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ORIGINAL ARTICLE

Revising the definition of vertical margin involvement following endoscopic polypectomy may reduce unnecessary surgery in patients with malignant colorectal polyps

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Abstract

Background and Study Aims: Endoscopically resected malignant colorectal polyps (MCPs) present a dilemma regarding whether the risk of residual disease justifies a major bowel resection. Overtreatment is common, and the vast majority of patients who undergo resection have no residual tumor. The aim of this study was to investigate whether revising the definition of vertical margin involvement following MCP polypectomy could reduce unnecessary surgery.

Patients and Methods: This was a cohort study of consecutive patients with MCPs treated at a tertiary hospital between 2004 and 2018. Data on demographics, index colonoscopy, polyp pathology, and any subsequent surgical resection were analyzed. Polypectomy resection margins were reviewed and measured to the nearest decimal place. The ability of existing guidelines (requiring a margin clearance of ≥ 1 mm) to predict residual disease was compared to a revised version requiring a margin clearance of ≥ 0.1 mm.

Results: A total of 129 patients with an MCP were included. Of these 129 patients, 77 (60%) underwent surgical resection, of which 62 (81%) had no residual tumor. Existing guidelines, requiring a margin clearance of ≥ 1 mm, classified 28 patients as being at "low risk" for residual disease. Of these, four underwent surgery, but none had residual tumor ($P = 0.031$). Revised guidelines, requiring a margin clearance of ≥ 0.1 mm, classified 44 patients as "low risk." Of these, in the 13 that had surgery, no residual tumor was found ($P = 0.003$).

Conclusions: Revising the definition of vertical margin involvement leads to more patients being correctly classified as being at low risk of residual disease. This has the potential to reduce unnecessary surgery in patients with MCPs.

Introduction

Malignant colorectal polyps (MCPs) are defined as endoscopically removed polyps in which a focus of neoplastic cells are seen to invade through the muscularis mucosa into the submucosa on histological examination. These early malignant lesions, estimated to account for approximately 10% of all screen-detected cancers,[1] are likely to be become increasingly common as bowel cancer screening programs expand worldwide.

Currently, the management of MCPs presents a dilemma for the multidisciplinary team (MDT). Clinicians must decide whether the risk of residual disease in the bowel wall or locoregional lymph nodes justifies a major bowel resection, with the inherent morbidity this entails, or whether the original polypectomy has been sufficient. Although guidelines exist in Australia to aid these decisions,[2] the underlying evidence base is poor, and key recommendations are based on historical data. It is now recognized that the risk of residual disease following polypectomy is very low, with large contemporary series reporting no evidence of residual tumor in over 80% of patients who undergo surgical resection.[3–5]

One way to address this issue of overtreatment might be to consider how the vertical margin of excision is defined following endoscopic polypectomy. Currently, existing Australian National Health and Medical Research Council (NHMRC) guidelines state that the resection margin must be clear of tumor by at least 1 mm before a strategy of surveillance can be considered. However, evidence is now accumulating that such a clearance may not be necessary as long as the distance between the invasive front and resection margin can be assessed and accurately measured. For example, a national cohort study in Scotland[6]

reported that a "positive" polyp resection margin was only associated with residual disease in the bowel wall if tumor cells extended into the diathermy burn zone. Similarly, updated national guidelines in Japan now state that the vertical margin of an MCP should only be considered positive if carcinoma is exposed at the submucosal margin.[7]

When designing the present study, we hypothesized that revising the definition of vertical margin involvement in this way would increase the number of patients that would be correctly classified as being at low risk of residual disease, thereby avoiding unnecessary surgery and reducing health-care costs. The aim of this study, therefore, was to compare the ability of the NHMRC guidelines with and without a revision of the vertical margin definition to predict the risk of residual disease in patients with MCPs.

Materials and methods

The study was carried out jointly by the Departments of Gastroenterology and Colorectal Surgery at Sir Charles Gairdner Hospital in Western Australia. A prospectively maintained database was used to record consecutive patients diagnosed with an MCP between March 2004 and August 2018. An MCP was defined as a colorectal polyp removed endoscopically, where subsequent histology confirmed the presence of adenocarcinoma invading through the muscularis mucosae. Cases that included a biopsy of a nonresected tumor and patients in whom a synchronous bowel cancer dictated the need for further treatment were excluded. Review and approval by the local Quality Improvement committee was obtained for the study, which fell under the auspices of a clinical audit.

The cohort. Information on patient demographics, details of the index colonoscopy, original polyp pathology, and subsequent surgical referral were recorded prospectively. For patients who went on to have surgery, the operative details, surgical outcomes, and pathology reports of the resected specimen were obtained. Residual disease was defined as histological evidence of adenocarcinoma in either the bowel wall or the locoregional lymph nodes or both. All patients, operative and nonoperative, were followed up according to local colorectal cancer surveillance guidelines, which included regular outpatient clinic visits, surveillance colonoscopy, and annual computed tomography (CT) scans. Information on date and cause of death was obtained from central health records, and follow up was considered complete on 1 October 2018, which served as the censor date.

Existing NHMRC guidelines. During the study period, patients were managed in accordance with contemporary National Medical and Research Council (NHMRC) Guidelines[2] which stated that an MCP can be designated as "low risk" and managed without surgical resection when all the following criteria are met: (i) A clear margin of excision of 1–2 mm, (ii) well or moderate differentiation, (iii) no evidence of lymphovascular invasion (LVI), and (iv) endoscopic assessment of complete excision. All other MCPs are automatically classified as "high risk" with a recommendation for surgical resection. At the time of manuscript preparation, the NHMRC Guidelines were updated, and the acceptable deep margin clearance was revised from 1–2 to ≥1 mm[8] (Table 1).

NHMRC guidelines with revised vertical margin criteria. The criteria used to define vertical margin involvement were the single factor altered in our revised version of the NHMRC guidelines. Instead of using a margin clearance of ≥ 1 mm, we designated all patients with a vertical margin clearance of any distance (≥ 0.1 mm) as "low risk" as long as the margin could be reliably measured and no other adverse prognostic factors were present such as deep submucosal invasion > 1000 μm, tumor budding, mucinous histology, poor differentiation, or LVI. If the vertical margin could not be adequately assessed because of specimen fragmentation or piecemeal resection, then the patients were automatically classified as "high risk," and surgical resection was recommended. Figure 1

Table 1 Summary description of the criteria currently used to recommend treatment for patients with endoscopically excised malignant colorectal polyps in Australia

Guideline	Risk Group	Criteria	Recommendation
NHMRC Guidelines 2011	Low	MCPs that fulfill all the following criteria: • Clear vertical margin of excision of 1-2 mm • Well or moderate differentiation • Lymphovascular invasion absent • Endoscopic assessment of complete removal	Surveillance
	High	MCPs that do not fulfill all the above criteria	Surgical resection
NHMRC Guidelines 2019	Low	MCPs that fulfill all the following criteria: • Clear vertical margin of excision of ≥ 1 mm • Superficial submucosal invasion < 1000 μm • Well or moderate differentiation • Lymphovascular invasion absent • No other high risk features • Endoscopic assessment of complete removal	Surveillance
	High	MCPs that do not fulfill all the above criteria	Surgical resection

The 2011 guidelines were in use during the study period and were subsequently updated in 2019.
MCP, malignant colorectal polyp; NHMRC, National Health and Medical Research Council.

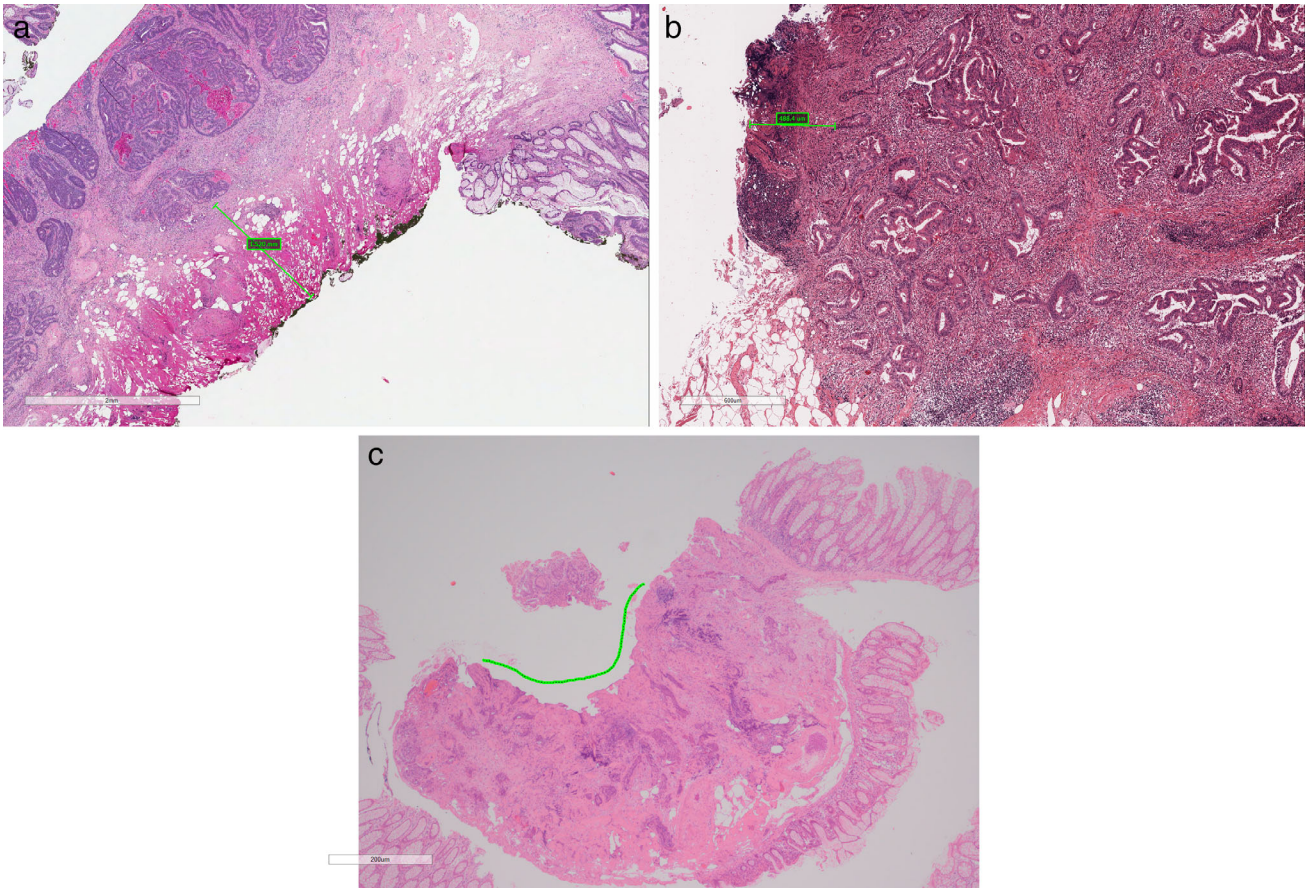

Figure 1 (a) An malignant colorectal polyp (MCP) with a vertical margin clearance of >1 mm (green line), classified as low risk by both the existing and revised versions of the guidelines. (b) An MCP with a margin clearance of <0.5 mm (green line), classified as high risk by the existing guidelines but low risk using our revised version. (c) An MCP with tumor extending to the inked diathermy margin (green line), classified as high risk by both the existing and revised version of the guidelines.

provides histopathology examples of different measured distances of vertical margin clearance in endoscopically excised MCPs.

Management strategies. It must be emphasized that the above risk classifications were applied retrospectively to the cohort. The original treatment decisions were taken by the colorectal MDT using the information that was available to them at the time. It should be stressed that, while contemporary guidelines broadly influenced these decisions, there were times when patient preference or fitness for major surgery resulted in a deviation from the recommended treatment.

Statistical analysis. Variables were grouped according to clinically relevant or previously published thresholds. Comparison between categorical and continuous variables was performed using the chi-square test for linear trend and the Mann–Whitney *U* test as appropriate. The accuracy of existing and revised guidelines was compared using chi-square tests. Patients in the nonoperative group who did not develop metastatic disease or die from colorectal cancer in the follow-up period were analyzed as having no residual disease. Survival differences were analyzed using Kaplan–Meier curves and log-rank tests. P values < 0.05 were considered statistically significant. Statistical analyses were performed using SPSS software (Version 24.0, IBM SPSS Inc., Chicago, IL, USA).

Results

A total of 129 patients with an MCP were included. The clinical and pathological characteristics of the cohort are shown in Table 2. There were 73 (57%) males and 56 (43%) females with a median age of 73 years (range 43–97). The malignant polyps were located predominantly in the left colon (64%) and rectum (16%). Most were polypoid (58%) lesions of ≥10 mm in size (82%), although polyps as small as 4 mm were found to contain a focus of adenocarcinoma. According to the original colonoscopy report, 57% of polyps were removed en bloc, while 43% were excised in a piecemeal fashion. When the specimens were examined in the laboratory, the reporting pathologist was able to discern a clear resection margin (≥0.1 mm) in 72 cases (56%), while in the remaining 57 cases (44%), the tumor either extended to the diathermy margin (19%) or was not assessable because of fragmentation or piecemeal excision (25%) (Table 2).

Table 2 Summary characteristics of the cohort of 129 patients with a malignant colorectal polyp

Variable		129 (%)
Age	Median (range)	72 (43–97)
Gender	Female	56 (43)
	Male	73 (57)
Polyp location	Right colon	25 (19)
	Left colon	83 (64)
	Rectum	21 (16)
Polyp size	<10 mm	23 (18)
	≥10 mm	106 (82)
Polyp morphology	Pedunculated	75 (58)
	Nonpedunculated	22 (17)
	Not classified	32 (25)
Polypectomy technique	En bloc	74 (57)
	Piecemeal	55 (43)
Assessment of resection completeness	Complete (En bloc)	68 (53)
	Complete (Piecemeal)	49 (38)
	Incomplete	1 (1)
	Not recorded	11 (9)
Polyp differentiation	Well	42 (33)
	Moderate	73 (57)
	Poor	12 (9)
	Not recorded	2 (2)
Lymphovascular invasion	No	88 (68)
	Yes	41 (32)
Vertical resection margin	Clear (≥0.1 mm)	72 (56)
	Involved to diathermy margin	25 (19)
	Not assessable[†]	32 (25)

[†]Specimens in which piecemeal excision or fragmentation prevented the reporting pathologist from reliably assessing the completeness of excision or accurately measuring the resection margin.

The management strategies originally followed in the cohort are shown in Figure 2. Of the 129 patients with an MCP, 77 (60%) underwent surgical resection, and 52 (40%) were managed nonoperatively. The reasons why management strategies deviated from the treatment recommended by contemporary guidelines were not always explicitly documented in the medical records. It was noted, however, that in the high-risk group, a number of patients refused an operation, while others had comorbidities that prevented major surgery. Of the 77 patients who underwent surgical resection, 62 (81%) had no evidence of residual disease. Of the 15 (19%) patients who did have a residual tumor, this was located in the bowel wall in six patients and the locoregional lymph nodes in nine patients (Fig. 2).

The median follow up for the survivors was 23 months (minimum 1; maximum 147). During the follow-up period, there were 14 deaths, of which only 1 was attributable to colorectal cancer. This particular patient was classified as high risk because of poor differentiation and mucinous histology but was turned down for surgery because of comorbid disease (alcohol-related liver cirrhosis) and died of metastatic colorectal cancer 19 months after the original polypectomy. The small number of events negated disease-specific survival analyses, but it was observed that overall survival was poorer in patients managed nonoperatively compared to those who underwent resection (82 *vs* 129 months, $P = 0.013$, log-rank test).

When existing NHMRC guidelines were applied to the cohort, 28 patients (22%) were classified as "low risk" and 101 patients (78%) as "high risk." Despite being originally classified as low risk, four patients proceeded to surgical resection, but none were found to have residual disease. The performance of existing NHMRC guidelines in predicting the risk of residual disease is shown in Table 3 ($P = 0.031$, chi square test). When NHMRC guidelines with revised vertical margin criteria were applied retrospectively to the cohort, 44 patients (34%) would have been classified as "low risk" and 85 patients (66%) as "high risk". None of the patients in this "low-risk" group who underwent surgical resection were found to have residual disease ($n = 13$). The performance of the revised NHMRC guidelines in predicting the risk of residual disease is also shown in Table 3 ($P = 0.003$, chi square test for linear trend).

The operative outcomes and associated health-care costs of the 13 patients who could have avoided major surgery if NHMRC guidelines with revised vertical margin criteria had been used to allocate treatment are summarized in Table 4. The median length of stay for these patients was 8 days (range 4–15 days), and six patients (46%) suffered a complication within 30 days of surgery. The total health-care cost of these operative episodes of care was calculated as $304 491 based on contemporary hospital financial records, which included theater, medical, nursing, and ward-based costs. In addition to the index operation, it was noted that one patient had a subsequent admission to reverse his loop ileostomy, and one patient developed an incisional hernia that required surgery 2 years later (Table 4).

Discussion

The present study was undertaken to investigate whether revising the definition of vertical margin involvement has the potential to reduce unnecessary surgery in patients with MCPs.

By changing the required margin clearance from greater than 1 mm to any accurately measurable distance (in practice, this equates to ≥ 0.1 mm), we were able to demonstrate an improved ability of the guideline to correctly classify which patients were at low risk of residual disease and who could potentially benefit from a nonsurgical approach to management. Indeed, if the original treatment strategies had followed the recommendations of our revised guidelines, a total of 13 patients could have avoided unnecessary major surgery. Although these absolute numbers are small, this represents a significant proportion of patients and, aside from the benefits of avoiding surgical morbidity, this change would have resulted in a substantial reduction in health-care costs.

The clinical utility of any MCP treatment guidelines will inevitably center around their ability to identify patients who can be safely treated without surgery. There must be a balance between classifying too few patients as low risk, leading to overtreatment and unnecessary surgery, *versus* classifying too many patients as low risk, leading to undertreatment.[9] It was noteworthy in the present study that no patient with a margin clearance of 0.1–1 mm and without other high-risk features had residual disease in the bowel wall of their resected specimens. This is an important point and suggests that revising the margin criteria

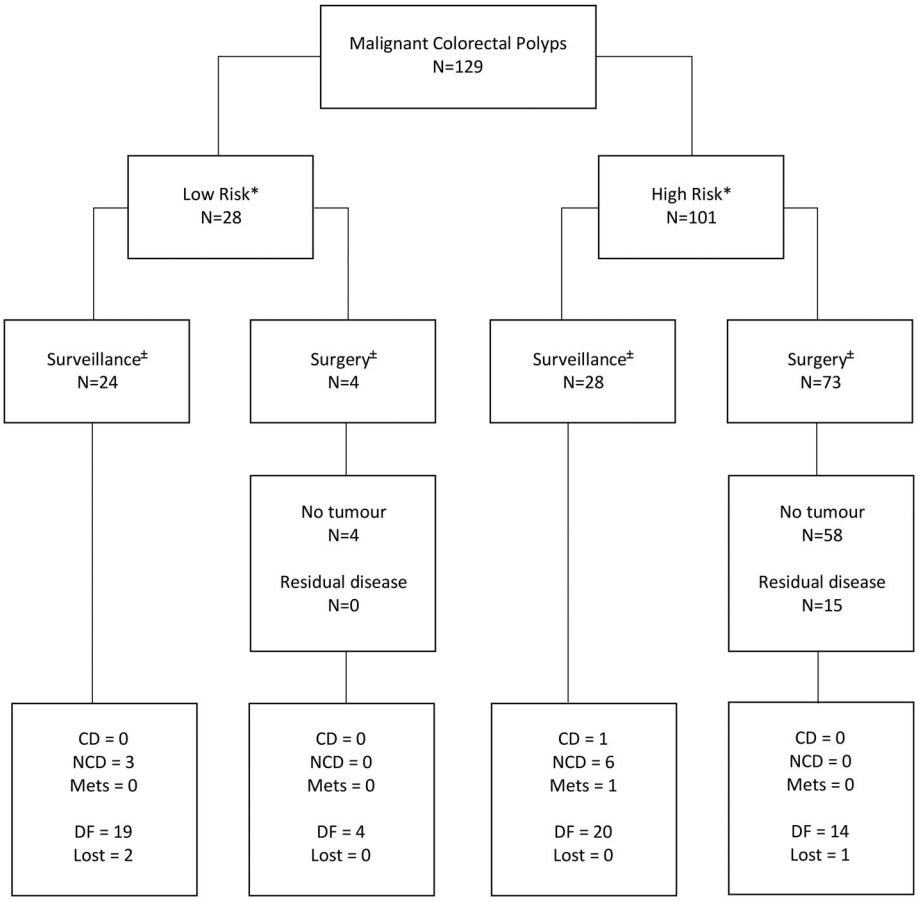

Figure 2 Flow diagram of the management strategies originally used in the cohort.

Table 3 The performance of the National Health and Medical Research Council (NHMRC) guidelines with and without revision of the vertical margin criteria in predicting the risk of residual disease or cancer recurrence in patients with malignant colorectal polyps

			Original treatment[†]			
		N (%)	No operation	Operation	*N* (%) with residual disease or cancer recurrence	*P* value[‡]
NHMRC guidelines (existing)	Low risk	28 (22)	24 (86)	4 (14)	0 (0)	0.031
	High risk	101 (78)	28 (28)	73 (72)	15 (15)	
NHMRC guidelines (revised vertical margin criteria)[§]	Low risk	44 (34)	31 (70)	13 (30)	0 (0)	0.003
	High	85 (66)	21 (25)	64 (75)	15 (18)	

[†]The original treatment allocation did not always conform to NHMRC guidelines because of individual patient factors such as patient preference or fitness for major surgery.

[‡]*P* values represent chi square tests.

[§]The revised criteria state that a vertical margin can be termed clear by any distance as long as it can be reliably assessed and measured.

would improve risk stratification but not at the expense of "misclassifying" patients who might benefit from surgery.

Our finding that a resection margin of less than 1 mm can still be acceptable is supported by a number of previous studies that have suggested, for early cancers, that only tumor cells at the true resection margin, or within the diathermy burn zone, should be considered for further resection. For example, the treatment algorithm proposed by the Scottish Screen-detected Polyp Cancer Study, following the analysis of 485 patients with MCPs, recommended that surveillance is adequate for any patient with a clear measurable resection margin (of any distance) and an absence of LVI.[6] This followed a similar study in the United Kingdom of 221 patients by Gill and coworkers who concluded that a clear resection margin of > 0 mm was sufficient to avoid surgery in patients with endoscopically resected MCPs.[10] Finally, an Australian study of 239 patients by Brown and colleagues,

Table 4 Summary of the operative outcomes and associated health-care costs of the 13 patients who could have avoided surgery if National Health and Medical Research Council (NHMRC) guidelines with revised vertical margin criteria had been used to allocate treatment

Patient ID	Age	Gender	Polypectomy vertical margin clearance (mm)	Operation	Approach	Length of stay (days)	Complication	Clavien-Dindo grade	Residual disease	Health-care cost†
1	73	Male	0.50	Subtotal colectomy	Open	6	None	—	No	$13 266
2	83	Female	<1.00	High anterior resection	Open	7	Ileus	1	No	$15 865
3	80	Female	1.50	High anterior resection	Open	11	None	—	No	$19 233
4	65	Female	0.50	Left hemicolectomy	Open	15	Ileus	1	No	$27 928
5	62	Female	1.00	High anterior resection	Laparoscopic	6	None	—	No	$20 289
6	73	Female	<1.00	High anterior resection	Laparoscopic	6	None	—	No	$21 256
7	82	Male	0.50	Left hemicolectomy	Open	13	Atrial fibrillation	1	No	$26 734
8	76	Male	1.00	Right hemicolectomy	Open	7	Blood transfusion	2	No	$20 082
9	67	Male	<1.00	High anterior resection	Laparoscopic	4	None	—	No	$16 002
10	55	Male	0.50	Right hemicolectomy	Laparoscopic	5	None	—	No	$15 090
11	52	Female	0.80	High anterior resection	Laparoscopic	13	Ileus	1	No	$58 032
12	81	Male	0.80	Low anterior resection and loop ileostomy	Open	8	Pneumonia	2	No	$32 117
13	55	Male	0.10	High anterior resection	Laparoscopic	4	None	—	No	$18 597
Total										$304 091

†Health-care costs in Australian dollars were calculated using the actual cost of each patient's episode of care and included theater, medical, nursing, and ward-based costs.

regarded as representing high-quality pathological reporting, observed that none of the intact MCPs with a clearance of between 0.1 and 1 mm showed residual carcinoma in the resected surgical specimens.[3]

Previous studies in this field have focused on the histopathological features associated with poor prognosis in patients with MCPs. This has resulted in the publication of a wide array of adverse features, including Haggitt level,[11] Kikuchi level,[12] poor differentiation,[13] tumor budding,[14] width and breadth of the invasive margin,[3] LVI,[15] and sessile morphology[16] amongst others. These reports have scientific value and have increased our understanding of MCP biology, but they have done less to improve risk stratification in "real-life" scenarios. The reasons for this are twofold. First, a number of these pathological features are not routinely reported and cannot therefore be used by local MDTs to recommend treatment. For example, the reporting pathologist cannot reliably determine a Haggitt level in polyps without a clearly defined stalk or report a Kikuchi level unless the specimen contains the entire submucosa and at least some muscularis propria. The second reason why previous reports have struggled to influence decision-making is the complexity of some of the proposed risk stratification tools.[14,17] The problem with using an approach whereby multiple prognostic features are combined into a cumulative "risk score" is that, when a patient is presented to the MDT, there can be difficulty in calculating the total score if individual components are unavailable or indeed determining what course of action a particular score dictates. In contrast, information regarding the margin of excision is routinely reported in all polypectomy specimens. Although historical reports often described the margin clearance in ambiguous terms, such as "< 1 mm," recent recommendations now suggest that pathologists should measure the margin clearance to within one decimal place.[18] Revising the definition of vertical margin involvement, therefore, is a potentially simple and easy method of improving risk stratification.

The major limitation of the present study was that our revised version of the NHMRC guidelines was applied to the cohort retrospectively and was therefore not responsible for treatment decisions taken at the time. Thus, the ability of our revision to reduce unnecessary surgery is inferred rather than proven. It must also be remembered that decisions around the treatment of individuals are multifactorial, taking into account not only the risk of residual disease but also fitness for major surgery and, perhaps most importantly, patient preference. The interpretation of risk varies from person to person, and it may be that one individual would accept a moderate risk of residual disease in order to avoid major surgery, while another may prefer the certainty of resection even if the risk of residual disease was low. Any guidelines for MCP management can therefore only act as an adjunct to clinical decision-making.

In summary, the present study has demonstrated that revising the definition of vertical margin involvement within existing NHMRC guidelines has the potential to reduce unnecessary surgery in patients with MCPs. This finding requires validation in prospective studies in order to establish this as best clinical practice for the management of MCPs.

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