Clinical Practice Guidelines - Gastrointestinal Disease Site

Guideline Title:	Microsatellite Instability and the Treatment of Stage II Colon Cancer - **Summary**	**Date:**	**(O):** **(R):**	Dec 31, 2020
Tumor Group:	G. I. Disease Site Group	**Page:**		1 of 10
Issuing Authority:	Dr. Jehan Siddiqui Clinical Chief, Cancer Care Program	**Date Signed:**		Feb 4, 202
Adapted From:	Up-To-Date "Adjuvant Chemotherapy for Resected Stage II Colon Cancer" guideline, August 2020 (20).			

Target Population:

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

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 immunohistochemistry (IHC) testing for microsatellite instability (MSI)/mismatch repair (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;
  - a high preoperative serum carcinoembryonic antigen (CEA) level (20-24).

  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-morbidities, age (>70 years) and anticipated life expectancy of the individual patient.

- Those patients having stage II colon cancer with proficient MMR (pMMR) status, with no other high risk features, should be offered six months of fluoropyrimidine-based chemotherapy (both fluoropyridime and leucovorin or single-agent capecitabine).
- Those patients with stage II low-risk (having no high-risk features) MSI-H/deficient MMR (dMMR) tumors will be followed with observation alone and do not require adjuvant chemotherapy.
- Those patients with stage II high-risk tumor features with MSI-H/dMMR will not receive adjuvant fluoropyrimidine-based chemotherapy. 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.
- Those patients with high-risk stage II colon cancer who are suitable for an oxaliplatin-containing chemotherapy may be offered the choice of three months of CAPOX (capecitabine, oxaliplatin), six months of CAPOX, or six months of FOLFOX (fluoropyridime, leucovorin, oxaliplatin) 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.

Supporting Evidence:

There are well-established clinical research data on the survival benefits of adjuvant chemotherapy following surgical resection for patients having stage III colon cancer. However, many of these same research studies have failed to demonstrate any significant survival advantage for the use of adjuvant chemotherapy in patients having surgically resected stage II colon cancer (1-6). Fluoropyridime-based adjuvant chemotherapy, following complete surgical resection, has been the standard of care for patients with stage III and selected 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 (7,8). Since chemotherapy is not without some risk of its own, it became important to identify which patients having stage II colon cancer should be offered adjuvant chemotherapy based upon their individual risk for relapse and death.

The American Joint Committee on Cancer (AJCC) 8th edition* for colon cancer staging uses the TNM staging to determine risk assessment after definitive surgery (i.e., tumor size and depth of penetration (T), number of lymph nodes involved (N), and the presence/absence of distant metastasis (M)) (9). 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 (10-12). These data have highlighted the inherent risk with

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

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.

Molecular Instability

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 (13). Microsatellites have been defined as 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 has been found to comprise approximately 15% of all CRCs (14). Microsatellite instability (MSI) occurs when there is a deficiency or mutation(s) of the DNA mismatch repair (MMR) genes which prevents normal cellular apoptosis from occurring (13). The two classifications of MSI include 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) (15). Those colon cancers which are known to be MSI-H are considered to have a deficient MMR status (dMMR) while those without a dMMR status are considered to have a proficient MMR status (also known as pMMR).

Recently, screening colon cancer tumors in patients with stage II disease has become an international standard of care. The immunohistochemistry (IHC) test is able to analyze stained tumor samples to detect the presence of MMR proteins (16). The IHC test is cost-effective and widely available and has been found to be sensitive and specific for dMMR and MSI, with >95% concordance across many tumor types.

Adjuvant Chemotherapy

Sufficient evidence exists which suggests that adjuvant fluoropyrimidine-based chemotherapy is ineffective for patients having MSI/dMMR stage II colon cancer. Nevertheless, the subgroup of greatest concern would be those having MSI/dMMR stage II colon cancer, with one or more high-risk features (i.e., T4 tumors). 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 the 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 absolute 7% increase in the probability of DFS at 5 years for those who received the oxaliplatin-containing regimen (5). Despite the fact that this finding did not reach statistical significance (hampered by small numbers of patients in this subset), 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 (20-24).

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 (6,17). This analysis concluded that regardless of the MMR status, there was a benefit with the use of an

oxaliplatin-containing regimen. The argument used to support their conclusion was that oxaliplatin forms platinum adducts with DNA which is unable to be repaired in a dMMR tumor.

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 II and III colon cancer (18). 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 (18). In addition, a shorter duration of adjuvant chemotherapy was associated with significantly lower incidence and severity of adverse events, such as neurotoxicity, 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. 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) (19). 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 (20-24).

Qualifying Statements:

Risk stratification is based upon the presence or absence of specific histopathological, clinical, and molecular characteristics. Unfortunately, there is no standardized definition for low versus high risk since risk factors have not been conclusively confirmed in prospective studies.

The decision of the Eastern Health G.I. Disease Site Group (GIDSG) is to test all patients pathologically staged as having stage II colon cancer for MSI/dMMR using IHC testing. Presently, IHC testing is unavailable in the province of Newfoundland and Labrador and therefore, surgical specimens must be sent out to other national and international facilities for testing results. However, this method frequently causes a treatment delay for eligible patients outside the recommended time window of commensing treatment within eight weeks of surgery date. In response to this concern, the pathology department within Eastern Health has agreed to arrange reflex (automatic) testing on the definitive surgical specimens of **all** patients with stage II colon

cancer. This will expedite the decision-making process to coincide with the patient's surgical recovery, so that the testing results should be available during the patient's first visit with the medical oncologist.

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.

Contact Information:

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Literature Support:

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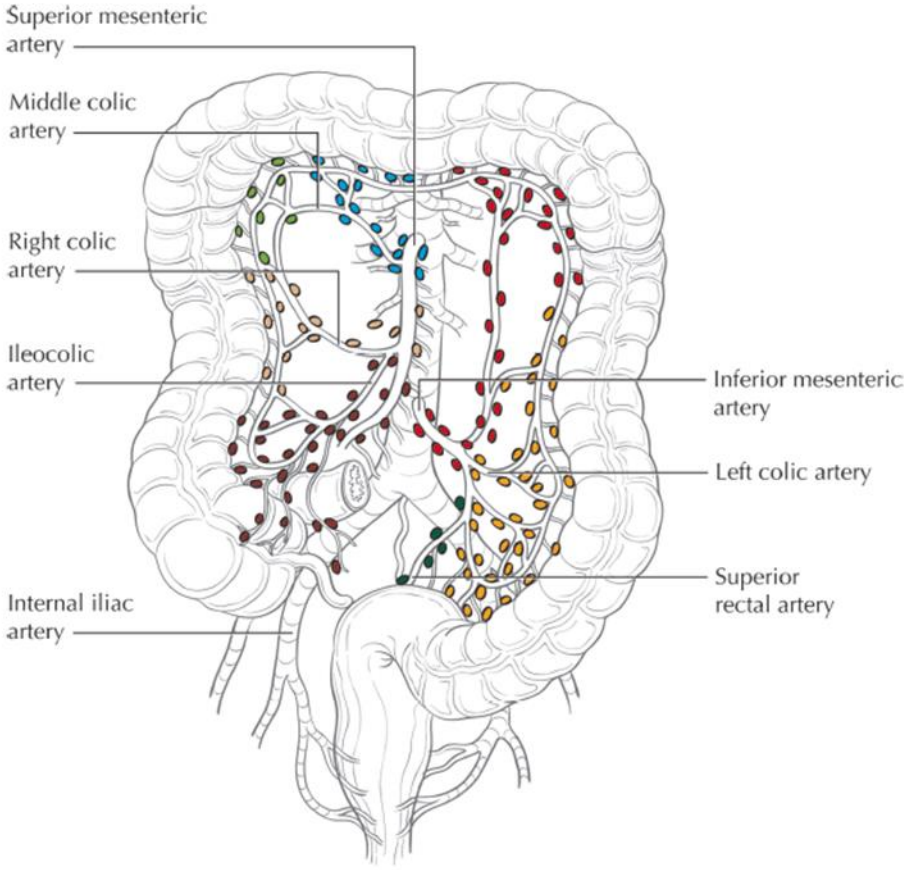
Appendix:

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



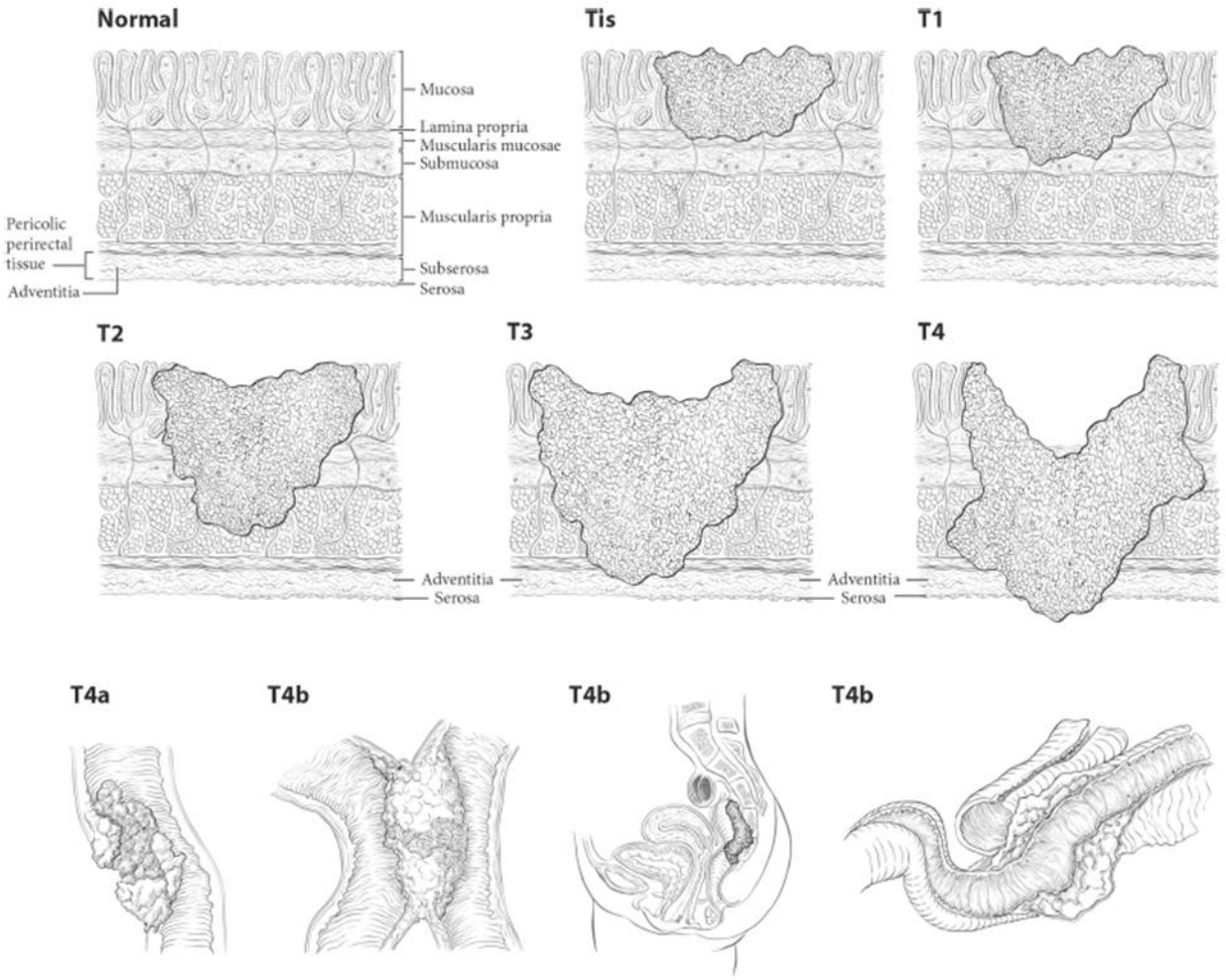


Fig. 20.5 T1–T3 as defined in Definition of Primary Tumor (T). T4 is a tumor that penetrates or perforates the visceral peritoneum in the parts of the colon or rectum covered only by peritoneum (T4a) or that invades an adjacent structure or organ (T4b)

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 pro- pria (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