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Clinical Practice Guidelines - Gastrointestinal Disease Site

Guideline Title:	Microsatellite Instability and the Treatment of Stage II Colon Cancer	**Date:**	**(O):**	Dec 31, 2020
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Tumor Group:	G. I. Disease Site Group	**Page:**		1 of 18
Issuing Authority:	Dr. Jehan Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**		Feb 4, 2022
Adapted From:	Up-To-Date "Adjuvant Chemotherapy for Resected Stage II Colon Cancer" guideline, August 2020 (44).			

Introduction:

Overall, colorectal cancer (CRC) is the third most commonly diagnosed cancer (excluding non-melanoma skin cancers) in Canada. It is also the second-leading cause of cancer deaths in men and the third-leading cause of cancer deaths in women (1). As a province, Newfoundland and Labrador led the country in having the highest colorectal incidence and mortality rates for both males and females for 2019 (1). The rates of CRC are expected to increase globally by as much as 60% by the year 2030 (2).

The goal of adjuvant systemic therapy following the primary surgical resection of non-metastatic colon adenocarcinoma is to improve survival outcomes by eradicating any remaining occult disease with the use of systemic cytotoxic therapy. Patients with resected stage III (lymph-node positive) colon cancer have clear and meaningful survival benefits with the use of adjuvant chemotherapy treatment, making it the standard of care in this setting. However, there is no strong evidence which demonstrates that all patients with resected stage II (lymph-node negative) colon cancer will achieve the same benefit. Recently, research has focused on identifying subsets of patients with high-risk stage II colon cancer who may benefit from adjuvant treatment consideration.

Questions:

1. How does the presence of microsatellite instability (MSI) affect the long-term outcomes of stage II colon cancer?

2. What pathological testing is offered in NL to determine whether there is a deficiency (or mutation) of the mismatch repair (dMMR) genes in colon cancer tumors?

3. What adjuvant chemotherapy options are available for use in stage II colon cancer?

Target Population:

These recommendations apply to patients with a pathological confirmed diagnosis of stage II colon cancer following definitive surgical resection.

Supporting Evidence:

It is well-established that the standard of care for stage III colon cancer is surgical resection, followed by adjuvant chemotherapy. Research has determined that the benefit of adjuvant chemotherapy in this patient population include a 22% to 32% overall survival (OS) advantage, and a 30% reduction in relative risk (RR) in disease recurrence (3). However, many of these same early research studies have failed to demonstrate that adjuvant chemotherapy has any significant survival benefit in the stage II resected colon cancer subset (4-9). The optimal research approach would involve studies designed for the stage II colon cancer population alone. These early research studies were burdened with significant limitations, having the inherent risk of introducing a confounding factor which could make any meaningful results difficult to interpret. These limitations included:

- incorporating patients having a rectal cancer in the study population, or
- incorporating both stage II and III subjects of colon cancer in the study population, or
- failing to provide a stratification of risk features in the stage II subset, which may indicate level of risk (low vs high).

In addition, significant advances were been made in the surgical and pathological staging of colon cancer during the time of these studies, which may have influenced the potential for understaging colon cancer patients, known as the *stage migration effect* (3). For example, the number of lymph nodes harvested during the resection of colon cancer has been studied extensively. Research evidence indicated that having 12 or greater lymph nodes removed during surgery had an association with improved survival and has subsequently become standard of care (10). However, previously, there was a wide variation in the surgical practice regarding the number of lymph nodes harvested (frequently <12) which potentially skewed the results of these early studies and meta-analyses. Hence, one must interpret the conclusions reached from early research data with some caution.

The 5-year survival rates for patients with non-metastatic colon cancer, treated with surgical resection alone, are 99% for stage I, 68% to 83% for stage II, and 45% to 65% for stage III (45). Fluoropyridime-based adjuvant chemotherapy following complete surgical resection has been the standard of care for patients with stage III and select stage II colon cancer for many years. However, the addition of adjuvant chemotherapy has been reported to provide only an incremental 5-year absolute survival benefit of less than 5% in patients with stage II disease, mainly due to the high cure rate with surgery alone (7,11). Furthermore, in recent studies, the addition of adjuvant oxaliplatin in this patient population failed to show additional absolute survival benefit (12-15). Since chemotherapy is not without some risk of its own, it became important to identify which patients with stage II colon cancer should be offered adjuvant chemotherapy based upon their individual risk of relapse and death.

The American Joint Committee on Cancer (AJCC) 8th edition staging manual* uses the TNM staging to determine risk assessment after definitive surgery for colon cancer (i.e., tumor size and depth of penetration (T), number of lymph nodes involved (N), and the presence/absence of distant metastasis (M)) (16). The AJCC 8th ed. staging manual uses three groups to describe stage II colon cancer pathologically: stage IIA (pT3N0), stage IIB (pT4aN0), and stage IIC (pT4bN0). The deeper the tumor penetration among these three groups corresponds with an increased risk for recurrence and death, and also reveals the considerable heteriogeneity within the stage II population. Several studies have shown that T4N0 (stage II) colon cancers have similar outcomes and also a higher risk of developing locoregional recurrence compared to those with early node-positive (stage IIIA, T3N1) disease (17-19). These data have highlighted the inherent risk with having a stage II T4 colon cancer similar to that seen in early node-positive stage III disease. This has also been used has the evidentiary base with which clinical researchers have lauded for the use of adjuvant chemotherapy in the T4 stage II subset, with the goal of reducing the risk of recurrence and death.

Risk stratification is based upon the presence or absence of specific histopathological, clinical, and molecular characteristics. There is no standardized definition for low versus high risk since risk factors have not been consistantly, or conclusively, confirmed in prospective studies. Each of the prominent international guideline developers have a slightly different definition of “high-risk” stage II colon cancer (44-48). However, many of these groups do agree on most of the “high-risk” features but differ on the ranking in importance of these features. There is consensus that as the number of high-risk characteristics increases, so to does the risk of recurrence and death.

Risk Assessment

The most common prognostic factors associated with a higher risk of recurrence in stage II resected colon cancer include:

- a T4 tumor;
- perforation at site of tumor location;
- inadequately sampled lymph nodes (<12);
- poorly differentiated (high grade) histology;
- microsatellite stability;
- lymphovascular invasion;
- perineural invasion;
- bowel obstruction;
- close, indeterminate, or positive resection margins; and
- a high preoperative serum carcinoembryonic antigen (CEA) level (44-48).

Given the current lack of consensus of high-risk recurrence features, the Eastern Health GI Disease Site Group has chosen to create a comprehensive list from those noted in the most recent and well established, pre-existing guidelines (44-48). Each oncologist must use independent medical judgement to identify the prognostic features which may present the highest risk of recurrence to the patient. In addition, medical oncologists must also consider a number of other patient-related factors to determine whether to offer systemic therapy including the patients’ performance status, pre-existing co-morbitities, age (>70 years) and anticipated life expectancy of the individual patient.

**See Appendix for AJCC 8th ed Colorectal Cancer Staging*

Molecular Instability

Techniques continue to be developed to help differentiate colorectal cancers at the molecular level. Tumorigenesis in CRC is a multi-step process involving triggering of oncogenes and deletion of tumor suppressor genes leading to chromosomal instability or microsatellite instability (20). Microsatellites are short, repetitive DNA sequences found throughout the tumor genome that are prone to mutations during the cellular replication process. While the vast majority of CRCs have chromosomal instability, microsatellite instability comprises approximately 15% of all CRCs (21). Microsatellite instability (MSI) occurs when there is a deficiency or mutation(s) of DNA mismatch repair (MMR) gene(s) (*MLH1*, *MSH2, MSH6* or *PMS2*) which prevent normal cellular apoptosis from occurring (20). The two classifications of MSI are MSI-high (MSI-H), which has been described has having high levels of instability and MSI-low (MSI-L), which is considered to have a low level of microsatellite instability (or microsatellite stable) (22). The MSI-H colon cancers are considered to have a deficient MMR status (dMMR) which arises due to a germline mutation in one of the MMR genes mentioned above, or from having the CpG island methylator phenotype (20,23). The CpG island methylator phenotype occurs when the CpG islands around the promoter region of *MLH1* and other genes become hypermethylated or abnormal which can promote tumor formation and cancer progression. However, some sporadic and familial colon cancers have been found where MSI-H and dMMR do not co-exist together signifying that exceptions exist potentially due to specific mutations or unidentified protein losses in the MMR pathway (23). Germline mutations in the MMR pathway have also been found in patients with hereditary Lynch syndrome, which is known to give rise to a variety of malignant tumors including colorectal cancer (previously known as “hereditary nonpolyposis colorectal cancer” (HNPCC)) (23). Colon cancers without a dMMR status are considered to have a proficient MMR status (pMMR).

Prognostic value of dMMR

Research studies suggest that tumor specimens having dMMR (or MSI-H) are more prevalent in stage II colon cancers than stage III disease (22% vs 12%, respectively; $P < 0.0001$), and are even less likely to be evident in stage IV tumors (3.5%) (24,25). The research findings of these studies suggest that in patients with stage II colon cancer, having dMMR is a prognostic indicator for more favorable outcomes. The results of a recent systematic review and meta-analysis concluded that the presence of MSI-H in stage II colon cancer was associated with a significantly reduced risk of relapse (HR 0.59, 95% CI: 0.45-0.77, $p<0.01$) and death (HR 0.64, 95% CI: 0.52-8.8, $p<0.01$) (26). Tumors with dMMR tended to be located on the right side of the colon, more likely to be diagnosed at a earlier pathological stage, and therefore less likely to develop lymph node spread and local/distant metastases compared to those having pMMR tumors (27,28).

Predictive value of dMMR

Recently researchers have suggested that dMMR status can also be used as a predictive indicator for a lack of response to fluoropyridime-based chemotherapy in stage II colon cancer patients (29). A landmark study which found that fluoropyridime-based chemotherapy failed to improve OS for those patients with dMMR/MSI-H stage II disease (HR 1.07, 95%CI 0.62 – 1.86; $p = 0.80$) (30). A later study revealed that patients with dMMR tumors, randomly assigned to surgery plus adjuvant chemotherapy (fluorouracil–based) or surgery alone, did not exhibit a difference in DFS (HR 1.10;95% CI, 0.42 – 2.91; $P = .85$) between the two arms (31). These results provide sufficient evidence to show restraint in choosing which patients with stage II colon cancer should receive adjuvant chemotherapy, especially when age, comorbidities and performance status are taken into consideration (32).

The best treatment choice for patients with high-risk stage II pMMR colon cancer is still a matter of debate. However, it does appear that patients diagnosed with low-risk stage II dMMR tumors of the colon have a favorable prognosis and are unlikely to gain meaningful benefit from receiving further adjuvant therapy following surgical resection. Definitive testing for the MMR status of stage II colon cancer is crucial in determining which patients with stage II colon cancer should be offered adjuvant chemotherapy.

Testing for dMMR

Recently, dMMR testing of tumors patients with stage II colon cancer has become an international standard of care. There are two techniques of testing to determine whether colon tumors have a deficiency in MMR or MSI which include:

1. immunohistochemistry (IHC), and
2. polymerase chain reaction (PCR).

The IHC test analyzes stained tumor samples to detect the presence of either of the four MMR proteins. It is most frequently used due to its low cost and wide availability, although individual interpretation of the percentage of protein expression has its limitations. However, testing all four MMR proteins can increase test sensitivity for detection of dMMR (23).

The PCR test is the gold standard for MSI testing and involves direct comparison of the lengths of microsatellites in the tumor with the patient's DNA. PCR has a number of advantages over IHC testing including:

- more objective measure of functional dMMR activity;
- better reproducibility between testing facilities;
- allows for identification of other abnormalities in mutations of the four MMR proteins, and
- allows for identification of MSI caused by other defects that result in dMMR (23,33).

The disadvantages for PCR-based testing are that it is much more labor-intensive than the IHC test and that it requires non-tumor tissue for comparison purposes (34). In addition, PCR is believed to be less effective at recognizing MSH6 abnormalities which has the potential to lead to lower MSI rate reporting (20). Despite their limitations, both IHC and PCR have been found to be sensitive and specific for dMMR and MSI, with >95% concordance across many tumor types (35-37).

Pre-existing Guidelines regarding MMR testing on Stage II Colon Cancer

Several well-established oncology guideline organizations have recommended testing for MSI and dMMR in stage II colon cancer patients (44-48). However, there is some disagreement as to which proportion or subgroups within the stage II population should be tested. Up-To-Date (UTD) and European Society of Medical Oncology (ESMO) agree that all stage II colon cancer patients should have their tumors tested using either available laboratory test (ie., PCR, IHC) while the National Comprehensive Cancer Network (NCCN) recommends that all newly diagnosed patients with colon cancer should be tested, regardless of stage (44-46). Cancer Care Ontario (CCO) and Alberta Health Services (AHS) recommend that only those 'high-risk' stage II patients who are being considered for adjuvant chemotherapy should be tested (47,48).

The Eastern Health G.I. Disease Site Group (GIDSG) has decided to test all patients with pathologic stage II colon cancer for MSI/dMMR using IHC staining. Presently, IHC testing is

unavailable in the province of Newfoundland and Labrador and therefore, surgical specimens must be sent out to other Canadian or international facilities for testing. However, this method may result in causing treatment delay for eligible patients outside the recommended time window of commensing treatment within eight weeks of surgery date. To minimize risk of exceeding the recommended timelines for starting adjuvant chemotherapy, Eastern Health's Department of Pathology has agreed to arrange reflex (automatic) testing on the definitive surgical specimens of **all** patients with stage II colon cancer. The goal is to have IHC testing results available during the patient's first visit with the medical oncologist.

Clinical Decision Support Tools in Colon Cancer (CDST)

Genetic expression assays were developed to aid in identifying an individualized risk of relapse and the benefit provided with chemotherapy, and have been commonly used in breast cancer for many years. Presently, five gene expression assays developed in the United States (US) are available for clinical use in stage II colon cancer to assess the risk of relapse, including the 12-gene recurrence score (Oncotype-DX Colon Cancer Assay) and the 18-gene expression profile (ColoPrint colon cancer recurrence assay) (44). However, none have received specific US Food and Drug Administration (FDA) approval for use in this population. In addition, none of these assays can predict which patients would benefit from chemotherapy in the stage II population. Clinically, these assays have had very limited use in Canada.

Other clinical decision support tools, such as web-based Adjuvant! Online, have been available for several years to aid physicians in calculating the relative risk of disease recurrence and mortality based on clinico-pathological features and the relative benefit provided by the addition of chemotherapy. However, these older tool models have become obsolete due to the introduction of molecular prognostic factors, such as dMMR and *BRAF* mutation status (44). A new CDST developed in western Canada, known as Oncopre, is an adjuvant chemotherapy benefit calculator for colon cancer which is gaining in popularity and meant to address the limitations of current CDSTs (38). It is available online at www.oncopre.com.

Adjuvant Chemotherapy

For most patients with stage II pMMR colon cancer, having no other high-risk features, the Eastern Health GIDSG recommends a fluoropyrimidime-based regimen such as intravenous 5-fluorouracil and leucovorin or oral single-agent capecitabine alone for six months. However, as mentioned previously, sufficient evidence exists which suggests that adjuvant fluoropyrimidine-based chemotherapy is ineffective for patients having MSI/dMMR stage II colon cancer. Nevertheless, patients with MSI/dMMR stage II colon cancer, with one or more high-risk features (i.e., T4 tumors), are a subset of this population for which there is greater concern due to the increased risk of recurrence and death, and are felt to warrant adjuvant chemotherapy. These patients comprise only 15% of all colon cancers and thus frequently their participation numbers are so small in large clinical studies, it often prevents any meaningful interpertation of the research data. However, it is commonly believed that the chemo-resistance to the fluoropyrimidine-based regimen exhibited by this subgroup can be overcome with the addition of oxaliplatin (eg. FOLFOX - fluoropyrimidine, leucovorin, oxaliplatin; CAPOX – capecitabine, oxaliplatin). This assumption has been based upon the exploratory analysis results of a high-risk stage II subgroup in the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, which showed an 7% increase of absolute benefit in DFS at 5 years for those who received the oxaliplatin-containing regimen (8). Despite the fact that this

finding did not reach statistical significance, many prominent guideline organizations recommend offering an oxaliplatin-containing regimen as an option during the treatment discussion for patients having stage II colon cancer with high-risk features (44-48).

Despite the lack of prospective clinical trials comparing an oxaliplatin-containing regimen (ie., FOLFOX) and a fluoropyrimidine-based regimen (ie., 5-FU/FA – 5-fluorouracil, leucovorin) head-to-head in stage II colon cancer patients with MSI/dMMR, some retrospective data have suggested a potential benefit exists with the use of a oxaliplatin-based regimen in this high-risk subgroup. Using the National Surgical Adjuvant Breast and Bowel (NSABP) C-07 clinical trial data, an analysis was conducted to determine whether there was a benefit with the addition of oxaliplatin to a fluoropyrimidine-based regimen for stage II and III colon cancer having dMMR (9,39). This analysis concluded that regardless of the MMR status, there was a benefit with the use of an oxaliplatin-containing regimen. The arguement used to support their conclusion was that oxaliplatin forms platinum adducts with DNA which is unable to be repaired in a dMMR tumor.

In addition, a subgroup analysis was conducted, after nearly 10 years of follow-up, using the MOSAIC clinical trial data of the patients with a known MMR status (n = 1008) (12). The translational analysis suggested that the addition of oxaliplatin was associated with a significant OS benefit in patients with dMMR (HR 0.42, 95% CI: 0.16 - 1.07, p=0.069), however the number of patients with dMMR was small and therefore underpowered. Finally, a retrospective study (n=433) of patients with resected dMMR colon cancer, of which 57% were stage II, looked at the oxaliplatin benefit for this population (40). Only 17% (n=41) of the stage II patients, who were considered to have high-risk features, were given the adjuvant oxaliplatin-based chemotherapy regimen (FOLFOX). The result was a trend toward better outcomes for the stage II subset who received FOLFOX compared to surgery alone (HR for relapse 0.13, 95% CI: 0.02 – 1.05, P=0.06) while fluoropyrimidine-based chemotherapy, without oxaliplatin, did not provide an advantage for either stage IIs or IIIs over surgery alone.

Pre-existing Guidelines regarding Treatment of Stage II Colon Cancer

There does appear to be a consensus among the most prominent international guideline developers that the presence of MSI/dMMR in stage II colon cancer patients is associated with fluoropyrimidine resistence and therefore unlikely to confer any meaningful benefit. However, there is some controversy among these same guideline developers regarding the recommended treatment for those with stage II dMMR colon cancer patients who have high-risk features (i.e., T4). The authors of the UTD guideline concluded that the best approach for treatment in these patients is uncertain, and therefore individualized consideration for adjuvant chemotherapy should be based on the number of high-risk features, overall medical condition, and age of the patient (44). They recommend that average-risk stage II colon cancer patients with pMMR should receive a fluoropyrimidine-based regimen (5FU/LV or capecitabine), while the option of a oxaliplatin-based regimen (e.g., FOLFOX) should be discussed with patients who have high-risk features and a dMMR status. The authors of the ESMO guideline also acknowledge this existing controversy and recommends chemotherapy for intermediate- and high-risk stage II patients (45). They suggest capecitabine as an option for those with intermediate-risk stage II disease, or for those deemed unfit for consideration of oxaliplatin therapy. For patients who are perceived to have benefit with the addition of oxaliplatin, ESMO recommends the medical oncologist have a discussion regarding the results of the MOSAIC trial. Conversely, NCCN recommends no adjuvant chemotherapy for all stage II colon cancer patients with MSI-H/dMMR tumors (46).

However, the authors do acknowledge and support the adage that it is "...reasonable to accept that the relative benefit of adjuvant therapy in stage III disease as indirect evidence of benefit for stage II disease, especially for those with high risk features" (41). The CCO guideline recommends fluoropyrimidine-based adjuvant monotherapy for stage II colon cancer patients having MSI-H/dMMR tumors. For those patients with high-risk features the treatment options are observation or the addition of oxaliplatin (ie., FOLFOX, CAPOX) (47). The authors also acknowledged that the data is lacking to support and guide this recommendation. The AHS guideline also recommends no adjuvant chemotherapy for stage II colon cancer patients unless they present with at least one or more 'high-risk' features (48). The authors recommends that a stage II colon cancer with high-risk features should be considered for adjuvant chemotherapy as used for stage III disease. They also note that the benefit of oxaliplatin is questionable.

Duration of Chemotherapy

The International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration was a prospective study which pooled the data from six individual clinical trials involving 12,834 patients having stage III colon cancer (42). Patients were randomly assigned to receive either three months or six months of a oxaliplatin-containing chemotherapy (either FOLFOX or CAPOX) to evaluate for noninferiority of adjuvant treatment. The primary endpoint was DFS. Noninferiority of three months of treatment versus six months of treatment was not confirmed in the overall population (HR 1.16; 95% CI 1.00 – 1.15). The findings suggested that three months of FOLFOX was found to be inferior to six months of this regimen. However, the three-month regimen of CAPOX was found to be noninferior to the six months of the same regimen especially in the earlier substages of stage III colon cancer. This suggested that three months of CAPOX was considered a sufficient duration of treatment for early stage III colon cancer, such as T1-3N1 disease (42). In addition, a shorter duration of adjuvant chemotherapy was associated with significantly lower incidence and severity of adverse events, such as neurotoxicity, palmer-plantar erythrodysesthesia (or hand-foot snydrome), mucositis, nausea, fatigue and diarrhea.

Four of the six clinical trials used in the IDEA collaboration included patients having high-risk stage II disease but without knowledge of MMR status. A planned analysis of this cohort found a primary endpoint of 80.7% for five-year DFS with three months of chemotherapy versus 83.9% with six months (HR 1.17; 80% CI, 1.05 – 1.31; *P* [for noninferiority] 0.39) (43). This suggested that noninferiority was not demonstrated since it crossed the noninferiority limit of 1.2 set by the researchers. The absolute difference in DFS between three months and six months of chemotherapy was very small at 3.2%. In addition, as seen in the stage III colon cancer cohort, there was a marked reduction in number and severity of adverse events in the three-month regimen compared to the six-month regimen. Therefore, three months of capecitabine and oxaliplatin (CAPOX) could be a a valid choice of treatment for some stage II patients. All five national and international guideline development organizations have acknowledged this evidence and all suggest that three months of oxaliplatin-containing chemotherapy should be an option for certain patients having high-risk stage II colon cancer (44-48).

In consideration of the evidence presented, the Eastern Health GIDSG has decided that three months of CAPOX, six months of CAPOX, as well as six months of FOLFOX are all valid options of treatment for patients having high-risk stage II colon cancer. The choice of regimen will be decided by the medical oncologist and the patient during the treatment discussion regarding their individualized risk of relapse.

The optimal choice and duration of adjuvant chemotherapy for stage II colon cancer remains unknown. However, the Eastern Health GIDSG strongly encourages all eligible patients with stage II colon cancer to participate in any available clinical trials.

Recommendations:

The following recommendations of the Eastern Health G. I. Disease Site Group apply to patients with a pathologically confirmed stage II colon cancer following definitive surgical resection:

- All patients having a pathologically confirmed stage II colon cancer should undergo IHC testing for MSI/MMR status.
- The Eastern Health GIDSG has provided a compilation of the most common prognostic factors associated with the increased risk of recurrence in surgically resected stage II colon cancer. They include:
  - a T4 tumor;
  - perforation at site of tumor location;
  - inadequately sampled lymph nodes (<12);
  - poorly differentiated (high grade) histology;
  - MSI/MMR status;
  - lymphovascular invasion;
  - perineural invasion;
  - bowel obstruction;
  - close, indeterminate, or positive margins; and
  - a high preoperative serum carcinoembryonic antigen (CEA) level (44-48).

  Oncologists are expected to use independent medical judgement to identify the combination of prognostic features which present the highest risk of recurrence to the patient.
- In addition, medical oncologists must also consider a number of other patient-related factors to determine whether to offer systemic therapy including the patients' performance status, pre-existing co-morbitities, age (>70 years) and anticipated life expectancy of the individual patient.
- Patients having stage II colon cancer with a pMMR status, with no other high-risk features, should be offered six months of fluoropyrimidine-based chemotherapy either 5-FU and leucovorin or single-agent capecitabine.
- Patients with stage II low-risk (having no high-risk features) dMMR tumors will be followed with observation alone and do not require adjuvant chemotherapy.
- Patients with stage II high-risk tumor features with dMMR will **NOT** receive adjuvant fluoropyrimidine-based chemotherapy alone. However, the medical oncologist may offer the patient the option of an oxaliplatin-containing regimen (if patient is deemed a suitable candidate), or observation alone.
- Patients with high-risk stage II colon cancer (regardless of MMR status) who are suitable for an oxaliplatin-containing chemotherapy may be offered the choice of three months of CAPOX, six months of CAPOX, or six months of FOLFOX at the discretion of the medical oncologist after a discussion of the existing evidence.
- All eligible patients with stage II colon cancer should be encouraged to participate in any available clinical trials.

Search Strategy:

Literature searches were conducted in PubMed, Embase, and the Cochrane Library, using keywords “colon cancer” AND “deficient mismatch repair” AND “treatment” as well as an extensive manual search of the reference lists of available literature articles. Guideline searches were also carried out on the websites of the world’s most highly respected cancer organizations and agencies. All selected literature articles and source guidelines were in English and dated after the year January 1, 2012 (unless the selection was an earlier landmark study) up to December 31, 2020. The inclusion/exclusion process consisted of selecting guidelines from reputable cancer organizations with preference given to those from Canadian sources where possible. Seven source guidelines were identified and conformed to our search criteria, from which five were selected due to currency, applicability and quality of content (44-48).

The five identified source guidelines (41-45) were put through the ADAPTE process (49) with an AGREE II assessment (50), and the Up-To-Date guideline was chosen to be adapted for use in our guideline (44). The Up-To-Date “Adjuvant chemotherapy for resected stage II colon cancer” was selected as the optimal choice due to its applicability, quality, and currency of content.

There has been much debate but no consensus on the ‘grading of evidence’ in Canada. Presently, Canadian experts in the field of guideline development are involved in an ongoing in-depth analysis of the functionality of grading. Until such time as a report is released of their findings, and a consensus reached on whether to assign a grade of recommendation to a guideline, this group has decided to forgo the use of grading.

No competing or conflicts of interest were declared.

Disclaimer:

These guidelines are a statement of consensus of the G. I. Disease Site Group regarding their views of currently accepted approaches to diagnosis and treatment. Any clinician seeking to apply or consult the guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment.

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Literature Support:

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Glossary:

AHS: Alberta Health Services

AJCC: American Joint Committee on Cancer

CAPOX: capecitabine and oxaliplatin

CCO: Cancer Care Ontario

CRC: colorectal cancer

DFS: disease-free survival

ESMO: European Society for Medical Oncology

5FU/FA: fluorouracil and folinic acid

FOLFOX: fluorouracil, folinic acid and oxaliplatin

IHC: immunohistochemistry

MMR, dMMR, pMMR: DNA mismatched repair gene; deficient mismatch repair gene; proficient mismatch repair gene

MSI: microsatellite instability

NCCN: National Comprehensive Cancer Network

OS: overall survival

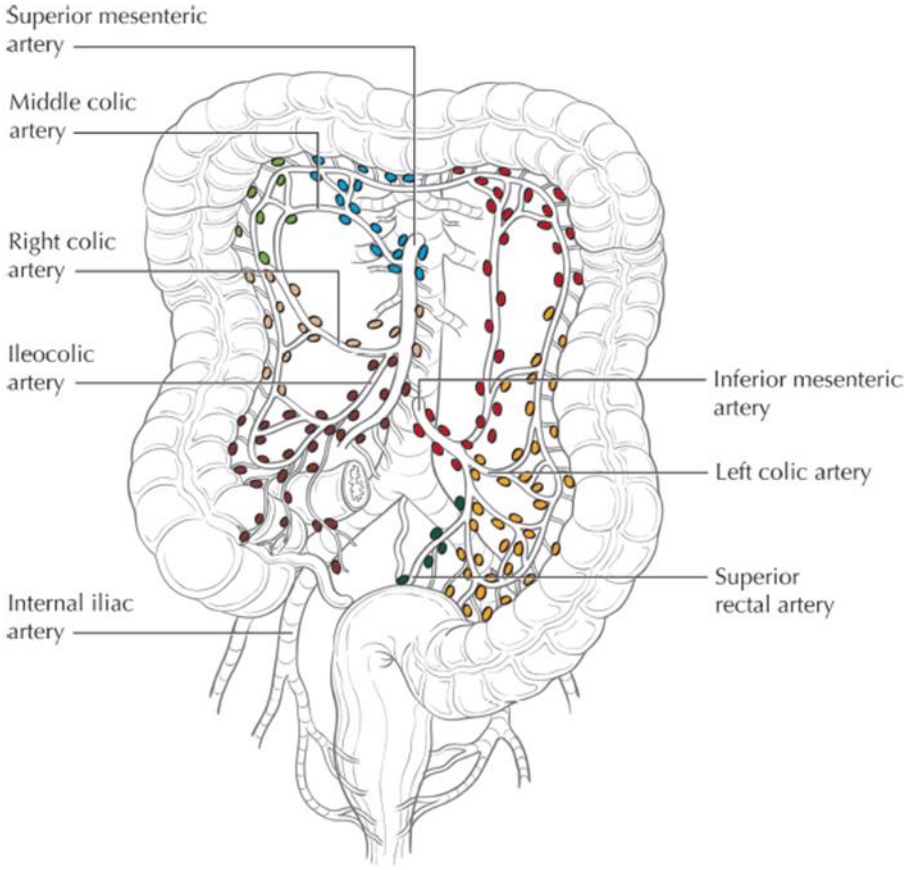
PCR: polymerase chain reaction

RR: risk of relapse

UTD: Up-To-Date

Appendix:

Fig. 20.4 The regional lymph nodes of the colon and rectum



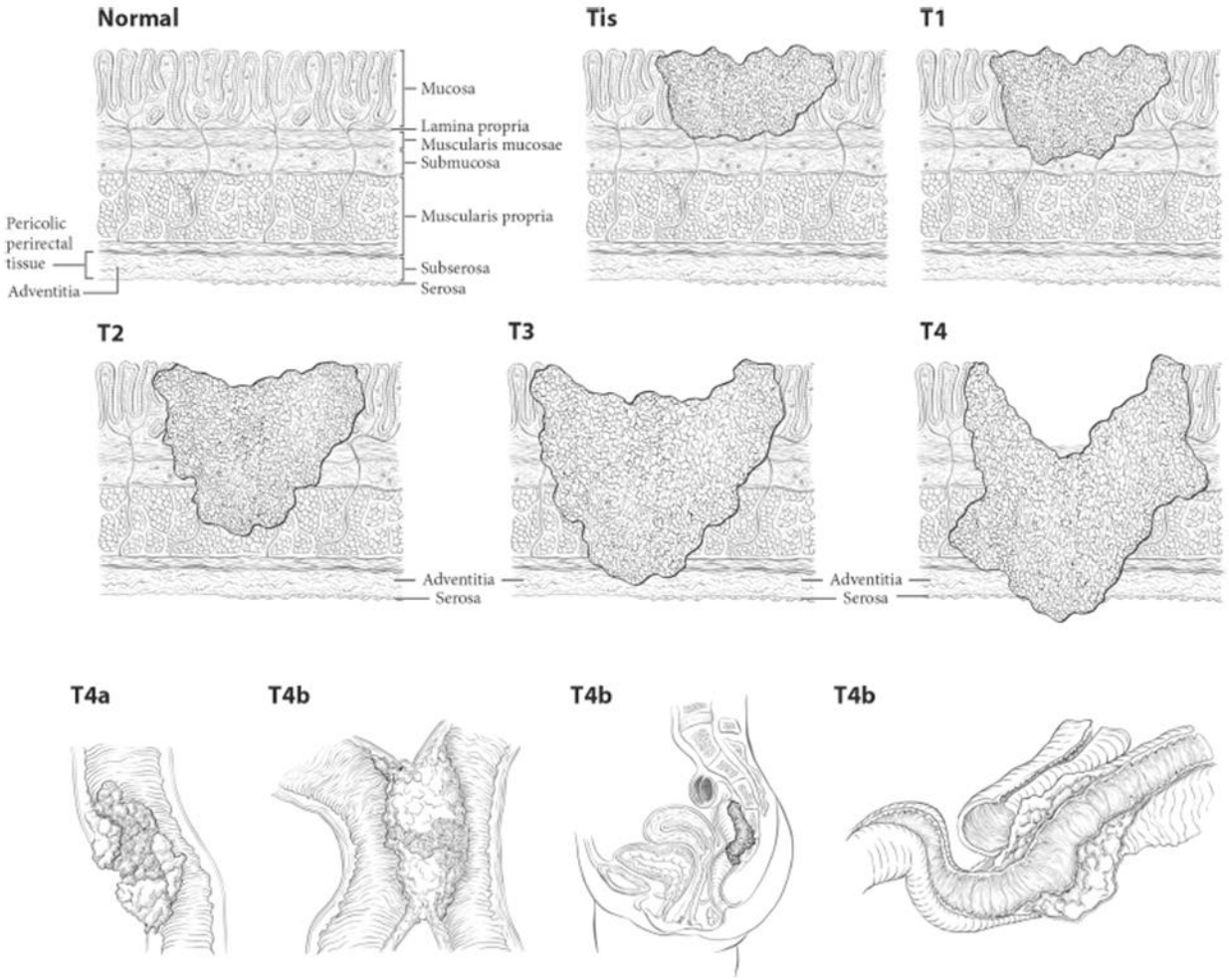


Fig. 20.5 T1–T3 as defined in Definition of Primary Tumor (T). T4 is a tumor that penetrates or perforates the visceral peritoneum in the parts of the colon or rectum covered only by peritoneum (T4a) or that invades an adjacent structure or organ (T4b)

DEFINITIONS OF AJCC TNM

Definition of Primary Tumor (T)

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
T2	Tumor invades the muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4	Tumor invades* the visceral peritoneum or invades or adheres** to adjacent organ or structure
T4a	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)
T4b	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 classification 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.

Definition of Regional Lymph Node (N)

N Category	N Criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One to three regional lymph nodes are positive in lymph nodes measuring ≥0.2 mm), or any of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the • subserosa • mesentery • or nonperitonealized pericolic, or perirectal/ mesorectal tissues.
N2	Four or more regional nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive

Definition of Distant Metastasis (M)

M Category	M Criteria
M0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs (This category is not assigned by pathologists.)
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
M1a	Metastasis to one site or organ is identified without peritoneal metastasis
M1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
M1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases

AJCC PROGNOSTIC STAGE GROUPS

When T is…	And N is…	And M is…	Then the stage group is…
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1–T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3–T4a	N1/N1c	M0	IIIB
T2–T3	N2a	M0	IIIB
T1–T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3–T4a	N2b	M0	IIIC
T4b	N1–N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

REGISTRY DATA COLLECTION VARIABLES

1. Tumor deposits
2. CEA levels: preoperative blood level recorded in nanograms per milliliter with fixed decimal point and five numbers (XXXX.X ng/mL)
3. Tumor regression score
4. Circumferential resection margin
5. Lymphovascular invasion
6. Perineural invasion
7. Microsatellite instability
8. KRAS and NRAS mutation
9. BRAF mutation

HISTOLOGIC GRADE (G)

G	G Definition
GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

HISTOPATHOLOGIC TYPE

Adenocarcinoma *in situ*
Adenocarcinoma
Medullary carcinoma
Mucinous carcinoma (colloid type; >50% extracellular mucinous carcinoma)
Signet ring cell carcinoma
Squamous cell (epidermoid) carcinoma
Adenosquamous carcinoma
High-grade neuroendocrine carcinoma (small cell carcinoma and large cell neuroendocrine carcinoma)
Undifferentiated carcinoma
Carcinoma, NOS