Update for Surgeons: Recent and Noteworthy Changes in Therapeutic Regimens for Cancer of the Colon and Rectum

Claudia Hriesik, MD, Ramesh K Ramanathan, MD, Steven J Hughes, MD, FACS

Colorectal cancer (CRC) is the third most common type of cancer, accounting for 11% of cancers diagnosed in men and women in the US (available at: http://www.cancer.org/cancerinfo/specific.asp). Approximately 130,000 new cases of CRC are diagnosed each year, circa 100,000 in the colon and the remainder in the rectum. CRC remains the second leading cause of cancer mortality,[1] emphasizing the need for improvements in therapeutic options.

For more than 3 decades, 5-FU had been the only known and applied chemotherapeutic agent with substantial activity against colorectal cancer,[2] but our increasing understanding of the molecular basis of cancer has recently led to development of new agents with antitumoral activity, including biologic-based therapy. These cancer drugs complement the action of 5-FU when used in combination or when used alone. Chemotherapy for CRC, as such, has undergone dramatic changes in the last few years. The speed of these advances has left many surgeons confused or uninformed of changes in the standard of care with respect to what patient should be offered what additional therapy, and what that therapy entails.

This review is designed to summarize literature not typically screened or readily available to surgeons, but essential to optimal surgical care of CRC patients. We summarize recent advancements in treatment regimen options and toxicities, novel therapeutics, patient selection, and future directions.

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From the Department of Surgery, Division of Surgical Oncology (Hriesik, Hughes) and Department of Medicine, Division of Hematology and Oncology (Ramanathan), University of Pittsburgh School of Medicine, and University of Pittsburgh Cancer Institute, Pittsburgh, PA.
Correspondence address: Steven J Hughes, MD, FACS, University of Pittsburgh, Scaife Hall, 3550 Terrace St, Pittsburgh, PA 15261. email: hughess2@upmc.edu

HISTORIC PERSPECTIVE

5-FU is the oldest chemotherapeutic still in use. First reported in the 1950s, it remains the backbone of colorectal cancer chemotherapy. Early experience demonstrated a clear benefit of this therapy in stage III and IV patients. In the 1980s, levamisole was noted to benefit 5-FU, given its immunostimulatory properties.[2,3] This drug combination reduced tumor recurrence by 40% and was regarded as gold standard therapy until 1996, when clinical trials found that leucovorin (folinic acid) in combination with 5-FU was more effective. Clear benefit for stage II patients was not established.[3] In addition, this well-tolerated regimen allowed a shorter treatment course of 6 months instead of the 12-month regimen consisting of 5-FU and levamisole. Until recently, this course of therapy was the standard of care for stage III and IV patients.

Recent chemotherapy trials have changed first-line therapy for CRC

Within the past decade, oxaliplatin (inhibition of DNA replication through the formation of bulky DNA adducts) and irinotecan (inhibition of DNA replication and transcription through topoisomerase interaction) have been shown to have activity against CRC. Several randomized clinical trials have been performed to test the efficacy and safety of both. Importantly, these trials first evaluated the effect of these agents in patients with measurable disease (palliative setting), and some of these now proved regimens have subsequently been evaluated in the adjuvant setting. In general, patient accrual to these trials, and treatment in general, is guided by disease stage at presentation (Table 1) and patient performance status (Table 2). The Eastern Cooperative Oncology Group or Karnofsky scale of patient performance status currently drive decision making. Typically, patients with poor performance as defined by an Eastern Cooperative Oncology Group score of 3 or greater (or the Karnofsky equivalent) are excluded from trials or standard therapies.

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Abbreviations and Acronyms

bFOL = bolus FOLFOX
CapeOx = capecitabine plus oxaliplatin
CRC = colorectal cancer
EGFR = epidermal growth factor receptor
FOLFIRI = 5-FU and irinotecan
FOLFOX = 5-FU, leucovorin, and oxaliplatin
IFL = 5-FU and leucovorin combined with irinotecan
IROX = irinotecan and oxaliplatin
LV = leucovorin
TTP = time to progression

New developments for first-line therapy of metastatic CRC

With the introduction of new drugs other than 5-FU, a number of developments have taken place in palliative treatment of advanced (defined as recurrent or metastatic, or both, CRC that is unresectable) CRC. To test the hypothesis that irinotecan prolongs survival, Saltz and colleagues[4] in 2000 compared the outcomes in 683 advanced CRC patients after therapy with bolus 5-FU and leucovorin (LV) (n = 452 patients) compared with patients treated with bolus 5-FU and LV combined with irinotecan (IFL) (n = 231 patients). This triple-agent therapy, as shown in Table 3, substantially improved disease-free survival from 4.3 months in the 5-FU/LV arm to 7 months in the irinotecan arm. Overall survival in the irinotecan group was 14.8 months compared with 12.6 months in the group not receiving irinotecan. The response rate was considerably higher, reaching 39% in the irinotecan group. The most common side effect in both trial arms was severe diarrhea, and this was reported more frequently among patients receiving irinotecan (Table 4). It was concluded that weekly therapy with IFL was well-tolerated and importantly, superior to the previously widely applied regimen consisting of 5-FU and LV alone. Based on the results of this study, IFL became the standard of care for patients with advanced, previously untreated CRC.

Similar supportive data for the efficacy of irinotecan in CRC was identified by Douillard and colleagues.[5] Unlike the US practice of bolus 5-FU administration, in Europe continuous IV schedules have been used. This trial investigated the efficacy of combination 5-FU and irinotecan (FOLFIRI) in patients with untreated metastatic CRC. A total of 387 patients were enrolled, 199 patients were assigned to the FOLFIRI treatment arm. This treatment group (FOLFIRI) experienced a substantially higher response rate of 49%, compared with a response rate of 31% in patients receiving 5-FU/LV. Overall survival measuring 17.4 months in the FOLFIRI arm was reflective of tumor response. Disease-free survival was similarly impacted, reaching 6.7 months after treatment with FOLFIRI compared with

Table 1. Current American Joint Commission on Cancer Staging of Colorectal Cancer

Stage	5-Year overall survival (%)
Stage 0	
Tis, N0, M0	
Stage I	93
T1, N0, M0	
T2, N0, M0	
Stage IIA	85
T3, N0, M0	
Stage IIB	72
T4, N0, M0	
Stage IIIA	83
T1, N1, M0	
T2, N1, M0	
Stage IIIB	64
T3, N1, M0	
T4, N1, M0	
Stage IIIC	44
Any T, N2, M0	
Stage IV	8
Any T, any N, M1	

M0, no distant metastases; M1, distant metastases present; N0, no regional lymph node involvement; N1, one to three nodes positive; N2, four or more lymph nodes positive; T1, tumor invades submucosa; T2, tumor invades muscularis propria; T3, tumor invades muscularis propria into the subserosa, or nonperitonealized pericolic tissues; T4, tumor directly invades other structures or organs or perforates visceral peritoneum.

Table 2. Comparison of Eastern Cooperative Oncology Group and Karnofsky Assessment of Patient Performance Status

ECOG status	Definition	Karnofsky status
0	No symptoms, fully active, able to work	100
1	Symptomatic, but not spending extra time in bed. Able to do light work	80 or 90
2	In bed < 50% of the day, unable to work, but can take care of self	60 or 70
3	In bed > 50% of the day, but not bedridden, limited self-care	40 or 50
4	Completely bedridden	20 or 30
5	Moribund, death	0–20

ECOG, Eastern Collaborative Oncology Group.