnel time[a]	Average hours	2.6	1.5	−1.1	131.9	75.0	−56.9
Diagnostic exams during stay:							
lab tests (biochemistry and coagulation)	Number – average per patient	11.5	0.4	−11.1	52.4	12.3	−40.1
Other visits	Number – average per patient	0.3	0.0	−0.3	9.2	–	−9.2
CT scan	Number – average per patient	0.2	0.0	−0.2	27.5	–	−27.5
X-ray	Number – average per patient	0.1	0.0	−0.1	2.2	–	−2.2
					1378.2	437.3	−940.9

[a] Excluding operating room time.

of economic resources is substantial, as these resources may be opportunistically used for more cost-effective alternative procedures. In addition, when considering the lack of superiority of the inpatient setting in terms of both efficacy and safety, it would appear to be cost-ineffective – and therefore not sustainable – when compared with an outpatient setting.

The main limitation of our study is clearly represented by the tertiary setting where it was located, i.e. outpatient management of ESD may not be feasible in many Western institutions lacking extensive experience in colorectal ESD, thus we cannot assure the reproducibility of these results in less experienced centers. However, colorectal ESD is a complex procedure with a well-defined learning-curve [17] that should remain restricted to selected tertiary level centers with adequate skills [1]. Such a policy is also important to minimize the adverse event rate: the 2.5% perforation rate observed in our tertiary centre is lower than the 5.1% recently reported in a systematic review [18], albeit resulting in a similar rate of surgery for adverse events (1.0%). The second limitation is the retrospective non-randomized nature of the study, which means that we cannot exclude that factors other than age and comorbidities may have interfered with the selection of the setting. However, the lack of difference in any lesion characteristics, as well as the equivalence of the main end-points between the two groups, seem to minimize the significance of this bias. Third, our cost-analysis is specific to the Italian system. However, we provided the analytical cost-related factors, so that any health system can adjust the final estimate to its cost assumptions. Fourth, we did not directly compare outpatient ESD with surgery. However, when simulating a comparison between endoscopic and surgical resection in a decision model, only a <76% endoscopic complete resection rate or a >12% endoscopic adverse event rate was required for surgery to be a cost-effective alternative to endoscopic resection [19]. Both the approximately 90% complete resection rate and the less than 3% adverse event rate observed in our outpatient arm would exclude a possible superiority of surgery as compared with ESD.

In the analysis of cost-effectiveness between ESD and surgery, we should also consider that 25% of patients in both groups had an invasive carcinoma. This percentage is higher than frequencies reported in a recent systematic review [19] showing an overall 8.0% and 7.7% rate of sm1 and sm2, respectively (without significant differences between European and Asian countries). Despite such an enriched-disease population, nearly one quarter of ESDs in our series were performed for low-grade dysplastic lesions that could have been equally treated with a simpler and more convenient piecemeal mucosal resection. In the future, such rate may be further reduced by stratifying lesions not only according to morphology and pit/vascular patterns, but also according to location, as recently shown by an Australian group [20]. Thus, we confirm

that colorectal ESD requires careful case selection to prevent over- and under-treatment even in expert centers. Despite the relatively high rate of invasive carcinoma, less than 10% of patients were referred for surgery due to unfavorable histopathology and this aspect should be also considered in the cost-effectiveness analysis.

If outpatient ESD is to be considered, some practical points of our protocol need to be underscored. Although patients were scheduled to have an outpatient procedure, they were only discharged after at least 6 h of post-procedure evaluation. This means that outpatient ESDs had to be scheduled in the morning. Moreover, all patients discharged the same day of the procedure received a structured telephone call after 24 and 48 h in order to re-evaluate clinical symptoms.

In conclusion, we have shown clinical equivalence between an outpatient and inpatient setting for colorectal ESD. Given the clear superiority of the outpatient setting in terms of cost-effectiveness, this strategy should be considered as first-line therapy for healthy patients (i.e., ≤79 years and ASA I/II) at an appropriately experienced and resourced tertiary care center.

Conflict of interest

None declared.

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