Guidelines

CSCO guidelines for colorectal cancer version 2024: Updates and discussions

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Submitted May 07, 2024. Accepted for publication May 17, 2024.
doi: 10.21147/j.issn.1000-9604.2024.03.01
View this article at: https://doi.org/10.21147/j.issn.1000-9604.2024.03.01

According to the latest global cancer statistics, colorectal cancer (CRC) is the most common malignancy of the digestive system and the second most lethal among all cancer types (1). In China, CRC is the second most prevalent cancer, following only after lung cancer (2). The first version of the Chinese Society of Clinical Oncology (CSCO) guideline was launched in 2017 and has been updated annually based on the latest findings of clinical research, drug accessibility and expert consensus (3-8). Here, we present the main updates of the 2024 version compared to the 2023 version.

Updates related to molecular pathological diagnosis of CRC

Polymerase epsilon and delta (POLE/POLD1) mutation and immunotherapy

POLE/POLD1 are DNA damage repair genes (9) and functionally guide DNA chain extension and DNA strand synthesis (10). In addition, *POLE/POLD1* are also essential for proofreading in DNA replication by recognizing and repairing the mismatched bases (11). Certain pathogenic mutations within the exonuclease domains of POLE/POLD1 can lead to DNA repair deficiencies and carcinogenesis via a hypermutator phenotype (12). Accumulative studies have revealed that tumors harboring POLE/POLD1 pathogenic mutations are associated with increased immunogenic mutations and higher tumor mutation burden (TMB) (13,14). The frequent immunogenic mutations and high levels of immune cell infiltration driven by POLE/POLD1 pathogenic mutations also increase the sensitivity of immunotherapy and contribute to better prognosis (9,15,16). Accordingly, 2%–8% of mismatch repair proficient/microsatellite stable (pMMR/MSS) CRC harbor functional somatic *POLE* mutations, while *POLD1* mutations are extremely rare (17,18). Based on the above-mentioned findings, *POLE/POLD1* mutation detection (either single gene sequencing or next-generation sequencing) is added as Class III recommendation for surgery/biopsy specimens of metastatic CRC (mCRC) in the 2024 version of CSCO guidelines.

Updates related to mCRC

Updates related to potentially resectable mCRC

FOLFOXIRI ± bevacizumab treatment in potentially resectable mCRC

In the management of potentially resectable mCRC, chemotherapy combined with targeted therapy is the standard regimen for conversion objectives. In a multi-center, randomized, phase III study (CAIRO5) comparing the effectiveness of current induction regimens, Bond *et al.* showed that FOLFOXIRI plus bevacizumab was the preferred treatment in patients with right-sided or RAS mutant-type primary tumor (19). Therefore, the evidence level of FOLFOXIRI ± bevacizumab recommendation is modified from Level 2A (2019 version) to Level 1A (2024

version) (both Class I recommendation).

Deletion of FOLFOXIRI + cetuximab in patients with potentially resectable mCRC with RAS/BRAF wild-type

Based on FOCULM study, mFOLFOXIRI plus cetuximab was recommended for patients with potentially resectable mCRC with RAS/BRAF wild-type in the 2021 version of CSCO guideline (6). The phase II FOCULM study showed that addition of cetuximab to mFOLFOXIRI significantly increased the rate of no evidence of disease, the objective response rate (ORR) and overall survival (OS) compared to chemotherapy only in potentially resectable colorectal liver-limited metastases with RAS/BRAF wild-type (20). However, whether FOLFOXIRI plus anti-epidermal growth factor receptor (EGFR) agent can be used as a standard regimen for mCRC patients with RAS/BRAF wild-type remains controversial due to negative results from several clinical trials.

At the 2023 European Society of Medical Oncology (ESMO) meeting, Mazard *et al.* reported a randomized phase II trial (PANIRINOX-UCGI28, No. NCT02980510) assessing FOLFIRINOX plus panitumumab *vs.* mFOLFOX6 plus panitumumab in mCRC patients whose RAS/BRAF status was determined by circulating DNA analysis (21). Patients were randomly assigned into FOLFIRINOX plus panitumumab or mFOLFOX6 plus panitumumab at a ratio of 2:1 (up to 12 cycles in each arm). The primary endpoint was similar between the two arms (complete response rate was 7.7% and 7.4% in the FOLFIRINOX-panitumumab arm and mFOLFOX6-panitumumab arm, respectively) at the time of data release among patients with non-liver-limited diseases. The secondary endpoints, including ORR, depth of tumor response (DpR), R0 resection rate and progression-free survival (PFS) were also comparable between the two arms.

The TRICE study (No. NCT03493048) is a randomized trial to investigate whether FOLFOXIRI plus cetuximab could offer additional benefits compared to FOLFOX plus cetuximab as first-line treatment in patients with initially unresectable mCRC with liver metastasis of RAS wild-type (22). In total, 146 patients were randomly assigned to FOLFOXIRI plus cetuximab treatment (triplet arm, 72 patients) or FOLFOX plus cetuximab treatment (doublet arm, 74 patients). The primary endpoint was ORR and the secondary endpoints included DpR, early tumor shrinkage (ETS), R0 resection rate, PFS, OS and treatment-related adverse events. The ORR was comparable between the two groups (84.7% and 79.7% in the triplet and doublet arms, respectively, P=0.43). Although three-drug chemotherapy plus cetuximab offered higher DpR (59.6% *vs.* 55.0%, P=0.039), other secondary endpoints (including R0 resection rate and PFS) were mostly comparable. Moreover, the incidence rate of grade 3–4 neutropenia and diarrhea was significantly higher in the triplet arm. Taken together, FOLFOXIRI plus cetuximab failed to increase ORR, R0 resection or PFS, but was associated with higher rates of adverse events.

Based on PANIRINOX-UCGI28 and TRICE studies, FOLFOXIRI plus cetuximab is deleted in the 2024 version of CSCO guideline for patients with potentially resectable mCRC with RAS/BRAF wild-type.

Updates related to unresectable mCRC

Updates of immunotherapy in second-line and above palliative treatment in microsatellite instability-high (MSI-H)/mismatch repair-deficient (dMMR) mCRC

Pembrolizumab has earned a Class I recommendation (Level 1A evidence) in the first-line palliative treatment in MSI-H/dMMR mCRC according to Keynote-177 study (6,23). In the 2023 version of CSCO guideline, nivolumab plus ipilimumab was added as Class III recommendation (Level 3 evidence) for MSI-H/dMMR mCRC as the first-line palliative treatment based on CheckMate 142 study (8). Immunotherapy of MSI-H/dMMR mCRC is mainly updated in second-line and above palliative treatment in the 2024 version. Envafolimab, serplulimab, tislelizumab, pucotenlimab, pembrolizumab and nivolumab are recommended for the second-line and above palliative treatment in MSI-H/dMMR mCRC who have not received immunotherapy (Level 2A evidence). The above-mentioned immune checkpoint inhibitors have earned their priority due to their approved treatment in adults with unresectable or metastatic MSI-H solid tumors and drug availability.

Updates related to combination of TAS-102 and bevacizumab

Trifluridine/tipiracil (TAS-102) is an orally administered drug composed of trifluridine (a thymidine analogue) and tipiracil (a thymidine phosphorylase inhibitor). Based on the results of phase III RECOURSE and TERRA trials, TAS-102 has been recommended as monotherapy in third-line treatment of refractory mCRC since the 2020 version of CSCO guideline (5,24,25).

Continuous inhibition of angiogenesis beyond disease progression seems as an effective strategy in refractory mCRC. Thus, a combination of TAS-102 and bevacizumab might give rise to active clinical outcomes. The phase III SUNLIGHT trial aimed to reveal the efficacy and safety of TAS-102 plus bevacizumab as compared to TAS-102 monotherapy in mCRC patients with no more than two previous chemotherapy regimens (26). The primary endpoint was OS in the full analysis set. The median OS was 10.8 [95% confidence interval (95% CI): 9.4–11.8] months in the combination group and 7.5 (95% CI: 6.3–8.6) months in the TAS-102 monotherapy group [hazard ratio (HR): 0.61, 95% CI: 0.49–0.77, P<0.001]. The median PFS was 5.6 (95% CI: 4.5–5.9) months in the combination group and 2.4 (95% CI: 2.1–3.2) months in the TAS-102 monotherapy group (HR: 0.44, 95% CI: 0.36–0.54, P<0.001). The survival benefits of TAS-102 plus bevacizumab were observed in almost all prespecified groups, stratified by sex, age, primary tumor location, number of metastatic sites, RAS mutation status and previous treatment of bevacizumab. The improved survival was achieved without notably increased toxicity risks. The safety profile of TAS-102 plus bevacizumab was consistent with previous observation and manageable.

Collectively, the addition of bevacizumab to TAS-102 represents a new standard in managing patients with mCRC who have progressed after two lines of therapy. Thus, TAS-102 combined with bevacizumab is recommended in third-line palliative treatment of mCRC (Class I recommendation, Level 1A evidence).

Updates on immunotherapy in pMMR/MSS mCRC

Immunotherapy is the standard first-line treatment in MSI-H/dMMR mCRC. For pMMR/MSS mCRC, several phase I/II trials have evaluated the efficacy of a combination of immune checkpoint blockade and angiogenesis inhibition (regorafenib or fruquintinib) in patients who fail the standard regimens (27-30). However, the ORR was unsatisfactory.

In a recent phase II study (CAPability-01 trial, No. NCT04724239), Wang *et al.* investigated the efficacy of a combination of programmed death 1 (PD-1) antibody (sintilimab), histone deacetylase inhibitor (HDACi) (chidamide) with or without bevacizumab in patients with advanced or metastatic pMMR/MSS CRC (31). The triplet arm showed significantly improved outcomes compared to the doublet arm, with a greater 18 weeks PFS rate (64.0% *vs.* 21.7%, P=0.003), higher overall response rate (44.0% *vs*. 13.0%, P=0.027) and longer median PFS rate (7.3 months *vs.* 1.5 months, P=0.006). The encouraging efficacy of CAPability-01 trial has fueled a phase III trial (CAPability-02).

Apart from the effectiveness of immunotherapy in pMMR/MSS mCRC patients who fail the standard treatment, several phase II studies have explored the potential efficacy of immunotherapy plus standard regimen as first-line palliative treatment.

A phase II randomized AtezoTRIBE study (No. NCT03721653) evaluated the addition of atezolizumab to FOLFOXIRI plus bevacizumab as first-line treatment in unresectable mCRC patients (32). Since neither MSI status nor RAS status was considered in selection criteria in AtezoTRIBE study, PFS was significantly increased in triplet arm than doublet arm in intention-to-treat (ITT) population (13.1 months *vs.* 11.5 months, P=0.015). However, PFS showed no statistical difference in analyzing pMMR/MSS mCRC patients (13.0 months *vs*. 11.5 months, P=0.073). Further analysis in pMMR/MSS unveiled that TMB and Immunoscore-IC [an index of CD8 and programmed death ligand 1 (PD-L1) cell densities and their proximity] may identify patients who can benefit from additional administration of atezolizumab.

In phase II CheckMate 9X8 study, researchers investigated whether the addition of nivolumab to standard first-line regimen might enhance anti-tumor activity (33). Similar to AtezoTRIBE study, MSI status was not selected in CheckMate 9X8 study. mCRC patients were randomized to receive mFOLFOX6 plus bevacizumab with and without nivolumab as first-line treatment. PFS by blinded independent central review (BIRC) was the primary endpoint, which was 11.9 months in both arms (HR: 0.81, 95% CI: 0.53–1.23, P=0.30) at 21.5-month minimum follow-up. Numerically higher PFS rate after 12 months (18 months: 28% *vs*. 9%) and higher ORR (60% *vs*. 46%) were observed in nivolumab plus standard regimen compared to standard regimen.

BBCAPX study (No. NCT05171660) is a phase II study to assess the efficacy and safety of sintilimab plus bevacizumab and CapeOx as first-line treatment in patients with pMMR/MSS mCRC with RAS mutant-type. According to the updated results released in American Society of Clinical Oncology (ASCO) meeting in 2023, 25 patients were enrolled after the assessment by CRC multidisciplinary team (34). ORR was one of the primary endpoints, which reached 84.0%. The median PFS was 18.2 months for the full analysis set and disease control rate

was as high as 100%. The high ORR and manageable safety profile of BBCAPX study has motivated a phase III, randomized, open-label and multicentric clinical trial (No. NCT04194359).

ASTRUM-015 is a phase II/III study comparing the efficacy of serplulimab (a PD-1 inhibitor) plus HLX04 (a bevacizumab biosimilar) and XELOX (group A) *vs*. bevacizumab and XELOX (group B) as first-line treatment for unresectable mCRC (without selection of MSI status). According to results released at the ASCO GI meeting in 2024, 114 patients were randomly assigned to the two groups and the primary endpoint was PFS assessed by independent radiographic review committee (35). Median PFS was prolonged in group A than in group B (17.2 months *vs*. 10.7 months, stratified HR: 0.60, 95% CI: 0.31−1.14, P=0.114). Serplulimab plus HLX04 and XELOX is a promising first-line treatment regimen that warrants further investigation in mCRC.

Taken together, a number of phase II studies have explored the addition of PD-1/PD-L1 antibodies to the first-line standard treatment in pMMR/MSS mCRC. The inconsistent results from phase II studies should be further confirmed by phase III studies.

Updates related to rectal cancer

Selective chemoradiotherapy as an alternative in highly selective locally advanced rectal cancer (LARC) with low risk of recurrence

Neoadjuvant chemoradiotherapy is the standard care of LARC. Although pelvic chemoradiotherapy can effectively decrease the local recurrence rate, it also brings about toxic effects that seriously affect physical function and quality of life. Due to the adverse effects of radiation, researchers are motivated to select rectal cancer patients with specific clinical stages who might safely skip radiotherapy. A multicenter, unblinded, noninferiority and randomized phase III trial (PROSPECT) compared the efficacy and safety of neoadjuvant FOLFOX (with selective chemoradiotherapy) and chemoradiotherapy in patients with rectal cancer (36). Patients with LARC who had been clinically diagnosed as T2 node-positive, T3 node-negative, or T3 node-positive and were candidates for neoadjuvant pelvic chemoradiotherapy followed by a sphincter-sparing surgery were enrolled and randomly assigned into the FOLFOX group (543 patients) and the chemoradiotherapy group (585 patients). Patients in the FOLFOX group received six cycles of mFOLFOX6 treatment and re-staged by pelvic imaging and rectal endoscopy who might subsequently underwent radical surgery or pelvic chemoradiotherapy based on tumor shrinkage. Specifically, patients who completed six cycles of mFOLFOX6 and whose primary tumor had decreased by at least 20% in size proceeded to surgery after assessment. While patients who were unable to complete at least five cycles of FOLFOX or whose primary tumor had decreased by less than 20% in size should receive chemoradiotherapy. Patients in the chemoradiotherapy group received pelvic radiotherapy and sensitizing fluoropyrimidine chemotherapy. The primary endpoint was disease-free survival (DFS). The 5-year DFS was 80.8% (95% CI: 77.9%−83.7%) in the FOLFOX plus selective chemoradiation group and 78.6% (95% CI: 75.4%−81.8%) in the chemoradiotherapy group, demonstrating the uninferiority of FOLFOX regimen plus selective chemoradiation. The secondary endpoints included OS, local recurrence, surgical completion, pathological remission and safety, which showed similar outcomes between the two groups.

According to the results of PROSPECT trial, FOLFOX regimen plus selective chemoradiotherapy is added as Class II recommendation in treating rectal cancer with T1−2 node-positive, T3 node-negative, or T3 node-positive and eligibility of sphincter-sparing surgery in the 2024 version of CSCO guidelines (Level 1B evidence). The results of PROSPECT trial emphasize the strict criteria of patient selection who might skip pelvic radiation. For patients with clinically diagnosed T4 tumor, four or more pelvic lymph nodes with a short axis larger than 10 mm or tumor visible within 3 mm of the radial margin, standard neoadjuvant chemoradiotherapy is necessary.

Updates related to neoadjuvant immunotherapy in pMMR/MSS LARC

Several phase II trials have evaluated the efficacy and safety of neoadjuvant immunotherapy combined with chemo-radiation in pMMR/MSS LARC. The pathological complete remission (pCR) ranged between 20% and 30% (37).

The UNION study (No. NCT04928807) reported at the 2023 ESMO meeting, is the first randomized and open-label phase III clinical trial to compare the efficacy and safety of short-course radiotherapy (SCRT) followed by immunochemotherapy *vs.* long-course chemoradiotherapy (LCRT) followed by chemotherapy for perioperative

treatment of LARC with clinical stage of T3–4 or node positive and lower edge of the tumor ≤10 cm from the anal verge (38). At the time of data release, 231 patients were enrolled and randomly assigned to SCRT combined with immunotherapy group (113 patients) and LCRT combined with chemotherapy (118 patients). The primary endpoint was blinded independent central review (BICR)-assessed pCR rate in the ITT population, which was significantly improved in the immunochemotherapy group (39.8%, 95% CI: 30.7–49.5) *vs.* chemotherapy group (15.3%, 95% CI: 9.3–23.0). The completion rate of surgery was higher in the immunochemotherapy arm (92.0%) compared to the chemotherapy arm (83.9%), with similar postoperative complication rates (38.1% *vs.* 40.8%). For safety profile, the incidence of grade ≥3 treatment-related adverse events (TRAEs) was similar between the two arms (29.2% in the immunochemotherapy arm and 27.2% in the chemotherapy arm). Experts in the guideline group have noticed the significantly improved pCR rate with acceptable tolerance of SCRT followed by immunochemotherapy and have thus added the results in the annotation of the updated guideline.

Acknowledgements

This work was supported by the Provincial Key R&D Program of Zhejiang Province (No. 2021C03125); National Natural Science Foundation of China (No. 82373415 and No. 82302489) 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: Chen L, Hu H, Yuan Y, Weng S. CSCO guidelines for colorectal cancer version 2024: Updates and discussions. Chin J Cancer Res 2024;36(3):233-239. doi: 10.21147/j.issn.1000-9604.2024.03.01

