



Clinical presentation and the early detection of colorectal cancer

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ABSTRACT

Colorectal cancer represents a major disease burden worldwide being responsible for considerable morbidity and mortality. The symptoms of colorectal cancer depend on tumor localization. The goal in developing molecular markers in the management of colorectal cancer represents the risk stratification in order to identify high-risk individuals, for the early detection of colon precancerous lesions and early staged colorectal cancers. Radical surgery treatment still represents the gold standard in the therapeutically asset in combination with the adjuvant chemoradiotherapy. It has been shown that more detailed postoperative examination of lymph nodes sections improves prognostic factor in colorectal cancer.

Keywords: Colorectal, Cancer, Early Detection, Biomarkers

INTRODUCTION

Colorectal cancer represents a major disease burden worldwide and is responsible for considerable morbidity and mortality. Therefore, the importance of the early detection and accentuation on implementing prevention guidelines in high risk individuals is of extreme value. The majority of these neoplasms arise sporadically due to multiple somatic and genetic instabilities.

Colorectal neoplasms represent a heterogeneous disease with respect to the anatomic location of the tumour, race, ethnicity differences, genetic and dietary interactions. According to Serbian national registry data, the incidence of colorectal cancer is 27.0 for overall population; whereas 33.5 for men and 21.6 amongst women.^{9,23} The most common type is colorectal adenocarcinoma. It has been estimated that 95% of colorectal cancer arises from adenomatous polyps. Histologically there are four types of possible tumor differentiation: well,

moderately, poorly and undifferentiated tumours. In predicting the outcome of this disease, the appropriate staging and lymphohematogeneous status represent the most important factors.

In the TNM staging system (Figure 1), the T describes the local extent of primary tumor at the time of diagnosis, before any treatment. The N symbol describes the status of the regional lymph nodes, and M symbol is for distant metastatic disease, including nonregional lymph nodes. The symbol 'p' refers to the pathological determination of the TNM in contrast to the clinical determination which is represented with 'c'.⁴

GJMEDPH 2015; Vol. 4, issue 4

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Conflict of Interest—none

Funding—none

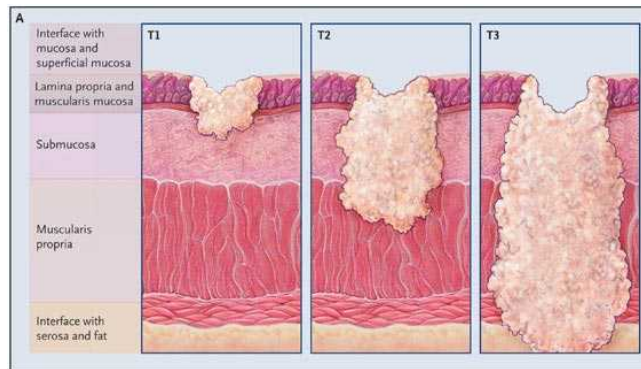


Fig 1: TNM stage of colorectal cancer

CLINICAL PRESENTATION OF COLORECTAL CANCER

The symptoms of colorectal cancer depend on tumor localization (Figure 2). In case of localization of the tumor in caecum and ascending colon the obstruction is usually not present due to relatively fluid stool in this region of colon. But, more often tumors of this region ulcerate so the blood in stool or defect in defecative mechanism is more characteristic. Consequently, in the laboratory findings there is usually evidence of blood loss and/or anaemia which should be triggering alarm in addition with physical examination on the process

in the above mentioned part of the colon. If the tumor is localized in the transverse colon the main symptom is obstruction with postprandial pain in the abdomen, meteorismus and diarrhea. In the worst case, it can presented with ileus and perforation. Carcinoma of the rectosigmoid part of colon presents with tenesmus or pain during defecation, thinner stool diameter and hematochesia.

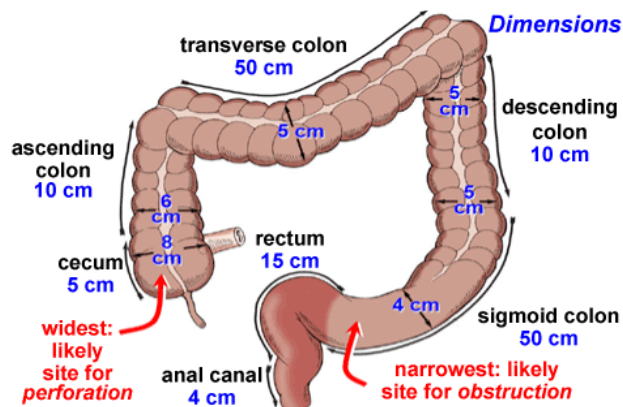


Fig 2: Dimensions of the large intestine linked to obstructive symptoms

COLORECTAL CLINICAL ANATOMY

Anatomic parts of the large intestines are as follow: the cecum, colon proper, rectum and anal canal. A surgical right part of the colon, the right colon consists of the cecum, ascending colon and hepatic

flexure. The left colon consists of the distal transverse colon, splenic flexure, descending and sigmoid colon. Layers of the colon and rectum are: 1) mucosa; 2) sub mucosa; 3) inner circular muscle; 4) outer longitudinal muscle and 5) serosa.

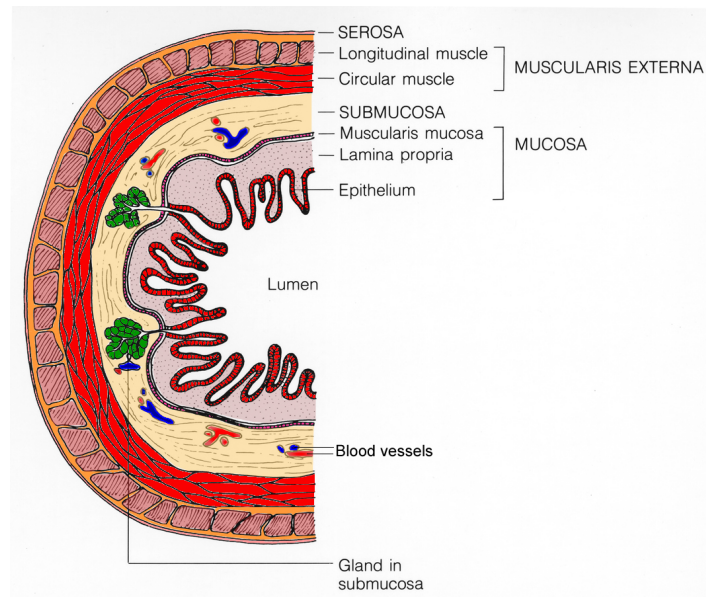


Fig 3: Layers of the colon wall

Generally, the arterial supply to the colon is as follows:

- 1) Superior mesenteric artery branches: a) ileocolic artery supplies blood flow to the terminal ileum and proximal ascending colon; b) right colic artery supplies the ascending colon; c) middle colon artery supplies the transverse colon.
- 2) Inferior mesenteric artery branches: a) left colic artery supplies the descending colon; b) sigmoidal branches supply the sigmoid colon; c) superior rectal artery supplies the proximal rectum. The terminal branches of each artery form anastomoses with the terminal branches of the adjacent artery and communicate via the marginal artery of Drummond (complete in only 15-20 % of people).
- 3) Internal iliac artery branches: a) middle rectal artery; b) internal pudendal artery branch. Inferior rectal artery supplies the distal part of rectum and anal canal.

A rich network of collaterals connects the terminal arterioles of each of these arteries, thus making the rectum relatively resistant to ischemia.

The veins of the colorectal area follow the above mentioned arteries, except for the inferior

mesenteric vein. The inferior mesenteric vein ascends in the retroperitoneal plane over the psoas muscle and continues posteriorly to the pancreas to conjoin the lienalis vein.

The rectum is drained by the superior rectal veins, which join the inferior mesenteric veins. That drainage leads to the portal system. The middle and inferior rectal veins drain into the iliac vein and thus drain into the systemic circulation.

The lymphatic drainage of the colorectal area consists of four lymph node groups: epicolic (beneath the serosa of the wall of the intestine); paracolic (on the marginal artery); intermediate (along the superior and inferior mesenteric artery) and central (at the radix of the superior and inferior mesenteric artery).

In the rectum and anal canal there are two extramural lymphatic plexuses. The first plexus which lies above the dentate line drains to the pelvic nodes. The second, which lies beneath the dentate line, drains to the inguinal nodes.

The sympathetic fibres represent the motoric innervations of the large intestine. These nerves arise from thoracic 6-12 and, lumbar 1-3 and act inhibitory. The parasympathetic fibres (stimulatory) arise from the vagus nerve and sacral 2-4 and they form nervi erigentes. From sacral 3-5 branches arises the innervation to the levator ani muscle. The



inferior rectal branch of the pudendal nerve provides the sensory innervations to the anal canal.

MOLECULAR MARKERS IN THE EARLY DETECTION OF COLORECTAL CANCER

The goal in developing molecular markers in the management of colorectal cancer represents the risk stratification in order to identify high-risk individuals, for the early detection of colon precancerous lesions and early staged colorectal cancers. Nowadays, new biomolecular markers and genes involved in colorectal carcinogenesis are being rapidly discovered.

Colonoscopy still represents the strongest diagnostic tool for colorectal cancer screening. It is also the therapeutic tool which allows the simultaneous removal of any spotted polyps before their transformation into malignant tissue. Colonoscopes measure 100–160 cm in length and are capable of examining the entire colon and terminal ileum.

Besides colonoscopy, in the early detection of this insidious disease, fecal occult blood test (FOBT) is widely used. Endoanal ultrasound is used to evaluate the layers of the anal canal.¹² Internal anal sphincter, external anal sphincter, and puborectalis muscle can be differentiated.

It has been recommended that CEA (carcinoembryonic antigen) levels should be measured prior the surgery as it is helpful in staging and surgical planning. Postoperatively CEA levels should be measured every 3 months in order to stage II and III patients for a minimum period of three years. Also, CEA represents the marker of choice in surveillance of metastatic disease in response to systemic therapy.^{14, 15}

Based on the Jass's molecular classification of colorectal cancer (2007) there are predominantly

five types: CpG island methylator phenotype (CIMP), microsatellite instability (MSI), KRAS, BRAF and methylation status of o-6-methylguanine DNA methyltransferase (MGMT). Recent studies suggest that there are more detailed molecular subgroups of colorectal cancer.¹⁶⁻¹⁹

The above mentioned prognostic markers are still investigated for its relevance and prognostic value in therapeutic approach.

TREATMENT OF COLORECTAL CANCER

Based on the International Union Against Cancer (UICC) / American Joint Committee on Cancer (AJCC) tumor staging system, when diagnosed at the early stage, complete tumor resection (RO) is of vital importance for local tumour control and long term survival.

Radical surgery treatment still represents the gold standard and the only therapeutical option that gives opportunity for healing. In addition to surgery, the adjuvant systemic chemotherapy definitely improves the overall survival in patients with localized colon cancer. Based on this data, it should be recommended in stage III and high-risk stage II individuals. It includes chemoradiotherapy and adjuvant chemotherapy.²⁰

The type of surgical approach depends on tumor stage and the presenting symptoms. In the elective setting there are various colon type surgical procedures depending on the tumor localization. They include: right, extended right, transverse, left, extended left, sigmoid, total and subtotal colectomy. The alternative is laparoscopic approach (Figure 4) which is more technically demanding but better correlates with the faster return of bowel habits, shorter hospital stay, lower percentage of postoperative hernias and site infection rate.



Fig 4: Laparoscopic resection of the colon cancer

For the rectosigmoid tumors the surgical procedures include: anterior, high anterior, low anterior, extended low anterior, abdominoperianal resection and Hartmann's procedure resection.

In an emergency setting the resection is often required because for acute symptoms such as

obstruction, perforation or haemorrhage. The principles of the operative approach is similar like in the elective procedures.

It has been shown that detailed postoperative examination of lymph nodes sections improves prognostic factor in colorectal cancer.²²

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