Original Research Article

An Algorithm for Evaluating the Risk of Submucosal Invasive Carcinoma in Large (≥20mm) Nonpedunculated Colonic Polyps

Tarkeshwar Kumar[1], Manoj Kumar[2], Baidyanath Rajak[3]

[1]Senior Resident, Department of General Surgery, Government Medical College and Hospital, Purnea, Bihar, India

[2]Senior Resident, Department of General Surgery, Government Medical College and Hospital, Purnea, Bihar, India

[3]Senior Resident cum HOD, Department of General Surgery, Government Medical College and Hospital, Purnea, Bihar, India

Abstract:

Background: Identification of submucosal invasive carcinoma (SMIC) in large (≥20mm) nonpedunculated colonic polyps (LNPCPs) guides the determination of the most effective approach for resection. The size, morphology and location of LNPCP affect the submucosal invasive carcinoma risk; nonetheless, there is presently no significant use of this knowledge that has streamlined the process for accessibility and widespread use. We created a decision-making system to facilitate the identification of LNPCP subtypes with heightened risk of possible submucosal invasive carcinoma.

Methodology: Individuals referred for resection of large nonpedunculated colonic polyps between one year were included in the study. Large nonpedunculated colonic polyps having submucosal invasive carcinoma were discovered from surgical results, biopsies of lesion or endoscopic resection specimens. A decision tree analysis of lesion features obtained through multivariate analysis was employed to provide a hierarchical classification of prevalence of submucosal invasive carcinoma.

Results: A total of 245 LNPCPs were examined: 12 (4.8%) were depressed ,104 (42.6%) were nodular, and 129 (52.6%) were flat.

Submucosal invasive carcinoma was verified in 27 of the large nonpedunculated colonic polyps (11.1%). It was correlated with proximal versus rectosigmoid location (OR 3.20 [95%CI 2.46–4.12]; P<0.001); granular versus nongranular appearance (OR 2.39 [95%CI 1.86–3.11]; P<0.001); flat versus depressed and nodular morphology OR 3.49 [95%CI 2.55–4.85] and (OR 35.69 [95%CI 22.5–56.4] respectively; P<0.001). Analysis using decision tree focused on submucosal invasive carcinoma revealed 8 terminal nodes: prevalence of SMIC was 20% in nodular proximal colon nongranular large nonpedunculated colonic polyps, 19% in nodular and rectosigmoid large nonpedunculated colonic polyps and 62% in depressed large nonpedunculated colonic polyps.

Conclusion: This decision making method streamlines the identification of large nonpedunculated colonic polyps with an elevated risk of possible submucosal invasive carcinoma. When integrated with optical assessment of surface, it enables precise lesion characterisation and resection decisions.

Keywords: Submucosal Invasive Carcinoma, Nonpedunculated Colonic Polyps, Algorithm, Resection.

Introduction

Large (≥20mm) nonpedunculated colonic polyps (LNPCPs) can be successfully and safely excised with endoscopic mucosal resection (EMR), resulting in a 98% cure rate and the avoidance of surgical intervention [1, 2, 3]. Nonetheless, the identification of submucosal invasive carcinoma continues to pose difficulties, especially in the presence of bulky tumours [4, 5].

Lesions with SMIC should ideally be removed en bloc to enable precise histological evaluation and meet the criteria if low-risk superficial SMIC is

present. Recent findings indicate that specific LNPCP factors, such as size, granularity, morphology and location affect the risk of SMIC. Upon analysing the intricate interplay of these variables, some LNPCP subtypes exhibit a markedly elevated submucosal invasive carcinoma risk. The implementation of this information is intrinsically complicated, obstructing its accessibility in practical situations. This issue continues to provide a significant difficulty for endoscopists, regardless of their experience and skill level. A streamlined approach to categorising subtypes of LNPCP with

varying submucosal invasive carcinoma risks would function as a mechanism to enhance focused optical assessment of surface and the judicious application of en bloc resection.

Methodology

Study design and patient selection: One year period, successive individuals were recruited from a single tertiary centre of referral. All large nonpedunculated colonic polyps were identified by a certified endoscopist (surgeons and gastroenterologists) and subsequently referred to our facility GMCH Purnea for evaluation of endoscopic resection. Prior to referral, the lesions were not confirmed as malignancies, and the endoscopist who referred the case believed that the LNPCP had likelihood of being benign. The exclusion criteria encompassed serrated histology and resections that were not performed because of technical limitations. Large nonpedunculated colonic polyps were not attempted due to inadequate lifting of submucosa and considerable fibrosis of submucosa in the group where invasive malignancy was greatly suspected.

Ethical permission from the institution was secured for registration of study, and informed consent was acquired. The study data was accessible to all authors, who also reviewed and gave approval for the final publication.

Procedure: A colonoscopy was conducted utilising Olympus 180/190 high-definition, varying stiffness colonoscopes (Japan, Tokyo, Olympus).

The investigator of study, a qualified gastroenterologist with specialist training and expertise in colon endoscopic resection and large nonpedunculated colonic polyps characterisation, or a senior fellow of interventional endoscopy working under close supervision carried out all endoscopic procedures. EMR was conducted systematically, incorporating subsequent advances as supporting data became available [6-9]. A subset of LNPCPs received endoscopic submucosal dissection (ESD) using a selective ESD technique (NCT02198729) [10]. Optical assessment was conducted utilising high-definition white light, narrow-band imaging (NBI), and near focus, upon their availability, to discern surface characteristics of SMIC. An investigation performed at our facility revealed that chromoendoscopy which is dye-based did not yield further advantages in the optical diagnosis of submucosal invasive carcinoma [11]. Consequently, this was not integrated into the usual procedures of our unit. LNPCPs were uniformly characterised according to the Kudo classification throughout the investigation period. Procedural documentation and LNPCP morphological descriptions were standardised to ensure consistency across proceduralists and reduce incomplete data. Specimens were gathered and prepared for histopathological examination, following the recommendations of the Australian Gastrointestinal Pathology Society [12]. The histopathological assessment was conducted by professional gastrointestinal pathologists, and consensus was reached where SMIC was diagnosed. Additionally, cases with diagnosed malignancy were deliberated at a interdisciplinary meeting attended by both gastroenterologists and pathologists.

Statistical Analysis: Version 29.0 of IBM SPSS Statistics (USA, New York, Armonk, IBM) was employed for data analysis. All the analyses were exploratory and adhered to guidelines of LNPCP. 2 tailed tests with a significance threshold of five percent were consistently applied. Continuous variables were presented as median (standard deviation [SD] or interquartile range [IQR]), while categorical variables were expressed as percentage and frequency. The size of LNPCP was summarised using median (IQR). Chi-squared tests assessed univariable associations between presence of SMIC and each categorical variable, whereas the Mann–Whitney test was utilised for size. Odds ratios (ORs) with 95% confidence intervals (CIs), derived from logistic regression analysis, quantified the strength of the associations of univariables. With a P value for elimination set at less than 0.1, the appropriate multivariate logistic regression model was found by using backward stepwise selection of variable, which included the major effects (colon side, morphology, granularity, and size) and their pairs of interactions.

Results

A total of 245 LNPCPs were analysed, with a median size of 35mm (IQR 25–50mm), having a granular appearance (n = 160; 65.4%), a prevalent position in the proximal part of colon (n = 167; 68.1%) and flat morphology (n = 129; 52.6%) (Table 1). SMIC was detected in 27 out of 245 large nonpedunculated colonic polyps (11.1%). Covert submucosal invasive carcinoma was identified in 42.8% of all malignancies and in 4.7% of all large nonpedunculated colonic polyps. Overt submucosal invasive carcinoma was observed in 6.3% of the large nonpedunculated colonic polyps.

Table 1: Baseline features of the 245 LNPCPs included in the study.

Features	N(%)
Granularity	
Granular	160 (65.4%)
Nongranular	85 (34.6%)
Location	
Rectosigmoid	78 (31.9%)
Proximal colon	167 (68.1%)
Morphology	
Depressed	12 (4.8%)
Flat	129 (52.6%)
Nodular	104 (42.6%)
Histopathology	
Submucosal invasive cancer	27 (11.1%)
Villous adenoma	2 (0.7%)
Tubulovillous adenoma	146 (59.6%)
Tubular adenoma	70 (28.5%)

SMIC was correlated with nodular (14/104; 13.8%) and depressed (7/12; 61.9%) morphologies compared to flat (6/129; 4.3%) morphology OR 35.69 [95%CI 22.5–56.4] and OR 3.49[2.55–4.85], respectively; P<0.001); proximal (12/167; 7.1%) versus rectosigmoid (15/78; 19.7%) colonic locations OR 3.20 [2.46–4.12]; P<0.001); and granular (13/160; 7.9%) versus nongranular (15/85; 17.2%) types. Appearance OR 2.39 [1.86–3.11]; P<0.001); and size ≥40mm (16/114; 14.1%) compared to <40mm (11/132; 8.6%) group OR 1.80 [1.34–2.25]; P<0.001) (Table 2).

Decision tree study focused on submucosal invasive carcinoma discovered 8 terminal nodes, referred to as "LNPCP subtypes": The incidence of SMIC was 62% in 12 depressed LNPCPs, 22% in 36 nodular rectosigmoid LNPCPs measuring ≥40mm, 12% in 16 nodular rectosigmoid LNPCPs measuring <40mm, and 20% in 13 nodular proximal colon nongranular LNPCPs. The minimal incidence (1%) was seen in 60 flat proximal colon granular LNPCPs. The decision tree utilising LNPCP size as a continuous variable was equal to the one employing dichotomised size, exhibiting a depth of 3. Table 2 displays the prevalence percentage of SMIC, along with the 95% confidence interval, for each LNPCP subtype within the investigation population.

Table 2: Distribution of characteristics of each LNPCPs according to status of SMIC, along with odds ratios and 95% confidence intervals obtained using multivariable regression analysis.

Presence of SMIC, n (%)				
Variable	Yes (Total 27)	No (Total 218)	Odds ratio (95% Confidence Intervals)	P value
Rectosigmoid location (vs. proximal)	15 (56.4%)	63(28.8%)	3.20 (2.46–4.12)	<0.001
Nongranular (vs. granular)	15 (53.5%)	70 (32.2%	2.39 (1.86–3.11)	<0.001
Depressed	7(26.7%)	5 (2.1%)	35.69 (22.5–56.4)	<0.001
Nodular	14 (52.7%)	90 (41.3%)	3.49 (2.55–4.85)	<0.001
Size ≥35mm (vs. <35mm)	17 (63.7%)	121(55.6%)	1.39 (1.07–1.81)	0.01
Size ≥40mm (vs. <40mm)	16 (58.6%)	98 (44.8%)	1.80 (1.34–2.25)	<0.001

Discussion

Identifying both overt and covert submucosal invasive carcinoma in large nonpedunculated colonic polyps continues to pose a significant difficulty. This issue affects endoscopists across all the levels of expertise and skill. Recently we have demonstrated that submucosal invasive carcinoma may be consistently identified in lesions that are flat via the invasive characteristic's expression on the lesion's surface; however, this accuracy is significantly reduced in bulky lesions. Although EMR is established as safe and successful for treating LNPCPs, individuals with submucosal invasive carcinoma are not deemed treated by resection in piecemeal, based on accepted guidelines [13-16]. Multiple factors contribute to SMIC estimate and can enhance visual diagnostics and optimise the resection technique. Existing methodologies are difficult to implement in practical environments. A straightforward method that may be readily implemented by all endoscopists is required.

Submucosal invasive carcinoma has been documented in 7.6%–8.5% of LNPCPs resected endoscopically and, when detected and adequately excised, may be curable. En bloc resection of

submucosal invasive carcinoma is treatable when positive histological characteristics are present, such as lack of poor differentiation, absence of lymphovascular invasion, and superficial invasion (<1000μm). In these instances, surgical resection is typically unnecessary [17]. Despite the unintentional piecemeal excision of SMIC, it appears that the same curative criteria applicable to en bloc resection are relevant, but data remain sparse. If submucosal invasive carcinoma is well-differentiated and exhibits no lymphovascular invasion, the likelihood of lymph node metastases is minimal. Moreover, if the deep margin is unremarkable, despite piecemeal resection, the likelihood of recurrence locally appears negligible [18].

The optical assessment of surface vascular and pit patterns of large nonpedunculated colonic polyps can precisely identify submucosal invasive carcinoma in lesions that are flat. The likelihood of optical evaluation failing to identify submucosal invasive carcinoma in a flat large nonpedunculated colonic polyps was 0.6% in a substantial prospective investigation; conversely, because of their substantial morphology hindering inspection, optical evaluation overlooked 5.9% of submucosal invasive carcinoma instances within nodular large nonpedunculated colonic polyps (P<0.001) [13]. A prospective series of 2277 large nonpedunculated colonic polyps revealed that the sensitivity of the Kudo pit pattern for diagnosing submucosal invasive carcinoma was merely 40.4%, with 138 out of 171 histologically confirmed tumours exhibiting benign surface characteristics. The instances of "covert" SMIC pose a considerable barrier in the identification and SMIC management in LNPCPs, underscoring the necessity of risk characterisation independent characteristics of surface.

The specific attributes of LNPCP, including granularity, location, shape and size determine the SMIC's baseline risk, regardless of surface vascular and pit patterns . Nodular or depressed morphology exhibits a higher likelihood of submucosal invasive carcinoma compared to flat lesions [19, 20]. Compared to their granular counterparts, nongranular large nonpedunculated colonic polyps have a higher likelihood of containing SMIC. LNPCPs situated in the part of colon located proximally have a minimal SMIC risk, whereas lesions in part of colon located distally, especially the rectosigmoid region, present a much higher risk [21]. The aggregate impact of these individual risk variables on SMIC risk is now well acknowledged. The interplay of these qualities is, however, intricate and challenging to implement in a practical context [22,23]. Furthermore, a straightforward algorithm for evaluating risk in a specific subtype of LNPCP has been absent.

Considering the intricate interplay of LNPCP attributes in forecasting SMIC risk, we employed a decision tree methodology to delineate subgroups exhibiting varying risks of SMIC, informed by polyp size, colonic location, granularity and morphology. The morphology of Paris has demonstrated inadequate interobserver agreement among specialists and was hence excluded as an autonomous indicator in the analysis using decision tree [24].

A novel algorithm provides accessible lesion-specific hazards of probable submucosal invasive carcinoma based on the subtype of large nonpedunculated colonic polyps. This can aid endoscopists in assessing the cancer risk in large nonpedunculated colonic polyps that is otherwise considered benign. Endoscopists must initially classify the LNPCP as depressed, flat, or nodular. Depressed LNPCPs necessitate no additional characterisation and exhibit a sixty-two percent prevalence of SMIC. In cases of such lesions, lacking surface characteristics indicative of invasion of deep submucosa, endoscopists should utilise an en bloc resection technique. Non depressed large nonpedunculated colonic polyps are categorised as either nodular or flat. Regardless of location or granularity, LNPCPs which are flat exhibit a lower incidence of SMIC (1.8%; nongranular ,4.3%: granular). Endoscopists must consider this profile of risk before initiating optical evaluation, which has proven to be extremely correct for lesions that are flat.

In the case of nodular lesions, location becomes the primary distinguishing factor. Nodular nongranular LNPCPs in the proximal part of colon have a high probability (20%) of submucosal invasive carcinoma, while nodular granular large nonpedunculated colonic polyps demonstrate a lower prevalence of submucosal invasive carcinoma (5%). Conversely, all rectosigmoid nodular large nonpedunculated colonic polyps are classified as high risk, regardless of their granularity or size (19%). Upon identification of high-risk subtypes of lesion, meticulous optical examination of their surface characteristics should be performed to rule out deep submucosal invasion. In the absence of these traits, an en bloc resection approach is necessary.

This algorithm for decision-making serves as a resource for endoscopists of varying expertise and training to assess the risk of possible malignancy in a low-grade neoplastic pancreatic cystic lesion that is otherwise considered benign. Risk assessments, requiring prior understanding of 12 subtypes of LNPCP, may now be performed on separate lesions by binary enquiries on LNPCP granularity, location, morphology and size. The presentation in flowchart form is user-friendly, with possible risk of SMIC frequently assessed using 1 to 3 LNPCP criteria. A comprehensive understanding of SMIC risk associated with an LNPCP is essential prior to

performing optical assessment of the surface of lesion. This is especially relevant to LNPCPs which are flat. The imprecision of optical assessment in LNPCPs which are nodular necessitates precise risk categorisation to guide the approach of resection.

The algorithm facilitates the identification of high-risk nodular lesions, enabling their targeting in proven en bloc selective resection regimens. A specific protocol conducted endoscopic submucosal dissection (ESD) on high-risk rectal lesions, encompassing Paris 0-Is or 0-IIa + Is nongranular laterally spreading tumours (LNPCPs) or 0-IIa + Is granular LNPCPs featuring a dominating nodule of ≥10mm. Selective resection effectively identified instances of SMIC, achieving curative oncologic excision in all cases that met the criteria for low-risk SMIC [10]. Although this approach is beneficial, it does not detect all the lesions having SMIC, highlighting the necessity of optical inspection of high-quality during assessment of lesion. This technique pertains exclusively to LNPCPs which are adenomatous , excluding lesions that are serrated from the conclusive assessment. Serrated lesions have a different carcinogenesis process and possess unique endoscopic characteristics and excision techniques, in contrast to adenomatous polyps [25]. Cytologic dysplasia present in the serrated lesions with are well-characterized premalignant lesions that can be detected endoscopically, in contrast to adenomas [26]. Moreover, it is essential to highlight that all large nonpedunculated colonic polyps indicated for resection endoscopically in our investigation were considered benign by the endoscopists who had referred the cases. Instances of overt malignancy were diagnosed by our facility at a later time. Thus, both overt and covert malignancies were included in the investigation to effectively develop an instrument that categorises the risk of possible malignancy in LNPCPs that were otherwise considered benign by endoscopists who had referred the cases.

The study's strength lies in the extensive cohort of large nonpedunculated colonic polyps that were prospectively gathered and characterised at a singular specialist centre of referral with significant proficiency in large nonpedunculated colonic polyps characterisation, evaluation, and resection.

A theoretical restriction is the diversity in identifying morphology and size of lesion in real-world scenarios; however, the algorithm has streamlined this process and does not depend on variables such as the Paris classification, which may exhibit poor concordance among proceduralists [24, 27]. We note, however, that this investigation lacks data on the consensus among our proceduralists concerning lesion characterisation. Being a derivation study ,it lacks external validation. External validation in an autonomous dataset is necessary to determine the generalisability of the

results and to acquire data on accuracy of algorithm. We acknowledge that our rate of SMIC (11%) surpasses that of prior studies; however, this is likely due to the inclusion of clearly malignant lesions brought to us for evaluation and endoscopic intervention, which we subsequently directed to surgical procedure.

As a tertiary centre of referral, we inevitably encounter referrer bias, as certain endoscopically resectable tumours identified by referrers might not have been deemed suitable for resection and were instead directly referred for surgical intervention. A recent study, however contentious among specialists, emphasised that insufficient retrieval of piecemeal resection specimens may theoretically contribute to overlooked foci of SMIC [28]. We acknowledge that a significant percentage of our EMR instances involved fragmented resections, hence lacking the histological precision achieved with a specimen of en bloc.

Conclusion

This investigation has established an algorithm to assess the probability of possible submucosal invasive carcinoma in a large nonpedunculated colonic polyps previously considered benign. The approach promotes a thorough evaluation of LNPCP before endoscopic resection and enhances decision-making confidence among endoscopists on treatment options.

References

1. Swan MP, Bourke MJ, Alexander S et al. Large refractory colonic polyps: is it time to change our practice? A prospective study of the clinical and economic impact of a tertiary referral colonic mucosal resection and polypectomy service (with videos) Gastrointest Endosc 2009; 70: 1128–1136.
2. Moss A, Williams SJ, Hourigan LF et al. Long-term adenoma recurrence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. Gut 2015; 64: 57–65.
3. Hassan C, Repici A, Sharma P et al. Efficacy and safety of endoscopic resection of large colorectal polyps: a systematic review and meta-analysis. Gut 2016; 65: 806–820 doi:10.1136/gutjnl-2014-308481.
4. Burgess NG, Hourigan LF, Zanati SA et al. Risk stratification for covert invasive cancer among patients referred for colonic endoscopic mucosal resection: a large multicenter cohort. Gastroenterology 2017; 153: 732–742.
5. Bogie RM, Veldman MH, Snijders LA et al. Endoscopic subtypes of colorectal laterally spreading tumors (LSTs) and the risk of

submucosal invasion: a meta-analysis. Endoscopy 2018; 50: 263–282 doi:10.1055/s-0043-121144.

6. Klein A, Bourke MJ. How to perform high-quality endoscopic mucosal resection during colonoscopy. Gastroenterology 2017; 152: 466–471 doi:10.1053/j.gastro.2016.12.029.

7. Jideh B, Bourke MJ. How to perform wide-field endoscopic mucosal resection and follow-up examinations. Gastrointest Endosc Clin N Am 2019; 29: 629–646 doi:10.1016/j.giec.2019.05.002.

8. Burgess NG, Bassan MS, McLeod D et al. Deep mural injury and perforation after colonic endoscopic mucosal resection: a new classification and analysis of risk factors. Gut 2017; 66: 1779–1789 doi:10.1136/gutjnl-2015-309848.

9. Tate DJ, Bahin FF, Desomer L et al. Cold-forceps avulsion with adjuvant snare-tip soft coagulation (CAST) is an effective and safe strategy for the management of non-lifting large laterally spreading colonic lesions. Endoscopy 2018; 50: 52–62.

10. Shahidi N, Vosko S, Gupta S et al. A rectum-specific selective resection algorithm optimizes oncologic outcomes for large nonpedunculated rectal polyps. Clin Gastroenterol Hepatol 2023; 21: 72–80 doi:10.1016/j.cgh.2022.04.021.

11. Sidhu M, Shahidi N, Vosko S et al. Incremental benefit of dye-based chromoendoscopy to predict the risk of submucosal invasive cancer in large nonpedunculated colorectal polyps. Gastrointest Endosc 2022; 95: 527–534 doi:10.1016/j.gie.2021.11.032.

12. Kumarasinghe MP, Bourke M, Brown I et al. Pathological assessment of endoscopic resections of the gastrointestinal tract: a comprehensive clinicopathologic review. Mod Pathol 2020; 33: 986–1006 doi:10.1038/s41379-019-0443-1.

13. Vosko S, Shahidi N, Sidhu M et al. Optical evaluation for predicting cancer in large nonpedunculated colorectal polyps is accurate for flat lesions. Clin Gastroenterol Hepatol 2021; 19: 2425–2434 doi:10.1016/j.cgh.2021.05.017.

14. Kaltenbach T, Anderson JC, Burke CA et al. Endoscopic removal of colorectal lesions—recommendations by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2020; 158: 1095–1129 doi:10.1053/j.gastro.2019.12.018.

15. Ferlitsch M, Moss A, Hassan C et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. Endoscopy 2017; 49: 270–297 doi:10.1055/s-0043-102569.

16. Bar-Yishay I, Shahidi N, Gupta S et al. Outcomes of deep mural injury after endoscopic resection: an international cohort of 3717 large non-pedunculated colorectal polyps. Clin Gastroenterol Hepatol 2022; 20: e139–e147 doi:10.1016/j.cgh.2021.01.007.

17. Beaton C, Twine CP, Williams GL et al. Systematic review and meta-analysis of histopathological factors influencing the risk of lymph node metastasis in early colorectal cancer. Colorectal Dis 2013; 15: 788– 797 doi:10.1111/codi.12129.

18. Gibson DJ, Sidhu M, Zanati S et al. Oncological outcomes after piecemeal endoscopic mucosal resection of large non-pedunculated colorectal polyps with covert submucosal invasive cancer. Gut 2022; 71: 2481–2488.

19. Kim BC, Chang HJ, Han KS et al. Clinicopathological differences of laterally spreading tumors of the colorectum according to gross appearance. Endoscopy 2010; 43: 100–107 doi:10.1055/s-0030- 1256027.

20. Kim KO, Jang BI, Jang WJ et al. Laterally spreading tumors of the colorectum: clinicopathologic features and malignant potential by macroscopic morphology. Int J Colorectal Dis 2013; 28: 1661–1666 doi:10.1007/s00384-013-1741-6.

21. Cronin O, Sidhu M, Shahidi N et al. Comparison of the morphology and histopathology of large nonpedunculated colorectal polyps in the rectum and colon: implications for endoscopic treatment. Gastrointest Endosc 2022; 96: 118–124 doi:10.1016/j.gie.2022.02.022.

22. Bogie RM, Veldman MH, Snijders LA et al. Endoscopic subtypes of colorectal laterally spreading tumors (LSTs) and the risk of submucosal invasion: a meta-analysis. Endoscopy 2018; 50: 263–282 doi:10.1055/s-0043-121144.

23. D'Amico F, Amato A, Iannone A et al. Risk of covert submucosal cancer in patients with granular mixed laterally spreading tumors. Clin Gastroenterol Hepatol 2021; 19: 1395–1401.

24. van Doorn SC, Hazewinkel Y, East JE et al. Polyp morphology: an interobserver evaluation for the Paris classification among international experts. Am J Gastroenterol 2015; 110: 180–18.

25. Bettington M, Walker N, Clouston A et al. The serrated pathway to colorectal carcinoma: current concepts and challenges. Histopathology 2013; 62: 367–386 doi:10.1111/his.12055.

26. Tate DJ, Jayanna M, Awadie H et al. A standardized imaging protocol for the endoscopic prediction of dysplasia within sessile serrated polyps (with video). Gastrointest Endosc 2018; 87: 222–231.

27. Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005; 37: 570–578 doi:10.1055/s-2005-861352.

28. Jacques J, Schaefer M, Wallenhorst T et al. Endoscopic en bloc versus piecemeal resection of large nonpedunculated colonic adenomas: a randomized comparative trial. Ann Int Med 2024; 177: 29–38 doi:10.7326/M23-1812.