25
Colon Cancer: Preoperative Evaluation and Staging

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Key Concepts

- Total colonic evaluation is recommended prior to surgical intervention to exclude synchronous tumors that may alter surgical plan.
- Evaluation for metastatic disease by cross-sectional imaging is recommended prior to surgical intervention, as it may alter treatment decisions.
- Preoperative carcinoembryonic antigen (CEA) level should be obtained, as changes in CEA may herald tumor recurrence.
- Tumor location should be identified preoperatively.
- Tumor grade, lymphovascular invasion, margin status, and immunohistochemical assessment of mismatch repair proteins may have prognostic significance and should be routinely reported.

Background

Colorectal cancer remains a challenging clinical entity worldwide—affecting more than one million individuals annually [1–3]. Marked geographic variations exist, with industrialized countries bearing significantly higher incidences that are believed to be attributed to a mix of diet and environment [2, 3]. In the United States, it is the third leading cause of cancer-related deaths and is the third most common cancer following lung cancer and prostate and breast cancers in men and women, respectively [2–4]. In recent years, it has been estimated that annually there are roughly 100,000 new cases of colon cancer and more than 40,000 cases of rectal cancer [5–7]. Fortunately, both the incidence and mortality of colorectal cancer have declined steadily in the past three decades—largely due to more effective screening programs and improvements in treatment modalities [5–7]. However, despite these measurable gains, there remain significant disparities in incidence and mortality, particularly among African Americans [8–10]. Overall, the lifetime risk of developing colorectal cancer in the United States is approximately 5 % with a likelihood rising notably after 50 years of age. It is estimated that up to 90 % of cases occur in individuals over the age of 50 [11].

Once the diagnosis of colon cancer is made, the goal of preoperative evaluation is to establish the location of the tumor, assess for metastatic disease and adjacent organ invasion, and identify other patient and tumor factors that may affect outcome or alter the medical or surgical approach to treatment. The primary importance of staging in colon cancer is to rule out additional pathology and distant metastatic disease (stage IV), which can affect treatment approach. This differs from rectal cancer where estimates of locoregional tumor stage have a greater effect on treatment planning.

Clinical Presentation

Colon cancer presents in three common ways: an asymptomatic lesion detected during routine screening examination; manifestation of vague but suspicious symptoms such as change in bowel habits, weight loss, and fatigue that lead to further investigation; and emergently, with perforation or obstruction.

Early colon cancers are often asymptomatic, which underscores the importance of routine screening. Even so, it is estimated that about 30 % of all cancers are diagnosed by endoscopy in the absence of symptoms [12]. Routine screening detects the majority of early cancers, but the definition of "effective screening" is in flux and overall compliance with colonoscopic screening in the United States is still quite low—below 50 % for most average risk adults. Rates of screening can vary widely between states and regions. The Centers for Disease Control and Prevention estimates that when surveyed for appropriate screening which could include fecal occult blood testing alone within 1 year, flexible sigmoidoscopy within 3 years, or colonoscopy within 10 years, the highest rates recorded are in the northeast topping out at 75 % and the lowest in the west with maximal screening

S.R. Steele et al. (eds.), *The ASCRS Textbook of Colon and Rectal Surgery*, DOI 10.1007/978-3-319-25970-3_25

compliance rates of 54 % [13]. When symptoms do occur, patients commonly present with abdominal pain, gastrointestinal bleeding, iron-deficiency anemia, change in bowel habits, or vague nonspecific symptoms such as lethargy, weight loss, and loss of appetite [4, 14, 15]. Symptoms will often manifest differently depending on tumor location and size. Late findings can include palpable abdominal mass, severe weight loss, intestinal obstruction, and, in rare cases, perforation leading to peritonitis or fistulization to adjacent organs.

Abdominal pain in the setting of colon cancer is often poorly localized and, therefore, a nonspecific finding. Patients may describe a vague visceral discomfort, which changes to crampy, colicky pain as luminal narrowing occurs—resulting in partial or complete colonic obstruction. While rectal bleeding is a common finding, its clinical manifestation can be varied; therefore, taking a careful history is imperative. Patients with distal, left-sided lesions will often present with bright red bloody stools, while more proximal lesions will cause melena or occult bleeding that results in iron-deficiency anemia [3, 14]. This anemia can ultimately result in dizziness, weakness, or generalized fatigue. Similarly, changes in bowel habits will be affected by tumor location within the colon. Typically, patients will report changes in the caliber, frequency, and consistency of their stools. This is more notable with left-sided lesions, which are more likely to cause narrowing of the colon lumen and impede passage of solid stool. Since the luminal diameter tends to be wider in the proximal colon and stool more liquid, alterations in stools generally coincide with large, exophytic lesions or cancers that obstruct the ileocecal valve.

Approximately 20–25 % of colon cancer will present with metastatic disease at the time of diagnosis; therefore, it is also critical to evaluate patients for signs and symptoms associated with metastatic disease. On the whole, widely advanced cancers can result in constitutional symptoms such as unintentional weight loss, cachexia, weakness, and anorexia [3].

Colon cancer typically spreads via lymphatic, hematogenous, or intraperitoneal extension, and the most common sites include the liver, lungs, and peritoneal surfaces. Spread to the brain or CNS and bones is less likely but possible. While symptoms of liver metastasis are uncommon, some patients may develop right upper quadrant pain, abdominal distention, anorexia, weakness, or jaundice when the burden of liver metastases is high. Direct local invasion of colon cancers into adjacent structures such as the small intestine, bladder, or abdominal wall can result to bowel obstruction, abscesses, pneumaturia, fecaluria, or enterocutaneous fistula. A Virchow node (left supraclavicular node) or Sister Mary Joseph node (umbilical nodule) is another uncommon finding that has been associated with the distant spread of colon cancer [3]. Patients who present with symptoms seem to be at much higher risk of having advanced disease at diagnosis than those for whom the primary is detected by routine screening. For example, in one study of over 1000 patients with colorectal cancer, only 217 were found during screening. Those that came to attention via symptoms were twice as likely to have a transmural tumor, twice as likely to present with stage III disease, and over three times as likely to have distant spread at diagnosis and have double the risk of recurrence [16].

Preoperative Evaluation

The evaluation of a patient with a new diagnosis of colon cancer should begin with a complete history and physical examination [11]. The history should focus on the duration and severity of symptoms associated with the primary tumor such as intestinal obstructive symptoms, anemia, and abdominal pain, as well as those associated with metastatic disease such as weight loss and fatigue. Information should also be obtained about any family history of colorectal cancer or other cancers known to be associated with inherited colon cancer syndromes. Finally, details regarding the patient's overall health will provide initial insight into their readiness for any surgical intervention. A focused physical examination can elucidate important signs such as a palpable mass, distant adenopathy, tenderness, or distention [11].

Assessment of Inherited Risk

The vast majority of colorectal cancers are sporadic in nature. However, there are factors associated with the development of colorectal cancer. Modifiable risk factors include low-fiber, high-fat diet, obesity, smoking, and heavy alcohol consumption. The primary inherent risk factor for colorectal cancer is increasing age; however, having a personal history of colorectal cancer, polyps, or inflammatory bowel disease will substantially increase risk. Approximately 5–10 % of colorectal cancers can be linked to discrete inherited syndromes, among which familial adenomatous polyposis (FAP) and Lynch syndrome are the most common. It is important to identify these risk factors, particularly inflammatory bowel disease, personal history of colorectal neoplasia, and presence of inherited colorectal cancer syndromes, as they will guide choice of therapy, surveillance strategies, and screening of at-risk relatives. For example, a patient with long-standing ulcerative colitis who is found to have a colon cancer should be considered for total proctocolectomy. A patient with colon cancer who is suspected of having Lynch syndrome should be considered for subtotal colectomy, as well as total abdominal hysterectomy and bilateral salpingo-oophorectomy in women.

Colonoscopy

If not completed at the time of diagnosis, a thorough endoscopic examination of the entire colon is critical as it provides added information about any synchronous cancers or polyps, which may need to be removed or marked preoperatively. The rate of synchronous cancers is understood to be about 5 %, and the overall rate of synchronous neoplasia that

would change operative approach is somewhat higher [17]. If a synchronous polypoid neoplasm is detected outside of the normal field of planned resection for the primary tumor, it is optimal to attempt complete endoscopic resection preoperatively. This will allow for histologic analysis—if cancer is found, then a more extensive colectomy than was originally planned may be indicated [4]. Colonoscopy allows for the localization and biopsy of the primary tumor; however, it is important to keep in mind that the flexible scope may not provide an exact measurement of distance. Therefore, it is important to assess known landmarks and whenever possible to mark the location of the cancer with an endoscopic tattoo, particularly if the cancer was contained within a polyp and therefore entirely resected. This is increasingly important for smaller lesions that may not be easily palpated at the time of surgery or if a laparoscopic approach is planned. It is not unusual for the endoscopist to resect a large polyp only to find an occult cancer within it requiring formal resection on pathology. Rapid reevaluation of the colon via colonoscopy with marking is essential. Typically, if the colon can be reevaluated within 2 weeks, a healing ulcer can be identified and tattooed.

Over time, a number of agents for endoscopic marking have been evaluated. Only India ink and SPOT (GI Supply, Camp Hill, PA) have been widely accepted. Both agents are colloid suspensions of fine carbon particles. India ink is suspended in a 0.9 % solution of saline at a 1:100 dilution and sterilized by autoclaving or being passed through a Millipore filter. SPOT is a marker composed of highly purified, fine carbon particles and is the only FDA-approved marking solution for endoscopic tattooing. Both have been tested extensively and are safe as well as durable. Identification of the endoscopic tattoo can be made well after the 1-year mark and commonly after 2 or more years. Other agents that have been used include methylene blue, hematoxylin, and toluene blue. Brevity of duration of marking and mucosal ulceration has limited use of these other agents. Technique of injection has been studied fairly extensively. Four-quadrant injection of 2–4 cm^3 of agent at or near the level of the lesion allows for accurate identification even if the lesion is on the mesenteric aspect of the colon lumen. Submucosal injection limits intraperitoneal spread that can make intraoperative identification confusing or difficult. Some advocate for placing a tattoo both proximally and distally to the tumor or polyp to help identify the extent or length of the lesion; however, this may confuse the surgeon if only one of the tattoo marks is visible. Other surgeons advocate marking only distal to the lesion. While there are no current recommendations regarding this aspect of marking, it seems clear that good documentation of technique in the report is mandatory and will limit misunderstandings or confusion [18]. Additional benefits of tattoo placement may include increased nodal harvest by virtue, most likely, of the ability to see and enumerate lymph nodes that take up the colloid carbon particles. A number of studies, both prospective as well as retrospective, have noted a significant increase in the number of specimens with >12 lymph nodes harvested when tattooing had taken place [19, 20].

An alternative to marking with tattoo is deployment of endoscopic metal clips followed by immediate plain radiograph. The colon outline is frequently visible due to retained air from colonoscopy. CT can also be obtained within a few days; the clips are usually retained and the tumor site can be clearly localized. Another strategy is to perform intraoperative colonoscopy to localize a small tumor. This can be performed immediately prior to operation or after exploration of the abdomen. The use of carbon dioxide as an insufflation gas is preferred, in order to limit bowel dilatation.

If colonoscopy cannot be completed preoperatively, then a suitable radiographic study, such as CT colonography or contrast enema, should be considered or intraoperative colonoscopy performed via the colon proximal to the tumor. For cases of obstructing cancers that preclude adequate endoscopic or radiographic assessment preoperatively, intraoperative colonic lavage and colonoscopy should be considered. If this is not possible, the proximal colon should be palpated intraoperatively, and if no obvious lesions are detected, a full colonoscopy should be performed when safe to do so after surgery [4].

Carcinoembryonic Antigen

Preoperative evaluation should also include routine laboratory studies, including a complete blood count (CBC) with focus on anemia that may need to be corrected before surgery. Another important test is the serum CEA level, which has been shown to provide some prognostic information [21]. CEA is a glycoprotein primarily involved in intercellular adhesion [22]. It is produced by columnar and goblet cells and can be found in normal colonic mucosa. Additionally, it can be found in low levels in the circulation of healthy individuals, but it is overexpressed in a variety of cancers, including colorectal cancer. Elevated serum levels may be identified in heavy smokers and in benign conditions such as pancreatitis and inflammatory bowel disease as well as malignancies outside of the gastrointestinal tract [22]; therefore, CEA is not a sensitive or specific screening tool for colorectal cancer [3, 23]. However, it is an important tool in CRC surveillance after surgical resection since its elevation may be the first indication of locally recurrent or metastatic disease [24].

Patients with preoperative serum CEA >5 ng/mL have a worse prognosis, stage for stage, than those with lower levels. Elevated preoperative CEA levels have been shown to be associated with poorer survival and increased recurrence in several studies; however, contradictory studies do exist [23, 25–29]. Therefore, there is currently insufficient evidence to support the use of elevated preoperative serum CEA levels as an absolute indication for adjuvant chemotherapy [4, 28].

Current American Society of Clinical Oncology (ASCO) guidelines recommend that serum CEA levels be obtained preoperatively in patients with demonstrated colorectal cancer for posttreatment follow-up and assessment of prognosis. Elevated preoperative CEA levels that do not normalize following surgical resection imply the presence of persistent disease. Furthermore, serial testing of CEA levels should be performed for 5 years for patients with stage II and III disease in those eligible for surgery or chemotherapy if metastatic disease is discovered. Rising CEA levels after surgical resection imply recurrent disease and should prompt consideration of radiologic and endoscopic evaluation to look for treatable disease [28].

Radiographic Evaluation

Preoperative radiographic imaging is fundamental for initial staging of newly diagnosed or recurrent colon cancers [4]. Computed tomography (CT) scans are the most widely used studies in this setting as they provide valuable preoperative information about liver or lung metastasis and are cost effective. This test should be done with both oral and intravenous contrast if there is no contraindication (anaphylaxis to contrast or renal insufficiency) to maximize accuracy of visualization of the abdominal viscera as well as highlight vascular structures and better determine the relationships between lymphatics, ureters, and vessels [30]. Additionally, cross-sectional imaging also facilitates more precise tumor location and delineates the extent of any extracolonic invasion of adjacent organs or the abdominal wall, all of which are important for operative planning [31]. In these cases, the appropriate consulting services can be mobilized if necessary for en bloc resections. CT scan has a sensitivity ranging from 75–90 % for detecting distant metastasis; however, the ability to accurately detect nodal involvement or small peritoneal metastasis is poor. The routine use of CT for imaging of the chest remains controversial for initial staging of colon cancer, as compared to rectal cancers. In asymptomatic patients in whom the suspicion of lung metastasis is low, a plain chest X-ray will suffice. Any suspicious findings on chest X-ray can be investigated with a noncontrast chest CT scan.

As imaging technology has improved, so has the sensitivity of CT scans for identifying liver metastases. However, there are studies that suggest that contrast-enhanced magnetic resonance imaging (MRI) is particularly valuable in evaluating smaller suspicious liver lesions (especially in the presence of fatty liver changes) with sensitivities up to 97 % [3, 32]. In routine clinical practice, MRI should be reserved for the evaluation of suspicious liver lesions not clearly characterized on CT scan and for operative planning prior to liver metastasectomy.

Positron emission tomography–computed tomography (PET/CT) scan has emerged as a useful imaging modality in the evaluation of many cancers. However, for initial staging of colorectal cancer, the routine use of PET/CT remains controversial. While it has been shown to be more sensitive in the detection of liver metastases as well as extrahepatic disease as compared with routine CT scan, other studies suggest that it does not add significant information [14, 33–35]. The strongest evidence for use of PET/CT in the management of colorectal cancer is in the evaluation of patients with recurrent disease [34–36]. It is often more helpful as an adjunct to conventional imaging studies in patients suspected of having metastasis, especially those with a rising CEA level [31, 37]. Additionally, in patients with potentially resectable metastatic disease, PET/CT has been shown in a randomized trial to reduce the number of unnecessary laparotomies [38].

Preoperative Evaluation of Coexisting Medical Conditions

Regardless of the operative approach, colorectal procedures carry inherent risks, which can be divided into procedure-specific risks and cardiopulmonary risks. Therefore, a thorough history and physical examination encompassing the patient's comorbidities is also vital. This is immensely important because surgical morbidity and mortality can be greatly improved by a careful assessment of organ-specific risks and, if feasible, preoperative optimization. Additionally, a detailed knowledge of the patient's prior abdominal surgery will aid in the appropriate operative planning.

Routine preoperative testing should be obtained and should include a CBC, a metabolic panel, type and screen, and a 12-lead electrocardiogram in older patients with cardiac risk factors. Liver function tests are not sensitive for liver metastasis and, therefore, are not required in the initial preoperative testing. Similarly, nutritional panels are not generally required unless there are significant concerns for underlying malnutrition. Complete optimization of nutritional parameters, either parenterally or enterally, typically takes weeks, which would delay surgery unnecessarily.

There are several classification systems that have been reported, which aim to gauge the overall risk of the surgical patient. The American Society of Anesthesiologists (ASA) classification is the simplest and most commonly used system, which highlights the patient's underlying illnesses that may impact outcomes from surgery [39, 40]:

- ASA I—a normal healthy patient
- ASA II—a patient with mild systemic disease
- ASA III—a patient with severe systemic disease
- ASA IV—a patient with severe systemic disease that is a constant threat to life
- ASA V—a moribund patient who is not expected to survive without the operation
- ASA E—emergency

The preoperative cardiac assessment should include a history of recent or remote myocardial infarction, angina, valvular disease, arrhythmias, or heart failure. Baseline functional status should also be quantified using metabolic equivalents (METs) [41]. Perioperative risk of an adverse cardiac event can then be estimated using the Goldman cardiac risk index or the revised cardiac risk index (Table 25-1), which are among the most widely used tools for cardiac risk assessment [39].

Chronic obstructive pulmonary disease (COPD), obesity, obstructive sleep apnea, pulmonary hypertension, recent respiratory infection, and smoking are some of the most important pulmonary risk factors that should be considered prior to surgery. These comorbidities can be gleaned from a thorough history and should prompt further investigation; however, this testing should be selective. The routine use of chest X-ray varies by institution and is often of limited value for the evaluation of significant pulmonary disease; therefore, this study should be reserved for patients with known cardiopulmonary disease or those older than 50 years of age as recommended by the American College of Physicians [42]. Because CXR is a part of staging of colon cancer, it is necessarily included in the preoperative evaluation. Pulmonary function testing and baseline arterial blood gases are not indicated routinely prior to abdominal surgery [43]. Complex patients with high-risk underlying pulmonary illnesses should be referred for pulmonary consultation prior to surgery for medical optimization and to outline appropriate perioperative strategies.

Smoking cessation should be emphasized but should not delay surgery, as any substantial benefits would not be realized for several weeks. However, there may be measurable gains in improving postoperative wound healing [44]. A recent meta-analysis of randomized trials demonstrated that smoking cessation was associated with a 41 % relative risk reduction in postoperative pulmonary complications [44].

In patients with renal insufficiency, care must be taken with choosing preoperative bowel preparation, and special attention must be paid to perioperative fluid balances. Additionally, diuretics, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers should be held the day prior to surgery to minimize the risk of profound hypotension during surgery.

Staging of Colon Cancer

The preferred staging system for colon and rectal cancers is the TNM staging system put forth by the American Joint Committee on Cancer and the International Union Against Cancer (UICC) [4, 36]. This system, which is summarized in Table 25-2, consists of three categories: tumor depth of invasion, nodal involvement, and distant metastasis. Based on the clinical and pathologic data, the combination of these categories forms the final stage, which correlates with the overall prognosis. Recent analysis of survival outcomes in a large group of patients with invasive colon cancer from the Surveillance, Epidemiology, and End Results (SEER) population-based database has led to the revision of the CRC TNM staging system in the 7th edition of the *AJCC Cancer Staging Manual* [45]. These changes include [6]:

- Stage II is further subdivided into IIA (T3N0), IIB (T4aN0), and IIC (T4bN0).
- Satellite tumor deposits in the pericolonic adipose tissue are classified as N1c.
- Several stage III groups have been revised based on survival outcomes.
- N1 and N2 subcategories are further subdivided according to the number of involved nodes to reflect prognosis.
- T4 lesions are subdivided as T4a (tumor penetrates the surface of the visceral peritoneum) and as T4b (tumor directly invades adjacent organs or structures).

Table 25-1. Revised cardiac risk index (RCRI)

Risk factors	
1. High-risk type of surgery (intraperitoneal, intrathoracic, or suprainguinal vascular procedures)	
2. Ischemic heart disease	
3. Congestive heart failure	
4. History of cerebrovascular disease	
5. Insulin therapy for diabetes	
6. Preoperative serum creatinine > 2.0 mg/dL	
Risk classification (*one point is assigned to each risk factor present*)	*Rates of major cardiac complications*[a] (%)
Class I (0 points)	0.50
Class II (1 point)	1.30
Class III (2 points)	3.60
Class IV (≥3 points)	9.10

[a]Major cardiac complications include myocardial infarction, pulmonary edema, ventricular fibrillation or primary cardiac arrest, and complete heart block
Adapted from Lee, TH et al., Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery Circulation 1999;100(10):1043–9 [63]

TABLE 25-2E. TNM classification and AJCC 7th edition staging of colon cancer

Primary tumor staging (*T*)			
T0		No evidence of primary tumor	
Tis		Carcinoma in situ	
T1		Tumor invades submucosa	
T2		Tumor invades the muscularis propria	
T3		Tumor invades through the muscularis propria into the pericolonic tissue	
T4a		Tumor penetrates to the surface of the visceral peritoneum (serosa)	
T4b		Tumor invades and/or is adherent to other organs or structures	
Regional lymph node staging (*N*)			
N0		No regional lymph node metastasis	
N1a		Metastasis in one regional lymph node	
N1b		Metastasis in 2–3 regional lymph nodes	
N1c		Tumor deposits in subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastases	
N2a		Metastasis in 4–6 regional lymph nodes	
N2b		Metastasis in seven or more regional lymph nodes	
Distant metastasis staging (*M*)			
M0		No distant metastasis	
M1a		Metastasis confined to one organ or site	
M1b		Metastasis in more than one organ/site or the peritoneum	
Stage	*T*	*N*	*M*
0	Tis	N0	M0
I	1–2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1–T2	N1–N1c	M0
	T1	N2a	M0
IIIB	T3–T4a	N1–N1c	M0
	T2–T3	N2a	M0
	T1–2	N2b	M0
IIIC	T4a	N2a	M0
	T3–T4a	N2b	M0
	T4b	N1–N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

With permission from Chang GJ et al., Practice parameters for the management of colon cancer. Dis Colon Rectum 2012;55(8):834. © Wolters Kluwer [4]

- M1 is subdivided into M1a (single metastatic site) and M1b (metastasis to more than one organ or the peritoneum).

The completeness of resection should also be noted by the surgeon [4, 6, 46]:

- R0—complete tumor resection with negative margins
- R1—incomplete tumor resection with microscopic involvement of the margin
- R2—incomplete tumor resection with gross residual disease that was not resected

In addition to the aforementioned components of the TNM staging system, there are several other histologic criteria that should be reported routinely. These include histologic grade, tumor ("satellite") deposits, lymphovascular invasion, perineural invasion, and margin status (distal, proximal, and radial). Each of these features provides important prognostic information.

Histologic Grade

Histologic grade has consistently been shown to be a stage-independent prognostic factor and is determined by the degree of differentiation in the colon tumor. While most systems stratify cancers into four grades, ranging from well differentiated (grade 1) to undifferentiated (grade 4) [46], histologic assessment is often plagued by interobserver variability. Consequently, the AJCC has recommended a two-tiered system for reporting: low grade (well and moderately

differentiated) and high grade (poorly differentiated and undifferentiated) [21, 46, 47].

There are histologic variants such as mucinous adenocarcinomas and signet ring cell adenocarcinomas that are also important in assessing overall prognosis. Mucinous adenocarcinomas are characterized by extracellular mucin in greater than 50 % of the tumor volume. When compared with conventional invasive adenocarcinomas, mucinous adenocarcinomas typically behave more aggressively, especially in patients without microsatellite instability (MSI). Signet ring cell adenocarcinomas are rare but when they occur in the colon, they carry a worse prognosis as compared with conventional adenocarcinomas [14]. These tumors are characterized histologically by greater than 50 % tumor cells with signet ring features—prominent intracytoplasmic mucin vacuole that pushes the nucleus to the periphery [47].

Lymph Node Evaluation

Other than radial margin status, lymph node status is the most important prognostic factor following resection of colon cancer [14]. The identification of at least 12 lymph nodes has been suggested as a key quality indicator in the resection of colon cancers [6]. While there are patient-related factors that influence lymph node yield, the completeness of mesenteric resection and the interest of the pathologist in obtaining the maximal number for nodes for examination are also paramount. Numerous studies have shown that increasing the number of lymph nodes examined is associated with improved survival in stage II and stage III patients [48]. Tumor deposits that are found in the pericolonic fat that do not show any evidence of residual lymph node are not counted as lymph nodes replaced by tumor and are designated as N1c. The number of these nodules should be reported as they confer a poor prognosis [6, 49].

During the past 20 years, there has been interest in improving harvest of at-risk lymph nodes and in better identification of tumor in lymph nodes. Some investigators have proposed injection of vital dye around the tumor at the time of operation as a method of identifying lymph nodes at greatest risk for metastases (sentinel node mapping).

Studies of sentinel lymph node mapping have focused on the detection of metastatic lesions in nodes that would ordinarily be missed by routine nodal retrieval and pathologic processing. However, with few exceptions, the "sentinel" nodes retrieved in these studies have been subjected to ultra-processing (microsectioning, immunohistochemical analysis, or RT-PCR), while other "nonsentinel" nodes have been examined by bivalving and hematoxylin and eosin staining only, biasing the results heavily in favor of sentinel lymph node mapping. Even with this bias, results have varied widely in the literature, with false-negative rates (patients with negative "sentinel" nodes and positive "nonsentinel" nodes/total patients with positive nodes) of 9–60 % [50–52]. Variation in reported success rates may also result from different methods of data analysis and presentation.

The ultimate goal of any protocol examining lymph nodes in nonstandard fashion is to identify patients with occult nodal metastases, to treat them with chemotherapeutic agents, and to improve survival. At present, there is no definitive evidence that treatment of patients with occult nodal metastases with chemotherapy improves survival.

Margin Status

Surgical resection with curative intent requires removal of the entire tumor as well as the associated lymphatics and nodal basin at risk, which will vary based on the location of the primary tumor. It would seem obvious that it is of critical importance to resect the entire tumor when operating for colon cancer. However, the concept that the radial margin of resection is important was largely ignored by the surgical and pathology communities until recently. Just as with rectal cancer, it is important to ink the radial margin of resection and assess it histologically, as it has profound prognostic significance and will drive some decisions regarding adjuvant treatment and can be used as an assessment of surgical quality. It should be noted that the visceral peritoneum is not considered a surgical margin. However, pathologists often have difficulty in assessing this layer in relation to margin status, making inking of the nonperitonealized radial margin all the more critical.

The proximal and distal margin of resection should also be measured and reported. Traditionally, some authors have advocated obtaining a 5 cm segment of normal bowel on the proximal and distal sides of the tumor to avoid local failure [4, 46, 53]. However, this recommendation has little to do with the primary tumor, as colon cancers do not often spread longitudinally in the wall of the bowel in occult fashion. Rather, the recommendation arises from the need to resect mesentery surrounding the tumor to ensure adequate removal of at-risk lymph nodes. Adequate resection of the mesentery, including named feeding vessels, will result in devascularization of the colon surrounding the tumor, thus mandating resection of the colon rendered ischemic.

Other Prognostic Features

The presence of lymphovascular and perineural invasion has been shown to be significantly associated with poorer prognosis [21, 46, 54–57]. Tumor budding refers to small clusters of undifferentiated cancer cells ahead of the invasive front of the lesion. While this is not a routinely examined pathologic parameter, there is increasing evidence that the quantitative

assessment of tumor budding reflects clinical aggressiveness of colon cancers. This has also been shown by some to be a poor prognostic feature [46, 54].

DNA Mismatch Repair/Microsatellite Instability

A germ line mutation in one of the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) is typically found in Lynch syndrome. In sporadic colon cancers, mismatch repair defects occur in approximately 20 % of cases and results from the hypermethylation of *MLH1* [3, 58]. Patients with dropout of *MLH1* on immunohistochemistry (IHC) can be accurately identified as either a sporadic or germ line mutation by staining for *BRAF*. If *BRAF* is mutated as well, then a sporadic mutation is 96 % likely in MLH1 [59]. Typically, tumors found to be lacking in MMR expression are subject to *BRAF* analysis. If *BRAF* mutation is detected, then Lynch syndrome is unlikely, and in most cases, the patient can be considered to have a sporadic cancer and genetic testing will cease. However, if *BRAF* is normal, then Lynch syndrome is likely and genetic counseling and testing should be considered.

The presence of MMR proteins in tumor tissue can be assessed by IHC and should be done routinely in patients suspected of having Lynch syndrome, based on the clinical criteria [36]. In many hospitals, IHC testing for MMR is done routinely for patients under the age of 50. Increasingly, because of the prognostic implications, many urge IHC for MMR proteins to be assessed on all patients with colorectal cancer in an effort to align pathology with prognosis and therapy.

MSI is another indicator of DNA repair defects caused by defective mismatch repair proteins. It is typically assessed by PCR amplification of repeated single nucleotide units of DNA, or microsatellites, in tumor tissue. Tumors are characterized as MSI high (MSI-H) or MSI low (MSI-L) based on the number of microsatellite sequences that appear. If the tumor has two or more mutated sequences, it is termed MSI-H, while if only one sequence is mutated, it is classified as MSI-L. Finally, if no mutation is present, then the tumor is microsatellite stable (MSS) [47, 60]. Recent studies demonstrate that stage II patients with MSI-H tumors did not have the same survival benefit from 5-FU-based adjuvant chemotherapy as compared with those that had MSI-L and MSS tumors although differences were slight [36, 50–52, 61–63].

Summary

Assessment of the patient and the tumor preoperatively is increasingly important. Today, treatment decisions are made by careful preoperative evaluation of the health of the patient, the genetics of the tumor, and the extent of disease. A sophisticated, organized, and educated approach to preoperative evaluation yields the best long-term results.

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