ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2018 November 10; 9(7): 123-166

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

Contents

Volume 9 Number 7 November 10, 2018

ORIGINAL ARTICLE

Basic Study

Case Control Study

Retrospective Cohort Study

CASE REPORT

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Oncology*, Zhao-Hua Zhong, PhD, Professor, Department of Microbiology, Harbin Medical University, Harbin 150081, Heilongjiang Province, China

AIM AND SCOPE

World Journal of Clinical Oncology (*World J Clin Oncol*, *WJCO*, online ISSN 2218-4333, DOI: 10.5306) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

WJCO covers a variety of clinical medical topics, including etiology, epidemiology, evidence-based medicine, informatics, diagnostic imaging, endoscopy, tumor recurrence and metastasis, tumor stem cells, radiotherapy, chemotherapy, interventional radiology, palliative therapy, clinical chemotherapy, biological therapy, minimally invasive therapy, physiotherapy, psycho-oncology, comprehensive therapy, and oncology-related nursing. Priority publication will be given to articles concerning diagnosis and treatment of oncology diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

We encourage authors to submit their manuscripts to *WJCO*. We will give priority to manuscripts that are supported by major national and international foundations and those that are of great clinical significance.

INDEXING/ABSTRACTING

World Journal of Clinical Oncology (*WJCO*) is now abstracted and indexed in PubMed, PubMed Central, Scopus, and Emerging Sources Citation Index (Web of Science), China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

EDITORIAL BOARD MEMBERS
All editorial board members resources online at http://www.wjgnet.com/2218-4333/editorialboard.htm

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Journal of Clinical Oncology
Baishideng Publishing Group Inc
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7901 Stoneridge Drive,
Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
Fax: +1-925-2238243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
November 10, 2018

INSTRUCTIONS TO AUTHORS
http://www.wjgnet.com/bpg/gerinfo/204

ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Clinical Oncology

Submit a Manuscript: http://www.f6publishing.com

World J Clin Oncol 2018 November 10; 9(7): 133-139

DOI: 10.5306/wjco.v9.i7.133

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Case Control Study

Mismatch repair protein expression and intratumoral budding in rectal cancer are associated with an increased pathological complete response to preoperative chemoradiotherapy: A case-control study

Leonardo S Lino-Silva, Armando Gamboa-Domínguez, Diego Zúñiga-Tamayo, Rosa A Salcedo-Hernández, Lucely Cetina, David Cantú-de-León

Leonardo S Lino-Silva, Surgical Pathology, Instituto Nacional de Cancerología, Mexico City 14080, Mexico

Armando Gamboa-Domínguez, Diego Zúñiga-Tamayo, Surgical Pathology, Instituto Nacional de ciencias Médicas y Nutrición salvador Zubirán, Mexico City 14080, Mexico

Rosa A Salcedo-Hernández, David Cantú-de-León, Surgical Oncology, Instituto Nacional de Cancerología, Mexico City 14080, Mexico

Lucely Cetina, Medical Oncology, Instituto Nacional de Cancerología, Mexico City 14080, Mexico

ORCID number: Leonardo S Lino-Silva (0000-0002-7394-5123); Armando Gamboa-Domínguez (0000-0002-1983-0384); Diego Zúñiga-Tamayo (0000-0001-5774-8421); Rosa A Salcedo-Hernández (0000-0003-4537-8034); Lucely Cetina (0000-0003-2018-7338); David Cantú-de-León (0000-0002-6693-8347).

Author contributions: Lino-Silva LS, Gamboa-Domínguez A and Zúñiga-Tamayo D contributed equally to this work; Salcedo-Hernández RA, Cetina L and Cantú-de-León D designed research, Lino-Silva LS, Gamboa-Domínguez A, Zúñiga-Tamayo D and Salcedo-Hernández RA wrote the paper.

Institutional review board statement: This work was authorized by the institutional review board of the National Cancer Institute of Mexico with the number REV/16/87.

Informed consent statement: A waiver form informed consent was provided due the retrospective nature of the study and data were collected from clinical files and pathology database.

Conflict-of-interest statement: The authors declared no potential conflicts of interest.

STROBE Statement: This study was conducted in line with the STROBE statement.

Manuscript source: Unsolicited manuscript

Correspondence to: Leonardo S Lino-Silva, MSc, Academic Research, Doctor, Gastrointestinal Pathology Division, Instituto Nacional de Cancerología de México (Mexico's National Cancer Institute), Av. San Fernando # 22, Sección XVI, Tlalpan, Mexico City 14080, Mexico. saul.lino.sil@gmail.com
Telephone: +52-55-34265921

Received: July 6, 2018
Peer-review started: July 6, 2018
First decision: August 6, 2018
Revised: August 18, 2018
Accepted: October 24, 2018
Article in press: October 24, 2018
Published online: November 10, 2018

Abstract

AIM

To determine whether the association of rectal adenocarcinoma with a defective-mismatch repair system (dMMR) was associated with a pathological complete response (pCR) to preoperative chemoradiotherapy.

METHODS
A case-control study was designed with the aim of determining if patients with rectal adenocarcinoma with dMMR had an associated high pCR rate in response to neoadjuvant chemoradiotherapy (nCRT).

RESULTS
Seventy-two cases with pCR were compared against 144 controls without pCR. Across 216 cases, the mean age was 56.8 years, 140 (64.8%) were men, and 63 (29.2%) demonstrated the dMMR system. The pCR was associated with G1 tumors, dMMR, the absence of vascular invasion, and low tumor budding in the pretreatment biopsy. In a multivariant analysis, the factors associated with pCR were dMMR (OR: 2.61; 95%CI: 1.355-5.040, P = 0.004) and a low degree of tumor budding (OR: 2.52; 95%CI: 1.366-4.894, P = 0.025).

CONCLUSION
We found an independent association between dMMR and a low rate of tumor budding, with a higher rate of pCR, in the basal biopsies of patients with rectal carcinoma subjected to nCRT.

Key words: Rectal cancer; Chemoradiotherapy; Tumor budding; Mismatch repair; Pathological complete response

Core tip: Defective Mismatch repair (dMMR) and a low number of buds in the pretreatment biopsy were independently associated with a high rate of the pathological complete response. Tumor budding and MMR status should be considered as tools to be implemented in studies that predict the pathological response to preoperative chemo-radiotherapy in rectal cancer.

Lino-Silva LS, Gamboa-Domínguez A, Zúñiga-Tamayo D, Salcedo-Hernández RA, Cetina L, Cantú-de-León D. Mismatch repair protein expression and intratumoral budding in rectal cancer are associated with an increased pathological complete response to preoperative chemoradiotherapy: A case-control study. *World J Clin Oncol* 2018; 9(7): 133-139 Available from: URL: http://www.wjgnet.com/2218-4333/full/v9/i7/133.htm DOI: http://dx.doi.org/10.5306/wjco.v9.i7.133

INTRODUCTION

Rectal carcinoma is the third most common cancer, only after lung, breast, and prostate cancers, but it is the second leading cause of cancer-related mortality[1]. The treatment in locally advanced stages is neoadjuvant chemoradiotherapy (nCRT), with the aim of decreasing the tumor size, inducing favorable changes in staging (downstaging), increasing the probability of anal sphincter preservation, and decreasing the local recurrence rate and the possibility of a pathological complete response (pCR)[2], which is defined as the absence of neoplastic cells in both the rectal wall and lymph nodes. A pCR is reported in between 10% and 30% of these patients, and it is suggested that it is associated with a better oncologic outcome, a low local recurrence and an improved survival[3-4].

Unfortunately, the pCR is only indicated by a histopathological study of the surgical specimen, and in theory, elements that anticipate a pCR in the pretreatment biopsy would be very useful because elements, such as preoperative biopsy findings (post-nCRT), endoscopic examination, or imaging studies after completion of nCRT, are not sensitive or specific enough to predict pCR.

Identifying characteristics of the tumors that will respond completely to nCRT could help avoid the radical resection of the rectum, a procedure that reduces the quality of life of the patient. Several histopathological, immunohistochemical, and molecular markers have been analyzed, but with contradictory results[5].

The fundamental damage caused by nCRT is direct nuclear damage, and then, some studies have associated the mismatch repair system (MMR) status with pCR with inconclusive results[6]. During DNA damage, the presence of proteins, such as MSH2, MSH6, MLH1, and PMS2 (associated with the MMR), increases[7]. We hypothesized that deficient MMR (dMMR) neoplastic cells may be especially prone to death from agents that induce genetic damage, such as nCRT. Other factors that might predict this response are the immune response to the tumor and the tumor budding (individual neoplastic cells at the tumor stroma).

Our aim was to determine if rectal adenocarcinomas with a dMMR system were associated with a higher pCR rate to nCRT compared to cases that were MMR-efficient (eMMR). Second, we evaluated the association between the inflammatory tumoral response and intratumoral budding with the pCR rate.

MATERIALS AND METHODS

A case-control study was performed

Ethical statement: This work was authorized by the ethics and research committee of our institution, with a waiver of informed consent, because of its retrospective nature (Instituto Nacional de Cancerología, approval number: Rev/16/21).

Inclusion criteria: From a prospective maintained rectal cancer database from 2010 to 2016 at one large cancer center (INCan), we searched for patients with stage Ⅲ adenocarcinoma of the lower two-thirds of the rectum that received and completed nCRT and were subjected to radical rectal surgery. For each case, the

initial biopsy (pre-nCRT) was retrieved, and the MMR protein status was determined by immunohistochemistry in this tissue. For all the cases, the pathological material from the surgical specimens were available, and all the resections were systematically evaluated according to the procedure recommended by Quirke and were standardized in our institution with the entire rectal wall examination in the case of a macroscopic absence of a tumor (in other words, the totality of the rectal wall was pathologically examined)[8,9]. We excluded patients who had previously undergone chemotherapy or radiotherapy for another neoplasm.

Case definition: Individuals with rectal cancer after nCRT who do not have histological evidence of cancer in both the rectum and lymph nodes of the surgical specimen (pCR, ypT0N0M0).

Controls definition: Individuals with rectal cancer who had histological evidence of residual neoplasm after nCRT. We took two controls per case that were matched by sex and age (± 5 years).

The outcome of interest was the presence or absence of pCR. An odds ratio (OR) of 2.0, for the primary objective, was the base for the sample size calculation, considering an alpha-value of 95%, a beta-value of 80%, a known proportion of MMR of 14%[10], and a 15% loss; the calculated number of cases per group was 72.

The clinical, demographic, and histopathological data were retrieved from the selected cases and controls. The cancer staging was determined preoperatively based on the Tumor Node Metastasis (TNM) classification of the American Joint Committee on Cancer (seventh edition)[11]. The expression of the MMR proteins was evaluated separately and independently by three pathologists with experience in gastrointestinal pathology who were blinded to the clinical data. If discordance was found, a consensus was achieved in a multi-observer microscope. The expression was evaluated according to the following criteria[12]: (1) The nuclear expression of all markers in each sample, allowing for the classification of adenocarcinoma, as with an efficient MMR system (eMMR); and (2) The absence of the nuclear expression of any of the markers in each sample, allowing for the classification of adenocarcinoma, as with a dMMR.

Additionally, for the MMR evaluation, each case the inflammatory infiltrate was categorized as present (either peritumoral in the form of lymphoid aggregates, or intratumoral) or absent. The evaluation of intratumoral budding was carried out by examining 0.785 mm^2 of the peritumoral stroma of the biopsy specimen, following the guidelines described by Lugli *et al*[13]. We defined low intratumoral budding as the presence of 0 to 4 buds/0.785 mm^2, and high intratumoral budding occurred when there were ⩾ 5 buds/0.785 mm^2.

Statistical analysis

Data analysis was performed using the statistical package SPSS 22.0 (IBM, California, United States). The ORs were calculated and contrasted with the Mantel-Haenszen method, with a significance level of 0.05. For the comparison of the numerical variables, we used a *t* test to compare the means, the Mann-Whitney test for medians and the chi-square test or Fischer's exact test for categorical variables. A multivariate analysis was performed with a conditional logistic regression to determine the independent predictors of pCR, with the variables at a significance level of $P < 0.05$ in the univariate analysis as components of the regression model.

RESULTS

Population and clinical characteristics

Seventy-two cases with pCR were evaluated, and two controls were selected per case, totaling 144 controls, for a total sample of 216 cases. The mean age was 56.8 ± 12.5 years, with 192 (88.9%) cases younger than 40 years. Of the 216 cases, 140 (64.8%) were men.

All the cases were in stage Ⅲ and at the time of the presentation, 123 cases (56.9%) had a cT3 stage rectal tumor, whereas 44 (20.4%) had cT2, 31 (14.4%) had cT4a, and 18 (8.3%) were cT4b. Seventy-seven (35.6%) patients were classified as having nodal disease by radiological studies and endoscopic ultrasound.

Pathological features

Of the total tumors, 109 were histologically grade 3, corresponding to 50.5%, whereas grade 1 was presented in 57 (26.4%) cases. Regarding budding, there was a mean of 6.3 ± 5.7 buds per 0.785 mm^2 (range, 0-45). In 23 (10.6%) cases, lymphovascular invasion was identified.

For tumor-associated inflammatory infiltrate, mainly lymphocytes and plasma cells were observed; in 41 (19%) cases, nodular lymphoid aggregates were immediately adjacent to the neoplastic cells. The mean number of intratumoral lymphocytes was 1.69 ± 1.74 / mm^2 (range, 0 to 10).

Of the 216 cases, a dMMR system was demonstrated in 63 (29.2%) patients, with the main alterations in the co-absence of PMS2 and MLH1 expression (74.6%) followed by an isolated loss of MSH6 expression (25.4%) and an isolated loss of MSH2 expression (17.4%).

Univariant analysis

The basal characteristics of the patients are summarized in Table 1, which shows that the tumors with a higher pCR rate were associated with grade 1 tumors, dMMR, an increased presence of intratumoral lymphocytes, and the absence of vascular invasion in the pretreatment biopsy. Factors that were statistically associated with the presentation of pCR were dMMR, the absence of lymphovascular invasion, and low intratumoral budding

Table 1 Clinical-pathological characteristic of 216 patients with rectal carcinoma with preoperative chemo-radiotherapy, divided by type of pathological response *n* (%)

	No pathological complete response group (controls) (*n* = 144)	Pathological complete response group (cases) (*n* = 72)	*P*
Median age (yr ± SD)	56.67 ± 11.94	57.22 ± 13.65	0.759[3]
Sex			
Female	48 (33.3)	24 (33.3)	1.0[1]
Male	96 (66.7)	48 (66.7)	
Histologic grade			
G1	30 (20.8)	27 (37.5)	
G2	44 (30.6)	6 (8.3)	< 0.001[1]
G3	70 (48.6)	39 (54.2)	0.147[1]
Budding			
Low (0-4 buds)	63 (43.8)	44 (61.6)	0.016[1]
High (5 or more buds)	81 (56.2)	28 (38.4)	
Missmatch repair status			
MMR proficient	112 (77.8)	41 (56.9)	0.001[1]
MMR defective	32 (22.2)	31 (43.1)	
CDX2 expression			
Absent	8 (5.6)	7 (9.7)	0.195[1]
Present	136 (94.4)	65 (90.3)	
MLH1			
Non expressed	23 (16)	26 (36.1)	0.001[1]
Normal	121 (84)	46 (63.9)	
PMS2			
Non expressed	23 (16)	26 (36.1)	0.001[1]
Normal	121 (84)	46 (63.6)	
MSH2			
Non expressed	11 (7.6)	0	0.010[2]
Normal	133 (92.4)	72 (100)	
MSH6			
Non expressed	12 (8.3)	4 (5.6)	0.587[2]
Normal	132 (91.7)	68 (94.4)	
Lymphovascular invasion			
Absent	130 (90.3)	63 (87.5)	0.105[1]
Present	14 (9.7)	9 (12.5)	

[1]Value calculated form *Chi square* test with the first group as the reference; [2]Values calculated from *Fischer's exact* test; [3]Value calculated from a Student *t*-test. MMR: Mismatch repair system; SD: Standard deviation.

(Table 2).

Multivariate analysis

The factors associated with pCR were a dMMR status and a low degree of budding (Table 2).

DISCUSSION

We found an independent prognostic value of dMMR and intratumoral budding in pretreatment biopsies of patients with rectal adenocarcinoma treated with nCRT. The rest of the factors examined did not correlate with pCR. Our study is the first to demonstrate the independent predictive value of intratumoral budding for increased pCR in these patients.

To date, no clinical, endoscopic, pathological, radiological or molecular features have been sensitive and specific enough to predict pCR. Several studies report promising results and a few have investigated the pretreatment histopathological features. Some of the characteristics associated with pCR are early T and N stage, small tumor size, histologic low-grade and low carcinoembryonic antigen serum levels[14,15]. However, these results are controversial[16].

We found that a dMMR status was associated with pCR. This is explained by the fact that the ability of a cell to survive is affected by defects in DNA repair against damage. These mechanisms in the rectal cancer response have been poorly studied because of the consensus that in colon cancer a dMMR is associated with poor response to fluoropyrimidine[17]. In the setting of concomitant radiation, the impact of fluoropyrimidine given to dMMR tumors is controversial, and the predictive and prognostic roles of MMR genes in colorectal cancer are still unclear[18]. Huh *et al*[19] evaluated MMR protein expression in 209 patients with locally advanced rectal cancers treated with nCRT and subsequent surgery, where a pCR of 14.4% was observed. They did not observe any differences in the MMR protein expressions between patients with pCR and patients without pCR. In another study, de Rosa *et al*[6], studied 62 dMMR colorectal cancers and identified 29 with stage Ⅱ-Ⅲ cancers who received nCRT and surgical resection and found that 8 (27.6%) had a pCR; this pCR was elevated compared to a rate of 18% reported by Brouquet *et al*[20]. As is clear, there is some evidence pointing out the possible value

Table 2 Analysis of 216 patients with rectal carcinoma with preoperative chemo-radiotherapy, regarding their association with presence of complete pathological response

	Univariate analysis			Multivariate analysis[1]		
	OR	*P*	95%CI	OR	*P*	95%CI
MMR status (defective *vs* proficient)	2.64	0.002	1.438-4.870	2.61	0.004	1.355-5.040
Lymphovascular invasion (present *vs* absent)	0.7	0.094	0.066-2.860			
Histologic Grade (G1-G2 *vs* G3)	1.24	0.442	0.709-2.203			
Tumor budding [Low budding (0-4 buds) *vs* High budding (5 or more buds)]	2.495	0.017	1.278-4.881	2.52	0.025	1.366-4.894
Inflammatory infiltrate (present *vs* absent)	1.194	0.624	0.587-2.429			

[1]Adjusted by MMR status and high tumor budding. OR: Odds ratio; CI: Confidence interval; MMR: Mismatch repair system.

of MMR proteins in the prediction of pCR. We found an increase in the pCR in patients with the dMMR system.

We found that 29% of our cases showed dMMR, which was a higher number than most reported studies. However, this high dMMR prevalence was according to the dMMR prevalence in Latin American studies[10,21].

Tumor budding is observed in approximately 40% of colorectal cancer cases, and several publications have informed the prognostic value of tumor budding in stage Ⅱ[22,23]. However, it has not been studied in patients prone to receive nCRT, and its predictive value for pCR has not been studied. Tumor budding has been studied in both biopsies and surgical specimens, and there is a lot of controversy about where and how to measure tumor buds[13]. In our study, we reported the number of buds in the intratumoral stroma of the biopsies and dichotomized the tumor budding into two grades. The consensus recommends the evaluation in the invasive front of the surgical specimens, which clearly demonstrates its prognostic significance, even when evaluated in biopsy specimens[24].

It is believed that tumor budding represents the first step in cancer metastasis and is considered a histological representation of the epithelial-mesenchymal transition (EMT). This hypothesis has not been validated thus far, and the mechanisms by which the bud cells separate from the main tumor are unclear. Individual cells at the stroma are thought to migrate through the extracellular matrix, invade lymphovascular structures, and form colonies of metastatic tumors in the lymph nodes and distant sites[24]. Additionally, tumor cells that undergo EMT are characterized by a gene expression switch from genes associated with epithelial differentiation to genes associated with mesenchymal properties[25]. We think that these events give neoplastic cells an intrinsic capacity to resist nCRT. Although the underlying mechanisms are not clear, this is a future line of investigation.

The last outcome evaluated by our study was the inflammatory infiltrate, which did not demonstrate an association with pCR. This parameter was very difficult to evaluate because of the complexity of the cellular response at tumor invasion. More complex studies specifically aimed to explore this response are needed.

The main limitation of our study was the unexplored reproducibility of the intratumoral budding in the literature in general, especially in the biopsy specimens. MMR protein evaluation is also a potential source of bias because, sometimes, the heterogeneous immunohistochemical reaction of the proteins is difficult to interpret. However, the standardized technique in our center (with external validation at UK-NEQAS), the consensus evaluation of the reaction, and the evaluation in whole tissue slides decreased this bias.

In conclusion, the response of rectal cancer to nCRT is a variable and very complex phenomenon. There is no individual molecular or genetic mechanism clearly associated with pCR. The key action that may help to predict pCR is a model that involves the combination of data from imaging, endoscopy, immunohistochemistry, gene expression, and histopathological data (such as intratumoral budding and dMMR).

ARTICLE HIGHLIGHTS

Research background

Several histopathological, immunohistochemical, and molecular markers have been analyzed in rectal carcinoma in an attempt to predict the pathological complete response (pCR) to neoadjuvant chemoradiotherapy (nCRT) with contradictory results.

Research motivation

Identifying characteristics of tumors that will respond to nCRT could help avoid surgery.

Research objectives

To determine whether the association of rectal adenocarcinoma with a defective-Mismatch repair system (dMMR) are associated with the rate of pCR. To identify histologic features in the diagnostic biopsy associated with the rate of pCR.

Research methods

A case-control study design paired 2:1 was performed.

Research results

The pCR was associated with well-differentiated tumors, dMMR, the absence of vascular invasion, and low tumor budding in the diagnostic biopsy. In the multivariant analysis, the factors independently associated with the pCR were dMMR and a low degree of tumor budding.

Research conclusions

Tumors with pCR were associated with the dMMR status and low tumor

budding in the diagnostic biopsy.

Research perspectives

Adding the status of both MMR and tumor budding to the current and future prognostic indexes could help predict the pCR of a rectal adenocarcinoma and evaluate alternative strategies for the care of these patients.

REFERENCES

1 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]

2 **Janjan NA**, Khoo VS, Abbruzzese J, Pazdur R, Dubrow R, Cleary KR, Allen PK, Lynch PM, Glober G, Wolff R, Rich TA, Skibber J. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer: the M. D. Anderson Cancer Center experience. *Int J Radiat Oncol Biol Phys* 1999; **44**: 1027-1038 [PMID: 10421535 DOI: 10.1016/S0360-3016(99)00099-1]

3 **Yeo SG**, Kim DY, Kim TH, Chang HJ, Oh JH, Park W, Choi DH, Nam H, Kim JS, Cho MJ, Kim JH, Park JH, Kang MK, Koom WS, Kim JS, Nam TK, Chie EK, Kim JS, Lee KJ. Pathologic complete response of primary tumor following preoperative chemoradiotherapy for locally advanced rectal cancer: long-term outcomes and prognostic significance of pathologic nodal status (KROG 09-01). *Ann Surg* 2010; **252**: 998-1004 [PMID: 21107110 DOI: 10.1097/SLA.0b013e3181f3f1b1]

4 **García-Aguilar J**, Hernandez de Anda E, Sirivongs P, Lee SH, Madoff RD, Rothenberger DA. A pathologic complete response to preoperative chemoradiation is associated with lower local recurrence and improved survival in rectal cancer patients treated by mesorectal excision. *Dis Colon Rectum* 2003; **46**: 298-304 [PMID: 12626903 DOI: 10.1007/s10350-004-6545-x]

5 **Kim NK**, Hur H. New Perspectives on Predictive Biomarkers of Tumor Response and Their Clinical Application in Preoperative Chemoradiation Therapy for Rectal Cancer. *Yonsei Med J* 2015; **56**: 1461-1477 [PMID: 26446626 DOI: 10.3349/ymj.2015.56.6.1461]

6 **de Rosa N**, Rodriguez-Bigas MA, Chang GJ, Veerapong J, Borras E, Krishnan S, Bednarski B, Messick CA, Skibber JM, Feig BW, Lynch PM, Vilar E, You YN. DNA Mismatch Repair Deficiency in Rectal Cancer: Benchmarking Its Impact on Prognosis, Neoadjuvant Response Prediction, and Clinical Cancer Genetics. *J Clin Oncol* 2016; **34**: 3039-3046 [PMID: 27432916 DOI: 10.1200/JCO.2016.66.6826]

7 **Lynch HT**, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. *Clin Genet* 2009; **76**: 1-18 [PMID: 19659756 DOI: 10.1111/j.1399-0004.2009.01230.x]

8 **Quirke P**, Steele R, Monson J, Grieve R, Khanna S, Couture J, O'Callaghan C, Myint AS, Bessell E, Thompson LC, Parmar M, Stephens RJ, Sebag-Montefiore D; MRC CR07/NCIC-CTG CO16 Trial Investigators; NCRI Colorectal Cancer Study Group. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet* 2009; **373**: 821-828 [PMID: 19269520 DOI: 10.1016/S0140-6736(09)60485-2]

9 **Lino-Silva LS**, García-Gómez MA, Aguilar-Romero JM, Domínguez-Rodríguez JA, Salcedo-Hernández RA, Loaeza-Belmont R, Ruiz-García EB, Herrera-Gómez Á. Mesorectal pathologic assessment in two grades predicts accurately recurrence, positive circumferential margin, and correlates with survival. *J Surg Oncol* 2015; **112**: 900-906 [PMID: 26487289 DOI: 10.1002/jso.24076]

10 **Gupta S**, Ashfaq R, Kapur P, Afonso BB, Nguyen TP, Ansari F, Boland CR, Goel A, Rockey DC. Microsatellite instability among individuals of Hispanic origin with colorectal cancer. *Cancer* 2010; **116**: 4965-4972 [PMID: 20665498 DOI: 10.1002/cncr.25486]

11 **Edge SB,** Byrd DR, Compton CC. American Joint Committee on Cancer (AJCC) Cancer Staging Manual. 7th ed. Chicago IL: Springer, Inc: 2010, 123-129

12 **Nowak JA**, Hornick JL. Molecular Evaluation of Colorectal Adenocarcinoma: Current Practice and Emerging Concepts. *Surg Pathol Clin* 2016; **9**: 427-439 [PMID: 27523970 DOI: 10.1016/j.path.2016.04.007]

13 **Lugli A**, Kirsch R, Ajioka Y, Bosman F, Cathomas G, Dawson H, El Zimaity H, Fléjou JF, Hansen TP, Hartmann A, Kakar S, Langner C, Nagtegaal I, Puppa G, Riddell R, Ristimäki A, Sheahan K, Smyrk T, Sugihara K, Terris B, Ueno H, Vieth M, Zlobec I, Quirke P. Recommendations for reporting tumor budding in colorectal cancer based on the International Tumor Budding Consensus Conference (ITBCC) 2016. *Mod Pathol* 2017; **30**: 1299-1311 [PMID: 28548122 DOI: 10.1038/modpathol.2017.46]

14 **Garland ML**, Vather R, Bunkley N, Pearse M, Bissett IP. Clinical tumour size and nodal status predict pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer. *Int J Colorectal Dis* 2014; **29**: 301-307 [PMID: 24420737 DOI: 10.1007/s00384-013-1821-7]

15 **Qiu HZ**, Wu B, Xiao Y, Lin GL. Combination of differentiation and T stage can predict unresponsiveness to neoadjuvant therapy for rectal cancer. *Colorectal Dis* 2011; **13**: 1353-1360 [PMID: 21689282 DOI: 10.1111/j.1463-1318.2011.02570.x]

16 **Kalady MF**, de Campos-Lobato LF, Stocchi L, Geisler DP, Dietz D, Lavery IC, Fazio VW. Predictive factors of pathologic complete response after neoadjuvant chemoradiation for rectal cancer. *Ann Surg* 2009; **250**: 582-589 [PMID: 19710605 DOI: 10.1097/SLA.0b013e3181b91e63]

17 **Ribic CM**, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM, Hamilton SR, Laurent-Puig P, Gryfe R, Shepherd LE, Tu D, Redston M, Gallinger S. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003; **349**: 247-257 [PMID: 12867608 DOI: 10.1056/NEJMoa022289]

18 **Yoon YS**, Yu CS, Kim TW, Kim JH, Jang SJ, Cho DH, Roh SA, Kim JC. Mismatch repair status in sporadic colorectal cancer: immunohistochemistry and microsatellite instability analyses. *J Gastroenterol Hepatol* 2011; **26**: 1733-1739 [PMID: 21615788 DOI: 10.1111/j.1440-1746.2011.06784.x]

19 **Huh JW**, Kim HC, Kim SH, Park YA, Cho YB, Yun SH, Lee WY, Park HC, Choi DH, Park JO, Park YS, Chun HK. Mismatch Repair Gene Expression as a Predictor of Tumor Responses in Patients With Rectal Cancer Treated With Preoperative Chemoradiation. *Medicine (Baltimore)* 2016; **95**: e2582 [PMID: 26817916 DOI: 10.1097/MD.0000000000002582]

20 **Brouquet A**, Mortenson MM, Vauthey JN, Rodriguez-Bigas MA, Overman MJ, Chang GJ, Kopetz S, Garrett C, Curley SA, Abdalla EK. Surgical strategies for synchronous colorectal liver metastases in 156 consecutive patients: classic, combined or reverse strategy? *J Am Coll Surg* 2010; **210**: 934-941 [PMID: 20510802 DOI: 10.1016/j.jamcollsurg.2010.02.039]

21 **Egoavil CM**, Montenegro P, Soto JL, Casanova L, Sanchez-Lihon J, Castillejo MI, Martinez-Canto A, Perez-Carbonell L, Castillejo A, Guarinos C, Barbera VM, Jover R, Paya A, Alenda C. Clinically important molecular features of Peruvian colorectal tumours: high prevalence of DNA mismatch repair deficiency and low incidence of KRAS mutations. *Pathology* 2011; **43**: 228-233 [PMID: 21436632 DOI: 10.1097/PAT.0b013e3283437613]

22 **Betge J**, Kornprat P, Pollheimer MJ, Lindtner RA, Schlemmer A, Rehak P, Vieth M, Langner C. Tumor budding is an independent predictor of outcome in AJCC/UICC stage II colorectal cancer. *Ann Surg Oncol* 2012; **19**: 3706-3712 [PMID: 22669453 DOI: 10.1245/s10434-012-2426-z]

23 **Okuyama T**, Oya M, Ishikawa H. Budding as a risk factor for lymph node metastasis in pT1 or pT2 well-differentiated colorectal adenocarcinoma. *Dis Colon Rectum* 2002; **45**: 628-634 [PMID: 12004212 DOI: 10.1007/s10350-004-6259-0]

24 **Lugli A**, Karamitopoulou E, Zlobec I. Tumour budding: a promising parameter in colorectal cancer. *Br J Cancer* 2012; **106**:

1713-1717 [PMID: 22531633 DOI: 10.1038/bjc.2012.127]
25 **Bhangu A**, Wood G, Mirnezami A, Darzi A, Tekkis P, Goldin R. Epithelial mesenchymal transition in colorectal cancer: Seminal role in promoting disease progression and resistance to neoadjuvant therapy. *Surg Oncol* 2012; **21**: 316-323 [PMID: 22981546 DOI: 10.1016/j.suronc.2012.08.003]

P- Reviewer: Arias F **S- Editor**: Dou Y **L- Editor**: A
E- Editor: Bian YN

Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com