COLORECTAL CANCER NATIONAL CLINICAL PRACTICE GUIDELINES

NATIONAL INTEGRATED
CANCER CONTROL PROGRAM

Colorectal Cancer National Clinical Practice Guidelines

Published by:
National Integrated Cancer Control Program
Disease Prevention and Control Bureau
Department of Health
San Lazaro Compound, Rizal Avenue, Sta. Cruz
Manila 1003, Philippines

An electronic copy of this publication can be downloaded at: www.doh.gov.ph

Suggested citation. Department of Health. (2022). *Colorectal Cancer National Clinical Practice Guidelines*. Manila, Philippines.

Editorial and Publication Team

Colorectal Cancer Guideline Development Group

Technical Advisory Group

Chair: Dr. Nilo C. de los Santos
East Avenue Medical Center

Co-chair: Dr. Clarito U. Cairo, Jr.
Department of Health

Members: Ms. Alma B. Abainza-Sanchez
Philippine Health Insurance Corporation

Dr. Allan Troy D. Baquir
East Avenue Medical Center

Dr. Samuel S. Duran
East Avenue Medical Center

Steering Committee

Chair: Dr. Omar O. Ocampo

Members: Ms. Maria Dolores R. Manalastas
Dr. Marc Anthony C. Cepeda
Dr. Catherine S. Co
Dr. Joseph Roy F. Fuentes
Dr. Mary Claire V. Soliman
Dr. Warren R. Bacorro
Dr. Misael C. Cruz
Dr. Sarah Preza-Carmona
Dr. Felix L. Domingo Jr.
Dr. Ruth Anne Manansala-Kong
Dr. Herdee Gloriane C. Luna
Dr. Ma. Pamela D. Patdu
Dr. Grace S. Nilo

Consensus Panel

Chair: Dr. Mark Anthony G. Fontanilla

Members: Dr. Marichona C. Naval
Ms. Alyanna Riel C. Panlilio
Dr. Manuel Francisco T. Roxas
Dr. Marc Paul J. Lopez
Dr. Tito Apollo A. Quitoriano
Dr. Carlo Angelo C. Cajucom
Dr. Fernando Antonio B. Roque

Dr. Maximino G. Bello III
Dr. Jose Roel E. Resubal
Dr. Henri Cartier S. Co
Dr. Ira Inductivo-Yu
Dr. Felipe Gozar L. Duque
Dr. Patricia Ann Cabral-Prodigalidad
Dr. Anarose C. Alvarado
Dr. Marie Ruth A. Echavez

Evidence Review Experts

Principal Investigator:	Dr. Omar O. Ocampo
Technical Lead:	Dr. Cherie Grace G. Quingking
Technical Co-lead:	Dr. Jane Eflyn Lardizabal-Bunyi
	Mr. Teddy S. Dizon
Support Team:	Dr. Rosally P. Zamora
	Ms. Hygeia Grace C. Agosto
	Ms. Jennel Mae T. Pimentel

Implementing Agencies

East Avenue Medical Center
Healthcare Practice and Policy Management (HPPM), Inc.

Funding Agency

Department of Health

Partner Agencies and Societies

Table of Contents

Abbreviations and Acronyms

5FU	5-fluorouracil
5-FU/LV	5-fluorouracil plus leucovorin
AGREE II	Appraisal of Guidelines, Research and Evaluation II
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
ASCRS	American Society of Colon and Rectal Surgeons
ASTRO	American Society for Radiation Oncology
CEA	carcinoembryonic antigen
cGy	centigray
CRC	colorectal cancer
CRM	circumferential resection margin
CSS	cause-specific survival
CT	computed tomography
DFS	disease-free survival
EGFR	epidermal growth factor receptor
EMR	endoscopic mucosal resection
EMVI	extramural vascular invasion
ESD	endoscopic submucosal dissection
ESMO	European Society for Medical Oncology
FIT	fecal immunochemical test
FOBT	fecal occult blood test
FOLFIRI	combination of leucovorin, 5-fluorouracil, and irinotecan
FOLFOX	combination of leucovorin, 5-fluorouracil, and oxaliplatin
gFOBT	guaiac fecal occult blood test
GPS	Good Practice Statement
HPB	hepatobiliary
HR	hazard ratio
IORT	intraoperative radiotherapy
KCE	Belgian Health Care Knowledge Centre
MDT	multidisciplinary team
MIS	minimally invasive surgery
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability
NACT	neoadjuvant chemotherapy
NCCN	National Comprehensive Cancer Network
NHMRC	National Health and Medical Research Council

NICE	National Institute for Health and Care Excellence
NOM	nonoperative management
OS	overall survival
pCR	pathologic complete response
PET/CT	positron emission tomography / computed tomography
PFS	progression-free survival
PNI	perineural invasion
QoE	quality of evidence
QoL	quality of life
QUADAS	Quality Assessment of Diagnostic Accuracy Studies
RCT	randomized controlled trial
RR	recurrence rate
RT	radiotherapy
SAGES	Society of American Gastrointestinal Endoscopic Surgeons
SIGN	Scottish Intercollegiate Guidelines Network
SoR	strength of recommendations
SM3	inferior third of the submucosa
TAMIS	transanal minimally invasive surgery
TEMS	transanal endoscopic microsurgery
TEO	transanal endoscopic operation
TME	total mesorectal excision
TNM	tumor, node, metastasis
TNT	total neoadjuvant therapy
UICC	Union for International Cancer Control
USPSTF	United States Preventive Services Taskforce
VEGF	vascular endothelial growth factor

Acknowledgments

The Department of Health (DOH) with technical assistance from East Avenue Medical Center (EAMC) and Healthcare Practice and Policy Management (HPPM), Inc. developed the Colorectal Cancer (CRC) National Clinical Practice Guideline (NCPG).

The Technical Advisory Group composed of EAMC, DOH, and Philippine Health Insurance Corporation (PhilHealth) representatives serves as the oversight committee ensuring quality and inclusive development of the guideline.

EAMC contracted HPPM as an independent study group to provide highly technical assistance to develop the CRC NCPG through a series of consultations and evidence reviews.

The following partner organizations contributed to the success of this publication:

- East Avenue Medical Center (EAMC)
- Department of Health – National Integrated Cancer Control Program (DOH-NICCP)
- Philippine Health Insurance Corporation (PhilHealth)
- Philippine Society of Colon and Rectal Surgeons (PSCRS)
- Philippine Society of Medical Oncology (PSMO)
- Philippine Radiation Oncology Society (PROS)
- Philippine Society of Gastroenterology (PSG)
- Philippine Society of Hospice and Palliative Medicine (PSHPM)
- Philippine Academy of Family Physicians (PAFP)
- Philippine Cancer Society (PCS)
- Philippine College of Surgeons Cancer Commission (PCS Cancer Commission)
- Philippine Society of General Surgeons (PSGS)
- Philippine Society of Pathologists (PSP)

Contributors

These guidelines were a collaborative effort between various guideline committees, methodologists, and systematic reviewers. The consensus panel/committee included colorectal cancer advocates, program managers of colorectal cancer program, and primary healthcare givers. All contributors completed the declaration of interest form.

The Technical Advisory Group (TAG) consisted of the following individuals: Dr. Nilo C. de los Santos (EAMC), Dr. Clarito U. Cairo, Jr. (DOH), Ms. Alma B. Abainza-Sanchez (PhilHealth), Dr. Allan Troy D. Baquir (EAMC), and Dr. Samuel S. Duran (EAMC).

The Steering Committee was headed by Dr. Omar O. Ocampo (EAMC) was composed of representatives, namely: Ms. Maria Dolores R. Manalastas (DOH), Dr. Marc Anthony C. Cepeda (PhilHealth – Research Division), Dr. Catherine S. Co (PSCRS), Dr. Joseph Roy F. Fuentes (PSCRS), Dr. Mary Claire V. Soliman (PSMO), Dr. Warren R. Bacorro (PROS), Dr. Misael C. Cruz (PROS), Dr. Felix L. Domingo, Jr. (PSG), Dr. Sarah Preza-Carmona (PSG), Dr. Ruth Anne Manansala-Kong (PAFP), Dr. Grace S. Nilo (PCS), Dr. Ma. Pamela D. Patdu (PCS), and Dr. Herdee Gloriane C. Luna (PCS).

With a background in clinical epidemiology, evidence-based medicine, medical informatics, and public health, Healthcare Practice and Policy Management, Inc. provided the technical guidance for the development of these national clinical practice guidelines. Dr. Cherie Grace G. Quingking, Dr. Jane Eflyn Lardizabal-Bunyi, and Dr. Rosally P. Zamora provided the oversight as methodologists, evidence review experts and technical writers for the NCPG. Dr. Omar O. Ocampo, the Project Lead and Steering Committee Chair provided his expertise as technical reviewer and subject matter expert. Technical and administrative support, coordination, and review services were provided by Mr. Teddy S. Dizon, Ms. Hygeia Grace C. Agosto and Ms. Jennel Mae T. Pimentel.

The Consensus Panel contributed by reviewing the evidence base and affirming recommendation statements. The panel was headed by Dr. Mark Anthony G. Fontanilla (EAMC), and included the following members: Dr. Marichona C. Naval (EAMC), Ms. Alyanna Riel C. Panlilio (DOH), Dr. Manuel Francisco T. Roxas (PCS Cancer Commission), Dr. Marc Paul J. Lopez (PCS Cancer Commission), Dr. Tito Apollo A. Quitoriano (PSGS), Dr. Carlo Angelo C. Cajucom (PSGS), Dr. Fernando Antonio B. Roque (PSMO), Dr. Maximino G. Bello III (PSMO), Dr. Jose Roel E. Resubal (PROS), Dr. Henri Cartier S. Co (PROS), Dr. Ira Inductivo-Yu (PSG), Dr. Felipe Gozar L. Duque (PSG), Dr. Patricia Ann Cabral-Prodigalidad (PSG), Dr. Anarose C. Alvarado (PSP), and Dr. Marie Ruth A. Echavez (PSHPM).

Executive Summary

Colorectal Cancer (CRC) is the second leading cause of cancer mortality globally, accounting for an estimated 935,173 cancer-related deaths in 2020. Approximately 1.9 million new cases of CRC were diagnosed in 2020 globally, making it the third most commonly encountered type of cancer. In the Philippines, CRC is the fourth leading cause of cancer death and accounts for 9.9% of cancer mortality. In 2020, an estimated 17,364 Filipinos were diagnosed with CRC, responsible for 11.3% of new cases of cancer for that year.

Considering the implementation of the National Integrated Cancer Control Act (Philippines Republic Act No. 11215) and Universal Health Care Act (Philippines Republic Act No. 11223), DOH provides support to develop the national clinical practice guidelines. The set standards for clinical care aims to progressively realize the highest attainable quality of health care services in the Philippines.

National clinical practice guideline (NCPG) development for the management of CRC in the Philippines synthesized the most recent high-quality source guidelines with recommendations reflecting new evidence generated. Program implementers, policy makers, and experts in colorectal surgery, medical oncology, radiation oncology, gastroenterology, pathology, and other relevant stakeholders were consulted in generating clinical questions that should be addressed by the Philippine NCPG for CRC through a process of prioritization and consensus-building. A consensus panel composed of stakeholders in the management of CRC validated the findings from a review of evidence.

This Guideline will aid in standardizing the care provided to patients with CRC in the Philippines, and ensure that screening, diagnosis, treatment, and surveillance are appropriate and contextualized to local policies, needs, and capabilities.

Colorectal Cancer NCPG Summary

The Guideline Development Group used the ADAPTE methodology to generate and finalize the recommendations for CRC NCPG, covering screening, diagnosis, clinical management, surveillance, and pathology reporting. The ADAPTE process results in the adoption and adaption of recommendations from the American Society of Colon and Rectal Surgeons (ASCRS) Clinical Practice Guidelines for the Management of Colon and Rectal Cancer, American Society of Clinical Oncology (ASCO) Colorectal Cancer Guidelines, National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, and NCCN Guidelines Colon and Rectal Cancer.

Table 1. Colorectal Cancer NCPG Summary

CLINICAL QUESTIONS	RECOMMENDATIONS	SoR	QoE
1. Among adult patients newly diagnosed with colon adenocarcinoma, is PET/CT scan the recommended initial modality for clinical staging compared with chest and abdominopelvic CT scan with contrast?	PET/CT scan is not recommended as initial modality for routine colon cancer staging and detection of distant metastasis.	Strong	Moderate
	PET/CT scan does not supplant a contrast-enhanced diagnostic CT scan or MRI. It should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or MRI or in patients with strong contraindications.	Strong	Low
	Chest, abdomen, and pelvic CT scan are recommended to initially evaluate local extent of tumor as well as invasion into nearby organs or structures, assess for nodal metastasis and identify distant metastatic disease to lungs, liver, peritoneal cavity and other organs.	Strong	Low
2. Among adult patients with cT1N0M0 colon adenocarcinoma, is endoscopic excision non-	For cT1N0M0 colon adenocarcinoma, endoscopic excision is not inferior to oncologic resection. However,	Strong	Moderate

inferior to oncologic resection?	endoscopic excision is dependent mainly on malignant polyp histopathological features and completeness of excision.		
3. Among adult patients with resectable stage I-III colon adenocarcinoma, should minimally invasive surgery be offered over open surgery?	When expertise and capability are available, a minimally invasive approach to elective colectomy for colon adenocarcinoma is acceptable.	Strong	High
4. Among adult patients with reliable pre-operative imaging showing unresectable locally advanced colon adenocarcinoma, does neoadjuvant chemotherapy followed by surgery yield better outcomes than upfront surgery followed by adjuvant chemotherapy?	Neoadjuvant chemotherapy is an option for locally advanced colon adenocarcinoma.	Good practice statement	
	Patients with unresectable locally advanced colon adenocarcinoma should be considered for neoadjuvant therapy to attempt to convert to resectability.	Strong	Moderate
	Neoadjuvant chemotherapy can result in tumor regression and may facilitate margin-negative excision of initially unresectable locally advanced colon adenocarcinoma.	Strong	Moderate
5. Among adult patients with stage II colon adenocarcinoma with high-risk features for recurrence, is oxaliplatin-based adjuvant chemotherapy recommended than 5FU/leucovorin or capecitabine monotherapy?	Oxaliplatin-based adjuvant chemotherapy is recommended for stage II colon adenocarcinoma patients with high-risk feature(s).	Strong	Low
6. What is the preferred sequence of treatment for resectable and potentially resectable stage IV colon adenocarcinoma?	Patients with initially resectable colon adenocarcinoma with liver or lung metastasis can be treated with upfront surgical resection followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by surgery.	Strong	Moderate
	Patients with resectable distant metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one	Strong	Low

	operation or as a staged approach, depending on the complexity of the metastasectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.		
	For patients with resectable colon adenocarcinoma and peritoneal metastasis without extra-abdominal disease, cytoreductive surgery with or without intraperitoneal chemotherapy should be considered in multidisciplinary setting with appropriate expertise.	Strong	Moderate
	A six-month course of systemic chemotherapy can be considered for most patients undergoing liver or lung resection to increase the likelihood of eradication of residual microscopic disease.	Strong	Low
7. Among adult patients newly diagnosed with rectal adenocarcinoma, is pelvic MRI the recommended modality for clinical locoregional staging over endorectal ultrasound?	Pelvic MRI (rectal cancer protocol) is the preferred modality for clinical locoregional staging of newly diagnosed rectal adenocarcinoma. Endorectal ultrasound may be considered when differentiating between early T stages or when MRI is contraindicated or not available.	Strong	Moderate
8. Among adult patients with cT1N0M0 rectal adenocarcinoma, should local excision +/- adjuvant treatment (radiotherapy or chemoradiotherapy) be offered as compared to oncologic resection?	Local excision is an appropriate treatment option for carefully selected patients with cT1N0 rectal adenocarcinoma with favorable clinical and histological features.	Strong	Moderate
	For high-risk patients who refuse or are medically unfit for radical resection, adjuvant chemoradiation should be recommended after local excision and should be followed by surveillance for a potentially salvageable recurrence.	Strong	Moderate

9. Among adult patients with resectable stage I-III low to mid rectal adenocarcinoma, should minimally invasive surgery be offered over open surgery?	Minimally invasive surgical approach following standard oncologic techniques of total mesorectal excision (TME) can be considered and should be performed by experienced surgeons with technical expertise.	Strong	High
10. Among adult patients with Stage II or III rectal adenocarcinoma, is neoadjuvant short course radiotherapy comparable to long course chemoradiotherapy?	Neoadjuvant short course radiation therapy and long course chemoradiation therapy are comparable for Stage II or III rectal adenocarcinoma in terms of outcomes such as survival, recurrence, and complications.	Strong	High
11. Among adult patients diagnosed with cT4b, cN2 or unresectable nonmetastatic rectal adenocarcinoma, does total neoadjuvant therapy yield better outcomes than neoadjuvant short course radiation therapy or long course chemoradiation therapy + adjuvant chemotherapy?	Considerations for total neoadjuvant therapy over standard neoadjuvant therapy (short course radiation therapy or long course chemoradiation therapy) for cT4b, cN2 or unresectable nonmetastatic rectal adenocarcinoma must be based on a multidisciplinary team evaluation.	Strong	Low
12. Among adult patients with rectal adenocarcinoma with complete clinical response following neoadjuvant therapy, is “watch and wait” management approach comparable to oncologic resection?	Patients with a complete clinical response to neoadjuvant therapy should be offered oncologic resection.	Strong	Moderate
13. What is the preferred sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma?	Referral to a multidisciplinary team in a Center of Excellence to determine the sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma is recommended.	Good practice statement	
14. Among adult patients with locally advanced colon and rectal adenocarcinoma, does a multidisciplinary team (MDT) approach	The treatment of patients with resectable stage IV colorectal adenocarcinoma should be individualized and based on a comprehensive MDT discussion.	Strong	Moderate

yield better outcomes than a non-MDT approach?	Optimum therapeutic strategy and centralization of care is best carried out by an adequately trained MDT which should include a surgeon, medical oncologist, radiation oncologist, diagnostic radiologist, gastroenterologist, pathologist, and other needed specialists as necessary.	Strong	Low
	An MDT approach is strongly recommended for all locally advanced and advanced colorectal adenocarcinoma to determine the best treatment options.	Strong	Moderate
15. Among adult patients with unresectable stage IV colon or rectal adenocarcinoma, does the addition of targeted therapy or immunotherapy to chemotherapy yield better outcomes compared to systemic chemotherapy alone?	Anti-VEGF therapy may be added to doublet or triplet chemotherapy, regardless of molecular status of the colorectal cancer.	Strong	Moderate
	Among adults with left-sided colon and rectal cancers with KRAS/NRAS WT molecular status, anti-EGFR therapy is recommended.	Strong	Moderate

Background

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer mortality globally, accounting for an estimated 935,173 cancer-related deaths in 2020. Approximately 1.9 million new cases of CRC were diagnosed in 2020 globally, making it the third most commonly encountered type of cancer. In the Philippines, CRC is the fourth leading cause of cancer death and accounts for 9.9% of cancer mortality. In 2020, an estimated 17,364 Filipinos were diagnosed with CRC, responsible for 11.3% of new cases of cancer for that year.

Considering the implementation of the National Integrated Cancer Control Act (Philippines Republic Act No. 11215) and Universal Health Care Act (Philippines Republic Act No. 11223), DOH provides support to develop the national clinical practice guidelines. The set standards for clinical care aims to progressively realize the highest attainable quality of health care services in the Philippines.

In a scoping study of current practices in NCPG development conducted by Silvestre et al (2017), 87 NCPGs from the disciplines of medicine, surgery, obstetrics, gynecology, and pediatrics were appraised. They found out that only 11 out of 48 of the most burdensome disease conditions in the Philippines have existing local NCPGs and there was a large variation in the processes utilized for NCPG development, in terms of: criteria used, format of manuscripts, and sufficiency of documentation. Prioritization of the development of NCPGs for the high-burden conditions was one of the recommendations of the study. The said study and the operational issues encountered since the issuance of Administrative Order (AO) 2018-0019 informed the Revised Guidelines on National Clinical Practice Guidelines Development, Adoption and Dissemination or AO No. 2021-0020. This AO aims to set the operational framework for practice guideline development, adoption, and dissemination; and to update the standardized process of practice guideline prioritization, generation, appraisal and approval, dissemination, and monitoring and evaluation.

New clinical evidence is being published so fast that it is nearly impossible for any clinician to keep track of new developments and to place those developments within a comprehensive framework. This has led to variations in practice and patient outcomes. Therefore, there is a need to develop NCPG for CRC that will help improve effectiveness and quality of care, maintain consistency in clinical practice, and decrease preventable and costly mistakes and adverse events.

In the local setting, there have been clinical practice guidelines that were formulated by various specialty societies. The Philippine Journal for Surgical Specialties published their recommendations in 2005, which were then updated in 2013 by members of the Philippine College of Surgeons and Philippine Society of Colon and Rectal Surgeons. However, these recommendations were applicable for the management of curable rectal cancer only.

On the other hand, the Philippine Society of Gastroenterology and Philippine Society of Digestive Endoscopy created consensus guidelines for the management of CRC in 2017. Several institutions in the country were surveyed regarding attitudes and practices towards CRC care among patients and at-risk individuals.

In 2019, the Civic Action Committee of the Philippine Society of Gastroenterology produced a Handbook on Colorectal Cancer with the aim of disseminating it as a guide for physicians, internists, and gastroenterologists. The scope of the said handbook was the screening and diagnosis, therapeutic management, and surveillance of patients. Epidemiology of the disease, such as: incidence, mortality, and risk factors, were also discussed to provide information on the aspects that predispose an individual to develop CRC.

Guideline Development Process

Phase 1 – Preparation Phase

Establishment of the Guideline Development Group

The guideline development group was composed of policy makers, program managers, surgeons, medical oncologists, radiation oncologists, gastroenterologists, pathologists, palliative care specialist, family physician and advocacy group. The multidisciplinary and multispecialty professionals composed the relevant working groups of the CRC NCPG, the Technical Advisory Group (TAG), the Steering Committee (SC), the Evidence Review Experts (ERE), and the Consensus Panel (CP).

The TAG and the SC comprised the lead NCPG developers. The TAG has the oversight function to ensure a quality and inclusive NCPG development process. Nominated members for the TAG included representatives from East Avenue Medical Center, the Department of Health, and the Philippine Health Insurance Corporation.

The multidisciplinary SC drafted the scope and target audience of the NCPG. They also identified, ranked, and finalized the clinical questions on screening, diagnosis, clinical management, surveillance, and pathology reporting of CRC in the Philippines. The SC identified, invited, reviewed, and managed the COI of the relevant working groups, such as the steering committee, evidence reviewers, consensus panelists, and facilitators.

The ERE provided technical assistance in evidence review ranging from the development of the clinical questions, search and identification of evidence, appraisal of relevant literature to answer clinical questions, and synthesis of evidence

summaries as the basis of recommendation statements. The ERE for this Guideline included consultants with backgrounds in clinical epidemiology, information specialists, medical informatics, and public health.

The CP was a wider group of CRC stakeholders. Establishing a more open and diverse group of stakeholders for the CP — including multidisciplinary healthcare practitioners, patient advocates, DOH program managers, and other technical content experts — was aimed at promoting transparency, introducing different perspectives to CRC management, and safeguarding against conflicts of interest. The CP reviewed and revised the recommendation statements and voted on adopting these statements into the Guideline.

Declaration and Management of Conflicts of Interest

The CRC NCPG Guideline Development Group utilized the PhP 2,000,000 DOH sub-allotment to develop the guideline. The stakeholder of the working groups that composed the Guideline Development Group (GDG) declared no true conflict of interests related to this material. The stakeholders included in the guideline development groups were requested to provide a summary of their conflicts of interest (COI) related to CRC. These COIs may be classified into financial and non-financial (or intellectual) COI. COIs were reviewed by the ERE, and admission of a stakeholder to the GDG was contingent on the stakeholder having no or minimal COI, following recommendations in the DOH CPG Manual (DOH [Philippines] 2018). Conflicts of interest(s) and how COIs were managed are presented in Annex A.

Identification of the Scope of the NCPG

The PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes and Health Care Setting (ADAPTE Collaboration, 2009). These five items aided the selection and framing of clinical questions on Population; Intervention of interest – screening, diagnostics, and treatment/management; Professionals to whom the guideline will be targeted; specific Outcomes; and Health care setting and context that the guideline will be implemented.

Generation of NCPG questions

The methodology of clinical question generation is based on frameworks of clinical practice guidelines (CPG), agenda-setting, and consensus-building (Murphy et al, 1998; The James Lind Alliance, 2020; WHO, 2014). For CPG question development guidelines, we specifically referred to guidance published by the WHO in 2014. Due to the COVID-19 pandemic and mobility restrictions at the time of guideline development, all methods of communication were virtual; no face-to-face, physical gatherings were conducted.

PIPOH framework was used by the TAG and the SC in defining the scope of this Guideline, which refers to Population, Intervention, Professionals, Outcomes, and Health Care Setting (ADAPTE Collaboration, 2009).

Table 2. PIPOH Framework for the Colorectal Cancer NCPG Development

Framework	Scope
Population	Sporadic colorectal cancer (Stages I-IV)
Intervention	Screening, diagnosis, treatment, and surveillance
Professionals	Physicians/medical doctors, allied health professionals, and health policy maker
Outcomes	Diagnostic accuracy, disease free survival,
Health Care Setting	Tertiary hospitals

These guidelines included relevant questions on screening, diagnosis, treatment, and surveillance of colorectal cancer. The objectives are the following:

1. To present and synthesize the best available evidence on the screening, diagnosis, treatment, and surveillance of colorectal cancer;
2. To standardize the screening, diagnosis, treatment, and surveillance of colorectal cancer in the Philippines for the reduction of the burden of disease; and,
3. To complement the existing DOH program mandates on cancer control by providing evidence to its statements for policy implementation.

The generation of CPG questions is an essential early step in CPG development. These questions were used as the basis for the subsequent systematic review of the evidence base on CRC (WHO, 2014). CPG questions generated by the SC were agreed to focus on evidence uncertainties, areas of controversy in the management of CRC and known variations of clinical practice and care especially in the resources available in the Philippine setting. The SC was then convened in virtual workshops where the final questions were formulated in PICO (Population, Intervention, Comparator, and Outcome) format, reviewed, and prioritized according to a consensus. Technical working groups were assigned for further review and revision to reach the final PICO format of the clinical questions. The final list of PICO elements for each CPG question is located in Annex C.1-3.

Phase 2 – Evidence Synthesis

Overview of Evidence Synthesis Methods

Considering the time and resources to produce quality CPGs, it is recommended that existing guidelines be adapted to reduce duplication of effort and update existing guidelines in a shorter period of time. In this CPG development process, guideline

adaptation by the ADAPTE method was considered to address specific health questions generated. Independent methodologists and reviewers determined if adaptation of any existing CPG was feasible and consequently created the evidence base and recommendation matrix.

The ERE utilized the ADAPTE method to review existing guidelines for inclusion in the evidence base and drafting of recommendation matrix. The ADAPTE collaboration has developed a systematic approach to aid in the adaptation of guidelines (ADAPTE Collaboration, 2009). The systematic approach aids in the use and modification of existing guidelines to customize an existing guideline to suit the local context while addressing relevant health questions. A systematic search of existing guidelines in multiple databases, including PubMed, Google Scholar and Scopus®. Search terms and limits are provided in Annex B.2. Updated versions of the guidelines were also searched to ensure currency of the recommendations.

Assessment of the guidelines yielded from the systematic search were then given consideration for adaptation by assessment if it meets the qualities of a high-quality guideline using the Appraisal of Guidelines Research and Evaluation (AGREE) instrument as well as if it can address the specific clinical questions. The AGREE II instrument provides a framework for assessing the quality of CPGs (Brouwers et al, 2013). The 23 items in the AGREE instrument assess the methods used for developing the guideline and quality of reporting. Assessment is focused on the rigor and overall score. The domains and criteria for the AGREE II tool are shown in Annex D. The guidelines were assessed for guideline quality, currency, content, consistency, and applicability (ADAPTE Collaboration, 2009). The characteristics and contents of the source guidelines are summarized in Annex B.5.

Phase 3 – Evidence to Recommendations

The ERE drafted the initial recommendation statements to include level of evidence based on the source guidelines and its references. All guidelines included utilized by recommended Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for evaluation of level of evidence (Schünemann et al, 2013). This is the tool developed by the GRADE working group in evaluating the quality of the evidence and is summarized and defined in Table 3 below.

Table 3. Quality of Evidence Grades (Schünemann et al, 2013)

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: The true effect

	may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

The recommendation matrix developed was for finalization of the CP who were provided by the ERE with a guide on determining the strengths of recommendation (Schünemann et al, 2013). Recommendations may either be *strong* or *weak*. *Strong* recommendations refer to issues where the guideline development group may be confident that the benefits outweigh the risks or costs of an intervention, or vice versa, whereas *weak* recommendations are those where there is appreciable uncertainty on the calculus of benefits and risks. A summary of the implication of recommendation strength on each type of guideline user based on WHO which is reproduced in full in Table 4.

Table 4. Implications of Strong and Weak Recommendations for Different Users of Guidelines (WHO, 2014)

	Strong Recommendation	**Weak Recommendation**
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.
For policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about

		the management options has taken place.

Phase 4 – Consensus Development

The result of ADAPTE evidence evaluation and recommendation synthesis was presented to the CP, composed of CRC management stakeholders, from health care practitioners to patient advocates to program implementers, for validation. The results of the systematic literature review and recommendation synthesis were forwarded to the members of the CP for review, either individually or together with their affiliated organizations. The suggested recommendations were also reiterated to the CP.

Nominal group techniques were applied to direct the discussions (Delbecq et al, 1986). After presentation of the evidence and recommendations, stakeholders were requested one-by-one to provide their inputs on each recommendation within a set time limit. The CP was allowed to revise the recommendation statements for adaptation within reasonable limits as long as the revision did not alter the value of the underlying evidence. The content and strength of each recommendation was then put to a vote for finalization, consensus was set at 80% agreement on a specific recommendation. If the CP was unable to reach the consensus marker, the cycle of discussions then voting was repeated up to two times.

Patient Values, Preferences, and Other Considerations

As there are no patient nor patient groups present within the SC or CP, results based on a systematic review of patient or family values, was assessed vis-à-vis the recommendations of the GDG after consensus made**.**

The SC and CP thoroughly discussed the applicability of the recommendations using several criteria, such as improvement of treatment outcomes, acceptability to local professional practice, public health impact, and healthcare cost based on lived experiences.

Ethics review was sought and approved by the DOH Single Joint Review Board.

External evaluation was sought by the guideline development group through a public forum with the general surgeons where feedbacks were documented and directly incorporated in the final manuscript.

The DOH as funding agency and EAMC as fund manager did not influence the editorial independence of the GDG.

Dissemination and Use of the Guideline

The value of a CPG is fully appreciated when it is widely adopted, and adoption is contingent on access and distribution of the CPG to its target audience. This clinical practice guideline is available on the DOH website.

The GDG will work closely with DOH and other partners to ensure wide dissemination of the guideline through different events: (1) Presentation in professional society's scientific fora; (2) Distribution of the guideline will be done electronically through DOH and partner society websites; (3) Monitoring/assessment on the uptake of the guideline will be done through monitoring the number of downloads and request for distribution, and; (4) Health outcomes will be monitored during the first three years of guideline distribution specifically on number of cases identified, treated and surveillance for recurrence reported.

The NCPG recommendations are valid until new significant evidence emerges that would require a change in recommendation. The ERE recommends revisiting the Guidelines regularly every three years. The research recommendations may be considered by policymakers and program managers for future research funding as part of the continuous quality improvement of healthcare services in the country.

References

ADAPTE Collaboration. (2009). The ADAPTE Process: Resource Toolkit for Guideline Adaptation. *Version 2.0*, 1–95. http://www.g-i-n.net

Brouwers, M., Kho, M., Browman, G., Cluzeau, F., Feder, G., Fervers, B., Hanna, S., & Makarski, J. (2013). *Appraisal of Guidelines for Research & Evaluation II: AGREE II Instrument*. https://doi.org/10.1503/cmaj.090449

Christie, C. A., & Barela, E. (2005). *The Delphi technique as a method for increasing inclusion in the evaluation process*. Canadian Journal of Program Evaluation, 20(1), 105–122

Cloa, M. S., Galang, J. A. G., Ismael, A. E., Daez, M. L. O., Sy, P. P., & Mina, Y. L. (2017). The joint Philippine Society of Gastroenterology (PSG) and Philippine Society of Digestive Endoscopy (PSDE) consensus guidelines on the management of colorectal carcinoma. *Philippine Journal of Internal Medicine, 55*(1), 1-16

Co, C., Roxas, M., Chang, R., Parreno-Sacdalan, M., Crisostomo, A., Cajucom, C., Lopez, M., Monroy III, H., & Daez, M. (2013). Evidence Based Clinical Practice Guideline on Curable Rectal Cancer – An Update. *Philippine Journal of Surgical Specialties, 68(3), 75-89.* https://pcs.org.ph/assets/journals/PJSS-68-3-Jul-Dec-2013-1.pdf

Delbecq, A., Van de Ven, A., & Gustafson, D. (1975). *Group Techniques for Program Planning; a guide to nominal group and Delphi processes.* Glenview IL, Scott Foresman and Company

Department of Health Philippines. (2018). Manual for Clinical Practice Guideline Development

Division of Cancer Prevention and Control, Centers for Disease Control and Prevention. (2021). *What is Colorectal Cancer?* CDC. https://www.cdc.gov/cancer/colorectal/basic_info/what-is-colorectal-cancer.htm

GRADE Working Group. (2004). Grading quality of evidence and strength of recommendations. *Bmj*, *328*(7454), 1490

Holey, E. A., Feeley, J. L., Dixon, J., & Whittaker, V. J. (2007). An exploration of the use of simple statistics to measure consensus and stability in Delphi studies. *BMC medical research methodology*, *7*(1), 1-10

Miguel, R. T. D., Silvestre, M. A. A., Salaveria-Imperial, M. L. A., Tolosa, M. T. S., Eubanas, G. A. S., & Dans, L. F. (2021). Disclosures of conflicts of interest in clinical practice guidelines. *Clinical Epidemiology and Global Health*, *9*, 355-359

Murphy, M., Black, N., Lamping, D., McKee, C., Sanderson, C., Askham, J., & Marteau, T. (1998). Consensus development methods, and their use in clinical guideline development. *Health Technology Assessment*, *2*(3). https://doi.org/10.4135/9781848608344.n24

National Institute for Health and Care Excellence. (2014). *Developing NICE guidelines: the manual*. http://www.nice.org.uk/process/pmg20

Philippine Society of Gastroenterology. (2019). *Colorectal Cancer Handbook*

Schively, C. (2007). A quantitative analysis of consensus building in local environmental review. *Journal of Planning Education and Research*, *27*(1), 82-98

Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013). *GRADE Handbook*. https://gdt.gradepro.org/app/handbook/handbook.html

Schünemann, H. J., Wiercioch, W., Brozek, J., Etxeandia-Ikobaltzeta, I., Mustafa, R. A., Manja, V., ... & Akl, E. A. (2017). GRADE Evidence to Decision (EtD) frameworks for adoption, adaptation, and de novo development of trustworthy recommendations: GRADE-ADOLOPMENT. *Journal of clinical epidemiology*, *81*, 101-110.Scottish Intercollegiate Guidelines Network (SIGN). (2015, November). SIGN 50: a guideline developer's handbook. Edinburgh. http://www.sign.ac.uk

The Global Cancer Observatory, International Agency for Research on Cancer, World Health Organization. (2020). *Colorectal Cancer.* https://gco.iarc.fr/today/data/factsheets/cancers/10_8_9-Colorectum-fact-sheet.pdf

The Global Cancer Observatory, International Agency for Research on Cancer, World Health Organization. (2021). *Philippines*. https://gco.iarc.fr/today/data/factsheets/populations/608-philippines-fact-sheets.pdf

The James Lind Alliance. (2020). *The James Lind Alliance Guidebook (9th ed.).* http://www.jla.nihr.ac.uk/jla-guidebook/

Wang, Z., Norris, S. L., & Bero, L. (2018). The advantages and limitations of guideline adaptation frameworks. *Implementation Science*, *13*(1), 1-13

World Health Organization. (2014). *Handbook for guideline development (2nd ed.).* http://www.who.int/kms/handbook_2nd_ed.pdf

Clinical Practice Guidelines

Colorectal Cancer National Clinical Practice Guidelines Recommendations

Clinical Question 1: Among adult patients newly diagnosed with colon adenocarcinoma, is PET/CT scan the recommended initial modality for clinical staging compared with chest and abdominopelvic CT scan with contrast?

Recommendation 1a.

PET/CT scan is not recommended as initial modality for routine colon cancer staging and detection of distant metastasis.

Strong recommendation, Moderate-quality evidence

Recommendation 1b.

PET/CT scan does not supplant a contrast-enhanced diagnostic CT scan or MRI. It should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or MRI or in patients with strong contraindications.

Strong recommendation, Low-quality evidence

Recommendation 1c.

Chest, abdomen, and pelvic CT scan are recommended to initially evaluate local extent of tumor as well as invasion into nearby organs or structures, assess for nodal metastasis and identify distant metastatic disease to lungs, liver, peritoneal cavity, and other organs.

Strong recommendation, Low-quality evidence

Consensus Issues

The Consensus Panel voted to adopt the recommendations of the American Society of Colon and Rectal Surgeons (ASCRS) for Recommendation 1a and the recommendations of the National Comprehensive Cancer Network (NCCN) for Recommendations 1b and 1c. Chest and abdominopelvic CT scan with contrast are the recommended initial modalities when determining the clinical stage of newly diagnosed colon adenocarcinoma unless there are strong contraindications such as allergy to the use of iodine contrast dye. PET/CT scan is not a routine pre-operative work-up for colon cancer.

Summary of Evidence

The main recommendation that PET/CT scan is not advocated as part of the recommended initial work-ups in the diagnosis and staging of CRC was based on the source guideline (ASCRS) which was adapted from both the NCCN and European

Society for Medical Oncology (ESMO) guidelines. The recommended initial workups include colonoscopy with biopsy, abdominopelvic CT scan, chest CT scan, and CEA determination. As stated in ASCRS, based on several prospective studies and a review on chest staging modalities for patients with CRC, there was no evidence demonstrating the superiority of PET/CT scan over contrast-enhanced CT scan for the detection of liver, lung or peritoneal metastases (Engelmann et al, 2014; Pfannenberg et al, 2009; Elekonawo et al, 2014; Parnaby et al, 2012).

NCCN stated that PET/CT scan may be considered if abnormalities (considered suspicious but inconclusive for distant metastases) are seen on CT scan or MRI provided that the information would change the management, i.e., curative resection is being considered.

Research Recommendation

The GDG recommended no additional research.

References

Argilés, G., Tabernero, J., Labianca, R., Hochhauser, D., Salazar, R., Iveson, T., ... & Arnold, D. (2020). Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Annals of Oncology*, *31*(10), 1291-1305

Elekonawo, F. M., Starremans, B., Laurens, S. T., Bremers, A. J., de Wilt, J. H., Heijmen, L., & de Geus-Oei, L. F. (2020). Can [18F] F-FDG PET/CT be used to assess the pre-operative extent of peritoneal carcinomatosis in patients with colorectal cancer?. Abdominal Radiology, 45(2), 301-306

Engelmann, B. E., Loft, A., Kjær, A., Nielsen, H. J., Berthelsen, A. K., Binderup, T., ... & Højgaard, L. (2014). Positron emission tomography/computed tomography for optimized colon cancer staging and follow up. Scandinavian journal of gastroenterology, 49(2), 191-201

Lopes, G., Stern, M. C., Temin, S., Sharara, A. I., Cervantes, A., Costas-Chavarri, A., ... & Correa, M. C. (2019). Early detection for colorectal cancer: ASCO resource-stratified guideline. *Journal of global oncology*, *5*, 1-22

National Comprehensive Cancer Network. (2022). *Colon Cancer Version 1.2022*

Parnaby, C. N., Bailey, W., Balasingam, A., Beckert, L., Eglinton, T., Fife, J., ... & Watson, A. J. M. (2012). Pulmonary staging in colorectal cancer: a review. Colorectal Disease, 14(6), 660-670

Pfannenberg, C., Königsrainer, I., Aschoff, P., Öksüz, M. Ö., Zieker, D., Beckert, S., ... & Königsrainer, A. (2009). 18F-FDG-PET/CT to select patients with peritoneal carcinomatosis for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Annals of surgical oncology, 16(5), 1295-1303

Vogel, J. D., Felder, S. I., Bhama, A. R., Hawkins, A. T., Langenfeld, S. J., Shaffer, V. O., ... & Paquette, I. M. (2022). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer. Diseases of the Colon & Rectum, 65(2), 148-177

Clinical Question 2: Among adult patients with cT1N0M0 colon adenocarcinoma, is endoscopic excision non-inferior to oncologic resection?

Recommendation 2a.

For cT1N0M0 colon adenocarcinoma, endoscopic excision is not inferior to oncologic resection. However, endoscopic excision is dependent mainly on malignant polyp histopathological features and completeness of excision.

Strong recommendation, Moderate-quality evidence

Consensus Issues

Both the American Society of Colon and Rectal Surgeons (ASCRS) and National Comprehensive Cancer Network (NCCN) define a malignant polyp as a pT1 adenocarcinoma arising in an adenomatous polyp, invading through the muscularis mucosa and into the submucosa. NCCN adds that pTis (carcinoma-in-situ) is not considered a "malignant polyp" since it has not yet penetrated the submucosa, hence, not considered capable of regional nodal metastasis.

The Consensus Panel voted to adopt the recommendation of the ASCRS. The panel concluded that expertise on the conduct of endoscopic excision, as well as quality assurance and auditing should be considered in the decision to do endoscopic excision for malignant polyp.

Summary of Evidence

The source guideline (ASCRS) recommends that a malignant polyp may be adequately treated by endoscopic excision or may require oncologic colon resection based on the histopathological features. This recommendation was based on two retrospective studies and one cohort study. NCCN guideline was also considered in this NCPG's review of evidence.

Among patients with malignant polyps in the colon, an initial non-piecemeal endoscopic excision with adequate margin was shown to be curative in more than 80% of patients (Butte et al, 2012; Gill et al, 2013; Richards et al, 2018). A review on patients with a malignant polyp who underwent endoscopic excision and subsequent colectomy found residual cancer at the polypectomy site or regional lymph nodes in 0-21% (Butte et al, 2012). Recommended endoscopic excision techniques that have been used to avoid colectomy among patients with low-risk malignant colon polyps were: the traditional colonoscopic polypectomy techniques, endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), or combined endoscopic and laparoscopic surgery techniques (CELS).

ASCRS describes the histopathological features that should be taken into consideration when endoscopic excision versus oncologic resection is being

considered for malignant polyp: (1) adequate polypectomy excision margin, (2) depth of submucosal (SM) invasion of cancer cells, (3) degree of cellular differentiation, (4) lymphovascular or perineural invasion (LVI or PNI), and (5) amount of tumor budding. Several studies have shown that tumor budding was a histologic feature associated with adverse outcome that may preclude polypectomy as an adequate treatment of endoscopically removed malignant polyps (NCCN, 2022).

Similarly, NCCN provides favorable and unfavorable histologic features for endoscopic excision. The favorable histologic features are: grade 1 or 2 histology, well- or moderately differentiated histology, no LVI or PNI, and negative margin of excision. Unfavorable histologic features are: grade 3 or 4 histology, poor differentiation, LVI or PNI, and a “positive margin” of excision. However, there is no consensus in both ASCRS and NCCN as to the definition of what constitutes a positive margin of excision. In NCCN, a positive margin has been defined as: (1) tumor <2 mm from the transected margin, (2) tumor <1 mm from the transected margin, and (3) tumor cells present within the diathermy of the transected margin. ASCRS maintains that the definition of a negative polypectomy excision margin is a point of debate, even including earlier reports based on the study of Volk et al (1995) indicating the need for a ≥2 mm excision margin to newer studies reporting low risk of residual cancer to even <1 mm margin.

A malignant polyp may have a pedunculated or sessile shape which the Haggitt classification had used to stratify the risk of lymph node metastasis based on the level of malignant invasion (Haggitt et al, 1985). For Haggitt levels 1 to 3 (defined as carcinoma invading through the muscularis mucosae into the submucosa but limited to the head, neck, or any part of the stalk of a pedunculated polyp, respectively), the risk of lymph node metastasis is negligible; while for Haggitt level 4 (defined as carcinoma in the submucosa at base of a pedunculated or sessile polyp) the risk of lymph node metastasis may be as high as 25%. ASCRS mentions that it is generally accepted that complete endoscopic excision of a pedunculated malignant polyp with Haggitt levels 1 to 3 invasion is adequate, provided that no unfavorable histologic feature is present; but not for patients with Haggitt level 4 invasion or any malignant polyp with unfavorable histologic feature due to high risk of recurrence or higher occurrence of nodal or even systemic metastasis. Although NCCN mentions that malignant sessile polyps with grade I or II histology, negative excision margins, and no LVI or PNI can be successfully treated with endoscopic polypectomy, the patient must be aware that endoscopic excision is associated with higher incidence of adverse outcomes such as higher residual and recurrent disease, greater risk of hematogenous metastasis, and higher mortality rates compared to oncologic resection (NCCN, 2022).

Finally, for those with fragmented specimen or margin which cannot be properly assessed, or those with unfavorable histologic feature, NCCN recommends that subsequent colectomy with en bloc removal of regional lymph nodes should be

considered (i.e., oncologic resection) after thorough assessment of the clinical stage and extent of disease.

Other guidelines mentioning the same recommendation were the American Society of Clinical Oncology (ASCO), Belgian Health Care Knowledge Centre, and European Society for Medical Oncology. ASCO recommends that benefits and potential harms should be noted. With benefits include reducing the risk of the development of malignancy by removing polyps that may be precursors, the potential harms are general risks of endoscopy (e.g., perforation and bleeding).

Research Recommendation

The GDG recommended no additional research.

References

Argilés, G., Tabernero, J., Labianca, R., Hochhauser, D., Salazar, R., Iveson, T., ... & Arnold, D. (2020). Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, *31*(10), 1291-1305

Butte, J. M., Tang, P., Gonen, M., Shia, J., Schattner, M., Nash, G. M., ... & Weiser, M. R. (2012). Rate of residual disease after complete endoscopic resection of malignant colonic polyp. *Diseases of the colon & rectum, 55*(2), 122-127

Gill, M. D., Rutter, M. D., & Holtham, S. J. (2013). Management and short-term outcome of malignant colorectal polyps in the north of England 1. *Colorectal Disease, 15*(2), 169-176

Haggitt, R. C., Glotzbach, R. E., Soffer, E. E., & Wruble, L. D. (1985). Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology, 89*(2), 328-336

Lopes, G., Stern, M. C., Temin, S., Sharara, A. I., Cervantes, A., Costas-Chavarri, A., ... & Correa, M. C. (2019). Early detection for colorectal cancer: ASCO resource-stratified guideline. *Journal of global oncology*, *5*, 1-22

National Comprehensive Cancer Network. (2022). *Colon Cancer Version 1.2022*

Peeters, M., Leroy, R., Robays, J., Veereman, G., Bielen, D., Ceelen, W., & Belgian Health Care Knowledge Center (KCE). (2014). Colon cancer: diagnosis, treatment and follow-up. Good Clinical Practice (GCP). Brussels, Belgium: Belgian Health Care Knowledge Centre

Richards, C. H., Ventham, N. T., Mansouri, D., Wilson, M., Ramsay, G., Mackay, C. D., ... & Steele, R. J. C. (2018). An evidence-based treatment algorithm for colorectal polyp cancers: results from the Scottish Screen-detected Polyp Cancer Study (SSPoCS). *Gut, 67*(2), 299-306

Vogel, J. D., Felder, S. I., Bhama, A. R., Hawkins, A. T., Langenfeld, S. J., Shaffer, V. O., ... & Paquette, I. M. (2022). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer. *Diseases of the Colon & Rectum, 65*(2), 148-177

Volk, E. E., Goldblum, J. R., Petras, R. E., Carey, W. D., & Fazio, V. W. (1995). Management and outcome of patients with invasive carcinoma arising in colorectal polyps. *Gastroenterology, 109*(6), 1801-1807

Clinical Question 3: Among adult patients with resectable stage I-III colon adenocarcinoma, should minimally invasive surgery be offered over open surgery?

Recommendation 3a.

> When expertise and capability are available, a minimally invasive approach to elective colectomy for colon adenocarcinoma is acceptable.
>
> *Strong recommendation, High-quality evidence*

Consensus Issues

The Consensus Panel voted to adopt the recommendation of the American Society of Colon and Rectal Surgeons (ASCRS) and the National Comprehensive Cancer Network (NCCN). The panel concluded that both the capability of centers and expertise of surgeons should be considered when providing minimally invasive surgical (MIS) approach on an elective oncologic resection for colon cancer.

Summary of Evidence

The ASCRS and NCCN recommendation was based on several randomized controlled trials and a meta-analysis comparing MIS versus open approach for oncologic resection of localized colon cancer. Laparoscopic approach with experienced surgeons demonstrated equivalent long-term oncological outcomes (overall survival, disease-free survival, recurrence rate, and time to recurrence), comparable surgical outcomes (lymph node harvest and length of resection margins), and improvements in short-term outcomes (surgical incision length, use of parenteral narcotics and oral analgesia, amount of blood loss, duration of hospital stay, recovery period, and postoperative complications) than open approach. ASCRS guideline likewise highlighted a randomized controlled trial showing that robotic surgery, although associated with longer operative time and higher cost, has the same rate of complications and equivalent short-term related outcomes compared with laparoscopic approach for right colectomy for colon cancer; however, for left colectomy for colon cancer, at present, evidence to support recommendations are limited to case reports or series. On deciding whether a laparoscopic (multiport, single-port, or hand-assisted) or robotic approach is more appropriate, the guideline maintains that MIS procedures should achieve the same goals as that of open surgery; and when this is not possible, conversion to open surgery is recommended. NCCN highlighted that routine use of MIS is generally not recommended for tumors that: are acutely obstructed or perforated, are clearly locally invasive into nearby structures or cT4, and has prohibitive abdominal adhesions.

In addition, the ASCRS and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) have recommended minimum requirements that surgeons must meet before they can perform laparoscopic surgery with curative intent in patients with cancer. Adequate training for laparoscopic colorectal surgery is described as

completion of at least completed 50 cases, as SAGES guidelines suggest. Other key guidelines with the same recommendation include American Society of Clinical Oncology (ASCO), Scottish Intercollegiate Guidelines Network, and Belgian Health Care Knowledge Centre. Lastly, ASCO guidelines highlights that the resources of the facilities should be considered.

Research Recommendation

The GDG recommended to conduct a costing study of adopting minimally invasive approach in the management of colon adenocarcinoma.

References

Costas-Chavarri, A., Nandakumar, G., Temin, S., Lopes, G., Cervantes, A., Cruz Correa, M., Engineer, R., Hamashima, C., Ho, G. F., Huitzil, F. D., Malekzadeh Moghani, M., Sharara, A. I., Stern, M. C., Teh, C., Vázquez Manjarrez, S. E., Verjee, A., Yantiss, R., & Shah, M. A. (2019). Treatment of Patients with Early-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline. *Journal of Global Oncology, 5*, 1–19

Dong, B., Luo, Z., Lu, J., Yang, Y., Song, Y., Cao, J., & Li, W. (2018). Single-incision laparoscopic versus conventional laparoscopic right colectomy: A systematic review and meta-analysis. *International Journal of Surgery, 55*, 31-38

Katsuno, G., Fukunaga, M., Nagakari, K., Yoshikawa, S., Azuma, D., & Kohama, S. (2016). Short-term and long-term outcomes of single-incision versus multi-incision laparoscopic resection for colorectal cancer: a propensity-score-matched analysis of 214 cases. *Surgical endoscopy, 30*(4), 1317-1325

Lopes, G., Stern, M. C., Temin, S., Sharara, A. I., Cervantes, A., Costas-Chavarri, A., ... & Correa, M. C. (2019). Early detection for colorectal cancer: ASCO resource-stratified guideline. *Journal of global oncology*, *5*, 1-22

Miyo, M., Takemasa, I., Ishihara, H., Hata, T., Mizushima, T., Ohno, Y., ... & Mori, M. (2017). Long-term outcomes of single-site laparoscopic colectomy with complete mesocolic excision for colon cancer: comparison with conventional multiport laparoscopic colectomy using propensity score matching. *Diseases of the Colon & Rectum, 60*(7), 664-673

Peeters, M., Leroy, R., Robays, J., Veereman, G., Bielen, D., Ceelen, W., & Belgian Health Care Knowledge Center (KCE). (2014). Colon cancer: diagnosis, treatment, and follow-up. *Good Clinical Practice (GCP)*. Brussels, Belgium: Belgian Health Care Knowledge Centre

Society of American Gastrointestinal and Endoscopic Surgeons. (2012). Guidelines for laparoscopic resection of curable colon and rectal cancer. *Guidelines for Laparoscopic Resection of Curable Colon and Rectal Cancer*

Vogel, J. D., Felder, S. I., Bhama, A. R., Hawkins, A. T., Langenfeld, S. J., Shaffer, V. O., ... & Paquette, I. M. (2022). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer. *Diseases of the Colon & Rectum, 65*(2), 148-177

Clinical Question 4: Among adult patients with reliable pre-operative imaging showing unresectable locally advanced colon adenocarcinoma, does neoadjuvant chemotherapy followed by surgery yield better outcomes than upfront surgery followed by adjuvant chemotherapy?

Recommendation 4a.

Neoadjuvant chemotherapy is an option for locally advanced colon adenocarcinoma.

Good Practice Statement

Recommendation 4b.

Patients with unresectable locally advanced colon adenocarcinoma should be considered for neoadjuvant therapy to attempt to convert to resectability.

Strong recommendation, Moderate-quality evidence

Recommendation 4c.

Neoadjuvant chemotherapy can result in tumor regression and may facilitate margin-negative excision of initially unresectable locally advanced colon adenocarcinoma.

Strong recommendation, Moderate-quality evidence

Consensus Issues

The Consensus Panel (CP) voted to adopt the recommendations of the American Society of Colon and Rectal Surgeons (ASCRS) and emphasized the importance of margin-negative oncologic resection for colon cancer. The CP had included a good practice statement that neoadjuvant chemotherapy (NAC) is an option for locally advanced colon cancer, which is supported also by evidence stated in source guideline. The CP highlighted that the definition of unresectable colon cancer should be included. In this guideline, patients with colorectal cancer fixed to critical structures (e.g., IVC and pelvic sidewall) are then considered locally "unresectable" for cure (Mathis et al, 2008).

Summary of Evidence

The recommendations were based on source guidelines (ASCRS) from National Comprehensive Cancer Network (NCCN) recommendation, one systematic review, and two prospective studies (FOxTROT and PRODIGE 22). Margin-negative oncologic resection is extremely important in colon cancer treatment as positive surgical margin is associated with significantly worse outcomes in terms of disease progression, disease-free survival, and overall survival. Resectability can be identified by contrast-enhanced abdominal CT scan or MRI before surgical exploration and may

facilitate operative planning and referral to a multispecialty surgical team, as needed. For locally advanced colon cancers preoperatively, NAC can be considered as an option for cT4b or bulky nodal disease as this can result in tumor regression and may facilitate complete oncologic resection (Arrendondo et al, 2017; de Gooyer et al, 2020).

In a systematic review by Arrendondo et al (2020) which included six studies, NAC resulted in: tumor volume reduction in two-thirds of patients, major pathological tumor regression in 4-37% of cases which significantly improved three-year disease-free survival in responders compared with non-responders (94% vs 63%, $p = 0.005$); and a 23% lower three-year mortality rate in matched patients with cT4b tumors who received neoadjuvant compared with adjuvant chemotherapy (HR 0.77, 95% CI 0.6–0.98; $p = 0.04$); however, no benefit was noted for cT3 nor cT4a tumors.

Likewise, tumor regression was demonstrated in both the FOxTROT trial and PRODIGE 22 trial. In the FOxTROT trial, colon cancer patients treated with NAC (3 cycles) followed by surgery and adjuvant chemotherapy (9 cycles) showed: significant T and N stage downstaging ($p < 0.001$), a pathological complete response rate of 3.8%, and a trend toward less recurrent or persistent disease at two years (14.0% vs. 17.5%) as compared to patients who received adjuvant chemotherapy (Seymour et al, 2019). The PRODIGE 22 trial, which randomized colon cancer patients to surgery followed by adjuvant chemotherapy (12 cycles) or NAC (4 cycles) followed by surgery and then adjuvant chemotherapy (8 cycles) showed that tumor regression grades 1 - 2 (44% vs 8%, $p < 0.001$) was more likely to be achieved and had a significantly increased rate of pTNM downstaging among patients in the NAC arm (Karoui et al, 2020). Furthermore, a systematic review of 20 trials has shown that neoadjuvant use of a combination of 5-FU, oxaliplatin, and irinotecan plus bevacizumab or cetuximab (for KRAS wild-type cancers) resulted in an overall response rate of 55-85%, a conversion to resectability in 10-61%, and an R0-resection rate of as high as 54% (Bolhuis et al, 2020).

Research Recommendation

The GDG recommended no additional research.

References

Arredondo, J., Baixauli, J., Pastor, C., Chopitea, A., Sola, J. J., González, I., ... & Hernández-Lizoain, J. L. (2017). Mid-term oncologic outcome of a novel approach for locally advanced colon cancer with neoadjuvant chemotherapy and surgery. *Clinical and Translational Oncology, 19*(3), 379-385

Arredondo, J., Pastor, E., Simó, V., Beltrán, M., Castañón, C., Magdaleno, M. C., ... & Ielpo, B. (2020). Neoadjuvant chemotherapy in locally advanced colon cancer: a systematic review. *Techniques in coloproctology, 24*(10), 1001-1015

Bolhuis, K., Kos, M., van Oijen, M. G., Swijnenburg, R. J., & Punt, C. J. (2020). Conversion strategies with chemotherapy plus targeted agents for colorectal cancer liver-only metastases: a systematic review. *European Journal of Cancer, 141*, 225-238

de Gooyer, J. M., Verstegen, M. G., Radema, S. A., Verhoeven, R. H., Verhoef, C., Schreinemakers, J. M., & de Wilt, J. H. (2020). Neoadjuvant chemotherapy for locally advanced T4 colon cancer: a nationwide propensity-score matched cohort analysis. *Digestive surgery*, *37*(4), 292-301

Foxtrot Collaborative Group. Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol.* 2012;13:1152–1160

Karoui, M., Rullier, A., Piessen, G., Legoux, J. L., Barbier, E., De Chaisemartin, C., ... & Taieb, J. (2020). Perioperative FOLFOX 4 versus FOLFOX 4 plus cetuximab versus immediate surgery for high-risk stage II and III colon cancers: a phase II multicenter randomized controlled trial (PRODIGE 22). *Annals of surgery*, *271*(4), 637-645

Mathis, K. L., Nelson, H., Pemberton, J. H., Haddock, M. G., & Gunderson, L. L. (2008). Unresectable colorectal cancer can be cured with multimodality therapy. *Annals of surgery*, *248*(4), 592-598

Seymour, M. T., Morton, D., & International FOxTROT Trial Investigators. (2019). *FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer*

Vogel, J. D., Felder, S. I., Bhama, A. R., Hawkins, A. T., Langenfeld, S. J., Shaffer, V. O., ... & Paquette, I. M. (2022). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer. *Diseases of the Colon & Rectum*, 65(2), 148-177

Clinical Question 5: Among adult patients with stage II colon adenocarcinoma with high-risk features for recurrence, is oxaliplatin-based adjuvant chemotherapy recommended than 5FU/leucovorin or capecitabine monotherapy?

Recommendation 5a.

Oxaliplatin-based adjuvant chemotherapy is recommended for stage II colon adenocarcinoma patients with high-risk feature(s).

Strong recommendation, Low-quality evidence

Consensus Issues

The Consensus Panel voted to adopt the recommendations of American Society of Colon and Rectal Surgeons (ASCRS) that an adjuvant chemotherapy for stage II colon adenocarcinoma patients with high-risk features for recurrence may offer a survival benefit.

Summary of Evidence

ASCRS defines high-risk stage II colon cancers to include those that present clinically with intestinal obstruction or perforation; or on histopathology have inadequately sampled lymph nodes (less than 12 lymph nodes in the resection specimen), a close indeterminate or positive resection margin, T4b tumor depth of invasion, poorly differentiated/undifferentiated histology, lymphovascular invasion, perineural invasion, with high-level tumor budding, or are microsatellite stable/mismatch repair proficient.

Based on the ASCRS guideline, there are conflicting data regarding the role of adjuvant chemotherapy in stage II colon cancer. While the initial subgroup analysis of the MOSAIC trial suggested a benefit of adding oxaliplatin to adjuvant treatment for high-risk stage II colon cancer patients, a more recent analysis of these data showed no benefit to adding oxaliplatin in the adjuvant treatment of either low or high-risk stage II disease (Andre et. al 2009, Tournigand et al, 2012). However, the ASCRS has recommended that oxaliplatin-based adjuvant chemotherapy for high-risk stage II colon cancer patients may offer a survival benefit. The expected five-year survival for a patient with a well-differentiated T3 colon cancer can be as high as 90% whereas for poorly differentiated T4b colon cancer can be as low as 74% (Kuceiko et al, 2020). In a 2016 retrospective study by Casadaban et al for stage II colon cancer patients included in the National Cancer Database (NCDB), the use of adjuvant chemotherapy was associated with improved survival irrespective of pathological risk factors. Most studies based on NCDB data suggest that there is minimal to no benefit to adjuvant treatment in patients with “low-risk” stage II colon cancer, while stage II patients with one or more high-risk features have a risk of recurrence which approaches stage IIIa colon cancer, hence, adjuvant chemotherapy is routinely considered (Kumar et. al, 2015).

ASCRS 2022 provided a recommendation based on moderate quality evidence based on a pooled analysis of five prospective trials and analysis of NCDB. In the pooled analysis of five prospective trials on adjuvant chemotherapy in patients with stage II colon cancer in which fluorouracil-based was compared with oxaliplatin-based treatment, the addition of oxaliplatin resulted in an improvement in five-year disease-free recurrence (10.3% vs 15.3%, $p < 0.05$) but no difference in five-year mortality rate (9.4% - 10.2%, $p > 0.05$) (Shah et al, 2016).

Other guidelines with the same recommendation cited were National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO). NCCN specifically mentions that NCCN Panel supports the conclusion of the 2004 American Society of Clinical Oncology Panel and believes that it is reasonable to accept the relative benefit of adjuvant chemotherapy in stage III disease as indirect evidence of benefit for stage II disease, especially for those with high-risk features. Meanwhile, ESMO recommended that patients with high-risk stage II disease (pT4 or <12 lymph nodes or multiple intermediate risk factors, regardless of MSI) may be considered for the addition of oxaliplatin in the adjuvant chemotherapy.

Research Recommendation

The GDG recommended no additional research.

References

André, T., Boni, C., Navarro, M., Tabernero, J., Hickish, T., Topham, C., ... & De Gramont, A. (2009). Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *Journal of Clinical Oncology*, *27*(19), 3109-3116

André, T., De Gramont, A., Vernerey, D., Chibaudel, B., Bonnetain, F., Tijeras-Raballand, A., ... & De Gramont, A. (2015). Adjuvant fluorouracil, leucovorin, and oxaliplatin in stage II to III colon cancer: updated 10-year survival and outcomes according to BRAF mutation and mismatch repair status of the MOSAIC study. *Journal of Clinical Oncology*, *33*(35), 4176-4187

Argilés, G., Tabernero, J., Labianca, R., Hochhauser, D., Salazar, R., Iveson, T., ... & Arnold, D. (2020). Localised colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Annals of Oncology*, *31*(10), 1291-1305

Casadaban, L., Rauscher, G., Aklilu, M., Villenes, D., Freels, S., & Maker, A. V. (2016). Adjuvant chemotherapy is associated with improved survival in patients with stage II colon cancer. *Cancer*, *122*(21), 3277-3287

Kucejko, R. J., Holleran, T. J., Stein, D. E., & Poggio, J. L. (2020). How soon should patients with colon cancer undergo definitive resection? *Diseases of the Colon & Rectum*, *63*(2), 172-182

Kumar, A., Kennecke, H. F., Renouf, D. J., Lim, H. J., Gill, S., Woods, R., ... & Cheung, W. Y. (2015). Adjuvant chemotherapy use and outcomes of patients with high-risk versus low-risk stage II colon cancer. *Cancer*, *121*(4), 527-534

National Comprehensive Cancer Network. (2022). *Colon Cancer Version 1.2022*

Niedzwiecki, D., Bertagnolli, M. M., Warren, R. S., Compton, C. C., Kemeny, N. E., Benson III, A. B., ... & Colacchio, T. A. (2011). Documenting the natural history of patients with resected stage II adenocarcinoma of the colon after random assignment to adjuvant treatment with edrecolomab or observation: results from CALGB 9581. *Journal of clinical oncology*, *29*(23), 3146

Shah, M. A., Renfro, L. A., Allegra, C. J., André, T., De Gramont, A., Schmoll, H. J., ... & Sargent, D. J. (2016). Impact of patient factors on recurrence risk and time dependency of oxaliplatin benefit in patients with colon cancer: analysis from modern-era adjuvant studies in the adjuvant colon cancer end points (ACCENT) database. *Journal of Clinical Oncology*, *34*(8), 843

Tournigand, C., André, T., Bonnetain, F., Chibaudel, B., Lledo, G., Hickish, T., ... & De Gramont, A. (2012). Adjuvant therapy with fluorouracil and oxaliplatin in stage II

and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. *Journal of clinical oncology*, *30*(27), 3353-3360

Vogel, J. D., Felder, S. I., Bhama, A. R., Hawkins, A. T., Langenfeld, S. J., Shaffer, V. O., ... & Paquette, I. M. (2022). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer. *Diseases of the Colon & Rectum*, 65(2), 148-177

Clinical Question 6: What is the preferred sequence of treatment for resectable and potentially resectable stage IV colon adenocarcinoma?

Recommendation 6a.

Patients with initially resectable colon adenocarcinoma with liver or lung metastasis can be treated with upfront surgical resection followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by surgery.

Strong recommendation, Moderate-quality evidence

Recommendation 6b.

Patients with resectable distant metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the metastasectomy or colectomy, comorbid diseases, and surgeon expertise.

Strong recommendation, Moderate-quality evidence

Recommendation 6c.

Patients with resectable colon adenocarcinoma and peritoneal metastasis without extra-abdominal disease, cytoreductive surgery with or without intraperitoneal chemotherapy should be considered in multidisciplinary setting with appropriate expertise.

Strong recommendation, Moderate-quality evidence

Recommendation 6d.

A six-month course of systemic chemotherapy can be considered for most patients undergoing liver or lung resection to increase the likelihood of eradication of residual microscopic disease.

Strong recommendation, Moderate-quality evidence

Consensus Issues

The Consensus Panel (CP) voted to adopt the recommendations of the American Society of Colon and Rectal Surgeons (ASCRS) and the National Comprehensive Cancer Network (NCCN).

The CP highlighted that the standard of care for patients with colon cancer with resectable metastatic disease is surgical resection of both the primary tumor and the distant metastasis and agrees with the ASCRS recommendation that the treatment of patients with resectable stage IV colon cancer should be individualized and based on

a comprehensive multidisciplinary team discussion together with the hepatobiliary or thoracic surgeons.

Summary of Evidence

For patients with resectable primary colon cancer and with resectable liver or lung metastasis, the NCCN (2022) recommends the following options: (1) synchronous or staged colectomy with liver or lung resection followed by adjuvant chemotherapy (oxaliplatin-based is preferred), (2) neoadjuvant chemotherapy (NAC) for 2 to 3 months (oxaliplatin-based is preferred) followed by synchronous or staged colectomy with liver or lung resection, then adjuvant chemotherapy, or (3) colectomy followed by systemic chemotherapy and a staged liver or lung resection followed by adjuvant chemotherapy. Overall, combined neoadjuvant and adjuvant chemotherapy should not exceed six months.

The role of systemic chemotherapy in the setting of resectable liver metastases was shown in the European Organization for Research and Treatment intergroup trial 40983 study where patients with up to four resectable liver metastases were randomly assigned to either liver surgery alone (i.e., no neoadjuvant or adjuvant chemotherapy); or to six cycles of neoadjuvant 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), followed by liver metastasectomy, and then six cycles of adjuvant FOLFOX (Nordinger et al, 2008; Nordinger et al, 2013). At three-year follow-up, there was a 7% better progression-free survival in the perioperative chemotherapy group compared with the surgery-alone group (35% vs 28%, p = 0.04). At a median follow-up of 8.5 years (interquartile range 7.6–9.5), five-year overall survival did not significantly differ among treatment groups (51% for those who received perioperative chemotherapy and 48% among those who underwent surgery alone).

ASCRS recommended that in patients with resectable colon cancer and peritoneal metastases, the initial treatment options should include systemic chemotherapy and/or resection of the peritoneal metastases with or without intraperitoneal chemotherapy. Systemic chemotherapeutic agents and targeted biologic therapies have improved outcomes of patients with colorectal cancer-associated carcinomatosis, with a median survival in the range of 16-24 months (Zani et al, 2013). In the first randomized trial of cytoreductive surgery and intraperitoneal chemotherapy versus systemic oxaliplatin-based chemotherapy by Cashin et al (2016), two- and five-year overall survival rates were 54% and 38% (p = 0.04) and 33% and 4% (p = 0.02), respectively.

The PRODIGE-7 multi-center randomized, controlled trial that compared cytoreduction alone (n = 132) versus combined cytoreduction and hyperthermic intraperitoneal chemotherapy (HIPEC) (n = 133) raised doubts about the value of HIPEC which showed no overall survival benefit (41-42 months in both arms) with the addition of HIPEC. The addition of HIPEC resulted in higher rates of severe adverse events (Quinet, et al, 2021).

A retrospective study of 553 Japanese patients who underwent colorectal cancer lung metastasectomy: segmentectomy (n = 98) or wedge resection (n = 455), reported five-year recurrence-free survival in 49% and 36% and five-year overall survival in 80% and 68% (Shiono et al, 2017). A variety of lung metastasectomy excision types were performed in 522 Spanish patients, with the median disease-free and disease-specific survival being 28 and 55 months, respectively, with the best outcomes in patients who had a major resection with lymphadenectomy (Hernández et al, 2016).

Research Recommendation

The GDG recommended no additional research.

References

Bakkers, C., van Erning, F. N., Rovers, K. P., Nienhuijs, S. W., Burger, J. W., Lemmens, V. E., ... & de Hingh, I. H. (2020). Long-term survival after hyperthermic intraperitoneal chemotherapy using mitomycin C or oxaliplatin in colorectal cancer patients with synchronous peritoneal metastases: A nationwide comparative study. *European Journal of Surgical Oncology*, *46*(10), 1902-1907

Cashin, P. H., Mahteme, H., Spång, N., Syk, I., Frödin, J. E., Torkzad, M., ... & Graf, W. (2016). Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases: a randomised trial. *European Journal of Cancer*, *53*, 155-162

Gonzalez, M., & Gervaz, P. (2015). Risk factors for survival after lung metastasectomy in colorectal cancer patients: systematic review and meta-analysis. *Future oncology*, *11*(2s), 31-33

Gonzalez, M., Poncet, A., Combescure, C., Robert, J., Ris, H. B., & Gervaz, P. (2013). Risk factors for survival after lung metastasectomy in colorectal cancer patients: a systematic review and meta-analysis. *Annals of surgical oncology*, *20*(2), 572-579

Hernández, J., Molins, L., Fibla, J. J., Heras, F., Embún, R., Rivas, J. J., ... & Canalís, E. (2016). Role of major resection in pulmonary metastasectomy for colorectal cancer in the Spanish prospective multicenter study (GECMP-CCR). *Annals of Oncology, 27*(5), 850-855

Lee, W. S., Yun, S. H., Chun, H. K., Lee, W. Y., Yun, H. R., Kim, J., ... & Shim, Y. M. (2007). Pulmonary resection for metastases from colorectal cancer: prognostic factors and survival. *International journal of colorectal disease*, *22*(6), 699-704

National Comprehensive Cancer Network. (2022). *Colon Cancer Version 1.2022*

Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G. J., Schlag, P. M., Rougier, P., ... & Australasian Gastro-Intestinal Trials Group. (2008). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *The Lancet*, *371*(9617), 1007-1016

Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G. J., Schlag, P. M., Rougier, P., ... & Australasian Gastro-Intestinal Trials Group. (2013). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *The lancet oncology*, *14*(12), 1208-1215

Quénet, F., Elias, D., Roca, L., Goéré, D., Ghouti, L., Pocard, M., ... & Patrick, R. A. T. (2021). Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. *The Lancet Oncology*, *22*(2), 256-266

Shiono, S., Okumura, T., Boku, N., Hishida, T., Ohde, Y., Sakao, Y., ... & Kondo, H. (2017). Outcomes of segmentectomy and wedge resection for pulmonary metastases from colorectal cancer. *European Journal of Cardio-Thoracic Surgery, 51*(3), 504-510

Vogel, J. D., Felder, S. I., Bhama, A. R., Hawkins, A. T., Langenfeld, S. J., Shaffer, V. O., ... & Paquette, I. M. (2022). The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer. *Diseases of the Colon & Rectum*, 65(2), 148-177

Zani, S., Papalezova, K., Stinnett, S., Tyler, D., Hsu, D., & Blazer III, D. G. (2013). Modest advances in survival for patients with colorectal-associated peritoneal carcinomatosis in the era of modern chemotherapy. *Journal of Surgical Oncology*, *107*(4), 307-311

Clinical Question 7: Among adult patients newly diagnosed with rectal adenocarcinoma, is pelvic MRI the recommended modality for preoperative clinical locoregional staging over endorectal ultrasound?

Recommendation 7a.

Pelvic MRI (rectal cancer protocol) is the preferred modality for preoperative clinical locoregional staging of newly diagnosed rectal adenocarcinoma. Endorectal ultrasound may be considered when differentiating between early T stages or when MRI is contraindicated or not available.

Strong recommendation, Moderate-quality evidence

Consensus Issues

The Consensus Panel (CP) voted to adopt the recommendation of the American Society of Colon and Rectal Surgeons (ASCRS) and National Comprehensive Cancer Network (NCCN). They recognized the role of pelvic magnetic resonance imaging (MRI) with rectal cancer protocol for locoregional staging (T and N stage) of low to mid rectal adenocarcinoma preoperatively. In addition, they also pointed out the role of endorectal ultrasound (EUS) if pelvic MRI cannot be offered due to any contraindication or unavailability. Aside from pelvic MRI (preferred) or EUS, other important pre-operative workups for diagnosis and staging of rectal cancer include colonoscopy and proctoscopy with biopsy; contrast-enhanced abdominopelvic CT scan, chest CT scan and CEA determination.

Summary of Evidence

Determining the clinical stage of rectal cancer is highly important since it will direct decisions regarding choice of initial treatment, either surgery or neoadjuvant therapy. Both the ASCRS and NCCN have recommended pelvic MRI with contrast over EUS as the preferred modality for pre-operative locoregional staging of rectal cancer. MRI with contrast staging of rectal adenocarcinoma, using standardized technical protocols and reporting templates, is considered the preferred modality for clinical locoregional staging of newly diagnosed patient. It can accurately assess the depth of tumor penetration (T stage), presence of locoregional nodal metastases (N stage), and the relationship between lesions within the mesorectum and the mesorectal fascia; hence, it can help ascertain surgical clearance of the circumferential resection margin (CRM) prior to oncologic resection. NCCN defines a clear or negative CRM as >1 mm from mesorectal fascia and levator muscles, and not invading into the intersphincteric plane; while an involved or threatened CRM is within 1 mm of mesorectal fascia, or within 1 mm from levator muscles for distal rectal cancer. In addition, pelvic MRI can fully image high, obstructing, or bulky rectal cancer tumors including regions beyond the immediate area of the primary tumor, such as tumor deposits and vascular invasion which the EUS can have limitations.

Endorectal ultrasound (EUS) is most useful in differentiating between early T stages (i.e., T1 versus T2), thus, is considered complementary to MRI for such purposes and when MRI is contraindicated (i.e., when implantable medical devices are present) or unavailable.

Falleti et al (2018) have demonstrated pelvic MRI to be accurate for the prediction of T and N stage and, pre-operatively, the disease-free survival (HR, 1.65; 95% CI, 1.01-2.69; P < .05) and local recurrence (HR, 3.50; 95% CI, 1.53-8.00; P < .05). Clinical nodal (cN) staging is comparable with pelvic MRI (Sensitivity = 66%, Specificity = 76%) and EUS (Sensitivity = 67%, Specificity = 78%), but the cN staging accuracy may be further improved in MRI by incorporating criteria such as a spiculated border and mixed signal intensity.

Research Recommendation

The GDG recommended no additional research.

References

Beets-Tan, R. G., Lambregts, D. M., Maas, M., Bipat, S., Barbaro, B., Curvo-Semedo, L., ... & Blomqvist, L. (2018). Magnetic resonance imaging for clinical management of rectal cancer: updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. *European radiology*, *28*(4), 1465-1475

Brown, G., Richards, C. J., Bourne, M. W., Newcombe, R. G., Radcliffe, A. G., Dallimore, N. S., & Williams, G. T. (2003). Morphologic predictors of lymph node status in rectal cancer with use of high-spatial-resolution MR imaging with histopathologic comparison. *Radiology*, *227*(2), 371-377

Faletti, R., Gatti, M., Arezzo, A., Stola, S., Benedini, M. C., Bergamasco, L., ... & Fonio, P. (2017). Preoperative staging of rectal cancer using magnetic resonance imaging: comparison with pathological staging. *Minerva Chirurgica*, *73*(1), 13-19

Fowler, K. J., Kaur, H., Cash, B. D., Feig, B. W., Gage, K. L., Garcia, E. M., ... & Carucci, L. R. (2017). ACR appropriateness criteria® pretreatment staging of colorectal cancer. *Journal of the American College of Radiology*, *14*(5), S234-S244

Garcia-Aguilar, J., Pollack, J., Lee, S. H., Hernandez de Anda, E., Mellgren, A., Wong, W. D., ... & Madoff, R. D. (2002). Accuracy of endorectal ultrasonography in preoperative staging of rectal tumors. *Diseases of the colon & rectum*, *45*(1), 10-15

Glynne-Jones, R., Wyrwicz, L., Tiret, E., Brown, G., Rödel, C. D., Cervantes, A., & Arnold, D. (2017). Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. *Annals of Oncology*, 28, iv22-iv40

Kim, J. H., Beets, G. L., Kim, M. J., Kessels, A. G., & Beets-Tan, R. G. (2004). High-resolution MR imaging for nodal staging in rectal cancer: are there any criteria in addition to the size? *European journal of radiology*, *52*(1), 78-83

Klessen, C., Rogalla, P., & Taupitz, M. (2007). Local staging of rectal cancer: the current role of MRI. *European radiology*, *17*(2), 379-389

Marusch, F., Koch, A., Schmidt, U., Zippel, R., Kuhn, R., Wolff, S., ... & Lippert, H. (2002). Routine use of transrectal ultrasound in rectal carcinoma: results of a prospective multicenter study. *Endoscopy*, *34*(05), 385-390

Mir, Z. M., Yu, D., Merchant, S. J., Booth, C. M., & Patel, S. V. (2020). Management of rectal cancer in Canada: an evidence-based comparison of clinical practice

guidelines. *Canadian Journal of Surgery*, 63(1), E27

National Comprehensive Cancer Network. (2022). *Rectal Cancer Version 1.2022*

Wo, J. Y., Anker, C. J., Ashman, J. B., Bhadkamkar, N. A., Bradfield, L., Chang, D. T., ... & Das, P. (2021). Radiation therapy for rectal cancer: Executive summary of an ASTRO clinical practice guideline. *Practical radiation oncology*, 11(1), 13-25

You, Y. N., Hardiman, K. M., Bafford, A., Poylin, V., Francone, T. D., Davis, K., ... & Feingold, D. L. (2020). The American society of colon and rectal surgeons clinical practice guidelines for the management of rectal cancer. *Diseases of the Colon & Rectum*, 63(9), 1191-1222

Clinical Question 8: Among adult patients with cT1N0M0 rectal adenocarcinoma, should local excision +/- adjuvant treatment (radiotherapy or chemoradiotherapy) be offered as compared to oncologic resection?

Recommendation 8a.

Local excision is an appropriate treatment option for carefully selected patients with cT1N0 rectal adenocarcinoma with favorable clinical and histological features.

Strong recommendation, Moderate-quality evidence

Recommendation 8b.

For high-risk patients who refuse or are medically unfit for radical resection, adjuvant chemoradiation should be recommended after local excision and should be followed by surveillance for a potentially salvageable recurrence.

Strong recommendation, Moderate-quality evidence

Consensus Issues

The Consensus Panel (CP) voted to adopt the recommendation of American Society of Colon and Rectal Surgeons (ASCRS) and National Comprehensive Cancer Network (NCCN) that local excision is an appropriate treatment modality for carefully selected cT1N0 rectal cancer patients without high-risk features for recurrence.

Summary of Evidence

The source guidelines of the above recommendation are ASCRS and NCCN.

Local excision is an appropriate treatment option among carefully selected cT1N0 rectal cancer patients with favorable clinical and histopathological features which include small (<3 cm), well- or moderately differentiated (grade 1 or 2 histology) adenocarcinomas limited to less than 30% of the rectal circumference, no lymphovascular or perineural invasion (LVI or PNI), SM1 or SM2 depth of submucosal invasion of cancer cells, without tumor budding on tissue biopsy, no clinical perirectal nodal involvement based on pelvic MRI or endorectal ultrasound evaluation, and are accessible transanally for full-thickness margin-negative excision. Haggitt et al (1985) stratified the risk of lymph node metastasis of cT1 tumor based on the shape of malignant polyp that may guide treatment decisions. For Haggitt levels 1 to 3 (defined as carcinoma invading through the muscularis mucosae into the submucosa but limited to the head, neck, or any part of the stalk of a pedunculated polyp, respectively), the risk of lymph node metastasis is negligible; thus, complete local excision of a pedunculated polyp with favorable clinical and histopathological features is adequate. Local excision can be done by conventional transanal excision for tumors that are located within 8 cm of the anal verge: or by using different transanal

endoscopic platforms such as transanal endoscopic microsurgery (TEMS), transanal endoscopic operations (TEO), or transanal minimally invasive surgery (TAMIS) for more proximal rectal lesions. It is recommended that the locally excised rectal tumor should be properly oriented and pinned before fixation and must be brought to the pathologist by the surgeon to facilitate an oriented histopathologic evaluation of the surgical margins.

The rate of local recurrence following local excision for cT1 rectal cancer (7% to 21%) remains higher than that after radical resection; thus, subsequent radical resection is typically recommended when pathologic examination reveals unfavorable histopathological features that may increase the risk of recurrence such as deeper T stage (T2 or higher), poorly differentiated or grade 3 or 4 histology, with LVI or PNI, SM3 depth of submucosal invasion, tumor budding, and inadequate excision margins. Furthermore, though local excision offers the advantages of minimizing operative risk and functional sequelae, it does not adequately remove or pathologically stage the mesorectal lymph nodes posing a risk for occult nodal metastasis, particularly for Haggitt level 4 (defined as carcinoma in the submucosa at base of a pedunculated or sessile polyp) in which the risk of lymph node metastasis is high. More recent studies showed that the risk of occult nodal metastasis from T1 lesion ranges from 6-11%, but with greater risk if unfavorable histopathological features are present; hence, for patients with Haggitt 4 malignant polyp with unfavorable histologic features, an oncologic resection is recommended.

For patients with high-risk T1 lesions who refuse radical resection or prioritize sphincter preservation, addition of adjuvant chemoradiation after adequate local excision has been considered. A systematic review comparing local excision with adjuvant chemoradiation versus radical resection among patients with pT1 rectal lesions showed a weighted average local recurrence rate of 10% (95% CI, 4-21) vs 6% (95% CI, 3-15). The need for surveillance after local excision is recommended to check on potentially salvageable recurrence. Thus, patients with Haggitt 4 classification or with unfavorable histopathological features undergoing local excision must be aware that the procedure is associated with higher incidence of adverse outcomes (e.g., higher residual and recurrent disease, greater risk of hematogenous metastasis, and higher mortality rates) compared to oncologic resection (NCCN, 2022).

Research Recommendation

The GDG recommended no additional research.

References

Borstlap, W. A. A., Coeymans, T. J., Tanis, P. J., Marijnen, C. A. M., Cunningham, C., Bemelman, W. A., & Tuynman, J. B. (2016). Meta-analysis of oncological outcomes after local excision of pT1–2 rectal cancer requiring adjuvant (chemo) radiotherapy or completion surgery. *Journal of British Surgery*, *103*(9), 1105-1116

Brunner, W., Widmann, B., Marti, L., Tarantino, I., Schmied, B. M., & Warschkow, R. (2016). Predictors for regional lymph node metastasis in T1 rectal cancer: a population-based SEER analysis. *Surgical endoscopy*, *30*(10), 4405-4415

Doornebosch, P. G., Tollenaar, R. A., & De Graaf, E. J. (2009). Is the increasing role of transanal endoscopic microsurgery in curation for T1 rectal cancer justified? A systematic review. *Acta Oncologica*, *48*(3), 343-353

Kidane, B., Chadi, S. A., Kanters, S., Colquhoun, P. H., & Ott, M. C. (2015). Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: a systematic review and meta-analysis. *Diseases of the Colon & Rectum*, *58*(1), 122-140

Nascimbeni, R., Burgart, L. J., Nivatvongs, S., & Larson, D. R. (2002). Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Diseases of the colon & rectum*, *45*(2), 200-206

National Comprehensive Cancer Network. (2022). *Rectal Cancer Version 1.2022*

Russo, S., Anker, C. J., Abdel-Wahab, M., Azad, N., Das, P., Dragovic, J., ... & Jabbour, S. K. (2019). Executive summary of the American Radium society appropriate use criteria for local excision in rectal cancer. *International Journal of Radiation Oncology* Biology* Physics*, *105*(5), 977-993

You, Y. N., Baxter, N. N., Stewart, A., & Nelson, H. (2007). Is the increasing rate of local excision for stage I rectal cancer in the United States justified? a nationwide cohort study from the National Cancer Database. *Annals of surgery*, *245*(5), 726

Clinical Question 9: Among adult patients with resectable stage I-III low to mid rectal adenocarcinoma, should minimally invasive surgery be offered over open surgery?

Recommendation 9a.

Minimally invasive surgical approach following standard oncologic techniques of total mesorectal excision (TME) can be considered and should be performed by experienced surgeons with technical expertise.

Strong recommendation, High-quality of evidence

Consensus Issues

The Consensus Panel voted to adopt the recommendation of the American Society of Colon and Rectal Surgeons (ASCRS) but emphasized that MIS approach for TME should be performed by experienced surgeons with technical expertise following standard oncologic principles.

Summary of Evidence

Based on the ASCRS guideline, minimally invasive surgery (MIS) for rectal cancer improves short-term perioperative outcomes. However, its long-term oncologic results remain unclear since several randomized, controlled trials (RCT) have raised concerns regarding the pathologic outcomes of laparoscopic resection for rectal cancer. Their findings showed that there is a concerning higher incidence of positive circumferential resection margin (CRM) with the laparoscopy group as compared to open surgery and the impact of these outcomes on long-term survival is still being clarified.

TME for adenocarcinoma of the middle third of the rectum should typically be performed as part of a low anterior resection. TME for adenocarcinoma of the lower third of the rectum should typically be performed as part of an ultra-low anterior resection or abdominoperineal resection (APR). For ultra-low anterior resection, distal mural margin of at least 2 cm is required, while for cancers located at or below the mesorectal margin, a 1 cm distal mural margin is generally acceptable. One of the most important parameters in TME surgery is achieving adequate CRM, as CRM positivity is associated with increased risk for local recurrence and decreased survival (5-year local recurrence: HR = 3.50; 95% CI, 1.53–8.00; $p < 0.05$; 5-year overall survival: HR = 1.97; 95% CI, 1.27–3.04; $p < 0.01$).

The primary landmark trials which randomly assigned patients with rectal cancer to laparoscopic versus open oncologic resection are the COLOR II, CLASSICC, COREAN, ACOZOG Z6051, and the ALaCaRT trials. Pathologic outcomes of concern were observed in several trials. The CLASICC trial reported that CRM positivity rate is slightly higher in the laparoscopic versus the open rectal cancer resection group (16%

versus 14%; p = 0.8) although not statistically significant. In the ACOSOG Z6051 trial, the composite primary end point (CRM >1 mm, negative distal margin, and TME completeness) was met in significantly fewer patients in the laparoscopic arm (81.7%; 95% CI, 76.8%–86.6% vs 86%; 95% CI, 82.5%–91.4%). In the ALaCaRT, successful resection was achieved in significantly fewer patients in the laparoscopic arm (82% vs 89%; risk difference of –7.0%; 95% CI, –12.4% to ∞; p = 0.38 for noninferiority) as well. Meta-analyses of RCTs have also reported significantly higher rates of incomplete resection (13.2% vs 10.4%; RR = 1.31; 95% CI, 1.05–1.64; p = 0.02) in the laparoscopic groups.

Nonetheless, the survival outcomes available based on the five landmark trials are still limited to less than a 5-year median follow-up duration. The three trials (COLOR II, CLASICC, and COREAN) demonstrated noninferiority of laparoscopy compared with open surgery for rectal cancer as the results showed no significant differences in 3-year local recurrence rates or 5-year disease-free survival (DFS) rates. In the ACOSOG Z6051 trial, laparoscopic and open rectal cancer resection showed no difference in 2-year DFS (79.5%; 95% CI, 74.4–84.9 vs 83.2%; 95% CI, 78.3–88.3), locoregional recurrence (4.6% vs 4.5%), and distant recurrence (14.6% vs 16.7%). Similarly, in the ALaCaRT trial, the two groups did not significantly differ in 2-year local recurrence rate or 2-year DFS rate.

Based on ASCRS guideline, data regarding robotic rectal cancer surgery have yet to mature. Meanwhile, initial reports of ROLARR trial and a meta-analysis from eight randomized trials comparing robotic and laparoscopic rectal cancer surgery showed no difference in the CRM positivity rate (5.1% robotic versus 6.3% laparoscopic; adjusted OR = 0.78; 95% CI, 0.35–1.76; p = 0.56) with similar pathologic outcomes including resection margin status and number of harvested lymph nodes, but no comparisons of oncologic outcomes were reported.

Research Recommendation

The GDG recommended no additional research.

References

Alberda, W. J., Verhoef, C., Nuyttens, J. J., van Meerten, E., Rothbarth, J., de Wilt, J. H., & Burger, J. W. (2014). Intraoperative radiation therapy reduces local recurrence rates in patients with microscopically involved circumferential resection margins after resection of locally advanced rectal cancer. *International Journal of Radiation Oncology* Biology* Physics*, *88*(5), 1032-1040

Bonjer, H. J., Deijen, C. L., Abis, G. A., Cuesta, M. A., Van Der Pas, M. H., De Lange-De Klerk, E. S., ... & Haglind, E. (2015). A randomized trial of laparoscopic versus open surgery for rectal cancer. *New England Journal of Medicine*, *372*(14), 1324-1332

Fleshman, J., Branda, M., Sargent, D. J., Boller, A. M., George, V., Abbas, M., ... & Nelson, H. (2015). Effect of laparoscopic-assisted resection vs open resection of stage II or III rectal cancer on pathologic outcomes: the ACOSOG Z6051 randomized clinical trial. *Jama*, *314*(13), 1346-1355

Guillou, P. J., Quirke, P., Thorpe, H., Walker, J., Jayne, D. G., Smith, A. M., ... & MRC CLASICC trial group. (2005). Short-term endpoints of conventional versus laparoscopic-assisted surgery in patients with colorectal cancer (MRC CLASICC trial): multicentre, randomised controlled trial. *The lancet*, *365*(9472), 1718-1726

Hyngstrom, J. R., Tzeng, C. W. D., Beddar, S., Das, P., Krishnan, S., Delclos, M. E., ... & Rodriguez-Bigas, M. A. (2014). Intraoperative radiation therapy for locally advanced primary and recurrent colorectal cancer: ten-year institutional experience. *Journal of surgical oncology*, *109*(7), 652-658

Jeong, S. Y., Park, J. W., Nam, B. H., Kim, S., Kang, S. B., Lim, S. B., ... & Oh, J. H. (2014). Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomised controlled trial. *The Lancet Oncology*, *15*(7), 767-774

Jiang, J. B., Jiang, K., Dai, Y., Wang, R. X., Wu, W. Z., Wang, J. J., ... & Li, X. M. (2015). Laparoscopic versus open surgery for mid-low rectal cancer: a systematic review and meta-analysis on short-and long-term outcomes. *Journal of Gastrointestinal Surgery*, *19*(8), 1497-1512

Martínez-Pérez, A., Carra, M. C., Brunetti, F., & De'Angelis, N. (2017). Pathologic outcomes of laparoscopic vs open mesorectal excision for rectal cancer: a systematic review and meta-analysis. *JAMA surgery*, *152*(4), e165665-e165665

Stevenson, A. R., Solomon, M. J., Lumley, J. W., Hewett, P., Clouston, A. D., Gebski,

V. J., ... & ALaCaRT Investigators. (2015). Effect of laparoscopic-assisted resection vs open resection on pathological outcomes in rectal cancer: the ALaCaRT randomized clinical trial. *Jama*, *314*(13), 1356-1363

van der Pas, M. H., Haglind, E., Cuesta, M. A., Fürst, A., Lacy, A. M., Hop, W. C., ... & COlorectal cancer Laparoscopic or Open Resection II (COLOR II) Study Group. (2013). Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. *The lancet oncology*, *14*(3), 210-218

Vennix, S., Pelzers, L., Bouvy, N., Beets, G. L., Pierie, J. P., Wiggers, T., & Breukink, S. (2014). Laparoscopic versus open total mesorectal excision for rectal cancer. *Cochrane Database of Systematic Reviews*, (4)

Clinical Question 10: Among adult patients with Stage II or III rectal adenocarcinoma, is neoadjuvant short course radiotherapy comparable to long course chemoradiotherapy?

Recommendation 10a.

> Neoadjuvant short course radiation therapy and long course chemoradiation therapy are comparable for Stage II or III rectal adenocarcinoma in terms of outcomes such as survival, recurrence, and complications.
>
> *Strong recommendation, High-quality evidence*

Consensus Issues

The Consensus Panel voted to adopt the recommendation of the American Society of Colon and Rectal Surgeons (ASCRS) and American Society for Radiation Oncology (ASTRO).

Summary of Evidence

For patients with clinical stage II-III low and midrectal cancer, neoadjuvant radiation therapy (RT) is recommended. Multiple prospective trials have demonstrated that neoadjuvant RT decreases the risk of local recurrence, even in the era of total mesorectal excision (TME). These results were confirmed by several meta-analyses, which consistently found that the hazard ratio for local recurrence with RT was approximately 0.5 compared with surgery alone.

The two most commonly used neoadjuvant therapy regimen are the short-course RT (5 Gy daily for 5 days without chemotherapy) and long-course chemoradiation therapy (CRT) (1.8-2 Gy per fraction over 5 to 6 weeks, for a total of 45-50.4 Gy with concurrent 5-fluorouracil-based chemotherapy). Two randomized trials that compared neoadjuvant short-course RT and long-course chemoradiation therapy (CRT) that reported long-term oncologic outcomes are the Polish trial and the Trans-Tasman Radiation Oncology Group trial (TROG) 01.04 which showed similar rates of local recurrence, development of distant metastasis in 5 years, and overall survival. While the rates of high-grade late toxicity did not significantly differ in either trial, significantly less acute toxicity was associated with short-course RT than with long-course CRT (3% versus 18%, $p < 0.001$ in the Polish trial and 1.9% versus 28%, $p < 0.001$ in the TROG 01.04 trial). There is also no difference in the rates of complete R0 resection and rates of sphincter preservation in the pooled analysis in either trial.

Neoadjuvant short-course RT or long-course CRT are recommended equally. This is based on high-quality evidence that either approach improves local control, and randomized studies suggesting similar efficacy and patient-reported Quality of Life outcomes for either treatment.

Research Recommendation

The GDG recommended to conduct a costing study on the neoadjuvant short course radiotherapy for the management of patients with stage II and III rectal adenocarcinoma.

References

Ansari, N., Solomon, M. J., Fisher, R. J., Mackay, J., Burmeister, B., Ackland, S., ... & Ngan, S. Y. (2017). Acute adverse events and postoperative complications in a randomized trial of preoperative short-course radiotherapy versus long-course chemoradiotherapy for T3 adenocarcinoma of the rectum. *Annals of surgery*, *265*(5), 882-888

Bujko, K., Nowacki, M. P., Kępka, L., Olędzki, J., Bębenek, M., Kryj, M., & Polish Colorectal Study Group. (2005). Postoperative complications in patients irradiated pre-operatively for rectal cancer: report of a randomised trial comparing short-term radiotherapy vs chemoradiation. *Colorectal Disease*, *7*(4), 410-416

Bujko, K., Nowacki, M. P., Nasierowska-Guttmejer, A., Michalski, W., Bebenek, M., & Kryj, M. (2006). Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Journal of British Surgery*, *93*(10), 1215-1223

Folkesson, J., Birgisson, H., Pahlman, L., Cedermark, B., Glimelius, B., & Gunnarsson, U. (2005). Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol*, *23*(24), 5644-5650

McLachlan, S. A., Fisher, R. J., Zalcberg, J., Solomon, M., Burmeister, B., Goldstein, D., ... & Ngan, S. Y. (2016). The impact on health-related quality of life in the first 12 months: A randomised comparison of preoperative short-course radiation versus long-course chemoradiation for T3 rectal cancer (Trans-Tasman Radiation Oncology Group Trial 01.04). *European journal of cancer*, *55*, 15-26

Ngan, S. Y., Burmeister, B., Fisher, R. J., Solomon, M., Goldstein, D., Joseph, D., ... & Mackay, J. (2012). Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol*, *30*(31), 3827-33

OCUM group Ruppert R http://orcid. org/0000-0001-5070-2009 Junginger T junginger@ uni-mainz. de Ptok H Strassburg J Maurer CA Brosi P Sauer J Baral J Kreis M Wollschlaeger D Hermanek P http://orcid. org/0000-0003-2676-9486 Merkel S. (2018). Oncological outcome after MRI-based selection for neoadjuvant chemoradiotherapy in the OCUM Rectal Cancer Trial. *Journal of British Surgery*, *105*(11), 1519-1529

Park, J. H., Yoon, S. M., Yu, C. S., Kim, J. H., Kim, T. W., & Kim, J. C. (2011). Randomized phase 3 trial comparing preoperative and postoperative

chemoradiotherapy with capecitabine for locally advanced rectal cancer. *Cancer*, *117*(16), 3703-3712

Peeters, K. C., Marijnen, C. A., Nagtegaal, I. D., Kranenbarg, E. K., Putter, H., Wiggers, T., ... & Dutch Colorectal Cancer Group. (2007). The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Annals of surgery*, *246*(5), 693-701

Pietrzak, L., Bujko, K., Nowacki, M. P., Kepka, L., Oledzki, J., Rutkowski, A., ... & Polish Colorectal Study Group. (2007). Quality of life, anorectal and sexual functions after preoperative radiotherapy for rectal cancer: report of a randomised trial. *Radiotherapy and oncology*, *84*(3), 217-225

Roh, M. S., Colangelo, L. H., O'Connell, M. J., Yothers, G., Deutsch, M., Allegra, C. J., ... & Wolmark, N. (2009). Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *Journal of clinical oncology*, *27*(31), 5124

Sauer, R., Liersch, T., Merkel, S., Fietkau, R., Hohenberger, W., Hess, C., ... & Rödel, C. (2012). Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin oncol*, *30*(16), 1926-1933

Sebag-Montefiore, D., Stephens, R. J., Steele, R., Monson, J., Grieve, R., Khanna, S., ... & Parmar, M. (2009). Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *The Lancet*, *373*(9666), 811-820

Taylor, F. G., Quirke, P., Heald, R. J., Moran, B. J., Blomqvist, L., Swift, I. R., ... & Brown, G. (2014). Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *Journal of Clinical Oncology*, *32*(1), 34-43

van Gijn, W., Marijnen, C. A., Nagtegaal, I. D., Kranenbarg, E. M. K., Putter, H., Wiggers, T., ... & Dutch Colorectal Cancer Group. (2011). Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *The lancet oncology*, *12*(6), 575-582

Zhou, Z. R., Liu, S. X., Zhang, T. S., Chen, L. X., Xia, J., Hu, Z. D., & Li, B. (2014). Short-course preoperative radiotherapy with immediate surgery versus long-

course chemoradiation with delayed surgery in the treatment of rectal cancer: a systematic review and meta-analysis. *Surgical oncology*, *23*(4), 211-221

Clinical Question 11: Among adult patients diagnosed with cT4b, cN2 or unresectable nonmetastatic rectal adenocarcinoma, does total neoadjuvant therapy yield better outcomes than neoadjuvant short course radiation therapy or long course chemoradiation therapy + adjuvant chemotherapy?

Recommendation 11a.

Considerations for total neoadjuvant therapy over standard neoadjuvant therapy (short course radiation therapy or long course chemoradiation therapy) for cT4b, cN2 or unresectable nonmetastatic rectal adenocarcinoma must be based on a multidisciplinary team evaluation.

Strong recommendation, Low-quality evidence

Consensus Issues

The Consensus Panel voted to adopt the recommendation of the American Society of Colon and Rectal Surgeons (ASCRS) and National Comprehensive Cancer Network (NCCN) but emphasized the importance of multidisciplinary team (MDT) evaluation when multimodality therapy for nonmetastatic locally advanced rectal adenocarcinoma is recommended.

Summary of Evidence

Total neoadjuvant therapy (TNT) is a treatment strategy for locally advanced rectal adenocarcinoma, which delivers both neoadjuvant systemic chemotherapy and chemoradiotherapy (CRT) prior to oncologic resection. TNT may either refer to induction systemic chemotherapy followed by long course CRT, or to long course CRT followed by consolidation systemic chemotherapy prior to oncologic resection. The treatment is given for a total duration that should not, in general, exceed six months. This treatment strategy was developed to address micro-metastases earlier than the adjuvant setting and have the ability to deliver all planned systemic therapy to a greater proportion of patients.

The efficacy and safety of TNT was assessed in the EXPERT and EXPERT-C trials that enrolled rectal cancer patients with poor-risk disease characterized by low-lying, cT4 or cN2 rectal cancer, or a threatened circumferential resection margin (CRM) as evaluated by pelvic MRI. The pooled analysis revealed a five-year progression-free survival and overall survival rates of 66.4% and 73.3%, respectively. Encouragingly high pathologic complete response (pCR) rates for TNT were also reported at 24% in EXPERT and 29% in CONTRE.

Several trials have been conducted comparing TNT with standard neoadjuvant therapy. A comparison was made between TNT and CRT with adjuvant chemotherapy in the Spanish GCR-3 trial and a retrospective cohort analysis. The pCR rates were similar between the two in the Spanish GCR-3 trial, while TNT produced a higher pCR

rate (36% vs 21%) in the cohort analysis.

The different sequences of introducing TNT have been described in several guidelines but comparative data regarding long-term toxicity and survival rates are limited. Hence, a multidisciplinary team discussion is recommended to tailor the management to the individual patients with locally advanced rectal cancer who will be subjected to multimodality treatment.

Research Recommendation

The GDG recommended no additional research.

References

Cercek, A., Goodman, K. A., Hajj, C., Weisberger, E., Segal, N. H., Reidy-Lagunes, D. L., ... & Saltz, L. B. (2014). Neoadjuvant chemotherapy first, followed by chemoradiation and then surgery, in the management of locally advanced rectal cancer. *Journal of the National Comprehensive Cancer Network*, *12*(4), 513-519

Chau, I., Brown, G., Cunningham, D., Tait, D., Wotherspoon, A., Norman, A. R., ... & Oates, J. (2006). Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging–defined poor-risk rectal cancer. *Journal of Clinical Oncology*, *24*(4), 668-674

Fernandez-Martos, C., Garcia-Albeniz, X., Pericay, C., Maurel, J., Aparicio, J., Montagut, C., ... & Minsky, B. D. (2015). Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: long-term results of the Spanish GCR-3 phase II randomized trial. *Annals of Oncology*, *26*(8), 1722-1728

Fernández-Martos, C., Pericay, C., Aparicio, J., Salud, A., Safont, M., Massuti, B., ... & Alonso, V. (2010). Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging–defined, locally advanced rectal cancer: grupo cáncer de recto 3 study. *Journal of Clinical Oncology*, *28*(5), 859-865

Marechal, R., Vos, B., Polus, M., Delaunoit, T., Peeters, M., Demetter, P., ... & Van Laethem, J. L. (2012). Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: a randomized multicentric phase II study. *Annals of oncology*, *23*(6), 1525-1530

National Comprehensive Cancer Network. (2022). *Rectal Cancer Version 1.2022*

Nogué, M., Salud, A., Vicente, P., Arriví, A., Roca, J. M., Losa, F., ... & AVACROSS Study Group. (2011). Addition of bevacizumab to XELOX induction therapy plus concomitant capecitabine-based chemoradiotherapy in magnetic resonance imaging–defined poor-prognosis locally advanced rectal cancer: the AVACROSS study. *The oncologist*, *16*(5), 614-620

Perez, K., Shah, N., Pricolo, V., Vrees, M., Roth, L., Schechter, S., ... & Sikov, W. M. (2014). *Complete neoadjuvant therapy in rectal cancer (CONTRE): A Brown University Oncology Research Group phase II study*

Clinical Question 12: Among adult patients with rectal adenocarcinoma with complete clinical response following neoadjuvant therapy, is "watch and wait" management approach comparable to oncologic resection?

Recommendation 12a.

Patients with a complete clinical response to neoadjuvant therapy should be offered oncologic resection.

Strong recommendation, Low-quality evidence

Consensus Issues

The Consensus Panel (CP) voted to adopt the recommendation of the American Society of Colon and Rectal Surgeons (ASCRS) that oncologic resection should be offered in patients with rectal adenocarcinoma with complete clinical response following neoadjuvant treatment. They agreed that a "watch and wait" management is an option only for patients who are medically unfit to undergo or refusing oncologic resection.

Summary of Evidence

Complete clinical response (cCR) after neoadjuvant therapy can be assessed clinically by checking for the absence of: (1) a palpable tumor on digital rectal examination, (2) a visible pathology other than a flat scar on endoscopy, and (3) evidence of disease on cross-sectional imaging (CT scan, MRI, or PET). ASCRS guideline recommends that a patient with cCR following neoadjuvant therapy should typically be offered oncologic resection to confirm if the patient achieved pathologic complete response (pCR) which is associated with excellent long-term outcomes. The pCR rate following neoadjuvant chemoradiation therapy has been associated with rate up to 20% or higher.

The need for oncologic resection among patients with cCR has been put into question, particularly in situations where sphincter preservation would be jeopardized or an abdominoperineal resection would be the surgical option, which could result in a permanent stoma for the patient. However, the correlation between cCR and pCR is poor, and there is currently no reliable method to accurately confirm pCR unless evaluating a total mesorectal excision specimen histologically.

Clinical and endoscopic evaluation cannot predict who among the patients with cCR will have a pCR. In a correlation study, 75% of patients with no disease identified by clinical and endoscopic evaluation had pathologic foci of tumor found at the time of resection; while in another study, 61% of patients with a pCR after neoadjuvant therapy had a residual mucosal abnormality preoperatively. Since patients with no mural disease may still harbor lymph node metastasis, and clinical and endoscopic

assessment of response alone cannot reliably predict pCR, the need for oncologic resection cannot be dismissed.

With the inherent risks of oncologic resection and reluctance of patients to undergo radical resection, a “watch and wait” nonoperative approach has been explored in selected patients who achieved a cCR despite concerns regarding oncologic sufficiency. A pooled 2-year local recurrence rate of 15.7% (95% CI, 11.8–20.1) was observed with a salvage surgery possible in 83.8 to 95.4% in patients with a local recurrence.

Comparison of outcomes between the “watch and wait” patients and patients with pCR who underwent radical resection showed no differences in the overall survival (OS) in an early meta-analysis; but in recent studies, a retrospective study showed inferior 5-year OS (73%; 95% CI, 60%–89% vs 94%; 95% CI, 90%–99%) and worse disease-free survival (75%; 95% CI, 62%–90% vs 92%; 95% CI, 87%–98%) among “watch and wait” patients. Furthermore, a significantly higher rate of development of distant metastasis was seen among patients subjected to “watch and wait” treatment approach who developed local recurrence (36%) compared to those who did not (1%) ($p < 0.001$).

Research Recommendation

The GDG recommended no additional research.

References

Appelt, A. L., Pløen, J., Harling, H., Jensen, F. S., Jensen, L. H., Jørgensen, J. C., ... & Jakobsen, A. (2015). High dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *The lancet oncology*, *16*(8), 919-927

Beets-Tan, R. G. H., Leijtens, J., & Beets, G. L. (2011). *Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer*

Chadi, S. A., Malcomson, L., Ensor, J., Riley, R. D., Vaccaro, C. A., Rossi, G. L., ... & Renehan, A. G. (2018). Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis. *The lancet Gastroenterology & hepatology*, *3*(12), 825-836

Cui, J., Fang, H., Zhang, L., Wu, Y. L., & Zhang, H. Z. (2016). Advances for achieving a pathological complete response for rectal cancer after neoadjuvant therapy. *Chronic Diseases and Translational Medicine*, *2*(01), 10-16

Dattani, M., Heald, R. J., Goussous, G., Broadhurst, J., São Julião, G. P., Habr-Gama, A., ... & Moran, B. J. (2018). Oncological and survival outcomes in watch and wait patients with a clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and pooled analysis. *Annals of surgery*, *268*(6), 955-967

Dossa, F., Chesney, T. R., Acuna, S. A., & Baxter, N. N. (2017). A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. *The lancet Gastroenterology & hepatology*, *2*(7), 501-513

Habr-Gama, A., Gama-Rodrigues, J., São Julião, G. P., Proscurshim, I., Sabbagh, C., Lynn, P. B., & Perez, R. O. (2014). Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *International Journal of Radiation Oncology* Biology* Physics*, *88*(4), 822-828

Habr-Gama, A., Perez, R. O., Nadalin, W., Sabbaga, J., Ribeiro Jr, U., e Sousa Jr, A. H. S., ... & Gama-Rodrigues, J. (2004). Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Annals of surgery*, *240*(4), 711

Hiotis, S. P., Weber, S. M., Cohen, A. M., Minsky, B. D., Paty, P. B., Guillem, J. G., ... & Wong, W. D. (2002). Assessing the predictive value of clinical complete

response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. *Journal of the American College of Surgeons*, *194*(2), 131-135

Kundel, Y., Brenner, R., Purim, O., Peled, N., Idelevich, E., Fenig, E., ... & Brenner, B. (2010). Is local excision after complete pathological response to neoadjuvant chemoradiation for rectal cancer an acceptable treatment option? *Diseases of the colon & rectum*, *53*(12), 1624-1631

Lambregts, D. M., Boellaard, T. N., & Beets-Tan, R. G. (2019). Response evaluation after neoadjuvant treatment for rectal cancer using modern MR imaging: a pictorial review. *Insights into imaging*, *10*(1), 1-14

Li, J., Liu, H., Yin, J., Liu, S., Hu, J., Du, F., ... & Zhang, X. (2015). Wait-and-see or radical surgery for rectal cancer patients with a clinical complete response after neoadjuvant chemoradiotherapy: a cohort study. *Oncotarget*, *6*(39), 42354

Ortega, C. D., & Perez, R. O. (2019). Role of magnetic resonance imaging in organ-preserving strategies for the management of patients with rectal cancer. *Insights into Imaging*, *10*(1), 1-16

Sammour, T., Price, B. A., Krause, K. J., & Chang, G. J. (2017). Nonoperative management or 'watch and wait' for rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy: a critical appraisal. *Annals of surgical oncology*, *24*(7), 1904-1915

Smith, F. M., Chang, K. H., Sheahan, K., Hyland, J., O'Connell, P. R., & Winter, D. C. (2012). The surgical significance of residual mucosal abnormalities in rectal cancer following neoadjuvant chemoradiotherapy. *Journal of British Surgery*, *99*(7), 993-1001

Smith, J. D., Ruby, J. A., Goodman, K. A., Saltz, L. B., Guillem, J. G., Weiser, M. R., ... & Paty, P. B. (2012). Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Annals of surgery*, *256*(6), 965-972

Smith, J. J., Strombom, P., Chow, O. S., Roxburgh, C. S., Lynn, P., Eaton, A., ... & Paty, P. B. (2019). Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA oncology*, *5*(4), e185896-e185896

Clinical Question 13: What is the preferred sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma?

Recommendation 13a.

Referral to a multidisciplinary team in a Center of Excellence to determine the sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma is recommended.

Good Practice Statement

Consensus Issues

The above recommendation is a good practice statement agreed upon by the members of the Consensus Panel (CP) based on the evidence presented. They did not vote on a sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma, but collectively recommended a multidisciplinary team (MDT) evaluation to determine the optimal sequence of curative-intent treatment for advanced rectal cancer.

Summary of Evidence

In 2018, the National Comprehensive Cancer Network (NCCN) panel recommended that a total neoadjuvant therapy approach be the treatment for resectable rectal adenocarcinoma with concomitant distant metastasis to the liver or lung. Initial treatment options include neoadjuvant chemoradiation therapy (CRT) for direct local treatment of the primary rectal cancer, neoadjuvant chemotherapy regimen to target metastatic disease, and curative-intent resection which is either staged (primary rectal first versus distant metastatic site first) or synchronous resection (distant metastases and primary rectal cancer). CRT, as an initial therapy, offers the advantage of a possible decreased risk of pelvic failure following surgery; however, it may cause a decrease in tolerance to systemic targeted therapy-containing adjuvant regimens, limiting subsequent treatment of systemic disease. Nevertheless, available data are very limited to help guide in decisions regarding optimal treatment approaches in this patient population.

The use of systemic therapy to surgery post-operatively (as adjuvant) or peri-operatively (neoadjuvant plus adjuvant) has also been considered among resectable stage IV rectal cancer. However, it produced varied outcomes showing a benefit in progression-free survival and disease-free survival but not in overall survival. The optimal sequencing of systemic therapy and resection remains unclear. Neoadjuvant therapy offers the potential advantages of earlier treatment of micrometastatic disease, determination of responsiveness to therapy, and avoidance of local therapy for those patients with early disease progression. The potential disadvantages, on the other hand, include missing the “window of opportunity” for resection due to the

possibility of disease progression or achievement of a complete response and development of liver steatohepatitis and sinusoidal liver injury for some chemotherapeutic agents.

With the very limited evidence available, a referral to an MDT in a Center of Excellence was recommended to determine the best sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma.

Research Recommendation

The GDG recommended no additional research.

References

Araujo, R., Gonen, M., Allen, P., Blumgart, L., DeMatteo, R., Fong, Y., ... & D'Angelica, M. (2013). Comparison between perioperative and postoperative chemotherapy after potentially curative hepatic resection for metastatic colorectal cancer. *Annals of surgical oncology*, *20*(13), 4312-4321

Bilchik, A. J., Poston, G., Adam, R., & Choti, M. A. (2008). Prognostic variables for resection of colorectal cancer hepatic metastases: an evolving paradigm. *Journal of Clinical Oncology*, *26*(33), 5320-5321

Bilchik, A. J., Poston, G., Curley, S. A., Strasberg, S., Saltz, L., Adam, R., ... & Rosen, L. S. (2005). Neoadjuvant chemotherapy for metastatic colon cancer: a cautionary note. *Journal of clinical oncology*, *23*(36), 9073-9078

Brandi, G., De Lorenzo, S., Nannini, M., Curti, S., Ottone, M., Dall'Olio, F. G., ... & Biasco, G. (2016). Adjuvant chemotherapy for resected colorectal cancer metastases: Literature review and meta-analysis. *World journal of gastroenterology*, *22*(2), 519

Choti, M. A. (2009). Chemotherapy-associated hepatotoxicity: do we need to be concerned? *Annals of surgical oncology*, *16*(9), 2391-2394

Ciliberto, D., Prati, U., Roveda, L., Barbieri, V., Staropoli, N., Abbruzzese, A., ... & Tagliaferri, P. (2012). Role of systemic chemotherapy in the management of resected or resectable colorectal liver metastases: a systematic review and meta-analysis of randomized controlled trials. *Oncology reports*, *27*(6), 1849-1856

Kemeny, N. (2006). Management of liver metastases from colorectal cancer. *Oncology (Williston Park, NY)*, *20*(10), 1161-76

Khoo, E., O'Neill, S., Brown, E., Wigmore, S. J., & Harrison, E. M. (2016). Systematic review of systemic adjuvant, neoadjuvant and perioperative chemotherapy for resectable colorectal-liver metastases. *Hpb*, *18*(6), 485-493

Kishi, Y., Zorzi, D., Contreras, C. M., Maru, D. M., Kopetz, S., Ribero, D., ... & Vauthey, J. N. (2010). Extended preoperative chemotherapy does not improve pathologic response and increases postoperative liver insufficiency after hepatic resection for colorectal liver metastases. *Annals of surgical oncology*, *17*(11), 2870-2876

Leonard, G. D., Brenner, B., & Kemeny, N. E. (2005). Neoadjuvant chemotherapy before liver resection for patients with unresectable liver metastases from colorectal carcinoma. *Journal of Clinical Oncology*, *23*(9), 2038-2048

Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G. J., Schlag, P. M., Rougier, P., ... & Australasian Gastro-Intestinal Trials Group. (2008). Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. *The Lancet*, *371*(9617), 1007-1016

Nordlinger, B., Sorbye, H., Glimelius, B., Poston, G. J., Schlag, P. M., Rougier, P., ... & Australasian Gastro-Intestinal Trials Group. (2013). Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. *The lancet oncology*, *14*(12), 1208-1215

Rubbia-Brandt, L., Audard, V., Sartoretti, P., Roth, A. D., Brezault, C., Le Charpentier, M., ... & Terris, B. (2004). Severe hepatic sinusoidal obstruction associated with oxaliplatin-based chemotherapy in patients with metastatic colorectal cancer. *Annals of Oncology*, *15*(3), 460-466

Van Vledder, M. G., De Jong, M. C., Pawlik, T. M., Schulick, R. D., Diaz, L. A., & Choti, M. A. (2010). Disappearing colorectal liver metastases after chemotherapy: should we be concerned? *Journal of Gastrointestinal Surgery*, *14*(11), 1691-1700

Vauthey, J. N., Pawlik, T. M., Ribero, D., Wu, T. T., Zorzi, D., Hoff, P. M., ... & Abdalla, E. K. (2006). Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. *Journal of clinical oncology*, *24*(13), 2065-2072

Wang, Z. M., Chen, Y. Y., Chen, F. F., Wang, S. Y., & Xiong, B. (2015). Peri-operative chemotherapy for patients with resectable colorectal hepatic metastasis: a meta-analysis. *European Journal of Surgical Oncology (EJSO)*, *41*(9), 1197-1203

Clinical Question 14: Among adult patients with locally advanced and advanced colon and rectal adenocarcinoma, does an MDT approach yield better outcomes than a non-MDT approach?

Recommendation 14a.

The treatment of patients with resectable stage IV colorectal adenocarcinoma should be individualized and based on a comprehensive multidisciplinary team (MDT) discussion.

Strong recommendation, Moderate-quality evidence

Recommendation 14b.

Optimum therapeutic strategy and centralization of care is best carried out by an adequately trained MDT which should include a surgeon, medical oncologist, radiation oncologist, diagnostic radiologist, gastroenterologist, pathologist, and other needed specialists as necessary.

Strong recommendation, Low-quality evidence

Recommendation 14c.

An MDT approach is strongly recommended for all locally advanced and advanced colorectal adenocarcinoma to determine the best treatment options.

Strong recommendation, Moderate-quality evidence

Consensus Issues

The Consensus Panel (CP) voted to adopt the recommendations of the American Society of Colon and Rectal Surgeons (ASCRS). Other guidelines mentioning the same recommendations that were considered were from: Hellenic Society of Medical Oncology (HeSMO) which was based on a recommendation from European Society for Medical Oncology (ESMO) as a source guideline, and two observational studies. HeSMO guideline, however, had low AGREE II score on rigor.

It was discussed that optimal management of patients with colorectal cancer for clinical input and collaboration among a team of clinicians is essential and includes expertise from surgery, medical oncology, radiation oncology, gastroenterology, diagnostic radiology, pathology, and other ancillary team members, such as hepatobiliary surgeon for patient with liver metastasis or thoracic surgeon for patient with pulmonary metastasis. The CP highlighted the inclusion of diagnostic radiologists in the multidisciplinary team. The discussion of management by a multidisciplinary team covers: preoperative clinical staging, modifying and individualizing multimodality treatment, planning technical aspects of surgery, and reviewing pathologic staging.

Summary of Evidence

Recommendation from ASCRS were based on cohort study which showed that the difference in overall survival (OS) was significant (p = 0.0001), although the difference in disease-free survival (DFS) was not (p = 0.21) (Lordan et al, 2009). Patients referred via the MDT had 1-, 3-, and 5-year OS rates of 89.6%, 67.5%, and 49.9% respectively and 1-, 3-, and 5-year DFS of 65.4%, 31%, and 27.2% respectively. Patients managed directly without MDT had 1-, 3-, and 5-year OS rates of 90.3%, 54.1%, and 43.3% respectively and 1-, 3-, and 5-year DFS rates of 70.3%, 37.6%, and 27.9% respectively.

A more recent systematic review by Munro et al (2015) showed the relationship between MDT discussion and outcome in patients with colorectal cancer as shown in Table 5.

Research Recommendation

The GDG recommended no additional research.

Table 5. Details of Studies on the Relationship between MDT Discussion and Outcome in Patients with Colorectal Cancer (Adapted from Munro et al)

Author	Country	Setting	Period	Patients	Comparison	Factors significant in MVA	Survival outcome	HR death any cause (95% CI)
Ye	China	Hospital-based	1999–2006	after radical resection for colorectal cancer	before MDT introduced in 2002 (n = 297) cf. after MDT (n = 298)	MDT, Age, Differentiation, Number of nodes examined, Stage	OS	0.62 (0.46 to 1.48)
Du	China	Hospital-based	2001–2005	with resectable locally advanced rectal cancer	contemporaneous patients: n = 101 were evaluated by MDT members and were treated with neoadjuvant chemotherapy; n = 162 were not evaluated	EMVI, pre-treatment CEA, pathological TNM stage	OS, DFS	0.88 (0.52 to 1.48)
Lordan	England	Hospital-based	1996–2006	with hepatic metastases from colorectal cancer who were referred for liver surgery	those who were referred by a team which contained a HPB surgeon (n = 108); those who were referred by teams lacking a HPB surgeon (n = 223)	recurrence, septicemia, pre-operative chemotherapy, referral via team with HPB surgeon, macroscopic invasion of diaphragm	OS, DFS	0.85 (0.60 to 1.19)
McDermid	Scotland	Surgeon-based	1997–2005	with resected colorectal cancers (excluding Dukes'A)	before MDT introduced in 2002 (n = 176) cf. after MDT (n = 134)	Age, stage, MDT	OS	0.73 (0.54 to 0.99)
Palmer	Sweden	Regional	1995–2004	with rectal cancer invading into adjacent organs	3 groups 1) n = 65 discussed at MDT appropriately staged 2) n = 99 appropriately staged not discussed at MDT 3) n = 139 not appropriately staged (whether or not discussed at MDT)	Age	OS (CSS for MVA)	0.95 (0.62 to 1.45)
Wille-Jorgensen	Denmark	Hospital	2001–2006	Rectal cancer	Before MDT introduced (n = 467) c.f. after MDT introduced (n = 344)	No MVA	OS	0.94 (0.79 to 1.12)

Abbreviations: OS, overall survival; DFS, disease-free survival; CSS, cause-specific survival; MVA, multivariate analysis; EMVI, extramural vascular invasion; HPB, hepatobiliary; CEA, carcinoembryonic antigen; HR, hazard ratio (event is death and comparator are no MDT discussion).

References

Lan, Y. T., Jiang, J. K., Chang, S. C., Yang, S. H., Lin, C. C., Lin, H. H., ... & Lin, J. K. (2016). Improved outcomes of colorectal cancer patients with liver metastases in the era of the multidisciplinary teams. *International journal of colorectal disease*, *31*(2), 403-411

Lordan, J. T., Karanjia, N. D., Quiney, N., Fawcett, W. J., & Worthington, T. R. (2009). A 10-year study of outcome following hepatic resection for colorectal liver metastases–the effect of evaluation in a multidisciplinary team setting. *European Journal of Surgical Oncology (EJSO)*, *35*(3), 302-306

Munro, A., Brown, M., Niblock, P., Steele, R., & Carey, F. (2015). Do Multidisciplinary Team (MDT) processes influence survival in patients with colorectal cancer? A population-based experience. *BMC cancer, 15*(1), 1-9

Richardson, B., Preskitt, J., Lichliter, W., Peschka, S., Carmack, S., de Prisco, G., & Fleshman, J. (2016). The effect of multidisciplinary teams for rectal cancer on delivery of care and patient outcome: has the use of multidisciplinary teams for rectal cancer affected the utilization of available resources, proportion of patients meeting the standard of care, and does this translate into changes in patient outcome? *The American Journal of Surgery*, *211*(1), 46-52

Schmoll, H. J., Van Cutsem, E., Stein, A. E. S. M. O., Valentini, V., Glimelius, B., Haustermans, K., ... & Cervantes, A. (2012). ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. *Annals of oncology*, *23*(10), 2479-2516

Clinical Question 15: Among adult patients with unresectable stage IV colon or rectal adenocarcinoma, does the addition of targeted therapy or immunotherapy to chemotherapy yield better outcomes compared to systemic chemotherapy alone?

Recommendation 15a.

> Anti-VEGF therapy may be added to doublet or triplet chemotherapy, regardless of molecular status of the colorectal cancer.
>
> *Strong recommendation, Moderate-quality evidence*

Recommendation 15b.

> Among adults with left sided colon and rectal cancers with KRAS/NRAS WT molecular status, anti-EGFR therapy is recommended.
>
> *Strong recommendation, Moderate-quality evidence*

Consensus Issues

The Consensus Panel (CP) adopted the recommendations from American Society of Clinical Oncology (ASCO) with citation from National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO), and National Institute for Health and Care Excellence (NICE).

Summary of Evidence

Among adult patients with unresectable stage IV colon or rectal adenocarcinoma, the primary recommendations for first-line treatment options depend on resources available. See Table 6.

The first set of treatment recommendations state that clinicians should recommend doublet chemotherapy with fluoropyrimidine (5-FU or capecitabine) and oxaliplatin (FOLFOX or CapeOX) or 5-FU and irinotecan (FOLFIRI) for patients able to tolerate intensive chemotherapy and when resources are available (Cassidy et al, 2008; Tournigand et al, 2004). Using doublet chemotherapy is supported by strong evidence, according to most guidelines (Benson et al, 2018; Cancer Council Australia, 2017; NICE, 2010; Van Cutsem, 2016). For patients unable to tolerate intensive chemotherapy or in limited-resource settings where it should be available, 5-FU/leucovorin or capecitabine are acceptable treatment options (O'Connell, 1989). Doublet chemotherapy is not available in basic, and typically not available in limited-resource settings. Capecitabine may not be cost-effective in resource-constrained settings (Toumazis et al, 2017).

Targeted therapies such as anti-VEGF and anti-EGFR agents may be added to doublet chemotherapies in maximal settings. The recommendation to add the anti-VEGF antibody bevacizumab to chemotherapy is moderate, based on available

guidelines and panel consensus. Anti-VEGF therapy may be added to the doublet or triplet chemotherapy, irrespective of molecular status of the cancer. While the evidence is strong and it is listed as an option by NCCN and ESMO, the absolute clinical benefit in addition to chemotherapy is modest (Hurwitz et al, 2004; Meyerhardt et al, 2012; Petrelli et al, 2013; Saltz et al, 2008). NICE does not recommend anti-VEGF therapy as cost effective for treatment of patients with late-stage CRC (NICE, 2010).

Research Recommendation

The GDG recommended to conduct a costing study on immunotherapy as part of the standard of care among adult patients with unresectable stage IV colon or rectal adenocarcinoma.

Table 6. First-line Systemic Treatments for Patients with Late-stage Colorectal Cancer (Adapted from Treatment of Patients with Late-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline)

Rec	Population	ASCO Resource Levels				Strength of Recommendation
		Basic	Limited	Enhanced	Maximal	
2.1	*RAS* unknown	Palliative care	Single-agent fluoropyrimidine if available; if not, referral to other facility	Doublet chemotherapy	Doublet chemotherapy ± anti-VEGF (bevacizumab)	Strong
						Moderate (chemotherapy + anti-VEGF)
2.2	*RAS* WT and right-sided primary tumor	N/A	N/A	Doublet chemotherapy	Doublet chemotherapy ± anti-VEGF (bevacizumab)	Strong (chemotherapy)
						Moderate (chemotherapy + anti-VEGF)
2.3	*RAS* WT and left-sided primary tumor	N/A	N/A	Doublet chemotherapy	Doublet chemotherapy ± anti-EGFR or doublet chemotherapy ± anti-VEGF (bevacizumab)	Strong (chemotherapy)
						Moderate (chemotherapy + anti-EGFR)
						Moderate (chemotherapy + anti-VEGF)
2.4	*RAS* WT ± *BRAF* MUT, patients with good PS and without major comorbidities, and/or when tumor shrinkage is the goal	N/A	N/A	Triplet chemotherapy	Triplet chemotherapy ± anti-VEGF (bevacizumab)	Strong (chemotherapy)
						Moderate (chemotherapy + anti-VEGF)
2.5	*RAS* WT and	N/A	Single-agent	Single-agent	Single-agent	Strong (chemotherapy)

	preexisting neuropathy, elderly, comorbidities, or not candidates for aggressive chemotherapy		fluoropyrimidine	fluoropyrimidine	fluoropyrimidine ± anti-VEGF (bevacizumab)	Moderate (chemotherapy + anti-VEGF)
2.6	*RAS* WT and preexisting neuropathy, elderly, comorbidities, or not candidates for chemotherapy	N/A	N/A	N/A	Anti-EGFR monotherapy	Moderate
2.7	*RAS* WT and very poor performance status (PS, 3-4) or comorbidities	Supportive care only				Strong
2.8	Any *RAS* status and dMMR or MSI-H and patients not candidates for intensive chemotherapy	N/A	N/A	N/A	Immune checkpoint inhibitors[a]	Moderate
2.9	*RAS* MUT	N/A	N/A	Doublet chemotherapy	Doublet chemotherapy ± anti-VEGF (bevacizumab)	Strong (chemotherapy) Moderate (chemotherapy +anti-VEGF)
2.10	*RAS* MUT and patients with good PS and without major comorbidities, or when tumor	N/A	N/A	May offer triplet chemotherapy	May offer triplet chemotherapy ± anti-VEGF (bevacizumab)	Strong (chemotherapy) Moderate (chemotherapy +anti-VEGF)

	shrinkage is the goal					
2.11	*RAS* MUT and preexisting neuropathy, elderly, comorbidities, or not candidates for aggressive chemotherapy	N/A	Single-agent fluoropyrimidine	Single-agent fluoropyrimidine	Single-agent fluoropyrimidine ± anti-VEGF (bevacizumab)	Strong (chemotherapy) Moderate (chemotherapy +anti-VEGF)
2.12	Patients treated with oxaliplatin-based doublet or triplet chemotherapy ± anti-VEGF therapy				Discontinue oxaliplatin after a period of induction if stable disease or response; maintenance single-agent fluoropyrimidine ± anti-VEGF therapy; if progression, then reintroduce the first-line therapy or a second-line therapy	Moderate
2.13	Metachronous metastases, prior oxaliplatin-based chemotherapy for early-stage disease (resectable) ≤12(aka			Doublet irinotecan-based chemotherapy	Doublet irinotecan-based chemotherapy	Strong

	within) months of mCRC diagnosis					
2.14[b]	Her2 + Pertuzumab for Her-2 amplified and RAS and BRAF WT for which intensive therapy is not recommended			Trastuzumab + Pertuzumab	Trastuzumab + Pertuzumab	
2.15[b]	Her2 + Pertuzumab for Her-2 amplified and RAS and BRAF WT for which intensive therapy is not recommended			Trastuzumab + Lapatinib	Trastuzumab + Lapatinib	
2.16[b]	Her2 + Pertuzumab for Her-2 amplified and RAS and BRAF WT for which intensive therapy is not recommended			Fam-Trastuzumab-deruxtecan-nxki	Fam-Trastuzumab-deruxtecan-nxki	

Abbreviations: aka, also known as; anti-EGFR, anti–epidermal growth factor medical therapy; BRAF, v-raf murine sarcoma viral oncogene homolog B1; CT, computed tomography; dMMR, deficient mismatch repair; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; MSI, microsatellite instability; MSI-H, MSI-high; MUT, mutation (or mutated); N/A, not available; PS, performance status; RAS, RAS gene; Rec, recommendation; VEGF, vascular endothelial growth factor; WT, wild-type.

[a]Qualifying statement for first-line immunotherapy: At the time of this writing, the US Food and Drug Administration had not approved the use of immune checkpoint inhibitors (eg, nivolumab or the combination of nivolumab plus ipilimumab) in first-line treatment of patients with mCRC.

[b] Recommendations from NCCN, 2022

References

Benson, A. B., Venook, A. P., Al-Hawary, M. M., Cederquist, L., Chen, Y. J., Ciombor, K. K., ... & Freedman-Cass, D. A. (2018). NCCN guidelines insights: colon cancer, version 2.2018. *Journal of the National Comprehensive Cancer Network*, *16*(4), 359-369

Cancer Council Australia Colorectal Cancer Guidelines Working Party: Clinical practice guidelines for the prevention, early detection, and management of colorectal cancer: Short-form summary of NHMRC approved recommendations. Sydney, 2017. https://wiki.cancer.org.au/australia/Guidelines:Colorectal_ cancer

Cassidy, J., Clarke, S., Díaz-Rubio, E., Scheithauer, W., Figer, A., Wong, R., ... & Saltz, L. (2008). Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. *Journal of clinical oncology*, *26*(12), 2006-2012

Hurwitz, H., Fehrenbacher, L., Novotny, W., Cartwright, T., Hainsworth, J., Heim, W., ... & Kabbinavar, F. (2004). Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *New England journal of medicine*, *350*(23), 2335-2342

Meyerhardt, J. A., Li, L., Sanoff, H. K., Carpenter IV, W., & Schrag, D. (2012). Effectiveness of bevacizumab with first-line combination chemotherapy for Medicare patients with stage IV colorectal cancer. *Journal of clinical oncology*, *30*(6), 608

National Comprehensive Cancer Network. (2022). *Colon Cancer Version 1.2022*

National Comprehensive Cancer Network. (2022). *Rectal Cancer Version 1.2022*

National Institute for Health and Care Excellence: Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer. https://www.nice.org.uk/guidance/ta212

O'Connell, M. J. (1989). A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A mayo clinic/north central cancer treatment group study. *Cancer*, *63*(S6), 1026-1030

Petrelli, F., Borgonovo, K., Cabiddu, M., Ghilardi, M., Lonati, V., Maspero, F., ... & Barni, S. (2013). FOLFIRI-bevacizumab as first-line chemotherapy in 3500 patients with advanced colorectal cancer: a pooled analysis of 29 published trials. *Clinical colorectal cancer*, *12*(3), 145-151

Saltz, L. B., Clarke, S., Díaz-Rubio, E., Scheithauer, W., Figer, A., Wong, R., ... & Cassidy, J. (2008). Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *Journal of clinical oncology*, *26*(12), 2013-2019

Toumazis, I., Kurt, M., Toumazi, A., Karacosta, L. G., & Kwon, C. (2017). Comparative effectiveness of up to three lines of chemotherapy treatment plans for metastatic colorectal cancer. *MDM policy & practice*, *2*(2), 2381468317729650

Tournigand, C., André, T., Achille, E., Lledo, G., Flesh, M., Mery-Mignard, D., ... & de Gramont, A. (2004). FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *Journal of Clinical Oncology*, *22*(2)

Van Cutsem, E., Cervantes, A., Adam, R., Sobrero, A., Van Krieken, J. H., Aderka, D., ... & Arnold, D. (2016). ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Annals of Oncology*, *27*(8), 1386-1422

Screening, Pathology Reporting, And Surveillance

What are the recommended screening tests to detect Colorectal Cancer?

The primary aims of colorectal cancer screening are to reduce the morbidity and mortality of the disease through: (1) earlier detection of cancer, and (2) prevention of cancer through detection and removal of pre-malignant adenomas. Because there are multiple options for screening, the choice of a particular screening modality should include a conversation with the patient concerning their preference and availability. It is recommended that available resources should be a consideration since not all screening modalities may be available in centers or health facilities, such as CT colonography or virtual colonoscopy. The CP recommends, based on other guidelines, to start screening at age 50 years among average-risk individuals. Average-risk individuals are considered by National Comprehensive Cancer Network (NCCN) as those with: (1) no history of adenoma or SSP or CRC, (2) no inflammatory bowel disease, and (3) negative family of history for CRC or confirmed advanced adenoma (i.e., high grade dysplasia, >1 cm villous or tubulovillous histology) or advanced SSP (>1 cm, any dysplasia).

Table 7. Screening Modality and Schedule for Average Risk Individuals (Adapted from NCCN Guidelines Version 1.2022 Colorectal Cancer Screening)

Screening Test*	Sensitivity		Specificity		Recommen-ded Testing Interval**
	Colon Cancer	Adenomas	Colon Cancer	Adenomas	
Colonoscopy	94.7%	89-95% (>10 mm adenomas) 75%-93% (>6 mm adenomas)	-	89% (>10 mm adenomas) 94% (>6 mm adenomas)	Every 10 years
Flexible Sigmoidoscopy ***	58-75%	72-86%	-	92%	Every 5-10 years
CT Colonography	86-100%	89% (>10 mm adenomas) 86% (>6 mm adenomas)	--	94% (>10 mm adenomas) 88% (>6 mm adenomas)	Every 5 years

High sensitivity guiac-based test	50-75%	7-21% advanced neoplasia) 6-17% (advanced adenomas)	96-98%	96-99% advanced neoplasia) 96-99% (advanced adenomas)	Annually
Quantitative FIT (using OC-sensor)	74%	25% advanced neoplasia) 23% (advanced adenomas)	94%	96% advanced neoplasia) 96% (advanced adenomas)	Annually
Quantitative FIT (using OC-light)	81%	27% advanced neoplasia) 28% (advanced adenomas)	93%	95% advanced neoplasia) 94% (advanced adenomas)	Annually
mt-sDNA test****	92%	47% advanced neoplasia) 43% (advanced adenomas)	85%	89% advanced neoplasia) 89% (advanced adenomas)	Every 3 years

* A blood test that detects circulating methylated SEPT9 DNA has been FDA-approved for CRC screening for those who refuse other screening modalities.

** Frequency based upon normal (negative) results.

*** Data for the sensitivity and specificity of flexible sigmoidoscopy are for the entire colon and are based on the completion of colonoscopy for those found to have a distal colon lesion on flexible sigmoidoscopy.

**** Optimal FIT thresholds will vary across screening programs, taking into consideration available colonoscopy resources to investigate abnormal results, including false-positive tests.

What is the required information that should be included in the pathology report for colon and rectal cancer?

The panel recommends using the College of American Pathologists Version: Colon Rectum 4.0.1 (2017) histopathology handling and reporting.

Synoptic Reporting
All core and conditionally required data elements outlined on the surgical case summary from this cancer protocol must be displayed in synoptic report format. Synoptic format is defined as:

- Data element: followed by its answer (response), outline format without the paired "Data element: Response" format is NOT considered synoptic.

- The data element should be represented in the report as it is listed in the case summary. The response for any data element may be modified from those listed in the case summary, including “Cannot be determined” if appropriate.

- Each diagnostic parameter pair (Data element: Response) is listed on a separate line or in a tabular format to achieve visual separation. The following exceptions are allowed to be listed on one line:
    - Anatomic site or specimen, laterality, and procedure
    - Pathologic Stage Classification (pTNM) elements
    - Negative margins, as long as all negative margins are specifically enumerated where applicable

- The synoptic portion of the report can appear in the diagnosis section of the pathology report, at the end of the report or in a separate section, but all Data element: Responses must be listed together in one location.

Organizations and pathologists may choose to list the required elements in any order, use additional methods to enhance or achieve visual separation, or add optional items within the synoptic report. The report may have required elements in a summary format elsewhere in the report IN ADDITION TO but not as replacement for the synoptic report i.e., all required elements must be in the synoptic portion of the report in the format defined above.

Sample Synoptic Report

SURGICAL PATHOLOGY REPORT

Name: ---

Age/Sex: ---

Room No.: ---

Date Received: --/--/--

Referring Physician: Dr. ---

Date Reported: --/--/--

Clinical Impression: ---

Specimen No.:

Specimen: ---

Pathologist/s:

Procedure: ---

SURGICAL PATHOLOGY CANCER CASE SUMMARY

PROTOCOL FOR THE EXAMINATION OF SPECIMENS FROM PATIENTS WITH PRIMARY CARCINOMA OF THE COLON AND RECTUM

Data Element	Response
Procedure	
A. Tumor Site	
+ Tumor Location	
Tumor Size	
B. Histologic Type	
C. Histologic Grade	
D. Tumor Extension	
E. Lymphovascular Invasion	
Perineural Invasion	
F. + Tumor Budding	
G. + Type of Polyp in Which Invasive Carcinoma Arose	
H. Macroscopic Tumor Perforation	
I. + Macroscopic Intactness of Mesorectum	
J. Margins	
K. Treatment Effect	
L. Tumor Deposits	
Regional Lymph Nodes	
M. Pathologic Stage Classification (pTNM, AJCC 8th Edition)	
+ Additional Pathologic Findings	

N. + Ancillary Studies	
+ Comments	

Adapted from the College of American Pathologists Protocol for the Examination of Specimens from Patients with Primary Carcinoma of the Colon and Rectum: Resection, Including Transanal Disk Excision of Rectal Neoplasms. Version 4.0.0.0. Protocol Posting Date: June 2017.

Surgical Pathology Cancer Case Summary for Excisional Biopsy

Adapted from: Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum." College of American Pathologists (CAP), 2017.

COLON AND RECTUM: Excisional Biopsy (Polypectomy)

Note: This case summary is recommended for reporting biopsy specimens but is not required for accreditation purposes. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Select a single response unless otherwise indicated.

Tumor Site (Note A)
___ Cecum
___ Ileocecal valve
___ Right (ascending) colon
___ Hepatic flexure
___ Transverse colon
___ Splenic flexure
___ Left (descending) colon
___ Sigmoid colon
___ Rectosigmoid
___ Rectum
___ Other (specify): _____
___ Not specified

+ Specimen Integrity
+ ___ Intact
+ ___ Fragmented

+ Polyp Size
+ Greatest dimension (centimeters): ___ cm
+ Additional dimensions (centimeters): ___ x ___ cm
+ ___ Cannot be determined (explain): _____

+ Polyp Configuration
+ ___ Pedunculated with stalk
    + Stalk length (centimeters): ___ cm
+ ___ Sessile

+ Size of Invasive Carcinoma
+ Greatest dimension (centimeters): ___ cm

+ Additional dimensions (centimeters): ___x ___ cm
+ ___ Cannot be determined (explain): _____

Histologic Type (select all that apply) (Note B)
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Signet-ring cell carcinoma
___ Medullary carcinoma
___ Micropapillary carcinoma
___ Serrated adenocarcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Neuroendocrine carcinoma (poorly differentiated)
___ Squamous cell carcinoma
___ Adenosquamous carcinoma
___ Spindle cell carcinoma
___ Mixed adenoneuroendocrine carcinoma
___ Undifferentiated carcinoma
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined
[#] *Note: Select this option only if large cell or small cell cannot be determined*

Histologic Grade (Note C)
___ G1: Well, differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): _____
___ GX: Cannot be assessed
___ Not applicable

Tumor Extension (Note D)
___ Tumor invades lamina propria
___ Tumor invades muscularis mucosae
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Cannot be assessed

Margins (select all that apply)

Deep Margin (Stalk Margin)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
Distance of invasive carcinoma from margin (millimeters *or* centimeters):

___ mm *or* ___ cm
___ Involved by invasive carcinoma

Mucosal Margin (required only if applicable)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma
___ Involved by adenoma

Lymphovascular Invasion (select all that apply) (Notes D and E)
___ Not identified
___ Present
+ ___ Small vessel lymphovascular invasion
+ ___ Large vessel (venous) invasion
___ Cannot be determined

+ Tumor Budding (Note F)
+ ___ Number of tumor buds in 1 “hotspot” field (specify total number in area=0.785 mm^2):
+ ___ Low score (0-4)
+ ___ Intermediate score (5-9)
+ ___ High score (10 or more)
+ ___ Cannot be determined

+ Type of Polyp in Which Invasive Carcinoma Arose (Note G)
+ ___ Tubular adenoma
+ ___ Villous adenoma
+ ___ Tubulovillous adenoma
+ ___ Traditional serrated adenoma
+ ___ Sessile serrated adenoma/sessile serrated polyp
+ ___ Hamartomatous polyp
+ ___ Other (specify): _____

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Ulcerative colitis
+ ___ Crohn disease
+ ___ Other polyps (type[s]): _____
+ ___ Other (specify): _____

+ Ancillary Studies (Note N)
Note: For reporting molecular testing and immunohistochemistry for mismatch repair proteins, and for other cancer biomarker testing results, the CAP Colorectal Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.

+ Comment(s

Surgical Pathology Cancer Case Summary for Transanal Disc Excision

COLON AND RECTUM: Resection, Including Transanal Disc Excision of Rectal Neoplasms

Note: This case summary is recommended for reporting transanal disc excision specimens but is not required for accreditation purposes. Non-core data elements are indicated with a plus sign (+) to allow for reporting information that may be of clinical value.

Select a single response unless otherwise indicated.

Procedure
___ Right hemicolectomy
___ Transverse colectomy
___ Left hemicolectomy
___ Sigmoidectomy
___ Low anterior resection
___ Total abdominal colectomy
___ Abdominoperineal resection
___ Transanal disk excision (local excision)
___ Endoscopic mucosal resection
___ Other (specify): _____
___ Not specified

Tumor Site (select all that apply) (Note A)
___ Cecum
___ Ileocecal valve
___ Right (ascending) colon
___ Hepatic flexure
___ Transverse colon
___ Splenic flexure
___ Left (descending) colon
___ Sigmoid colon
___ Rectosigmoid
___ Rectum
___ Colon, not otherwise specified
___ Cannot be determined (explain): _____

+ Tumor Location (applicable only to rectal primaries) (Note A)
+ ___ Entirely above the anterior peritoneal reflection
+ ___ Entirely below the anterior peritoneal reflection
+ ___ Straddles the anterior peritoneal reflection
+ ___ Not specified

Tumor Size
Greatest dimension (centimeters): ___ cm
+ Additional dimensions (centimeters): ___ x ___ cm
+___ Cannot be determined (explain): _____

Macroscopic Tumor Perforation (Note H)
___ Not identified
___ Present
___ Cannot be determined

+ Macroscopic Intactness of Mesorectum (if applicable) (Note I)
+ ___ Complete
+ ___ Near complete
+ ___ Incomplete
+ ___ Cannot be determined

Histologic Type (Note B)
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Signet-ring cell carcinoma
___ Medullary carcinoma
___ Micropapillary carcinoma
___ Serrated adenocarcinoma
___ Large cell neuroendocrine carcinoma
___ Small cell neuroendocrine carcinoma
___ Neuroendocrine carcinoma (poorly differentiated) #
___ Squamous cell carcinoma
___ Adenosquamous carcinoma
___ Undifferentiated carcinoma
___ Other histologic type not listed (specify): _____
___ Carcinoma, type cannot be determined
Note: Select this option only if large cell or small cell cannot be determined

Histologic Grade (Note C)
___ G1: Well, differentiated
___ G2: Moderately differentiated
___ G3: Poorly differentiated
___ G4: Undifferentiated
___ Other (specify): _____
___ GX: Cannot be assessed
___ Not applicable

Tumor Extension

___ No evidence of primary tumor
___ No invasion (high-grade dysplasia)
___ Tumor invades lamina propria/muscularis mucosae (intramucosal carcinoma)
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades through the muscularis propria into pericolorectal tissue
___ Tumor invades the visceral peritoneum (including tumor continuous with serosal surface through area of inflammation)
___ Tumor directly invades adjacent structures (specify: _____)
___ Cannot be assessed

Margins (Note J)

Note: Use this section only if all margins are uninvolved and all margins can be assessed.

___ All margins are uninvolved by invasive carcinoma, high-grade dysplasia, intramucosal adenocarcinoma, and adenoma

Margins examined: _____

Note: Margins may include proximal, distal, radial or mesenteric, deep, mucosal, and others.

+ Distance of invasive carcinoma from closest margin (millimeters *or* centimeters): ___ mm *or* ___ cm
+ Specify closest margin: _____

Distance of tumor from radial margin (required only for rectal tumors) (millimeters *or* centimeters): ___ mm or ___ cm

+ Distance of tumor from distal margin (recommended for rectal tumors) (millimeters *or* centimeters):___ mm or ___ cm

Individual margin reporting required if any margins are involved or margin involvement cannot be assessed

For resection specimens only

Proximal Margin

___ Cannot be assessed
___ Uninvolved by invasive carcinoma
+ Distance of tumor from margin: ___ mm *or* ___ cm
___ Involved by invasive carcinoma

Distal Margin

___ Cannot be assessed
___ Uninvolved by invasive carcinoma
+ Distance of tumor from margin (millimeters *or* centimeters): ___ mm *or* ___ cm
___ Involved by invasive carcinoma

Radial or Mesenteric Margin
___ Not applicable
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
Distance of tumor from margin (required only for rectal tumors) (millimeters *or* centimeters): ___ mm *or* ___ cm
___ Involved by invasive carcinoma (tumor present 0-1 mm from margin)

+ Status of Non-Invasive Tumor at Margin(s)
+ ___ Involved by intramucosal adenocarcinoma
+ Specify margin(s): _____
+ ___ Involved by high-grade dysplasia
+ Specify margin(s): _____
+ ___ Involved by adenoma
+ Specify margin(s): _____

Other Margin(s) (required only if applicable)
Specify margin(s): _____
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

For transanal disk excision specimens only

Deep Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
+ Distance of tumor from margin (millimeters *or* centimeters): ___ mm *or* ___ cm
___ Involved by invasive carcinoma

Mucosal Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma, intramucosal adenocarcinoma, high-grade dysplasia, and adenoma
Distance of invasive carcinoma from closest mucosal margin (millimeters *or* centimeters): ___ mm *or* ___ cm
+ Specify location (e.g., o'clock position), if possible: _____
___ Uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest mucosal margin (millimeters *or* centimeters): ___ mm *or* ___ cm
+ Specify location (e.g., o'clock position), if possible: _____
Involved by:
___ Intramucosal adenocarcinoma

+ Specify location (e.g., o'clock position), if possible: _____
___ High-grade dysplasia
+ Specify location (e.g., o'clock position), if possible: _____
___ Adenoma
+ Specify location (e.g., o'clock position), if possible: _____
___ Involved by invasive carcinoma
+ Specify location (e.g., o'clock position), if possible: _____
___ Uninvolved by intramucosal adenocarcinoma, high-grade dysplasia, and adenoma

OR

Involved by:
___ Intramucosal adenocarcinoma
+ Specify location (e.g., o'clock position), if possible: _____
___ High-grade dysplasia
+ Specify location (e.g., o'clock position), if possible: _____
___ Adenoma
+ Specify location (e.g., o'clock position), if possible: _____

Treatment Effect (Note K)
___ No known presurgical therapy
___ Present
+ ___ No viable cancer cells (complete response, score 0)
+ ___ Single cells or rare small groups of cancer cells (near complete response, score 1)
+ ___ Residual cancer with evident tumor regression, but more than single cells or rare small groups of cancer cells (partial response, score 2)
___ Absent
+ ___ Extensive residual cancer with no evident tumor regression (poor or no response, score 3)
___ Cannot be determined

Lymphovascular Invasion (select all that apply) (Note E)
___ Not identified
___ Present
+ ___ Small vessel lymphovascular invasion
+ ___ Large vessel (venous) invasion)
+ ___ Intramural
+ ___ Extramural
___ Cannot be determined

Perineural Invasion (Note E)
___ Not identified
___ Present
___ Cannot be determined

+ Tumor Budding (Note F)
+ ___ Number of tumor buds in 1 “hotspot” field (specify total number in area=0.785 mm^2): _____
+ ___ Low score (0-4)
+ ___ Intermediate score (5-9)
+ ___ High score (10 or more)
+ ___ Cannot be determined

+ Type of Polyp in Which Invasive Carcinoma Arose (Note G)
+ ___ None identified
+ ___ Tubular adenoma
+ ___ Villous adenoma
+ ___ Tubulovillous adenoma
+ ___ Traditional serrated adenoma
+ ___ Sessile serrated adenoma/sessile serrated polyp
+ ___ Hamartomatous polyp
+ ___ Other (specify): _____

Tumor Deposits (Note L)
___ Not identified
___ Present
Specify number of deposits: ____
___ Number cannot be determined (explain): _____
___ Cannot be determined

Regional Lymph Nodes

___ No lymph nodes submitted or found

Lymph Node Examination (required only if lymph nodes present in specimen)

Number of Lymph Nodes Involved: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Examined: ____
___ Number cannot be determined (explain): _____

Pathologic Stage Classification (pTNM, AJCC 8th Edition) (Note M)
Note: Reporting of pT, pN, and (when applicable) pM categories is based on information available to the pathologist at the time the report is issued. Only the applicable T, N, or M category is required for reporting; their definitions need not be included in the report. The categories (with modifiers when applicable) can be listed on 1 line or more than 1 line.

TNM Descriptors (required only if applicable) (select all that apply)

___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)

___ pTX: Primary tumor cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
___ pT1: Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
___ pT2: Tumor invades the muscularis propria
___ pT3: Tumor invades through the muscularis propria into pericolorectal tissues
___ pT4: Tumor invades[#] the visceral peritoneum or invades or adheres[##] to adjacent organ or structure
___ pT4a: Tumor invades[#] through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
___ pT4b: Tumor directly invades[#] or adheres[##] to adjacent organs or structures

[#] *Direct invasion in T4 includes invasion of other organs or other segments of the colorectum as a result of direct extension through the serosa, as confirmed on microscopic examination (for example, invasion of the sigmoid colon by a carcinoma of the cecum) or, for cancers in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria (i.e., respectively, a tumor on the posterior wall of the descending colon invading the left kidney or lateral abdominal wall; or a mid or distal rectal cancer with invasion of prostate, seminal vesicles, cervix, or vagina).*

[##] *Tumor that is adherent to other organs or structures, grossly, is classified cT4b. However, if no tumor is present in the adhesion, microscopically, the classification should be pT1-4a depending on the anatomical depth of wall invasion. The V and L classifications should be used to identify the presence or absence of vascular or lymphatic invasion whereas the PN prognostic factor should be used for perineural invasion.*

Regional Lymph Nodes (pN)

___ pNX: Regional lymph nodes cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1: One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative

___ pN1a: One regional lymph node is positive
___ pN1b: Two or three regional lymph nodes are positive
___ pN1c: No regional lymph nodes are positive, but there are tumor deposits in the subserosa, mesentery, or nonperitonealized pericolic, or perirectal/mesorectal tissues.
___ pN2: Four or more regional lymph nodes are positive
___ pN2a: Four to six regional lymph nodes are positive
___ pN2b: Seven or more regional lymph nodes are positive

Distant Metastasis (pM) (required only if confirmed pathologically in this case)
___ pM1: Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
___ pM1a: Metastasis to one site or organ is identified without peritoneal metastasis
___ pM1b: Metastasis to two or more sites or organs is identified without peritoneal metastasis
___ pM1c: Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

Specify site(s), if known: _____

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Adenoma(s)
+ ___ Ulcerative colitis
+ ___ Crohn disease
+ ___ Diverticulosis
+ ___ Dysplasia arising in inflammatory bowel disease
+ ___ Other polyps (type[s]): _____
+ ___ Other (specify): _____

+ Ancillary Studies (Note N)

Note: For reporting molecular testing and immunohistochemistry for mismatch repair proteins, and for other cancer biomarker testing results, the CAP Colorectal Biomarker Template should be used. Pending biomarker studies should be listed in the Comments section of this report.

Reference

Kakar, S., Shi, C., Berho, M.E., Driman, D.K., Fitzgibbons, P., Frankel, W.L., Hill, K.A., Jessup, J., Krasinskas, A.M., & Washington, M.K. (2017). *Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum.* College of American Pathologists (CAP)

What are the recommended surveillance modalities for stage I-III colorectal adenocarcinoma who received guideline recommended treatment?

The purpose of surveillance after definitive therapy of colon and rectal cancer (CRC) is early identification of those patients who might potentially be cured by further surgical intervention and to screen for second primary cancers and polyps. Considerations for surveillance should also be tempered by the ability and appropriateness of further major surgical resection and/or adjuvant therapy for an individual patient. Possible harms should also be considered which include radiation exposure with repeated CT scans, psychological stress associated with surveillance visits and scans, and stress and risks from following up on false-positive results.

For stage I CRC, the recommendations of American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN) and New Zealand Ministry of Health with Te Aho O Te Kahu on polyp surveillance guidelines were included as source guidelines. NCCN recommends that a less intensive surveillance schedule is appropriate because of the low risk of recurrence and the harms associated with surveillance (Table 8). ASCO recommends that posttreatment surveillance be done only for higher-risk disease (e.g., rectal cancer treated with endoscopic or trans-anal excision, colon cancers treated with endoscopic resection alone, and patients who did not undergo guideline-based treatment) for whom surveillance-based detection as is used for higher-stage disease might reveal a potentially salvageable recurrence.

Table 8. Surveillance Modalities for Stage I Colorectal Cancer*

Intervention	Colon	Rectal
Proctoscopy	-	Every 3-6 months for the first 2 years then every 6 months for a total of 5 years for rectal cancer with trans-anal local excision only
Colonoscopy	If advanced adenoma, at 1 year after surgery If no advanced adenoma, repeat in 3 years then every 5 years	If advanced adenoma, at 1 year after surgery If no advanced adenoma, repeat in 3 years then every 5 years

*Source: NCCN Colon 2022, NCCN Rectal 2022

Table 9 summarizes the new guidelines recommended by New Zealand Ministry of Health with Te Aho O Te Kahu on polyp surveillance after complete removal of adenomas and serrated polyps. This advice was developed in recognition of the: (1) low risk of future colorectal cancer for some groups of patients identified as having adenomas, and (2) colorectal cancer risk associated with some serrated polyps.

Table 9. Surveillance Intervals Based on Findings at High-Quality Colonoscopy on Polyp Surveillance Guidelines (Adapted from Te Aho O Te Kahu and New Zealand Ministry Of Health Polyp Surveillance Guidelines)

1 Year	3 Years	5 Years
Adenomas* ≥10 adenomas***	Adenomas* 5-9 adenomas <10mm Adenoma ≥10mm Tubulovillous adenoma or Villous adenoma Adenoma with HGD	Adenomas* 3-4 adenomas <10mm
Serrated polyps* Serrated polyposis syndrome – initial interval after polyp clearance***	Serrated polyps* ≥5 SSL <10mm SSL≥10mm SSL with dysplasia Traditional serrated adenoma	Serrated polyps* 1-4 SSL <10mm HP ≥10mm

Abbreviations: SSL, sessile serrated lesion=sessile serrated adenoma/polyp; HGD, high grade dysplasia; HP, Hyperplastic polyp.

* If there are both adenoma <10mm and SSL <10 mm, sum up the numbers and apply follow-up interval for SSL.

** A three-year follow-up interval is favoured if concern about consistency in distinction between sessile serrated lesion and hyperplastic polyp locally.

*** Consider further specialist referral.

After potentially curative treatment for a stage II or III colon cancer, post-treatment surveillance is recommended. In this guideline, NCCN recommendations for surveillance of Stage II-III CRC were adopted as shown on Table 9.

It should be noted that the use of PET/CT scans for surveillance is not recommended, but NCCN panel highlighted that in the scenario of an elevated CEA with negative, good-quality CT scans, the use of PET/CT scan in identifying surgically curable disease can be considered. A recent systematic review and meta-analysis found 11 studies (510 patients) that addressed the use of PET/CT scan in this setting showing pooled estimates of sensitivity and specificity for the detection of tumor recurrence were 94.1% (95% CI, 89.4–97.1%) and 77.2% (95% CI, 66.4– 85.9), respectively (Lu et al, 2013).

Table 10. Surveillance Modalities for Stage II-III Colorectal Cancer*

Intervention	Interval	
	Years 1-2	**Years 3-5**
History and Physical Examination	Every 3-6 months	Every 6 months
CEA	Every 3-6 months	Every 6 months
CT scan of the chest-abdominal-pelvic imaging	Every 6-12 months	
Colonoscopy	At 1 year following surgery except if no preoperative colonoscopy due to obstructing lesion, then colonoscopy in 3-6 months If with advanced adenoma, repeat in 1 year If no advanced adenoma, repeat in 3 years, then every 5 years	
PET/CT scan	Not recommended	

*Source: NCCN Colon 2022, NCCN Rectal 2022

References

Lu, Y. Y., Chen, J. H., Chien, C. R., Chen, W. T. L., Tsai, S. C., Lin, W. Y., & Kao, C. H. (2013). Use of FDG-PET or PET/CT to detect recurrent colorectal cancer in patients with elevated CEA: a systematic review and meta-analysis. *International journal of colorectal disease*, *28*(8), 1039-1047

Meyerhardt, J. A., Mangu, P. B., Flynn, P. J., Korde, L., Loprinzi, C. L., Minsky, B. D., ... & Benson III, A. B. (2013). Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. *Journal of Clinical Oncology*, *31*(35), 4465-4470

National Comprehensive Cancer Network (NCCN). (2022). *NCCN Clinical Practice Guidelines in Oncology*; NCCN Guidelines Colon Cancer Version 1.2022

National Comprehensive Cancer Network (NCCN). (2022). *NCCN Clinical Practice Guidelines in Oncology*; NCCN Guidelines Rectal Cancer Version 1.2022

Te Aho O Te Kahu. (2020). *Update on Polyp Surveillance Guidelines*. Wellington: Te Aho O Te Kahu

Annexes

Annex A. GDG COI Declaration and Management

Annex A.1. Technical Advisory Group COI Declaration and Management

Name	Affiliation	Conflict of Interest		
		Intellectual	Monetary	Management
Dr. Nilo C. de los Santos	East Avenue Medical Center	None	None	May participate in the guideline development
Dr. Clarito U. Cairo, Jr.	Department of Health	None	None	May participate in the guideline development
Ms. Alma B. Abainza-Sanchez	Philippine Health Insurance Corporation	None	None	May participate in the guideline development
Dr. Samuel S. Duran	East Avenue Medical Center	None	None	May participate in the guideline development
Dr. Allan Troy D. Baquir	East Avenue Medical Center	None	None	May participate in the guideline development

Annex A.2. Steering Committee COI Declaration and Management

Name	Affiliation	Conflict of Interest		
		Intellectual	Monetary	Management
Dr. Omar O. Ocampo	East Avenue Medical Center	None	None	May participate in the guideline development
Ms. Maria Dolores R. Manalastas	DOH-Cancer Control Program	None	None	May participate in the guideline development
Dr. Marc Anthony C. Cepeda	PhilHealth - Research Division	None	None	May participate in the guideline development
Dr. Catherine S. Co	Philippine Society of Colon and Rectal Surgeons	None	None	May participate in the guideline development
Dr. Joseph Roy F. Fuentes	Philippine Society of Colon and Rectal Surgeons	None	None	May participate in the guideline development
Dr. Mary Claire V. Soliman	Philippine Society of Medical Oncology	Moderate	Moderate	Allowed partial participation
Dr. Warren R. Bacorro	Philippine Radiation Oncology Society	None	None	May participate in the guideline development
Dr. Misael C. Cruz	Philippine Radiation Oncology Society	None	None	May participate in the guideline development
Dr. Sarah Preza-Carmona	Philippine Society of Gastroenterology	None	None	May participate in the guideline development
Dr. Felix L. Domingo Jr.	Philippine Society of Gastroenterology	None	None	May participate in the guideline development
Dr. Ruth Anne Manansala-Kong	Philippine Academy of Family Physicians	None	None	May participate in the guideline development
Dr. Herdee Gloriane C. Luna	Philippine Cancer Society	None	None	May participate in the guideline development

Dr. Ma. Pamela D. Patdu	Philippine Cancer Society	None	None	May participate in the guideline development
Dr. Grace S. Nilo	Philippine Cancer Society	None	None	May participate in the guideline development
Dr. Yasmin M. Lee-Catalan	Philippine Society of Medical Oncology	Excessive	Excessive	Not included as part of SC
Dr. June Michael V. Razon	Philippine Society of Hospice and Palliative Medicine	Excessive	Excessive	Not included as part of SC
Dr. Dennis L. Sacdalan	Philippine Cancer Society	Excessive	Excessive	Not included as part of SC

Annex A.3. Consensus Panel COI Declaration and Management

Name	Affiliation	Conflict of Interest		
Dr. Mark Anthony G. Fontanilla	East Avenue Medical Center	**Intellectual**	**Monetary**	**Management**
Dr. Marichona C. Naval	East Avenue Medical Center	None	None	May participate in the guideline development
Ms. Alyanna Riel C. Panlilio	Department of Health	None	None	May participate in the guideline development
Dr. John Juliard L. Go	World Health Organization - WPRO	None	None	Did not participate in any CP session; Excluded
Dr. Manuel Francisco T. Roxas	Philippine College of Surgeons Cancer Commission	None	None	May participate in the guideline development
Dr. Marc Paul J. Lopez	Philippine College of Surgeons Cancer Commission	None	None	May participate in the guideline development
Dr. Tito Apollo A. Quitoriano	Philippine Society of General Surgeons	None	None	May participate in the guideline development
Dr. Carlo Angelo C. Cajucom	Philippine Society of General Surgeons	None	None	May participate in the guideline development
Dr. Fernando Antonio B. Roque	Philippine Society of Medical Oncology	None	None	May participate in the guideline development
Dr. Maximino G. Bello III	Philippine Society of Medical Oncology	None	None	May participate in the guideline development
Dr. Jose Roel E. Resubal	Philippine Radiation Oncology Society	None	None	May participate in the guideline development
Dr. Henri Cartier S. Co	Philippine Radiation Oncology Society	None	None	May participate in the guideline development
Dr. Ira Inductivo-Yu	Philippine Society of	None	None	May participate in the

	Gastroenterology			guideline development
Dr. Felipe Gozar L. Duque	Philippine Society of Gastroenterology	None	None	May participate in the guideline development
Dr. Patricia Ann Cabral-Prodigalidad	Philippine Society of Gastroenterology	None	None	May participate in the guideline development
Dr. Anarose C. Alvarado	Philippine Society of Pathologists	None	None	May participate in the guideline development
Dr. Marie Ruth A. Echavez	Philippine Society of Hospice and Palliative Medicine	None	None	May participate in the guideline development

Annex B. Summary of ADAPTE Evidence

Annex B.1. NCPG PIPOH Framework

Framework	Scope
Population	Sporadic colorectal cancer (Stages I-IV)
Intervention	Screening, diagnosis, treatment, and surveillance
Professionals	Physicians/medical doctors, allied health professionals, and health policy maker
Outcomes	Diagnostic accuracy, disease free survival,
Health Care Setting	Tertiary hospitals

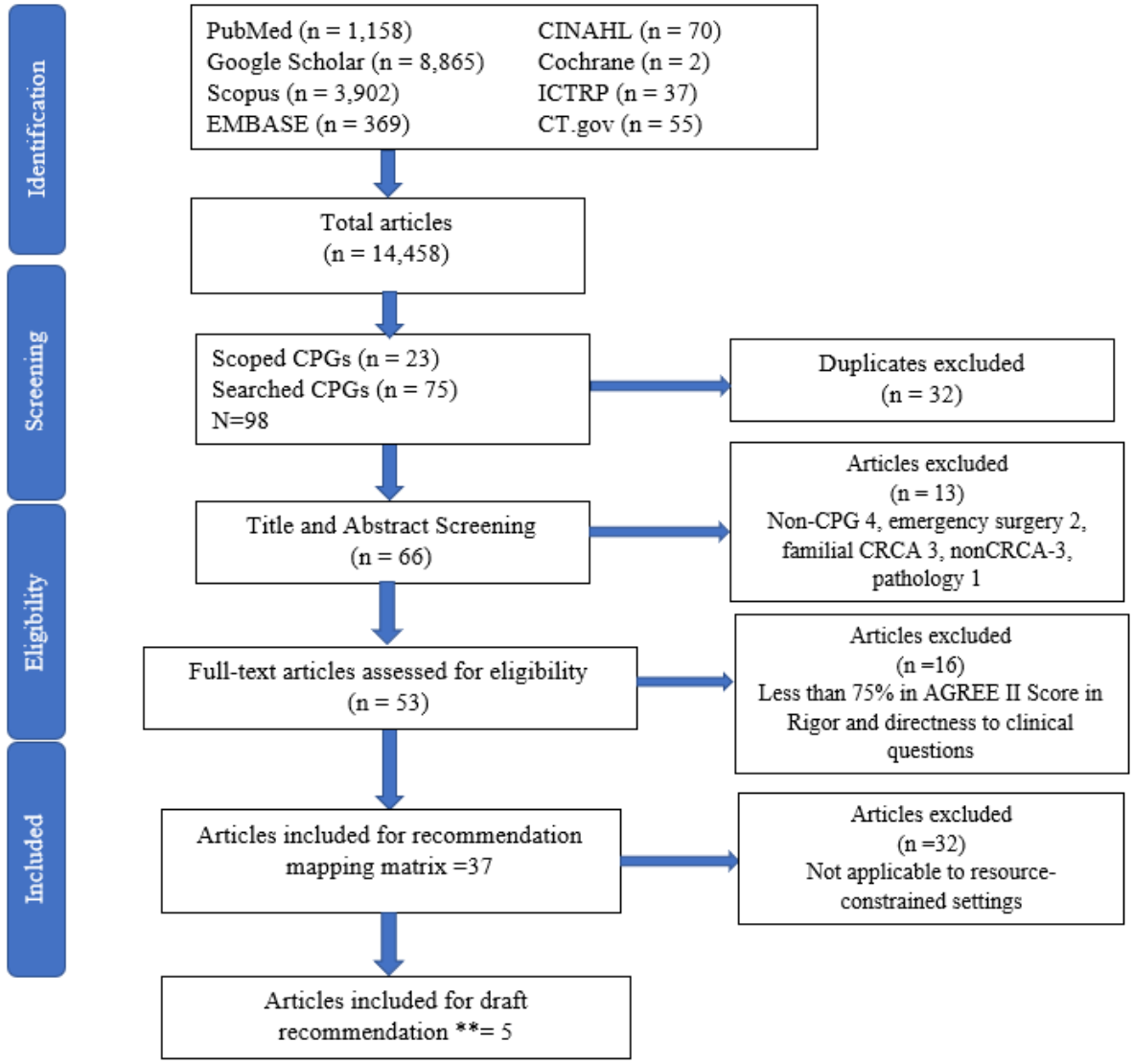
Annex B.2. Search Strategy

Utilizing the PICO for key search terms of each clinical question, search strategy was conducted with the following study type filters used, database and filter for dates of publication.

Database	Year of Publication	Search string
Pubmed	2011-2021	“Colon Cancer” OR “Rectal Cancer” OR “Colorectal Cancer” AND “Clinical Practice Guidelines”
Scopus	2011-2021	“Colon Cancer” OR “Rectal Cancer” OR “Colorectal Cancer” AND “Clinical Practice Guidelines”
Google Scholar	2011-2021	“Colon Cancer” OR “Rectal Cancer” OR “Colorectal Cancer” AND “Clinical Practice Guidelines”
Guidelines International Network (GIN)	2011-2021	“Colorectal Cancer”
The National Institute for Health and Care Excellence (NICE)	2011-2021	“Colorectal Cancer”
New Zealand Guidelines Group (NZGG)	2011-2021	“Colorectal Cancer”
Scottish Intercollegiate Guidelines Network (SIGN)	2011-2021	“Colorectal Cancer”

Annex B.3. PRISMA Flow

(INCLUSION/EXCLUSION) *



** updated versions were included for CPGs published in 2022*

*** 3 with AGREE II score on RIGOR Domain >75%, 2 with <75% AGREE II score*

Annex B.4. AGREE II Guideline Evaluation

Source Guidelines	Scope and Purpose	Stakeholders	Rigor	Applicability	Independence	Overall Score
The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer (2022)	77.78	72.22	98.96	16.67	100.00	83.33
NCCN guidelines: Colon Cancer, Version 1.2022	72.22	63.89	68.75	62.50	66.67	83.33
NCCN guidelines: Rectal cancer, version 1.2022	72.22	63.89	62.50	25.00	58.33	75.00
Treatment of Patients with Late-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline (ASCO2020)	86.11	94.44	98.96	70.83	95.83	83.33
The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Rectal Cancer (ASCRS2020)	63.89	66.67	88.54	20.83	50.00	75.00

Annex B.5. Source Guidelines Characteristics

Title	CODE	Publisher	Country Language	Publication Date	Search Duration	Recommendation Standards (AGREE)	AGREE II SCORE (Rigour)
Treatment of Patients With Late-Stage Colorectal Cancer: ASCO Resource-Stratified Guideline	ASCO2020	American Society of Clinical Oncology	USA, English	2020	07/21 to 03/22	ASCO (rating provided by Expert Panel)	96.88
The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Rectal Cancer	ASCRS2020	The American Society of Colon & Rectal Surgeons, Inc.	USA, English	2020	07/21 to 03/22	GRADE	88.54
The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the Management of Colon Cancer	ASCRSColon 2022	The American Society of Colon & Rectal Surgeons, Inc.	USA, English	2022	07/21 to 03/22	GRADE	98.96
NCCN Guidelines: Rectal Cancer Version.1.2022	NCCNRectal 2022	NCCN	USA, English	February 25, 2022	07/21 to 03/22	NCCN Categories of Evidence & Consensus	62.50
NCCN Guidelines: Colon Cancer Version 1.2022	NCCNColon 2022	NCCN	USA, English	February 25, 2022	07/21 to 03/22	NCCN Categories of Evidence and Consensus	68.75

Annex C. NCPG Questions in PICO Framework

The Steering Committee identified and developed the key guideline questions as a guide for evidence review as basis for the recommendations of the Consensus Panel. The key questions were formulated using the PICO (Population, Intervention, Comparator, and Outcome) format.

Annex C.1. Colon Cancer

1. Among adult patients newly diagnosed with colon adenocarcinoma, is PET/CT scan the recommended initial modality for clinical staging compared with chest and abdominopelvic CT scan with contrast?

Population	Intervention	Comparator	Outcome
Adult patients newly diagnosed with colon adenocarcinoma	PET-CT	Chest and abdominopelvic CT scan with contrast	Staging, detecting distant metastasis: accuracy, (sensitivity / specificity / +LR / -LR of diagnostic test being evaluated / PPV / NPV), cost-benefit, adverse events

2. Among adult patients with cT1N0M0 colon adenocarcinoma, is endoscopic excision non-inferior to oncologic resection?

Population	Intervention	Comparator	Outcome
Adult patients newly diagnosed with malignant polyp (cT1N0M0) in the colon	Endoscopic resection *recommended margins (2 mm vs 1 mm)	Oncologic resection	3-5 year overall survival, disease free survival, recurrence rate, mortality, morbidity, cost-benefit, adverse events

3. Among adult patients with resectable stage I-III colon adenocarcinoma, should minimally invasive surgery be offered over open surgery?

Population	Intervention	Comparator	Outcome
Adult patients with resectable stage I-III colon adenocarcinoma	Minimally invasive surgery (laparoscopic/robotic)	Open surgery	Equivalence or non-inferiority, 5-year overall survival, disease free survival, recurrence rate, mortality, morbidity, cost-benefit, adverse events

4. Among adult patients with reliable preoperative imaging showing unresectable locally advanced colon adenocarcinoma, does neoadjuvant chemotherapy followed by surgery yield better outcomes than upfront surgery followed by adjuvant chemotherapy?

Population	Intervention	Comparator	Outcome
Adult patients with locally unresectable colon adenocarcinoma with no distant metastasis	Neoadjuvant therapy followed by surgery +/- intra-operative RT	Upfront surgery followed by adjuvant chemotherapy	3 year and 5-year overall survival, disease free survival, QoL, recurrent rate, downstaging, downsizing, R0 resection, mortality, morbidity, adverse events

5. Among adult patients with stage II colon adenocarcinoma with high-risk features for recurrence, is oxaliplatin-based adjuvant chemotherapy recommended than 5FU/leucovorin or capecitabine monotherapy?

Population	Intervention	Comparator	Outcome
Adult patients with stage II high-risk colon adenocarcinoma	Oxaliplatin-based systemic chemotherapy	Capecitabine or 5FU/leucovorin	Overall survival, disease-free survival, recurrence rate, adverse events

6. What is the preferred sequence of treatment for resectable and potentially resectable stage IV colon adenocarcinoma?

Population	Intervention	Comparator	Outcome
Adult patients with curable stage IV colon adenocarcinoma	Upfront surgery 1. Simultaneous resection (colon adenocarcinoma and/or distant metastasis) 2. Distant metastasis first 3. Resection of primary tumor first	Systemic chemotherapy first	Overall survival, disease free survival, morbidity, mortality, adverse events

Annex C.2. Rectal Cancer

1. Among adult patients newly diagnosed with rectal adenocarcinoma, is pelvic MRI the recommended modality for preoperative clinical locoregional staging over endorectal ultrasound?

Population	Intervention	Comparator	Outcome
Adult patients newly diagnosed with rectal adenocarcinoma	Pelvic MRI	Endorectal ultrasound	Locoregional staging (T and N stage), circumferential resection margin, pelvic lymph nodes (mesorectal, lateral pelvic, inguinal)

2. Among adult patients with cT1N0M0 rectal adenocarcinoma, should local excision +/- adjuvant treatment (radiotherapy or chemoradiotherapy) be offered as compared to oncologic resection?

Population	Intervention	Comparator	Outcome
Adult patients newly diagnosed with malignant polyp (cT1N0M0) in the rectum	Local excision (Transanal excision/Endoscopic Excision/TEMS/TEO/TAMIS) +/- adjuvant RT or +/- adjuvant chemo-RT	Oncologic transabdominal resection (low anterior resection, abdominoperineal resection)	Equivalence or non-inferiority, 3-5 year overall survival, disease free survival, recurrence rate, mortality, morbidity, cost-benefit, adverse events

3. Among adult patients with resectable stage I-III low to mid rectal adenocarcinoma, should minimally invasive surgery be offered over open surgery?

Population	Intervention	Comparator	Outcome
Adult patients with resectable stage I-III rectal adenocarcinoma	Minimally invasive surgery (laparoscopic/robotic)	Open surgery	Equivalence or non-inferiority, 5-year overall survival, disease free survival, recurrence rates mortality, morbidity, cost-benefit, adverse events

4. Among adult patients with Stage II or III rectal adenocarcinoma, is neoadjuvant short course radiotherapy comparable to long course chemoradiotherapy?

Population	Intervention	Comparator	Outcome
Adult patients newly diagnosed with Stage II or III (T3 or T4 or N+, M0) rectal adenocarcinoma	1. Short course radiotherapy (standard) 2. Short course radiotherapy (long wait)	Long course chemoradiotherapy	3–5-year overall survival, 3–5-year local recurrence rate, complications, complete clinical response, complete pathologic response, sphincter preservation rate, acute and ate toxicity, cost-benefit, adverse events

5. Among adult patients diagnosed with cT4b, cN2 or unresectable nonmetastatic rectal adenocarcinoma, does total neoadjuvant therapy yield better outcomes than neoadjuvant short course radiation therapy or long course chemoradiation therapy + adjuvant chemotherapy?

Population	Intervention	Comparator	Outcome
Adult patients diagnosed with cT4b or cN2 or unresectable, nonmetastatic rectal adenocarcinoma	Total neoadjuvant therapy (short course radiotherapy, long course chemoradiotherapy, induction chemotherapy, consolidation chemotherapy)	Neoadjuvant short course RT or long course chemo + adjuvant chemo	3–5-year Overall survival, 3–5-year local recurrence rate, complications, complete clinical response, complete pathologic response, sphincter preservation rate, acute and ate toxicity, cost-benefit, adverse events

6. Among adult patients with rectal adenocarcinoma with complete clinical response following neoadjuvant therapy, is “watch and wait” management approach comparable to oncologic resection?

Population	Intervention	Comparator	Outcome
Adult patients with rectal adenocarcinoma with apparent complete clinical response following neoadjuvant therapy	“Watch and wait” management approach	Oncologic resection	3–5-year overall survival, disease free survival, recurrence rate, mortality, morbidity, cost-benefit, adverse events

7. What is the preferred sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma?

Population	Intervention	Comparator	Outcome
Adult patients with curable stage IV rectal adenocarcinoma	Upfront surgery (colon adenocarcinoma and/or distant metastasis) Upfront radiotherapy (Long-course chemoradiotherapy /Short-course radiation therapy)	Upfront systemic chemotherapy	Overall survival, disease free survival, morbidity, mortality, adverse events, recurrence rate

Annex C.3. Colorectal Cancer

1. What is/are the recommended screening modality/ies for colon and rectal cancer among average-risk patients?

Population	Intervention	Comparator	Outcome
Patients with average risk for colorectal cancer	FOBT/ FIT; Barium enema; Flexible sigmoidoscopy; Colonoscopy; CT colonography		Diagnostic accuracy

2. Among adult patients with locally advanced and advanced colon and rectal adenocarcinoma, does an MDT approach yield better outcomes than a non-MDT approach?

Population	Intervention	Comparator	Outcome
Adult patients with locally advanced and advanced colon and rectal adenocarcinoma	MDT	No MDT	Clinical staging, multimodality treatment decision, pathologic staging, overall survival, disease free survival, quality of life

3. What are the important pathological parameters in colorectal cancer that should be reported as part of minimum data set?

Population	Intervention	Comparator	Outcome
Adult patients with colorectal cancer who underwent oncologic resection	*Histopathology reporting*		

4. What are the recommended surveillance modalities for stage I-III colorectal adenocarcinoma who received guideline recommended treatment?

Population	Intervention	Comparator	Outcome
Adult patients with early stage colorectal adenocarcinoma and Stage I-III colorectal adenocarcinoma who received guideline recommended treatment	PET-CT	Chest, abdominal and pelvic CT	Equivalence or superiority, overall survival, disease-free survival, detection of recurrence, reduction of costs, reduction of risks of tests

5. Among adult patients with unresectable stage IV colon or rectal adenocarcinoma, does the addition of targeted therapy or immunotherapy to chemotherapy yield better outcomes compared to systemic chemotherapy alone?

Population	Intervention	Comparator	Outcome
Adult patients with unresectable stage IV colon or rectal adenocarcinoma	Addition of targeted therapy +/- immunotherapy	Systemic chemotherapy only	Overall survival, disease free survival, quality of life, conversion to resectable disease, adverse events

Annex C.4. Source Guideline Content Comparison

CRC NCPG Questions and Recommendations		Content Comparison				
		A check (✓) indicates inclusion of the relevant discussion in the guideline.				
		ASCO 2020	**ASCRS Colon 2022**	**ASCRS Rectal 2020**	**NCCN Colon 2022**	**NCCN Rectal 2022**
Among adult patients newly diagnosed with colon adenocarcinoma, is PET/CT scan the recommended initial modality for clinical staging compared with chest and abdominopelvic CT scan with contrast?	PET/CT scan is not recommended as initial modality for routine colon cancer staging and detection of distant metastasis.		✓			
	PET/CT scan does not supplant a contrast-enhanced diagnostic CT scan or MRI. It should only be used to evaluate an equivocal finding on a contrast-enhanced CT scan or MRI or in patients with strong contraindications.				✓	
	Chest, abdomen, and pelvic CT scan are recommended to initially evaluate local extent of tumor as well as invasion into nearby organs or structures, assess for nodal metastasis and identify distant metastatic disease to lungs, liver, peritoneal cavity and other organs.				✓	
Among adult patients with cT1N0M0 colon adenocarcinoma, is	For cT1N0M0 colon adenocarcinoma, endoscopic excision is not inferior to oncologic resection. However,		✓		✓	

endoscopic excision non-inferior to oncologic resection?	endoscopic excision is dependent mainly on malignant polyp histopathological features and completeness of excision.					
Among adult patients with resectable stage I-III colon adenocarcinoma, should minimally invasive surgery be offered over open surgery?	When expertise and capability are available, a minimally invasive approach to elective colectomy for colon adenocarcinoma is acceptable.		✓		✓	
Among adult patients with reliable pre-operative imaging showing unresectable locally advanced colon adenocarcinoma, does neoadjuvant chemotherapy followed by surgery yield better outcomes than upfront surgery followed by adjuvant chemotherapy?	Neoadjuvant chemotherapy is an option for locally advanced colon adenocarcinoma.	Good Practice Statement				
	Patients with unresectable locally advanced colon adenocarcinoma should be considered for neoadjuvant therapy to attempt to convert to resectability.		✓			
	Neoadjuvant chemotherapy can result in tumor regression and may facilitate margin-negative excision of initially unresectable locally advanced colon adenocarcinoma.		✓			
Among adult patients with stage II colon	Oxaliplatin-based adjuvant chemotherapy is recommended for		✓			

adenocarcinoma with high-risk features for recurrence, is oxaliplatin-based adjuvant chemotherapy recommended than 5FU/leucovorin or capecitabine monotherapy?	stage II colon adenocarcinoma patients with high-risk feature(s).					
What is the preferred sequence of treatment for resectable and potentially resectable stage IV colon adenocarcinoma?	Patients with initially resectable colon adenocarcinoma with liver or lung metastasis can be treated with upfront surgical resection followed by adjuvant chemotherapy or neoadjuvant chemotherapy followed by surgery.		✓		✓	
	Patients with resectable distant metastatic disease and a primary tumor in place should have both sites resected with curative intent. These can be resected in one operation or as a staged approach, depending on the complexity of the metastasectomy or colectomy, comorbid diseases, surgical exposure, and surgeon expertise.		✓		✓	
	For patients with resectable colon adenocarcinoma and peritoneal metastasis without extra-abdominal		✓		✓	

	disease, cytoreductive surgery with or without intraperitoneal chemotherapy should be considered in multidisciplinary setting with appropriate expertise.					
	A six-month course of systemic chemotherapy can be considered for most patients undergoing liver or lung resection to increase the likelihood of eradication of residual microscopic disease.		✓		✓	
Among adult patients newly diagnosed with rectal adenocarcinoma, is pelvic MRI the recommended modality for clinical locoregional staging over endorectal ultrasound?	Pelvic MRI (rectal cancer protocol) is the preferred modality for clinical locoregional staging of newly diagnosed rectal adenocarcinoma. Endorectal ultrasound may be considered when differentiating between early T stages or when MRI is contraindicated or not available.			✓		✓
Among adult patients with cT1N0M0 rectal adenocarcinoma, should local excision +/- adjuvant treatment (radiotherapy or chemoradiotherapy) be	Local excision is an appropriate treatment option for carefully selected patients with cT1N0 rectal adenocarcinoma with favorable clinical and histological features.			✓		✓
	For high-risk patients who refuse or are medically unfit for radical resection,			✓		✓

offered as compared to oncologic resection?	adjuvant chemoradiation should be recommended after local excision and should be followed by surveillance for a potentially salvageable recurrence.					
Among adult patients with resectable stage I-III low to mid rectal adenocarcinoma, should minimally invasive surgery be offered over open surgery?	Minimally invasive surgical approach following standard oncologic techniques of total mesorectal excision (TME) can be considered and should be performed by experienced surgeons with technical expertise.			✓		
Among adult patients with Stage II or III rectal adenocarcinoma, is neoadjuvant short course radiotherapy comparable to long course chemoradiotherapy?	Neoadjuvant short course radiation therapy and long course chemoradiation therapy are comparable for Stage II or III rectal adenocarcinoma in terms of outcomes such as survival, recurrence, and complications.			✓		
Among adult patients diagnosed with cT4b, cN2 or unresectable nonmetastatic rectal adenocarcinoma, does total neoadjuvant therapy yield better outcomes than	Considerations for total neoadjuvant therapy over standard neoadjuvant therapy (short course radiation therapy or long course chemoradiation therapy) for cT4b, cN2 or unresectable nonmetastatic rectal adenocarcinoma must be based on a multidisciplinary team evaluation.			✓		✓

neoadjuvant short course radiation therapy or long course chemoradiation therapy + adjuvant chemotherapy?						
Among adult patients with rectal adenocarcinoma with complete clinical response following neoadjuvant therapy, is “watch and wait” management approach comparable to oncologic resection?	Patients with a complete clinical response to neoadjuvant therapy should be offered oncologic resection.			✓		
What is the preferred sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma?	Referral to a multidisciplinary team in a Center of Excellence to determine the sequence of treatment for resectable and potentially resectable stage IV rectal adenocarcinoma is recommended.	Good Practice Statement				
Among adult patients with locally advanced colon and rectal adenocarcinoma, does a multidisciplinary team	The treatment of patients with resectable stage IV colorectal adenocarcinoma should be individualized and based on a comprehensive MDT discussion.		✓			

(MDT) approach yield better outcomes than a non-MDT approach?	Optimum therapeutic strategy and centralization of care is best carried out by an adequately trained MDT which should include a surgeon, medical oncologist, radiation oncologist, diagnostic radiologist, gastroenterologist, pathologist, and other needed specialists as necessary.		✓			
	An MDT approach is strongly recommended for all locally advanced and advanced colorectal adenocarcinoma to determine the best treatment options.		✓			
Among adult patients with unresectable stage IV colon or rectal adenocarcinoma, does the addition of targeted therapy or immunotherapy to chemotherapy yield better outcomes compared to systemic chemotherapy alone?	Anti-VEGF therapy may be added to doublet or triplet chemotherapy, regardless of molecular status of the colorectal cancer.	✓				
	Among adults with left-sided colon and rectal cancers with KRAS/NRAS WT molecular status, anti-EGFR therapy is recommended.	✓				

Annex D. AGREE II Reporting Checklist (Self-Evaluation)

TITLE OF CPG: _____

EVALUATOR: _____ **DATE:** _____

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
DOMAIN 1. SCOPE AND PURPOSE			
1. THE OVERALL OBJECTIVE(S) OF THE GUIDELINES IS (ARE) SPECIFICALLY DESCRIBED.	□ Health intent □ Expected benefit or outcome □ Target		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
2. THE HEALTH QUESTION(S) COVERED BY THE GUIDELINE IS (ARE) SPECIFICALLY DESCRIBED)	□ Target population □ Intervention or exposure □ Comparisons □ Outcomes □ Health care setting or context		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
3. THE POPULATION (PATIENT, PUBLIC, ETC.) TO WHOM THE GUIDELINE IS MEANT TO APPLY IS SPECIFICALLY DESCRIBED.	□ Target population □ Clinical condition □ Severity/stage □ Comorbidities □ Excluded populations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 2. STAKEHOLDER INVOLVEMENT			
4. THE GUIDELINE DEVELOPMENT GROUP INCLUDES INDIVIDUALS FROM ALL RELEVANT PROFESSIONAL GROUPS.	□ Name of participant □ Discipline/content expertise □ Institution □ Geographical location □ A description of the member's role in the guideline development		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
5. THE VIEWS AND PREFERENCES OF THE TARGET POPULATION (PATIENTS, PUBLIC, ETC.) HAVE BEEN SOUGHT.	□ Statement of type of strategy used to capture patient/public views and preferences □ Methods by which preferences and views were sought		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Outcomes/ information gathered on patient/public information □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations		
6. THE TARGET USERS OF THE GUIDELINE ARE CLEARLY DEFINED.	□ The intended guideline audience □ How the guideline may be used by its target audience		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 3. RIGOUR OF DEVELOPMENT			
7. SYSTEMATIC METHODS WERE USED TO SEARCH FOR EVIDENCE.	□ Named electronic databases or evidence source where the search was performed □ Time periods searched □ Search terms used □ Full search strategy included		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
8. THE CRITERIA FOR SELECTING THE EVIDENCE ARE CLEARLY DESCRIBED.	□ Target population □ Study design □ Comparisons □ Outcomes □ Language □ Context		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
9. THE STRENGTHS AND LIMITATIONS OF THE BODY OF EVIDENCE ARE CLEARLY DESCRIBED. TOOLS EXIST THAT CAN FACILITATE THE REPORTING OF THIS CONCEPT.	□ Study design included in body of evidence □ Study methodology limitations □ Appropriateness/ relevance of primary and secondary outcomes considered □ Consistency of results across studies		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Direction of results across studies □ Magnitude of benefit vs magnitude of harm □ Applicability to practice context.		
10. THE METHODS FOR FORMULATING THE RECOMMENDATIONS ARE CLEARLY DESCRIBED. SPECIFY AREAS OF DISAGREEMENTS AND METHODS USED TO RESOLVE THEM.	□ Recommendation development process □ Outcomes of the recommendation development process □ How the process influenced the recommendations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
11. THE HEALTH BENEFITS, SIDE EFFECTS, AND RISKS HAVE BEEN CONSIDERED IN FORMULATING THE RECOMMENDATIONS.	□ Supporting data and report of benefits □ Supporting data and report of harms/side effects/ risks □ Reporting of the balance/trade-off between benefits and harms/side effects/risks □ Recommendations reflect considerations of both benefits and harms/side effects/risks		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
12. THERE IS AN EXPLICIT LINK BETWEEN THE RECOMMENDATIONS AND THE SUPPORTING EVIDENCE.	□ How the guideline development group linked and used the evidence to inform recommendations. □ Link between each recommendation and key evidence □ Link between recommendations and evidence summaries/or evidence tables in the results section of the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
13. THE GUIDELINE HAS BEEN EXTERNALLY REVIEWED BY EXPERTS PRIOR TO ITS PUBLICATION.	□ Purpose and intent of the external review □ Methods taken to undertake the external review		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Description of the external reviewers □ Outcomes/information gathered from the external review □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations.		Comments:
14. A PROCEDURE FOR UPDATING THE GUIDELINE IS PROVIDED.	□ A statement that the guideline will be updated □ Explicit time interval or explicit criteria to guide decisions about when an update will occur □ Methodology for the updating procedure		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 4. CLARITY OF PRESENTATION			
15. THE RECOMMENDATIONS ARE SPECIFIC AND UNAMBIGUOUS.	□ A statement of the recommended action □ Intent or purpose of the recommended action □ Relevant population □ Caveats or qualifying statements, if relevant □ If there is uncertainty about the best care option, the uncertainty should be stated in the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
16. THE DIFFERENT OPTIONS FOR MANAGEMENT OF THE CONDITION OR HEALTH ISSUE ARE CLEARLY PRESENTED.	□ Description of management options □ Population or clinical situation most appropriate to each option		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
17. KEY RECOMMENDATIONS ARE EASILY IDENTIFIABLE.	□ Recommendations in a summarized box, typed in bold, underlined, or presented as flow charts or algorithms □ Specific recommendations grouped together in one section		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 5. APPLICABILITY			
18. THE GUIDELINE DESCRIBES FACILITATORS AND BARRIERS TO ITS APPLICATION.	□ Types of facilitators and barriers that were considered □ Method by which information regarding the facilitators and barriers to implementing recommendations were sought. □ Information/ description of the types of facilitators and barriers that emerged from the injury □ How the information influenced the guideline development process and/or formation of the recommendations		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
19. THE GUIDELINE PROVIDES ADVICE AND/OR TOOLS ON HOW THE RECOMMENDATIONS CAN BE PUT INTO PRACTICE.	□ Additional materials to support the implementation		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
20. THE POTENTIAL SOURCE IMPLICATIONS OF APPLYING THE RECOMMENDATIONS HAVE BEEN CONSIDERED.	□ Types of cost information that were considered □ Methods by which the cost information was sought		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	□ Information/ description of the cost information that emerged from the inquiry □ How the information gathered was used to inform the guideline development process and/or formation of the recommendations.		
21. THE GUIDELINE PRESENTS MONITORING AND/OR AUDITING CRITERIA.	□ Criteria to assess guideline implementation or adherence to recommendations □ Criteria for assessing impact of implementing the recommendations □ Advice on the frequency and interval of measurement □ Operational definitions of how the criteria should be measured.		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
DOMAIN 6. EDITORIAL INDEPENDENCE			
22. THE VIEWS OF THE FUNDING BODY HAVE NOT INFLUENCED THE CONTENT OF THE GUIDELINE.	□ The name of the funding body or source of funding □ A statement that the funding body did not influence the content of the guideline		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
23. COMPETING INTERESTS OF GUIDELINE DEVELOPMENT GROUP MEMBERS HAVE BEEN RECORDED AND ADDRESSESD.	□ Types of competing interests considered □ Methods by which potential competing interests were sought □ a description of the competing interests □ How the competing interests influenced the guideline process and		1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:

CHECKLIST ITEM AND DESCRIPTION	REPORTING CRITERIA	PAGE NO.	LIKERT SCALE
	development of recommendations		
OVERALL GUIDELINE ASSESSMENT			
1. RATE THE OVERALL QUALITY OF THIS GUIDELINE			1 Strongly Disagree | 2 | 3 | 4 | 5 | 6 | 7 Strongly Agree Comments:
2. I WOULD RECOMMEND THIS GUIDELINE FOR USE.			YES YES WITH MODIFICATTION NO