CHAPTER 2
Diagnosis and initial evaluation

Risk factors

Risk factors for colon cancer include genetic factors such as ethnicity, age, sex, and family history, as well as lifestyle factors. In Asian countries and specific regions, high incidences are related to economic development, urbanization, and a Western lifestyle.[1–4]

Individuals with any of the following history are considered to be at high risk for colon cancer and should be actively screened. In addition, those with inherited syndromes should be referred for genetic counseling:

- Personal medical history of adenoma, colon cancer or inflammatory bowel disease, such as Crohn's disease or ulcerative colitis.
- Family history of adenoma or colon cancer.
- Hereditary syndromes (2-5%): Lynch syndrome or hereditary non-polyposis colon cancer (2-4%), familial adenomatous polyposis and its variants (1%), Turcot syndrome, MUTYH-associated polyposis syndrome, Peutz-Jeghers disease.

Diagnosis

Because of the specific topic of this treatment update report, we will not address the basics of screening, specific diagnosis, or symptoms of uncomplicated colon cancer. However, we cannot define the current treatment of colon cancer without first establishing the basic principles of its staging.

Following the diagnosis of a colon tumor, a clinical examination and laboratory tests are necessary to correctly assess the patient's general condition and characteristics before defining the definitive therapeutic approach. Evidence IIA.

It is essential to perform a cancer-related history analysis, including specific symptoms, personal clinical history, family history, physical examination, and perioperative risk, before planning treatment. Evidence IB.[1]

An objective way to assess preoperative risk is to analyze the general condition according to the Eastern Cooperative Oncology Group.[2]

In addition to the complete physical examination, the humoral examination includes general laboratory tests, coagulation tests, liver function, kidney function, and proteinogram. Evidence IIA. Likewise, carcinoembryonic antigen (CEA) should be evaluated before surgery and during postoperative follow-up for early detection of metastatic disease. Evidence IIIA.[1]

The preoperative CEA level is important to define the oncological prognosis of each case. A level >5 ng/ml suggests a worse outcome.[5]

According to a multivariate analysis of over 130,000 patients included in the National Cancer Database, preoperative CEA is an independent predictive factor of overall survival (OS) in patients with stage I, II, and III colon cancer. Patients with elevated CEA have a 62% increased risk of death compared with patients with normal CEA. Although CEA is considered an important predictor, there is no complete consensus on the cutoff value. In stage IV patients, decreased CEA in response to chemotherapy has been associated with improved survival.[5–10]

Histological classification of colon carcinoma

Approximately 95% of malignant neoplasms of the colon are adenocarcinomas.[11–13] According to their histological characteristics, carcinomas are classified as:

a) Adenocarcinoma: the usual form of malignant neoplasia originating in the colonic glandular epithelium.
b) Mucinous or colloid adenocarcinoma: more than 50% of the lesion is made up of lakes of extracellular mucin containing malignant epithelium forming acini, epithelial strips or loose cells. It is frequently associated with microsatellite instability.
c) Signet ring cell adenocarcinoma: more than 50% of the neoplastic cells show abundant intracellular mucin and the nucleus is located peripherally in a characteristic ring shape, regardless of the presence of extracellular mucin lakes. Some show microsatellite instability.
d) Adenosquamous carcinoma: features of squamous carcinoma and adenocarcinoma coexist in separate areas of the same tumor or are intermingled. More than an occasional focus of squamous differentiation is required to define this subtype.
e) **e)** Medullary carcinoma: characterized by a covering of malignant cells with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm, surrounded by an intense lymphocytic infiltrate. It is a rare variant that is invariably associated with microsatellite instability and has a better prognosis than poorly differentiated and undifferentiated carcinoma.
f) f) Undifferentiated carcinoma: malignant epithelial tumor without any type of cellular olodifferentiation (glandular, squamous or neuroendocrine), beyond the epithelium itself. These tumors are genetically different and are typically associated with microsatellite instability.

Degree of cell differentiation

According to the degree of histological differentiation, adenocarcinoma can be:

- Well differentiated (G1): more than 95% of the tumor forms glands.
- Moderately differentiated (G2): 50 to 95% of the tumor forms glands.
- Poorly differentiated (G3): less than 50% of the tumor forms glands.

It is necessary to determine the level of infiltration of the colonic wall (affectation of the submucosa, muscularis propria, perivisceral fat, serosa, or other organ by contiguity), the presence of lymph node metastasis (regional disease) and distant metastasis (disseminated disease).[1,2,14]

Histological prognostic factors

Histopathological factors that have been definitively proven to be prognostic are pTNM, the presence of residual tumor after a curative procedure (R1 or R2 resection), and vascular and/or lymphatic invasion. Histological grade, margin status (radial, distal, and deep), and the presence of residual tumor after neoadjuvant therapy are also sufficiently proven.

Promising, but not yet sufficiently proven in the clinical context, are the histological characteristics associated with microsatellite instability (MSI): peritumoral lymphoid response, mucinous and medullary histological type, high MSI grade, and tumor border configuration (infiltrative vs. expansive).[1,2,14]

Histological evaluation and report

Histopathology reports non-mucinous adenocarcinoma in 89.2%, mucinous adenocarcinoma in 9.3%, and signet ring cells in 1.5%. The histology report is of particular importance and should be performed immediately after surgery to determine lymph node involvement and tumor extension into the colon wall and adjacent structures, as well as to establish the need for biopsies due to suspected distant invasion (e.g. liver, peritoneum).

Although the analysis of this aspect exceeds the objectives of this report, it is important to define a correct histological report because the choice of postoperative treatment will depend on it. A standard histological evaluation should include:[1,2,4,14]

- Morphological description of the specimen
- Type of surgery performed
- Location and size of the tumor
- Presence of macroscopic or microscopic tumor perforation
- Histological grade and type
- Definition of T stage (extension of the tumor into the colon wall and involvement of adjacent structures)
- Distance of the tumor to the resection margins (proximal, distal and radial)
- Presence of tumor deposits
- Perineural and/or lymphovascular invasion
- Presence of tumor budding
- Evaluation of N stage (site and number of resected regional nodes and their tumor involvement)
- Evaluation of M stage (involvement of other distant organs, e.g. peritoneum, liver, lung, defining whether metastases were biopsied or resected)
- Tumor status with respect to mismatch repair (MMR) and microsatellite instability (MSI).

Pathologic stage should be reported according to the 8th edition of the Union for International Cancer Control (UICC) classification.

According to the American Society of Colon and Rectal Surgeons (ASCRS) practice parameters, a standard histologic surgical report should include a description of the type of surgery, tumor morphology (size, location and integrity), histologic grade and type, penetration into the wall of the colon and adjacent organs, description of margins, tumor deposits, perineural and lymphovascular invasion, tumor budding, description of lymph nodes, distant organ involvement, and MMR/MSI status. Evidence 4A.[1]

Genomic and chromosomal instability in colon cancer

There are two main types of genomic instability in CRC: MSI and chromosomal instability (CIN). MSI leads to a high rate of point mutations, while CIN refers to an increased rate of accumulation of chromosomal disorders.[15-17]

Microsatellites are very short regions of DNA that are repeated in tandem and that can be located within genes and constitute non-coding regions of the genome. MSI occurs in 15% of CRCs and is the result of the inactivation of the MMR system, either by mutations in these genes or by hypermethylation of the promoter of the MLH1 gene, one of the genes of this system. The main function of the post-replication mismatch repair system is to eliminate base-base pairings and insertion/deletion bonds that arise as a consequence of DNA polymerase dysfunction during DNA synthesis.[16]

Defective MMR facilitates malignant transformation by allowing rapid accumulation of mutations that inactivate genes that perform key functions in the cell. Defective MMR genes, by failing to produce the proteins responsible for correcting nucleotide mismatches during DNA replication, also promote mutations in other genes. But genes that have microsatellites in their own coding sequence are also involved. There is a hereditary form of colorectal cancer, hereditary non-polypoid colorectal cancer (HNPCC) or Lynch syndrome, which accounts for 3 to 5% of all CRC and is the most frequent entity within the hereditary CRC syndrome. In this syndrome, MSI is due to mutations in the MMR genes.

The predisposition to cancer observed not only in HNPCC but also in other cancer syndromes caused by germline mutations in genes regulating DNA fidelity [e.g., Li-Fraumeni syndrome (TP53, CHK2), Nijmegen syndrome (NBS1), Bloom syndrome (BLM), and ataxia telangiectasia (ATR/ATM)] demonstrates that inactivation of mechanisms regulating genomic stability constitutes a primary event in carcinogenesis. MMR-deficient cells display a mutator phenotype in which the spontaneous mutation rate is very high and can be 100- to 1000-fold higher than in normal cells.[17,18]

Virtually all CRCs exhibit either MSI or CIN, suggesting that genomic instability is not only common but also fundamental in the genesis of CRC.

CIN is the most common type of instability in CRC and occurs in approximately 85% of colon tumors. Aneuploidy, characterized by changes in the structure and number of chromosomes, is considered a hallmark of CIN, although more precise information is still lacking.[18]

Evaluation of tumor extension

Before evaluating tumor extension, the macroscopic and microscopic type of the lesion, location, initial resectability, and association with polyps or second tumors should be evaluated. Evidence IA.[1]

The colon should be evaluated with a complete colonoscopy to rule out synchronous tumors, which are present in 4% of patients with Stage I and II. The incidence of synchronous adenomas is 30% to 50%.[1]

Proximal and distal endoscopic tattooing of early tumors should be performed routinely to facilitate their intraoperative localization, particularly during minimally invasive surgery. In patients with obstructive colon cancer, where proximal endoscopic evaluation is impossible, virtual colonoscopy is highly effective (sensitivity 94%) in detecting synchronous tumors or adenomas, which affect the surgical plan in 2% to 21% of patients.[14]

High histological grade and poor cell differentiation have been shown to be predictors of poor outcome and should therefore be taken into consideration before recommending any type of treatment.

The histological diagnosis of malignancy should be confirmed whenever possible before treatment. Methods for diagnosis and preoperative confirmation of malignancy are beyond the scope of this report and their approach could be considered a topic in itself.

The outcome of colon cancer is strongly related to the stage of the disease. Early-stage colon cancer is potentially curable and is associated with excellent OS, unlike what occurs in patients with metastatic disease. Approximately 20% of new colon cancers present synchronous metastases at the time of diagnosis, with the most frequently affected organs being the liver (17%), peritoneum (5%), lung (5%) and lymph nodes (3%).[19]

Preoperative assessment of tumor extent is essential to determine whether resection of the primary tumor alone will be necessary and, if there are distant metastases, whether they will be amenable to resection or systemic therapy.

Computed tomography of the chest, abdomen and pelvis with oral and intravenous contrast is the preferred method for initial staging. It allows for the assessment of the locoregional extension of the tumor and its possible complications (obstruction, perforation, fistula or abscess), as well as distant metastases. However, the sensitivity for peritoneal metastases is relatively low. Evidence IIB.[1,20–23]

Magnetic resonance imaging may replace computed tomography in patients with iodine allergy or renal failure with a glomerular filtration rate less than 30 ml/min. It is also useful for better definition of peritumoral soft tissues

when CT results are inconclusive. Abdominal MRI may also be combined with chest CT for initial staging. Evidence 2A.[1] Fluorodeoxyglucose positron emission tomography (FDG PET/CT), used in selected nonmetastatic cases, has a negative predictive value of 93% for advanced adenomas and 100% for tumors. However, neither NCCN nor ESMO recommend staging with PET/CT. Another option to rule out synchronous lesions is intraoperative colonoscopy, or postoperative colonoscopy in a period close to surgery.[24,25]
For ESMO, PET/CT does not add relevant information in the routine initial evaluation for staging localized colon tumors. It should be reserved for patients who initially present with distant metastases and for decision making in surgical treatment of those with Stage IV. Evidence IIA.[14]
Table 2.1 shows the different studies available for staging colon cancer and their level of evidence, according to ESMO.

Table 2.1. Levels of evidence and grades of recommendation in the staging of colon cancer.

Test	Level of evidence. Grade of recommendation
Complete colonoscopy	I. A
Imaging studies	
Computed tomography	
- Lung	I. B
- Abdomen	I. B
- Pelvis	I. B
Virtual colonoscopy	I. A
Magnetic resonance imaging	II. A
Laboratory	
Cell count	II. A
Coagulation	II. A
Liver function	II. A
Kidney function	II. A
Albumin	III. A
CEA	III. A

CEA: Carcinoembryonic antigen.

Recommendations

- Preoperative evaluation should include a complete physical examination, complete laboratory tests, CEA determination, abdominal, chest, and abdominopelvic CT with oral and intravenous contrast. Evidence III A.
- In the absence of an indication for urgent tumor resection, a complete colonoscopy is recommended to confirm the diagnosis and rule out synchronous tumors. If a complete colonoscopy is not possible, an alternative is to combine a left-sided colonoscopy with a CT-guided colonoscopy. Evidence IA.
- In the event that colonoscopy cannot be performed before the surgical procedure, a complete colonoscopy should be performed between 3 and 6 months after tumor resection. Evidence IVC.

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