Guidelines

CSCO guidelines for colorectal cancer version 2022: Updates and discussions

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Colorectal cancer (CRC) is the third most common cancer worldwide and the second most common in tumor-related mortality by Global Cancer Statistics 2020 (1). Recent data show that the incidence and mortality of CRC in China are increasing (2-4), with the number of new cases and deaths reaching 607,900 and 261,777 in 2019. The Chinese Society of Clinical Oncology (CSCO) published the first version guidelines in April 2017 and updated annually according to the latest clinical data and the changes in China's national conditions (5-8). Here we present the main updates of the 2022 version compared with the previous version.

Updated highlights of guidelines from version 2021 to 2022

In general, this year's guideline updates are limited, mainly involving imaging diagnosis, postoperative adjuvant chemotherapy, palliative second-line and third-line immunotherapy for patients with high microsatellite instability (MSI-H)/deficient mismatch repair (dMMR), and postoperative circulating tumor deoxyribonucleic acid (ctDNA) monitoring.

Imaging diagnosis

After discussion by the expert panel of the guidelines, in the diagnosis of CRC, class I recommendation was modified to "high-resolution plain computed tomography (CT) or contrast-enhanced CT of the chest and enhanced CT of the abdominal/pelvic cavity" for the staging diagnosis of patients diagnosed by colonoscopy. For patients with iodine contrast agent allergy, class II recommendation "high-resolution plain chest CT and enhanced abdominal/pelvic magnetic resonance imaging (MRI)" could be used. Considering the imaging diagnosis of lung, peritoneal and ovarian metastasis, continuous thin transverse, coronal, and sagittal reconstruction images could be used for differential diagnosis of lung metastasis of CRC if possible (9); enhanced abdominal and pelvic CT was recommended to diagnose ovarian metastasis and peritoneal implantation metastasis. When CT does not confirm the diagnosis of ovarian metastasis, pelvic MRI or gynecological ultrasound was recommended to assist the diagnosis. MRI was suggested including T2-weighted, diffusion-weighted imaging (DWI) and multiphasic T1-weighted enhanced imaging sequences (10).

Postoperative adjuvant chemotherapy

In adjuvant therapy after radical resection of CRC, the description of low-risk stage II patients was changed from "$T_3N_0M_0$, dMMR" to "$T_3N_0M_0$, dMMR, regardless of the clinical high-risk factors such as poor histological differentiation, lymphatic/vascular invasion, nerve invasion, preoperative intestinal obstruction or perforation of tumor site, positive resection margin or insufficient safety

distance, less than 12 lymph nodes dissected (11)". In addition, based on results of the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration, 3 months of CapeOX (capecitabine + oxaliplatin) adjuvant chemotherapy was recommended for all high-risk stage II patients, and 6 months of CapeOX was no longer emphasized for $T_4N_0M_0$ patients (12).

Second-line and third-line palliative treatment for MSI-H/dMMR patients

In the second-line and third-line palliative treatment for MSI-H/dMMR patients, class II recommendation was modified from "programmed cell death protein 1 (PD-1) inhibitors with no restriction on the types" to "PD-1/programmed cell death ligand 1 (PD-L1) inhibitors". Meanwhile, because pembrolizumab, nivolumab and envafolimab have been approved for the treatment of unresectable or metastatic MSI-H/dMMR patients with solid tumors, including advanced CRC patients who failed to respond to standard treatments (13,14), the above three PD-1/PD-L1 inhibitors were preferentially recommended for second-line and third-line therapies.

Postoperative ctDNA monitoring during follow-up of CRC

Recent studies have shown that dynamic ctDNA monitoring is helpful for early warning of postoperative recurrence and metastasis (15-17), but whether it should be routinely used for postoperative follow-up and guidance of treatment remains controversial and requires further evidence.

Combination of PD-1 inhibitors and anti-angiogenetic tyrosine kinase inhibitors (TKIs) was not included in 2022 version of CSCO guidelines

A phase Ib trial (REGONIVO, EPOC 1603) which applied the combination therapy of regorafenib and nivolumab to metastatic colorectal cancer (mCRC) patients who had failed to respond to standard treatments was first reported by Japanese researchers at the American Society of Clinical Oncology (ASCO) 2019 annual meeting (18). The treatment regimen was regorafenib (80−160 mg once daily for 21 d on/7 d off, every 4 weeks) combined with nivolumab (3 mg/kg intravenously every 2 weeks). Twenty-four CRC patients with microsatellite stablility (MSS) achieved 33.3% objective response rate (ORR). The median progression-free survival (PFS) in CRC patients was 7.9 months and 12-month PFS rate was 41.8%. These prominent data held great promise to improve the efficacy of immunotherapy in mCRC patients with MSS status. Since then, several similar single-arm exploratory trials were published in large international conferences including ASCO, European Society of Medical Oncology (ESMO) and ASCO-Gastrointestinal Cancers Symposium (ASCO-GI). At the 2021 ASCO meeting, Fakih *et al.* reported a phase II trial (NCT04126733) based on North American population, in which regorafenib and nivolumab were used. Among the 70 MSS mCRC patients who failed to standard treatments, only 7.1% ORR was achieved, with a disease control rate (DCR) of 38.6% at 40 weeks, a median PFS of 8.0 weeks and a median overall survival (OS) of 51.8 weeks. Among them, ORR in patients with liver metastasis was 0, which was significantly different from the previous REGONIVO study in the Japanese population.

A phase Ib trial (NCT03903705) of fruquintinib plus sintilimab, reported by Prof. Li at the 2021 ASCO meeting, showed that fruquintinib (with two different administration regimens: 3 mg once daily continuously; 5 mg once daily for 14 d on/7 d off, every 3 weeks) combined with sintilimab (200 mg intravenously every 3 weeks) in 44 mCRC patients who failed to standard treatments achieved 22.7% ORR and 86.4% DCR, with a median PFS of 5.6 months and a median OS of 11.8 months, among which the 5 mg fruquintinib group had better data.

The REGOTORI study (NCT03946917) (19), reported by Prof. Xu at the 2020 ESMO meeting, included 42 mCRC patients with MSS who had received ≥2 previous lines of chemotherapy. Among 33 patients with at least one imaging tumor assessment, ORR and DCR were 15.2% and 36.4%, respectively, when using the combination of regorafenib (80 mg once daily for 21 d on/7 d off, every 4 weeks) and toripalimab (3 mg/kg intravenously every 2 weeks). A median PFS of 2.1 months and a median OS of 15.5 months were reported.

The LEAP-005 study (NCT03797326), presented at the 2021 ASCO meeting, showed that pembrolizumab (200 mg intravenously every 3 weeks) combined with lenvatinib (20 mg once daily continuously) resulted in 22% ORR and 47% DCR with a median PFS of 2.3 months and a median OS of 7.5 months in the third-line treatment of MSS mCRC patients.

According to the results of the above single-arm trials, the combination of PD-1 inhibitors with anti-angiogenetic TKIs in patients with late line MSS mCRC who failed to

the standard treatments was highly inconsistent. Even though using the same combination regimen, inconsistent data were obtained from different populations. The scheduled phase III trials of regorafenib combined with nivolumab in comparison with regorafenib have not initiated due to various reasons, and currently only one phase III clinical trial LEAP-017 (NCT04776148) is ongoing. The LEAP-017 study is a 1:1 randomized controlled phase III trial scheduled to enroll 434 patients with non-MSI-H/proficient mismatch repair (pMMR) who have failed to standard treatments from 117 centers of 15 countries. The experimental group was treated with pembrolizumab (400 mg intravenously every 6 weeks) combined with lenvatinib (20 mg once daily continuously), while the control group was treated with standard third-line drug regorafenib (160 mg once daily for 21 d on/7 d off, every 4 weeks) or TAS-102 (trifluridine and tipiracil hydrochloride, 35 mg/m^2 twice a day for d 1–5, d 8–12, repeated every 4 weeks). The primary endpoint was OS, and the secondary endpoints were PFS, ORR, DCR and safety. Therefore, experts in the guideline group decided, based on the current data, not to add the combined regimen of PD-1 inhibitor and anti-angiogenetic TKIs to the third-line palliative treatment in 2022 version CSCO guidelines for the time being, pending the results of phase III clinical trial of LEAP-017.

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Footnote

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

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