Guidelines

CSCO guidelines for colorectal cancer version 2023: Updates and insights

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Submitted May 09, 2023. Accepted for publication May 29, 2023.
doi: 10.21147/j.issn.1000-9604.2023.03.02
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2023.03.02

Colorectal cancer (CRC) is the second most common cancer and the most common type of gastrointestinal cancer with rapidly increasing incidence and mortality in China (1,2). Since the first edition of the Chinese Society of Clinical Oncology (CSCO) guideline was published in 2017, the guideline has been updated annually according to the latest results of clinical research at home and abroad, the accessibility of drugs and the opinions of CSCO experts (3-7). Here, we present the main updates of the 2023 version compared to the 2022 version.

Updates related to diagnosis of CRC

Imaging diagnosis of liver metastases

Increasing evidences have shown that chemotherapy may lead to liver steatosis or liver fibrosis and even cirrhosis due to hepatic sinusoidal obstruction. Therefore, liver metastases may not be shown by computed tomography (CT) after chemotherapy. Further diagnosis is recommended by liver cell-specific contrast agent-enhanced magnetic resonance imaging (MRI) (class II recommendation), and liver contrast-enhanced ultrasound is recommended if necessary (class III recommendation) (8,9).

Location of lower margin of rectal cancer

The location of the lower edge and the quadrant of rectal cancer are independent predictors of positive pathological circumferential resection margin (pCRM). It is recommended that the distance between the lower edge of the tumor and the lower edge of the external sphincter as well as the lower edge of the puborectalis muscle should be marked. Simultaneously, the quadrant of the tumor is recommended to be marked in the clockwise direction, especially when the tumor involves the anterior quarter quadrant (10 o'clock to 2 o'clock in clockwise position) (10,11).

T staging of rectal cancer

This update further clarified the diagnostic criteria of clinical TN staging of rectal cancer. In particular, T4b rectal cancer can be diagnosed if rectal cancer invaded pelvic structures including pelvic organs (ureter, bladder, urethra, prostate, seminal vesicle, uterus, cervix, vagina, ovary, small intestine, colon, etc.), pelvic bones (direct invasion but not hematogenous spread), pelvic floor muscles (isiciococcygeus, piriformis muscle, obturator muscle, levator ani muscle, puborectalis muscle, external sphincter, etc.), sciatic and sacral nerves, sacrospinous or sacrotuberous ligament, external mesorectal vessels, fat and other structures (12).

N staging of rectal cancer

The clinical diagnosis of lymph node metastasis in rectal

cancer impacts the treatment strategy, especially the presence of non-regional and lateral lymph node metastasis. Lymph node metastasis of rectal cancer is diagnosed according to the following criteria: short diameter ≥5 mm, irregular shape, unclear boundary, and heterogeneous signal or echo (13). Regional lymph nodes which are reported as cN staging are recommended to be labeled, including mesorectal nodes and nodes in the mesocolon of the distal sigmoid colon nodes (along the superior rectal artery and vein), obturator nodes, and internal iliac nodes. Non-regional lymph nodes, including external iliac, common iliac and inguinal lymph nodes, are reported as cM staging. In the case of rectal cancer extending into the anal canal below the level of the dentate line (the puborectalis muscle), inguinal nodes may still be considered regional nodes and reported as cN-stage. Until now, there is no widespread consensus on the criteria for lateral lymph node metastasis. According to the consensus of Chinese experts, the threshold of lateral lymph node suspected metastasis is 5−10 mm in short diameter, and the threshold of diagnosis is ≥10 mm in short diameter. Similarly, there is no widely accepted standard for the diagnosis of residual tumors after neoadjuvant therapy. Lower rectal cancer or cT3−4 can be considered as a high-risk factor for pelvic lateral lymph node metastasis. The location of clinically suspected or diagnosed lateral lymph nodes is recommended to be marked, including obturator nodes, internal iliac nodes, and external iliac nodes (14,15).

Safe surgical resection plane: mesorectal fascia (MRF) and anal canal

Evidence is mounting that high-resolution MRI is an effective way to determine the safe surgical resection plane to reduce the rate of positive pCRM. Positive MRF (MRF+) was defined as the distance between primary rectal cancer, metastatic lymph nodes, extramural vascular invasion (EMVI) and MRF≤1 mm. When >1 mm, MRF− was diagnosed. It is recommended that radiologists mark whether the lower rectal cancer or anal canal cancer involves the internal sphincter, the internal and external sphincter space, the external sphincter, the puborectalis muscle, or the levator ani muscle as anal+/− according to the coronal high-resolution MRI parallel to the anal canal (12,16).

Evaluation of effect of neoadjuvant therapy

Up to now, there is no widely accepted diagnostic criteria for evaluating the efficacy of chemoradiotherapy for rectal cancer. The recommended main methods and quantitative indicators to assess the effect of chemoradiotherapy for rectal cancer are as follows: the axial small field-of-view (FOV) high-resolution T2 weighted imaging (T2WI) nonfat-suppressed sequence, diffusion-weighted imaging (DWI) sequence, and apparent diffusion coefficient (ADC) values as well as the change of ADC values before and after chemoradiotherapy (12,17,18). The accuracy of combined omics (clinical characteristics, radiomics and pathomics) models for evaluating the therapeutic effect of rectal cancer has been continuously confirmed, but it has not yet been applied in clinical practice. To avoid the interference of inflammatory edema of the bowel wall and peri-intestine on imaging evaluation after neoadjuvant therapy, the interval between chemoradiotherapy and imaging scan is recommended to be 6−8 weeks. Additional monitoring time points of more than 8 weeks are recommended depending on the treatment regimens (19). To evaluate the therapeutic efficacy of rectal cancer, the following reference criteria can be considered: the cT and cN staging, EMVI, tumor diameter or volume, tumor high signal on DWI, and ADC value of tumors in pre-chemoradiotherapy. After chemoradiotherapy, rectal tumors regression, the regression within metastatic lymph nodes in the mesorectum and EMVI are presented as fibrous tissues or mucus replacing all or part of the tumor tissue, changes in tumor diameter or volume, and changes in ADC value which can be used to evaluate the therapeutic effect (12,17,20,21). The pre- and post-treatment images are recommended to compare to diagnose the clinical complete response (cCR) of rectal cancer. In MR images, the absence of tumor signals in high-resolution T2WI nonfat-suppressed sequence and in DWI sequence, in combination with ADC in the primary tumor region, would be one of the standards to diagnose cCR. When it's difficult to diagnose cCR with MRI, the positron emission tomography (PET) can be used for auxiliary diagnosis (12,21,22).

Updates related to treatment of mismatch repair-deficient (dMMR)/microsatellite instability-high (MSI-H) CRC

Preoperative neoadjuvant immunotherapy

Since the efficacy of immune checkpoint inhibitors is clear for patients with advanced dMMR/MSI-H CRC, researchers are with great interest in exploring immune

checkpoint inhibitors for non-metastatic dMMR/MSI-H CRCs. The NICHE trial is the first exploratory neoadjuvant immunotherapy study to evaluate the efficacy of a single dose of ipilimumab (1 mg/kg, i.v. on d 1) combined with two doses of nivolumab (3 mg/kg, i.v. on d 1 and d 15) with a response rate of 100% and pathological complete response (pCR) rate of 69% in 32 patients with dMMR CRC (78% stage III) (23). To further investigated the efficacy of same combination, Chalabi and colleagues administrated the NICHE-2 trial for a larger cohort of patients with non-metastatic dMMR colon cancers. A total of 112 patients (87% stage III, with 74% having high risk) were treated with one dose of ipilimumab (1 mg/kg, i.v. on d 1) and two doses of nivolumab (3 mg/kg, i.v. on d 1 and d 15). The co-primary endpoints were safety, feasibilitiy and 3-year disease-free survival (DFS). Major pathologic response (MPR) and pCR rates in post-treatment surgical specimen were considered as the secondary endpoints. At the time of data release, NICHE-2 confirmed the previously reported pathologic response to short-term neoadjuvant nivolumab plus ipilimumab with an MPR rate of 95% (including 67% pCR) in the per-protocol (PP) population (n=107) and 98% of patients underwent surgery without delay. At a median follow-up of 13.1 (range 1.4–57.4) months, none of the patients had disease recurrence and 61% of patients experienced an immune-related adverse event of any grade, but they were grade 3 or 4 in only four patients. Only two patients had an immune-related adverse event leading to a delay in surgery of at least 2 weeks (24). The PICC study is a single-center, parallel-group, non-comparative, randomized, phase 2 clinical trial aimed to investigate the efficacy and safety of PD-1 blockade with toripalimab with or without the COX-2 inhibitor celecoxib, as neoadjuvant treatment for dMMR/MSI-H, locally advanced CRCs. The majority of participants had T4 or N2 disease and were randomly assigned to receive six cycles of toripalimab (3 mg/kg, i.v. on the d 1 of each 14-day cycle) with or without celecoxib (200 mg orally twice daily) before surgery. Hu and colleagues reported a pCR of 88% [15 of 17 patients; 95% confidence interval (95% CI), 64–99] of patients with toripalimab plus celecoxib and 65% (11 of 17 patients; 95% CI, 38–86) of patients with toripalimab alone. Both treatment regimens were with manageable adverse events and without treatment-related surgical delays (25).

Recently, one of the Memorial Sloan-Kettering Cancer Center (MSKCC) clinical trials reported the remarkable efficacy of the PD-1 inhibitor dostarlimab in patients with dMMR, locally advanced rectal cancer without exposure to immunotherapy, chemotherapy or radiotherapy before. Sixteen patients were recruited and treated with dostarlimab (500 mg, i.v. every 3 weeks). Twelve of these patients received the drug for 6 months and completed the nine planned cycles of dostarlimab. The percentage of the 12 consecutive patients achieving a cCR was 100% (95% CI, 74–100) and during the median follow-up period of one year, no patients required surgery, chemotherapy or radiotherapy. Acceptable toxicity occurred in 12 of the 16 patients (75%; 95% CI, 48–92) without any grade 3 or higher adverse events (22). Simultaneously, Chen and his colleague initiated a study to evaluate the neoadjuvant sintilimab monotherapy for patients with dMMR/MSI-H locally advanced rectal cancer (26). This open-label, single-arm, phase 2 study was conducted at the Sun Yat-sen University Cancer Center, Guangzhou, China. Of the 17 patients who received at least one dose of sintilimab (200 mg, i.v. once every 3 weeks) included, one patient was excluded from efficacy because of loss to follow-up. Of the remaining 16 patients, six underwent surgery, of whom 3 had a pCR, nine achieved a cCR and chose the watch-and-wait strategy and one had a serious adverse event and discontinued treatment. In total, a complete response was noted for 12 patients (75%; 95% CI, 47–92). After a median follow-up of 17.2 months, all patients were alive and none had disease recurrence (26).

Although there are no large randomized controlled studies, the highly consistent results of these phase 2 studies have emphasized the efficacy of immunotherapy in patients with dMMR/MSI-H CRCs. Consequently, the CSCO expert group recommended that immune-checkpoint inhibitors (anti PD-1 ± CTLA-4 antibody) therapy followed by radical surgery was added as class II recommendation for cT4b, dMMR/MSI-H colon cancers without emergency. For patients with dMMR/MSI-H rectal cancer, especially those with difficulty in preserving anal sphincter or unable to achieve R0 resection of T4b, a multidisciplinary team meeting after neoadjuvant immunotherapy can be considered to evaluate the timing and plan of surgery. The specific drug selection of neoadjuvant immunotherapy can refer to the MSKCC clinical trial. Considering the accessibility of drugs, similar immune-checkpoint inhibitors or participation in clinical trials may also be allowed.

Regimens for palliative treatment group

For patients with metastatic dMMR/MSI-H CRC in

palliative care, pembrolizumab has earned a class I recommendation as the first-line palliative treatment based on the results of Keynote-177 (6). At the American Society of Clinical Oncology (ASCO) annual meeting in 2022, the five-year follow-up results of CheckMate 142 clinical trial was reported. In its first-line therapy cohort, patients with metastatic dMMR/MSI-H CRC were treated with nivolumab (3 mg/kg, i.v) every 2 weeks plus low-dose ipilimumab (1 mg/kg, i.v) every 6 weeks until disease progression. During a long-term follow-up of approximately five years, nivolumab plus ipilimumab demonstrated sustained overall survival (OS) and progression-free survival (PFS) benefits (48-month OS rate: 72%, 95% CI, 57–83; 48-month PFS rate: 51%, 95% CI, 34–66) (27). Since ipilimumab has been approved in China, this dual immuno-oncology combination regimen was added as class III recommendation in palliative first-line treatment for metastatic dMMR/MSI-H CRC patients (Level 3 evidence).

For patients with advanced dMMR/MSI-H cancers who had never received immunotherapy before, anti-PD-1/PD-L1 antibody was added as class II recommendation (Level 2A evidence) in the second-line and third-line palliative treatment. Pembrolizumab, envafolimab, serplulimab and tislelizumab were recommended as a priority for they have been approved for the treatment of adult patients with unresectable or metastatic MSI-H advanced solid tumors (including patients with advanced CRC who had failed standard therapy before). In addition, based on the results of back-line therapy cohort of CheckMate 142 and the availability of ipilimumab in China, nivolumab ± ipilimumab was also recommended.

Updates related to combination of TAS-102 and bevacizumab

Trifluridine/tipiracil (TAS-102) plus bevacizumab has been shown efficacy in previous phase 2 studies including patients with unresectable metastatic CRC (mCRC) (28-32). Recently, the results of two phase 3 studies further highlight the efficacy of TAS-102 plus bevacizumab for mCRC.

SOLSTICE is a randomized, open-label phase 3 study aimed to investigate first-line TAS-102 plus bevacizumab *vs*. capecitabine plus bevacizumab in patients with unresectable mCRC ineligible for intensive treatment. Participants were randomly allocated (1:1) to these two regimens with a primary endpoint of investigator-assessed PFS. After a median follow-up of 16.6 (95% CI, 16.5–17.1) months, the investigator-assessed median PFS was 9.4 (95% CI, 9.1–10.9) months in patients with TAS-102 plus bevacizumab and 9.3 (95% CI, 8.9–9.8) months in patients with capecitabine plus bevacizumab. The common grade 3 adverse events including neutropenia, decreased neutrophil count and anemia occurred more commonly in the TAS-102 plus bevacizumab group, but lower rates of hand-foot syndrome compared with capecitabine plus bevacizumab. Although the results of SOLSTICE revealed that first-line TAS-102 plus bevacizumab was not superior to capecitabine plus bevacizumab for unresectable mCRC, TAS-102 plus bevacizumab could represent a feasible alternative for this population (33).

At the American Society of Clinical Oncology-Gastrointestinal Cancers Symposium (ASCO-GI) annual meeting in 2023, the latest results of SUNLIGHT study were presented, of which mCRC patients with RAS wild-type or mutation who had been treated with 1–2 lines of chemotherapy in an advanced setting were randomly assigned (1:1) to received TAS-102 with or without bevacizumab. The primary endpoint was OS in full analysis set with a total of 492 patients. At the time data release, the median OS was 10.8 months with the bevacizumab combination regimen (n=246) *vs.* 7.5 months with TAS-102 alone (n=246) [hazard ratio (HR): 0.61; 95% CI: 0.49–0.77; P<0.001]. In the secondary endpoint analysis, the median PFS was 5.6 months with the TAS-102 plus bevacizumab *vs*. 2.4 months with TAS-102 monotherapy (HR: 0.44; 95% CI: 0.36–0.54; P<0.001). Notably, the survival benefit was also observed across all subgroups irrespective of sex, age, location of primary tumor, *RAS* mutation status and whether patients had received prior treatment with bevacizumab. The safety profile of these agents was consistent with that previously observed and was manageable (34).

In view of the above data, the combination of TAS-102 plus bevacizumab represents a new standard regimen for the treatment of patients with mCRC who have progressed after two lines of therapy (from class III recommendation to class II recommendation, Level 2A evidence) in the third-line palliative treatment group. And for patients who are not suitable for intensive treatment (MSS or MSI-L/pMMR, regardless of *RAS*/*BRAF* gene status), TAS-102 plus bevacizumab was added as class III recommendation (Level 3 evidence) in the first-line palliative treatment group.

Acknowledgements

This study was supported by the Provincial Key R&D Program of Zhejiang Province (No. 2021C03125) and Beijing Xisike Clinical Oncology Research Foundation (No. Y-tongshu2021/ms-0003).

Footnote

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

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Cite this article as: Mi M, Weng S, Xu Z, Hu H, Wang Y, Yuan Y. CSCO guidelines for colorectal cancer version 2023: Updates and insights. Chin J Cancer Res 2023;35(3):233-238. doi: 10.21147/j.issn.1000-9604.2023.03.02

