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## Colorectal Carcinoma in Children and Adolescents

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### A. Introduction

Although colorectal carcinoma (CRC) is one of the most common malignant tumors in adults, it is extremely uncommon in children and adolescents. CRC is a malignant epithelial tumor arising from the glandular epithelium of the intestinal mucosa. According to a recent publication that described a search of the Survival Epidemiology and End Result (SEER) public access database, less than 200 CRC patients younger than 19 years of age were reported from 1973 to 2006.<sup>1</sup>

Therefore, the calculated age-adjusted incidence rate is 802 per million. Because CRC is so uncommon in young people, most pediatric oncologists will see a few cases in their lifetime. However, the management of these cases poses a significant challenge. Several features differentiate CRC in young people from that which occurs in adults. Adults have a higher prevalence of left side tumors, while up to 60% of the tumors in the pediatric population arise on the right side.<sup>1,2</sup> In addition, genetic predisposition plays an important role in the pathogenesis of these tumors in children and should always be considered when evaluating a child with a possible epithelial gastrointestinal (GI) tumor.<sup>2</sup> On the other hand, adults usually present lifestyle-related risk factors such as smoking and poor dietary habits, which are seen less frequently in children and adolescents.

Hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) are the most important cancer predisposition syndromes associated with CRC. HNPCC and FAP are inherited in an autosomal dominant fashion and account for approximately 2 and 0.1–1% of all adult cases of CRC, respectively. Other polyposis syndromes include the Peutz-Jeghers syndrome and juvenile polyposis coli.

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## A. References

<sup>1</sup>Sultan I, Rodriguez-Galindo C, El-Taani H, et al. Distinct features of colorectal cancer in children and adolescents: a population-based study of 159 cases. *Cancer*. 2010. 1;116(3):758-65.

<sup>2</sup>Saab R, Furman WL. Epidemiology and management options for colorectal cancer in children. *Paediatr Drugs*. 2008;10(3):177-92.

## B. Familial Adenomatous Polyposis

FAP is generally caused by germline inactivating mutations in the adenomatous polyposis coli gene (APC). APC is a tumor suppressor gene and is a member of the WNT pathway located at 5q21.<sup>1</sup> FAP is a dominantly inherited syndrome affecting 1 in 7000 individuals with high penetrance; affected patients have a nearly 100% chance of developing CRC at an early age. Affected patients may present hundreds to thousands of precancerous colonic polyps (adenomas). Children with this mutation should undergo frequent colonoscopy screening from age 10 to age 14. Ideally, annual sigmoidoscopy should start by the age of 10, and prophylactic colectomy should be considered at age 15 or as soon as polyps are identified. Prophylactic total colectomy (extended to the rectum in some instances) is the recommended surgical procedure. Patients with FAP are also susceptible to extracolonic malignancies such as hepatoblastoma and thyroid malignancies. Two clinical variants of FAP, which have the same risk of progression to CRC, and extraintestinal tumors have been clinically identified. Gardner syndrome, one of the clinical variants of FAP, also presents with osteomas, desmoid tumors, epidermoid cysts, fibromas, and congenital hypertrophy of the retinal pigment epithelium. The other FAP variant, Turcot syndrome, involves multiple brain tumors (medulloblastoma, glioma, and ependymoma) and usually occurs in pediatric patients in conjunction with FAP.<sup>1-3</sup>

Mutations on chromosome 1p33-34 involving the *MUTYH* gene (OMIM n. 608456) are associated with a relatively milder form of polyposis termed *MUTYH*-associated polyposis (MAP). These mutations may be present in 10–30% of patients without a mutation in *APC*; *MUTYH* mutations are important biomarkers that are useful for identifying FAP patients, especially those with an attenuated phenotype. All patients, including those with attenuated phenotypes and those with classical FAP, need strict surveillance.

In fact, many authors have even considered recommending upper gastrointestinal (GI) tract surveillance because some reports have identified cases of upper GI adenomas/polyps, although these usually occur in the adult years.<sup>4</sup>

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## B. References

<sup>1</sup>Saab R, Furman WL. Epidemiology and management options for colorectal cancer in children. *Paediatr Drugs*. 2008;10(3):177-92.

<sup>2</sup>Vasen HF, Moslein G, Alonso A, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut*. 2008;57(5):704-13.

<sup>3</sup>Signoroni S, Vitellaro M, Sala P, Bertario L. Biomarkers in familial adenomatous polyposis: role and significance. *Front Biosci (Schol Ed)*. 2010;2:413-21.

<sup>4</sup>Bouguen G, Manfredi S, Blayau M, et al. Colorectal adenomatous polyposis Associated with MYH mutations: genotype and phenotype characteristics. *Dis Colon Rectum*. 2007;50(10):1612-7.

## C. Hamartomatous Polyposis Syndromes

The hamartomatous polyposis syndromes are a rare group of hereditary autosomal dominant disorders comprising less than 1% of all hereditary colorectal cancers.<sup>1</sup> These benign proliferations have malignant potential and may develop into colorectal or extracolonic cancers. Early detection is crucial for establishing proper surveillance to minimize the risk of carcinoma. The hamartomatous polyposis syndromes include juvenile polyposis syndrome (JPS); PTEN hamartoma tumor syndrome, which includes Cowden syndrome (CS) and Bannayan-Riley-Ruvalcaba syndrome (BRRS); and Peutz-Jeghers syndrome (PJS).<sup>1</sup>

### C.1 Juvenile Polyposis Syndrome

The most frequent clinical situation in JPS is solitary juvenile polyps; however, their risk of developing into CRC is likely minimal. Solitary polyps are usually found in the rectosigmoid area in children under the age of 10 years, although they can develop at any age.

This condition is usually considered to be separate from JPS. A diagnosis of JPS is established when at least 1 of the following criteria<sup>3,4</sup> are met:

- a) At least 3–10 polyps detected during colonoscopy;
- b) Polyps located outside of the colon;
- c) Any number of polyps in a patient with a family history of juvenile polyps.

A family history of juvenile polyps is noted in 20–50% of patients with JPS, and JPS exhibits an autosomal dominant pattern of inheritance with variable penetrance.<sup>4,5</sup> Three genes, all of which are members of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily of proteins, have been associated with JPS: SMAD4, BMPR1A, and ENG. Individuals with JPS are at risk not only for the development of CRC but also for gastric, small bowel, and pancreatic cancers.

## *C.2 PTEN Hamartoma Tumor Syndromes: Cowden Syndrome and Bannayan-Riley-Ruvalcaba Syndrome*

Both Cowden and Bannayan-Riley-Ruvalcaba syndromes have been associated with the PTEN tumor suppressor gene, which is located on chromosome 10q22-23. Cowden Syndrome (CS) is a rare autosomal dominant syndrome presenting with macrocephaly, mucocutaneous lesions (such as facial trichilemmoma), acral keratosis, and papillomatous papules. CS may also be associated with cancer in other areas such as the breast, thyroid, and endometrium, and the incidence of gastrointestinal polyps in CS is approximately 30%. Bannayan-Riley-Ruvalcaba Syndrome (BRRS) is an autosomal dominant disease presenting with macrocephaly, developmental delays, pigmented speckling of the penis, lipomas, and hamartomatous polyps of the intestine, the latter of which occur in approximately 50% of the cases. The risk of GI carcinoma in CS is not known, and its occurrence is based upon case reports. Gynecological cancer has been reported in patients with BRRS; however, the risk of other non-intestinal cancers is not fully known.

### C.3 Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is an autosomal dominant syndrome characterized by mucocutaneous pigmentation and intestinal hamartomatous polyps. Pigmentation is typically observed around the lips but may also affect the buccal mucosa, hands, feet, genitals, and areas around the nose and eyes. This quite typical presentation should always be considered by the pediatrician because pigmentation typically presents in early childhood and tends to be milder after the onset of puberty. Mutations in the *LKB1/STK11 gene*<sup>6</sup> were implicated in the development of PJS in approximately 80% of patients. Hamartomatous polyps in PJS may involve the whole intestinal tract may be limited to a specific area, occasionally causing abdominal pain secondary to intussusception. On other occasions, polyps may present with anemia caused by gastrointestinal bleeding. Approximately one third of PJS patients are diagnosed in the first decade of life, and the remaining patients present by the second or third decade of live. A diagnosis of PJS is supported by the presence of hamartomatous polyps and 2 of the following criteria:<sup>7</sup>

- a) A family history of PJS;
- b) The presence of mucocutaneous pigmentation and small-bowel polyps.

Individuals with PJS are at risk for the development of cancers, including intestinal and extraintestinal tumors, usually occurring beyond the pediatric age group. Cancers that affect the digestive tract include colorectal, gastric, small intestinal, esophageal, and pancreatic cancers. Extraintestinal tumors include lung, breast, ovarian, testicular, and endometrial cancers.

## C.4 Hereditary Non-Polyposis Colorectal Cancer

Hereditary non-polyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is an uncommon autosomal dominant hereditary condition accounting for 1–5% of all CRCs.<sup>8</sup> It is caused by a mutation in one of several DNA mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, or *PMS2*. Mutations in these genes lead to microsatellite instability (MSI). Affected patients are typically diagnosed with CRC earlier than those with sporadic CRC; however, they are usually diagnosed in older patients (beyond the pediatric age range). However, because these patients have an estimated 80% risk of developing colorectal cancer, it is important to identify affected families in order to establish intensive surveillance programs. The prevalence of HNPCC in children and adolescents with CRC is not known, and reports only comprise single case reports.

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## C. References

- <sup>1</sup>Manfredi M. Hereditary hamartomatous polyposis syndromes: understanding the disease risks as children reach adulthood. *Gastroenterol Hepatol (N Y)*. 2010;6(3):185-96.
- <sup>2</sup>Jass JR, Williams CB, Bussey HJ, Morson BC. Juvenile polyposis--a precancerous condition. *Histopathology*. 1988;13(6):619-30.
- <sup>3</sup>Giardiello FM, Hamilton SR, Kern SE, et al. Colorectal neoplasia in juvenile polyposis or juvenile polyps. *Arch Dis Child*.1991;66(8):971-5.
- <sup>4</sup>Chow E, Macrae F. A review of juvenile polyposis syndrome. *J Gastroenterol Hepatol*. 2005;20(11):1634-40.
- <sup>5</sup>Attard TM, Young RJ. Diagnosis and management of gastrointestinal polyps: pediatric considerations. *Gastroenterol Nurs*. 2006;29(1):16-22; quiz 3-4.
- <sup>6</sup>Hemminki A, Hoglund P, Pukkala E, et al. Intestinal cancer in patients with a germline mutation in the down-regulated in adenoma (DRA) gene. *Oncogene*. 1998.5;16(5):681-4.
- <sup>7</sup>Giardiello FM, Welsh SB, Hamilton SR, et al. Increased risk of cancer in the Peutz-Jeghers syndrome. *N Engl J Med*. 1987;316(24):1511-4.
- <sup>8</sup>Gryfe R. Inherited colorectal cancer syndromes. *Clin Colon Rectal Surg*. 2009 Nov;22(4):198-208.

## **D. Clinical Features of Colorectal Carcinoma in Young Patients**

Despite the limited evidence available, most series report that childhood and adolescent CRC behaves more aggressively than CRC in adults. More aggressive histotypes such as poorly differentiated (signet-ring) or mucinous adenocarcinomas are observed more frequently in children and adolescents. In addition, microsatellite instability has been noted in younger patients,<sup>1</sup> and younger patients tend to present with a more advanced clinical stage. Indeed, fewer than 20% of children/adolescents present with localized disease, and there is an increased prevalence of metastatic disease in this age group,<sup>2</sup> which may be related to more aggressive tumors. Other authors have hypothesized that diagnostic delays may also partially explain the advanced disease at diagnosis.<sup>3-5</sup> Recent reports have shown that the median lag time (time between the onset of symptoms and diagnosis) is 3 months for patients younger than 20 years old compared to 1 month for those over 20.<sup>4</sup>

Signs and symptoms of CRC depend on the tumor location. Patients with a tumor in the left colon usually present with a change in bowel habits and hematochezia, whereas those with a tumor in the right colon usually present with chronic anemia or an abdominal mass. It is probable that GI symptoms such as abdominal pain, constipation, or diarrhea may be underestimated since they are seldom associated with CRC in children. Patients who present with these features are not often suspected as being malignant by doctors or patients, which may explain the delayed diagnosis in this age group. In addition, because of the technical limitations of fiberoptic examination of the right colon, young patients may only undergo rectosigmoidoscopy, and right side tumors may be underdiagnosed. Right side tumors may occur relatively more frequent in children than in adults.<sup>6</sup>

In more advanced cases, bowel perforation may occur with tumors on both sides and is related to poor prognosis because of peritoneal seeding.

It is important to create a registry of CRC patients with rare tumors so that larger numbers of patients can be identified worldwide. The available pediatric evidence for CRC is scant. A literature review<sup>7</sup> and a population-based study using the SEER data<sup>2</sup> that were recently published may contain the most comprehensive data about this tumor in children. In the latter study, the clinical features and outcomes of 159 patients less than 20 years old and those of a large adult cohort (over 550,000 cases) were compared, and the survival rate was found to be poorer for pediatric cases than for adults. In the SEER study, the survival estimates at 5 and 10 years were 40% and 31%, respectively, for children/adolescents and 60% and 54%, respectively, for adults.<sup>2</sup> Another factor contributing to poor prognosis in children may be that pediatric surgeons have limited experience in this area; indeed, most series report suboptimal resection rates. Adult studies have shown a correlation between the surgeon's experience and overall prognosis.<sup>8</sup>

### *D.1 Extent of Disease Evaluation*

Diagnostic investigations include a digital rectal exam, which adolescents occasionally find difficult to accept, a fecal occult blood test, complete blood cell counts, and abdominal imaging. This includes an abdominal ultrasound, which may show an abdominal mass but is not specific enough for diagnosis. Only a colonoscopy with biopsy can provide a confirmatory diagnosis and represents the gold standard. However, many young children present with abdominal emergencies caused by obstruction, bleeding, or perforation. The diagnosis is often made by the surgeon in the operating room after an emergency laparotomy.

As soon as the diagnosis is confirmed, the tumor should be staged based on information from the surgical report, histopathological data, and imaging studies. These include a computed tomography (CT) scan of the chest and abdomen. Because the tumor tends to disseminate via the lymph nodes, it is important to carefully assess the extension and the number of affected nodes, which are features associated with a poorer prognosis. Special attention should be paid to the liver during imaging evaluations because it is the most common metastatic site. In girls, the ovaries may be a metastatic site and should always be considered. Tumor markers such as carcinoembryonic antigen (CEA) in plasma and, less significantly, CA 19-9 and CA 242 may be elevated (especially for adenocarcinoma). These markers may be used to monitor the outcome and assess the treatment response in patients with metastatic disease. Occasionally, elevated CEA during a follow-up examination may predict the occurrence of metastatic relapse. However, CEA is not a reliable tumor marker because it produces many false positive and false negative test results. As described previously in this chapter, a genetic predisposition for CRCs should always be determined in young patients.

The most common staging system is the TNM (tumors/nodes/metastases) system described by the American Joint Committee on Cancer<sup>9</sup> (**D. Table 1**). This staging system is based on the level of invasion of the primary tumor (mucosa, submucosa, muscularis propria, serosa, or beyond) and the number of lymph node metastases. Older staging systems such as the Dukes and the Astler-Coller classifications are less frequently used these days.

## D. Table 1

The AJCC TNM staging system for CRC.<sup>9</sup>

### Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Carcinoma in situ: intraepithelial or invasion of lamina propria<sup>a</sup>
- T1 Tumor invades submucosa
- T2 Tumor invades muscularis propria
- T3 Tumor invades through the muscularis propria into the pericolorectal tissues
- T4a Tumor penetrates to the surface of the visceral peritoneum<sup>b</sup>
- T4b Tumor directly invades or is adherent to other organs or structures<sup>b,c</sup>

### Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in 1-3 regional lymph nodes
- N1a Metastasis in one regional lymph node
- N1b Metastasis in 2-3 regional lymph nodes
- N1c Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
- N2 Metastasis in four or more regional lymph nodes
- N2a Metastasis in 4-6 regional lymph nodes
- N2b Metastasis in seven or more regional lymph nodes

### Distant Metastasis (M)

- M0 No distant metastasis
- M1 Distant metastasis
- M1a Metastasis confined to one organ or site (eg, liver, lung, ovary, nonregional node)
- M1b Metastases in more than one organ/site or the peritoneum

## D. Table 2

Prognostic stages according to the AJCC TNM staging system for CRC.<sup>9</sup>

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	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-T2	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

## D. References

- <sup>1</sup>Kam MH, Eu KW, Barben CP, Seow-Choen F. Colorectal cancer in the young: a 12-year review of patients 30 years or less. *Colorectal Dis.* 2004;6(3):191-4.
- <sup>2</sup>Sultan I, Rodriguez-Galindo C, El-Taani H, et al. Distinct features of colorectal cancer in children and adolescents: a population-based study of 159 cases. *Cancer.* 2010;116(3):758-65.
- <sup>3</sup>Karnak I, Ciftci AO, Senocak ME, Buyukpamukcu N. Colorectal carcinoma in children. *J Pediatr Surg.* 1999;34(10):1499-504.
- <sup>4</sup>Chantada GL, Perelli VB, Lombardi MG, et al. Colorectal carcinoma in children, adolescents, and young adults. *J Pediatr Hematol Oncol.* 2005;27(1):39-41.
- <sup>5</sup>Lamego CM, Torloni H. Colorectal adenocarcinoma in childhood and adolescent. Report of 11 cases and review of the literature. *Pediatr Radiol.* 1989;19(8):504-8.
- <sup>6</sup>Ferrari A, Rognone A, Casanova M, et al. Colorectal carcinoma in children and adolescents: the experience of the Istituto Nazionale Tumori of Milan, Italy. *Pediatr Blood Cancer.* 2008;50(3):588-93.
- <sup>7</sup>Saab R, Furman WL. Epidemiology and management options for colorectal cancer in children. *Paediatr Drugs.* 2008;10(3):177-92.
- <sup>8</sup>Simons AJ, Ker R, Groshen S, et al. Variations in treatment of rectal cancer: the influence of hospital type and caseload. *Dis Colon Rectum.* 1997;40(6):641-6.
- <sup>9</sup>Greene FL. American Joint Committee on Cancer, & American Cancer Society. AJCC cancer staging handbook: *From the AJCC cancer staging manual.* New York: Springer; 2002.

## E. Treatment

There are no prospective studies for CRC in young patients. Surgery is a key component of CRC treatment. Close cooperation with surgeons and oncologists is essential for improving the outcomes for children and adolescents with CRC. In children with known polyposis syndromes, a tumor can be diagnosed earlier when it develops within a polyp, and these children can often be cured by polypectomy during colonoscopy. However, in most children, radical surgery is necessary to obtain a radical resection of all tumor manifestations even if radical procedures such as wide or multivisceral resections and peritonectomy are needed. In most cases, the resection of the section of colon containing the tumor with sufficient margins en-bloc with mesentery and lymph nodes (radical colectomy) is needed. A colostomy is usually performed in most patients to relieve obstruction.

The indication for adjuvant treatment should follow treatment recommendations based on adult experience and considering the staging of the individual patient. The 5-year survival rate of children with early stage tumors (TNM stage T1-2, N0, M0) is over 90%, and in these cases, no adjuvant therapy is recommended after surgery. Two features facilitate the categorization of a patient with stage II CRC as a high-risk patient: a pT4 tumor and a low frequency of satellite instability (MSI-Low). However, in young patients, it may be important to categorize those with pT3 tumors, a high histological grade (3-4 for MSI-High), perforation or occlusion, less than 12 lymph nodes studied, and undetermined or compromised surgical margins (and perhaps those where the margin is close) as high-risk patients. We believe this is a crucial topic because the minimal effect that adjuvant chemotherapy could have would be justified in children in whom a long life is expected. Determination of mismatch repair (MMR) is crucial because tumors that are MMR deficient (dMMR) have a better prognosis and are more sensitive to chemotherapy than MMR proficient (pMMR) tumors. There is no current consensus on the best method for estimating MMR: Some centers use immunohistochemistry (approximately 50% of centers in the USA), while others use PCR techniques or a combination of both.

Adjuvant treatment modalities include chemotherapy, radiotherapy, and more recently, biological targeted therapy. Postoperative radiotherapy has been typically used for rectal cancer in combination with 5FU-based chemotherapy. However, recent experience in pre-operative radiotherapy for advanced adult cases might suggest a role for this therapy in decreasing the risk of recurrence following surgery, or occasionally to allow for a less invasive surgical procedure.<sup>1,2</sup> The use of radiotherapy for colon cancer is complicated by the occurrence of radiation-induced enteritis and is limited by the difficulties in targeting the tumor volume.

Treatment of node-negative patients at stage T3–4 is controversial. Newer agents such as capecitabine, oxaliplatin, irinotecan, cetuximab, or bevacizumab have proven to be active in advanced disease and are now under evaluation in the adjuvant setting.<sup>3-5</sup> For patients with resected CRC with lymph node involvement (stage III), adjuvant chemotherapy based on 5-fluorouracil/folinic acid (5FU/FA) is recommended.<sup>1,6</sup> Liver metastasis should be approached with a tumor resection with radical intent, and other treatments such as cryoablation, radiofrequency ablation, and chemoembolization should be used occasionally for unresectable tumors.

### *E.1 Treatment of Stage II (High Risk) and Stage III*

Adjuvant therapy has proven to be effective in terms of improving the survival of these patients. It is clear today that combinations including oxaliplatin are superior to those containing only fluoropyrimidines and leucovorin. Regimens such as FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or XELOX (capecitabine and oxaliplatin) are recommended, while those including irinotecan, bevacizumab, cetuximab or panitumumab have not been shown to be superior to the above-mentioned combination.

### *E.2 Treatment of Stage IV*

The treatment objectives in these patients include cure, life prolongation, or palliation. Therefore, we have selected the following situations, which are common treatment dilemmas in the management of these patients. We will assume here that the primary tumor is under control, including those presenting synchronically or metachronically.

### *E.3 Liver Metastasis*

The study of liver anatomy and liver segmentation together with the development of liver imaging techniques including positron emission tomography (PET)-CT, multislice CT with volumetric reconstruction, liver angioresonance, and intraoperative ultrasound have revolutionized the treatment of liver metastasis in colorectal cancer. Curative strategies: Complete resection with clear margins is necessary for a cure.

Even though it is undisputable that cases with less than 3 metastases and unilobar involvement are candidates for curative treatment, all other patients should be evaluated for curative treatment in a personalized fashion. Occasionally, 2-step surgical procedures may be required for patients with multiple metastases or more than 2 compromised lobes. A series examining patients with multiple bilobar metastases showed that up to 1 in 5 patients in whom more than 20 metastases were resected were able to achieve a long-term survival of more than 10 years.<sup>7</sup> A recent review of the MD Anderson Hospital database included more than 1600 patients who were treated with surgery. Of the 159 patients who had between 4 and 12 metastases, half were alive at 5 years (22% were disease-free). This is an indicator of extensive preoperative and intraoperative evaluation as well as the efficacy of preoperative chemotherapy because all patients responded to chemotherapy. The author concluded that tumor biology might be more important than the number and location of metastases in these cases. Although extra-hepatic extension is a relative contraindication for resection of liver metastasis, if complete resection can be accomplished, the long-term survival is similar to that of patients with liver involvement only. In occasional selected patients, the combination of surgery and radiofrequency ablation of non-resectable metastasis achieved a 22% survival rate at 4 years, which is more favorable than that the 5% survival rate achieved with chemotherapy alone.

Preoperative chemotherapy may shrink the metastatic tumor making it amenable for surgery. This modality has been erroneously denominated as neoadjuvant, a term that should be reserved for the treatment of a primary tumor. Response to chemotherapy may be associated with improved survival. However, liver toxicity is associated with certain chemotherapy drugs such as oxaliplatin, which can cause sinusoidal obstruction and perisinusoidal fibrosis, or irinotecan, which can cause liver steatosis. All of these features may alter liver regeneration after surgery. If bevacizumab is administered, at least 12 weeks should be allowed to elapse before surgery. When cetuximab is used, all skin lesions should be inactive before surgery in order to avoid the risk of infection during postoperative care.

#### *E.4 Lung Metastasis*

This complication is more common in rectal cancer because the hemorrhoidal veins may metastasize directly to the liver without the first step at the liver. Patients with lung metastasis who have had their disease completely resected have cure rates similar to those with isolated liver metastasis. PET-CT may be useful for patients presenting with less than 3 lesions (all smaller than 15 mm), especially when they are unilateral. In cases with extensive lung metastases, for example, those with more than 10 lung nodules, a balance between resectability and lung function should be achieved. However, the survival rate is lower in patients with extensive lesions. When there is mediastinal involvement, there is little hope for a cure.

#### *E.5 Metastasis to the Liver and the Lung*

In selected patients, combined resection of lung and liver metastases (either simultaneously or sequentially) may result in long-term survival. Surgeons should begin with the lesion that can be more easily resected with less morbidity.

Occasionally, this means that a second surgical procedure needs to be scheduled. Hence, if one starts with the most difficult surgery, complications may prevent the performance of the second one. Thus, there is no single unanimously accepted procedure. For example, in patients with lung involvement that is limited to the right base, it is possible to access to both organs in the same procedure. However, most patients require sequential procedures.

## *E.6 Peritoneal Involvement*

Although peritoneal involvement can be noted in any gastrointestinal tumor, it is more common in tumors of the right colon, especially those in the appendix. Peritoneal carcinomatosis caused by a secreting adenocarcinoma is referred to as pseudomyxoma peritonei and it can originate from the appendix, ovary, or any organ capable of giving rise to a mucosecreting adenocarcinoma. Paul H. Sugarbaker designed a strategy for the management of these tumors that includes peritonectomy together with intraoperative chemotherapy with or without hyperthermia. This procedure requires high surgical skill and very careful patient selection (disease extension, patient age, and comorbidities must be carefully considered). Surgical complications may occur, but up to one-third of patients can be cured with this modality.

## *E.7 Unresectable Metastatic Disease*

Palliation and life prolonging therapy are the treatments of choice for most of these patients. It is not reasonable to translate the results obtained in clinical trials to patients who would not qualify for these therapies, so the presence of comorbidities, liver function, and performance status should be carefully considered to determine the optimal therapy. It is necessary to recognize that many young patients with disseminated disease may be candidates for treatment because they do not have most these limitations;

however, it is difficult to determine the best therapy for these patients. It is obviously important to consider other treatments that the patient received previously in order to select the most appropriate agents. In naive patients with good performance and no comorbidities, different chemotherapy combinations can be used because there seems to be no difference in life expectancy depending on the regimen used. The usual regimens include a combination of fluorouracil and leucovorin (which can be substituted with capecitabine) associated with oxaliplatin (FOLFOX, FLOX, XELOX, or Bifol) or irinotecan (FOLFIRI, IFL, or XELIRI). Some authors recommend the use of oxaliplatin first. Of all the combinations, FOLFOX is the most commonly used in Europe and can be considered as a first-line regimen based on the results of the European C95 study, which compared FOLFOX4 with 5Fu-Leucovorin. The US N9741 study compared FOLFOX4 with IFL or a combination of irinotecan and oxaliplatin (IROX), and the NCCTG N9741 study compared FOLFOX4 and IFL. In all studies, FOLFOX was superior to irinotecan-containing regimens.

Other authors maintain that the choice of a specific regimen plays only a minor role in the outcome, especially after the results of Protocol 9901 from the Grupo Oncologico Dell'Italia Meridionale (GOIM) as well as of those from studies by the Groupe Cooperateur Multidisciplinaire en Oncologie (GERCOR) and from the GOIM that failed to show any significant difference in the progression-free interval or survival among any of the regimens.

In patients that relapsed after treatment with oxaliplatin, a schema using single-agent irinotecan or associated to fluoropyrimidines is recommended (FOLFIRI, IFL, or XELIRI). In patients that relapsed after an irinotecan-containing regimen, oxaliplatin-containing regimens (FOLFOX) may be used. In some of these patients, bevacizumab may be added if it is not contraindicated based on the results of a study by the Eastern Cooperative Oncology Group (E3200), which showed an approximately 2-month survival advantage (12.9 months vs. 10.8 months). These results were not replicated by first-line treatments.

Patients without mutations in *KRAS* benefit, both in first- and second-line treatments, from the administration of cetuximab in association with irinotecan in terms of progression-free survival and eventually in overall survival (CRYSTAL study), whereas association with oxaliplatin (COIN and OPUS studies) failed to show similar results. As discussed by Grothey and Lenz,<sup>8</sup> it is possible that the efficacy of cetuximab may be related to the continuous infusion of fluorouracil and, to a lesser degree, oxaliplatin or irinotecan. These authors postulated that prolonged infusions of fluorouracil may inhibit the enzyme thymidylate synthase, which in turn may be inhibited by blockage of the epidermal growth factor receptor (EGFR), thereby potentiating the effect of prolonged infusions of 5-FU and not affecting its administration in bolus injections.

Resistance to cetuximab has been extensively studied, and it is now understood that the most sensitive tumors are those that lack *KRAS*, *BRAF*, *PTEN*, and *PIK3CA* mutations. On the other hand, any alteration in these targets may elicit resistance to EGFR blockage. From a practical point of view, cetuximab and panitumumab can be used interchangeably; however, cetuximab may be used in cases of progression.

### E. Table 1

Description of chemotherapy regimens used for the treatment of colorectal carcinoma

<b>1. Combination of 5-Fluoruracil/Leucovorin</b>
<ul style="list-style-type: none"> <li>• Weekly 5-FU Initial dose, 500 mg/m<sup>2</sup> by I.V. bolus 1 hour after leucovorin infusion Leucovorin 20 mg/m<sup>2</sup> as a 2-hour I.V. infusion over 2 hours Repeat cycle every week</li> <li>• Mayo Clinic regimen 5-FU 425 mg/m<sup>2</sup> daily by I.V. bolus 1 hour after start of leucovorin on days 1 through 5 Leucovorin 20 mg/m<sup>2</sup> daily by I.V. bolus on days 1 through 5 Repeat cycle in weeks 4 and 8; then every 5 weeks</li> <li>• Roswell Park regimen 5-FU 500 mg/m<sup>2</sup> by I.V. bolus 1 hour after start of leucovorin on days 1, 8, 15, 22, 29, and 36 Leucovorin 500 mg/m<sup>2</sup> I.V. over 2 hours on days 1, 8, 15, 22, 29, and 36 Repeat cycle every 8 weeks</li> </ul>

## 2. Combinations with Oxaliplatin

- FOLFOX4  
Oxaliplatin 85 mg/m<sup>2</sup> I.V. over 2 hours on day 1  
Leucovorin 200 mg/m<sup>2</sup> I.V. over 2 hours (on days 1 and 2); then  
5-FU 400 mg/m<sup>2</sup> by I.V. bolus, followed by 600 mg/m<sup>2</sup> by continuous I.V. infusion over 22 hours on days 1 and 2  
Repeat cycle every 14 days
- FOLFOX6  
Oxaliplatin 100 mg/m<sup>2</sup> I.V. over 2 hours on day 1  
Leucovorin 400 mg/m<sup>2</sup> I.V. over 2 hours on day 1; then  
5-FU 400 mg/m<sup>2</sup> by I.V. bolus, then 1,200 mg/m<sup>2</sup> daily for 2 days (total 2,400 mg/m<sup>2</sup> over 46 to 48 hours) by continuous I.V. infusion  
Repeat cycle every 14 days. If no toxicity greater than grade 1 occurs after first two cycles, increase 5-FU dosage to 3,000 mg/m<sup>2</sup>
- FLOX  
Oxaliplatin 85 mg/m<sup>2</sup> over 1 hour (30 to 90 minutes) on day 1  
FU 500 mg/m<sup>2</sup> as a bolus infusion ( 5 minutes), followed 30 minutes later by bolus FA 60mg/m<sup>2</sup> (10 minutes) on days 1 and 2.  
Repeat cycle every 14 days

## 3. Regimens with Irinotecan

- Irinotecan single agent  
Irinotecan 125 mg/m<sup>2</sup> I.V. over 90 minutes on days 1, 8, 15, and 22  
Repeat cycle every 6 weeks.

Alternatively

- Irinotecan 300 to 350 mg/m<sup>2</sup> I.V. over 90 minutes on day 1  
Repeat cycle every 21 days.
- FOLFIRI  
Irinotecan 180 mg/m<sup>2</sup> I.V. over 90 minutes on day 1  
Leucovorin 400 mg/m<sup>2</sup> I.V. over 90 minutes on day 1  
5-FU 400 mg/m<sup>2</sup> by I.V. bolus on day 1, followed by 1,200 mg/m<sup>2</sup> daily for 2 days (total 2,400 mg/m<sup>2</sup> over 46 hours) by continuous I.V. infusion  
Repeat cycle every 14 days.

## 4. Regimens with Cetuximab

- FOLFIRI + Cetuximab (for wild-type KRAS gene only)  
Irinotecan 180 mg/m<sup>2</sup> I.V. over 90 minutes on day 1  
Leucovorin 400 mg/m<sup>2</sup> I.V. over 90 minutes on day 1  
5-FU 400 mg/m<sup>2</sup> by I.V. bolus on day 1, followed by 1,200 mg/m<sup>2</sup> daily for 2 days (total 2,400 mg/m<sup>2</sup> over 46 hours) by continuous I.V. infusion  
Repeat cycle every 2 weeks with:  
Cetuximab 400 mg/m<sup>2</sup> I.V. loading dose over 120 minutes on day 1; then  
Cetuximab 250 mg/m<sup>2</sup> I.V. over 60 minutes weekly

## 5. Regimens with Bevacizumab

- FOLFOX4 plus bevacizumab  
Oxaliplatin 85 mg/m<sup>2</sup> I.V. over 2 hours on day 1  
Leucovorin 200 mg/m<sup>2</sup> I.V. over 2 hours (on days 1 and 2); then  
5-FU 400 mg/m<sup>2</sup> by I.V. bolus, followed by 600 mg/m<sup>2</sup> by continuous I.V. infusion over 22 hours on days 1 and 2  
Bevacizumab 10 mg/kg I.V. infusion over 90 minutes on day 1  
Repeat cycle every 14 days

## 6. Regimens with Capecitabine

- Capecitabine  
Capecitabine 850 to 1,250 mg/m<sup>2</sup> P.O. twice daily on days 1 through 14, followed by 7 days rest  
Repeat every 21 days.
- CapeIRI (capecitabine, irinotecan)  
Capecitabine 1,000 mg/m<sup>2</sup> P.O. twice daily on days 1 through 14  
Irinotecan 250 mg/m<sup>2</sup> I.V. over 90 minutes on day 1  
Repeat cycle every 3 weeks.
- CapeOX (XELOX) (capecitabine [Xeloda], oxaliplatin)  
Oxaliplatin 130 mg/m<sup>2</sup> I.V. over 2 hours on day 1  
Capecitabine 850 to 1,000 mg/m<sup>2</sup> P.O. twice daily from evening of day 1 to morning of day 15  
Repeat cycle every 21 days.

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## E. References

- <sup>1</sup>Minsky BD, Cohen AM, Enker WE, Kelsen DP, Kemeny N, Frankel J. Efficacy of postoperative 5-FU, high-dose leucovorin, and sequential radiation therapy for clinically resectable rectal cancer. *Cancer Invest.* 1995;13(1):1-7.
- <sup>2</sup>Minsky BD, Cohen AM, Enker WE, Sigurdson E. Phase I/II trial of pre-operative radiation therapy and coloanal anastomosis in distal invasive resectable rectal cancer. *Int J Radiat Oncol Biol Phys.* 1992;23(2):387-92.
- <sup>3</sup>Rothenberg ML, Oza AM, Bigelow RH, et al. Superiority of oxaliplatin and fluorouracil-leucovorin compared with either therapy alone in patients with progressive colorectal cancer after irinotecan and fluorouracil-leucovorin: interim results of a phase III trial. *J Clin Oncol.* 2003;21(11):2059-69.
- <sup>4</sup>Goyle S, Maraveyas A. Chemotherapy for colorectal cancer. *Dig Surg.* 2005;22(6):401-14.
- <sup>5</sup>Saltz LB. Adjuvant therapy for colon cancer. *Surg Oncol Clin N Am.* 2010;19(4):819-27.
- <sup>6</sup>Madajewicz S, Petrelli N, Rustum YM, et al. Phase I-II trial of high-dose calcium leucovorin and 5-fluorouracil in advanced colorectal cancer. *Cancer Res.* 1984;44(10):4667-9.
- <sup>7</sup>Minagawa M, Yamamoto J, Miwa S, et al. Selection criteria for simultaneous resection in patients with synchronous liver metastasis. *Arch Surg.* 2006 Oct;141(10):1006-12; discussion 13.
- <sup>8</sup>Grothey A, Lenz HJ. Explaining the unexplainable: EGFR antibodies in colorectal cancer. *J Clin Oncol.* 2012;30(15):1735-7.