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Colon cancer: the 2023 Korean clinical practice guidelines for diagnosis and treatment

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Colorectal cancer is the third most common cancer in Korea and the third leading cause of death from cancer. Treatment outcomes for colon cancer are steadily improving due to national health screening programs with advances in diagnostic methods, surgical techniques, and therapeutic agents. The Korea Colon Cancer Multidisciplinary (KCCM) Committee intends to provide professionals who treat colon cancer with the most up-to-date, evidence-based practice guidelines to improve outcomes and help them make decisions that reflect their patients' values and preferences. These guidelines have been established by consensus reached by the KCCM Guideline Committee based on a systematic literature review and evidence synthesis and by considering the national health insurance system in real clinical practice settings. Each recommendation is presented with a recommendation strength and level of evidence based on the consensus of the committee.

Keywords: Colonic neoplasms; Diagnosis; Genetics; Therapy; Humans

INTRODUCTION

Colorectal cancer is the third most common cancer in Korea. It accounts for 10.9% of all cancer deaths, the third highest mortality rate among all cancers [1]. Treatment outcomes for colon cancer have steadily improved, with a 5-year survival rate of about 72% [2]. Various diagnostic and therapeutic approaches have been proposed in recent years. Personalized precision medicine based on genetic information is also being pursued. However, the safety and effectiveness of new treatments need to be verified. In addition, there are different views on optimal drug selection, timing, treatment sequence, and duration, which need to be established based on scientific evidence. In recognition of the need for a multidisciplinary colorectal cancer guideline that reflects the latest knowledge in the Korean health insurance system and the actual situation in the field, a multidisciplinary committee composed of experts from various medical departments specializing in colorectal cancer care was organized to develop evidence-based practice guidelines for the diagnosis and treatment of colon cancer.

METHODS

Methodology

The guidelines were developed by both adapting previous guidelines and *de novo* development through brainstorming by the members of the development committee. These guidelines have 7 newly developed key questions (KQs) and 10 updated KQs selected from the previous version. The systematic review followed the methodology outlined by Cochrane [3]. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology was adopted to assess the quality of evidence and determine the strength of the recommendation (SoR) [4].

Synthesis of evidence

Literature search

A literature search was conducted through MEDLINE (PubMed) using primary search terms derived through discussions with methodology experts (Supplementary Material 1). A systematic literature search was conducted in MEDLINE, Embase, Cochrane, and KoreaMed databases for articles updated since the references used in the previous guideline version through August 2022 and from inception until August 2022 for *de novo* KQs. The retrieved articles were screened by applying inclusion and exclusion criteria

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in a PICOS (population, intervention, comparator, outcomes, and study design) format by at least 2 committee members assigned to each KQ. The literature selection process was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [5] flow diagram (Supplementary Fig. 1).

Assessment of risk of bias

The quality of the literature was assessed independently by at least 2 reviewers for each KQ using assessment tools selected according to the study design (Table 1) [6–10]. Discrepancies in the assessment results were resolved by discussion. The results of the individual evidence quality assessments are presented in Supplementary Fig. 2 [11–220].

Level of evidence

The level of evidence (LoE) was determined according to the GRADE group's criteria [4]. This assessment was done in consultation with a methodology expert and individual KQ members (Table 2).

Table 1. Tools for assessing risk of bias

Study type	Tool
Randomized controlled study	Cochrane RoB 2 [6]
Nonrandomized controlled study	ROBINS-I [7]
Diagnostic study	QUADAS-2 [8]
Cross-sectional study	QUADAS-C [9]
Systematic review	AMSTAR 2 [10]

RoB, Risk-of-Bias Tool for Randomized Trials; ROBINS-I, Risk of Bias in Nonrandomized Studies of Intervention; QUADAS, Quality Assessment of Diagnostic Accuracy Studies; QUADAS-C, QUADAS-Comparative; AMSTAR, A Measurement Tool to Assess Systematic Reviews.

Formulation of recommendations

Investigation of the values and preferences of the target population

A 19-question survey of health outcome priorities and preferences was administered to 56 patients diagnosed and treated for colon cancer of all stages.

Strength of recommendations

Each KQ member developed draft recommendations and SoR based on the GRADE grid method by considering the strengths and limitations of the evidence, the magnitude and balance of benefits and harms, patient values and preferences, physician barriers, financial factors, and applicability in their practice setting using a summary of the evidence and the LoE [221] (Table 3).

Recommendation consensus

The draft recommendations and SoR were discussed in a development committee meeting and a consensus was reached through a blind vote of all members conducted on August 28, 2023. The internal committee recommendation grading process was attended by at least 70% of all committee members. The committee's decision was deemed a consensus if at least 70% of the votes were cast on an individual item and at least 70% of the votes were in favor. If less than 70% of the votes were in favor, the development committee members considered amendments and a second vote was taken.

Table 2. Level of evidence

Level of evidence	Definition
High	High evidence from a well-conducted RCT/meta-analysis with low risk of bias in study design and conduct, or from an observational study with no bias in study design or conduct and an effect size rated as very large
Moderate	Evidence from an RCT/meta-analysis with bias in study design and conduct, or from an observational study with no bias in study design or conduct and a large effect size
Low	Evidence from an RCT/meta-analysis with study design and conduct flaws raised in more than one item, or from an observational study with no study design or conduct flaws
Very low	Evidence from observational studies with study design and conduct flaws, case reports, or poorly systematized observational studies

RCT, randomized controlled trial.

Table 3. Strengths of the recommendations and implications for clinical practice

Strength of recommendation	Definition
Strong recommendation	Strongly recommended in most clinical situations, given the benefits and harms of the treatment, level of evidence, values and preferences, and resources
Conditional recommendation	The use of these treatments may depend on the clinical situation or patient/societal values. They might be used selectively or conditionally
Conditional against	In some situations or conditions, implementation is not recommended because harms of the treatment may outweigh its benefits based on the clinical situation and/or patient/social value
Strong against	It is not recommended in most clinical situations because the harms of the treatment outweigh the benefits, considering the clinical situation and/or patient/social value

Endorsement process

External expert review

Twenty-three external experts in fields related to colon cancer diagnosis and treatment who were not members of the development committee were selected to evaluate the recommendations and assess their acceptability. They reviewed the KQs, the objectivity of the recommendation, the overall balance of benefits and harms from the evidence assessment, recommendation direction and SoR based on the strengths and limitations of the evidence.

Public hearing

Public hearings were held to survey and incorporate feedback on the direction of the recommendations and the SoRs.

Guideline update plan

When high-quality evidence is reported on new diagnostic methods, drugs, and therapies, the guideline will be revised by adding new recommendations or revising or supplementing existing recommendations. If new evidence is reported, the committee will evaluate the evidence and discuss how to revise the recommendations. If high-quality evidence is reported for un outcome with a current recommendation, the committee will consider raising the LoE for that recommendation.

RESULTS

Recommendation	Recommendation strength	Level of evidence	Method
Diagnosis			
KQ 1. What imaging studies should be performed if liver metastases are suspected on abdominal computed tomography (CT) for staging in a patient with colon cancer?			Updated
1-1. Liver magnetic resonance imaging (MRI) is recommended if metastases localized to the liver are suspected or if liver resection is considered.	Do (strong)	Low	
1-2. When liver metastases are suspected in patients with colon cancer, positron emission tomography (PET)-CT is recommended for radical treatment decisions.	Do (strong)	Low	
KQ 2. Is the addition of PET-CT more effective than CT alone in patients with metastatic colon cancer?			Updated
In patients with metastatic colon cancer, PET-CT is useful for detecting metastatic lesions not detected on contrast-enhanced CT. PET-CT is recommended for treatment decision-making in metastatic colon cancer.	Do (strong)	Very low	
KQ 3. What tests can be considered for proximal colon evaluation in patients with left obstructive colon cancer where evaluating the proximal colon on preoperative colonoscopy is difficult?			Updated
In patients with left obstructive colon cancer where the proximal segment is difficult to evaluate on preoperative colonoscopy, CT colonography, PET-CT, and completion colonoscopy may be considered for proximal evaluation.	Do (conditional)	Very low	
Intervention or surgery			
KQ 4. Following the endoscopic resection of colorectal submucosal cancer (cT1N0M0) with a histopathologic diagnosis of completely resected (margin negative) submucosal adenocarcinoma, what risk factors for lymph node metastasis should be considered for additional colectomy?			Updated
Further radical surgery should be considered in patients at high risk for lymph node metastasis, such as those with lymphovascular/perivascular involvement, poorly differentiated/undifferentiated, deep submucosal invasion, and high-tier tumor budding, even if complete resection is achieved endoscopically.	Do (strong)	Very low	
KQ 5. Does D3 lymph node dissection or complete mesocolic excision/central vessel ligation contribute to reduced recurrence and improved survival in surgery for right-sided colorectal cancer without distant metastases?			*De novo*
D3 lymph node dissection or complete mesocolic excision/central vessel ligation is recommended for nonmetastatic right-sided colon cancer.	Do (conditional)	Very low	
KQ 6. Is the use of self-expanding metallic stents (SEMS) for preoperative decompression recommended in obstructive colon cancer?			*De novo*
6-1. Preoperative stenting is not always recommended in operable obstructive right-sided colon cancer.	Do not (conditional)	Very low	
6-2. Preoperative stenting in operable obstructive left-sided colon cancer may be considered in selected cases.	Do (conditional)	Very low	

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Recommendation	Recommendation strength	Level of evidence	Method
Pathology			
KQ 7. What is the appropriate number of lymph node examinations for proper lymph node staging of stage II and III colon cancer?			Updated
For proper lymph node staging, the dissection and examinations of least 12 lymph nodes are recommended for pathologic diagnosis.	Do (strong)	Low	
KQ 8. Should microsatellite instability (MSI) testing be performed for all colon cancer patients to screen for Lynch syndrome?			*De novo*
MSI test is recommended for all patients with colon cancer to screen for Lynch syndrome.	Do (conditional)	Low	
KQ 9. Is *KRAS, NRAS,* or *BRAF* gene testing necessary to determine targeted therapy for epidermal growth factor receptor (EGFR) as first-line chemotherapy in patients with metastatic colon cancer?			Updated
KRAS, NRAS, and *BRAF* genetic testing are recommended to determine the appropriateness of EGFR-targeted therapy as first-line chemotherapy in patients with metastatic colon cancer.	Do (strong)	Moderate	
Chemotherapy			
KQ 10. Is adjuvant chemotherapy after curative resection necessary for high-risk stage II colon cancer patient?			Updated
Adjuvant chemotherapy after surgery is recommended for high-risk stage II colon cancer patients	Do (conditional)	Low	
KQ 11. Is 3 months of adjuvant chemotherapy with oxaliplatin oncologically safe for patients with stage III colon cancer compared to 6 months?			*De novo*
11-1. Three months of adjuvant chemotherapy with oxaliplatin may be considered for patients with low-risk stage III (pT1–3N1) after colon cancer surgery.	Do (conditional)	Low	
11-2. Three months of FOLFOX (folinic acid, fluorouracil and oxaliplatin) is not recommended as adjuvant chemotherapy in patients with high-risk stage III (pT4 or N2) after colon cancer surgery.	Do not (conditional)	Low	
KQ 12. Does immunotherapy provide a better response rate in patients with metastatic colon cancer with MSI-high (MSI-H)/ MMR protein deficiency (dMMR) than conventional chemotherapy?			*De novo*
Immunotherapy is recommended for patients with MSI-H/dMMR metastatic colon cancer.	Do (conditional)	Low	
KQ 13. In patients with locally advanced colon cancer, is the addition of neoadjuvant chemotherapy oncologically superior to surgery alone?			Updated
Neoadjuvant chemotherapy may be considered a treatment option for patients with locally advanced colon cancer to reduce recurrence rates.	Do (conditional)	Low	
Resectable metastastic colon cancer			
KQ 14. What is the appropriate treatment for patients with resectable colon cancer liver metastases?			Updated
14-1. For theradical treatment of patients with a single colon cancer liver metastasis of 3 cm or less, hepatectomy is more effective than radiofrequency thermotherapy (RFA).	Do (strong)	Very low	
14-2. In patients with resectable colon cancer liver metastases, simultaneous resection versus staged resection is an option.	Do (conditional)	Very low	
14-3. In patients with resectable colon cancer liver metastases, either surgery after neoadjuvant chemotherapy or upfront surgery can be considered.	Do (conditional)	Very low	
KQ 15. Does pulmonary metastasectomy improve survival in patients with colon cancer lung metastasis?			Updated
Pulmonary metastasectomy is considered for resectable colon cancer lung metastases.	Do (conditional)	Very low	
KQ 16. Do cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) improve survival in patients with colon cancer with peritoneal metastases?			*De novo*
CRS and selective HIPEC are recommended for patients with colon cancer with resectable peritoneal metastases	Do (conditional)	Low	
Unresectable metastatic colon cancer			
KQ 17. Is second-line palliative chemotherapy recommended for improving survival and quality of life in patients with metastatic colon cancer after the failure of first-line palliative chemotherapy?			Updated
Second-line palliative chemotherapy is recommended for patients with metastatic colon cancer that have failed first-line palliative chemotherapy to improve survival and quality of life.	Do (conditional)	Low	

DIAGNOSIS

Topic: **Diagnosis**

KQ 1. What imaging studies should be performed if liver metastases are suspected on abdominal CT for staging in a patient with colon cancer?

Recommendation 1-1.
Liver MRI is recommended if metastases localized to the liver are suspected or if liver resection is considered.
Strength of the recommendation: do (strong)
Level of evidence: low

Recommendation 1-2.
When liver metastases are suspected in patients with colon cancer, PET-CT is recommended for radical treatment decisions.
Strength of the recommendation: do (strong)
Level of evidence: low

The resection of liver metastases can improve prognosis. Determining treatment intent and resectability is important [222]. Meta-analyses have indicated that MRI outperforms CT in detecting small metastatic lesions and characterizing indeterminate lesions (Supplementary Figs. 3, 4) [11–18, 20–56, 223]. Therefore, MRI is the best option for accurately diagnosing liver metastases on a per-lesion basis. In situations where a treatment decision between curative and palliative therapy is required, it is important to determine the presence or absence of distant metastases at the patient level. PET-CT is recommended because of its high accuracy in per-patient analysis (Supplementary Fig. 5) [19, 40, 42–44, 46, 49, 50, 56]. PET-CT has the advantage of being able to accurately diagnose distant metastases to organs other than the liver. For both MRI and PET-CT, patient value and preference surveys showed that most patients were either in favor of additional testing or supportive of it at the discretion of their physicians, indicating that additional testing for an accurate diagnosis is supported by patients.

Topic: **Diagnosis**

KQ 2. Is the addition of PET-CT more effective than CT alone in patients with metastatic colon cancer?

Recommendation 2.
In patients with metastatic colon cancer, PET-CT is useful for detecting metastatic lesions not detected on contrast-enhanced CT. PET-CT is recommended for treatment decision-making in metastatic colon cancer.
Strength of recommendation: do (strong)
Level of evidence: very low

PET-CT has a higher diagnostic sensitivity for metastatic lesions than contrast-enhanced CT (Supplementary Fig. 6) [44, 47, 52, 60, 61, 63, 67, 71]. The concordance between PET-CT and contrast-enhanced CT for metastatic lesions ranges from 71% to 90% for liver metastases, with the concordance being lower for extrahepatic metastases than for liver metastases [47, 58, 65, 75]. Additional metastatic lesions can be detected by PET-CT. PET can also detect secondary or synchronous colon cancer [57, 58, 60, 63, 67]. PET-CT can detect additional extrahepatic metastases in 0.4 to 37.1% of cases compared to traditional diagnostics alone. PET-CT results led to treatment changes in 6.8%–53.9% of colon cancer patients [44, 47, 52, 57–75].

Topic: **Diagnosis**

KQ 3. What tests can be considered for proximal colon evaluation in patients with left obstructive colon cancer where evaluating the proximal colon on preoperative colonoscopy is difficult?

Recommendation 3.
In patients with left obstructive colon cancer where evaluating the proximal segment on preoperative colonoscopy is difficult, CT colonography, PET-CT, and completion colonoscopy may be considered for proximal evaluation.
Strength of recommendation: do (conditional)
Level of evidence: very low

In patients with obstructive colorectal cancer where the proximal colon could not be evaluated, CT colonography, PET-CT, and completion colonoscopy after stent insertion detected synchronous cancer in the proximal colon in 1.4%–15%, 4.1%– 9.7%, and 2.5%–10% of the cases, respectively, showing very high accuracy and leading to a change in the scope of surgery or a change in treatment for those patients [76–83, 85–91, 224].

CT colonography is a CT scan without the insertion of an endoscope, which allows for the evaluation of the inner colon using computerized techniques. This technique can be useful when the entire colon cannot be evaluated due to structural causes such as colonic obstruction or other technical difficulties [225]. PET-CT can detect suspected malignant lesions even when morphologic variation is severe or direct histologic examination is difficult. In addition to detecting proximal colorectal cancer, PET-CT can help detect metastatic lesions. In addition, if a preoperative abdominal CT scan suggests a proximal colon lesion and a histologic diagnosis is needed for treatment planning, completion of the colonoscopy which refers to preoperative full colonoscopic evaluation after effective stent placement with a small-diameter endoscope should be considered. Its benefits may be significant.

Additional testing to evaluate the proximal colon should be

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considered in patients with obstructive colorectal cancer when feasible, as the discovery of proximal lesions may alter the scope of surgery. Failure to diagnose them may result in the need for secondary surgery or the failure of radical therapy.

INTERVENTION OR SURGERY

Topic: Surgery

KQ 4. Following the endoscopic resection of colorectal submucosal cancer (cT1N0M0) with a histopathologic diagnosis of completely resected (margin negative) submucosal adenocarcinoma, what risk factors for lymph node metastasis should be considered for additional colectomy?

Recommendation 4.
Further radical surgery should be considered in patients at high risk for lymph node metastasis, such as those with lymphovascular/perivascular involvement, poorly differentiated/undifferentiated, deep submucosal invasion, and high-tier tumor budding, even if complete resection is achieved endoscopically.
Strength of recommendation: do (strong)
Level of evidence: very low

Submucosal cancers of the colon are those in which the infiltration of cancer cells is confined to mucosal and submucosal layers. The need for further radical resection has long been debated. A lymph node metastasis rate of around 10% has been reported [226]. Tumors are generally classified as high-risk for lymph node metastasis if there is margin involvement, lymphovascular/vascular invasion, poorly differentiated/undifferentiated, deep submucosal involvement, or high-tier tumor budding, which has recently been reported to increase the risk of lymph node metastasis [92–102, 104–113, 115–119]. The presence of each risk factor is associated with a more than 3-fold increase in the odds ratio for lymph node metastasis risk (Supplementary Fig. 7) [92–95, 97–102, 105–108, 110–112, 115, 116, 118, 119]. Therefore, we recommend radical resection with lymph node dissection in high-risk patients with any 1 risk factor after endoscopic resection for submucosal cancer and surveillance rather than further radical resection in low-risk patients without all the above findings.

Limited imaging tests are currently available to determine the presence of lymph node metastases in colorectal cancer. When deciding on further radical surgery, considering the patient's general condition and risk of lymph node metastasis is recommended. The decision should be made after full consultation with the medical team and the patient.

Topic: Surgery

KQ 5. Does D3 lymph node dissection or complete mesocolic excision/central vessel ligation contribute to reduced recurrence and improved survival in surgery for right-sided colorectal cancer without distant metastases?

Recommendation 5.
D3 lymph node dissection or complete mesocolic excision/central vessel ligation is recommended for surgery for nonmetastatic right-sided colon cancer.
Strength of recommendation: do (conditional)
Level of evidence: very low

Meta-analysis studies showed that patients who underwent extensive lymphadenectomy (D3 lymph node dissection or complete mesocolic excision/central vessel ligation) had statistically significant survival benefits over patients who did not undergo extensive lymphadenectomy, including longer overall survival (OS) (risk ratio [RR], 0.78; 95% confidence interval [CI], 0.67–0.92), better disease-free survival (DFS; RR, 0.68; 95% CI, 0.55–0.84), higher cancer-specific survival (CSS; RR, 0.27; 95% CI, 0.13–0.57), and lower recurrence rate (RR, 0.55; 95% CI, 0.43–0.70) (Supplementary Fig. 8) [120–126, 128, 227–229]. However, meta-analysis studies and prospective randomized clinical trials (RCTs) comparing short-term postoperative outcomes between extensive lymphadenectomy and no extensive lymphadenectomy did not show significant differences in outcomes related to complications such as anastomotic leakage, postoperative recovery, or reoperation [230, 231]. D3 lymph node dissection or complete mesocolic excision/central vessel ligation is recommended as it has a lower recurrence rate, a survival benefit, and minimal harm compared to no extensive lymphadenectomy.

Nonetheless, mandatory implementation of D3 lymph node dissection or complete mesocolic excision with central vessel ligation may not be recommended for early-stage colon cancer patients lacking preoperative lymph node metastases and exhibiting tumor invasion limited to the submucosal layer. Likewise, such procedures may be unsuitable for individuals at high surgical risk due to advanced age or comorbidities.

Topic: Intervention

KQ 6. Is the use of SEMS for preoperative decompression recommended in obstructive colon cancer?

Recommendation 6-1.
Preoperative stenting is not always recommended in operable obstructive right-sided colon cancer.
Strength of recommendation: do not (conditional)
Level of evidence: very low

Recommendation 6-2.
Preoperative stenting in operable obstructive left-sided colon cancer may be considered in selected cases.
Strength of recommendation: do (conditional)
Level of evidence: very low

Meta-analysis studies showed a lower rate of stoma formation in the SEMS group of patients with right-sided obstructive colon cancer than in the emergency surgery (ES) group (Supplementary Fig. 9) [129–136]. However, most studies had few cases of stoma formation in each group. Thirty-day mortality was lower in the SEMS arm, and there was no significant difference in the open conversion rate (Supplementary Fig. 9) [129–136]. In terms of oncologic outcomes, 3-year DFS was higher in the SEMS arm (RR, 1.23; 95% CI, 1.02–1.49; P=0.03), while no significant difference in 5-year DFS or 5-year OS (Supplementary Fig. 10) [129, 131–135]. The serious complication of bowel perforation may occur during SEMS insertion, although it is not frequent. In many cases of right-sided colon cancer, primary anastomosis without stoma creation is possible without preoperative decompression. In clinical practice, SEMS insertion is limited by the patient's visit time, emergency level, and the human and material resources of the institution. Because the benefits of the procedure do not outweigh the harm it may cause and the resources it requires, SEMS insertion for preoperative decompression is not always recommended for surgically curable obstructive right-sided colon cancer.

In patients with left-sided obstructive colon cancer, the SEMS group showed significantly lower rates of stoma formation and overall complication but higher primary anastomosis rates than the ES group (Supplementary Fig. 11) [137, 138, 140–153]. Regarding oncologic outcomes, the recurrence rate in the SEMS group was significantly higher than in the ES group (RR, 1.39; 95% CI, 1.09–1.78; P=0.006) when data were analyzed by including only RCTs. Three-year DFS, 5-year DFS, 3-year OS, and 5-year OS showed substantial heterogeneity, although no significant differences were seen between the 2 groups (Supplementary Fig. 12) [137, 138, 141, 142, 145, 146, 148–152, 232]. While SEMS insertion has demonstrated superiority over ES in short-term outcomes such as the stoma formation rate, overall complications, and primary anastomosis rate in patients with left-sided obstructive colon cancer, there are concerns about recurrence. A significant difference in the recurrence rate depending on the occurrence of perforation was reported in a SEMS group [135]. In operatively curable obstructive left colon cancer, SEMS insertion may be considered by experienced interventionists in selected patients, as adequate preoperative decompression with SEMS insertion increases the likelihood of primary anastomosis without creating a stoma.

PATHOLOGY

Topic: Pathology

KQ 7. What is the appropriate number of lymph node examinations for proper lymph node staging of stage II and III colon cancer?

Recommendation 7.
For proper lymph node staging, the dissection and examinations of at least 12 lymph nodes are recommended for pathologic diagnosis.
Strength of recommendation: do (strong)
Level of evidence: low

There are limitations in that each previous study had a different patient population and that the number of lymph node examinations was decided according to various self-criteria, making it difficult to conduct a comprehensive analysis. However, most studies classified patients based on 12 lymph nodes. Thus, the present meta-analysis was performed based on 12 lymph nodes. The meta-analysis showed a significant reduction in overall mortality (hazard ratio [HR], 0.78; 95% CI, 0.72–0.85) with increases in the number of lymph nodes dissected (Supplementary Fig. 13) [154, 158, 162–164]. Lee et al. [158] found reductions in the recurrence rate with increasing numbers of lymph nodes dissected (HR, 0.59; 95% CI, 0.41–0.85). However, their study was limited by very low quality of evidence. Patient values and preferences surveys also suggest that patients would prefer to have more than 12 lymph nodes removed, as curing and minimizing recurrence are top priorities in colon cancer treatment.

Topic: Pathology

KQ 8. Should MSI testing be performed for all patients with colon cancer to screen for Lynch syndrome?

Recommendation 8.
MSI test is recommended in all patients with colon cancer to screen for Lynch syndrome.
Strength of recommendation: do (conditional)
Level of evidence: low

Microsatellite instability (MSI) testing can detect abnormalities in the number of microsatellites repeats in the sequences of patients with Lynch syndrome or sporadic tumors. It has a theoretical sensitivity of 100% for colon cancer caused by Lynch syndrome. In a meta-analysis, patients with positive MSI accounted for approximately 11% of all colon cancer patients and approximately 22% of all colon cancer patients who met the revised Bethesda guidelines criteria and required genetic testing to confirm Lynch syndrome (Supplementary Fig. 14A, B) [165–173]. Among patients ulti-

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mately diagnosed with Lynch syndrome after screening with MSI testing and genetic testing for confirmation, 22% did not meet the revised Bethesda guidelines criteria (Supplementary Fig. 14C) [165–167, 169, 173].

In a survey of patient values and preferences, 59% of patients agreed with the use of MSI testing to screen for Lynch syndrome, 30% preferred their physician's judgment, and 7% preferred genetic testing to confirm Lynch syndrome without screening.

Topic: Pathology

KQ 9. Is *KRAS, NRAS,* or *BRAF* gene testing necessary to determine targeted therapy for EGFR as first-line chemotherapy in patients with metastatic colon cancer?

Recommendation 9.
KRAS, NRAS, and *BRAF* genetic testing are recommended to determine the appropriateness of EGFR-targeted therapy as first-line chemotherapy in patients with metastatic colon cancer.
Strength of recommendation: do (strong)
Level of evidence: moderate

Meta-analysis results in this study confirmed a difference in progression-free survival (PFS) with the use of anti-EGFR antibody in both *KRAS* wide type (WT) and mutant type (MT) tumors. In *KRAS* WT, the use of anti-EGFR antibody was associated with PFS benefits (HR, 0.66; 95% CI, 0.58–0.74) and OS (HR, 0.76; 95% CI, 0.67–0.86). In MT tumors, the use of targeted therapy adversely affected PFS (HR, 1.22; 95% CI, 1.06–1.41) with no significant difference in OS. The survival benefit of using anti-EGFR antibody based on *KRAS* testing was 24% for OS and 22% to 34% for PFS (Supplementary Fig. 15A, B) [174, 175, 177, 178]. Targeted therapy had PFS benefits in *NRAS* WT tumors (HR, 0.72; 95% CI, 0.58–0.89) and OS (HR, 0.77; 95% CI, 0.64–0.93), while in *NRAS* MT, there was no significant difference in PFS or OS (Supplementary Fig. 15C) [176]. The survival benefit of using anti-EGFR antibody with *NRAS* testing was 23% for OS and 28% for PFS.

Analyses showed that *BRAF* WT had superior PFS and OS in patients treated with targeted therapies compared to MT (Supplementary Fig. 15D) [179, 180]. However, these studies did not compare outcomes with and without targeted therapies. Thus, the survival benefit associated with *BRAF* testing and using targeted therapies is unknown. An analysis of randomized studies of *RAS*-WT/*BRAF*-MT patients found no difference in OS or PFS with or without anti-EGFR antibody treatment [233]. These results suggest that *BRAF* genetic testing can be used as a rationale for avoiding targeted therapies in *BRAF* MT patients undergoing first-line chemotherapy.

The sensitivity and specificity of both *RAS* and *BRAF* genetic testing are >95%. Thus, the likelihood of misusing targeted therapies due to incorrect genetic testing results is low. Although there is a cost associated with the test, 96% of patients agreed with testing in a survey on patient values and preferences. A 2012–2013 survey of more than 300 oncologists in 5 European countries found that 99.3% of the physicians performed *KRAS* genetic testing before using anti-EGFR antibody [234].

CHEMOTHERAPY

Topic: Chemotherapy

KQ 10. Is adjuvant chemotherapy after curative resection necessary for high-risk stage II colon cancer patients?

Recommendation 10.
Adjuvant chemotherapy after surgery is recommended for high-risk stage II colon cancer patients.
Strength of recommendation: do (conditional)
Level of evidence: low

High-risk stage II colon cancer is defined as having at least one of the following risk factors: T4 tumor, bowel obstruction or perforation, lymphatic or vascular invasion, perineural invasion, lymph node yield of fewer than 12, poorly differentiated tumor, and positive margins. In high-risk stage II colon cancer, when comparing the adjuvant chemotherapy group to the surgery alone group, a statistically significant increase in OS was seen (HR, 0.62; 95% CI, 0.46–0.95) but no significant difference in DFS (HR, 0.76; 95% CI, 0.57–1.02) or recurrence-free survival (RFS; HR, 1.01; 95% CI, 0.79–1.29) (Supplementary Fig. 16A–C) [181–187, 235]. One prospective study reported adverse effects of adjuvant chemotherapy after surgery for high-risk stage II colon cancer that included elevated alanine aminotransferase and aspartate aminotransferase levels, decreased appetite, diarrhea, and nausea (Supplementary Fig. 16D) [186]. However, the number of events was low. In addition, such risks were not thought to outweigh the survival benefit. Curing and minimizing recurrence were top priorities for patients in the survey, with 86% of all respondents agreeing that they would accept the adverse effects of chemotherapy to improve survival outcomes.

Topic: Chemotherapy

KQ 11. Is 3 months of adjuvant chemotherapy with oxaliplatin oncologically safe for patients with stage 3 colon cancer compared to 6 months?

Recommendation 11-1.
Three months of adjuvant chemotherapy with oxaliplatin may be considered for patients with low-risk stage III (pT1–3N1) after colon cancer surgery.
Strength of recommendation: do (conditional)
Level of evidence: low

Recommendation 11-2.
Three months of FOLFOX is not recommended as adjuvant chemotherapy for patients with high-risk stage III (pT4 or N2) after colon cancer surgery.
Strength of recommendation: do not (conditional)
Level of evidence: low

Meta-analysis showed that in patients with stage III colon cancer, 3 months of adjuvant chemotherapy significantly reduced the incidence of peripheral neuropathy without compromising OS compared to 6 months of adjuvant chemotherapy (Supplementary Fig. 17A, B) [188, 192, 236, 237]. While RFS was not significantly different between 3 or 6 months of CAPOX (capecitabine and oxaliplatin) or FOLFOX in patients with low-risk stage III, 3 months of FOLFOX led to inferior outcomes in patients with high-risk stage III (HR, 1.37; 95% CI, 1.11–1.69) (Supplementary Fig. 17C) [189–191, 238]. Therefore, adjuvant chemotherapy for 3 months is preferred for patients with low-risk stage III, showing a significant reduction in peripheral neuropathy without affecting survival outcome. In high-risk stage III, FOLFOX showed a clear disadvantage in RFS despite a reduction in peripheral neuropathy. Therefore, FOLFOX for 3 months is not recommended given its oncologic hazard.

Topic: Chemotherapy

KQ 12. Does immunotherapy provide better response rates in patients with metastatic colon cancer with MSI-H/dMMR than conventional chemotherapy?

Recommendation 12.
Immunotherapy is recommended for patients with MSI-H/dMMR metastatic colon cancer.
Strength of recommendation: do (conditional)
Level of evidence: low

Keynote-177, a randomized phase III study, compared immunotherapy (pembrolizumab) with conventional chemotherapy (FOLFOX or FOLFIRI [folinic acid, fluorouracil, and irinotecan] ± bevacizumab or cetuximab) [194]. PFS (HR, 0.59; 95% CI, 0.45–0.79) and the overall response rate (RR, 1.36; 95% CI, 1.02–1.81) were significantly improved in the pembrolizumab arm (Supplementary Fig. 18A, B) [194]. However, OS was not significantly different between the 2 groups (HR, 0.74; 95% CI, 0.53–1.03) (Supplementary Fig. 18B) [194]. Quality of life was significantly better in the pembrolizumab arm (Supplementary Fig. 18C) [193]. Phase II studies and retrospective studies also showed improved survival with immunotherapy in patients with MSI-H/dMMR metastatic colon cancer. PFS rates of 13 months and OS of 47 months were reported with pembrolizumab or nivolumab, whereas PFS of 6 to 7 months and OS of 13 to 28 months were reported with a conventional chemotherapy [195, 239–242].

In the Keynote-177 study, the incidence of grade 3 or higher treatment-related adverse events was also significantly lower in the pembrolizumab arm (22% vs. 66%; RR, 0.30; 95% CI, 0.22–0.42) (Supplementary Fig. 18A) [194]. The CheckMate 142 and Keynote-164 studies also reported less frequent adverse events in the pembrolizumab arm than in the conventional chemotherapy arm [195, 239]. Thus, immunotherapy can reduce treatment harm and improve survival and quality of life, consistent with patient values.

However, in Korea, immunotherapy for metastatic colon cancer is not covered by national health insurance. In addition, it is expensive, resulting in economic inequalities. For this reason, we reached a consensus with a conditional recommendation. If the national health insurance system changes its policy in the future, the SoR may be upgraded.

Topic: Chemotherapy

KQ 13. In patients with locally advanced colon cancer, is the addition of neoadjuvant chemotherapy oncologically superior to surgery alone?

Recommendation 13.
Neoadjuvant chemotherapy may be considered a treatment option in patients with locally advanced colon cancer to reduce recurrence rates.
Strength of recommendation: do (conditional)
Level of evidence: low

A randomized phase III study has compared 6 weeks of neoadjuvant chemotherapy followed by surgery to 18 or 24 weeks of adjuvant chemotherapy following surgery in patients with colon cancer clinically staged as T3–4, N0–2, or M0 on imaging studies. The study found that residual disease or recurrence rates at 2 years were significantly lower in the neoadjuvant chemotherapy group (16.9% vs. 21.5%; RR, 0.72; 95% CI, 0.54–0.98), although there was no difference in OS or CSS (Supplementary Fig. 19A) [196]. No statistically significant differences in postoperative complications, including anastomotic leakage and intra-abdominal abscess were seen (Supplementary Fig. 19B) [196]. In a survey of patient values and preferences, 36% agreed with preoperative chemotherapy and 59% said it depended on their surgeon's judgment.

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Given the lack of evidence for neoadjuvant chemotherapy in nonmetastatic colon cancer and the limitations of the radiologic diagnosis of lymph node metastases, overtreatment in node-negative patients is a concern. Thus, patients selection should be done carefully.

Although neoadjuvant chemotherapy has an unclear survival benefit, it was shown to reduce recurrence rates. In a comparison of groups that did and did not receive neoadjuvant chemotherapy, no significant differences were found in terms of postoperative complications, overall treatment duration, or cost, supporting the option of preoperative chemotherapy in select patients with locally advanced colon cancer to reduce recurrence rates.

RESECTABLE METASTATIC COLON CANCER

Topic: Resectable liver metastases

KQ 14. What is the appropriate treatment for patients with resectable colon cancer liver metastases?

Recommendation 14-1.
For the radical treatment of patients with a single colon cancer liver metastasis of 3 cm or less, hepatectomy is more effective than RFA.
Strength of recommendation: do (strong)
Level of evidence: very low

Recommendation 14-2.
In patients with resectable colon cancer liver metastases, simultaneous resection versus staged resection is an option.
Strength of recommendation: do (conditional)
Level of evidence: very low

Recommendation 14-3.
In patients with resectable colon cancer liver metastases, either surgery after neoadjuvant chemotherapy or upfront surgery can be considered.
Strength of recommendation: do (conditional)
Level of evidence: very low

All previous studies comparing hepatectomy and RFA were all retrospective. Because RFA was performed in high-risk patients, the results regarding treatment complications and survival outcomes should be cautiously interpreted [199, 203, 205]. The local recurrence rate was significantly lower in the resection group than in the RFA group (RR, 0.14; 95% CI, 0.05–0.38) (Supplementary Fig. 20) [199, 203, 205]. Although few major complications have been reported, it is difficult to conclude treatment-related harms due to bias in subject selection. Given the local recurrence rate, resection is the treatment of choice for resectable colon cancer liver metastases. Other modalities such as RFA, stereotactic body radiation therapy, microwave ablation, and cryoablation may be considered depending on surgical risk. However, there is insufficient evidence on the effectiveness and side effects of those modalities.

Whether simultaneous resection is more effective than staged resection remains inconclusive, with both approaches being used in real-world practice. OS and DFS were not significantly different between simultaneous versus staged resection. Simultaneous resection was not associated with a higher risk of complications compared to staged resection in a prospective randomized study (Supplementary Fig. 21) [197, 198, 204, 209]. Patient values and preferences surveys also showed that minimizing recurrence (43.0%) and the surgeon's judgment (39.3%) were the most important factors in deciding the timing of surgery. Clinically, the decision between simultaneous and staged resection can be made selectively based on clinical settings.

No statistical difference in 3-year DFS, 5-year DFS, or 5-year OS was found in a comparison of surgery after neoadjuvant chemotherapy versus upfront surgery (Supplementary Fig. 22A) [84, 200, 201, 206–208]. Postoperative complications tended to be higher in the surgery after neoadjuvant chemotherapy group than in the upfront surgery group. However, the difference did not appear to be significant, although some studies reported the contrary results (Supplementary Fig. 22B) [201, 202, 206–208]. In a survey of patient values and preferences, 26.8% responded that they would like to reduce the extent of surgery by receiving neoadjuvant chemotherapy, and 51.8% agreed that it was up to their surgeon. Surgery after neoadjuvant chemotherapy has the advantage of confirming chemosensitivity. However, it may make it more difficult to locate the lesion and increase the risk of postoperative complications. There is no difference in benefits or risks. Thus, either treatment can be chosen depending on the patient's condition.

Topic: Resectable lung metastases

KQ 15. Does pulmonary metastasectomy improve survival in patients with colon cancer lung metastasis?

Recommendation 15.
Pulmonary metastasectomy is considered for patients with resectable colon cancer lung metastases.
Strength of recommendation: do (conditional)
Level of evidence: very low

Studies on pulmonary metastasectomy for colon cancer are scarce because the patient population is heterogeneous, with different indications for local and systemic treatment depending on the number and extent of metastases at diagnosis. Two treatments are often combined in practice. Nevertheless, pulmonary metastasectomy for colon cancer is widely performed in clinical practice. A meta-analysis showed a trend toward better survival in patients

who underwent lung resection compared to patients treated without surgical resection (RR, 0.72; 95% CI, 0.51–1.03; P = 0.07) (Supplementary Fig. 23A) [211–213], although the difference was not statistically significant. Median survival was significantly longer in patients who underwent resection than in patients treated without surgical resection (RR, 0.76; 95% CI, 0.01–1.42; P = 0.02) (Supplementary Fig. 23B) [210, 211].

Pulmonary metastasectomy can be considered if the primary lesion has already been resected or is planned to be resected, pulmonary function is good, the risk of lung resection is low, and pulmonary metastatic lesions are resectable.

Topic: Resectable peritoneal metastasis

KQ 16. Do CRS and HIPEC improve survival in patients with colon cancer with peritoneal metastases?

Recommendation 16.
CRS and selective HIPEC are recommended for patients with colon cancer with resectable peritoneal metastases.
Strength of recommendation: do (conditional)
Level of evidence: low

Patients with colorectal cancer with peritoneal metastases typically are not expected to survive more than one year without treatment. However, even palliative chemotherapy can improve median survival from 12 months to 16 months [243]. Several studies demonstrated a significant survival benefit for patients who underwent CRS followed by HIPEC compared to palliative chemotherapy (HR, 0.55; 95% CI, 0.32–0.95) (Supplementary Fig. 24A) [215, 217–220]. When the incidence of grade 3 or higher complications was compared, no significant difference was seen between CRS followed by HIPEC and palliative chemotherapy (Supplementary Fig. 24B) [219].

However, the results recently reported from a phase III trial and prospective study that analyzed the effectiveness of CRS followed by HIPEC versus CRS alone in colorectal cancer with peritoneal metastases showed no additional survival benefit in patients who received CRS with oxaliplatin-based HIPEC compared to the CRS alone group (Supplementary Fig. 25A) [214, 244]. In a comparison of grade 3 or higher complications between the 2 groups, no difference in the rate of complications within 30 days was seen (Supplementary Fig. 25B) [214]. Therefore, in patients with colon cancer with resectable peritoneal metastases, CRS should be the cornerstone of treatment. The effectiveness of HIPEC remains unclear. Considering that high morbidity and mortality are associated with CRS, it is important to select candidates who might achieve the best outcomes.

UNRESECTABLE METASTATIC COLON CANCER

Topic: Palliative chemotherapy

KQ 17. Will second-line palliative chemotherapy improve survival and quality of life in patients with metastatic colon cancer after the failure of first-line palliative chemotherapy?

Recommendation 17.
Second-line palliative chemotherapy is recommended for patients with metastatic colon cancer that have failed first-line palliative chemotherapy to improve survival and quality of life.
Strength of recommendation: do (conditional)
Level of evidence: low

In metastatic colorectal cancer patients with disease progression after first-line palliative chemotherapy, treatment with irinotecan significantly improved survival compared with best supportive care (RR, 1.7; 95% CI, 1.24–2.35) (Supplementary Fig. 26A) [216]. Chemotherapy was also associated with fewer tumor-related side effects and better quality of life, although it showed side effects (Supplementary Fig. 26B, C) [216]. In patients with metastatic colon cancer who have failed first-line palliative chemotherapy, the priority in deciding on second-line palliative chemotherapy is to improve survival and quality of life. Therefore, second-line chemotherapy should be considered for patients with metastatic colorectal cancer.

CONCLUSION

These guidelines emphasize the importance of a personalized treatment plan based on a multidisciplinary approach to the management of colon cancer that takes the patient's values, preferences, and the evolving landscape of diagnostic and treatment options into consideration.

The recommended surgical technique for nonmetastatic right-sided colon cancer is complete mesocolic excision/central vessel ligation to reduce recurrence and improve survival outcomes. At least 12 lymph nodes should be examined for lymph node staging. In the management of obstructive colon cancer, decompression with preoperative stenting is not always necessary for right-sided colon cancer. However, it is recommended for left-sided colon cancer for adequate decompression with SEMS insertion. Adjuvant chemotherapy is recommended for patients with high-risk stage II and III after surgery. In low-risk stage III, 3 months of adjuvant chemotherapy with oxaliplatin may also be considered.

For metastatic colon cancer, liver MRI or PET is recommended

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to determine resectability and radical treatment decision. MSI testing and *KRAS, NRAS,* or *BRAF* gene testing are required when considering various treatment options. Resection may be considered for resectable liver or lung metastases. CRS and selective HIPEC are recommended for resectable peritoneal metastases. Immunotherapy provides better response rate than conventional chemotherapy in metastatic colon cancer patients with MSI-H/dMMR.

ARTICLE INFORMATION

Disclaimer

The 2023 Colon Cancer Korean Clinical Practice Guidelines are intended to guide the clinical practice of colon cancer based on published medical evidence for diagnosis and treatment. In actual clinical practice, the specific treatment of various clinical situations may differ from these guidelines. The guidelines should not interfere with or limit them. These guidelines do not have legal status. They are not binding. Users are responsible for patient outcomes in actual clinical practice.

Conflict of interest

Je-Ho Jang is an Editorial Board member of *Annals of Coloproctology*, but was not involved in in the peer reviewer selection, evaluation, or decision process of this article. To identify other potential conflicts of interest for all members who participated in the development of guidelines, we examined whether they were employed by a related company, received sponsorship or honoraria of more than KRW 10 million, conducted research funded by a specific institution or pharmaceutical company or received rights to economic benefits, or had intellectual property rights such as patents or royalties in the last 2 years. No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization: HSR, JMK, HJK, WBJ, BCK, JHK, SKM; Data curation: all authors; Formal analysis: HJK; Funding acquisition: JMK; Investigation: all authors; Methodology: HJK, WBJ; Project administration: JMK, HJK; Visualization: all authors; Writing–original draft: all authors; Writing–review & editing: HSR, JMK. All authors read and approved the final manuscript.

Supplementary materials

Supplementary Material 1. Literature search terms for each key questions (KQs).

Supplementary Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for each key questions (KQs).

Supplementary Fig. 2. Risk of bias assessment for each key questions (KQs) using QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies 2), QUADAS-C (QUADAS-Comparative), ROBINS-I (Risk of Bias in Nonrandomized Studies of Intervention), and Cochrane RoB 2 (Risk-of-Bias Tool for Randomized Trials 2).

Supplementary Fig. 3. Forest plots of (A) per-patient and (B) per-lesion sensitivity and specificity of computed tomography for detecting liver metastasis.

Supplementary Fig. 4. Forest plots of (A) per-patient and (B) per-lesion sensitivity and specificity of magnetic resonance imaging for detecting liver metastasis.

Supplementary Fig. 5. Forest plots of (A) per-patient and (B) per-lesion sensitivity and specificity of FDG positron emission tomography–computed tomography for detecting liver metastasis.

Supplementary Fig. 6. Forest plots of sensitivity and specificity of (A) positron emission tomography–computed tomography and (B) computed tomography for detecting metastatic lesions.

Supplementary Fig. 7. Forest plots for the association between lymph node metastasis and (A) lymphovascular invasion, (B) differentiation, (C) depth of invasion (≥1,000 μm), and (D) tumor budding.

Supplementary Fig. 8. Forest plots of 3- and 5-year (A) recurrence rate, (B) disease-free survival, (C) overall survival, and (D) cancer-specific survival in extensive lymphadenectomy (D3 lymph node dissection or complete mesocolic extension/central vessel ligation) versus no extensive lymphadenectomy for right-sided colon cancer.

Supplementary Fig. 9. Forest plots of (A) the stoma formation rate, (B) 30-day mortality, and (C) open conversion rate in self-expanding metallic stents versus emergency surgery for right-sided obstructive colon cancer.

Supplementary Fig. 10. Forest plots of (A) the R0 resection rate,

(B) 3-year disease-free survival, (C) 5-year disease-free survival, and (D) 5-year overall survival in self-expanding metallic stents versus emergency surgery for right-sided obstructive colon cancer.

Supplementary Fig. 11. Forest plots of (A) the stoma formation rate, (B) primary anastomosis rate, (C) overall complication rate, and (D) 30-day mortality in self-expanding metallic stents versus emergency surgery for left-sided obstructive colon cancer.

Supplementary Fig. 12. Forest plots of (A) 3-year disease-free survival (DFS), (B) 3-year overall survival (OS), (C) 5-year DFS, (D) 5-year OS, and (E) recurrence rate in self-expanding metallic stents versus emergency surgery for left-sided obstructive colon cancer.

Supplementary Fig. 13. Forest plot of overall and disease-free survival in lymph node yields of more than 12 versus less than 12.

Supplementary Fig. 14. Forest plots of (A) microsatellite instability/mismatch repair deficiency positivity, (B) positivity for revised Bethesda guidelines for Lynch syndrome in colon cancers, and (C) false-negative rate of revised Bethesda guidelines in genetically confirmed Lynch syndrome patients.

Supplementary Fig. 15. Forest plots of progression-free survival (PFS) and overall survival (OS). (A) PFS and (B) OS according to KRAS status. (C) PFS and OS according to NRAS status. (D) PFS and OS according to BRAF status.

Supplementary Fig. 16. Forest plots of (A) disease-free survival, (B) recurrence-free survival, (C) overall survival, and (D) adverse effects in patients receiving adjuvant chemotherapy versus no adjuvant chemotherapy for high-risk stage II colon cancer patients.

Supplementary Fig. 17. Forest plots of (A) overall survival and recurrence-free survival, (B) peripheral neuropathy in stage III colon cancer patients receiving 3 months versus 6 months of adjuvant chemotherapy, and (C) recurrence-free survival in patients receiving 3 months of adjuvant chemotherapy according to risk stratifications and regimens.

Supplementary Fig. 18. Forest plots of (A) overall and progression-free survival, (B) overall response rate and grade 3 or higher adverse events, and (C) quality of life in patients with metastatic colon cancer with microsatellite instability-high/MMR protein deficiency receiving immunotherapy versus conventional chemotherapy.

Supplementary Fig. 19. Forest plots of (A) oncologic and (B) postoperative outcomes in neoadjuvant chemotherapy followed by surgery versus upfront surgery in patients with locally advanced colon cancer.

Supplementary Fig. 20. Forest plot of marginal recurrence and local recurrence-free survival in hepatectomy versus radiofrequency thermotherapy in patients with resectable colon cancer liver metastases.

Supplementary Fig. 21. Forest plots of (A) oncologic outcomes and (B) postoperative complications in simultaneous versus staged resection in patients with resectable colon cancer liver metastases.

Supplementary Fig. 22. Forest plots of (A) oncologic outcomes and (B) postoperative complications in upfront surgery versus surgery following neoadjuvant chemotherapy in patients with resectable colon cancer liver metastases.

Supplementary Fig. 23. Forest plots of (A) overall survival and (B) median overall survival in patients with pulmonary metastasectomy with resectable colon cancer pulmonary metastases.

Supplementary Fig. 24. Forest plots of (A) overall survival and (B) adverse events in patients with colorectal cancer peritoneal metastasis receiving cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus palliative chemotherapy.

Supplementary Fig. 25. Forest plots of (A) overall survival and (B) adverse events in patients with colorectal cancer peritoneal metastasis receiving cytoreductive surgery and hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone.

Supplementary Fig. 26. Forest plots of (A) overall survival, (B) quality of life, and (C) adverse events in second-line palliative chemotherapy for metastatic colon cancer after failure of first-line palliative chemotherapy.

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