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Extensive colectomy in colorectal cancer and hereditary nonpolyposis colorectal cancer – long-term results

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ABSTRACT

Background: Colorectal cancer survival is better in hereditary nonpolyposis colorectal cancer patients than in sporadic colorectal cancer patients and even for hereditary nonpolyposis colorectal cancer with colorectal cancer is not consensual that extensive colectomy is preferable to partial colectomy. This study analyzes and compares the long-term results of these two groups of patients submitted to curative subtotal colectomy or total colectomy.
Methods: Between 2002 and 2018, 68 patients with colorectal cancer without familial adenomatous polyposis were submitted to a total or subtotal colectomy in a single tertiary center. The patients were divided in two groups: hereditary nonpolyposis colorectal cancer patients (with Amsterdam criteria) and sporadic colorectal cancer patients (the others). The presence of Amsterdam criteria for hereditary nonpolyposis colorectal cancer and germline mutation for mismatch repair genes was confirmed by clinical records. Results and survival were analyzed following surgery.
Results: We obtained a sporadic colorectal cancer group with 31 patients and a hereditary nonpolyposis colorectal cancer group with 37 patients. The two groups differ in age but not in gender, tumor stage or surgical morbidity. The overall survival and disease-free survival were good in both groups but even better for hereditary nonpolyposis colorectal cancer group with statistical significance when comparing the two groups.
Conclusion: Total or subtotal colectomy for colorectal cancer provides a good survival. These surgical procedures should be considered the first option for colorectal cancer in young

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hereditary non polyposis colorectal cancer patients. In those cases, they provide good long-term results, avoiding the risk of metachronous colorectal cancer and the surveillance is restricted only to the remaining need for rectum.

Colectomia extensa em cancro colorretal e cancro colorretal hereditário sem polipose – resultados a longo prazo

Palavras-chave:
Cancro colorretal
HNPCC
Síndrome de Lynch
Instabilidade
Genes de reparação do ADN
Colectomia total

RESUMO

Introdução: A sobrevivência do cancro colorretal é melhor em pacientes com cancro colorretal hereditário não associado a polipose do que em pacientes com cancro colorretal esporádico. Mesmo em casos de cancro colorretal hereditário sem polipose, a preferência pela colectomia total em relação à parcial não é consensual na literatura. Este estudo analisa e compara os resultados a longo prazo destes dois grupos de pacientes submetidos à colectomia curativa subtotal ou total.

Métodos: Entre 2002 e 2018, 68 pacientes com cancro colorretal sem polipose adenomatosa familiar foram submetidos a colectomia total ou subtotal em um único centro terciário. Os pacientes foram divididos em dois grupos: aqueles com cancro colorretal hereditário sem polipose (de acordo com os critérios de Amsterdão) e os com cancro colorretal esporádico (os demais). Os critérios de Amsterdão para cancro colorretal hereditário sem polipose e a presença de mutação germinativa para os genes de reparação de ADN foram confirmados por consulta dos registros clínicos. Os resultados e a sobrevivência foram analisados após a cirurgia.

Resultados: No presente estudo, 31 pacientes foram incluídos no grupo de cancro colorretal esporádico e 37 no grupo de cancro colorretal hereditário sem polipose. Diferenças significativas foram observadas em relação à idade, mas não ao género, estadio do tumor ou morbilidade cirúrgica. A sobrevivência global e a sobrevivência livre de doença foram boas em ambos os grupos, mas os resultados foram ainda melhores no grupo de cancro colorretal hereditário sem polipose, com significado estatístico.

Conclusão: A colectomia total ou a colectomia subtotal para o cancro colorretal proporcionam uma boa sobrevivência e devem ser consideradas a primeira opção de tratamento em pacientes jovens com cancro colorretal hereditário sem polipose. Nestes pacientes, uma cirurgia cólica mais extensa permite a obtenção de bons resultados a longo prazo; reduz o risco de cancro colorretal metácrono e restringe a vigilância endoscópica ao reto remanescente.

Introduction

Hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) is a genetic disease of autosomal dominant inheritance due to germline mutations in mismatch repair (MMR) genes MLH1, MSH2, MSH6, PMS2 or epigenetic silencing of MSH2 via inherited EPCAM mutations,[1,2] which carries a cumulative risk by age 70 years of 26%–80% for colorectal cancer (CRC).[3] Mutation carriers also are at risk for several extra-colonic cancers, particularly cancers of the endometrium, ovary, urothelium, small bowel, stomach and brain.[4]

Its prevalence in the general population is about 1 in 500, and it causes about 2%–3% of all colorectal cancers. The mutation in one of four genes of the DNA mismatch repair system also confers a markedly increased risk for other types of cancer, namely of endometrium.[5,6]

The presence of HNPCC is suspected when a patient develops cancer at an unusually young age or because of familial clustering. Usually patients with CCR who meet the Amsterdam criteria (Table 1) are HNPCC patients by definition.[7] In families that meet the Amsterdam criteria, the probability of having a mutation in MLH1, MSH2 genes is high (50%–92%).[8,9]

Currently the Amsterdam criteria also still covers families with no evidence of a DNA repair defect in a tumor, in which the increased tumor risk is probably due to genetic causes that have not yet been identified.[10] The familial nature of colon cancer is also caused, to an unknown extent, by simple coincidence. HNPCC patients also include those who meet the weaker criteria of the Bethesda Guidelines[11] (Table 1) and have a tumor with an MMR defect. The Bethesda Guidelines

Table 1 – Amsterdam II Criteria and Revised Bethesda Guidelines.

Amsterdam II Criteria (Vasen et al.[7])
All criteria must be met:
Three or more relatives with histologically confirmed colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis, one affected relative being a first-degree relative of the other two; FAP should be excluded;
Two or more successive generations are affected;
At least one relative was diagnosed before the age of 50 years

Revised Bethesda Guidelines (Rodriguez-Bigas et al.[11])
One or more of the following criteria must be met:
Colorectal cancer before the age of 50 years;
Synchronous or metachronous colorectal cancer or other HNPCC-related tumors[a], regardless of age;
Colorectal cancer with MSI-high morphology[b] before the age of 60 years;
Colorectal cancer (regardless of age) and a first-degree relative with colorectal cancer or an HNPCC-related tumor before the age of 50 years;
Colorectal cancer (regardless of age) and two or more first- or second-degree relatives diagnosed with colorectal cancer or an HNPCC-related tumor (regardless of age)

FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; MSI, microsatellite instability.
[a] HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir–Torre syndrome, and carcinoma of the small bowel.
[b] Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring cell differentiation, or medullary growth pattern.

have a higher sensitivity but lower specificity than the Amsterdam criteria regarding evidence of a mutation in an MMR gene. All patients carrying a cancer-causing germline mutation in an MMR gene (almost half of HNPCC patients) can also be said to have Lynch syndrome. However, in clinical practice the terms "HNPCC" and "Lynch syndrome" are usually used synonymously.[12]

Usually for Lynch syndrome confirmation, the tumor tissue is analyzed for evidence of deficient mismatch repair. If such evidence is found, a genetic mutation is sought. The identification of a pathogenic mutation by genetic test confirms the diagnosis in the patient and enables predictive testing of other family members.[13]

Yet, the identification of MMR gene mutation is not always achieved and the diagnosis, the therapeutic plan and surveillance are made taking into account the other cardinal features besides the earlier average age of cancer onset, including CRC mainly in right colon, accelerated carcinogenesis, high risk for metachronous colorectal cancers, specific pathology features for HNPCC colorectal cancers (they are more often poorly differentiated and have an excess of mucoid and signet cell features, a Crohn-like reaction and an excess of infiltrating lymphocytes within the tumor)[14] and importantly, an increased survival when compare with sporadic colorectal cancer patients.

These aspects have clinical implications for HNPCC patients with CRC management namely, extension of surgical resection, the need of chemotherapy in CRC Stage III and frequency of screening colonoscopies when partial colectomy is done to detriment of a total or subtotal colectomy.[15] In fact, the concept that more extensive colonic resection in the CRC and in particular in the HNPCC does provide survival advantage is not proven and the surgical policy varies in different centers. For this specific reason we carry out the present study which aims to analyze long-term results after total or subtotal colectomy in colorectal cancer, especially concerning patients with Amsterdam criteria and based on results achieved to determinate the most appropriate extension of surgical resection in this group of patients.

Methods

Database design, patient population and inclusion criteria

The study was an open observational study without a control group. All patients were 20 years of age or older at inclusion. Age at inclusion was the patient age when they were submitted to elective total/subtotal colectomy or colectomy totalization. We included all patients with colon cancer without familial adenomatous polyposis (FAP) submitted to a curative total, subtotal colectomy or colectomy totalization between December 2002 and April 2018 in a single tertiary referral center. Other diagnosed neoplasia, presence of rectal cancer, clinical Stage IV and R1/R2 surgery were exclusion criteria but not the clinical patient history of previous colonoscopy with polypectomy or a previous surgery for CRC.

The patients were divided in two groups: HNPCC patients (patients with Amsterdam criteria) and SCRC patients (the others). All the patients have a colon cancer diagnosis without other neoplasm. All patients were subjected to follow-up according to international guidelines. The patients were followed until the last update of information, and scored as alive without disease, alive with disease and dead.

The following information was used for this report: gender, presence of Amsterdam criteria, genetic variant when identified, age at surgery, age and stage of previous CRC and surgery type and date if any, surgery extension and date, surgery morbimortality cancer stage, numbers of months between surgery and last observation or dead. When calculating survival, each patient was scored once only, irrespective of how many surgeries for cancer the patient might have had.

Diagnosis

Total colonoscopy with a biopsy-proven adenocarcinoma, chest, abdominal and pelvic computed tomographic scan, and serum carcinoembryonic antigen (CEA) level.

Surgical procedures

Surgery consisted mainly of total or subtotal colectomy. For patients with previous partial colectomy the surgery realized was totalization of colectomy.

The term of "subtotal colectomy" is used for the authors only for the extensive colectomy in which part of the sigmoid and sigmoid arteries were spared in a near total colectomy.

For authors the synonymous of "partial colectomy" are "segmental colectomy". This term includes "right colectomy", "left colectomy", "sigmoidectomy" or "transverse colectomy".

Regarding the selection of the operative procedure, we considered the presence of CRC with Amsterdam criteria, synchronous CRC, metachronous CRC or CRC with polyps not removable by colonoscopy.

Resected specimen samples – H&E staining; analysis for deficient of MMR

Standard pathological tumor staging of the resected specimen was performed in accordance with the guidelines of the American Joint Committee on Cancer (http://www.cancerstaging.net).

Tumor tissue was analyzed for evidence of loss of mismatch repair protein expression by immunohistochemistry or by microsatellite instability test. When positive the pathogenic mutation by genetic test (denaturing high performance liquid chromatography analysis and DNA sequencing) was realized.

Adjuvant chemotherapy protocol

Post-surgery patients with pathological Stage III were administered adjuvant chemotherapy protocol for 6 months performed preferably with 5-FU or a combination of 5-FU and oxaliplatin (one of the followed regimens: mFolFOX6 – 200 mg/m^2 folinic acid (FA) day 1, 400 mg/m^2 5-FU bolus day 1, continued infusion for 46 h of 2400 mg/m^2 5-FU and 85 mg/m^2 oxaliplatin, 14/14 day cycle; CapeOx: 1000 mg/m^2 capecitabine twice a day, days 1–14, 130 mg/m^2 oxaliplatin day 1, 21/21 day cycle; 5-FU/FA: 200 mg/m^2 FA day 1, 400 mg/m^2 5-FU bolus day 1, continued infusion for 46 h of 2400 mg/m^2 5-FU, 14/14 day mFolFOX6 or CapeOX were the preferred regimens. When the administration of oxaliplatin is not possible due to side effects of the drug or the comorbidities of the patient, one of followed regimens was used: 5-fluorouracil/folinic acid (5-FU/FA) 200 mg/m^2 folinic acid (1 h infusion prior to 5-FU) and 400 mg/m^2 5-FU per day intravenously once daily × 5 every 5 weeks or 1000 mg/m^2 capecitabine twice a day × 5 every 5 weeks.

Survival and disease recurrence definitions

Disease recurrence was evaluated according to location: locoregional (LR), systemic (DR) or mixed. All surviving patients were followed-up and their current status was confirmed. None of the patients were lost from follow-up. Disease-free survival (DFS) was calculated from the date of surgery to the date of progression (local or distant), and overall survival (OS) was calculated from the date of surgery to the date of death or last follow-up.

Statistical analysis

The HNPCC group and the SCRC group were compared in relation to age (Student's *t*-test) and in relation to sex, stage and morbidity (Chi-square test).

Overall survival and disease-free survival were estimated in the 68 patients studied and also in the two groups using the Kaplan–Meier method.

The difference in survival rates between the two groups was tested for significance using the log-rank test. Survival was compared with the log rank test.

The statistical analysis was made with SPSS statistical software (version 21.0 for Windows; SPSS Inc., Chicago, IL). All statistical tests were conducted at a two-sided level of significance of 0.05.

Ethics approval

This project was approved by the Research Ethics Health Committee. Patient informed consent for the use of clinical and genetic information was obtained.

Results

Description of study population and clinical parameters

This cohort study gathered 72 consecutive patients with CRC treated with total, subtotal colectomy or totalization of colectomy at one single University Hospital. After the exclusion of 4 patients with *p* Stage IV, 68 patients were included in the present analysis, with a median age of years 58.7 (range 30–86 years). The male to female ratio was 1.72:1. Patients were divided in two groups – HNPCC group (patients with Amsterdam criteria): 37 and SCRC group (the others): 31. The clinical parameters are summarized in Table 2.

Surgery

Total colectomy was performed in 42 (61.7%) patients; subtotal colectomy in 17 (25%) patients and totalization of colectomy in 9 (13.2) patients. In 26 (38.2%) patients the surgical approach was laparoscopic. The perioperative morbidity of the series was 23.5%, with 5 (7.3%) abdominal or pelvic abscesses, 5 (7.3%) anastomotic leaks, that included 8 (11.7) reoperations (due to five leakages and three abdominal abscesses), without re-admissions or mortality (Table 3).

Table 2 – Clinical parameters.

	Entire sample($n=68$)	HNPCC group($n=37$)	SCRC group($n=31$)	p
Age	58.7	52.3	66.5	<0.001
Male	43	25	18	0.59
Previous CRC	9	7	2	
Synchronous CRC	20	12	6	
CRC + polyps	43	21	22	
CRC location				
Right colon	31	18	13	
Transverse colon	13	5	8	
Left colon	19	11	8	
Sigmoid colon	14	6	8	
Time between diagnosis and surgery (days)	42	41	43	

Table 3 – Surgical parameters.

	Entire sample$n=68$ (%)	HNPCC group$n=37$ (%)	SCRC group$n=31$ (%)	p
Surgery				
Total/colectomy	42	23	19	
Subtotal/colectomy	17	7	10	
Totalization/of/colectomy	9	7	2	
Morbidity				
Postoperative ileus	16 (23.5%)	9 (24.3%)	7 (22.5%)	
Abdominal/infection	6	4	2	
Abscess	3	1	2	
Anastomotic leak	2	1	1	
Reintervention				0.87
With temporary stoma	5	3	2	
With abdominal/washout	3	1	2	
Readmission	0	0	0	
Posterior surgery for stoma closure	5	3	2	
Mortality	0	0	0	

p=0.87 (includes morbidity, reintervention, readmission and posterior surgery for stoma closure), not only reintervention.

Table 4 – Pathologic and genetic parameters.

	Entire sample($n=68$)	HNPCC group($n=37$)	SCRC group($n=31$)	p
Tumor grade				
G1	3	0	3	
G2	60	33	27	
G3	5	4	1	
Crohn-like reaction	10	8	2	
Mucinous tumor	15	9	6	
"Ring signet cells" presence	3	3	0	
Tumor stage				0.70
Stage I	24	12	12	
Stage II	23	12	11	
Stage III	22	13	8	
MMR gene mutation				
MLH1	1	1	0	
MSH2	8	8	0	
MSH6	3	3	0	
PMS2	0	0	0	
EPCAM mutation	2	2	0	

Pathology of resected specimens and genetic test

Stage distribution is shown in Table 4. The average number of dissected lymph nodes in the surgical specimens was 23 (range 18–55). All resected specimens were R0.

Genetic mutation was identified in 14 patients of 37 with Amsterdam criteria.

Clinical outcome

Table 5 shows long-term clinical outcome, relapse of disease and survival.

The mean of patients follow-up was 79.5 months (range 6–190).

Table 5 – Long-term results after extensive colectomy in CRC. Mean of follow-up: months 79.5 (range 6–190).

	Entire sample ($n=68$)	HNPCC group ($n=37$)	SCRC group ($n=31$)	p
Bowell movements per day	1.7	1.7	1.8	
Surgery related with total/subtotal colectomy or totalization of colectomy	5	3	2	
OS				0.001
1 year	100%	100%	100%	
2 year	100%	100%	100%	
3 year	96.3%	100%	92.6%	
5 year	89.9%	100%	79.5%	
DFS				0.013
1 year	97.0%	100%	93.4%	
2 year	97.0%	100%	93.4%	
3 year	91.4%	96.2%	86.0%	
5 year	87.2%	96.2%	77.2%	

Concerning functional results: these patients have not dietary restriction, regular medication for stool regulation, night time defecation, use of pad daytime or at night, soiling or seepage during day time or night or urgency of defecation.

Also, they have not any social handicap.

The 24 h stool frequency was 1.7.

Five of the 68 patients had other surgical procedures related with the total/subtotal colectomy or totalization of colectomy. For example, intestinal reconstruction (HNPCC-3 and SCRC-2).

For global sample 5 year OS was 89.9% and 5 year DFS was 87.2%.

When compared OS and DFS for HNPCC and SCRC groups, survival was significantly higher in HNPCC group ($p=0.001$ and $p=0.013$).

From total sample (68 patients) only nine patients (13.2%) developed distant metastases (3 hepatic metastases, 3 pulmonary metastases; 1 hepatic and pulmonary metastases and 1 hepatic and retroperitoneal lymph node metastases): 7 died and 2 were alive with pulmonary metastases.

Discussion

CCR is one of the most frequent worldwide cancers. In the case of non-metastatic colon cancer, segmental colectomy continues to be the treatment plan corner stone followed by adjuvant chemotherapy for tumor Stages III.[16] Most of CRC are sporadic cancers but circa 3% are HNPCC with a more favorable survival. So, in those cases therapy, surveillance and genetic counseling are necessarily different.

The first problem that arises is the HNPCC identification in population with CRC. We know that a large number of clinicians are still not sensitized for screening and in most centers the systematic detection of microsatellite instability in patients with colon cancer and age under 70 years is not yet implemented. In the other hand, about 15% of sporadic cancer shows microsatellite instability and there are patients with Amsterdam criteria in which microsatellite instability is negative. For that reason, in our center the policy adopted for patients with Amsterdam criteria regardless the identification or not of the genetic mutation that have the first CRC was a more extensive colectomy instead a segmental colectomy. This explains why a considerable number of patients with Amsterdam criteria and microsatellite instability negative test were submitted to a more extensive colectomy in our sample.

The second issue is related with the concept that more extensive colonic resection in the CRC and in particular in the HNPCC does provide survival advantage. Surgical management of colon cancer for patients with Lynch Syndrome who carry a mismatch repair gene mutation is controversial. Actually, current recommendations in the USA, suggest that persons with Lynch syndrome undergoing surgical resection of a colon cancer should be offered to extensive resection rather than a segmental resection, even though this policy has not previously been proven to be superior to a policy of 1–2 yearly colonoscopic surveillance.[17] Despite this recommendation, the extent of resection performed varies between centers in the USA. For example, the Cleveland Clinic performed total colectomy for 16 of 33 CRC patients from Amsterdam criteria-positive families compared with seven of 60 from clinics elsewhere in the USA.[18] In Europe, on the basis of a decision analysis study[9] and the documented high risk of a metachronous cancer, current guidelines recommend the option of extensive resection be discussed with patients, particularly those under the age of 50 years.[19] In fact, there are no controlled studies available that address the question of whether radical surgery is appropriate. Any decision on radical surgery, up to and including colectomy, would need to take into account the risk of surgery, the patient's age and sex, long-term medical prognosis, and the quality and capacity to do annual colonoscopy surveillance with preventive adenoma removal. In fact, the decision to remove more or less of the colon involves the consideration of a relatively high risk of metachronous Colorectal Cancer (CRC) with the impact of more extensive surgery quality of life.[20] The relatively high risk of metachronous CRC, i.e. primary CRC diagnosed more than 12 months after the first diagnosis of primary colon cancer, (16% after 10 years)[21] supports a more aggressive primary surgical approach involving the removal of all, or at least most, of the colon after diagnosis.[22] The functional consequence of an increase in bowel frequency and possible negative impact on quality of life might be balanced against the reduction in risk of metachronous CRC afforded by more extensive surgery, particularly if the person is aged less than 60 years at the time of surgery.[23] On the other hand, surveillance of the remaining colon and rectum will be required after most surgery and the inconvenience of yearly colonoscopy (with the requirement for standard bowel preparation rather than enema preparation) may be offset by the better functional outcome after segmental surgery. This clinical equipoise is reflected in world

surgical opinion[4,24] and our opinion is in favor of a more extensive surgery.

Based on these assumptions we analyzed first the long-term overall results of our sample and then the same sample divided into two groups: patients in two groups with Amsterdam criteria that we named HNPCC group and the other patients with CRC but without criteria of Amsterdam where the surgery was more extensive due to the presence of metachronous neoplasms or the presence of polyps that could not be endoscopically easily removed.

As the first analysis of the overall sample we can consider as good the results of patients treated with a more extensive surgery. The morbidity of the surgery was the expected, without definitive stomas and without mortality. The mean of movements bowel number per day were 1.7, without dietary restriction, need of medication for stool regulation or social handicap; there were few subsequent abdominal surgeries related to the total/subtotal colectomy; the overall survival and disease-free survival were good (5 year, OS: 89.9%; 5 year, DFS: 87.2%). So, in our series morbidity and functional quality of a more extensive surgery were acceptable without a negative burden.

In the other hand, the division of the sample into two groups allowed us to obtain two groups with differences in age as expected but without significant differences in sex, surgery, surgical complications and stage, which allows us to state that the survival and survival of the first group is significantly better than that of the second group. This is in accordance with the statement that CRC in HNPCC patients have better prognosis and probably is not fundamental to characterized patient gene mutation to adopt a more extensive surgery since patient shows Amsterdam criteria.

Finally, the third aspect the CRC treatment of HNPCC patient: patients with microsatellite-unstable tumors have a better prognosis than those with stable tumors (probably due to an immune response to tumor cells). This means that there may be less benefit from adjuvant therapy. Several retrospective studies have shown that patients with microsatellite-unstable Stage II and III colon cancer do not benefit from adjuvant 5-FU-based chemotherapy.[25] Ongoing research is investigating whether this is also true for colon cancers in HNPCC patients. This aspect was not considered in our series. All the patients with tumor Stage III were treated with adjuvant chemotherapy which does not interfere with the results presented.

The strength of our study includes long mean follow-up, data and surgery realized in a single center. There are some limitations inherent to this study: the small number of patients and a small number of patients with genetic mutation confirmation. This is a technical difficulty that we face in the last years in our center. We intend in the future revised all Formalin-Fixed Paraffin-Embedded blocks of tumor resected specimens (FFPE tissue sample) from the Pathology Department at our Hospital and repeated the microsatellite instability analysis by immunohistochemistry and by PCR. In meantime the missing know of genetic mutation status has not prevented that it may be considered a good policy to adopt a more extensive colic surgery whenever the patient presents Amsterdam criteria.

The virtue of this study is warning the need for large-scale studies to confirm the advantage of more extensive colon surgery for patients with CRC, especially for the first CRC in patients with Amsterdam criteria.

Conclusion

Total or subtotal colectomy in CRC provides a good survival. These surgical procedures should be considered the first option for colorectal cancer in young HNPCC patients. In those cases, they provide good long-term results, avoiding the risk of metachronous CRC and surveillance is restricted only to the remaining rectum.

Conflicts of interest

The authors declare no conflicts of interest.

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