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Therapeutic Strategies in Colonic Cancer

D. Dinu[1], R. Birla[1], A. Caragui[2], S. Constantinoiu[1]

[1]"Carol Davila" University of Medicine and Pharmacy, Department of General and Esophageal Surgery
"Sf. Maria" Clinical Hospital, Bucharest, Romania
[2]Department of General and Esophageal Surgery, "Sf. Maria" Clinical Hospital, Bucharest, Romania

Rezumat

Strategia terapeutică în cancerul colonic

Cancerul de colon (CC) este cea mai frecventă boală malignă a tubului digestiv, reprezentând 13% din totalul neoplaziilor. Scopul studiului este evaluarea strategiei terapeutice actuale la pacienții cu CC. Mortalitatea prin această boală este în scădere în multe din țările vestice; aceasta putând fi atribuită screeningului pentru CC, rezecției adenoamelor, detectării precoce a unor leziuni canceroase și folosirii unor opțiuni terapeutice cât mai individualizate. Tratamentul bolii este multimodal incluzând secvențe terapeutice diverse: chirurgie, chimioterapie, radioterapie, imunoterapie. Progresele actuale în cercetarea mecanismelor carcinogenezei în CC fac posibilă folosirea informației genetice în scopul stabilirii unor factori de prognostic și predicție pentru selecția pacienților pentru o terapie individualizată. Metodele actuale de evaluare a CC permit stabilirea unei stategii terapeutice individualizate, ceea ce ar conduce la rezultate optime.

Cuvinte cheie: cancer de colonic, strategia terapeutică

Abstract

Colonic cancer is the most common malignancy of the digestive tract, representing 13% of all malignancies. The aim of the study is to evaluate the current therapeutic strategy in patients with CC. Mortality from the disease is declining in many Western countries; this may be the result of screening for CC, resection of adenomas, early detection of tumoral lesions and the use of individualized therapeutic strategies. The multimodal treatment of the disease includes different sequences such as: surgery, chemotherapy, radiotherapy, immunotherapy. Current advances in the research of mechanisms of carcinogenesis in CC make it possible to use genetic information in order to establish the prognostic and predictive factors for selecting the patients for individualized therapy. The current methods of CC evaluation allow the planning of individualized therapeutic strategies, which would lead to optimal results.

Key words: colonic cancer, therapeutic strategy

Introduction

The treatment of Colonic Cancer (CC) is multimodal. Recent decades were marked by the progresses made in imaging and staging, surgery, anesthesia, medical oncology, radiation therapy, and last but not least in the molecular biology of CC, and all of these have influenced treatment modalities. Normally, a multidisciplinary team consisting of oncologists, surgeons, radiotherapists, radiologists and physicists, pathologists examines the case, reviews the pre-treatment investigations and elaborates a

Corresponding author: Dinu Daniela Elena, MD
Department of General and Esophageal Surgery, "Sf. Maria" Clinical Hospital
37-39, I. Mihalache Blvd., district 1
Bucharest, Romania
E-mail: chirurgie_esofagiana_sfmaria@yahoo.com

specific protocol of treatment for a particular patient, given the generally accepted treatment guidelines that are based on the efficacy of the multimodal treatment. An honest and explicit discussion with the patient is essential in determining the future therapeutic approach and it is also necessary for obtaining informed consent.

Early colon cancer treatment

5-year survival rate in CC is different, depending on the TNM stage established when the disease is diagnosed, post therapeutic outcome being more favorable when the disease is diagnosed in an early stage. CC may be asymptomatic for a long time, so screening addresses to apparently healthy individuals. Screening tests are used for early detection of some lesions that otherwise would not be detected or that would be detected in more advanced stages. (1)

In accordance with international guidelines, screening tests are structured according to the patients' personal risk of disease. Age is considered a major risk factor for sporadic colon cancer: 70% of patients with colon cancer are older than 65 years and the disease is rare for those under 40 years (2,3,4). On the other hand, it is known that the evolution sequence for CC is represented by the progression from adenoma to cancer. Screening is able to decrease mortality by resection of adenomatous polyps. Individualized screening is considered if we are aware of a personal history of adenomas, colon cancer, inflammatory bowel disease or family history of polyps or CC.

Principles of screening

The purpose of screening is to detect early precancerous or malignant lesions that can be treated curatively. In the European Union the recommendations are:

1. Fecal occult blood test (FOBT) is indicated for patients between 50-74 (70) years. In the average-risk population, guaiac test (FOBT) reduced mortality by about 15% in different age groups. The benefit appears to be greater when comparing annual testing with the biannual testing. Immunochemical testing (detection of human Hb) appears to be superior to FOBT regarding the detection rate and the positive predictive value for adenomas and cancer; testing interval shall not exceed three years (1,5,6,7,8).
2. Flexible sigmoidoscopy (RSS) reduces the incidence and mortality of CC when performed in an organized screening program, the optimum interval being under 10 years. The recommended age range is between 55 and 64 years. After the age of 74 years screening through the RSS should be discontinued because of the increased number of comorbidities in this group.
3. There is limited evidence that screening colonoscopy reduces mortality by CC.

New screening technologies are now being evaluated: CT colonography, stool DNA testing and videocapsule endoscopy, but have not proven yet the effectiveness as a screening tool in the average-risk population.

Treatment of malignant polyps

Complete endoscopic polypectomy is indicated whenever the morphological appearance of the polyp allows it to be performed safely. The presence of invasive carcinoma in the resected polyp imposes the detection of some extra histopathological features that may help in indicating the following course of treatment: oncologic surgical resection or colonoscopic surveillance. Unfavorable histopathological criteria that determine the necessity of colon resection are: lymphatic or venous invasion, degree of differentiation G3, neoplastic submucosal invasion, neoplastic invaded resection margins. Note that the absence of these parameters, especially the last two, does not exclude the possibility of remote dissemination, so it requires further investigation and subsequent supervision. (4)

Treatment of localized disease

Surgical treatment

About half of patients with CC are treated surgically, this being the only curative method. The goal of surgery is represented by an extended resection of a colonic segment that carries the neoplastic lesion together with the adjacent lymph nodes. The extent of the colonic resection is determined by the distribution of blood supply and the distribution of locoregional lymph nodes. Although the resected colonic segment must be at least 5 cm above and under the tumor, resection limits are dictated by arterial pedicle ligation. Surgical resection is the foundation of curative treatment for localized colon cancer and for selected patients with metastatic disease. Approximately 75% of patients are candidates for potentially curative surgical resection at the moment of diagnosis. The aim of surgery is to achieve an oncologic resection, ideally a R0 resection with minimal complications, such as infection, bleeding, sexual and urinary dysfunction. A proper abdominal exploration should be performed in order to establish intraoperatively the extension of the disease: in the liver, greater omentum, diaphragm, abdominal or pelvic wall. The involved segment of colon should be resected en bloc together with a 2-5 cm limit with any local structures or organs invaded by the primary tumor. The vascular pedicles and lymphatic drainage basins of the involved bowel segment must be excised in a curative resection. According to the NCCN, the minimum required number of lymph nodes to be removed is 12, in order to perform a proper evaluation of nodal involvement. Bowel continuity should be restored when possible, without tension and with a good vascularization of the anastomotic partners. Selection of the appropriate surgical procedure is based on the location of the primary tumor and the presence of synchronous lesions or the presence of a hereditary cancer syndrome (9).

Right colectomy is performed for cecum, ascending colon and hepatic angle cancer. In this resection the ileocolic artery is ligated and resected at its origin, respectively the right colic artery if it is present. The extent of ileal resection is 10-15 cm from the ileocecal valve. The transverse colon is sectioned proximally from the right branch of the middle colic artery,

which may be ligated if needed. Extended right colectomy or transverse colectomy can be performed for tumors of the middle third of the transverse colon. In extended right colectomy we also ligate the middle colic artery, while in transverse colectomy we only ligate the middle colic artery. Reestablishing the continuity of the colon is done by ileocolic anastomosis and in transverse colectomy the restoration of the colonic integrity is obtained by performing a tension-free colo-colic anastomosis. Splenic angle tumors can be treated by a subtotal colectomy or by a splenic loop colectomy if the colonic mobility allows it. Descending and proximal sigmoid colon tumors are solved by a left colectomy. In case of a left colectomy the inferior mesenteric artery is ligated at its origin. Some sigmoid cancers can benefit from a segmental sigmoid resection with ligation of the sigmoidian arteries. In patients with synchronous colon cancer or hereditary cancer a total colectomy with ileoanal anastomosis is the most justified option. To clearly define stage II versus stage III, the resected segment must contain at least 12 lymph nodes.

Laparoscopic approach

Laparoscopic approach became a frequent modality for many types of abdominal surgical procedures. In laparoscopic colectomy the vascular pedicles are approached at their origin respecting the no touch isolation principles of open surgery. This method may be carried out safely for CC, in particular for those of the left colon. (10) For cancers situated on the right side the anastomosis is usually carried out extra-abdominally, so a minimal celiotomy is required. This technique decreases length of hospitalization, pain intensity, reduces the duration of postoperative ileus. Laparoscopy must meet certain criteria: lack of severe adhesions if the patient underwent previously major abdominal surgery, the laparoscopic approach is not suited for locally advanced tumors or complicated CC (acute intestinal obstruction or perforation), experienced surgeons in laparoscopic and oncological surgery. Long-term results in terms of oncology are similar both in the conventional approach and laparoscopic.

Occlusive colorectal cancers can be treated in one or two steps. Procedures may include an initial colostomy, followed by colonic resection after a few weeks or Hartmann technique – tumor resection and colostomy followed by anastomosis and colostomy removal. Single step surgery implies colic segmental resection after intraoperative colonic lavage and, in some cases, subtotal colectomy with ileorectal anastomosis. In order to treat the acute occlusion and later perform the resection and anastomosis, endoscopic stenting can be used. Occlusive right colon cancers can be treated using resection and anastomosis in the same step. (11)

The surgical treatment depending on the stage:

$T_{is}N_0M_0$ - simple polypectomy, segmental resection for larger lesions that cannot be resected en bloc;

$T_{1-2}N_0M_0$ - wide surgical resection with lymphadenectomy and anastomosis, without adjuvant chemotherapy;

$T_3N_0M_0$, $T_{4a-b}N_0M_0$ - wide surgical resection with anastomosis, adjuvant chemotherapy is recommended for high-risk patients;

Any T, N_{1-2}, M_0 - wide surgical resection with anastomosis with adjuvant chemotherapy.

The prognosis depends on the TNM stage - parietal tumor penetration, presence of invaded nodes. However there are additional parameters: vascular and perineural invasion, appearance of resection margins (tumor infiltration), lymphoid inflammatory response, P53, K-RAS expression of bcl-2, TGF-alpha, EGFR, Ki67 proliferative index and aneuploidy, intestinal obstruction and perforation are clinical indicators of poor prognosis.

Complementary treatment

Postoperative standard adjuvant treatment is recommended in patients with stage III colonic cancer if they are able to tolerate a scheme that combines oxaliplatin with a fluoropyrimidine. The recommended duration of adjuvant treatment is 6 months and it should be started as soon as the patient recovers after surgery, optimally within the first 6 weeks after surgery. (4) Adjuvant systemic therapy is administered after the primary tumor is resected in order to reduce the risk of relapse and death. Generally, adjuvant treatment is recommended for stage III patients and for high-risk stage II patients. Selection of high-risk stage II patients for further disease progression is of most importance. The general consensus suggests that patients with stage II are at risk of relapse if they have: resected lymph nodes under 12, poorly differentiated tumors, vascular and perineural invasion, pT_4, tumor obstruction or perforation, young age.

Many studies argue that other molecular factors should be analyzed in order to assess the prognosis of patients in stage II. Of more importance of these factors is the loss of heterozygosity 18q (18qLOH), the status of KRAS, BRAF, PIK3CA (4). Integration of genomic changes in different prognostic molecular tests provides data that allow selection of patients at risk for further disease progression (Oncotype DX, COLO-PRINT)

Complementary treatment options

The benefits of different oxaliplatin combinations were demonstrated in three major trials (MOSAIC, NSABPC07, ROSWELL-PARK). The MOSAIC study (12) that used the FOL / FOX scheme (oxaliplatin and 5-FU / LV) showed significant increase in the range of survival (DFS) at 3 years, reducing the risk of disease recurrence by 23% compared to the control group (LV, 5FU (5). Assessment at 6 years confirmed DFS benefit ratio in adjuvant treatment FOL-FOX (4) and an advantage was observed in overall survival (OS), but mainly for patients with stage III disease (13). MOSAIC study findings were confirmed by other studies.

XELOXA study assessed the efficacy of the combination of capecitabine with oxaliplatin (XELOX) in patients in stage III disease. The oral administration form of the drug was well tolerated and was superior to endovenous administration. If neurotoxicity appears, oxaliplatin administration should be stopped and treatment should continue with fluoropyrimidine because its effect represents two thirds of the effect of FOL-FOX / XELOX schemes. (14)

In particular situations monotherapy with capecitabine or 5-FU / leucovorin may be an alternative scheme. Some trials have shown that capecitabine is an active agent with acceptable toxicity and may reduce costs compared to endovenous treatment (15).

Post-therapeutic surveillance

Despite optimal therapeutic approach at the moment of diagnosis- with appropriate surgery, with or without adjuvant chemotherapy- 30-50% of patients with colon cancer will present disease progression and often some of these patients will die because of their disease. Local recurrence is more common for rectal cancer (40-50%) in patients without neo-adjuvant treatment and about half of the patients with CC develop metastases in the liver or show recurrence. The detection of disease progression as soon as possible is the main goal of post-therapeutic surveillance. Patient follow-up can be time and money consuming, that is why it must be justified by evidence and clear procedures. In the past 10 years, 4 studies showed improved survival in patients who had a more intense follow-up / monitoring compared to those with little or no supervision. The estimated overall survival benefit was between 7-13%. (16)

Surveillance led to early detection of recurrent disease and, especially in isolated locoregional recurrence detection, to a slight, insignificant increase in detecting liver metastases. Reduction in mortality was 9-13%, comparable to adjuvant chemotherapy in stage III. Despite improving survival and reducing mortality due to surveillance, globally there was a low concern for follow-up on patients with CC, one of the reasons possibly being the lack of a generally accepted follow-up algorithm. After a meta-analysis of several studies that included more than 20,000 patients it was shown that 82% of recurrences in stage III and 74% of stage II patients are diagnosed in the first 3 years after the primary tumor resection. (17) Surveillance is standard practice after finishing the multimodal treatment and consists of periodic visits and investigations that usually take place in a specialized center. The recommendations proposed are the following (18): intensive surveillance, clinical examination and CEA determination are recommended every 3, 6 months during the first 3 years after surgery and every 6 to 12 months 4 and 5 years postoperatively, colonoscopy should be performed annually during the first 3-5 years after surgery, thorax and abdominal CT every 6 to 12 months during the first 3 years after surgery (CEUS for replacing CT scan).

Despite the progress made, the compliance of the population regarding follow-up remains low and in this context the family physician should have an important role. (19)

Survivors of CC represent the third group of long term cancer survivors in Western countries (about 11% of the population). Important in their care are: surveillance in order to prevent recurrence or development of a new cancer, treatment of related cancer sequelae, evaluation of late medical and psychological effects. Most long-term survivors of CC have a good quality of life after treatment, but there are still many problems. Some patients may have impaired transit, diarrhea, constipation, colicky pain. Right hemicolectomy may cause loose stools, but this is reversed in time. It is of high importance to achieve dietary counseling especially in the first months after surgery. Survivors who have underwent chemotherapy with FOL-FOX may present polyneuropathy symptoms. (20). Many survivors with CC are over 65 years of age and reintegration in the work field is not a problem, but for young people reintegration and financial problems represent issues to be considered. High rates of mental depression in survivors were reported and it was found that psychosocial interventions are more limited. Most of the CC survivors die from other causes, therefore, surveillance for general medical problems - cardiovascular disease, diabetes, kidney disease, chronic lung disease, should receive the same attention as cancer surveillance.

Metastatic disease

25% of CC patients present metastases at the moment of the diagnosis and 50% of them will develop metastases. Clinical or biochemical suspicion of metastatic disease is confirmed by CT imaging, MRI, ultrasound or FDG PET that are useful in order to determine the extent of the disease. Histology of the primary tumor or metastasis is always required before starting chemotherapy. For metachronous metastases, HP confirmation must be obtained. Assessment of general condition, vital organ function and concomitant non-malignant diseases determine the therapeutic strategy for patients with metastatic CC. General condition of the patient and the predictive factors are important in choosing the optimal treatment. Most patients with metastatic disease do not have initial indication for resection, but some of them may become resectable after a favorable response to combined chemotherapy.

Resectable metastatic disease

10% of the 25% of patients with isolated metastases have surgical indication. Surgical resection should be considered for solitary or localized liver metastases because it offers the best chance of survival at 5 years, ranging from 30-35% to less than 50% in some selected series. Unfortunately, 60-75% of these patients will develop recurrence after resecting the liver metastases. (21)

Classic criteria for resectability of liver metastases were: 4 metastases, absence of extrahepatic metastasis and a minimum safety margin of 1 cm. Currently, these criteria are only indicative and the purpose is to achieve a R0 resection, the only potentially curative one. Currently, liver metastases are considered resectable when preoperative evaluation estimates that the lesions can be resected completely, at least two adjacent liver segments being preserved entirely with competent vascular and biliary drainage. In patients with normal liver, minimum liver outstanding volume that allows safe resection is 25-30%, while in patients with chronic liver disease or multiple courses of chemotherapy minimum volume is advisable to represent 30-40% of the total functional liver. In some specialized centers resection of liver metastases in serial interventions is performed because of the interval of time that allows regeneration of liver parenchyma.

For patients with resectable liver metastases, perioperative

chemotherapy with FOLFOX regimen improves progression-free survival at 3 years with 7-8%. Where perioperative chemotherapy was not given, postoperative adjuvant treatment is recommended with FOLFOX. Initially unresectable liver metastases can become resectable after chemotherapy and surgical indication is made after multidisciplinary consultation. Standard chemotherapy regimens used are: FOLFIRI or FOLFOX with the addition of a monoclonal antibody (bevacizumab or cetuximab) show increased efficiency. Surgery can be carried out under safe conditions, 4 weeks after the final cycle of chemotherapy ± Cetuximab and 5-8 weeks of chemotherapy + bevacizumab.

Radiofrequency ablation of liver metastases (up to 3-4 cm in diameter depending on the technical performance of the device) alone or in combination with surgical resection and systemic treatment is studied as an alternative or complementary method to surgical resection.

Resection of lung metastasis increases 5-year survival.

Inoperable metastatic disease

Optimal therapeutic strategy for patients with unresectable metastatic CC is evolving rapidly. The goal of treatment is prolonging survival, healing, relief of symptoms, improving quality of life. Due to the new treatment applied in recent years in metastatic CC median survival reached almost 24 months.

For the last 40 years, 5FU remained the standard agent in the treatment of advanced CC without surgical or radiotherapy control. The first palliative line of chemotherapy is a fluoropyrimidine endovenous or per os in different combinations and at different periods. The response rate varies widely, but is generally between 10-15%.

Combined chemotherapies of 5FU / LV / oxaliplatin FOL-FOX or 5FU / LV / irinotecan FOL-FIRI increase survival without progression of the disease and also determine a better survival than 5FU - Leucovorin. FOL-FOX and FOL-FIRI have similar efficacy, but different toxicity profile - alopecia and diarrhea for irinotecan and polyneuropathy for oxaliplatin. Both regimens consist of one application for 48 hours to 2 weeks.

The combination of capecitabine with oxaliplatin (CAPOX-capecitabine 2000 mg/m^2/day - days 1-14 and oxaliplatin 130 mg/m^2/day-first day) repeated after 3 weeks is an alternative to the combination of 5-fluorouracil + oxaliplatin infusion with the same effectiveness and safety.

The 3 weeks interval regime that consists of capecitabine / irinotecan (capecitabine and irinotecan 2000 mg/m^2/day-days 1-14 250 mg/m^2/day in the first day) appears to be more toxic than 5-fluorouracil/LV/irinotecan. This scheme is less standardized and uses a lower dose regimen (capecitabine and irinotecan 200 mg/m^2/day 1600 mg/m^2/day-2 weeks 1 day repeat 3 weeks).

The optimal duration of chemotherapy for metastatic CC remains controversial. The choice is either between a fixed period of treatment (3-6 months) or until disease progression or toxicity is observed. Reintroduction of combined chemotherapy is indicated for disease progression. Second-line chemotherapy should be proposed for patients with good performance status and good organ function. In patients refractory to fluoropyrimidine monotherapy second line treatment should associate oxaliplatin or irinotecan. In patients refractory to CAPOX or FOLFOX, irinotecan regimen is proposed as a second line. Monotherapy with irinotecan (350 mg/m^2 to 3 weeks) or FOLFIRI are the options. In patients refractory to FOLFIRI, FOLFOX or CAPOX the proposed second line treatment is a combination of monoclonal antibodies (21).

Monoclonal antibodies against vascular endothelial growth factor (VEGF), and against epidermal growth factor (EGFR) in combination with chemotherapy would be taken into account in these patients, because it improves the results in selected patients with metastatic CC.

Bevacizumab is an anti-VEGF antibody that in the case of metastatic CC increases the efficiency of an active cytotoxic regimen, increases overall survival, progression-free survival and the response rate of the first-line chemotherapy in combination with fluoropyrimidine + oxaliplatin, respectively, and in combination with FOLFOX in the second line treatment. Bevacizumab has some side effects: hypertension, proteinuria, arterial thrombosis, mucosal bleeding, gastrointestinal perforation and delayed wound healing. Bevacizumab is usually associated with a cytotoxic agent (fluoropyrimidin + /- oxaliplatin or irinotecan) until disease progression is observed, toxicity, or the metastases become resectable. AntiEGFR antibodies - Cetuximab and Panitumumab are active as monotherapy in refractory to chemotherapy metastatic CC. AntiEGFR antibody activity is limited to tumors exhibiting wild type KRAS gene. The combination of cetuximab and irinotecan has become the reference treatment in refractory to chemotherapy metastatic CC with KRAS wild-type. AntiEGFR antibodies must not be combined with bevacizumab. The efficiency of antiEGFR antibodies is limited to KRAS wild-type tumors and should not be used in patients with KRAS mutation. Approximately 40% of metastatic CC exhibit KRAS mutations, and 5-10% of CC exhibit mutations in the BRAF gene. KRAS and BRAF mutations are mutually exclusive. AntiEGFR antibody activity in refractory to chemotherapy CC is also limited to tumors with wild-type BRAF gene. AntiEGFR antibodies can cause acneiform eruptions, hypomagnesaemia. Cetuximab is a chimeric antibody that gives allergic reactions more frequently than Panitumumab, human monoclonal antibody.

In patients with unresectable metastases of CC, suffering from symptoms of the primary tumor (bleeding, occlusion) the resection of the primary tumor is taken into account before starting the chemotherapy. In patients with metastatic rectal cancer, that exhibit symptoms of the primary tumor, radiation (possibly in combination with chemotherapy) should be taken into account in order to control the symptoms (21).

Conclusions

Establishing therapeutic strategy must take into account not only the TNM staging but histopathological, immunohistochemical and genetic prognostic factors, selecting the patients

at high risk of further disease progression for adjuvant therapy. The current methods of CC evaluation allow the planning of individualized therapeutic strategies, which would lead to optimal results. Selecting chemotherapy protocols should be based on predictive factors of response to the proposed adjuvant treatment.

References

1. Popescu Alina, Sporea I. Screening for colonic cancer between ideal and practical possibilities. Timișoara: Editura Mirton; 2009.
2. American Cancer Society Guidelines. American Cancer Society recommendations for colorectal cancer early detection http://www.cancer.org.
3. Schmoll HJ, Van Cutsem E, Stein A, Valentini V, Glimelius B, Haustermans K, et al. ESMO consensus guidelines for management of patients with colon and rectal cancer: a personalized approach to clinical decision making. Ann Oncol. 2012;23(10): 2479-516.
4. Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandalà M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24 Suppl 6:vi64-72.
5. Rockey DC, Auslander A, Greenberg PD. Detection of upper gastrointestinal blood with fecal ocult blood tests. Am J Gastroenterol. 1999;94(2):344-50.
6. Kronborg O1, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colo-rectal cancer with fecal occult blood test. Lancet. 1996;348(9040):1467-71.
7. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of fecal occult blood screening for colorectal cancer. Lancet. 1996;348(9040):1472-7.
8. Kewenter J, Brevinge H, Engarțs B, Haglind E, Ahrén C. Results of screening,rescreening and follow-up in detection of colorectal cancer by fecal ocult blood testing. Results for 68308 subjects. Scand J Gastroenterol. 1994;29(5):468-73.
9. Cameron JL, Cameron AM. Current Surgical Therapy, 11-edition. Elsevier; 2014.
10. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med. 2004;350(20):2050-9.
11. Hewett PJ, Allardyce RA, Bagshaw PF, Frampton CM, Frizelle FA, Rieger NA, et al. Short-term outcomes of the Australasian randomized clinical study comparing laparoscopic and conventional open surgical treatments for colon cancer: the ALCCaS trial. Ann Surg. 2008;248(5):728-38.
12. André T, Boni C, Mounedji-Boudiaf L, Navarro M, Tabernero J, Hickish T, et al. Oxaliplatin, fluorouracil and leucovorin as adjuvant treatment for colon cancer. N Engl J Med. 2004;350 (23):2343-51.
13. André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27(19):3109-16.
14. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. J Clin Oncol. 2011 10;29(11):1465-71.
15. Twelves C, Wong A, Nowacki MP, Abt M, Burris H 3rd, Carrato A, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352(26):2696-704.
16. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev 2007:CD002200.
17. Sargent DJ, Patiyil S, Yothers G, Haller DG, Gray R, Benedetti J, et al. End points for colon cancer adjuvant trials: observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. J Clin Oncol. 2007;25(29):4569-74. Epub 2007 Sep 17.
18. Tsikitis VL, Malireddy K, Green EA, Christensen B, Whelan R, Hyder J, et al. Postoperative surveillance recommendations for early stage colon cancer based on results from the clinical outcomes of surgical therapy trial. J Clin Oncol. 2009;27(22): 3671-6.
19. Grunfeld E1, Earle CC. The interface between primary and oncology specialty care: treatment through survivorship.J Natl Cancer Inst Monogr. 2010;2010(40):25-30.
20. Howell D, Hack TF, Oliver TK, Chulak T, Mayo S, Aubin M, et al. Models of care for post-treatment follow-up of adult cancer survivors: a systematic review and quality appraisal of the evidence. J Cancer Surviv. 2012;6(4):359-71.
21. Van Cutsem E1, Nordlinger B, Cervantes A; ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. Ann Oncol. 2010;21 Suppl 5:v93-7.