

# Improving assessment and management of large non-pedunculated colorectal lesions in a Western center over 10 years: lessons learned and clinical impact



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## ABSTRACT

**Background and study aims** Outcomes of endoscopic assessment and management of large colorectal (CR) non-pedunculated lesions (LNPLs) are still under evaluation, especially in Western settings. We analyzed the clinical im-

part of changes in LNPL management over the last decade in a European center.

**Patients and methods** All consecutive LNPLs  $\geq 20$  mm endoscopically assessed (2008–2019) were retrospectively included. Lesion, patient, and resection characteristics were compared among clinically relevant subgroups. Multivariate logistic regression (for predictors of submucosal invasion [SMI] and recurrence), Kaplan-Meier curves and ROC curves (for temporal cut-offs in trends analyses) were used.

**Results** A total of 395 LNPLs were included (30 mm [range 20–40]; SMI=9.6%; primary endoscopic resection [ER]=88.4%). Pseudo-depression and JNET classification independently predicted SMI beyond single morphologies/location. After complete ER, involvement of ileocecal valve/dentate line, piece-meal resection and high-grade dysplasia independently predicted recurrence. Rates of 5-year recurrence-free, surgery-free and cancer-free survival were 77.5%, 98.6% and 100%, respectively, with 93.8% recurrences endoscopically managed and no death attributable to ER or CR cancer (versus 3.4% primary surgery mortality). ROC curves identified the period  $\geq 2015$  (following Endoscopic Submucosal Dissection [ESD] introduction and education on pre-resective lesion assessment) as associated with improved lesions' characterization, increased en-bloc resection of SMI lesions (87.5% vs 37.5%;  $p=0.0455$ ), reduced primary surgery (7.5% vs 16.7%;  $p=0.0072$ ), surgical referral of benign lesions (5.1% vs 14.8%;  $p=0.0019$ ), and recurrences.

**Conclusions** ESD introduction and educational interventions allowed ER of more complex lesions, offset by increased complementary surgery for complications or intrinsic histological risk. Nevertheless, overall, they have reduced surgery demand and increased appropriateness and safety of LNPL management in our center.

## Introduction

Large ( $\geq 20$  mm) non-pedunculated colorectal (CR) lesions (LNPLs) harbor a significant risk of malignancy and are associated with technical difficulty in achieving complete endoscopic

resection (ER) [1–3]. Technological improvements (e.g. endoscopic submucosal dissection [ESD]) and a deeper comprehension of the biological behavior of cancer precursors have enabled endoscopists to consider ER for lesions of increasing complexity. However, these procedures have a longer training

curve, are more resource-intensive, carry a higher risk of adverse events (AEs), and their long-term advantages over surgery are still debated [4–8].

Selection of the correct therapeutic approach strictly relies on the capability of endoscopists to identify lesions at higher risk of superficial submucosal invasion (SMI) that warrant en-bloc (EB) resection to ensure precise histological evaluation and endoscopic curability, but currently available predictors have suboptimal performance [1, 7, 9–12].

Moreover, long-term results of endoscopic management are heterogeneous, mainly derived from Eastern experience, where ESD is more widely available and outcomes have proven to be different from those in Western series [8, 13–16].

Finally, analysis of quality improvement in this area is usually restricted to learning curves of single resection techniques [17, 18].

Our aim was to describe endoscopic assessment and management of all consecutive LNPLs treated in a single European referral center over 10 years, to analyze: 1) pre-resection prediction of SMI; 2) outcomes of treatment according to resection technique; and 3) temporal trends of clinically relevant performance measures while expertise improved.

## Patients and methods

A retrospective search of prospectively collected endoscopic and histological databases of Sant'Andrea Hospital, an academic, referral center for endoscopic management of CR lesions, was executed from January 2008 to April 2019.

Procedures were executed by the same five endoscopists (SA, VDC, GDA, MR and EDG) over time, all of whom were experienced in endoscopic luminal resection. LNPLs were treated through: 1) endoscopic mucosal resection (EMR) when the lesion was lifted through submucosal fluid injection and finally resected through a snare; 2) ESD, when fluid submucosal injection was used to expand the submucosal space, which was then accessed through an endoscope equipped with a transparent hood for careful manual dissection through a knife; and 3) hybrid procedures, when a part of the lesion was dissected through a knife and another part resected through snaring (usually a peripheral dissection and a central snaring [19, 20]).

All consecutive LNPLs  $\geq 20$  mm were included, notwithstanding primary treatment (e.g. surgical versus [vs.] endoscopic, EMR vs. ESD), provided that endoscopic assessment and definitive histology were both available.

Excluded lesions were: 1)  $< 20$  mm; 2) pedunculated; 3) had obvious deep invasion (e.g. ulcerated); or 4) were in patients with inflammatory bowel diseases or genetic syndromes.

Morphology and superficial pattern were extracted from the databases and all images and videos were reevaluated by agreement of four trained endoscopists unaware of histology. Each lesion was categorized using JNET classification [21, 22] for vascular pattern and one modified Paris classification [23], to further include sessile lesions (sessile [S]; sessile with pseudodepression [S-PD]; LST granular, homogeneous [LST-GH] or mixed [LST-GM]; LST non-granular, flat-elevated [LST-NG-FE] or pseudodepressed [LST-NG-PD]). Pseudodepression [23] (PD) was furthermore independently dichotomised as present/

absent. As for lesion size, an endoscopic estimate initially was used as a reference, but was subsequently systematically compared to the histopathological report, with any significant disagreement leading to lesion exclusion.

The study was approved by local Institutional Review Board.

## Definitions

Histological diagnosis followed World Health Organization definitions [24].

Submucosal invasion (SMI) was categorized as “high-risk” for lymph node metastasis when at least one of the universally adopted histological risk factors (i.e. G3 differentiation, submucosal invasion  $> 1000$   $\mu\text{m}$ , lymphovascular invasion and tumor budding) [2, 25] was identified, or “low-risk” when all the above-mentioned parameters were excluded. In case of SMI lesions, we defined “accurate histological stratification” when all risk factors [2, 25] were reported in the histological report.

Surgery was defined as “primary” when indicated soon after endoscopic assessment without any attempt of endoscopic resection, and “complementary” when executed after primary endoscopic resection.

ER was deemed “curative” after a macroscopically complete resection of lesions with intramucosal dysplasia or “low-risk” SMI and “non-curative” after an incomplete resection, a resection of “high-risk” SMI lesions or SMI lesions resected piecemeal (PM) [26].

Post-treatment follow-up (FU) data were registered: recurrence; surgery for recurrences; and cancer-specific mortality. FU was analyzed only for non-surgically resected patients, endoscopically treated before June 2018 (allowing  $> 12$  months FU at analysis time). At the moment of data extraction, all patients were contacted through phone calls to update clinical follow-up and register subsequent endoscopic examinations performed in other centers. Endoscopic follow-up was required for analysis of recurrence. For surgically treated and lost-to-FU patients, data on mortality were retrieved from health databases.

We defined as “potentially preventable” surgeries executed for 1) primary referral of benign lesions (BLs); 2) PM resection of invasive lesions (ILs); 3) complications; and 4) recurrences.

## Statistical analysis

Categorical variables were compared through the  $\chi$ -squared test, while continuous variables with t-test or Mann-Whitney test, as appropriate.

When analyzing associations between continuous variables and an outcome of interest, receiver operating characteristic (ROC) curves were used to identify cut-offs discriminating different outcome prevalences, which were used to dichotomize continuous variables.

Multivariate logistic regression models were built using a stepwise method, with a  $P$ - to enter  $< 0.05$  and a  $P$  to stay  $< 0.1$ . Results were expressed as odds ratio (OR) and 95% confidence interval (CI).

Recurrence-, surgery-, and cancer-free survival was evaluated using Kaplan-Meier curves. The influence of independent variables was evaluated by stepwise Cox-proportional-hazards

regression. Outcomes were expressed as adjusted survival probabilities at mean of covariates.

For trends analysis, we paired each procedure with a time lag (years) from inception of the study and analyzed this continuous variable in ROC curves to explore cut-offs separating periods with different prevalences of binary performance measures (i. e. presence/absence of an outcome).

$P < 0.05$  was considered statistically significant.

## Results

A total of 395 patients (age 70 [interquartile range (IQR) 62–76], male 57.5%) with LNPLs (30 mm [IQR 20–40]) were evaluated during the study period (► **Table 1**).

Identification/exclusion of patients is summarized in **Supplementary Table 1**.

### Characteristics of included lesions

#### Differences according to location

Colonic vs rectal lesions are compared in **Supplementary Table 2**, showing a significantly different distribution of morphological types and histologies through the colon.

#### Invasive lesions (ILs) versus benign lesions (BLs)

38/395 (9.6%) lesions presented as submucosally invasive.

Characteristics of ILs and BLs are compared in ► **Table 1** (significant differences shown in **Supplementary Fig. 1**). ILs were more frequent among older patients ( $\geq 74$  years,  $P = 0.03$ ) and among larger lesions ( $\geq 40$  mm,  $P = 0.001$ ), distal lesions ( $P = 0.0134$ ) and those with pseudodepression ( $P < 0.0001$ ). SMI was significantly different among the various morphologies, ranging from 1.9%, 2.7% and 7.6% of LST-GH, LST-NG-FE and sessile lesions, to 11.9%, 28.1% and 35% of LST-GM, S-PD and LST-NG-PD respectively ( $P < 0.0001$ ).

JNET classification was available for 294 lesions (74.4%). All lesions with Pattern 1 (21/21) corresponded to a serrated histology. All lesions with Pattern 3 (3/3) were invasive beyond muscularis propria. 53.6% of JNET 2b and 3.3% of JNET 2a lesions were found with SMI ( $P < 0.0001$ , ► **Table 1** and **Supplementary Fig. 1**).

#### Predictors of invasiveness

We used variables associated to SMI at univariate analysis to build multivariate logistic regression models. In the simplest model (M1), considering pre-resection variables available for all lesions, pseudodepression (OR = 7.5 [CI 3.6–15.6]) and dimension  $\geq 40$  mm (OR = 2.4 [CI 1.2–5]) were the only independent predictors of SMI, beyond other single morphological characteristics. The addition of JNET classification and non-lifting sign to this model (M2) resulted in only a JNET 2b/3 (OR = 51.8 [CI 12.5–215.5]) and PD (OR = 4.6 [CI 1.1–19.7]) independently predicting SMI (► **Table 1** and **Supplementary Fig. 1**).

As diagnostic tests (**Supplementary Table 3**), both predictive models had a high negative predictive value for SMI (96.9% for M1 and 98.2% for M2), with a lower positive predictive value.

## Management

After endoscopic assessment, primary surgical referral was 11.6%, more frequently for ILs than BLs (31.6% vs 9.5%;  $P = 0.0002$ ).

Among patients in whom an ER was first attempted (N = 349), there were 31 incomplete resections (8.9%; 9 endoscopically retreated), and nine perforations (2.6%; 6 endoscopically managed). Both events were significantly more frequent among ILs (► **Table 2**).

Need for complementary surgery after ER was significantly higher among ILs than BLs (69.2% vs 5.6%,  $P < 0.0001$ ), due to the relatively higher rate of adverse events, but also to presence among SMI lesions of two (7.6%) piecemeal resections and seven (26.9%) high-risk histologies after a complete ER.

Among ILs managed by primary endoscopic resection (N = 26), eight patients did not undergo subsequent surgery (surgical sparing = 30.8%), four for being unfit despite high-risk histology while four (15.4%) had curative ERs.

#### Resection technique

Lesions that were larger, flat, with more dangerous morphology (e. g. nodules/PD) or superficial pattern (i. e. JNET 2B/3), involving “risky hotspots” (i. e. dentate line, ileocecal valve or appendix) and with more advanced histology were relatively more frequent among patients treated through ESD rather than EMR (**Supplementary Table 4**).

There was a higher rate of EB resection among ESDs (**Supplementary Table 4**). Incomplete resections, recurrences and surgeries for recurrence were similar among the two techniques. There was a trend towards a more frequent need for complementary surgery following ESD, due to the relatively higher rate of surgery for perforation (3.6% vs 0.3%,  $P = 0.01$ ) and for high-risk histology after a complete endoscopic resection (7.5% vs 1.7,  $P = 0.01$ ). Conversely, among ESDs there was a higher prevalence of ILs not undergoing complementary surgery (7.5% vs 1.4%,  $p = 0.007$ ) and of ILs with a curative endoscopic resection (5.6% vs 0.3%,  $P = 0.0007$ ; **Supplementary Table 4**).

## Follow-up

#### Endoscopically managed patients

Among non-operated patients with a complete ER (N = 307), 244 underwent any clinical FU while 14 (5.4%) were lost-to-FU.

#### Recurrence

Among patients with endoscopic FU (N = 204; median 16 months [IQR 10–34]), recurrence was found in 42 (20.5%) after a median interval of 7 months [IQR 4–13] from index procedure. Considering also patients experiencing  $> 1$  recurrence (N = 19, maximum 3 per patient), endoscopic treatment of recurrence was possible in 60/64 cases (93.8%), while 4 patients (9.5%) were finally sent to surgery.

A ROC curve identified a dimension  $\geq 30$  mm as best (area under the curve [AUC] = 0.702,  $P < 0.0001$ ) separating recurrent (28.9%) vs non-recurrent (9.9%) lesions ( $P = 0.0008$ ). Risk

► **Table 1** Characteristics of included lesions, comparisons based on histology (invasive vs. benign) and multivariate analysis of predictors of submucosal invasion.

Variable	All patients (N=395)				
Age [IQR], years	70 [62–76]				
Male sex	228 (57.7%)				
Dimensions [IQR], mm	30 [20–40]				
Reason of the exam: screening	96 (24.3%)				
Histology	LGD: 221 (55.9%)				
	HGD: 136 (34.4%)				
	T1 or superior: 38 (9.6%)				
Variable	Invasive Lesions (N=38)	Benign Lesions (N=357)	P value	Multivariate M1 <sup>1</sup> OR [CI]	Multivariate M2 <sup>2</sup> OR [CI]
Age ≥ 74 years <sup>3</sup>	19 (50.0%)	114 (31.9%)	0.0252 <sup>4</sup>	NS	NS
Sex (Male)	22 (57.9%)	206 (57.7%)	0.9819		
Colon: Rectum	27 (71.1%) : 11 (28.9%)	268 (75.1%) : 89 (24.9%)	0.5887		
Proximal: Distal	16 (42.1%) : 22 (57.9%)	224 (62.7%) : 133 (37.3%)	0.0134 <sup>4</sup>	NS	NS
Dimensions ≥ 40 mm <sup>3</sup>	19 (50.0%)	91 (25.5%)	0.0014 <sup>4</sup>	OR 2.4 [1.2–5]	NS
Sessile: LST	16 (42.1%) : 22 (57.9%)	108 (30.4%) : 247 (69.9%)	0.1413		
Composite Morphology				NS	NS
▪ S	7 (18.4%)	85 (24.1%)	<0.0001 <sup>4</sup>		
▪ S-PD	9 (23.7%)	23 (6.5%)			
▪ LST-GH	2 (5.3%)	106 (30.1%)			
▪ LST-GM	12 (31.6%)	89 (25.3%)			
▪ LST-NG-FE	1 (2.6%)	36 (10.2%)			
▪ LST-NG-PD	7 (18.4%)	13 (3.7%)			
▪ NA	0	5			
Pseudodepression (+)	25 (65.8%)	68 (19%)	<0.0001 <sup>4</sup>	OR 7.5 [3.6–15.6]	OR 4.6 [1.1–19.7]
Adenomatous: Serrated	38 (100%) : 0 (0%)	322 (90.2%) : 35 (9.8%)	0.0435 <sup>4</sup>	NS	NS
JNET Classification <sup>5</sup>					
▪ JNET 1	0 (0%)	21 (7.8%)	<0.0001 <sup>4</sup>	/	1
▪ JNET 2A	8 (30.8%)	234 (87.3%)			
▪ JNET 2B	15 (57.7%)	13 (4.9%)		/	OR 51.8 [12.5–215.5]
▪ JNET 3	3 (11.5%)	0 (0%)			
▪ NA	12	89			

LST, laterally spreading tumor; S, sessile; PD, pseudodepression; GH, granular, homogeneous; GM, granular, mixed; NG-FE, non-granular-flat elevated; NG-PD, non-granular-pseudodepressed; NA, not available; NS, not significant; JNET, Japan NBI Expert Team Classification of vascular pattern.

<sup>1</sup> Model 1 (included observations = 390): model fit  $P < 0.0001$ ; % of cases correctly classified = 90.26%; AUC = 0.777

<sup>2</sup> Model 2 (including JNET and non-lifting sign, included observations = 269): model fit  $P < 0.0001$ ; % of cases correctly classified = 95.91%; AUC = 0.914

<sup>3</sup> ROC curve analyses identified an age ≥ 74 (Area under the curve [AUC] = 0.576,  $P = 0.13$ ) and a diameter ≥ 40 mm (AUC = 0.587,  $P = 0.1$ ) as the cut-offs better separating an invasive versus a benign histology.

<sup>4</sup> statistically significant ( $P < 0.05$ )

<sup>5</sup> proportion of lesions with available data

► **Table 2** Endoscopic management of lesions.

Variable	Invasive Lesions (N = 38)	Benign Lesions (N = 357)	P value
Primary Surgery	12 (31.6%)	34 (9.5%)	0.0002 <sup>1</sup>
Endoscopic Treatment	26 (68.4%)	323 (90.5%)	0.0002 <sup>1</sup>
Non-lifting sign (+)	6 (23.1%)	17 (5.2%)	0.0004 <sup>1</sup>
Technique			0.0026 <sup>1</sup>
▪ EMR	16 (61.5%)	279 (86.6%)	
▪ ESD	6 (23.1%)	24 (7.5%)	
▪ Hybrid techniques	4 (15.4%)	19 (5.9%)	
Complications			
▪ Perforations	3 (11.5%)	6 (1.9%)	0.0028 <sup>1</sup>
▪ Incomplete Resections	10 (38.5%)	21 (6.5%)	<0.0001 <sup>1</sup>
▪ EB : PM resection <sup>2</sup>	10 (62.5%) : 6 (37.5%)	148 (49%) : 154 (51%)	0.2936
▪ Curative ER	4 (15.4%)	302 (93.5%)	<0.0001 <sup>1</sup>
▪ Non-curative ER	22 (84.6%)	21 (6.5%)	
▪ R+	9	21	
PM resections	2		
High-risk histology	11		
▪ SMI > 1000 µm	7		
▪ LVI+	3		
▪ G3 differentiation	1		
Complementary surgery <sup>3</sup>	18 (69.2%)	18 (5.6%)	<0.0001 <sup>1</sup>

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EB, en-bloc; PM, piecemeal; ER, endoscopic resection; R+, residual tumor due to perforation or incomplete resection; SMI, submucosal invasion; LVI, lymphovascular invasion; G3, poor differentiation.

Among all patients for which an endoscopic resection was first attempted (N=349), there were 31 incomplete resections (8.9%), 9 perforations (2.6%) and 36 (10.9%) complementary surgeries. All three events were significantly more frequently among ILs.

<sup>1</sup> statistically significant ( $P < 0.05$ )

<sup>2</sup> proportion of complete endoscopic resections (excluded incomplete procedures): N = 16 for ILs and 302 for BLs

<sup>3</sup> reasons for complementary surgery were 1) among ILs: 1 perforation, 8 incomplete resections, 7 non-endoscopically curable T1, 2 piecemeal resections of ILs; 2) among BLs: 2 perforations, 14 incomplete resections, 2 patients' choice.

factors for recurrence were: PM resection (31.2% vs 7.5%,  $P < 0.0001$ ), a higher number of fragments (9.6%, 23.5% and 30.9% for lesions removed EB, in 2 pieces and  $\geq 3$  pieces,  $P = 0.0014$ ), involvement of "risky hotspots" and high-grade (HG) versus low-grade (LG) dysplasia (28.6% vs 16.1%,  $P = 0.0354$ ; ► **Table 3**).

No association with resection techniques nor morphology was found.

### Multivariate logistic regression of variables associated with recurrence

The involvement of "risky hotspots" (OR=6.3 [CI 1.8–21.8]), a PM vs EB resection (OR=5.6 [CI 2.3–13.7]) and a HG vs LG dysplasia (OR=2.7 [CI 1.2–5.7]) were found to be independent predictors of recurrence (► **Table 3** and **Supplementary Fig. 1**).

### Cancer-specific mortality

No CRC-related death was found in the whole cohort of patients with clinical follow-up (median = 36 months [IQR 19–70]).

Among patients lost to follow-up, three deaths were registered far from endoscopic resection (excluding endoscopy-related events), with removed lesions further excluding cancer-specific mortality (20–25 mm LGD lesions, removed EB).

### Adjusted survival curves

Adjusted rates of 1-year recurrence-free survival, surgery-free and CRC-free survival were 88.9%, 99.7%, and 100%, respectively. Five-year survival rates were 77.5%, 98.6%, and 100%, respectively.

► **Table 3** Comparisons of characteristics of recurrent versus not recurrent lesions during endoscopic follow-up.

Variable	Recurrent (N=42)	Not Recurrent (N=163)	P value	Prevalence of recurrence (% of pts with variable)	Multivariate analysis <sup>1</sup> OR [CI]
Age [IQR], years	69 [61–74]	69 [61–74]	0.8747		
Dimensions [IQR], mm	35 [30–45]	28 [20–35]	<0.0001 <sup>2</sup>		NS
Dimensions ≥30 mm <sup>3</sup>	33 (78.6%)	81 (49.7%)	0.0008 <sup>2</sup>	28.9% vs. 9.9%	NS
Colon : Rectum	31 (73.8%): 11 (26.2%)	114 (69.9%): 49 (30.1%)	0.6238		
Proximal : Distal	24 (57.1%): 18 (42.9%)	94 (57.7%): 69 (42.3%)	0.9511		
Sessile: LST	9 (21.4%): 33 (78.6%)	54 (33.1%): 109 (66.9%)	0.1438		
Composite Morphology			0.1008		
▪ S	7 (16.7%)	40 (24.5%)			
▪ S-PD	2 (4.8%)	14 (8.6%)			
▪ LST-GH	18 (42.9%)	46 (28.2%)			
▪ LST-GM	14 (33.3%)	39 (23.9%)			
▪ LST-NG-FE	1 (2.4%)	18 (11%)			
▪ LST-NG-PD	0 (0%)	6 (3.7%)			
Pseudodepression (+)	9 (21.4%)	29 (17.8%)	0.5895		
Adenomatous: Serrated	41 (97.6%): 1 (2.4%)	144 (88.3%): 19 (11.7%)	0.0715	22.2% : 5%	NS
Dysplasia			0.0619		
▪ LGD	20 (47.6%)	104 (63.8%)		16.1%	1
▪ HGD	22 (52.4%)	55 (33.7%)	HGD vs. LGD, p = 0.0354 <sup>2</sup>	28.6%	OR 2.7 [1.2–5.7]
▪ T1	0 (0%)	4 (2.5%)		0%	NS
▪ PM: EB	35 (83.3%): 7 (16.7%)	77 (47.2%): 86 (52.8%)	<0.0001 <sup>2</sup>	31.2% : 7.5%	OR 5.6 [2.3–13.7]
Number of pieces			0.0014 <sup>2</sup>		NS
▪ 1	9 (21.4%)	85 (52.1%)		9.6%	
▪ 2	4 (9.5%)	13 (8%)		23.5%	
▪ ≥3	29 (69%)	65 (39.9%)		30.9%	
Involvement of dentate line. appendix. ileocecal valve (+)	7 (16.7%)	7 (4.3%)	0.0047 <sup>2</sup>	50% vs. 18.3%	OR 6.3 [1.8–21.8]
Technique			0.5066		
▪ EMR	36 (85.7%)	138 (84.7%)			
▪ ESD	2 (4.8%)	15 (9.2%)			
▪ Hybrid procedures	4 (9.5%)	10 (6.1%)			

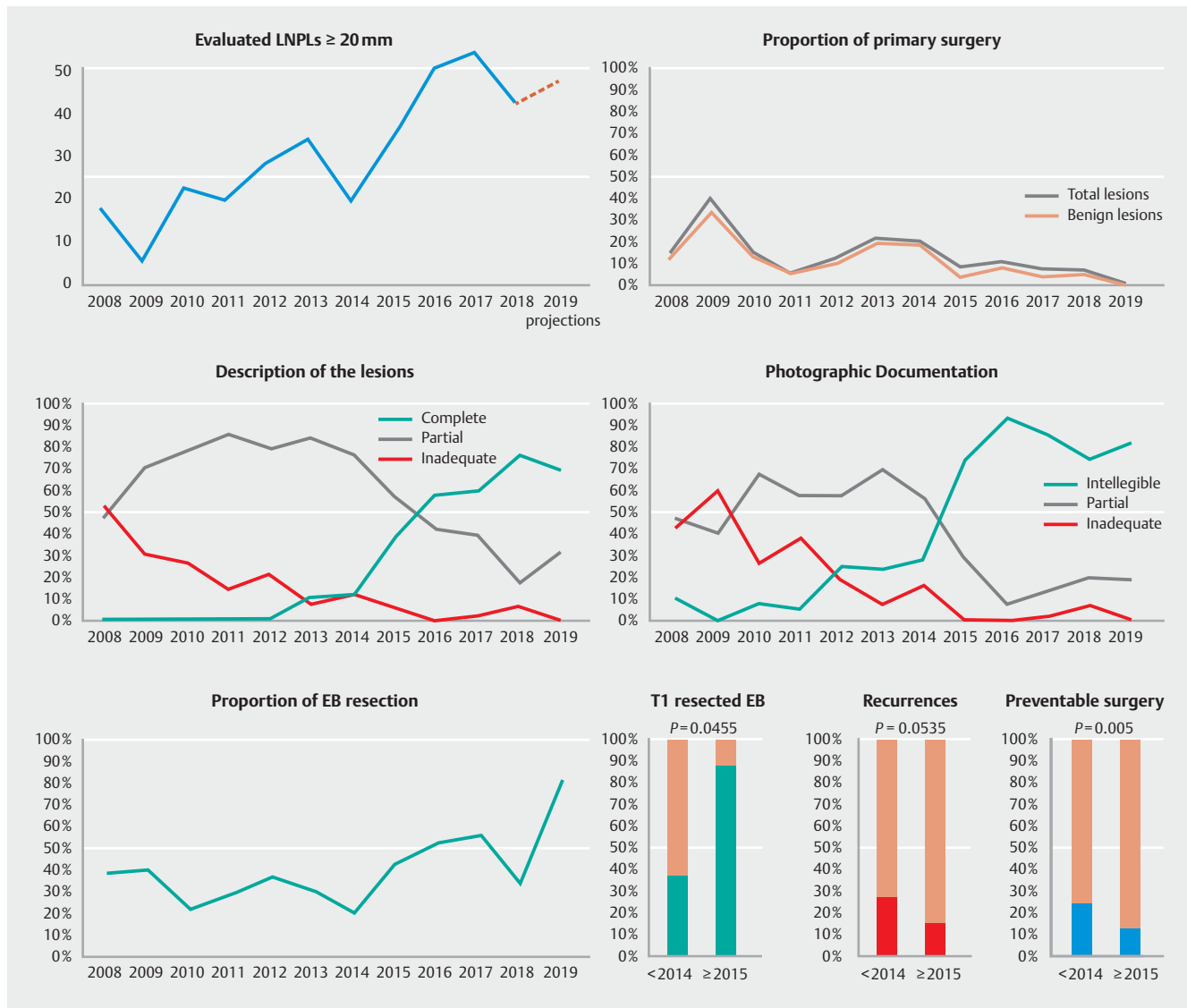
LST, laterally spreading tumor; S, sessile; PD, pseudodepression; GH, granular, homogeneous; GM, granular, mixed; NG-FE, non-granular-flat elevated; NG-PD, non-granular-pseudodepressed; NA, not available; LGD, low-grade dysplasia; HGD, high-grade dysplasia; T1, submucosal invasion following TNM staging; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; EB, en-bloc resection; PM, piecemeal resection.

Involvement of risky hotspots, histology with HGD and a PM resection were independent significant predictors of recurrence at multivariate analysis.

<sup>1</sup> model fit  $P < 0.0001$ ; % of cases correctly classified = 80.98%; AUC = 0.755

<sup>2</sup> statistically significant ( $P < 0.05$ )

<sup>3</sup> A ROC curve identified a dimension of the lesion  $\geq 30$  mm as best (AUC = 0.702,  $P < 0.0001$ ) separating recurrent (28.9%) vs. non-recurrent (9.9%) lesions ( $P = 0.0008$ ).



► **Fig. 1** Temporal trends for performance measures. At the top-left, absolute number of evaluated large ( $\geq 20$  mm) non-pedunculated colorectal lesions. Subsequently; proportion of primary surgery, reporting of lesions, photographic documentation and proportion of en-bloc (EB) resection where represented as rate per year over the study period. At bottom-right, rates of submucosally invasive lesions resected EB, recurrent lesions and “potentially preventable surgery” separated according to two time intervals (before and after 2015, cut-off identified through ROC curve analysis as explained in the text).

### Surgically managed patients

Among 88 operated patients, three (3.4%) died within 30 days of surgery. All of them (median age = 71) were in the group of primary elective surgery (SMI histology 3/3).

### Trends over time

Temporal trends of performance measures related to the assessment and management of LNPLs were evaluated graphically (► **Fig. 1**) and through ROC curve analysis (► **Table 4**).

ROC curves repeatedly identified 2015 (following ESD introduction and education on pre-resective lesion assessment) as the year better separating procedures with a complete description of the lesion (OR = 37.8 [16.9–84.4],  $P < 0.0001$ ), an adequate iconographic documentation (OR = 23.3 [13.8–39.4],  $P <$

0.0001) and availability of JNET classification (OR = 13.43 [7.3–24.9],  $P < 0.0001$ ). These 3 outcomes were present in 60.5%, 82.3% and 93.5% of procedures  $\geq 2015$ .

After 2015, primary surgery was less indicated, both overall (7.5% vs 16.7%,  $P = 0.0072$ ) and especially for BLs (5.1% vs 14.8%,  $P = 0.0019$ ). EB removal of lesions with invasive histology was more frequent (87.5% vs 37.5%,  $P = 0.0455$ ) and the rate of recurrence was lower (15% vs 26%,  $P = 0.0535$ ). Finally, the overall rate of “potentially preventable” surgery was significantly lower  $\geq 2015$  (12.6% vs 23.3%,  $P = 0.005$ ) (► **Table 5**).



► **Table 4** Temporal trends of performance measures.

Outcome	Identified Cut-off	AUC	P Value	Odds Ratios; P value
Adequate iconographic documentation	≥2015	0.840	<0.001 <sup>1</sup>	OR = 23.3 [13.8–39.4]. <0.0001
Completeness of report (location + morphology + dimensions + superficial pattern)	≥2015	0.866	<0.0001 <sup>1</sup>	OR = 37.8 [16.9–84.4]. <0.0001
JNET classification available	≥2015	0.801	<0.001 <sup>1</sup>	OR = 13.43 [7.3–24.9]. <0.0001
Outpatients management of lesions	≥2012	0.564	<0.042 <sup>1</sup>	OR = 3.1 [1.5–6.1]. 0.0015
Primary surgery	≥2015	0.625	0.002 <sup>1</sup>	OR = 0.4 [0.2–0.8]. 0.0055
Benign lesions sent to primary surgery	≥2015	0.640	0.0022 <sup>1</sup>	OR = 0.3 [0.1–0.7]. 0.0029
Resections at index colonoscopy	≥2019	0.521	NS	NS
En-bloc removal of invasive lesions <sup>2</sup>	≥2015	0.650	NS	OR = 11.7 [0.9–147.6]. 0.0578
Incomplete resections	≥2014	0.587	NS	NS
Perforation	≥2018	0.510	NS	NS
Accurate histological stratification of T1 lesions	≥2014	0.600	NS	NS
Recurrence <sup>3</sup>	≥2015	0.571	NS	OR = 0.5 [0.3–1]. 0.0554
Surgery for recurrence <sup>3</sup>	≥2014	0.598	NS	NS
“Non-curative endoscopic resection”	≥2015	0.563	NS	OR = 0.6 [0.3–1.05]. 0.0722
“Potentially preventable surgeries”	≥2015	0.602	0.0043 <sup>1</sup>	OR = 0.5 [0.3–0.8]. 0.0056

JNET, Japan NBI Expert Team Classification of vascular pattern; NS, not significant.

We paired each procedure with a time lag (years) from inception of the study and analyzed this continuous variable through ROC curves to explore cut-offs separating periods with different prevalences of binary performance measures (ie, presence/absence of an outcome). For each outcome, the identified cut-off and significance of the model are provided (as area under the curve (AUC) and P value); In the rightmost column, odds ratios (OR) are reported, as a measure of the increased or decreased probability to detect the outcome in the temporal interval following the identified cut-off.

<sup>1</sup> statistically significant ( $P < 0.05$ )

<sup>2</sup> among patients with complete endoscopic resection

<sup>3</sup> among patients with endoscopic resection undergoing follow-up

## Discussion

According to our study, implementation of technological and educational interventions over time has resulted in a substantial improvement in endoscopic management of LNPLs in our center. The unique methodology used in this paper has underscored how not only specific interventions led to an increased confidence in handling these lesions and choosing the most appropriate therapeutic strategy, but even how this has translated into measurable changes in relevant clinical outcomes.

Endoscopic resection of these lesions often requires adoption of advanced endoscopic techniques (e.g. ESD), whose limits [4–6] impose a rigid selection of lesions [7, 27]. Characteristics associated with a higher probability of SMI have shown suboptimal accuracy, deriving from heterogeneous series, usually including specific subtypes of lesions (e.g. only LSTs [1, 28]), specific resection techniques (e.g. only ESDs [9, 10] or EMRs [12, 19, 29]) and finally, not always including risk factors in a multivariate analysis [9, 12, 30]. In our series of consecutive LNPLs, potentially free of selection bias beyond referral, we confirmed the majority of known risk factors, with SMI rates according to single morphologies consistent with those summarized in a recent meta-analysis [1]. We further explored recently

advocated factors (e.g. lesions distal to splenic flexure were morphologically more complex and histologically advanced [1, 30]), but when included in a multivariate model, only a few variables independently predicted SMI. Irregularity in superficial pit/vascular pattern seems to be the strongest SMI predictor. However, JNET classification was not available for all lesions, and published experiences have demonstrated that interobserver agreement is suboptimal, with specific training required to reach acceptable accuracy [21, 31, 32]. This could suggest that if the endoscopist has sufficient training/experience with pit/vascular pattern interpretation, this should be the most considered parameter, along with presence of pseudodepression. However we also created a simpler model suggesting that size ≥40 mm and pseudodepression (evaluable without specific training) can nonetheless predict SMI histology better than other currently considered factors, including superficial morphology. Advance in the field of artificial intelligence will surely improve pre-resection assessment of LNPLs [19, 33], integrating all morphological aspects into a risk estimate helping the endoscopist to adopt the most appropriate therapeutic strategy.

As for resection techniques, the dispute between ESD and EMR is still open. While larger/more specific series evaluating efficacy and safety of single techniques exist [12–14, 19, 34–



► **Table 5** Differences in lesion characteristics, management, and outcomes before and after 2015.

Variable	Lesions managed <2015 (N = 180)	Lesions managed ≥ 2015 (N = 215)	P value
Assessment			
Indication, screening	32 (17.8%)	64 (29.8%)	0.0057 <sup>1</sup>
Colon, rectum	128 (71.7%), 52 (28.9%)	167 (77.7%), 48 (22.3%)	0.1357
Proximal, distal	104 (57.8%), 76 (42.2%)	136 (63.3%), 79 (36.7%)	0.2674
Sessile, LST	65 (36.5%), 113 (63.5%)	59 (27.4%), 156 (72.6%)	0.0543
Composite morphology			0.0169 <sup>1</sup>
▪ S	47 (26.7%)	45 (21%)	
▪ S-PD	18 (10.2)	14 (6.5%)	
▪ LST-GH	47 (26.7%)	61 (28.5%)	
▪ LST-GM	50 (28.4%)	51 (23.8%)	
▪ LST-NG-FE	10 (5.7%)	27 (12.6%)	
▪ LST-NG-PD	4 (2.3%)	16 (7.5%)	
▪ NA	4	1	
Dysplasia			0.0384 <sup>1</sup>
▪ LGD	88 (48.9%)	133 (61.9%)	
▪ HGD/Tis	74 (41.1%)	62 (28.8%)	
▪ T1 or superior	18 (10%)	20 (9.3%)	
Pseudodepression (+)	46 (25.6%)	47 (21.9%)	0.3893
Non-lifting sign (+)	14 (9.2%)	9 (4.5%)	0.0820
Completeness of report	7 (3.9%)	130 (60.5%)	<0.0001 <sup>1</sup>
Adequate iconographic documentation	30 (16.7%)	177 (82.3%)	<0.0001 <sup>1</sup>
JNET classification available	93 (51.7%)	201 (93.5%)	<0.0001 <sup>1</sup>
Management regimen <sup>2</sup>	N = 149	N = 199	0.1839
▪ Outpatients	43 (28.9%)	75 (37.7%)	
▪ Day Hospital	35 (23.5%)	46 (23.1%)	
▪ Hospitalized	71 (47.7%)	78 (39.2%)	
Treatment			
Primary surgery	30 (16.7%)	16 (7.5%)	0.0072 <sup>1</sup>
BLs sent to primary surgery	24/162 (14.8%)	10/195 (5.1%)	0.0019 <sup>1</sup>
Endoscopic treatment	150 (83.3%)	199 (92.6%)	0.0072 <sup>1</sup>
Endoscopic technique			<0.0001 <sup>1</sup>
▪ EMR	145 (97.3%)	150 (75.4%)	
▪ ESD	1 (0.7%)	29 (14.6%)	
▪ Hybrid techniques	3 (2%)	20 (10.1%)	
Perforation	4 (2.7%)	5 (2.5%)	0.9285
Incomplete resections	17 (11.3%)	14 (7%)	0.1629
EB resection <sup>3</sup>	54/133 (40.6%)	104/185 (56.2%)	0.0061 <sup>1</sup>
EB removal of ILs <sup>3</sup>	3/8 (37.5%)	7/8 (87.5%)	0.0455 <sup>1</sup>
Complementary surgery	19 (12.7%)	17 (8.5%)	0.2105

► **Table 5** (Continuation)

Variable	Lesions managed <2015 (N = 180)	Lesions managed ≥2015 (N = 215)	P value
Recurrence <sup>4</sup>	27/104 (26%)	15/100 (15%)	0.0535
Surgery for recurrence <sup>4</sup>	4/118 (3.4%)	2/127 (1.6%)	0.3594
“Non-curative” ER	24/150 (16%)	19/199 (9.5%)	0.0698
“Potentially preventable surgery”	42 (23.3%)	27 (12.6%)	0.0050 <sup>1</sup>

LST, laterally spreading tumor; S, sessile; PD, pseudodepression; GH, granular, homogeneous; GM, granular, mixed; NG-FE, non-granular-flat elevated; NG-PD, non-granular-pseudodepressed; NA, not available; LGD, low-grade dysplasia; HGD, high-grade dysplasia; T1, submucosal invasion following TNM staging; JNET, Japan NBI Expert Team Classification of vascular pattern; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; BLs, benign lesions; EB, en bloc; ILs, invasive lesions; FU, follow-up; ER, endoscopic resection; PM, piecemeal.

From 2015 primary surgery was overall less indicated (7.5% vs. 16.7%,  $P=0.0072$ ) as well as a lower proportion of benign lesions was sent to primary surgery (5.1% vs. 14.8%,  $P=0.0019$ ). Moreover, the proportions of en-bloc removal of lesions with invasive histology was higher (87.5% vs. 37.5%,  $P=0.0455$ ) and the rate of recurrence lower (15% vs. 26%,  $p=0.0535$ ). The overall rate of “potentially preventable” surgeries was significantly lower >2015 (12.6% vs. 23.3%,  $P=0.005$ )

<sup>1</sup> statistically significant ( $P<0.05$ )

<sup>2</sup> proportion of lesions with available data

<sup>3</sup> proportion of complete endoscopic resection

<sup>4</sup> proportion of complete endoscopic resections undergoing endoscopic follow-up (for recurrences) or any clinical follow-up (for surgery)

39, it remains difficult to demonstrate the impact of these techniques and of their learning curve on patients' long-term outcomes in real-life cohorts. In our experience, ESD was not per se associated with better outcomes but, compared to EMR, seems to have allowed the treatment of larger and more complex lesions. This was obviously paired with a higher need for subsequent surgery, due to a higher proportion of SMI lesions, a higher rate of AEs but above all to a higher detection of “high-risk” lesions for lymph node metastasis despite complete endoscopic resection. Of note, increasing the possibility of diagnosing NC-ERs at histology, to allow access to further treatments, is one precise expected advantage of ESD [40]. Taking all of this into consideration, at first glance, ESD seems to be a staging procedure, and the endoscopist must accept a non-irrelevant rate of subsequent surgery (17% in our series), which is closely connected to the greater complexity of lesions approached, for which the alternative would be a primary surgical referral. However, our data suggest that the rate of ILs for which surgery can be avoided thanks to ESD is not negligible, and is significantly higher than among EMRs. This is particularly important considering the lack of endoscopy-related and cancer-related mortality versus the 3.4% of surgery-related mortality in our cohort. In this scenario, every effort must be encouraged to attempt a primary ER for lesions without signs of deep SMI.

Endoscopic resection of LNPLs also involves the issue of recurrence, especially in the setting of PM resections [12, 16, 41]. In our cohort, we confirm that after complete ER, a recurrence may be found in almost one-quarter of patients, but is endoscopically manageable in the majority of cases. Even if our median endoscopic follow-up was relatively short (16 months [IQR 10–34]), data from the literature are reassuring because 96% of recurrences occur within 6 months after index resection, and only 2% of recurrences can be expected after 12 months [34], as also suggested by our median time-to-recurrence of 7 months (IQR 4–13). Our multivariate analysis identified independent predictors of recurrence, both known (PM vs

EB resection) and poorly reported (grading of dysplasia and involvement of “risky hotspots”). This may suggest that lesions with HG dysplasia or involving dentate line or ileocecal valve might deserve a tighter FU even when resected en bloc. The finding of recurrences after en bloc resections should not be a surprise, since “en-bloc” is an endoscopic definition, while histology must still be taken into account for subsequent patient management; moreover, histological definition of complete resection can be hampered by presence of cautery artefacts [42]; however, we cannot exclude a learning curve effect on these data.

We found that during the last 10 years, management of LNPLs in our center has significantly improved, with decreased surgical referral and more appropriate assessment and treatment of lesions with higher risk of SMI. We reached these conclusions after analyzing trends in performance measures over time through an original, but still precise, statistical method. This method identified the turning point of our quality improvement process to be in 2015, corresponding to about 1 year after the first rectal ESD was performed in our center, and probably linked to increasing confidence with the technique. Moreover, in 2015, an educational intervention on endoscopic pre-resection assessment was completed for both tutors and trainees, and our practice was audited and statistically assessed [40]. We strongly believe that these two aspects (technical and educational) go hand-in-hand in terms of improving proficiency of decision-making and management, as recommended by international position statements [4].

This study has limitations. First, even if the prospectively collected databases allowed the inclusion of all consecutive LNPLs, the retrospective nature did not permit evaluation of every outcome (e.g. minor complications). Second, as expected from a real-life series, included lesions were not homogeneous, potentially affecting analysis of risk factors and permitting only indirect considerations about resection techniques. Third, some

parameters (JNET classification) were not available for all lesions.

Nevertheless, this study represents deep insight on real-life management of all consecutive LNPLs evaluated in a single institution, potentially free of any selection bias. All available records, images, and videos were blindly reevaluated to confirm morphology and superficial pattern. All lesions for which a pre-resection assessment is relevant to therapeutic strategy (i. e. both LSTs and sessile) were included, excluding only pedunculated polyps, which are always manageable EB. We used multivariate analyses in order to eliminate confounders. Moreover, while literature on quality improvement in this field is mainly about the learning curve of single resection techniques [8], this is the only available study in which statistical methods were adopted to evaluate temporal trends of performance measures relevant to patient outcomes.

## Conclusion

In conclusion, management of LNPLs is still challenging and strongly depends on the ability to predict advanced histology and adverse outcomes, for which we provided multivariate models valuable both for primary screening centers and tertiary referral centers, further suggesting predictors to be explored in dedicated prospective cohorts. If SMI is no longer an a priori indication for surgery, it deserves advanced endoscopic management in referral centers, including advanced resection techniques. Reduction in primary surgical referrals is clearly paired with an increased need for secondary surgery both for complications and intrinsic histological risk, but nevertheless allows a net reduction in surgeries, and in their consequential burden in morbidity or mortality [19,43]. Centers that invest in education and technical improvements, with shared efforts by all involved specialists (endoscopists, surgeons, histopathologists) in a multidisciplinary setting, offer more appropriate and personalized management of LNPLs that leads to better outcomes for patients.

## Acknowledgements

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## Competing interests

The authors declare that they have no conflict of interest.

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#### CORRECTION

**Giuseppe Vanella, Chiara Coluccio, Giulio Antonelli et al. Improving assessment and management of large non-pedunculated colorectal lesions in a Western center over 10 years: lessons learned and clinical impact**

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In the paragraph Results on page E1254 interquartile range (IQR) was added two times.

In the paragraph recurrence on page E1254 interquartile range (IQR) was added two times.

In **Table 1** to Multivariate M1<sup>1</sup> and Multivariate M2<sup>2</sup> OR (CI) was added. HR was changed into OR.

In **Table 3** to Multivariate analysis 1 OR (CI) was added. HR was changed into OR.

In **Fig. 1** values were corrected. Correct is:  $P=0.0535$  and  $P=0.005$ ; the a heading within the figure was changed in “Photographic Documentation”.

In the footnotes of **Table 5**, in line 7 were changed the last figures in 12.6% vs 23.3%,  $P=0.005$ .