Journal of Surgery
[Jurnalul de Chirurgie]

Review Article Open Access

Therapeutic Management of Colon Cancer

Ana-Maria Todosi[1,2], Mihaela Mădălina Gavrilescu[1,2] and Viorel Scripcariu[1,2]

[1]"Gr. T. Popa" University of Medicine and Pharmacy, Iași, Romania
[2]I-st Clinic of Oncologic Surgery, Iași Regional Cancer Institute, Romania

Abstract

Colorectal cancer is a major public health problem worldwide, and a major cause of mortality and morbidity. Correct pretherapeutic staging has the role of guiding the management of colon cancer patients. The diagnosis is guided by the clinical symptoms. Chemotherapy is an important part of colon cancer treatment. Chemotherapy regimens are adapted to tumor stage and patient status and have various side effects and variable survival outcomes. International guidelines recommend different treatments depending on the presence or absence of metastases. The primary goal of treatment in nonmetastatic colon cancer is surgical removal of the tumor which could be the first step of the complex therapy or preceded by neoadjuvant therapy, depending on pretherapeutic staging. In resectable nonmetastatic tumors the preferred surgical procedure is colectomy with en bloc removal of regional lymph nodes. The extent of colectomy should be based on tumor location. The management of metastatic colon cancer also targets the therapeutic approach of the metastatic disease. Therapy is standardized and applied according to tumor stage. Surveillance has a major role in therapeutic success, reason why a time schedule and a protocol adapted to the primary lesion are essential. The goal of implementing the recommendations of international guidelines for the treatment of colon cancer is to provide a uniform treatment for this disease in view of improving overall survival of patients.

Keywords: Colon Cancer; Management; International guidelines

Introduction

According to the World Health Organization in 2010 cancer overtook ischemic heart disease as a leading cause of death [1]. Colorectal cancer (CRC) is a major public health problem worldwide, representing a major cause of death and morbidity. Worldwide, CRC is the fourth leading cause of deaths [2], the third most common cancer in men (663,000 cases, 10% all cancer cases), and the second most common cancer in women (571,000 cases, 9.4% of all cancer cases) [3].

Clinical Diagnosis of Colon Cancer

Alarm clinical signs are those which make a person seek medical attention, and thus the diagnosis is symptomatic in 71% of cases. Abdominal pain in the colon area is vague, or in progressively worsening episodes which subside after bowel movement, suggesting a tension in the colonic area upstream a stenosing lesion. Most frequently, pain reveals a right colon cancer. A change in bowel habits is common and includes rebel diarrhea, habitual constipation or alternating diarrhea and constipation. Changes in bowel habits and rectum bleeding most frequently are suggestive of left colon cancer. Intestinal bleeding is less abundant, but repeated, spontaneous or favored by anticoagulant therapy. The tumor is rarely accessible to palpation. Rectal or vaginal examination may reveal a tumor prolapsed into the Douglas pouch or the presence of peritoneal carcinomatosis lymph nodes. Colon cancer may suspected be in the presence of lung or liver metastases, perforation with manifestations of peritonitis, or stenosis with clinical picture of obstruction. Symptoms like anemia or unexplained fever may guide diagnosis [4].

Pretreatment Staging

Preoperative staging of patients presenting with resectable invasive colon cancer requires the following investigations: total colonoscopy with biopsy, complete blood count, biochemistry, carcinoembryonic antigen, and chest-abdominal-pelvic computed tomography (CT). CT scan should be with contrast, and if the contrast is contraindicated an abdominal-pelvic MRI with contrast should be performed [5].

Neoadjuvant Treatment

Chemotherapy is an important part in the treatment of colon cancer. Fluoropyrimidines, e.g., 5-fluorouracil (5-FU), administered both intravenously and orally, are extensively used first-line chemotherapeutic agents in the treatment of CRC. The most used are the regimens consisting in 48-hour bolus and intravenous 5-flurouracil/Leucoverin (5-FU/LV) every two weeks. Combinations of 5-FU/LV/Oxaliplatin (FOLFOX) or 5-FU/LV/irinotecan (FOLFIRI) have a much higher response rate, a longer disease-free interval and longer survival. FOLFOX and FOLFIRI have a similar activity but different toxicity: alopecia and diarrhea for irinotecan and polyneuropathy for oxaliplatin. The combination capecitabine plus oxaliplatin (CAPOX) is an alternative to the combination 5-FU/oxaliplatin. The second-line chemotherapeutic agents are oxaliplatin and irinotecan. In patients refractory to FOLFOX or CAPOX an irinotecan-based regimen is proposed as second-line treatment [6].

Monoclonal antibodies against epidermal growth factor (EGF), vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2) inhibitors in combination with chemotherapeutic agents should be considered in the treatment of metastatic colon cancer. Bevacizumab (rhuMab -VEG, Avastin®) is a recombinant, humanized monoclonal antibody that binds to VEGF receptor. VEGF stimulates endothelial cells growth being expressed in 50% of cases, and correlates with a poor prognosis. 5-FU/LV plus bevacizumab as first-line

***Corresponding author:** Ana-Maria Todosi , Str General Henry Mathias Berthlot 2-4, Clinica I Chirurgie Oncologică, Institutul Regional de Oncologie Iaşi, Romania, Tel: 0040741667683; 0040 (0) 374 27 88 10; Fax: 0040 (0) 374 27 88 02; E-mail: todosi_anamaria@yahoo.com

Received May 04, 2014; **Accepted** June 18, 2014; **Published** September 20, 2014

Citation: Todosi AM, Gavrilescu MM, Scripcariu V. Therapeutic Management of Colon Cancer. Journal of Surgery [Jurnalul de chirurgie] 2014; 10(3): 213-216 DOI: 10.7438/1584-9341-10-3-2.

treatment showed: response rates of 17% for 5-FU/LV alone and 40% for 5FU/LV plus bevacizumab; time to disease progression 5.2 *vs.* 9.0 months and median survival 13.8 *vs.* 21.5 months, respectively. Cetuximab (Erbitux®) is a monoclonal antibody with highly specificity and high affinity for EGFR causing a direct inhibition of angiogenesis. It demonstrated response rates of 17% in association with irinotecan in pretreated patients refractory to irinotecan and 5-FU. Irinotecan ± Bevacizumab/Cetuximab association in CRCs refractory to irinotecan resulted in a partial response of 35% and 23%, and a time to disease progression of 5.8 and 4.0 months, respectively [7].

Recommendations from International Guidelines

Management of no metastatic colon cancer

According to the National Comprehensive Cancer Network (NCCN) guidelines the treatment options for colon cancer depend on the histopathological stage [5]. In resectable non-metastatic colon cancer the surgical procedure of choice is colectomy with regional lymph node removal. The extent of colectomy should be based on tumor location, part of the intestine and vascular arch containing the regional lymph nodes being removed. Other lymph nodes, such as those at the origin of the feeding vessels (e.g., apical nodes) and other lymph nodes located outside the resection field should have biopsy or be removed. To be curative removal should be complete, and positive lymph nodes left behind signifies incomplete resection (R2). Laparoscopic colectomy is an option in the surgical management of colon cancer.

Adjuvant treatment of resectable colon cancer has gained and increasing interest. The choice of adjuvant therapy for patients with non-metastatic colon cancer depends on the stage of disease.

- Patients with stage I colon cancer do not require adjuvant treatment
- Patients with low-risk stage II are eligible for clinical trials, observed without adjuvant therapy or administration of capecitabine or 5-FU/LV. Latest trials do not consider oxaliplatin based chemotherapy, and consequently FOLFOX (infused 5-FU, leucovorin, oxaliplatin) is a therapeutic option for these patients.
- Patients with high-risk stage II are defined as having a poor prognosis. The high-risk features include T4 tumors (stage IIB/IIC), poorly differentiated histology, except for patients with high frequency of microsatellite stability, lymphovascular or perineural invasion, bowel obstruction, lesion with localized or closed perforation, positive or indeterminate margins, or insufficient number of lymph nodes (<12 nodes) can be candidates for adjuvant chemotherapy with 5-FU/L, capecitabine, FOLFOX, capecitabine/oxaliplatin (CapeOx) or FLOX.
- For stage III patients the recommendations are 6 month-adjuvant chemotherapy after surgery. Therapeutic options are FOLFOX or CapeOX; bolus 5-FU/LV/oxaliplatin; or a single chemotherapeutic agent, 5-FU/LV or capecitabine, in patients in which oxaliplatin is presumed to be ineffective [5].
- According to ESMO (European Society for Medical Oncology) guidelines the treatment of colon cancer should be based on stage-specific strategies. As to surgical treatment, one of its objectives is the resection of the involved colon segment together with the draining lymph nodes. The extent of surgical resection is determined by blood transfusions and lymph node distribution. Resection should include a segment of colon at least 5 cm on either side pf the tumor. The laparoscopic approach was accepted especially in left colon surgery in which it has proven its benefits. ESMO guidelines recommend the following treatment options:
- Stage 0 - (i): local excision or polypectomy, (ii) segmental resection for larger lesions not amenable to local excision.
- Stage I: wide surgical resection with anastomosis
- Stage II: (i) wide surgical resection with anastomosis; (ii) after surgery, patients considered at high risk should receive adjuvant therapy (stage II). All patients should be evaluated for entry into randomized clinical trials evaluating new therapeutic options for adjuvant treatment
- Stage III: (i) wide surgical resection with anastomosis; (ii) after surgery, the standard treatment is a doublet schedule with oxaliplatin and 5-FU/folinic acid (LV) (FOLFOX4 or FLOX). When oxaliplatin is contraindicated, monotherapy with intravenous 5-FU/LV or oral fluoropyrimidines (capecitabine) can be administered. The benefits of doublet scheme with oxaliplatin and 5-FU/LV (FOLFOX scheme) have been demonstrated by a number of clinical trials that showed a significant increase in disease-free interval after 3 years, and a 23% reduction in relapse rate compared to patients receiving only 5FU/LV [8].

Management of Metastatic Colon Cancer

Approximately 50-60% of the patients with colorectal cancer develop metastases and of these 80-90% have unresectable liver metastases. About 20% to 34% of patients present synchronous liver metastases. Although the standard treatment for patients with liver metastases is surgical resection, they may benefit from targeted treatment instead of surgery.

Port-a-cath implantation into the hepatic artery during surgery for liver resection with administration of chemotherapeutic agents may be an option. The administration of 5-FU with or without LV using a hepatic artery catheter proved superior to systemic chemotherapy, with a liver disease-free interval of 2 years.

Radiation delivered directly to the liver by arterial radioembolization with yttrium -90 microspheres is a therapeutic option. External beam radiation therapy can be used in very carefully selected cases, when the patient has a limited number of liver or lung lesions or is symptomatic. Tumor ablation can be a treatment option in patients who do not require hepatic resection because of comorbidities, location of tumors, or inadequate liver size after ablation. Approximately 17 % of patients with metastatic colon cancer have peritoneal carcinomatosis, in 2% the peritoneum being the sole site of metastasis. The treatment of peritoneal carcinomatosis is palliative rather than curative consisting of systemic therapy. Another treatment strategy could be hyperthermic intraoperative intraperitoneal chemotherapy [5].

Therapeutic Indications and Surveillance

- **Tis, T1, N0, M0** - no treatment; surveillance by colonoscopy at 1 year, if advanced adenoma repeat in 1 year, if no advanced adenoma repeat in 3, then every 5 years.
- **T2, N0, M0** - no treatment; surveillance by colonoscopy at 1 year, if advanced adenoma repeat in 1 year, if no advanced adenoma repeat in 3, then every 5 years.
- **T3, N0, M0** no high-risk - clinical trial/observation/capecitabine or 5FU/leucoverin
- **T3, N0, M0** high-risk for systemic recurrence; **T4, N0, M0** - capecitabine or 5-FU/LV, or FOLFOX, or CapeOX, or FLOX, or clinical trial, or observation.
- Surveillance for stages T3N0M0 and T4N0M0 includes history and physical examination every 3-6 months for the first 2 years, then every 6 months for 5 years; carcinoembryonic antigen every 3-6 months for the first 2 years, then every 6 months for

5 years; chest-abdominal-pelvic CT annually for up to 5 years in patients at high risk for recurrence; colonoscopy in 1 year, if no preoperative colonoscopy due to obstructive lesion, and in case of preoperative colonoscopy in 3-6 months, repeated at 1 year if advanced adenoma or at 3 years and then every 5 years if not advanced adenoma; PET-CT is not routinely recommended.

- **T1-3, N1-2, M0** or **T4, N1-2, M0** – FOLFOX, or CapeOX, or FLOX, or capecitabine or 5-FU/LV
- Surveillance includes history and physical examination every 3-6 months for the first 2 years, then every 6 months for 5 years; carcinoembryonic antigen every 3-6 months for the first 2 years, then every 6 months for 5 years; chest-abdominal-pelvic CT annually up to 5 years for patients at high risk for recurrence; colonoscopy in 1 year, if no preoperative colonoscopy due to obstructive lesion, and in case of preoperative colonoscopy in 3-6 months, repeated at 1 year if advanced adenoma or at 3 years and then every 5 years if not advanced adenoma; PET-CT is not routinely recommended.
- **Any T, any N, M1**: suspected or proven metastases, synchronous tumors - diagnosis by colonoscopy, chest-abdominal-pelvic CT, blood count, biochemistry, carcinoembryonic antigen, determination of KRAS gene status (if K-RAS is non-mutated, BRAF testing), needle biopsy if clinically indicated, PET-CT if M1 disease can be surgically approached, multidisciplinary assessment including a surgeon experienced in the resection of liver and pulmonary metastases

Resectable Synchronous Liver and/or Lung Metastases

1) colectomy with resection of liver or lung metastases followed by chemotherapy FOLFOX or CapeOx;

2) neoadjuvant treatment for 2-3 months (FOLFIRI or FOLFOX or CapeOx ± bevacizumab);

3) FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± Cetuximab if K-RAS is wild-type) followed by synchronous colectomy and resection of metastatic disease.

4) colectomy followed by chemotherapy (for 2-3 months) FOLFIRI or FOLFOX or CapeOx ± bevacizumab or FOLFIRI or FOLFOX ± panitumumab or FOLFIRI ± Cetuximab (KRAS wild-type) and resection of metastatic disease.

Surveillance includes history and physical examination every 3-6 months for 2 years, then every 6 months for 5 years; carcinoembryonic antigen every 3-6 months in the first 2 years, then every 6 months for 3-5 years; chest-abdominal-pelvic CT every 3-6 months in the first 2 years, then every 6-12 months for 5 years; colonoscopy in 1 year, if no preoperative colonoscopy due to obstructive lesion, and in case of preoperative colonoscopy in 3-6 months, repeated at 1 year if advanced adenoma or at 3 years and then every 5 years if not advanced adenoma [9];

Unresectable synchronous liver and/or lung metastases:

1) FOLFIRI or FOLFOX or CapeOx ± bevacizumab

2) FOLFIRI or FOLFOX ± Panitumumab

3) FOLFIRI ± cetuximab (K-RAS wild-type)

4) FOLFOXIRI ± bevacizumab

5) Colon resection should be considered only if there is imminent risk of obstruction or significant bleeding.

Reassess for conversion to resectable every two months, if resectability is a reasonable goal. If the lesions are resectable perform synchronous resection of colon and metastases followed by chemotherapy regimens recommended for advanced disease. If metastases remain unresectable chemotherapy for metastatic disease should be administered. Surveillance of patients with unresectable metastases is the same as for those with resectable metastases.

Synchronous Abdominal/Peritoneal Metastases

1) When nonobstructing administer chemotherapy regimens for advanced disease.

2) the presence of obstruction or imminent obstruction requires colon resection, or colostomy, or bypass surgery to prevent obstruction or stenting, followed by chemotherapy for advanced disease.

Recurrent Colon Cancer

When there is an elevation in serum carcinoembryonic antigen, the recommendations are: physical examination, colonoscopy and chest-abdominal-pelvic CT. If the results of these imaging investigations are negative should consider a PET-CT, with reassessment in case of negative results in 3 months by chest-abdominal-pelvic CT. If a tumor recurrence is found administer the treatment recommended for metastatic disease [9].

Conclusions

Colon cancer is a major public health problem. The treatment of this cancer is standardized, and the recommendations from international guidelines are specific to tumor stage. An effective treatment heavily depends on accurate staging of patients and the administration of the treatment regimens adequate for each patient category. Oncologic surveillance plays a very important role in therapeutic success, being based on a time-schedule and a protocol adapted according to the

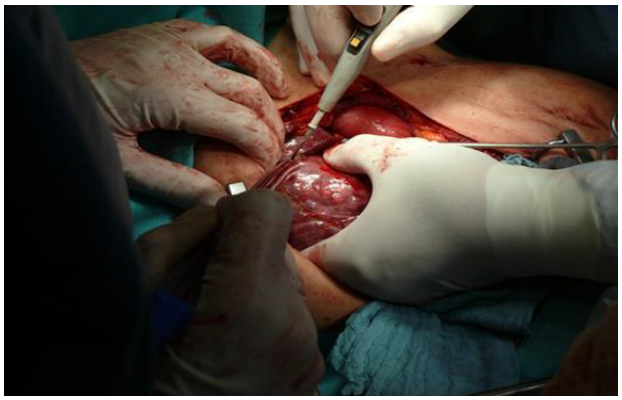

Figure 1: Surgical treatment of liver metastases in colon cancer – before resection (Collection of V Scripcariu).

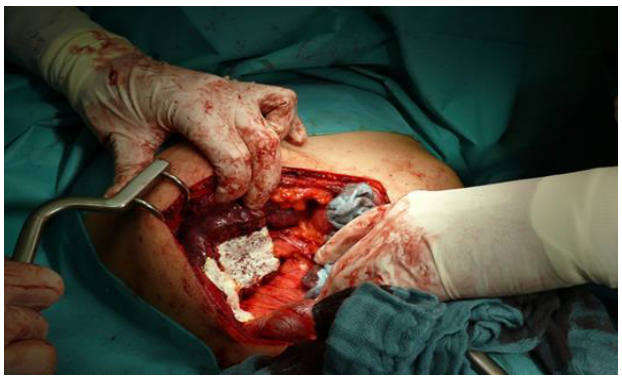

Figure 2: Surgical treatment of liver metastases in colon cancer – after resection (Collection of V Scripcariu).

primary lesion. The goal of implementing the recommendations of international guidelines for the treatment of colon cancer is to provide a uniform treatment for this disease in view of improving overall survival of patients.

Conflict of interest

The authors have no conflicts of interest to declare.

Note: The corresponding author is a PhD student at the "Gr. T. Popa" University of Medicine and Pharmacy Iasi. This paper is the result of research during the doctoral internship within the project "Inter-university partnership for increasing the medical doctoral quality and interdisciplinary through doctoral scholarships - DocMed.net" POSDRU/107/1.5/S/78702.

Acknowledgement

Thanks AMPOSDRU for supporting the research for this study.

References

1. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, et al. (2010) Annual report to the nation on the status of cancer, 1975-2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. See comment in PubMed Commons below Cancer 116: 544-573.
2. Haggar FA, Boushey RP (2009) Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. See comment in PubMed Commons below Clin Colon Rectal Surg 22: 191-197.
3. Globocan 2008. Colorectal cancer.
4. Viguier J, Bourlier P, Karsenti D, de Calan L, Danquechin Dorval E (2003) Cancer du côlon. Encycl Méd Chir (Editions Scientifiques et Médicales Elsevier SAS, Paris, tous droits réservés), Gastro-entérologie, 9-068-A-10, 18.
5. National Comprehensive Cancer Network: NCCN Practice Guidelines in Oncology v.3 2013.
6. Van Cutsem E, Nordlinger B, Cervantes A; ESMO Guidelines Working Group (2010) Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. See comment in PubMed Commons below Ann Oncol 21 Suppl 5: v93-97.
7. Miron L, Marinca M (2006) [Sistematic treatment of metastatic colorectal cancer: actual standards, future options]. J Chir (3) 260-264.
8. Labianca Rs, Nordlinger B, Beretta GD, Brouquet A, Cervantes A; ESMO Guidelines Working Group (2010) Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up. See comment in PubMed Commons below Ann Oncol 21 Suppl 5: v70-77.
9. National Comprehensive Cancer Network: NCCN Practice Guidelines in Oncology v.2 2014.