# COLON CANCER

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## ANATOMY OF THE COLON

The colon is a part of the gastrointestinal tube, which is constituted by the oesophagus, the stomach, the ileum and the colon or large intestine. The colon itself is constituted by different tracts, the caecum, the ascending colon, the transverse colon, the descending colon, the sigmoid colon and the terminal part, the rectum, which communicates with the outer through the anus. The gastrointestinal tract absorbs from the food we eat the nutritional elements (vitamins, minerals, carbohydrates, fats, proteins and water), and holds the residuals until the organisms discharges them, through the anal canal, as faeces.

## THE DISEASE

Colorectal cancer has a high incidence in Western countries, representing the second cause of morbidity for neoplasm in both sexes in Europe as well as in the USA, (9,4% of all tumours in men, 10,1% in women). Colorectal cancer must be regarded as one of the most frequent causes of death in the Italian population (together with rectal cancer, with 19000 deaths and 34000 new cases per year, it is the second cause of death related to tumour after lung cancer, with 30000 deaths). From these pieces of information comes the necessity of a precise program of prevention in order to lessen the incidence of this tumour, mostly considering the high possibility of preventing it in pre-neoplastic benignant and malignant phase, but also considering the possibility of an early diagnose of the disease already developed but not yet spread.

## KNOWN CAUSES

The majority of colorectal cancers develop from the malignant transformation of the so called adenomatous or gland-like “polyps”, small outgrowths of the mucosa, benign itself at least at the beginning, due to the proliferation of the mucosal cells. According to its morphological features, the single polyp can be defined sessile (with a flat base) or peduncolated (attached to the intestinal wall by a stalk). Only adenomatous polyps are at risk for malignant transformation: the so called hyperplastic polyps (characterised by a rapidly proliferating mucosa) and the hamartomatous polyps (also called youth polyps or Peutz-Jeghers polyps) have no malignant potentials. The probability for an adenoma of the colon to evolve into an invasive form of cancer depends on the time it has to grow and start its transformation (dysplasia) and also on the size the polyp reaches in time: the probability of finding neoplastic spots in the polyp is minimal for a size of less than 1 cm, low for a size of 1-2,5 cm, whereas it becomes high for a polyp of more than 2,5 cm. Once transformed into a carcinomatous tissue, the affected mucosa can substitute the entire polyp and infiltrate the visceral wall. It is clear the importance of eliminating all the polyps before they can evolve into malignant lesions, avoiding a neoplasm of the colon.
It is possible, even if not so frequent, for the neoplasm to develop directly from the mucosa without the initial growth as a polyp; it appears then as a nodule or as an ulcer of the mucosa generally fragile and easily bleeding even spontaneously.

**There are many causes which cooperate to determine the disease:**

**-Nutritional factors**: many studies outline how a highly caloric, highly fat and fibres-less diet is associated to an increased frequency of intestinal tumours; on the other hand, a diet rich in fibres (characterised by a high consume of fruit and vegetables), salicylates and magnesium seems to have a protective role.
**-Genetic factors**: some genetically determined diseases are known to promote intestinal tumours: the hereditary adenomatous polyposis (such as Familial Adenomatous Polyposis or FAP, Gardner Syndrome, Turcot Syndrome) and the so called hereditary non polyposis colorectal cancer (HNPCC or Lynch Syndrome). These diseases are passed on by parents who carry specific genetic alterations, which could also be silent (non symptomatic). The probability of passing the altered gene to the children is of 50%, independently from the gender. Also the presence of a relative with colon cancer must lead to the suspect of a genetic disposition to develop such disease and to undergoing the necessary diagnostic exams, in time to discover the benign alterations (the risk of developing colon cancer is 2-3 times higher for first grade relatives of people with cancer or bowel polyps).
**-Non hereditary factors**: age (incidence is 10 times higher after 60 years in comparison to a 40 year old), inflammatory bowel diseases (Ulcerative Colitis for more than 10 years and, according to recent studies, even Crohn's Disease), a past history of colonic polyps or colorectal cancer are important.

## WHICH ARE THE SYMPTOMS

Polyps, benignant precursors of cancer, usually do not present symptoms if they do not reach considerable size to determine bowel obstruction: it is instead frequent the presence of occult blood in stool in healthy patients. The ascertained neoplasm instead determines different symptoms depending on its location: in the left colon, where faeces are more consistent, it will most likely determine obstruction disturbs with altered frequency of stool discharging, pains which are relieved by evacuation of the stools or gas emission, macroscopically evident bleed, loss of weight and asthenia; the progression of the disease can sometimes lead to bowel obstruction. Neoplasms located in the proximal tracts (caecum, ascending colon and transverse colon) reveal mostly with blood loss (anaemia), weight loss and asthenia, whereas obstruction disturbs are less frequent since the faeces in these tract are more liquid. It is not rare the diagnosis of right colon cancer after the finding of an abdominal mass or the finding of hepatic metastasis.

## HOW TO DIAGNOSE

The diagnostic steps must be guided by the evaluation of the emerging signs and symptoms during an accurate clinical examination with a rectal exploration
**clinical examination and clinical history:** body examination to verify general signs of health conditions, including the presence of eventual signs of disease, as the presence of masses or any other manifestation that can seem abnormal. Detailed history of the patient referring to old diseases and treatments undergone and indications of his lifestyle;
**research of occult blood in stool**: this test is based on the fact that malignant neoplasms and polyps bleed more easily than normal mucosa, and that the discovery of occult blood in the faeces leads to the diagnosis in an early phase of the disease. It consists in taking a faeces sample for at least three days, on which it is possible to determine the presence of blood not visible at bare eye. False positive samples are often present and mostly due to other sources of blood loss which, when present, could invalidate the test (gums, nose and mouth mucosa, haemorroids, anal fissures);

**rectal exploration**: wearing a disposable glove, the doctor inserts a lubricated finger in the rectum in search for the presence of any nodule or abnormal areas and ascertain the presence of blood mixed with the faeces or mucus eventually haematic;
**barium enema**: it consists of a series of radiographies of the colon, after accurate toilette of the viscer: barium is used as a radiological solution to obtain a radiographic image of the gastrointestinal tract; introduced in the colon through the anus, it coats the colon wall which is then put in tension by the introduction of air allowing the visualisation of the mucosal surface with opportune rotation of the patient;
**endoscopy**: endoscopy is a direct evaluation of the internal surface performed with sophisticate instruments with a micro-camera on one end which, after a good toilette of the intestine, is introduced through the anus and allows to check through the different tracts of the colon up to the caecum and the terminal ileum. It is so possible to ascertain the presence of polyps, tumours or abnormal areas: if a polyp or an abnormal area is found, the operator can perform a biopsy or remove the lesion and send it to a lab for hystological examination which can confirm the diagnosis;
**endoscopic biopsy**: it consists in taking a tissue sample which will be analysed with a microscope to reveal the presence of neoplastic cells;
**virtual colonoscopy**: it uses the images of a multislice CT (Computed Tomography) to reveal information on the internal structures of the colon. A computer elaborates the images to obtain a detailed representation in order to allow the diagnosis of presence of polyps or other abnormal tissue on the internal wall of the colon. It is an exam that can still present a discrete percentage of false positives for polyps and therefore it often requires to be confirmed by direct colonoscopy;
**tumour markers**: for colorectal cancer the dosage of tumour markers (CEA, Carcino-Embryo Antigen) has no diagnostic aim; its determination remains useful before treatment as a parameter to refer to during the follow-up (control of the therapeutic results).

**Other exams complete the staging of the disease**:

**hepatic ultrasound**: being the liver the first and most likely metastatic site (15-20% of patients have hepatic metastasis at the time of diagnosis), hepatic ultrasound is considered to be essential during the pre-operative evaluation;
**abdominal-pelvic CT**: it is no exam for primary level diagnosis whereas it is sometimes useful for a pre-operative staging in terms of local extension of the lesion and presence of distant metastasis;
**lung radiography**: it is a fundamental exam for the pre-surgical evaluation;
**magnetic resonance (MR)**: differently from CT, it is an exam which does not use radiation nor intravenous radiological solution, but uses a strong magnetic field: the images can be useful to the surgeon to better evaluate the relation between the disease and the near structures in the prospective of surgical treatment. In some cases can be used the i.v. injection of a substance (Gadolinium) to improve the quality of the image: the use of gadolinium is extremely safe and induces a change in the magnetic properties of water in different tissues, improving the visibility of tumors and diseases of Central Nervous System.
**PET scan (Positron Emission Tomography)**: using low doses of radioactive glucose, it is an exam which allows to measure the activity of the cells in the different parts of the body; metabolism in the areas of neoplastic tissue is generally more active than in the near areas, resulting evident at the exam; frequently also adenomatous polyps of discrete size but not yet cancerized are evident;
**PET-CT:** Integrated positron emission tomography (PET) and computed tomography (CT) is a new imaging modality offering anatomic and metabolic informations. The fusion of PET and CT images allows an accurate localization of the lesions, improves the staging of cancer through a

better anatomic localization and characterization of lesions and is superior to CT alone and PET alone. This technique is a useful tool to differentiate pathologic from physiologic FDG uptake (PET) and is often used in the surveillance of recurrent colorectal cancers after curative resections .

**bone scintigraphy**: it has very selected indications (staging of clinically advanced disease, bone located pain); it must not be used as a routine before surgery nor during follow-up;

**genetic tests**: the available genetic tests allow the definition of the genetic base of the disease, in particular the identification of the family members at risk. Therefore they should be used: to confirm a syndrome in an individual or in a family in the suspect of hereditary syndrome for colorectal cancer drawn from clinical findings, to outline the different genetic mutations in the individuals of a family known as carrier of an hereditary syndrome, to determine which individual in particular (in a family with an hereditary syndrome and a known genetic mutation) is the carrier of the mutated gene.

## THERAPY

Benign polyps of the bowel are removed during endoscopy. Removal must be complete to allow the Pathologist to give a precise diagnosis of radical treatment; in case of a stage A according to Dukes, removal is considered radical when borders are certainly free from infiltration in all the sections correctly directed. In case of a non certain eradication the Patient must undergo conventional surgery.

The therapy for colorectal cancer is essentially surgical: it consists in large removal of the intestinal tract where the tumour is located and removal of the lymph nodes of the same district (lymph nodes located on the lymphatic drainage system through which a tumour cell could “wonder” and reach a distant area passing by the different lymphatic stations). The intestinal canalization is then rebuild by means of a suture between the two visceral ends (anastomosis), which can be manually sutured or jointed with staplers which use metal clips.

In particular situations a local excision can be performed, in case of a tumour in a very early stage (usually cancerized polyps): an endoscopic polypectomy is performed (polyp removal with diathermic loop) or, if endoscopy cannot be performed because of the location and size of the lesion, a partial surgical resection of the visceral wall containing the tumour can be carried out, evaluating the stage of the disease with intra-operatory histology.

In case of advanced disease, when the tumour infiltration of the near tissues does not allow its removal, an intestinal by-pass can be performed suturing the tract above the tumour with the tract following the tumour in order to avoid intestinal obstruction. In particularly severe conditions a colonostomy or ileostomy could be necessary (the jointing of the intestinal tract, colon or ileum, to the abdominal wall for the discharge of the faeces, which are collected in a reservoir applied to the abdomen). Colonostomy or ileostomy could be necessary also to protect intestinal sutures particularly at risk for failing; this procedure could be performed even after surgery in case of post-operative failing.

In case of distant metastasis (for example liver metastasis) it is possible during surgery to evaluate these lesions with hepatic ultrasound and specific biopsy and, after an histological verification, proceed to remove the lesions. In some cases the presence of multiple hepatic nodules compromises their removal, therefore it could be possible to use radiofrequency ablation: this consists in the use of an needle which, under ultrasound control, is introduced in the centre of the lesion which is then “heated” by a radiofrequency generator, determining the necrosis of the surrounding tumour tissue.

## POST - OPERATIVE TREATMENT

After surgery the Oncologist could believe necessary to carry out a post-operative chemotherapy or a radiotherapy to destroy any remnant tumour cell. The post-operative treatment performed to increase the probability of healing is known as “adjuvant”.

### Chemotherapy

Chemotherapy is the therapeutic option which destroys tumour cells by means of drugs, which can be taken per os as pills, or injected intravenous or intramuscle. In these cases, chemotherapy is defined as a “systemic treatment”, because the drug enters the blood circulation, spreads into the organism and can reach and destroy the tumour cells that have disseminated.
Chemo-embolization of the hepatic artery can be used to treat the tumour that has reached the liver. It consists in guiding a catheter through the arterial branch up to the lesion and in introducing the drugs directly into the lesion, sparing the other body districts from the toxic drug effects.

### Radiotherapy

Radiotherapy consists in applying high frequency radiations to destroy the tumour cells and lessen the tumour size. Two types of radiotherapy exist: external radiotherapy: radiations can be conveyed by a machine extern to the body and directed on the part affected by the tumour; or internal/intra-cavity radiotherapy: the radioactive substance (isotope) can be directly introduced in the lesion or nearby. The choice of radiotherapy depends on the type and stage of the tumour.

### Biologic therapy

Biologic therapy aims to stimulate natural defences of the organism to fight the tumour through the administration of substances produced by the organism itself or synthetic substances (cetuximab Erbitux®, bevacizumab Avastin®). The function of these monoclonal antibodies is to bind the growth factor receptors of the tumour cells (Epidermal Growth Factors Receptors), avoiding their growth and multiplication.

## CONCLUSIONS AND ADVISES: EARLY DIAGNOSIS AND PREVENTION

Without any doubt colorectal cancer offers the possibility for early action and elimination of the benign precursors of the disease; yet polyps, most of all small ones, are totally asymptomatic, therefore it is advisable not to wait for symptoms to undergo diagnostic exams.
First of all, it is necessary to consult the family doctor, to outline risk factors or a family history of disease.
From 45 years onwards, a test for occult stool in blood can reveal small traces which could be the signal of a problem (watch out: not necessarily a tumour) to study better.
In cases of risk (familiarity, symptoms, positive occult blood in stool) **colonoscopy** is mandatory. For many it is an exam which determines greater worries and apprehensions than necessary, but it remains an essential instrument to prevent, diagnose and keep under control colorectal cancer. Besides the diagnosis, it allows individuation and removal of pre-cancer lesions as polyps during endoscopy, interrupting the sequence “polyp-cancer”. Diagnosis and therapy in one, that can prevent 80% of neoplasm.
Lifestyle has been object of numerous studies, underlining simple behaviour rules that seem to influence the development of a colorectal tumour: reduce the uptake of fat and alcohol, increasing the uptake of fibres and fruit; increase the uptake of magnesium (pasta, nuts) and vitamin C; use antioxidants (salicylates); maintain physical activity.

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