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ORIGINAL ARTICLE

Endoscopic submucosal dissection or piecemeal endoscopic mucosal resection for large superficial colorectal lesions: A cost effectiveness study

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Abbreviations: ASA, American Society of Anesthesiologists; CONECCT, COlorectal Neoplasia Endoscopic Classification to Choose the Treatment; CRC, Colorectal cancer; DRG, Diagnosis Related Groups; EMR, endoscopic mucosal resection; pEMR, piecemeal EMR; U-EMR, Universal-EMR; ENC, Examen National de Coûts; ESD, endoscopic submucosal dissection; S-ESD, Selective-ESD; U-ESD, Universal-ESD; ESGE, European Society of Gastrointestinal Endoscopy; FECCo, French Endoscopic submucosal Colorectal Cohort; JNET, Japan Narrow band imaging Expert Team; LST, laterally spreading tumour; LSL, laterally spreading lesion; NG, non-granular; GH, Granular homogeneous; GM, granular-nodular mixed (macronodule > 1 cm); PPV, Positive predictive value; SMIC, Submucosal Invasive Cancer; LR-SMIC, low-risk SMIC; HR SMIC, high-risk SMIC; IBD, Inflammatory bowel disease; SSL, Sessile serrated lesions; TEM, Transanal endoscopic microsurgery; USD, United States Dollar.

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KEYWORDS
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Cost effectiveness;
Colorectal neoplasms

Abstract
Background and aims: Endoscopic management is preferred to surgical management for large superficial colorectal lesions. However, the optimal endoscopic resection strategy (piecemeal endoscopic mucosal resection [pEMR] or endoscopic submucosal dissection [ESD]) is still debated from an economical point of view. To date, in France, there is no Health Insurance reimbursement rate for the hospital stays related to ESD. We searched to estimate the global cost of colorectal ESD and to define the most cost-effectiveness endoscopic strategy.
Methods: A model was created to compare the cost-effectiveness of ESD and pEMR according to optical diagnosis (Japan NBI Expert Team [JNET], laterally spreading tumour [LST], CONECCT). We distinguished three groups from the same multicentre ESD cohort and compared the medical and economic outcomes: real-life ESD data (Universal-ESD or U-ESD) compared to modelled selective ESD (S-ESD JNET; S-ESD LST; S-ESD CONECCT) and exclusive pEMR strategies (Universal-EMR or U-EMR).
Results: The en-bloc, R0, and curative resection rates were 97.5%, 86.5%, and 82.6%, respectively in the real life French ESD cohort of 833 colorectal lesions. U-ESD was the least-expensive strategy, with a global cost of 2,858,048.17 €, i.e. 3,431.03 €/patient and was also the most effective strategy because it avoided 774 surgeries, which was more than any other strategy. It outperformed S-ESD CONNECT (global cost = 2,951,411.44 €, and 3,543.11 €/patient, 765 surgeries avoided, S-ESD LST (global cost = 3,055,951.53 €, and 3,668.61 €/patient, 749 surgeries avoided), and S-ESD JNET (global cost = 3,547,426.97 € and 4,258.62 €/patient, 704 surgeries avoided) and U-EMR (global cost = 4,060,547.62 € and 4,874.61 €/patient, 620 surgeries avoided). Even though a model which optimized pEMR results (0% technical failure, 0% primary surgery), U-EMR strategy remained the most expansive strategy and the one that avoided the least surgeries.
Conclusion: ESD for all LSTs upper than 20 mm is more cost-effective than pEMR, and S-ESD.

Significance of the study

Overview

Piecemeal Endoscopic mucosal resection (pEMR) for treating Laterally spreading lesions (LSLs) is safe and effective. However, recurrence rate remains non negligeable and need further colonoscopic controls that offset the low initial procedure cost.

Concerning Endoscopic submucosal dissection (ESD), while initially criticized in Western countries for its technical difficulty, the development of countertraction techniques simplifies its practice and allocates similar results than Asian countries.

Several recent cost effectiveness studies show contradictory results between EMR and ESD.

New findings

A strategy using countertraction ESD for all lesions upper than 20 mm is more cost effective in our model to a selective strategy or an exclusive piecemeal EMR strategy in case of large superficial colorectal lesions.

In case of using a selective resection strategy, an optical diagnosis using a new classification (CONECCT) that combines overt and covert sign of carcinoma is superior to other classifications to predict presence of submucosal cancer and should be used to select high risk lesions for ESD.

Depending to the reimbursement scheme, a selective ESD (S-ESD) strategy using the CONECCT classification to select at-risk lesion could be the most cost-effective resection strategy.

Clinical practice impact

Using current data about EMR, use of ESD with countertraction for all LSLs is more cost effective than other strategies in case of large colorectal laterally spreading lesions and should be proposed for patients

Introduction

Organised colorectal cancer (CRC) screening has increased the detection rate of large superficial colorectal lesions [1—7]. Although endoscopic management is preferred to surgical management [8—11], the optimal endoscopic resection strategy (piecemeal endoscopic mucosal resection [pEMR] or endoscopic submucosal dissection [ESD]) is debated [12—17].

Despite its carcinological advantages, ESD is criticised in Western countries, particularly for colonic lesions, because of its technical difficulty, long procedure time, and higher perforation rate than pEMR. In recent years, the development of traction strategy has considerably simplified its practice[18—21].

The European Society of Gastrointestinal Endoscopy (ESGE) recommends a selective strategy, reserving ESD for lesions at high risk of submucosal cancer [22]. Reserving ESD

for lesions with superficial cancer is attractive but difficult in practice because of the difficulty of predicting submucosal cancer in a lesion at the time of colonoscopy. Optical diagnosis based on macroscopic signs, pitt and vascular patterns analysis allows high sensibility but poor specifity to identify Submucosal Invasive Cancer (SMIC) inside a large Laterally Spreading Lesion (LSL).

Increasing healthcare costs necessitate analysis of the optimal endoscopic resection strategy from both the patient's point of view and an economic standpoint. Three medico-economic studies have reported contradictory results regarding this issue [23–25].

In the era of systematic countertraction ESD, it is important to determine the most cost-effective endoscopic resection strategy according to real-time endoscopic optical diagnostic method, to clarify the lesions that would benefit from ESD and avoid surgery.

Patients and methods

Overview

Since 1 January 2017, all superficial colorectal lesions larger than 20 mm have been removed by ESD with double clip traction in our two centres.

We searched to know what would have been the medical and economic outcomes if all those same lesions had been treated by a selective ESD or an exclusive pEMR strategies.

A model was created to compare the cost-effectiveness of ESD and pEMR according to endoscopic classification (Japan NBI Expert Team [JNET] [26], laterally spreading tumour [LST] [27], CONECCT[28–30]) in real time before the procedure. We distinguished three groups from the same multicentre colorectal ESD cohort (Limoges University Hospital and Rennes University Hospital) and compared the medical and economic outcomes. We also compared our real-life ESD with double clip-and rubber-band countetraction data to modelled selective ESD and exclusive pEMR strategies.

Inclusion and exclusion criteria

All superficial lesions larger than 2 cm and resected by ESD were prospectively and consecutively included, between the 1st January 2017 and the 5th May 2021. All lesions unsuitable for pEMR were excluded, like neuroendocrine tumour (NET) cases, post-EMR or post-surgical recurrence, dysplasia in inflammatory bowel disease (IBD), cases with signs of deep invasion, tattooing under the lesion, lesions on radiation proctitis, appendicular or ileal invasion.

Objective

The objective of this study was to determine the most cost-effective endoscopic resection strategy (pEMR, selective ESD, or universal ESD) according to endoscopic classification (LST, JNET, or CONECCT). The primary efficacy criterion was absence of surgical management.

Analytical model

We distinguished and analysed three groups from the same cohort.

Fig. 1. Decision tree analysis.

(1) Universal ESD strategy (U-ESD): actual strategy applied to the French multicentre cohort. All lesions were removed by ESD.
(2) Selective ESD strategy (S-ESD): ESD was reserved for lesions considered at risk of submucosal cancer according to endoscopic classification.

Selective ESD according to JNET (S-ESD-JNET): only lesions meeting the endoscopic criteria of JNET IIb were treated by ESD. JNET IIa lesions with depression (Paris 0-IIc) were referred for primary surgery. JNET IIa lesions without depression area were removed by pEMR.
Selective ESD according to CONECCT (S-ESD-CONECCT): the CONECCT classification includes both overt and covert sign of carcinoma; and has higher interobserver agreement than other classifications[30,31]. Lesions with at least one CONECCT IIc criterion were removed by ESD. Lesions without one of the four criteria (CONECCT IIc = Paris 0-IIc, JNET IIb, LST NG or LST *G* + macronodule) were removed by pEMR.
Selective ESD according to LST (S-ESD-LST): only LST G with macronodule $>$ 1 cm and LST NG lesions were treated by ESD. LST-granular homogenous (LST-GH) and protruding lesions were treated by pEMR[27].

(1) Universal pEMR strategy (U-EMR): removal of all lesions by pEMR. Primary surgical indication was considered for lesions with depression area (Paris 0-IIc) because of the high positive predictive value (PPV) of this sign for submucosal cancer [32].

Model predictions

Endoscopic resections

Results for lesions treated by pEMR: The results of Klein *et al*. [33] were used to run the model. The procedure failure or incomplete resection rate was 9,3%. The 6-month and 18-month recurrence rate were respectively 5.2%, and 2%. The procedural failure rate was reduced to 4.5% by the S-ESD CONECCT strategy because CONECCT IIA lesions correspond to LST-GH lesions, which rarely present submucosal invasion [27] or fibrosis and are in our experience much easier to treat. This was made to favour the pEMR results. All patients in the pEMR group received colonoscopy at 6 and 18 months in accordance with the ESGE guidelines [34].

Outcomes of lesions treated by ESD: the ESD results were from two expert centres participating in the French Endoscopic Submucosal Dissection Colorectal Cohort (FECCo NCT04592003) that has been approved by ethical comity of the Limoges University Hospital. Only patients with an invaded lateral margin (R1 resection) received 6 months control colonoscopy. All patients with SMIC underwent control colonoscopy at 1 year according to ESGE guidelines. The other resected lesions with healthy margins (R0 resection) and without SMIC, were followed up by colonoscopy at 3 years according to ESGE guidelines.

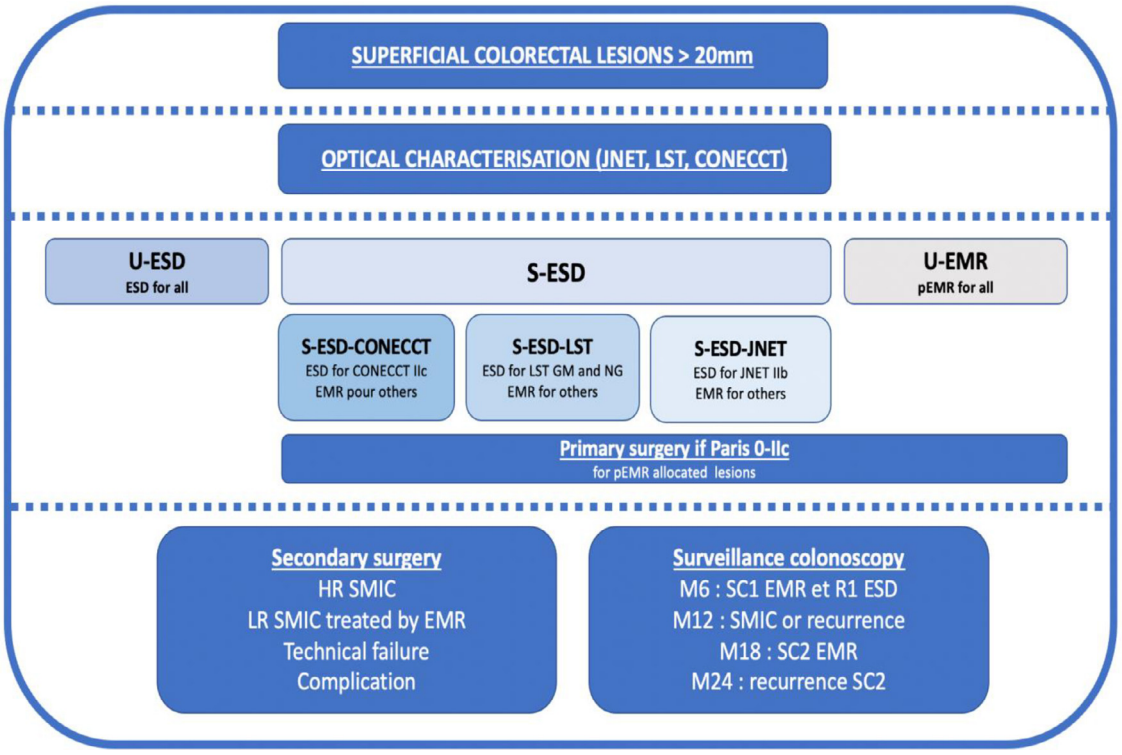

Fig. 1 Decision tree analysis. CONECCT IIc = macronodule $>$ 1 cm, Paris classification 0-IIc, LST NG or JNET IIb area.
LR-SMIC, low-risk submucosal invasive cancer (submucosal cancer $<$ 1000 μm + good differentiation + no budding + no lymphovascular emboli).
HR SMIC, high-risk submucosal invasive cancer (submucosal cancer $>$ 1000 μm, poor differentiation, budding, or lymphovascular emboli).
LST, laterally spreading tumour; NG, non-granular; GM, granular-nodular mixed (macronodule $>$ 1 cm); ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection.

Surgical indications

For lesions treated by pEMR: all lesions with SMIC (LR-SMIC or HR-SMIC) underwent salvage carcinologic surgery with lymph node dissection. (LR-SMIC $<$ 1000 μm, good differentiation, and absence of lymphovascular emboli and tumour budding; HR-SMIC $>$ 1000 μm, presence of lymphovascular budding, emboli, or dedifferentiation)

Secondary surgeries were mandatory for lesions not removed by pEMR. For rectal lesions, technical failure requires Transanal Endoscopic Microsurgery (TEM) in the first instance, followed by proctectomy if a histopathological criterion is met. Finally, lesions with depression area with Paris IIc component were considered for first-line surgical management as it was proposed by the Australian team in their medico-economic study [23].

We did not consider surgical management for adverse events or recurrence after EMR.

For lesions treated by ESD: lesions that could not be removed endoscopically (ESD followed by rescue pEMR) were treated surgically. Lesions with a high risk of lymph-node invasion (HR SMIC) were treated by secondary surgery. For rectal lesions, technical failure prompted management by TEM in the first instance, followed by proctectomy if a histological criterion was met.

Right hemicolectomy, left hemicolectomy, TEM, or laparoscopic proctectomy were considered salvage procedures depending on tumour location.

Cost analysis

The healthcare costs associated with the procedures are detailed below.

For lesions treated by pEMR: reimbursement is decided according to the diagnosis-related group (DRG). The prices are uniform for an ambulatory management or a stay of less than 2 days in the case of EMR and control colonoscopy; otherwise, prices are based on the overall costs.

For lesions treated by surgery: reimbursement for surgical procedures is complex because they vary according to comorbidities, adverse events, and transfer to intensive care. We therefore used a retrospective series from Limoges University Hospital and Bordeaux University Hospital, covering the same period, of patients treated by TEM, proctectomy, or right/left colectomy. We calculated the costs for the surgical groups based on the average stay valuation for each of the three surgeries.

For lesions treated by ESD: there is no standard reimbursement for colorectal ESD in France. A prospective microcosting analysis was performed of the costs of ESD plus those of the hospital stay, according to a national retrospective cost study in which the University Hospital of Limoges is participating (Appendix).

Healthcare costs related to post-procedural bleeding, work stoppage and nursing care costs at home following surgery were not considered.

ESD procedure

The lesions were obtained from two expert centres where endoscopic and procedural data are prospectively recorded.

Informed consent was obtained from each patient before the procedure.

All lesions were evaluated by an endoscopist with expertise in optical diagnosis and resection, accompanied or not by a trainee. Each operator selected the dissection knife and strategy to be used in the procedure. All operators participated in the development and democratization of the ESD with double clip and rubber-band countertraction strategy. A VIO 3 or VIO 300D electrosurgical unit was used.

The specimen was pinned on corks and fixed before being sent to the pathology department. Millimetre-long cuts were made according to Japanese standards before evaluation by pathologist with expertise in superficial tumours of the digestive tract.

Results

Results of the real-life U-ESD cohort

In the real-life prospective colorectal ESD cohort, 833 colorectal lesions in 802 patients were resected (*Fig. 2*), with a mean size of 59.4 mm. The baseline population characteristics and clinical, endoscopic, and histologic features of the resected lesions and procedural parameters are shown in *Table 1*. The en-bloc, R0, and curative resection rates were 97.5%, 86.5%, and 82.6%, respectively. The average procedure time was 69.5 min, and the average length of stay was 1.80 days. Also, 57 patients underwent secondary surgery, mostly due to one of the histological criteria being met. The recurrence rate was 1.1%. None of post procedural bleeding or perforation resulted in secondary salvage surgery. There were 68 (8.2%) lesions with at least submucosal SMIC invasion (24 LR-SMIC [2.9%] and 44 HR-SMIC [5.3%]), and 7 T2 lesions (0.8%). There were 100 lesions with a depressed area (Paris 0-IIc) and SMIC were present in 22 of them, including 11 HR-SMIC of rectal location. Only the CONECCT classification referred to ESD whole submucosal cancer (75/75), contrary to LST and JNET classifications that missed 24% and 27% of those lesions by orienting them to pEMR.

Cost

The average global cost of one ESD was estimated at 2268.40 € per stay. The procedure cost evaluated by microcosting was 1237.22 € and the hospital stay cost was estimated at 1031.18 € (Appendix) [35]. The overall costs including hospital admission and procedural costs for the surgical groups obtained from the average stay valuation and French reimbursements are shown in *Table 2*.

Analysis of modelled scenarios

-Medical outcomes (Table 3)

For the U-ESD, S-ESD, and U-EMR groups, technical efficiency, the number of primary or secondary surgeries, and the number of total colonoscopies (therapeutic or surveillance) are detailed in *Table 3*.

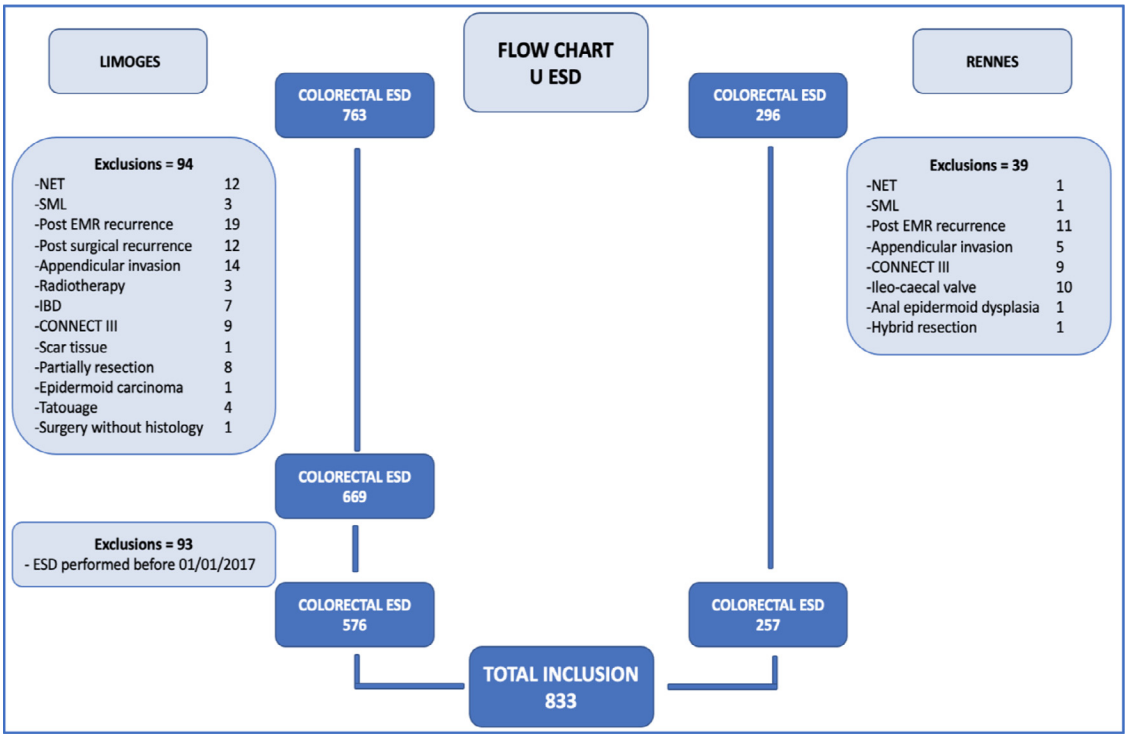

Fig. 2 Study flow chart.
ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; NET, neuroendocrine tumour; SML, submucosal lesion; IBD, inflammatory bowel disease.

Table 1 Population and lesion features of the real-life endoscopic submucosal dissection cohort.

Features	Number	Average
Population		
Patients	802	
Lesions	833	
Sexe (F/M)	337/465	42%/58%
Age		68.6
ASA		
1	77	13.7%
2	290	51.7%
3	184	32.8%
4	10	1.8%
NC	272	
Average length of stay (day		1.8
Anticoagulant	72	8.7%
Anti-agregant	143	17.2%
Lesions		
Rectum	286	34.3%
Pectineal line	75	9%
Colon	547	65.7%
Sigmoïde	103	12.4%
Left colon	40	4.8%
Left colonic angle	21	2.5%
Left Transverse colon	25	3%
Right Transverse colon	30	3.6%
Right colonic angle	98	11.8%
Right colon	106	12.7%
Ileo caecal valve	35	4.2%
Caecum	89	10.7%
Endoscopic characterization		
Type		
LST G	529	63.5%
LST GM	302	36.2%
LST NG	167	20%
LST NG pseudo depressed	58	7%
Protruding lesion	125	15%
Serrated lesion	12	1.5%
Classification de Paris		
0-Ip	15	1.8%
0-Is	117	14%
0-Is + 0-IIa	290	34.8%
0-Is + 0-IIc	21	2.5%
0-IIa	304	36.5%
0-IIb	7	0.8%
0-IIc	1	0.1%
0-IIa + 0-IIc	78	14.1%
JNET		
I	23	2.8%
IIa	533	64%
IIb	277	33.2%
CONECCT		
IS	30	3.6%
IIA	212	25.5%
IIC	591	70.9%
Features (next)	Number	Average
Submucosal cancers and T2 missed proportion		
CONECCT	0/75	0%
LST	18/75	24%
JNET	20/75	27%
SMIC and T2 prediction sensibility		
CONECCT	75/75	100%
LST	57/75	76%
JNET	55/75	73%
Anatomopathology		
Sessile Serrated lesion	15	1,8%
Low grade dysplasia	309	37.1%
High grade dysplasia	261	31.3%
In situ carcinoma pTis	173	20.8%
SMIC	68	8.2%
μm	34	4.10%
μm	34	4.10%
LR SMIC	24	2.90%
HR SMIC	44	5.30%
T2	7	0.8%
Poor differenciated	5	0.6%
Emboles	20	2.5%
Budding	17	2.1%
Procedure		
Size (mm)		59.4
Time (min)		69.5
Surface (mm2)		2574.2
Speed (mm2/min)		41.2
Fibrosis		
F0 No fibrosis	332	40.2%
F1 Moderated fibrosis	271	32.8%
F2 severe fibrosis	222	26.7%
NC	8	
Manœuvrability		
Good	594	72.4%
Poor	227	27.6%
NC	12	
Issues		
Monobloc	812	97.5%
R0	721	86.5%
Curative resection	688	82.6%
Safe lateral margin	735	88.2%
Safe deep margin	811	97.4%
Perforation	60	7.2%
Post procedure bleeding	53	6.5%
Secondary surgeries	57	6.8%
Complications	0	0%
Technical failures	11	1.3%
Histopathologic reasons	46	5.5%
Surveillance colonoscopy	453	54.3%
First control recurrence	5	1.1%

ASA, American Society of Anesthesiologists; LST, large spreading tumour; LST G, LST granular; LST NG, LST non-granular; LGD, low-grade dysplasia; HGD, high-grade dysplasia; Sm, submucosal; LR-SMIC, low-risk submucosal invasive cancer; HR SMIC, high-risk submucosal invasive cancer; NC, not characterised.

Table 2 Endoscopic and surgical overall hospital costs.

	Cost (Euros)
ESD	2 268.40
Standard colonoscopy	706.89
EMR	855.43
Colonic surgery	12 960.25
Proctectomy surgery	16 776.00
Transanal endoscopic microsurgery	3021.77

ESD, endoscopic submucosal dissection, EMR, endoscopic mucosal resection.

The U-ESD group had the lowest numbers of surgeries and colonoscopies. There were 59 surgical procedures in total, including 13 for technical failure and 46 for histopathological criteria. The total number of colonoscopies was 1017 (average of 1.22 colonoscopies per patient).

The U-EMR group had the highest number of surgeries and colonoscopies, with 213 surgeries (111 primary surgeries for Paris 0-IIc depressed lesions, 80 for technical failure, and 22 due to the patient meeting the histopathological criteria) and 2210 colonoscopies, (average of 2.65 colonoscopies per patient). There were 113 surgeries for low-risk lesions (SSL, LGD, HGD) and 24 for LR-SMIC. This resulted in 154 more surgeries, and 1193 more colonoscopies, compared to the U-ESD group.

In the S-ESD CONNECT group, there were 591 ESD and 242 pEMR attempts. This is the only group in which en-bloc resection by ESD was attempted for all submucosal invasive lesions (n = 75). pEMR is attempted only for low-risk lesions not requiring surgery due to pathological findings. Low-risk lesions were removed surgically in the S-ESD CONNECT group because of technical failure of pEMR. There were 68 surgeries (9 additional) and 1451 colonoscopies (434 additional; average of 1.74 colonoscopies per patient).

In the S-ESD LST group, there were 495 ESD attempts and 318 EMR attempts. There were 84 secondary surgeries, including 38 in cases meeting the histopathological criteria and 46 for technical failures (i.e. 25 additional surgeries).

Table 3 Outcomes of the various strategies.

	U ESD	SELECTIVE ESD CONNECT	SELECTIVE ESD LST	SELECTIVE ESD JNET	U EMR			
	U ESD	ESD CONNECT	EMR CONNECT	ESD LST	EMR LST	ESD JNET	EMR JNET	U EMR
ENDOSCOPIC RESECTIONS	833	591	242	495	338	277	530	733
Technical success	812	575	231	483	307	270	481	667
Technical failure	21	16	11	12	31	7	49	66
PRIMARY SURGERY	0	0	0	0	0	0	26	111
SECONDARY SURGERY	59	57	11	43	41	42	61	102
Technical failure	13	11	11	9	37	5	53	80
Histopathological reasons	46	46	0	34	4	37	8	22
SURGICAL REMOVED LESIONS	57	55	11	41	35	41	57	188
LR-SMIC lesions	0	0	0	0	4	0	9	24
Low risk lesions	6	4	11	4	17	2	37	113
TOTAL NUMBER OF SURGERIES	59	68	84	129	213			
TEM	5	4	11	12	53			
Proctectomy	32	32	34	35	39			
Left colectomy	8	10	11	21	41			
Right colectomy	14	22	28	61	80			
NUMBER OF ADDITIONAL SURGERIES	0	9	25	70	154			
TOTAL NUMBER OF COLONOSCOPIES (until 24 months)	1017	1451	1584	1902	2210			
NUMBER OF ADDITIONAL								

COLONOSCOPIES04345678851193AVERAGE NUMBER OF COLONOSCOPIES PER PATIENT1.221.741.902.282,65

ESD, endoscopic submucosal dissection; EMR, endoscopic mucosal resection; TEM, transanal endoscopic microsurgery; SMIC, submucosal invasive cancer; LR-SMIC, low-risk SMIC.

Low-risk lesions included sessile serrated lesions, low-grade dysplasia, high-grade dysplasia, and pTis.

There were 55 ESD and 18 pEMRs for SMIC lesions. There were 1584 colonoscopies (567 additional; average of 1.90 colonoscopies per patient).

The S-ESD JNET group included 277 ESD and 530 EMR attempts. Primary surgery in the EMR group for JNET IIA lesions with Paris 0-IIc depressed component was performed in 26 cases, and secondary surgery in 83 cases (58 for technical failure and 45 for histopathological criteria). There were 55 ESDs and 20 EMRs for SMIC lesions. Thirty-nine lesions removed surgically were low-risk lesions. Of the 59 SMIC lesions removed surgically, 9 were LR-SMIC. There were 1902 colonoscopies (885 additional; average of 2.65 colonoscopies per patient).

Cost-effectiveness of the various strategies (Table 4)

The least-expensive strategy was U-ESD, with a total cost of management of 2858,048.17 €, i.e. 3431.03 €/patient (Table 4). U-ESD was the most cost-effective strategy because it avoided 774 surgeries, which is more than any other strategy. It outperformed S-ESD CONNECT (global cost = 2951,411.44 €, and 3543.11 €/patient, 765 surgeries avoided), S-ESD LST (global cost = 3055,951.53 €, and 3668.61 €/patient, 749 surgeries avoided), and S-ESD JNET (global cost = 3547,426.97 € and 4258.62 €/patient, 704 surgeries avoided) and U-EMR (global cost = 4060,547.62 € and 4874.61 €/patient, 620 surgeries avoided).

Analytical model of the cost-effectiveness of strategies that increase pEMR success (Table 5)

Only surgeries for cases of technical failure of ESD plus failure of conversion to piecemeal EMR were retained in the analysis. In the scenario in which none of the lesions treated by pEMR exhibited technical failure or required primary surgery (Table 5), the S-ESD CONECCT strategy was the most cost-effective (lower cost than the U-ESD strategy with the same number of surgeries). The U-EMR strategy was still the most expensive and avoided the fewest surgeries.

Effect of varying the cost of endoscopic submucosal dissection (Table 6)

With reimbursement by the responsible agency of up to 2654.00 € (i.e. more than threefold the reimbursement for piecemeal EMR) the U-ESD strategy remained the cheapest and most cost-effective (***Table 6***).

When the reimbursement rate for ESD increased to 3000 € per ESD-related stay, the S-ESD CONECCT strategy became the less expensive strategy. In comparison, the U-ESD strategy was 83,683.93 € more expensive but avoided nine more surgeries; this equates to an incremental cost of 9298.21 € to avoid one surgery. The U-EMR strategy remained the most expensive.

Discussion

This study is one of the largest worlwilde series of colorectal ESD for large LSL. It confirms the excellent results obtained by our team using an adapted training program [36], and using a systematic countertraction system with clips and a rubber-band [18] [19] [21].

The carcinological results (en bloc, R0, and curative resection and recurrence) are similar to the Japanese results, but the procedure speed was twice faster that reported by the most recent Japanese study using the pocket creation method [37] [38].

At the medico-economic level, regardless of the scenario used to model the results of pEMR, the U-ESD strategy was the most cost-effective. The model showing the best results for pEMR [33] used the methodology of Bourke [23] (direct surgery for EMR of lesions with a Paris 0-IIc; recurrence rate = 5.2%, technical failure rate = 9.3%). Even increasing pEMR success (0% rate of primary surgery for Paris 0-IIc lesions, 0% technical failure rate, and 5.2% recurrence rate), the costs of the S-ESD and U-ESD strategies were similar, while the U-ESD and S-ESD CONECCT strategies avoid the largest number of surgeries.

Three medico-economic studies have compared these strategies. The results were similar between analyses based on the Japanese and Korean reimbursement systems. A Korean retrospective study [24] compared real-life data from patients treated with pEMR and ESD, and demonstrated a higher procedural cost for ESD, which was offset after 18 months by the cost of control colonoscopy in the pEMR group. Unfortunately, the results cannot be extrapolated to other studies because of the retrospective design and difference between lesions treated with ESD (higher% of SMIC) and pEMR (selection bias). An Australian study [23] favoured a selective strategy, reserving ESD for lesions at risk of SMIC. However, the cost of ESD was high (USD 4100 vs. USD 1135 for pEMR), and surgery was not considered for failed pEMR. By increasing the reimbursement difference between ESD and pEMR in this study (ESD model, 3000 €), the selective strategy using the CONECCT classification to select at-risk lesions was the most cost-effective. The U-EMR strategy is not favourable and therefore should not be used. A recent Japanese study [25] reported results similar to ours based on the Japanese and Swedish reimbursement systems.

Our results are robust because they are based on a real-life prospective cohort of ESD and use the best published pEMR data. However, the model is biased toward EMR because unlike the Japanese medico-economic study, it uses the most recent Australian results involving thermoablation of the margins. However, these have not been reproduced or independently validated by other teams [25,33] [39]. For example, an expert American team confirmed the effectiveness of thermoablation of the margins following pEMR but obtained a recurrence rate of 12% [40], two-fold higher than that of the Australian team. Moreover, the model did not consider indirect costs, like work stoppages (which are particularly important in the pEMR group due to higher rate of colonoscopies and surgeries), or postoperative nursing care at home. Recently, an Italian study confirms high impact of colonoscopies on work productivity [41].

Sending Paris 0-IIc lesions to primary surgery in the U-EMR strategy is a debatable approach. This choice, that may not reflect the practice of all centres practicing EMR, has been decided to respect the same analytical model than Bahin et al.[23]. However, even with a model that optimized pEMR approach (0% rate of primary surgery for Paris 0-IIc lesions, 0% technical failure rate, and 5.2% recurrence rate), this strategy was still the most expansive.

In our analytic model, all modelled lesions treated by pEMR containing SMIC, including LR-SMIC, were sent to secondary surgery even if there no precise guidelines on this topic. We kept in consideration that even if the deep margin is free of cancer, pEMR is a R1 technical resection. Furthermore, repeated snare excisions during pEMR could lead to a

Table 4 Cost-effectiveness of the various strategies.

	MODEL OF LITERATURE REAL DATA					
STRATEGY	TOTAL COST (EUROS)	INCREMENTAL COST (EUROS)	COST PER PATIENT (EUROS)	NUMBER OF SURGERIES AVOIDED	ADDITIONAL SURGERIES	INCREMENTAL COST EFFECTIVENESS
U-ESD	2858,048.17	–	3431.03	774	–	
S-ESD CONECCT	2951,411.44	93,363.27	3543.11	765	9	More expensive and fewer surgeries avoided
S-ESD LST	3055,951.53	197,903.36	3668.61	749	25	More expensive and fewer surgeries avoided
S-ESD JNET	3547,426.97	689,378.80	4258.62	704	70	More expensive and fewer surgeries avoided
U-EMR	4060,547.62	1202,499.45	4874.61	620	154	More expensive and fewer surgeries avoided

Table 5 Cost-effectiveness of strategies that increase pEMR performance (0% technical failure and 0% primary surgery rates).

	Model (0% technical failure and 0% primary surgery)					
	For pEMR allocated lesions					
STRATEGY	TOTAL COST (EUROS)	INCREMENTAL COST (EUROS)	COST PER PATIENT (EUROS)	NUMBER OF SURGERIES AVOIDED	ADDITIONAL SURGERIES	INCREMENTAL COST EFFECTIVENESS
S-ESD CONECCT	2840,382.29	–	3409.21	774	–	
U-ESD	2858,048.17	17,665.88	3431.03	774	0	More expensive and same number of surgeries avoided
S-ESD LST	2873,813.43	33,431.14	3449.96	770	4	More expensive and fewer surgeries avoided
S-ESD JNET	2904,521.75	64,139.46	3486.82	767	7	More expensive and fewer surgeries avoided
U-EMR	2988,139.94	147,757.65	3587.20	758	16	More expensive and fewer surgeries avoided

Table 6 Cost-effectiveness analysis of the strategies with an ESD cost of 3000 €.

	MODEL with ESD 3000 euros							
STRATEGY	GLOBAL COST (EUROS)	INCREMENTAL COST (EUROS)	COST PER PATIENT (EUROS)	NUMBER OF SURGERIES AVOIDED	ADDITIONAL SURGERIES	INCREMENTAL COST PER SURGERY AVOIDED (EUROS)	INCREMENTAL COST PER SURGERY AVOIDED PER PATIENT (EUROS)	INCREMENTAL COST EFFECTIVENESS
S-ESD CONECCT	3383,787.04	–	4062.17	765	–	–	–	–
U-ESD	3467,470.97	82,977.04	4162.63	774	−9	9219.67	11,07	More expensive but more surgeries avoided
S-ESD LST	3418,093.53	33,599.60	4103.35	749	16	–	–	More expensive and fewer surgeries avoided
S-ESD JNET	3750,080.17	365,586.24	4501.90	704	45	–		More expensive and fewer surgeries avoided
U-EMR	4060,547.62	676,053.69	4874.61	620	132	–		More expensive and fewer surgeries avoided

loss of carcinologic information (artefact of thermocoagulation, missing pieces) that could be detrimental for the patients in particular in presence of SMIC. Moreover, the same strategy was applied in the paper of Bahin et al., that is a referral paper on this topic. Finally, according to our knowledge, a majority of centres applied this strategy in daily practice.

The economic data of the ESD group were derived via a reliable microcosting methodology allowing for precise analysis of the reimbursement requirements, and showing that the U-ESD strategy is the most effective due to frequent avoidance of surgery, and relatively low numbers of recurrences and colonoscopies. Based on European guidelines recommending follow-up after pEMR at 6 and 18 months, and the higher number of costly surgeries in patients treated with pEMR, a reimbursement rate for ESD roughly approximating the cost of one pEMR and two follow-up colonoscopies was most cost-effective.

Endoscopic optical diagnosis remains difficult to differentiate lesions associated or non-associated with a risk of submucosal cancer. In one hand, many simple LGD and HGD lesions were classified as high risk, and in another hand, several submucosal cancers were missed except with CONECCT classification[26,27,42–46]. Submucosal cancer is not always visible, particularly in the presence of a macronodule more than 1 cm in diameter (protruding lesions and laterally spreading tumour-granular-nodular mixed [LST-GM]). This may explain the lower efficiency of strategies based on the JNET classification that does not take into account covert signs of carcinoma. With the U-ESD strategy, the algorithm is simplified—for an LST more than 2 cm in diameter, it is necessary to rule out the presence of deep cancer (JNET III), which is typically located within a depressed zone (Paris 0-IIc or 0-III); this is an indication for direct referral for surgery. If no sign of deep cancer is present, ESD with traction should be proposed. Management is subsequently guided by the results of the pathological analysis.

Performing a large number of ESDs, which have a lower risk of recurrence, could decrease the risk of interval colorectal cancer. Indeed, post-resection recurrences represent 30% of all cases of interval cancer [47,48]; these arise in particular due to the low acceptance by patients of iterative control colonoscopy after a pEMR (leading to a risk of loss to follow-up).

Validation of these results in other healthcare systems will be important before expanding indications for ESD. Our systematic double clip and rubber-band countertraction ESD strategy is innovative, effective, and inexpensive. The use of increasingly available tools that simplify the procedure [18,49–51] should not unreasonably elevate the cost of ESD given the inability at present to accurately target lesions with submucosal cancer; ESD should only be considered when high performance is expected, in terms of R0 resection and avoidance of perforation requiring surgery, given the major increase in costs related to surgery and control colonoscopy for non-R0 resection.

A weakness of our study concerns the expertise of the operators, where the management of large LSLs requires an expert centre [18,52–54]. Second, use of endoscopes with a zoom function might have helped the selection of patients not requiring ESD (improving results of selected strategies) but also increased the cost of the procedures (due to the

requirement for two endoscopes). Third, the cost estimated for the ESD procedure is a real cost in a country without dedicated reimbursement. However, this weakness can also be considered a strength because this is in fact the situation in many Western countries. The results could inform the creation of reimbursement tariffs for ESD according to pEMR and control colonoscopy tariffs. Finally, the outcomes of pEMR were modelled in the S-ESD or U-EMR groups based on the most robust available data. A second scenario was also modelled to improve the robustness of our results.

In conclusion, in the era of clip-and-rubber-band countertraction, ESD for all large LSLs is more cost-effective than pEMR, and can be superior to a S-ESD depending on the reimbursement scheme. The CONECCT classification, which combines overt and covert signs of carcinoma, is preferable to select lesions that will most benefit from an ESD. It is important that technological advances that facilitate ESD do not increase its cost unreasonably.

Credit author statement

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.clinre.2022.101969.

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