

# Updates in version 2020 of CSCO guidelines for colorectal cancer from version 2019

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According to the latest data released by the National Cancer Center, colorectal cancer (CRC) had the third highest incidence and the fifth highest mortality of all malignancies, with 388,000 new cases and 187,000 cancer deaths in China (1). The Chinese Society of Clinical Oncology (CSCO) originally published the English version of 2018 guideline concerning CRC and updated them in 2019 (2,3). According to the latest progress, clinical guidelines have been updated. Here, we present the main updates of the 2020 version compared to 2019 version.

## Updates related with molecular pathological section

Recommendation of “tumor budding” was added as class I in the microscopic examination of specimens after adenoma local excision and carcinoma radical resection. The recommendation of mismatch repair (MMR) protein expression is modified from class II to class I. Recommendations of “detection of microsatellite instability (MSI) status” and “detection of *RAS*+*BRAF* gene mutation” were added for the specimens after radical resection as class

I and class II, respectively. Recommendation of “detection of human epidermal growth factor receptor 2 (HER2) status and *NTRK* gene fusion” was added as class III for surgery/biopsy specimens of metastatic CRC after failure of standard treatment or before enrollment in clinical trials. World Health Organization (WHO) histological classification of CRC and the relationship between histological classification and histological grade were updated.

## Updates related with postoperative adjuvant therapy

Last June, the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration presented a prospective pooled analysis of four randomized trials investigating duration of adjuvant oxaliplatin-based therapy (3 vs. 6 months) for patients with high-risk stage II CRC. High-risk stage II disease was defined as T4, poorly differentiated, invasion (vascular/lymphatic/perineural), inadequate nodal harvest, obstruction or perforation before operation. A total of 3,273 patients from Italy, UK,

Denmark Spain, Australia, Sweden, Greece and Japan, were involved (TOSCA 1,268 cases, SCOT 1,078 cases, HORG 413 cases, ACHIEVE-2 514 cases). The primary disease-free survival (DFS) analysis for intent-to-treat (ITT) population showed a non-inferiority P value of 0.3851 (5-year DFS for 3-month group and 6-month group, 80.7% vs. 83.9%). While in the subgroup of patients with CapeOX regimen, a non-inferiority for 3-month CapeOX vs. 6-month CapeOX was reached, as 5-year DFS was 81.7% vs. 82.0% respectively. Due to significantly less toxicity of 3-month treatment, recommendation of 3-month CapeOX adjuvant chemotherapy was added for stage II CRC patients with high risk (4). Furthermore, according to the ACHIEVE-2 study based on the Asian, 3-month CapeOX is inferior to 6-month treatment for T4 patients, thus this recommendation is for stage II patients with high risk (except T4).

### Updates related with treatment of metastatic colon cancer

The CRC patients with potentially resectable metastases should be treated with higher intensity to achieve conversion. At present, bevacizumab and cetuximab have been covered by medical insurance in China, as a result, combination of two-drug chemotherapy and targeted therapy (bevacizumab or cetuximab) was recommended as class I and recommendation of two-drug chemotherapy alone was modified from class I to class II.

In the second-line and third-line palliative treatment for patients with *RAS* wild type and *BRAF*<sup>V600E</sup> mutation, several clinical trials have shown that *BRAF*<sup>V600E</sup>-mt CRC patients could benefit from triplet drug combination targeting *BRAF*, epidermal growth factor receptor (EGFR) and MEK. The BEACON study is a randomized controlled phase III clinical trial, which was designed to evaluate the efficacy and safety of cetuximab and encorafenib (a selective *BRAF* kinase inhibitor) with or without binimetinib (a MEK inhibitor) compared with traditional second-line or third-line chemotherapy. The enrolled participants were divided into three groups (three-drug group, dual-drug group and chemotherapy control group) at a ratio of 1:1:1. The median overall survival (OS) of patients receiving three-drug treatment was significantly prolonged than that of control group (9.0 vs. 5.4 months,  $P < 0.001$ ), which nearly doubled the OS and reduced the risk of disease death by 48%. The median OS of two-drug group was 8.4 months, which also reduced the risk of disease death by 40% compared with the control group.

The objective response rate (ORR) of the three-drug group and the two-drug group were 26% and 20%, which were much higher than the 2% of control group. The incidences of grade 3/4 adverse effects in the three-drug group, the two-drug group and the control group were 58%, 50% and 61%, respectively, all in line with expectations (5-7). For the first time, it was confirmed that the combination of multiple targeted drugs without chemotherapy can bring significant survival benefits to metastatic CRC patients with *BRAF* mutation. In addition, Corcoran *et al.* suggested that 43 patients receiving dabrafenib 150 mg bid plus trametinib 2 mg qd showed a 12% ORR, including one complete response (CR) (8). Another phase I/II trial reported that combination of dabrafenib, trametinib and panitumumab achieved 21% ORR and median progression-free survival (PFS) was 4.2 months (9). The main grade 3/4 adverse events were diarrhea, dermatitis acneiform, fatigue, pyrexia and rash. The above three clinical trials have all evaluated MEK inhibitors + *BRAF* inhibitors + anti-EGFR monoclonal antibodies. Although the specific drugs used are different, they still prove the efficacy of the combination of these three targeted drugs. Therefore, considering the drug availability, recommendation of dabrafenib + trametinib + cetuximab was added as class III (Level 2B evidence) in the second line and above treatment for patients with *RAS* wild type and *BRAF*<sup>V600E</sup> mutation.

In the third-line palliative treatment, recommendation of oral trifluridine/tipiracil (TAS-102) is added as class I recommendation (Level 1A evidence). TAS-102 is a combination of two active pharmaceutical ingredients: trifluridine (FTD), a nucleoside analog, and tipiracil, a thymidine phosphorylase inhibitor (TPI). Tipiracil prevents rapid metabolism of trifluridine, increasing the bioavailability of trifluridine. In the RECOURSE study, a phase III clinical trial, a total of 800 previously treated mCRC patients were enrolled and 534 participants received TAS-102 monotherapy. Comparing with placebo, the median PFS (2.0 vs. 1.7 months) and OS (7.1 vs. 5.3 months) of TAS-102 group were both significantly prolonged (10). Therefore, TAS-102 was approved in the United States, Europe and Japan, and was recommended by relevant guidelines. Based on the TERRA randomized clinical trial, oral TAS-102 monotherapy compared with placebo, resulted in significantly prolonged PFS (2.0 vs. 1.8 months) and OS (7.8 vs. 7.1 months) for Asian patients with metastatic CRC. And the main adverse event is hematological toxicity (11). Currently TAS-102 has been

proved by the National Medical Products Administration (NMPA) and will be available in China this year. Hence, regardless of *RAS* and *BRAF* gene status, TAS-102, along with regorafenib and fruquintinib, is positioned as the recommended class I drugs for the third-line treatment of metastatic CRC. TAS-102, 35 mg/m<sup>2</sup> (the maximum amount of 80 mg in a single dose) orally, twice a day, 1–5 and 8–12 d, 28 d per cycle.

There are 5% CRC harboring HER2 variation, including amplification, point mutation and gene fusion. The HERACLES trial showed that KRAS codon 12/13 wild-type, HER2-positive metastatic CRC patients receiving trastuzumab and lapatinib revealed 30% ORR and mPFS reached 21 weeks (12). Moreover, 57 HER2-amplified CRC patients enrolled in the MyPathway basket study, were treated with pertuzumab and trastuzumab as third-line therapy. And 18 (32%) patients achieved objective response, including one CR. Median PFS and OS were 2.9 months and 11.5 months, respectively (13). In 2019, the preliminary results of three single-arm studies of HER2-amplified mCRC were reported at the European Society for Medical Oncology (EMSO) conference. According to HERACLES-B study, 30 patients receiving pertuzumab and T-DM1 showed a 10% ORR and 80% disease control rate (DCR). The median PFS was 4.9 months, especially the patients with HER2 3+ (5.7 months) (14). In the TRIUMPH study, 18 participants were treated with the combination of pertuzumab and trastuzumab. And 35.3% of patients received objective response and 64.7% of patients had disease under control (15). Additionally, the MOUNTAINEER trial was designed to evaluate the efficacy of trastuzumab and tucatinib, a small molecule tyrosine kinase inhibitor (TKI) that is highly selective for HER2. Surprisingly, ORR and DCR reached 52.2% and 91%, which is the highest in current clinical trials. The survival data also showed that the median PFS and OS were 8.1 months and 18.7 months, respectively (16). Based on the results of the above clinical trials, coupled with the availability of most anti-HER2 agents in China, recommendation of anti-HER2 therapy was added as class III for patients with HER2 amplification (Level 2B evidence) in the third-line palliative treatment.

### Updates related with treatment of rectal cancer

Except for clinical trials, it is not recommended to use oxaliplatin, irinotecan, bevacizumab, cetuximab or panitumumab in combination with radiotherapy for rectal

cancer. However, for cT3/cT4N+ patients suffering technical difficulties for anal preservation, but with a strong desire to preserve the anus, recommendation of several high intensity treatments before the surgery was added. In the FOWARC study, a total of 495 patients with locally advanced rectal cancer undergoing neoadjuvant were randomly divided into three groups (De Gramont + radiotherapy, mFOLFOX6 + radiotherapy, and mFOLFOX6 alone group). The pathologic complete response (pCR) rates of these three groups were 14.0%, 27.5% and 6.6%, respectively (17). Similarly, CinClare study showed that comparing to capecitabine with concurrent radiotherapy followed by XELOX, under the guide of UGT1A1, the addition of irinotecan into capecitabine-based neoadjuvant radiochemotherapy could also potentially increase the pCR rate (33.8% vs. 17.5%) (18). And with the increase in the number of irinotecan administered weekly, pCR rate was gradually increased. In addition, total neoadjuvant therapy (TNT) also enables to achieve a 21.8% CR [pCR or sustained clinical CR (cCR)] rate (19,20).

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### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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