Guidelines

Updates in version 2019 of CSCO guidelines for colorectal cancer from version 2018

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According to the latest data from cancer registration center, there are estimated to be 3,929,000 individuals newly diagnosed with cancer and 2,338,000 deaths from this disease in China in 2015 (1). Among them, colorectal cancer (CRC) with 388,000 newly diagnosed cases and 187,000 deaths, stands the third place in incidence and the fifth place in mortality. The Chinese Society of Clinical Oncology (CSCO) has organized an expert committee to write and publish the Guideline for Colorectal Cancer in 2017. And its English version has already been published in March 2019 (2). According to the latest progress, the expert committee updated the guideline to the 2019 version in this April, and the summary of the main updates are as following.

Updates related with imaging diagnosis

Recommendation of computed tomography (CT) virtual colonoscopy (class II) was deleted and recommendation of plain chest CT was added as class II in the CRC diagnosis.

Recommendation of structured imaging report for rectal cancer was added, which needs to include tumor location, depth of tumor invasion and the relation to surrounding structures or organs (T stage), regional lymph node metastasis (N stage), extramural venous invasion (EMVI), circumferential resection margin (CRM), distant metastases (non-regional lymph node, liver, peritoneum and lung) as well as vascular and intestinal anatomical variation (3-5).

Updates related with molecular pathological diagnosis

KRAS, *NRAS* and *BRAF* gene mutation was recommended to be detected by direct DNA sequencing method or ARMS method. High-throughput sequencing or next-generation sequencing (NGS) technology, which has higher and faster throughput, has been increasingly applied to clinical genetic testing. The NGS platform and testing protocols adopted for mutation detection should be certificated. Only through strict quality control and standardized operation, the accuracy of testing results can be ensured.

Updates related with postoperative adjuvant therapy

Definition of stage II CRC with low risk [T3N0M0, defection of mismatch repair function (dMMR)], general

risk [T3N0M0/proficient in DNA MMR (pMMR) without clinical high-risk factors] and high risk (T3N0M0/pMMR with clinical high-risk factors, or T4N0M0) has been clarified. For stage II CRC patients with general risk, recommendation of the "observation" is modified from class I to class II.

In addition to irinotecan, S-1, TAS-102, bevacizumab, cetuximab, panitumumab, aflibercept and regorafenib, fruquintinib and all immune checkpoint inhibitors (pembrolizumab and nivolumab, etc.) were not recommended in adjuvant therapy.

Updates related with treatment of metastatic colon cancer

For the treatment of potentially resectable metastatic colon cancer with RAS/BRAF wide type, further stratification has been made according to the primary tumor location (the left-side *vs*. the right-side colon). Regardless of *RAS* and *BRAF* gene status, recommendation of FOLFOXIRI ± bevacizumab is modified from class II to class I (Level 2A evidence) (6).

In the first-line palliative treatment, the patients with both *RAS* and *BRAF* wide type who are suitable for intensive treatment are further stratified by the primary tumor location (the left-side *vs*. the right-side colon). For patients with left-sided colon cancer, doublet chemotherapy plus cetuximab is preferred. For patients with right-side colon cancer, doublet chemotherapy plus bevacizumab is preferred (7). For patients with right-side colon cancer who had contraindications of bevacizumab, doublet chemotherapy plus cetuximab are recommended as class II recommendation (Level 2A evidence). For these patients who are not suitable for intensive treatment, but with a high microsatellite instability (MSI-H) or dMMR, immune checkpoint inhibitors were recommended as class II (Level 2A evidence).

In the second-line palliative treatment, recommendation of immune checkpoint inhibitors was added as class II recommendation for patients with MSI-H or dMMR, regardless of *RAS*/*BRAF* gene status and the first-line regimen (Level 2A evidence) (8-10). Recommendation of irinotecan plus capecitabine ± bevacizumab is modified from class III to class II (Level 1B evidence) (11,12). For patients with *RAS* wild type and $BRAF^{V600E}$ mutation, phase II clinical trial, SWOG 1406 have revealed that BRAF inhibitor vemurafenib plus irinotecan and cetuximab (VIC) resulted in a prolongation of progression-free survival (PFS, 4.4 *vs*. 2.0 months) and a higher disease control rate (67% *vs*. 22%) than irinotecan plus cetuximab, so recommendation of VIC regimen was added as class III (Level 2B evidence) (13).

In the third-line palliative treatment, based on the FRESCO randomized clinical trial, oral fruquintinib compared with placebo, resulted in significantly prolonged PFS (3.7 *vs*. 1.8 months) and overall survival (OS) (9.3 *vs*. 6.6 months) for Chinese patients with metastatic CRC. Consequently, regardless of *RAS* and *BRAF* gene status, furquinitinib is recommended as class I recommendation (Level 1A evidence) (14). In addition, regardless of *RAS*/*BRAF* gene status and previous treatments, recommendation of immune checkpoint inhibitors was added as class II (Level 2A evidence) for MSI-H or dMMR tumors (8-10). And vemurafenib plus irinotecan and cetuximab was added as class III recommendation (Level 2B evidence) for patients with *RAS* wild type and $BRAF^{V600E}$ mutation (13).

Furthermore, in the footnotes, two points have been added that "In the first cycle of regorafenib, the dose titration can be used: 80 mg/d in the first week, 120 mg/d in the second week, 160 mg/d in the third week" (15) and "For the patients with homozygous or heterozygous variants of *UGT1A1*28* and **6*, the dose of irinotecan could be reduced".

Updates related with treatment of rectal cancer

For cT1N0 low rectal cancer patients with a strong desire to preserve the anus, "wait and watch" strategy was suggested as a class II recommendation, in case the tumor was evaluated as clinical complete remission (cCR) (16) after neoadjuvant chemoradiotherapy. Similarly, for cT3/cT4 N+ low rectal cancer patients with a strong desire to preserve the anus, recommendation of "wait and watch" was also added as class II if the tumor was evaluated as cCR after neoadjuvant chemoradiotherapy.

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Footnote

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

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