Original Article

Differential effect of tumor budding on the benefit of adjuvant chemotherapy in stage II colorectal cancer: a retrospective observational study

Xin Ran[1], Yan Chen[2], Chengxiang Liu[1], He Xiao[1], Xiaona Su[1], Zhuo Chen[1], Jia Du[1], Juan He[1], Peng Zhong[2], Mengxia Li[1], Nan Dai[1], Chuan Chen[1]

[1]Department of Cancer Center, Daping Hospital, Army Medical University, Chongqing, China; [2]Department of Pathology, Daping Hospital, Army Medical University, Chongqing, China

Contributions: (I) Conception and design: C Chen, N Dai; (II) Administrative support: C Chen, N Dai; (III) Provision of study materials or patients: X Su, Z Chen, J Du, J He, M Li; (IV) Collection and assembly of data: Y Chen, C Liu, P Zhong; (V) Data analysis and interpretation: H Xiao, X Ran; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Chuan Chen, PhD; Nan Dai, PhD. Department of Cancer Center, Daping Hospital, Army Medical University, 10 Changjiang Zhilu, Yuzhong District, Chongqing 400042, China. Email: sinkriver2012@tmmu.edu.cn; dn400042@tmmu.edu.cn.

Background: Tumor budding (TB) has been shown to be a poor prognostic indicator after colorectal cancer (CRC) surgery. The aim of the present study is to evaluate the predictive role of morphological features (e.g., the number, structure, and location of tumor buds, and their reaction with the extracellular mesenchyme) in postoperative adjuvant chemotherapy in surgically resectable stage II CRC.

Methods: Between 2016 and 2019, 336 patients with stage II CRC who underwent radical surgery were enrolled in this study. TB status was determined according to the criteria adopted at the 2016 International Tumor Budding Consensus Conference (ITBCC). We retrospectively recorded all the clinical and pathological data and assessed the effect of different types of TB status on patients' recurrence-free survival (RFS) and overall survival (OS).

Results: Of the 336 patients, 173, 88, and 75 were budding grade 1 (BD1), BD2, and BD3, respectively. The 5-year RFS rates were 84.6%, 81.2%, and 68.0% (P=0.01), and the 5-year OS rates were 91.0%, 83.3%, and 76.2% (P=0.007) in BD1, BD2, and BD3, respectively. TB grade was strongly associated with vascular invasion status and mucinous adenocarcinoma, and BD3 was detected in 51.7% of patients with positive vascular invasion. The multivariate analysis showed that only age, perineural invasion, and TB grade [BD2 *vs.* BD1, hazard ratio (HR) =1.468, 95% confidence interval (CI): 0.703–3.063, P=0.30; BD3 *vs.* BD1, HR =2.310, 95% CI: 1.154–4.625, P=0.01] had an independent effect on RFS. In addition, the Kaplan-Meier curve analysis showed that BD3 patients had the worst RFS (P=0.01). The OS of the adjuvant chemotherapy group was significantly improved compared to that of the surgery-only group in the BD1/2 patients (HR =0.278, 95% CI: 0.114–0.676, P=0.005) but not in the BD3 patients with significant interaction ($P_{interaction}$=0.03).

Conclusions: Our results indicate that TB could play a subsidiary role in selecting stage II CRC patients who could achieve a favorable prognosis with chemotherapy.

Keywords: Colorectal cancer (CRC); tumor budding (TB); adjuvant chemotherapy

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Introduction

One-third of patients with colorectal cancer (CRC) undergoing radical resection have stage II disease (1). Adjuvant therapy is commonly administered to selected stage II patients with clinical "high-risk" factors, including pT4 staging, poor differentiation, lymphovascular/perineural invasion, obstruction/perforation, and positive/insufficient lymph node margins (2,3); however, controversy remains as to which high-risk subset of stage II CRC patients could benefit from adjuvant therapy (4). Notably, the effective indicators used to predict who could benefit from postoperative adjuvant chemotherapy require further clarification. Thus, more studies need to be conducted to elucidate the role of adjuvant chemotherapy in stage II CRC patients. Further, controversy remains as to which patients need chemotherapy, and whether optimal postoperative adjuvant treatment decision factors can guide risk-stratified treatment strategies that seek to mitigate chemotherapy toxicity (5,6).

In recent years, molecular biomarkers (e.g., microsatellite instability status) that can predict prognosis or treatment responses in CRC patients have been intensively explored. However, very few studies have sought to identify pathological markers in early-stage CRC. A considerable number of studies have reported that tumor budding (TB) significantly shortens disease-free survival (DFS) in stage II CRC patients, and is thus clinically valuable in identifying high-risk stage II CRC patients (7-9). TB is emerging as an important prognostic factor for early-stage CRC patients, and in April 2016, the International Tumor Budding Consensus Conference (ITBCC) reached a consensus, establishing an international, evidence-based, standardized scoring system for CRC TB (8). Moreover, in 2017, the Union for International Cancer Control (UICC) published the tumor-node-metastasis (TNM) classification of malignant tumors (8th edition), in which TB was listed as a potential prognostic factor for tumors (9). In the current 5th edition of the World Health Organization's classification of tumors, TB is listed as a necessary and ideal diagnostic criterion for CRC. This consensus has laid a solid foundation for further exploring whether TB could be used as a predictive factor to select CRC patients who could benefit from appropriate adjuvant chemotherapy. However, most previous studies have only evaluated the prognostic impact of TB in retrospective studies. Currently, there is a lack of strong evidence as to whether the TB grading determined by the recommendation proposed at the 2016 ITBCC can be used to predict the benefit of postoperative adjuvant chemotherapy in stage II CRC patients (10,11).

This retrospective study mainly sought to elucidate the importance of TB grading based on the ITBCC criteria in predicting the efficacy of adjuvant chemotherapy with oxaliplatin and 5-fluorouracil (5-FU) in stage II microsatellite stable (MSS) CRC patients. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-278/rc).

Highlight box

Key findings

- The stage II colorectal cancer (CRC) patients with budding grade 1 or budding grade 2 (BD1 or BD2) evaluated according to the 2016 International Tumor Budding Consensus Conference guideline may benefit from adjuvant chemotherapy in terms of overall survival (OS).

What is known and what is new?

- Many researches have just reported that tumor budding is a strong independent prognostic factor for stage II CRC.
- Our study reveals that, in stage II CRC patients, the benefit from adjuvant chemotherapy with regard to OS was only observed in the BD1/2 subgroup but not in the BD3 patients compared to that of the surgery alone, which had a significant interaction effect.

What is the implication, and what should change now?

- Tumor budding should be considered as an important factor in selecting stage II CRC patients who could benefit from adjuvant chemotherapy.
- Prospective clinical trials based on tumor budding grades need to be conducted in the future to rigorously verify the predictive significance of this pathological marker for adjuvant chemotherapy in stage II CRC.

Methods

Patients

A total of 336 patients with stage II CRC (according to the 8th edition of the American Joint Committee on Cancer/UICC TNM system classification), who underwent radical surgery at the Third Affiliated Hospital of the Army Medical University between January 2016 and December 2019, were included in this retrospective study. To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) had a pathologically confirmed diagnosis of stage II CRC; (II) had no distant metastases; and (III) had complete clinicopathological data

and follow-up information available. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had undergone preoperative radiotherapy for multiple cancers; (II) had failed to complete adjuvant chemotherapy; and/or (III) had MLH1 or MSH2 immunoexpression deficiency. Patients with polyposis syndrome or inflammatory bowel disease were also excluded from the study.

Of the patients enrolled in the study, 212 were male, and 90 were aged >70 years. Clinicopathological data and surgical factors were collected for all patients, including age, sex, tumor size (<5 or ≥5 cm), tumor location (proximal, cecum to transverse colon; distal, descending colon to rectum), number of lymph nodes harvested, serum tumor markers, pathological T stage, pathological N stage, histological type, degree of differentiation, lymphatic invasion; vascular invasion, perforation obstruction, and TB status (number, structure, location, and extra mesenchymal reaction). Data on recurrence-free survival (RFS), overall survival (OS), and the incidence and severity of adverse events were also collected. RFS was defined as the interval between the date of the surgery and the date of first occurrence of relapse at any anatomic location or the date of death or last follow-up. OS was defined as the time from enrollment to the date of death or last follow-up.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Chinese ethical guidelines. The study was approved by the ethics committee of the Third Affiliated Hospital of Army Medical University (No. 317, 2023), and all patients signed an informed consent form.

TB assessment

Two pathologists scanned and observed tissue specimens from the largest section of the entire tumor, including the entire infiltrating margin. TB was analyzed in an independent state by counting the individual cancer cells at the invasive front or clusters of ≤4 cancer cells, irrespective of histological type. Hematoxylin and eosin (H&E)-stained tumor tissue sections were evaluated at medium power (×10 objective) to locate "hotspots" (the densest field of the TB in a single high-magnification field of view) at the front of tumor the invasion area. The number of tumor buds were read in a ×20 objective (0.785 mm^2) microscopic field of view, and TB with fewer than <5, 5–9, and ≥10 foci were classified as budding grade 1 (BD1), BD2, and BD3, respectively, as per the assessment criteria recommended in the international standards from the 2016 ITBCC (11). As BD1/2 had low heterogeneity and a high degree of consolidation, the TB grade for each patient were categorized into high budding (≥10) or low budding (<10) group. Cytokeratin staining was not used to identify hot spots or to count the number of buds. In our study, observer agreement on the interpretation of the "budding" parameter was crucial, and disagreement on the assessment of TB was observed in less than 10% of cases; any disputed cases were processed under a multi-camera microscope, and a consensus was reached at further review.

Adjuvant chemotherapy

Oxaliplatin and fluoropyrimidine should be candidates for adjuvant therapy in stage II tumors with high-risk factors (T4 or bowel obstruction, perforation, poorly differentiated tumors, or <10 examined lymph nodes). After the exclusion of ineligible patients, a total number of 336 patients were finally retained for the subsequent analysis. The treatment categories were divided into the following two groups: the surgery alone group and the adjuvant chemotherapy group. One hundred and forty-eight patients (148/336, 44.0%) received the adjuvant chemotherapy based on the combination of oxaliplatin and 5-FU. The following chemotherapy regimens was used: XELOX (n=27), mFOLFOX6 (n=63), capeOX (n=50), oral capecitabine alone (n=6), and FOLFIRI (n=2). Adjuvant therapy was commenced within 8 weeks of surgery, and chemotherapeutic agents were administered for 6 months; all patients in the chemotherapy group completed the dosing schedule of oxaliplatin and 5-FU combination adjuvant chemotherapy regimen (12-14).

Postoperative follow-up

All the patients underwent regular clinical examinations on an outpatient basis (every 2–4 months), and disease recurrence was assessed at each visit on the basis of physical examination findings, serum carcinoembryonic antigen level testing, barium enema angiography or colonoscopy, ultrasonography, and computed tomography scanning.

Statistical analysis

For the categorical variables, the χ^2 test or Fisher's exact probability test were used for comparisons between the subgroups with and without adjuvant chemotherapy. The

Kruskal-Wallis test was used to evaluate differences in the BD1–3 proportions among the various clinical subgroups, for which BD1–3 were considered an ordinal variable. Univariate and multivariate Cox regression was used to determine the prognostic factors for RFS and OS. To determine the predictive effect of TB grade in relation to the benefit of adjuvant chemotherapy, Cox regression analyses were performed for RFS and OS to examine the interaction between adjuvant chemotherapy and TB grades. The interaction analysis results were visualized in forest plots. Kaplan-Meier curves and log-rank tests were used to compare the differences in RFS and OS among the various subgroups. The Bonferroni method was used for the correction of multiple comparisons. All reported P values were two-sided. All the analyses were performed using R v4.2.3.

Results

Patient characteristics

A total of 470 patients with pathologically confirmed stage II CRC were preliminarily included in the study. After excluding ineligible patients for various reasons, a total of 336 patients were finally included in the analysis. Figure S1 provides a flowchart diagram to illustrate the process excluding ineligible patients in each step. The clinical information of the patients included in the final analysis is summarized in *Table 1*. This study included 278 patients with colon tumors and 58 patients with rectal tumors. The clinical stages at the baseline showed that more than half of patients were cT1–T3 (210 of 336, 62.5%) and only 4.2% of the patients (14 of 336) exhibited poor differentiation. Of the patients, 29 and 72 presented with positive vascular invasion and perineural invasion, respectively. The median follow-up time was 57.27 months (range, 1.45–91.30 months). During the follow-up, recurrence events were observed in 69 patients, and 50 patients succumbed to the disease. In this cohort, 148 patients underwent adjuvant chemotherapy. Most of the baseline characteristics of the adjuvant and non-adjuvant chemotherapy groups were comparable, except for perineural invasion, tumor location, and age (Table S1).

Pathological characteristics of TB

TB was counted in the hotspot area defined in the methods at a ×20 objective. The final TB status for each patient was divided into the following four categories: no TB, 0; low TB, 1–4; moderate TB, 5–9; and high TB, ≥10 (*Figure 1A-1D*). Based on the H&E evaluation, 173, 88, and 75 patients were assigned to the BD1, BD2, and BD3 categories, respectively. The Kruskal-Wallis test revealed that TB grade was strongly and significantly associated with vascular invasion status and mucinous adenocarcinoma (*Table 1*). For example, 51.7% of the patients with positive vascular invasion had BD3, while only 19.5% of the patients with negative vascular invasion had BD3. Additionally, the TB grades were also weakly, but significantly, associated with age and morphological type (*Table 1*). These results demonstrated that high TB may indicate more aggressive disease.

TB as an independent prognostic factor

The median follow-up time was 57.27 months (range, 1.45–91.30 months). The 3- and 5-year RFS rates were 87.46% [95% confidence interval (CI): 83.98–91.08%] and 79.90% (95% CI: 75.56–84.49%), and the 3- and 5-year OS rates were 92.23% (95% CI: 89.41–95.14%) and 85.62% (95% CI: 81.77–89.65%). In the whole population, there was no significant difference in the RFS rate between the oxaliplatin and 5-FU combination adjuvant chemotherapy group and the surgery-only group (78.9% *vs.* 80.7%, log-rank P=0.87). The univariate Cox regression showed that age, perineural invasion, intestinal obstruction, perforation, serum carcinoembryonic antigen before surgery, and TB grading were significantly associated with RFS (Table S2). However, after adjusting for other clinical factors, the multivariate Cox regression results showed that only age [≥70 *vs.* <70 years, hazard ratio (HR) =4.501, 95% CI: 2.205–9.189, P<0.001], perineural invasion (yes *vs.* no, HR =2.612, 95% CI: 1.397–4.882, P=0.003), and TB grading (BD2 *vs.* BD1, HR =1.468, 95% CI: 0.703–3.063, P=0.30; BD3 *vs.* BD1, HR =2.310, 95% CI: 1.154–4.625, P=0.01) remained significant. Moreover, the Kaplan-Meier curve analysis showed that BD3 patients had the worst RFS (*Figure 2A*). The stepwise comparisons demonstrated that BD3 patients had significantly shorter RFS than BD1 patients (P=0.01) but not BD2 patients (P=0.12), and the difference between the BD1 and BD2 patients was not significant (P=0.35). These results held true for OS (*Figure 2B*). The stepwise comparisons also demonstrated that only BD3 patients had significantly shortened OS than BD1 patients (P=0.006). The 3- and 5-year RFS and OS rates of the various clinical subgroups are set out in Tables S3,S4.

Table 1 Patient characteristics and proportions of TB grades in each subgroup

Clinical factors	Number of patients	BD1	BD2	BD3	Chi-squared	P value
Gender					0.056	0.81
Female	124	0.500	0.282	0.218		
Male	212	0.524	0.250	0.226		
Age (years)					4.086	0.04
≥70	90	0.411	0.333	0.256		
<70	246	0.553	0.236	0.211		
Tumor size (cm)					3.471	0.06
<5	205	0.463	0.307	0.229		
≥5	131	0.595	0.191	0.214		
Location					5.320	0.07
Distal colon	157	0.586	0.223	0.191		
Proximal colon	121	0.471	0.240	0.289		
Rectum	58	0.414	0.414	0.172		
T4					3.275	0.07
No	210	0.552	0.248	0.200		
Yes	126	0.452	0.286	0.262		
Morphological type					6.256	0.04
Lump	38	0.500	0.289	0.211		
Raised	54	0.667	0.204	0.130		
Ulcerative	244	0.484	0.270	0.246		
Differentiation					0.441	0.80
Middle	302	0.510	0.272	0.219		
Poor	14	0.571	0.000	0.429		
Well	20	0.550	0.300	0.150		
Vascular invasion					12.263	<0.001
No	307	0.537	0.267	0.195		
Yes	29	0.276	0.207	0.517		
Perineural invasion					2.539	0.11
No	264	0.534	0.261	0.205		
Yes	72	0.444	0.264	0.292		
Mucinous adenocarcinoma					6.454	0.01
No	320	0.497	0.275	0.228		
Yes	16	0.875	0.000	0.125		
Intestinal obstruction					1.658	0.19
No	236	0.487	0.284	0.229		
Yes	100	0.580	0.210	0.210		

Table 1 *(continued)*

Table 1 *(continued)*

Clinical factors	Number of patients	BD1	BD2	BD3	Chi-squared	P value
Perforation					0.496	0.48
No	324	0.515	0.269	0.216		
Yes	12	0.500	0.083	0.417		
Adjuvant chemotherapy					0.029	0.86
No	188	0.511	0.282	0.207		
Yes	148	0.520	0.236	0.243		
CEA (ng/mL)					0.179	0.67
>5	107	0.533	0.252	0.215		
≤5	229	0.507	0.266	0.227		
CA199 (U/mL)					1.451	0.22
>37	43	0.419	0.326	0.256		
≤37	293	0.529	0.253	0.218		
TB construction					3.472	0.06
Cluster	255	0.439	0.286	0.275		
Single-cell	27	0.593	0.296	0.111		
TB location					4.111	0.25
Muscularis propria	94	0.511	0.298	0.191		
Peritoneum	7	0.429	0.286	0.286		
Submucosa	38	0.474	0.316	0.211		
Subserosa	143	0.413	0.273	0.315		
TB stromal reaction					0.833	0.65
Fibrotic	86	0.477	0.221	0.302		
Inflammatory	166	0.434	0.313	0.253		
Myxoid	30	0.500	0.333	0.167		

TB, tumor budding; BD, budding grade; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199.

TB as a potential predictive factor

To elucidate the effect of TB on the benefit of adjuvant chemotherapy, a subgroup analysis was first performed of each BD category. As *Figure 3A-3D* show, in terms of RFS, no obvious beneficial effect was observed across the individual BD categories, and the combination subgroup comprising BD1 and BD2. Conversely, patients who underwent adjuvant chemotherapy were compared to those who did not undergo adjuvant chemotherapy, and a significantly decreased risk of death was observed in the BD1 subgroup (HR =0.265, 95% CI: 0.075–0.932, P=0.03), and a borderline significant decreased risk of death was observed in the BD2 subgroup (HR =0.337, 95% CI: 0.096–1.185, P=0.09). However, no such beneficial effect was observed in the BD3 subgroup (HR =1.109, 95% CI: 0.439–2.799, P=0.82) (*Figure 3E-3G*). The longer OS related to the administration of adjuvant chemotherapy was more pronounced in the combination BD1 and BD2 subgroup due to the larger sample size (HR =0.278, 95% CI: 0.114–0.676, P=0.005) (*Figure 3H*). Moreover, adjuvant chemotherapy was an independent prognostic factor (HR =0.302, 95% CI: 0.119–0.765, P=0.01) for OS after adjusted for other clinical factors excluding age (Table S5). However, adjuvant chemotherapy was not an independent prognostic factor for OS in the multivariate

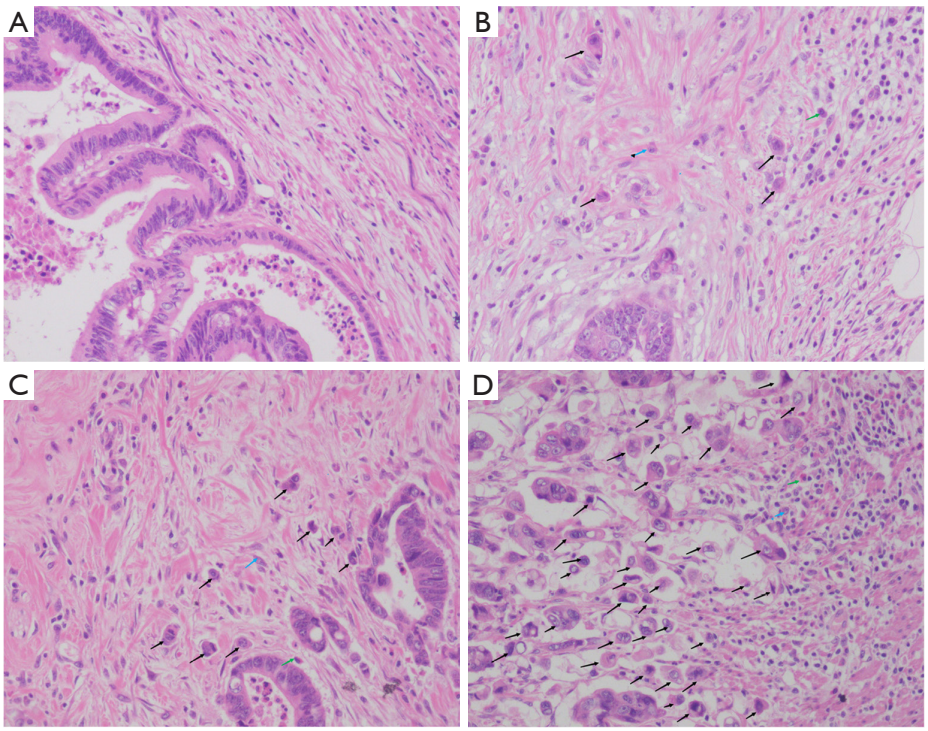

Figure 1 Representative images of TB: (A) no TB: 0 tumor buds; (B) low TB: 1–4 tumor buds; (C) moderate TB: 5–9 tumor buds; and (D) high TB: ≥10 tumor buds. The black arrows indicate tumor buds at the invasive lesion, the green arrows indicate the inflammatory cells and the blue arrows indicate the stromal cells (H&E staining, ×20 objective lens). TB, tumor budding; H&E, hematoxylin and eosin.

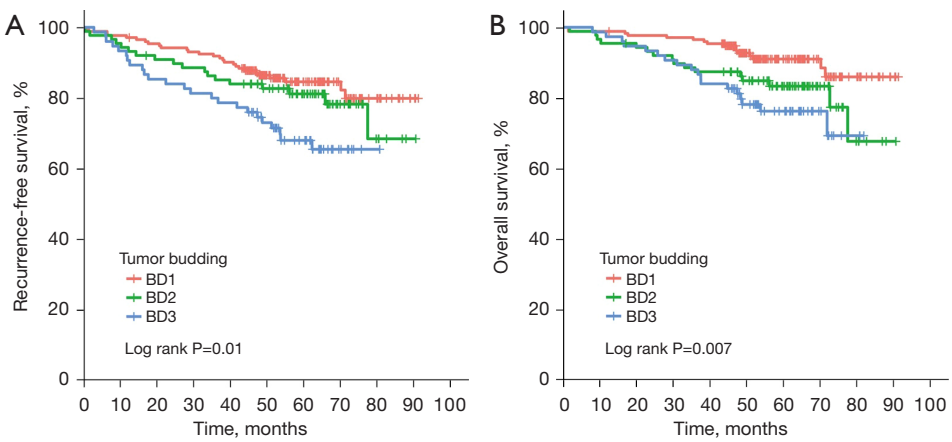

Figure 2 Kaplan-Meier curves to illustrate the prognostic effect of BD1–3 in stage II CRC patients for RFS (A) and OS (B). BD, budding grade; CRC, colorectal cancer; RFS, recurrence-free survival; OS, overall survival.

Cox regression analysis in which age was included as one of the covariates (Table S5).

Although no significant difference was found between the three categories of TB grade and adjuvant chemotherapy in terms of OS (*Figure 4A*), the interaction between BD1/2 *vs.* BD3 and adjuvant chemotherapy was significant in the Cox regression analysis (P=0.03) (*Figure 4B*). These results provide preliminarily evidence that patients with a TB count of <10 may benefit from adjuvant chemotherapy. The results of the interaction analysis of TB grade and RFS are

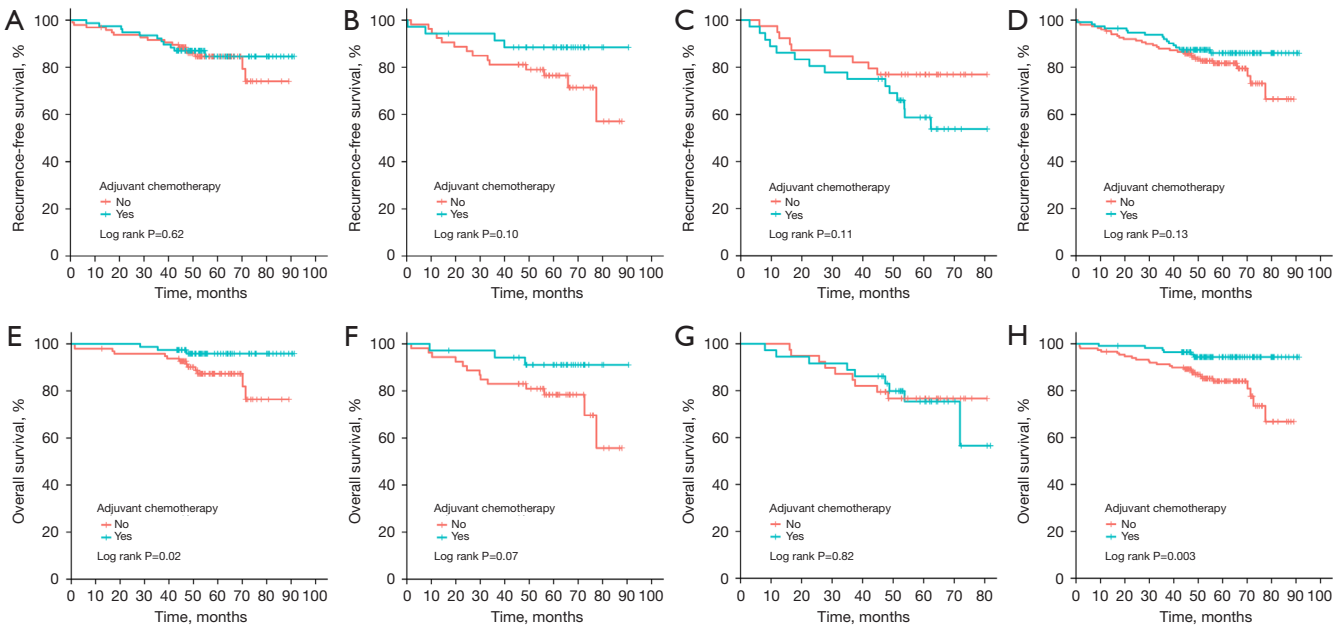

Figure 3 Kaplan-Meier curves to illustrate the differential effect size of benefit from adjuvant chemotherapy in different BD subgroups for RFS (A-D) and OS (E-H). The difference in the RFS of adjuvant chemotherapy *vs.* surgery alone in: (A) BD1 (n=173); (B) BD2 (n=88); (C) BD3 (n=75); and (D) BD1/2 (n=261). The difference in OS of adjuvant chemotherapy *vs.* surgery alone in: (E) BD1 (n=173); (F) BD2 (n=88); (G) BD3 (n=75); and (H) BD1/2 (n=261). BD, budding grade; RFS, recurrence-free survival; OS, overall survival.

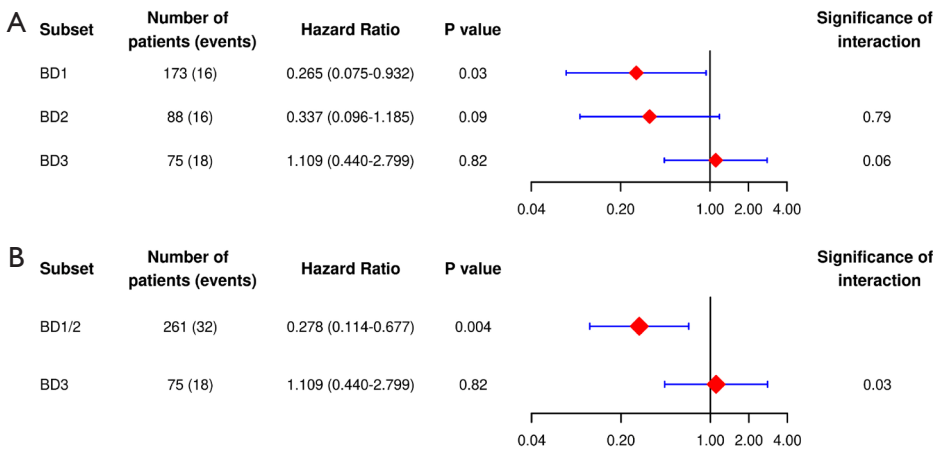

Figure 4 Forest plots to illustrate the differential effect size of benefit from adjuvant chemotherapy in different BD subgroups and their significance of interaction for OS. (A) Forest plot for individual BD group. (B) Forest plot for BD1/2 subgroup *vs.* BD3. BD, budding grade; OS, overall survival.

shown in Figure S2. However, unlike TB grade, TB location and stromal reaction were not found to be predictive factors in relation to the benefit of adjuvant chemotherapy for both RFS and OS (Figure S3).

Discussion

The present study confirmed that TB is a poor prognostic factor post-surgery in stage II CRC patients. BD3 was shown to be significantly associated with increased

recurrence and shorter OS, which is highly consistent with the findings of previous studies (15,16). As TB is a high-risk factor for stage II CRC surgery, it has been frequently hypothesized that patients with high-grade TB may benefit from appropriate adjuvant chemotherapy and the identification of TB may aid in decision making. Two clinical studies (10,11) examined whether high-grade TB should be included as a decision-making factor for adjuvant chemotherapy in stage II CRC, and reported that patients with stage II CRC with high-grade TB showed some improvements in RFS and OS following adjuvant therapy. However, these results were not statistically significant. Most recently, another study provided evidence that adjuvant chemotherapy is beneficial for patients with BD3 but not for those with BD1 or BD2 (17). Conversely, in our own cohort, the patients with BD3 did not benefit from adjuvant chemotherapy in terms of OS; however, a significant improvement in OS was observed in patients who received adjuvant chemotherapy in the BD1/2 subset. This is consistent with the responsiveness of TB to adjuvant chemotherapy in stage III CRC (18,19). Moreover, it is also supported by the capacity of TB status (based on biopsy specimens) to predict patients' pathological responses to neoadjuvant chemoradiotherapy (20).

Several clinical observations appear to indirectly support our results. Rogers *et al.* (20) reported that patients with rectal cancer who presented with TB in biopsy specimens did not show a pathological complete response following neoadjuvant chemoradiotherapy based on 5-FU; rather, these patients had poor treatment responses and adverse prognoses. The specificity and positive predictive values of TB in predicting a non-response to neoadjuvant chemoradiotherapy were both 100%. These results indicate that rectal tumors characterized by TB show some resistance to radiotherapy and chemotherapy. Two studies of stage III CRC also provide supportive evidence of a relationship between high-grade TB and resistance to cytotoxic drugs (18,19). Stage III CRC patients with high-grade TB may be resistant to 5-FU-based chemotherapy via the epithelial-mesenchymal transition (EMT) pathway (18). Low-risk (T1, T2, or T3, and N1) stage III CRC patients with low-grade TB had significantly higher 3-year DFS than those with high-grade TB after 5-FU-based chemotherapy (19). These clinical studies suggest that TB, at least in stage III CRC, should be considered an unfavorable pathological factor for 5-FU-based adjuvant chemotherapy. However, the mechanisms underlying the resistance to 5-FU remain unknown. Further experimental research is needed to confirm the link between TB and 5-FU efficacy.

In addition to the clinical observations mentioned above, it is widely accepted that TB reflects a morphological feature of EMT (21-23). A gene expression analysis confirmed a strong association between TB and CRC consensus molecular subtype 4 (CMS4; which is associated with EMT) with highly infiltrated stromal cells (24). Malignancies that develop EMT may be resistant to conventional chemotherapy (22,25). For example, a previous study has shown that EMT of CRC malignant cells characterized with highly expressed cancer stem cell markers CD44 and CD166 results in resistance to chemotherapy and radiotherapy (26). Given this clinical evidence, it is appropriate to speculate that TB as a cellular morphological phenotype may be resistant to adjuvant chemotherapy, which may in turn prevent CRC patients with high-grade TB from benefiting from conventional adjuvant chemotherapy.

There are some limitations in this study. First, it was only based on an analysis of clinical data; thus, further investigation into the mechanism by which TB leads to resistance to chemotherapy is needed to validate our results. Second, the present study was a retrospective study with a small sample size that was insufficient to support the analysis of the interactions; there were only 75 cases in the BD3 subgroup. Third, the heterogeneity of the adjuvant chemotherapy regimens might have affected the results. Strong evidence is needed to validate the exact effect of TB on adjuvant chemotherapy. Fourth, a significant proportion of the patients assigned to the surgery-only group did not receive adjuvant chemotherapy for physiological reasons (e.g., age, tumor location, or other). This resulted in a significant difference in the background of the patients in the chemotherapy and surgery-only groups. Despite the unavoidable limitations of this retrospective study, our findings suggested that adjuvant chemotherapy based on 5-FU and oxaliplatin had a significant benefit in the low TB group but not in the high TB group. Notably, patients with high-frequency microsatellite instability cancer were excluded from the study, as chemotherapy has been reported to be ineffective for this type of cancer (27,28).

Conclusions

In conclusion, our results indicate that TB should be considered as an important factor in selecting stage II CRC patients who could benefit from adjuvant chemotherapy.

Further clinical research must be performed to confirm our preliminary findings with the aim of eventually establishing TB as a predictive factor for adjuvant chemotherapy in stage II CRC.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-278/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-278/dss

Peer Review File: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-278/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-278/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and Chinese ethical guidelines. The study was approved by the ethics committee of the Third Affiliated Hospital of Army Medical University (No. 317, 2023), and all patients signed an informed consent form.

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