Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Pathological perspective of deficient mismatch repair in locally advanced colon cancer after neoadjuvant immunotherapy

Xiaowei Xue
Peking Union Medical College Hospital
Zhen Sun
Peking Union Medical College Hospital
Yan You
Peking Union Medical College Hospital
Yi Xiao
Peking Union Medical College Hospital
Weixun Zhou
zweixun@163.com

Peking Union Medical College Hospital

Research Article

Keywords: Colon cancer; Deficient mismatch repair; Neoadjuvant immunotherapy; Pathology.

Posted Date: May 21st, 2026

DOI: https://doi.org/10.21203/rs.3.rs-7880703/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Additional Declarations: No competing interests reported.

Abstract

Background

The role of neoadjuvant therapy in the treatment of locally advanced colon cancer has become increasingly prominent. However, radiographic assessment rarely provided an accurate prediction of pathological complete response. This study aims to improve preoperative clinical evaluation by investigating the histopathological differences in colon cancer after neoadjuvant therapy.

Method

This was a prospective observational study conducted at Peking Union Medical College Hospital. Patients were eligible for inclusion if they were locally advanced colon adenocarcinoma and treated with neoadjuvant therapy. Surgical specimens after neoadjuvant therapy were carefully examined by pathologists. According to the standard sampling method, the location of the tumor bed was identified and all tissues of the tumor bed were sent for microscopic examination.

Results

Of 32 patients, 16 (50%) were included in dMMR group. The difference in tumor location between these two groups was statistically significant (P<0.05). The dMMR group had a better pathological response, with a pCR rate of 62.5% and 3 cases (18.75%) of near pCR (TRG grade 1). In pMMR group, only 12.5% achieved pCR and 6.25% near pCR. The difference between the two groups was statistically significant (P<0.05). There was no statistical difference in gross findings of the surgical specimen between the two groups. However, there was a significant difference in the maximum diameter of residual tumor between the two groups (*P*<0.05). Histopathological examination revealed mucinous pools was predominant in 50% of dMMR tumors and fibrosis was the predominant pattern in 87.5% of pMMR tumors (*P*<0.05).

Conclusions

For patients with dMMR after neoadjuvant immunotherapy, histologic manifestations more frequently included large mucinous pools, leading to a gross overestimation of residual tumor.

Introduction

Colorectal cancer is a highly prevalent malignancy, ranking second in incidence in Western countries and showing a continuously increasing trend in developing countries. With the advancement of medical technology and widespread adoption of multidisciplinary comprehensive treatment strategies, the role of neoadjuvant therapy in the treatment of locally advanced colorectal cancer has become increasingly prominent. Neoadjuvant therapy for colon cancer has a limited therapeutic effect because it cannot be combined with radiotherapy; therefore, it is only supported by clinical evidence in patients with locally advanced colon cancer.

Substantial breakthroughs have been made in the neoadjuvant treatment of patients with deficient mismatch repair (dMMR) colorectal cancer, especially with the application of immune checkpoint inhibitors[1]. With the rise of immunotherapy, preoperative anti-PD-1 therapy has shown impressive efficacy, with pathological complete response (pCR) rates of 68%[2]. Surgeons were faced with the choice of whether and when to perform surgery after neoadjuvant therapy, which requires a clinical evaluation of the treatment effect. Currently, assessment relies primarily on imaging to observe tumor changes, supplemented by combined endoscopic and biopsy methods. However, radiographic assessments rarely provide an accurate prediction of pCR.

In this article, we review the histopathological differences between patients with dMMR colon cancer after neoadjuvant immunotherapy and patients with proficient mismatch repair (pMMR) colon cancer after neoadjuvant chemotherapy, with the aim of improving preoperative clinical evaluation.

Materials and Methods

Patients

Patients were eligible for inclusion if they were at least 18 years old and had previously untreated, locally advanced colon adenocarcinoma. All patients had colon adenocarcinoma confirmed by endoscopic biopsy, and mismatch repair protein expression was determined by immunohistochemistry. MMR protein antibodies MLH1 (clone number OTI4H4), MSH2 (clone number OTIR1B12), MSH6 (clone number EP49), and PMS2 (clone number OTI4B2) were purchased from Beijing Zhongshan Golden Bridge Biotechnology Co., Beijing, China. A secondary antibody (UltraPATH Plus DAB Staining Solution) and color development system (ZSGB-BIO UltraPATH, Beijing Zhongshan Golden Bridge Biotechnology Co., Beijing, China) were used for IHC staining. The absence of at least one of the four mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6) was indicative of dMMR, whereas expression of all four proteins was indicative of pMMR.

The patients were treated with neoadjuvant therapy, including single- or double-agent immunotherapy in the dMMR group and chemotherapy or chemotherapy combined with tyrosine kinase inhibitors in the pMMR group.

This study was approved by the Ethical Review Board of the Peking Union Medical College, Chinese Academy of Medical Sciences (approval number I-24PJ0062).

Pathological examination

Surgical specimens obtained after neoadjuvant therapy were carefully examined by pathologists. The location of the tumor bed was identified according to the standard sampling method, and all tissues from the tumor bed were submitted for microscopic examination. Gross observations of residual tumor morphology and size were recorded. Residual tumor tissue was examined under a microscope by two

independent pathologists (WXZ and YY), and tumor regression was graded according to the AJCC Cancer Staging system[3]. Histological changes reflecting treatment response were also evaluated.

Statistical analysis

Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation and were analyzed using independent-sample *t*-tests. Non-normally distributed variables are expressed as median (interquartile range) and compared using the Mann–Whitney U test. Categorical variables are summarized as frequencies (%) and analyzed using the chi-square test or Fisher's exact test, as appropriate. Statistical significance was set at a two-tailed *p*-value < 0.05. All analyses were performed using SPSS (version 26.0; IBM Corp., Armonk, NY, USA) or GraphPad Prism (version 9.5; GraphPad Software, San Diego, CA, USA).

Results

Demographic characteristics

This study included 16 patients with dMMR who underwent surgery after neoadjuvant therapy at the Peking Union Medical College Hospital between September 2023 and December 2024 as the dMMR group. Sixteen consecutive patients who underwent surgery after neoadjuvant therapy from July to November 2024 were included in the pMMR group.

Demographic and pathological characteristics of the patients are summarized in TABLE 1. There were nine men and seven women in the dMMR group, aged 35–76 years, with a median age of 56 years. There were 11 men and five women in the pMMR group, aged 42–74 years, with a median age of 57.5 years. There were no significant differences in sex or age between the two groups. The pattern of loss of expression in the dMMR group included loss of MLH1 and PMS2 expression in 10 cases, loss of MSH2 and MSH6 expression in four cases, and loss of PMS2 expression alone in two cases. In the dMMR group, 14 tumors were situated in the right colon (ranging from the cecum to the proximal transverse colon), whereas two tumors were found in the left colon (from the distal transverse colon to the sigmoid colon). In the pMMR group, three tumors were located in the right colon and 13 in the left colon, and the difference in tumor location between these two groups was statistically significant ($P < 0.05$). Before treatment, the histological types of the biopsies were colon adenocarcinoma, not otherwise specified. No special histological types, such as mucinous adenocarcinoma, were found. There were nine cases of well-moderately differentiated adenocarcinoma and seven cases of poorly differentiated adenocarcinoma in the dMMR group. In the pMMR group, 14 cases were moderately differentiated and two cases were poorly differentiated.

Pathological characteristics

R0 resection (no tumor at the margins of the resected specimen) was performed in all patients. The dMMR group had a better pathological response, with a pCR rate of 62.5% and three cases (18.75%) of

near pCR (tumor regression grade 1). In the pMMR group, only 12.5% of patients achieved pCR and one patient (6.25%) achieved near pCR. The difference between the two groups was statistically significant ($P < 0.05$).

Only one patient in the dMMR group had a single lymph node metastasis, whereas six patients in the pMMR group had lymph node metastases: three patients had one lymph node metastasis, one patient had two, and two patients had three. Although the numbers differed, the difference did not reach statistical significance.

Gross findings of the surgical specimens included uneven, irregular mucosa (FIGURE 1A), superficial ulcers without obvious tumors (FIGURE 1B), and a prominent tumor mass with or without ulceration (FIGURE 1C and D). In the dMMR group, 11 patients had tumor masses, of which six had a maximum diameter of ≥ 4cm. In the pMMR group, 10 patients had tumor masses, of which four had a maximum diameter of ≥ 4cm. No statistically significant differences were found between the two groups.

However, the microscopic residual tumor in the dMMR group measured < 1cm in five of six cases, whereas one case had a residual tumor measuring 2.3cm. In the pMMR group, 12 of 13 cases had residual tumors larger than 1cm, and the largest diameter was 5cm. There was a significant difference in the maximum diameter of the residual tumor observed under the microscope between the two groups ($P < 0.05$).

Histopathological examination revealed a definite posttreatment response in all tumor beds. Fibrosis and inflammation were the most common findings in patients with pMMR. Mucus pools, focal necrosis, calcification, and foam cell aggregation were also observed. In patients with dMMR, the most common findings were mucus pools, fibrosis, and inflammation. Necrosis, calcification, and foam cell aggregation were also observed. Foreign body granulomas were identified in two dMMR cases, showing epithelioid cells and multinucleated giant cells adjacent to necrosis, which were not found in pMMR cases. Mucinous pools (FIGURE 2) were predominant in 50% of the dMMR tumors. Fibrosis (FIGURE 3) was present in all dMMR cases but was the predominant pattern in only 25% of tumors. Fibrosis was predominant in 87.5% of pMMR tumors. Mucinous pools were found in only 12.5% of the pMMR cases and accounted for a small proportion of each tumor. A statistically significant difference was observed between the two groups ($P < 0.05$).

Discussion

In the present study, 87.5% of tumors in the dMMR group were located in the right colon, a substantially higher proportion than the 18.75% of tumors located in the right colon in the pMMR group. Furthermore, 43.75% of the tumors in the dMMR group were classified as poorly differentiated adenocarcinomas, in contrast to only 12.5% of tumors in the pMMR group. These differences were statistically significant and aligned with the findings of previous studies. Compared with the more prevalent pMMR in colorectal cancer, dMMR exhibits distinct clinicopathological characteristics. Patients with dMMR tended to be younger and more frequently diagnosed with tumors located in the right colon. Poorly differentiated

adenocarcinoma with prominent atypia and increased lymphocytic infiltration is the most common subtype observed in patients with dMMR. There was no statistical difference in gross findings of the surgical specimen between the two groups. However, the microscopic residual tumor in the dMMR group was less than 1cm in 5/6 cases. In the pMMR group, 12/13 cases had residual tumors larger than 1cm. There was a significant difference in the maximum diameter of residual tumor between the two groups. Histopathological examination revealed mucinous pools was predominant in 50% of dMMR tumors and fibrosis was the predominant pattern in 87.5% of pMMR tumors.

Numerous clinical trials have demonstrated that both the objective response and disease control rates of immunotherapy are significantly higher in patients with dMMR than in patients with pMMR[3,4]. Neoadjuvant therapy is predominantly utilized in patients with locally advanced colon cancer to achieve R0 resection. Immunotherapy has demonstrated remarkable efficacy in colorectal cancer[1,2,4], and neoadjuvant immunotherapy has become a treatment option for locally advanced dMMR colon cancers. In this study, the dMMR group demonstrated a superior response to neoadjuvant immunotherapy, with pCR and near-pCR rates of 81.25%. Nevertheless, two patients exhibited a partial response and one patient showed a poor response to treatment. The reasons for these variations require further investigation.

However, a prominent mass was often observed after neoadjuvant immunotherapy in the present study, leading to an overestimation of the residual tumor. Macroscopic observation of surgical specimens after neoadjuvant therapy often showed ulcers, uneven irregular mucosa, or only a scar with intact mucosa, which was considered a clinical complete response[5]. When there was a significant tumor mass, it was evaluated as a poor response to treatment[6]. These gross findings, which can be evaluated before surgery by endoscopy or imaging, serve as a clinical assessment of treatment response and are an important reference for surgical decision-making[5]. However, to date, this assessment often deviates from the actual pathological results. The macroscopic appearance of the residual tumor did not correspond to its histological appearance. We found that this inconsistency differed between the two tumor groups. The dMMR group tended to overestimate the residual tumor, whereas the pMMR group tended to underestimate it. In the dMMR group, there were five cases without obvious tumors on gross examination, all of which were pCR cases. Five of the 11 cases with a gross tumor size < 3cm were also pCR cases. Of the six patients with a gross tumor size ≥ 4cm, five had a residual tumor (< 0.5cm) under the microscope, and only one had a residual tumor measuring 2.3cm. By contrast, six patients in the pMMR group had no obvious tumors on gross examination, but four patients had residual tumors under the microscope, and three of them were TRG grade 2–3. All cases with macroscopic tumors had residual tumors ≥ 1cm. Among them, the residual tumor measured > 2cm under the microscope in all cases with macroscopic tumors ≥ 4cm, which corresponded to the gross results. A study reviewing endoscopic evaluation after neoadjuvant therapy in 74 patients found that pCR may be achieved in patients with dMMR despite the presence of residual tumor on endoscopy, limiting the reliability of endoscopic evaluation[7]. This phenomenon of false progression or false residual is especially common in patients with dMMR, which is consistent with our findings. Therefore, unlike pMMR tumors that appear to

respond well grossly but may still harbor residual tumors, gross tumor assessment after neoadjuvant immunotherapy in patients with dMMR may easily underestimate the treatment response.

Histological posttreatment reactions are more common in the form of large mucinous pools in patients with dMMR cancers. Histopathological patterns after neoadjuvant therapy include fibrosis, inflammation, mucinous pool formation, necrosis, calcification, cholesterol clefts, foam cells, and multinucleated giant cells[8], among which fibrosis, inflammation, and mucinous pool formation are common morphological changes observed in colorectal cancer. We observed that these three patterns were also common in our cases but differed notably between the two groups. Mucinous pools were found in 62.5% of dMMR cases and were predominant in 50% of the dMMR tumors. Fibrosis was present in all dMMR cases but was the predominant pattern in only 25% of tumors. In the pMMR group, fibrosis was not only present in all cases but was also the predominant pattern in 87.5% of cases. Mucinous pools were found in only 12.5% of cases and accounted for a small proportion of each tumor. Neoadjuvant chemoradiotherapy is widely used to treat locally advanced rectal cancers. Fibrosis after chemoradiotherapy has been observed in almost all tumors[9,10], whereas mucinous pools were found in 12%–33% of posttreatment tumors[9,11]. By contrast, mucinous pools were observed in 62.5% of patients with dMMR after neoadjuvant immunotherapy, and in most of them, these pools represented the dominant morphology of the tumor bed. It has been suggested that the mechanisms and microenvironments of immunotherapy may differ. The formation of mucinous pools is not fully understood, but the prevailing view is that it represents a posttreatment response[12]. No mucinous adenocarcinoma or abundant extracellular mucus was found in the biopsy specimens before treatment in any of our cases, suggesting that mucinous pools are not tumor products but rather treatment responses, which also supports the previous view. Deep mucinous pools (in the serosa and/or adipose tissue) are independent prognostic factors for poor disease-free survival in rectal cancer[13]. However, the prognostic significance of mucinous pools in patients with dMMR colon cancer after neoadjuvant immunotherapy remains unclear.

Collectively, these features suggest that the accuracy of clinical assessment of tumor response may be improved by identifying differences between mucus and tumor tissue. Magnetic resonance imaging can accurately evaluate the extent of mucinous pools in primary rectal cancer tissue, which is closely associated with the response to neoadjuvant therapy[14]. However, the clinical evaluation of colon cancer still relies on computed tomography. No study has reported the relation between mucinous pools and computed tomography findings, which hinders accurate restaging of patients with colon cancer after neoadjuvant treatment.

Considering the small proportion of dMMR colorectal cancers, the major limitation of this study was its relatively small sample size. However, the site of onset of dMMR tumors, the effect of neoadjuvant immunotherapy, residual tumor volume, and reactive histopathological patterns were relatively distinct from those in patients with pMMR in the present study, even though few cases have been reported. Therefore, it is necessary to investigate whether this phenomenon is common in larger cohorts.

Conclusion

For patients with dMMR after neoadjuvant immunotherapy, histologic manifestations more frequently included large mucinous pools, leading to a gross overestimation of residual tumor.

Declarations

Author contributions

Conception and design of study: Yi Xiao, Weixun Zhou. Data acquisition: Xiaowei Xue, Zhen Sun, Yan You. Analysis: Xiaowei Xue, Zhen Sun. Interpretation of data: Xiaowei Xue, Zhen Sun, Yan You. Drafting: Xiaowei Xue, Zhen Sun. Critical revision of manuscript for important intellectual content: Yi Xiao, Weixun Zhou.

References

1. Hu H, Kang L, Zhang J, et al. Neoadjuvant PD-1 blockade with toripalimab, with or without celecoxib, in mismatch repair-deficient or microsatellite instability-high, locally advanced, colorectal cancer (PICC): a single-centre, parallel-group, non-comparative, randomised, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2022;7(1):38-48. doi: 10.1016/S2468-1253(21)00348-4. Epub 2021 Oct 22. PMID: 34688374.
2. Chalabi M, Verschoor YL, Tan PB, et al. Neoadjuvant Immunotherapy in Locally Advanced Mismatch Repair-Deficient Colon Cancer. *N Engl J Med*. 2024;390(21):1949-1958. doi: 10.1056/NEJMoa2400634. PMID: 38838311.
3. Golshani G, Zhang Y. Advances in immunotherapy for colorectal cancer: a review. *Therap Adv Gastroenterol*. 2020;13:1756284820917527. doi: 10.1177/1756284820917527. PMID: 32536977; PMCID: PMC7268115.
4. Chen G, Jin Y, Guan WL, et al. Neoadjuvant PD-1 blockade with sintilimab in mismatch-repair deficient, locally advanced rectal cancer: an open-label, single-centre phase 2 study. *Lancet Gastroenterol Hepatol*. 2023;8(5):422-431. doi: 10.1016/S2468-1253(22)00439-3. Epub 2023 Mar 1. PMID: 36870360.
5. Williams H, Thompson HM, Lin ST, et al. OPRA Consortium. Endoscopic Predictors of Residual Tumor After Total Neoadjuvant Therapy: A Post Hoc Analysis From the Organ Preservation in Rectal Adenocarcinoma Trial. *Dis Colon Rectum*. 2024;67(3):369-376. doi: 10.1097/DCR.0000000000003096. Epub 2023 Nov 20. PMID: 38039292; PMCID: PMC10922113.
6. Pai RK, Pai RK. Pathologic assessment of gastrointestinal tract and pancreatic carcinoma after neoadjuvant therapy. *Mod Pathol*. 2018;31(1):4-23. doi: 10.1038/modpathol.2017.87. Epub 2017 Aug 4. PMID: 28776577.

7. Li YG, Han CC, Zhuang M, Zhao W, Hu G, Qiu WL, Wang XS, Tang JQ. Evaluating the predictive value of endoscopic findings for residual colorectal cancer following neoadjuvant combination immunotherapy. *World J Gastrointest Surg*. 2025;17(1):98263. doi: 10.4240/wjgs.v17.i1.98263. PMID: 39872770; PMCID: PMC11757185.
8. Hav M, Libbrecht L, Ferdinande L, Geboes K, Pattyn P, Cuvelier CA. Pathologic Assessment of Rectal Carcinoma after Neoadjuvant Radio(chemo)therapy: Prognostic Implications. *Biomed Res Int*. 2015;2015:574540. doi: 10.1155/2015/574540. Epub 2015 Oct 5. PMID: 26509160; PMCID: PMC4609786.
9. Fernández-Aceñero MJ, Estrada Muñoz L, Sastre Varela J, Corona Sánchez JA, Díaz Del Arco C, García Paredes B, Córdoba Largo S, Del Puerto Nevado L. Prognostic influence of histopathological regression patterns in rectal adenocarcinoma receiving neoadjuvant therapy. *J Gastrointest Oncol*. 2017;8(1):49-54. doi: 10.21037/jgo.2017.01.02. PMID: 28280608; PMCID: PMC5334051.
10. Tanaka S, Martling A, Lindholm J, Holm T, Palmer G. Remaining cancer cells within the fibrosis after neo-adjuvant treatment for locally advanced rectal cancer. *Eur J Surg Oncol*. 2015;41(9):1204-9. doi: 10.1016/j.ejso.2015.05.019. Epub 2015 Jun 12. PMID: 26108735.
11. Reynolds IS, McNamara DA, Kay EW, O'Neill B, Deasy J, Burke JP. The significance of mucin pools following neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *J Surg Oncol*. 2018;118(7):1129-1134. doi: 10.1002/jso.25247. Epub 2018 Sep 27. PMID: 30261095.
12. Reynolds IS, O'Connell E, Fichtner M, Kay EW, McNamara DA, Prehn JHM, Burke JP. Mucin Pools Following Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Marker of Response or Epiphenomenon? *Am J Surg Pathol*. 2020;44(2):280-287. doi: 10.1097/PAS.0000000000001373. PMID: 31567193.
13. Chen M, Wang C, Liu H, Liang Z, Ye F, Luo S, Liu Z, Hu H, Lai S, Hou Y, Kang L, Huang L. The Deepest Extent of Acellular Mucin Pools in Resected Locally Advanced Rectal Cancer With Pathological Complete Response After Preoperative Chemoradiotherapy: A Hidden Killer? *Am J Surg Pathol*. 2023 ;47(7):812-818. doi: 10.1097/PAS.0000000000002055. Epub 2023 May 17. PMID: 37194966.
14. Miyakita H, Sadahiro S, Ogimi T, Saito G, Okada K, Tanaka A, Suzuki T, Kajiwara H, Yamamuro H, Akiba T. Mucinous components assessed by magnetic resonance imaging in primary rectal cancer tissue before and after chemoradiotherapy and tumor response. *Int J Colorectal Dis*. 2018;33(8):1135-1138. doi: 10.1007/s00384-018-3047-1. Epub 2018 Apr 26. PMID: 29696349; PMCID: PMC6060831.
15. Jessup JM, Goldberg RM, Asare EA et al. Colon and Rectum. In MB Amin, SB Edge, FL Greene et al. eds. AJCC cancer staging manual. 8th ed. New York, NY: Springer, 2017; 251–274.

Tables

TABLE 1 Comparison of Clinical Features and Treatment Outcomes between dMMR and pMMR Patient Groups

Variables	Total	Group		P-value
		dMMR	pMMR	
Sex				
Male	16	9（56.25）	11（43.75）	0.4652
Female	16	7（68.75）	5（31.25）	
Age		55.81±11.91	59.56±9.825	0.3391
Tumor location				
Left	16	2（12.50）	14（87.50）	0.0002***
Right	16	13（81.25）	3（18.75）	
Treatment response				
pCR	12	10	2	0.0056**
TRG grade 1	4	3	1	
TRG grade 2	10	2	8	
TRG grade 3	6	1	5	
Pathological type				0.3096
Well-moderately differentiated	31	16	15	
Poorly differentiated	1	0	1	
Lymph node metastasis				0.1718
0	25	15	10	
1	4	1	3	
2	1	0	1	
3	2	0	2	
The main morphology of the tumor bed				0.0008***
Inflammation	6	4	2	
Fibrosis	18	4	14	
Mucus	8	8	0	
Gross features of tumor				0.8193
Mucosal irregularity	5	3	2	

Superficial ulcer	6	2	4	
Mass	1	2	2	
Mass with ulcer	4	9	8	
Remaining tumor				0.7097
Yes	21	11	10	
No	11	5	6	
Maximum diameter of residual tumor				0.0003***
None	12	10	2	
≤1cm	7	5	2	
1cm	13	1	12	

** indicates that difference is significant (P<0.01).

*** indicates significant difference (P < 0.001)

Figures

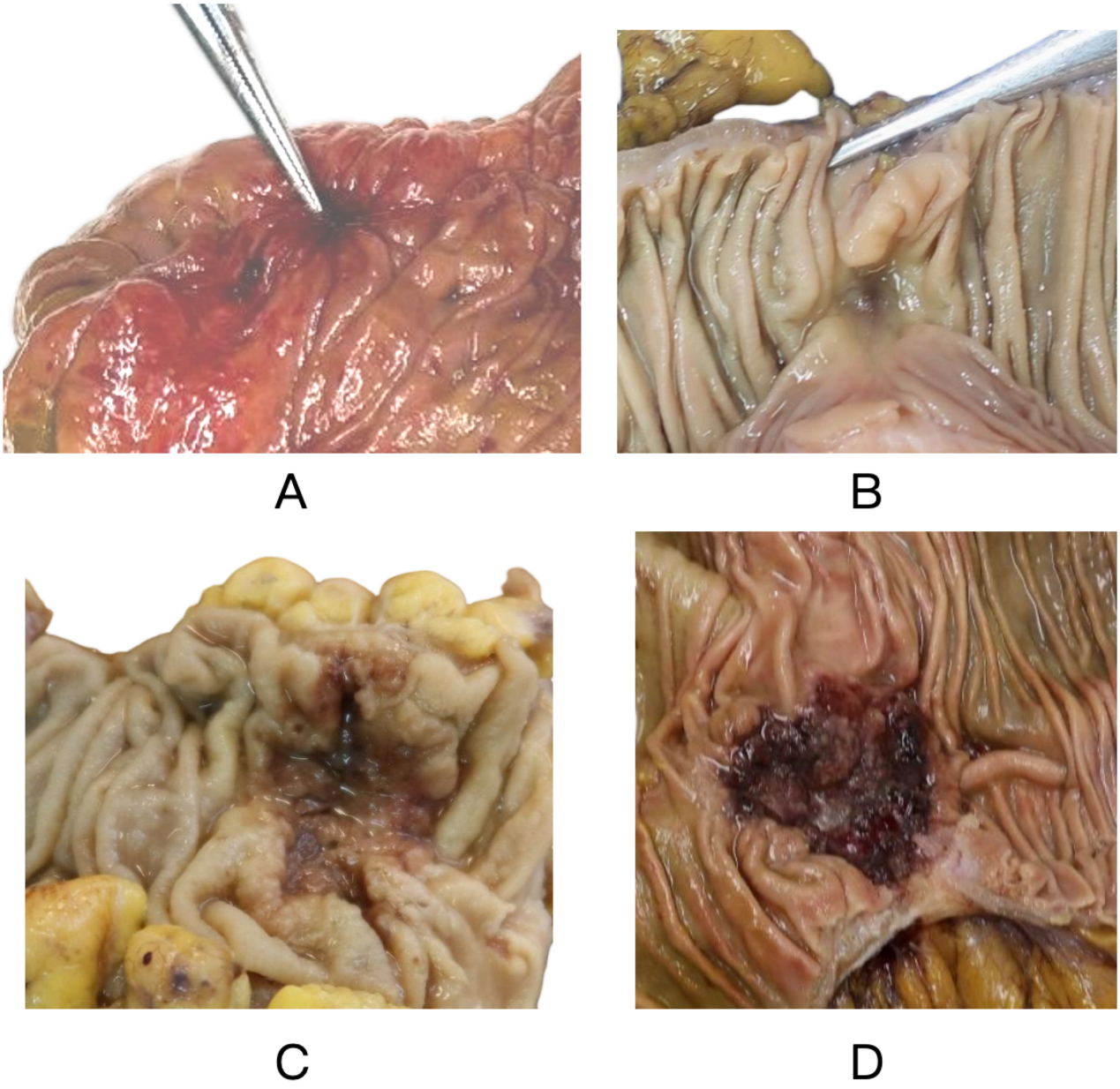


Figure 1

Gross findings of the surgical specimen. A: uneven irregular mucosa (dMMR case No. 8); B: superficial ulcers without obvious tumor (pMMR case No. 5); C: prominent tumor mass with ulcer (pMMR case No. 3); D: prominent tumor mass (dMMR case No. 16).

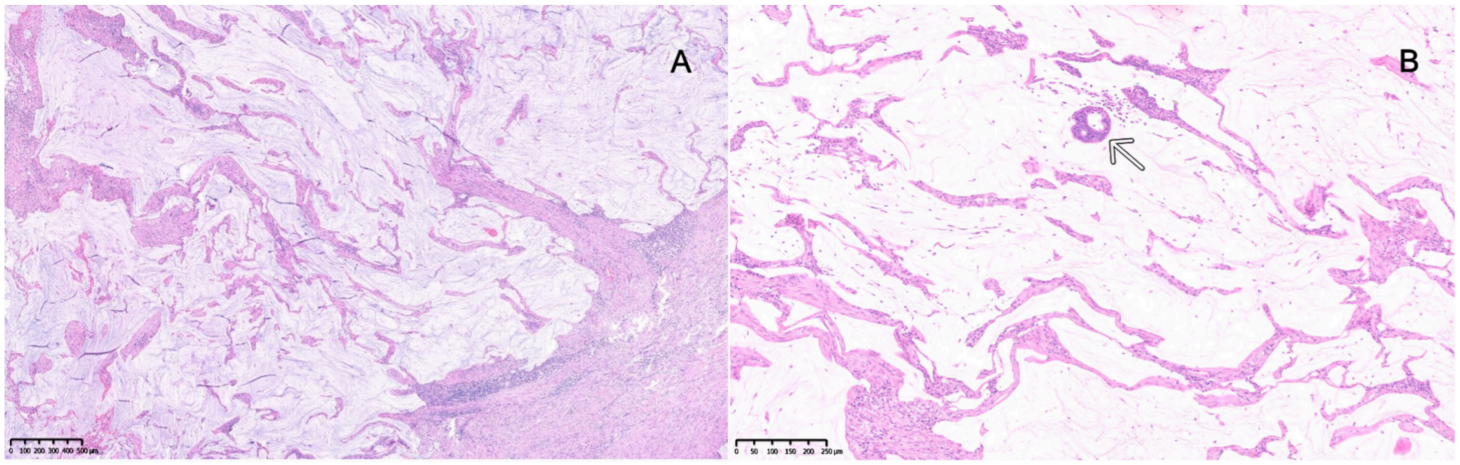


Figure 2

The histopathological pattern of mucinous pool. A, Large area of mucinous pool without tumor. B, A small amount of tumor tissue remained in mucinous pool (arrow).

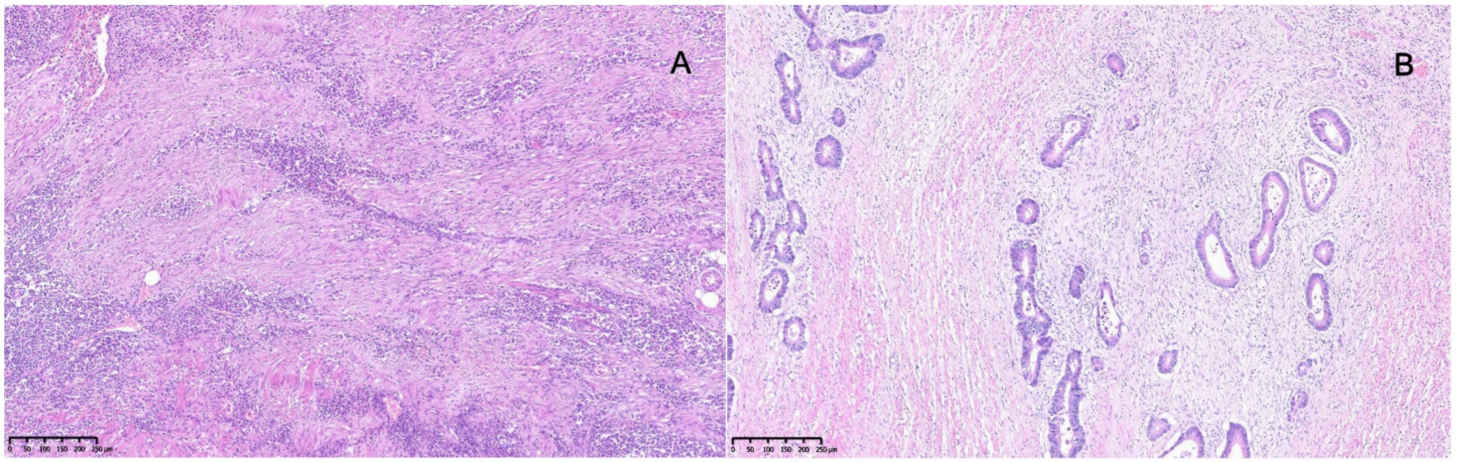


Figure 3

The histopathological pattern of fibrosis. A, Fibrosis without tumor. B, Fibrosis with resident tumor inside.