

Recent Achievements in Colorectal Adenocarcinoma's Diagnosis and Treatment. Surgical Point of View

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INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed cancer in both men and women in the US and it is the third cause of death throw cancer. Precancerous growths such as adenomatous polyps can be detected throw screening test, even if not all the polyps will become cancerous. By screening the patients considered at risk (familial syndromes) cancerous polyps can be detected at an early stage when the treatment is more likely to be curative.

Despite the improvements in the field of modern medicine and screening tests, 20% of patients with colorectal carcinomas have metastases at the moment of diagnosis. Depending of the stage of the neoplastic disease and applied treatment, the survival rate at 5 years is between 12% and 90% [1]. Colorectal cancer develops slowly from precancerous lesions so; early detection can

reduce the mortality. The peak incidence for colorectal cancer was found to be between ages of 61 and 70. If colorectal cancer is found at young patients we have to take in consideration pre-existing polyposis syndrome [2].

According to the GLOBOCAN there were 1.360.602 new cases of colorectal cancer worldwide and 447.136 new cases of colorectal cancer in Europe. Mortality is high, 693.933 deaths from colorectal cancer worldwide been estimated in 2012 and 214.866 deaths in Europe [3].

DIAGNOSTIC OF COLORECTAL ADENOCARCINOMAS

Early cases of colorectal adenocarcinomas could be asymptomatic for a long period. Patients at high risk (familial adenomatous polyposis, patients with anemic syndrome and positive test for occult digestive bleeding) should perform a colonoscopy, the gold standard for investigation of symptoms suggestive for colorectal cancer.

Patients with *advanced colorectal cancer* can present signs of malignancy impregnation such as weight loss, asthenia in addition to the symptoms given by the local presence of the tumor: abdominal pain, constipation or diarrhea. Furthermore, there are an increasing number of patients who present themselves to the doctor with digestive complications of the tumor such as: obstruction of the bowel, perforation or digestive bleeding.

There are some *serum markers* (carcinoembryonic antigen - CEA) which have been associated with colorectal cancer. Unfortunately, all these markers have a low probability to detect an early stage cancer. Furthermore, CEA specificity is limited, high levels of CEA being detected in patients with gastritis, peptic ulcer disease, diverticulitis, liver disease, diabetes. However, CEA levels are important after surgery, for the follow up of the patients with treated colorectal cancer [4-6].

Once the patient is diagnosed with colorectal cancer, further investigations will assist in *staging the disease* which is absolutely necessary for a proper management. In addition to the colonoscopy who can locate the tumor and establish if there are synchronous lesions, Computed Tomography (**CT**) will evaluate tumor relations with neighboring structures and the presence of distant metastases. For staging rectal tumors, endorectal ultrasound or Magnetic Resonance Imagings (**MRI**) are indicated [7]. Virtual colonoscopy (CT colography) provides a computer-simulated endoluminal perspective of the air-filled distended colon.

The AJCC (American Joint Committee on Cancer) staging system is used for the colorectal cancer [8]. The stages are defined by TNM (tumor-nodes-metastasis) score. The cancer is often staged twice: first before the treatment and then after the treatment. The most recent 2010 TNM staging classification includes a number of changes compared with the older 2002 classification [4-6].

Nowadays, it is taken in consideration that colorectal cancer is caused by a cascade of *genetic mutations*. Mutations and gene amplifications seem to be involved in gradual progression from

normal epithelial mucosa to adenoma and then to carcinoma. In the field of colorectal cancer diagnosis there have been detected some forms of genomic instability including Chromosomal Instability (**CIN**), Microsatellite Instability (**MSI**) and epigenetic silencing.

Chromosomal instability seems to be the most common genomic instability and it is inducing carcinoma through the loss or mutation of tumor suppressor genes such as APC, TP53 and through activation of oncogenes such as KRAS. CIN tumor marker is RAS family [9,10].

Some markers tests should be performed for patients with colorectal cancer. Patients who are being considered for anti-*EGFR* therapy should perform *RAS* mutational testing of colorectal carcinoma tissue. This analysis must include *KRAS* and *NRAS* codons 12, 13 of exon 2, 59, 61 of exon 3 and 117 and 146 of exon 4 [11,12]. *BRAF* V600 mutational analysis should be done in conjunction with deficient mismatch repair (dMMR)/Microsatellite Instability (**MSI**) testing for prognostic stratification [11,12]. dMMR/MSI testing must be performed in all colorectal cancers for prognostic stratification and identification of Lynch syndrome patients (*BRAF* mutation testing is not needed for Lynch syndrome if there is no MSI-H with loss of *MLH1*).

General indications for genetic testing have been proposed by the American Society of Clinical Oncology. First, patients who have a personal or family history of cancer should perform genetic testing. The second indication is the existence of genetic test whose results can be adequately interpreted. The third indication is that the test results will influence the treatment of the patient [11].

An individual with an inherited colon cancer syndrome should be recognized by [11]:

- Colon cancer diagnosed under the age of 45;
- Adenomas >2 cm diagnosed under the age of 40;
- Multiple colonic malignancies present, either synchronous or metachronous;
- Multiple primary cancers diagnosed, either colonic or extracolonic;
- 10 or more adenomas present over a lifetime, along with a family history of colon cancer;
- Multiple, closely related family members who have been diagnosed with colon cancer;
- Colon cancer in more than one generation of the individual's family;
- Clustering of extracolonic cancers in family members (especially gastric, breast, thyroid, and uterine).

The inherited colon cancer syndrome is classified by polyp histopathology. There are two types of disorders: ones that determine adenomatous histopathology and the other ones which determine hamartomatous polyps. Familial Adenomatous Polyposis (**FAP**), Gardner's syndrome, Turcot syndrome, MUTYH-Associated Polyposis (**MAP**) and Hereditary Nonpolyposis Colorectal Cancer (**HNPCC**) are syndromes characterized by the presence of adenomatous polyp while

Peutz-Jeghers, juvenile polyposis syndrome, Cowden disease and Bannayan-Ruvalcaba-Riley are syndromes characterized by hamartomatous polyps on the digestive tract. Genetic testing should be done when a patient has the clinical criteria for any of these syndromes [9].

TREATMENT OF COLORECTAL CANCER

Treatment of colorectal cancer is usually surgical based, depending on the stage of the cancer and, it may be combined with chemotherapy, radiotherapy and biological treatments [7,13]. The treatment for colorectal cancer depends on which part of the bowel is interested and how far the cancer has spread. If the cancer is detected early enough, the treatment can be done by *endoscopic approach*. When the endoscopic treatment is taken into consideration, some factors are mandatory: tumor size, histological type and invasion depth. Based on the guidelines, lesions with the following characteristics can be treated endoscopically: adenoma, mucosal carcinoma or submucosa carcinoma without massive invasion. [7,13]. Furthermore, the indications for colorectal Endoscopic Submucosal Dissection (**ESD**) are as follows: large size in which en bloc resection using snare endoscopic mucosal resection is difficult; mucosal lesions with fibrosis caused by biopsy, peristalsis of the lesions or chronic inflammation; local residual early cancer after endoscopic resection [10,13].

It is important to underline that even after complete endoscopic resection of submucosal carcinoma, some patients requires surgery because of the histopatological examination (microscopically positive resection specimen).

Surgery is the main therapeutic attitude, curative treatment being the goal. During the surgery, the tumor, adjacent lymph nodes and distant metastasis are removed and the continuity of the digestive tract is restored.

After a long time of debates and controversy, now it is established that laparoscopic colon surgery for cancer is the gold standard treatment [13,14]. Laparoscopic colon and rectal surgery in the hands of well-trained surgeons can be performed safely with short hospital stay, low analgesic requirements and acceptable complication rates [15].

The most important benefits of laparoscopic surgery include less pain, quicker return of bowel function, faster recovery and decreased wound infection rate. It has been proven that there are no differences in surgical resection margins or the number of lymph nodes harvested between laparoscopic and open approach. Also, the recovery of pulmonary function has been shown to be quicker after laparoscopic colectomy [16].

Regarding the long-term outcomes, the overall survival rate seems to be similar for patients who underwent laparoscopic surgery and open surgery for colorectal carcinoma [10,17].

The indications for performing a laparoscopic colon resection are similar with those of an open surgery. Neither obesity nor the presence of previous abdominal surgical incision is absolute contraindications; they just increase the risk of conversion to open surgery. The main

contraindications for laparoscopic approach in colorectal cancer include intestinal obstruction, cancer invasive into adjacent organs and pregnancy. Intestinal obstruction determines the small bowel to distend, reducing the ability to obtain an efficient pneumoperitoneum and sufficient intra abdominal space. Another contraindication is large masses (over 8 cm) which tend to be difficult to manipulate and often hide the correct anatomical planes [17].

Laparoscopic surgery for colorectal cancer should be performed only by experienced surgeons due to risks such as inadequacy of oncologic resection and perforation of the tumor. Also complications such as an stomotic leak, autonomic nerve damage and wound complications are common for both laparoscopic and open approach. There are some characteristic complications for laparoscopic colectomy such as “off screen injuries” which occur when the instruments are not visible on the screen (when they are introduced to the abdominal cavity or when the hot cautery is moved out of the screen view) and will usually produce small bowel injury. Also, the small bowel can be damaged when the bowel is moved from the operative field with graspers [18].

Nowadays, the standard treatment for rectal cancer consists in surgical removal of the rectum together with the surrounding fat tissue (mesorectum): Total Mesorectal Excision (**TME**) [7]. This procedure can be done by laparoscopic or by classic approach (laparotomy). As an alternative surgery, transanal TME is also described in the literature. Currently, this Natural Orifice Transluminal Endoscopic Surgery (**NOTES**) remains as an experimental technique due to the concerns over the operative platform, accidental organ injury and viscerotomy closure. The procedure involves creating a viscerotomy distal to an endoluminal purse-string suture using a transanal endoscope. After that, a total mesorectal excision can be performed with the coloanal anastomosis [19-21].

Transanal TME is a new procedure which can solve some difficulties during the pelvic dissection, particularly in obese, male patients with a bulky mesorectum and narrow pelvis. This type of surgery can be performed “purely” or as a “hybrid” procedure when associated with laparoscopic assistance. Regarding the oncological results, the follow up is too short for now, but short outcome results are encouraging for this approach. The most important complications cited are the urethral injury, pneumatosis of the small bowel mesentery, intraoperative bowel perforation [17].

Next level of treatment refers to *Multivisceral Resections* (**MVR**), this type of surgery being indicated for patients with locally advanced neoplasm, with invasion in neighbor organs. Not all the patients can benefit of this kind of treatment because it is associated with a high rate of morbidity and mortality. Many surgeons are reluctant to practice this treatment due to the technical complexity of these radical operations, despite favorable results remotely communicate by the literature: 36%-46% overall survival [22,23].

Only 10% of patients with colorectal carcinomas benefits of MVR. The most frequently resected organs are: the bladder, internal genitals organs, abdominal wall and the diaphragm. In colon cancer, the most frequently involved resection is those of small intestine and abdominal wall. By principle, the recommended approach is laparotomy even if laparoscopic approach seems to be feasible while the oncologic principles are respected. Laparoscopic technique is accompanied by a high rate of conversion to open approach.

MVR are contraindicated if the patients are diagnosed with visceral metastatic disease. Exception is only for peritoneal carcinomatosis when the MVR are associated with hyperthermic *intraperitoneal chemotherapy (HIPEC)*. This type of surgery should respect the oncological principles, but because of the high rate of complications patients must be carefully selected. Adequate lymphadenectomy is mandatory and oncological resection should involve complete removal of the mesocolon and thus removed all lymph node stations responsible for lymphatic drainage of the body: epicolic stations, paracolic and intermediates. After the removal of tumor block, the surgery continues with the reconstruction time: digestive anastomosis or gastrointestinal stoma, repair of bladder and ureter (if resected) [24-26].

The most frequent complication after MVR is wound infection, followed by intestinal obstruction, intraperitoneal abscess, anastomotic leak, enteral fistula, intraperitoneal hemorrhage and urinary fistula [27, 28].

The 5-year survival of patients with colorectal cancer stage T3 or T4 who benefit of multivisceral resection is between 30% and 77%, with lower survival rates for rectal tumors. The most important factors for prognosis are the age and the presence of lymph node metastases. The relative 5-year survival is significantly higher in tumors T3-T4aN0 (79.6%) compared with tumors invading or adherent to neighboring organs (58,4%) [29-34].

Tumoral Cytoreduction (**CR**) represents the surgical removal of macroscopic tumors (Figure 1). At the end of the surgery the team quantify the degree of cytoreductive surgery's success by calculating the score of "completeness of cytoreduction" (CC). Thus, we are talking of CC-0 in situations where after surgery there are no longer visible tumoral tissues (macroscopic). Score CC-1 is set when in the peritoneal cavity nodules <2.5 mm are remaining, still considered reactive to HIPEC. CC-3 score is established in cases with tumors > 2.5 cm or when in the abdomen and pelvis is a confluence of unresectable tumor [29-34].

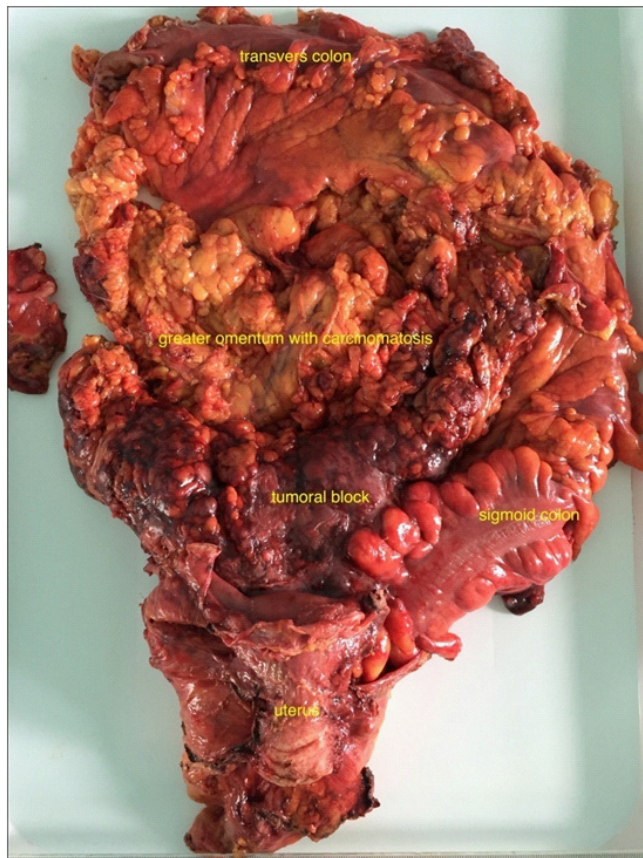


Figure 1: Multivisceral resection: “en block” resection of the sigmoid colon (primary adenocarcinoma) together with the rectum, uterus, greater omentum and transverse colon (invaded by the neoplastic process) (from the personal archive of the authors).

For colorectal cancer and peritoneal carcinomatosis the only way to ensure optimal results in terms of survival is to obtain a CC-0 score. This score is the main prognostic factor [29-34].

Intraperitoneal chemotherapy means that the peritoneal cavity is washed with cytotoxic substances (Figure 2). The most important advantage of intraperitoneal chemotherapy is that the systemic toxicity is reduced so exposure can be longer and higher doses of chemotherapy agents can be used. The chemotherapies used intraperitoneal for colorectal carcinomas are Mitomycin C or Oxaliplatin. Regarding the temperature for HIPEC, it has been shown that at a temperature more than 41°C, the chemotherapy drugs have selective toxicity on the tumor cells. Mechanism of action consists in denaturation of proteins, inhibition of oxidative metabolism, increase of pH, activation of apoptosis and lysosomal activation [35-37].

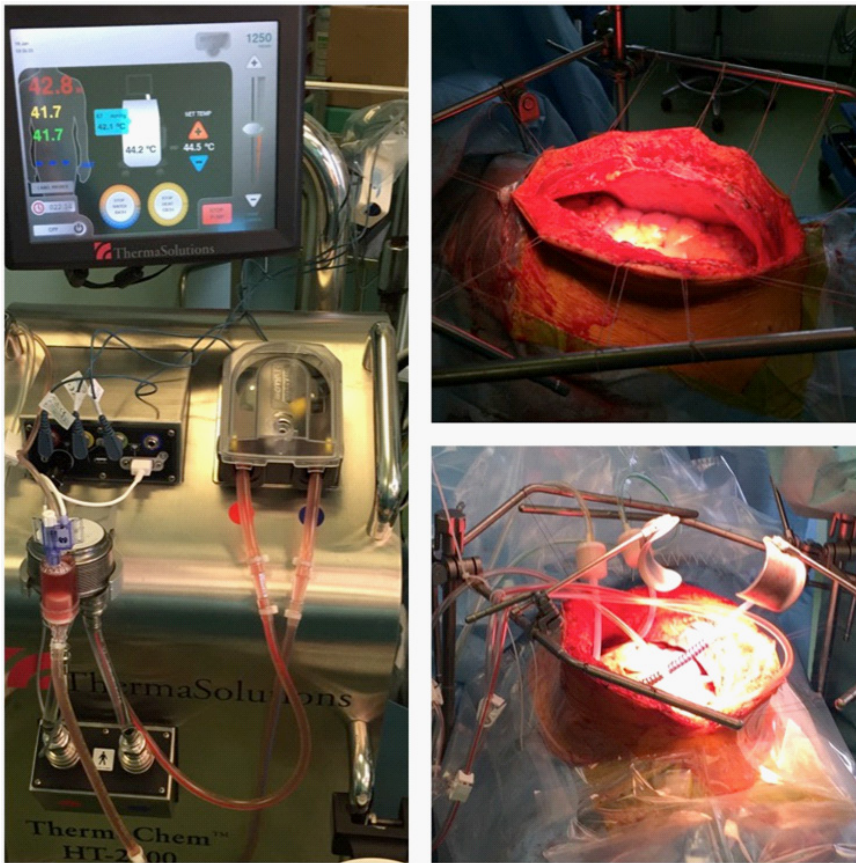


Figure 2: Intraoperative Hiperthermic Chemotherapy (HIPEC). Hiperthermia device, by Therma Solutions (left). Abdominal cavity prepared for HIPEC (right) (from the personal archive of the authors).

Selection of patients who may benefit from this treatment is essential. Diagnostic algorithm required for patients that are candidates for CR and HIPEC will include: medical history, clinical examination, carcinoembryonic antigen (CEA) (pathology non-mucinous), colonoscopy, complete thoraco-abdomino-pelvic scans (CT,PET-CT), biopsy (histopathological confirmation of the disease). Candidates for CR and HIPEC should not present major comorbidities and before surgery it is mandatory to know if the patient has any metastatic diseases, because extraperitoneal neoplastic dissemination diagnosed by CT are a contraindication for the procedure. It is considered that if the carcinomatosis index is more than 20 the procedure should not be done except for the appendicular pseudomixoma [35-37].

Regarding the histopathological exam, it must be proven by biopsy before the surgery. The best results are reported for moderately and well-differentiated adenocarcinoma. An absolute contraindication for this procedure are the presence of extra abdominal neoplasia or visceral/ lymph nodes metastasis (more than 3 liver metastasis) [35, 37].

In the case of colorectal cancer, reports in the literature indicate that CR followed by HIPEC may lead to an increase of median survival up to 62 months with a 5-year survival between 17-51% [35,37]. Without this procedure, when the treatment consists only in systemic chemotherapy, the median survival does not exceed 15 months [35].

Special situation implies patients diagnosed with liver metastases from colo-rectal origin. They can be synchronous, observed in the time of primary tumor diagnosis (20-30%) and metachronous, occurring at an interval of time after resection of the primary tumor (40-50%) [38-40]. Radical surgical resection represents the treatment of liver metastases. Currently, guided liver resections conducted according to international guidelines [41] represent the optimal technical approach with the best long outcome [42]. When this is not possible, limited resection or ablation of 'in situ' with radiofrequency or microwave may represent viable solutions [43,44]. Depending on the surgeon's preference, biological state of the patient and the quality of liver parenchyma, synchronous liver metastases detected simultaneously with the primary colon or rectum tumor can be resected at the same time with the colorectal adenocarcinoma or can be approached afterwards at 2-3 months from the main primary tumor resection [13,14,45]. In experienced, high volume centers, chemotherapy by direct infusion into the hepatic artery can be taken in account, as adjunctive therapy to systemic administration of cytostatic agents [13,14]. Oncological treatment, chemo-radiotherapy can be discussed in confront with the location of the primary tumor and the possibility of metastatic tumor resection, neoadjuvant or adjuvant indication given as appropriate [7,13]. Accompanied by chemotherapy, radical surgical treatment of liver metastases, with resection margins free of neoplastic disease (R0) can lead to 50% overall survival at 5 years [46-49].

For patients with multiple metastases, disseminated in both lobes and complex relationships with important vascular structures for which the standard resections mentioned above are not indicated, there are authors who have described new extended hepatic resections techniques, guided by ultrasound and completed with liver intraparenchymal dissection [50-52] his technique, called the authors "conservative but radical surgery " widens the practical indication of liver resections for patients mentioned above and also for those with cirrhotic liver parenchyma, for which extended an atomical resections would not be possible [53].

The presence of lung metastases, if resectable, is not a contraindication for radical surgery. First it is indicated to resect the primary tumor followed by lung and liver metastases, neoadjuvant or adjuvant treatment being integrated into the therapeutic management [7,13]. Patients with synchronous hepatic and pulmonary metastases, which benefit from hepatic and lung resections will have a survival rate at 5 years of 30% [54,55].

The role of *systemic chemotherapy* remains particularly important, contributing substantially to the completion of therapy, neoadjuvant or adjuvant by nature, depending on each case. Palliative chemotherapy is used when colorectal cancer is advanced and has already spread

to different parts of the body. In this situation, surgery cannot eliminate the cancer. Adjuvant chemotherapy is an oncological treatment given after the tumor is surgically removed. The surgery may not eliminate all the cancer cells, so the adjuvant chemotherapy treatment has the role to destroy the remnant tumor cells such as cells that may have metastasized or spread to the liver. Neoadjuvant chemotherapy is the oncological treatment which is given before the surgery. The main purpose of this type of treatment is to shrink the tumor so the surgeon can remove it completely during the surgery. The mostly used chemotherapy drug is 5-Fluorouracil (5-FU), already in use for many years. Nowadays, 5-FU is used in combination with folinic acid (leucovorin), for more efficiency. Xeloda is a pill based of 5-FU used for colorectal cancer that has spread to other organs. Also, Xeloda is used as adjuvant or neoadjuvant therapy with radiation therapy, to increase the effect of radiation. In the last period, new chemotherapy drugs are used for the treatment of colorectal cancer that has spread. Some of this is Vectibix, Erbitux, Avastin and Afibercept. All of these chemotherapy drugs are given along with 5-FU. Regorafenib is also a new drug used for the oncologic treatment of colorectal cancer which should be taken if the other drugs are not effective. Chemotherapy drugs have a lot of side effects because their mechanism is to kill the dividing cancer cell; unfortunately, they also kill the healthy cells. The most common side effects of chemotherapy are: nausea and vomiting, loss of appetite, hair loss, mouth sores, rash on the hands and feet, diarrhea, higher risk of infection (by immunosuppression), bleeding from minor injuries and anemia. Chemotherapy is not recommended for stage I of colon cancer and it is used as palliative treatment for patients with colorectal cancer stage IV [13].

NEW PERSPECTIVES FOR COLORECTAL CANCER DIAGNOSTIC AND TREATMENT

Nowadays, as medicine evolves, researchers are trying to improve the accuracy of colonoscopy and to detect colorectal cancer even earlier than is currently possible.

As we know, definitive staging of colorectal cancer is based on the histopathological examination of lymph nodes and the intestinal piece of resection. Discovering and improving new methods of diagnosis and staging would lead for more precisely surgical attitude in accordance with neoplastic disease. Nanotechnology has proven to be useful in the diagnosis and treatment of colorectal adenocarcinomas. Early diagnosis could be possible by using nanotechnology to discover precancerous or cancerous cells, at molecular levels, before a visible neoplastic growth has formed. In the near future, with the advance of nanotechnology it will be also possible to deliver chemotherapeutic drugs directly to the cancerous cells, overtaking the problems of resistance to chemotherapeutic agents and their adverse effects [56,57].

Regarding the MRI, widely used for colorectal cancer diagnosis and staging, nanoparticles may contribute to a significant improvement in quality of the image and diagnostic accuracy by improving the sensitivity and specificity [2]. Using imagistic techniques based on fluorescence detection could be the solution to detect lymph node metastasis, to do the mapping of peritoneal carcinomatosis and to determine the stage of “in situ” tumors [1,58,59].

Moreover, recent studies in the literature indicate that using nanoparticles in combination with cytostatic agents used in HIPEC would increase tumor penetration and apoptotic effect [1,60]. Other studies have shown the possibility of scheduled release of cytostatic agents (cisplatin, doxorubicin) using the physical properties of nanoparticles and their behavior under the action of hyperthermia and of ultrasound [1].

As mentioned above, nanotechnology has shown the potential and applicability in the diagnosis and treatment of cancer. Research in this area is focused on implementing nanotechnology in this sub domain, colorectal cancer representing one of the most accessible experimental models for the study of neoplasia [61]. *In-vitro* and *in-vivo* experimental models, although they are widely used, have limitations related to not being able to reproduce the same conditions as in humans [62]. That is why *ex-vivo* models are particularly important in research, providing close conditions to natural ones [63]. In this field, there are only a few such models, these being done under hypothermia or normothermia conditions.[63, 64] (Figure 3).

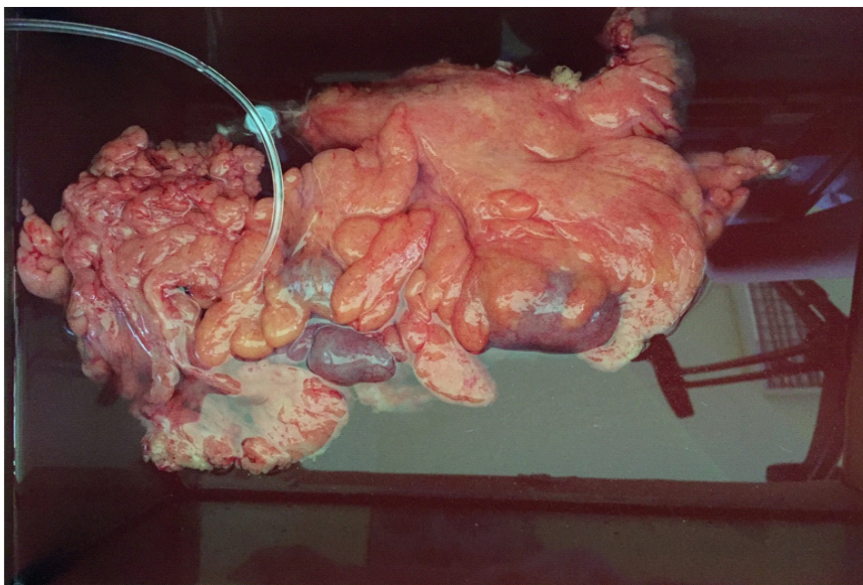


Figure 3: “Ex vivo” experimental model of right colon with adenocarcinoma. Viability was preserved by continuous perfusion of the ileo-colic vascular pedicle (from the personal archive of the authors).

The development of this field of research together with the progresses of the minimal invasive surgery could lead to an earlier diagnosis followed by a radical treatment, all of this translated in improved survival and quality of life.

However, for patients diagnosed in advanced stages, with metastatic or locally advanced, the development of new chemotherapeutic compounds and standardization of the HIPEC techniques, along with aggressive treatment of hepatic and pulmonary metastases could offer a real chance of survival.

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